THE REACTIONS OF SEMICARBAZONES, THIOSEMICARBAZONES AND RELATED COMPOUNDS, INCLUDING THE ACTION OF AMINES ON AMINOCARBOCARBAZONES.

A THESIS PRESENTED BY

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CONTENTS.

Page

General Introduction..... 1

PART 1.

The Action of Amines on Amino Carbocarbazones.

Introduction..... 4
Benzylamine.....Theoretical..... 11
.....Experimental..... 15
Aniline.....Theoretical..... 21
.....Experimental..... 22
B-Naphthylamine.....Theoretical..... 27
.....Experimental..... 28
Piperidine.....Theoretical..... 32
.....Experimental..... 33
Methylaniline.....Experimental..... 35
Dibenzylamine.....Experimental..... 36

PART 1 B.

The Action of Pyridyl Hydrazine on Semicarbazones

Introduction..... 38
Preparation of 2 Pyridyl Hydrazine..... 44
Benzophenone Semicarbazone..... 46
Benzaldehyde Semicarbazone..... 49
Acetophenone Semicarbazone..... 50
Benzoin Semicarbazone..... 51
p-Methoxy-Hydratropaldehyde Pyridyl Hydrazone.. 53
Benzoin Pyridyl Hydrazone..... 54
Methyl Cyclohexanone Pyridyl Hydrazone..... 56
Menthone Pyridyl Hydrazone..... 56

PART 2.

The Resolution of Racemic Aldehydes and Ketones via Active Semicarbazides.

Introduction..... 59
1.3-Methyl Cyclohexanone via δ-(∝ Phenylethyl) Semicarbazide..... 64
1.3-Methyl Cyclohexanone via δ (∝ Phenylethyl) Thiosemicarbazide..... 72
Camphor via δ-(∝ Phenylethyl) Semicarbazide..... 74
Camphor via δ-Camphyl Semicarbazide..... 81
Benzoin via δ-Camphyl Semicarbazide..... 87
Benzoin via δ (∝ Phenylethyl) Thiosemicarbazide. 91

PART 3.

Thiazole Formation from Thiosemicarbazones.

Introduction..... 97
Acetone Thiosemicarbazone and Active Ethyl Phenyl Chlor-Acetate..... 102
Ethyl ∝ Brom Methyl Ethyl Acetate..... 103
Ethyl ∝ Brom Iso Butyrate..... 105
Diethyl Brom Acetic Ester..... 106
Methyl Ethyl Brom Malonic Ester..... 107
Methyl Ethyl Sulphocyan Acetic Ester..... 109
Resolution of 2-Imino-5Methyl Thiazolidene..... 111

PART 4.

Reactions of Thiosemicarbazones with the Anhydrides of Unsaturated Acids.

Introduction..... 117
Maleic Anhydride and Thiosemicarbazide..... 121
Citraconic Anhydride and Thiosemicarbazide..... 124
Maleic Anhydride and Acetophenone Thiosemicarbazone..... 126
Maleic Anhydride and Methyl Cyclohexanone Thiosemicarbazone..... 129
Citraconic Anhydride and Benzaldehyde Thiosemicarbazone..... 131
Cinnamic Anhydride and Thiosemicarbazide..... 133
Crotonic Anhydride and Thiosemicarbazide..... 134

PART 5

The Action of Thiosemicarbazones on Halogeno-Aldehydes and Ketones.

Introduction..... 137
Benzaldehyde Thiosemicarbazone and Chloracetone..... 140
Acetone Thiosemicarbazone and Chloracetone..... 143
Acetophenone Thiosemicarbazone and Chloracetone..... 145
Acetone Thiosemicarbazone and Chloracetaldehyde..... 149
Benzal Thiosemicarbazone and Chloracetaldehyde..... 150

PART 6.

The Action of Halogens on Thiosemicarbazones.

Introduction..... 152
Acetophenone Thiosemicarbazone Mono-Bromide..... 154
Acetophenone Thiosemicarbazone Tri-Bromide..... 154
Acetophenone Thiosemicarbazone Mono-Iodide..... 155
Acetophenone Thiosemicarbazone Tri-Iodide..... 156
Benzal Thiosemicarbazone Di-Iodide..... 157
Benzal Thiosemicarbazone Tetra-Iodide..... 158
Acetone Thiosemicarbazone Mono-Iodide..... 158
Acetophenone δ-Benzyl Thiosemicarbazone Mono-Iodide..... 159
Benzal Semicarbazone Di-Iodide..... 161

APPENDIX.

Appendix..... 162
Hydrolysis of Acetophenone δ Benzyl Semicarbazone.. 163
Chloro-Methyl *l*-Menthyl Ether..... 165

GENERAL INTRODUCTION.

The work described in the following pages, mainly on the reactions of semicarbazones and thiosemicarbazones forms part of an investigation which has been followed for several years, under the direction of Professor F.J.Wilson, in the organic chemistry department of this college.

While the complete work is concerned with semicarbazones and related compounds it is convenient to divide it into several sections viz;-

Part 1.

(A) Action of Amines on Aminocarbocarbazones.

(B) Action of Pyridyl Hydrazine on Semicarbazones.

Part 2.

Resolution of Aldehydes and Ketones via Active Thiosemicarbazides and Semicarbazides.

Part 3

Thiazol Formation from Thiosemicarbazones.

Preparation of Optically Active Thiazoles.

Part 4

Action of Thiosemicarbazones on Anhydrides of Unsaturated Acids.

Part 5

Action of Thiosemicarbazones on Halogeno-Aldehydes and Ketones.

Part 6

Action of Thiosemicarbazones on Halogens.

Each section of the work is preceded by a brief introduction, in which previous publications, with some bearing on the subject, are discussed.

PART 1

THE ACTION OF AMINES ON AMINOCARBOCARBAZONES.

INTRODUCTION.

The action of amines on semicarbazones, $RR'C:N\cdot NH\cdot CO\cdot NH_2$;
2 substituted semicarbazones, $RR'C:N\cdot NR''\cdot CO\cdot NH_2$;
thiosemicarbazones, $RR'C:N\cdot NH\cdot CS\cdot NH_2$;
and semioxamazones, $RR'\cdot C:N\cdot NH\cdot CO\cdot CO\cdot NH_2$;
has been extensively investigated;-

Wilson, Hopper and Crawford, J.C.S., 1922, 121, 866.
Wilson and Crawford, J.C.S., 1925, 127, 103.
Wilson and Chapmam, J.C.S., 1931, 507.
Wilson, Baird and Burns. J.C.S., 1927, 2527.
Wilson and Pickering, J.C.S., 1924, 125, 1152.
Borsche and collaborators, Ber. 1901, 34, 4297.
1904, 37, 3177.
1905, 38, 831.

Borsche found that amines reacted with semicarbazones on heating, to form δ-aryl semicarbazones with liberation of ammonia as in the following general equation:-

$$CRR':N\cdot NH\cdot CO\cdot NH_2 + R''NH_2 = CRR':N\cdot NH\cdot CO\cdot NHR'' + NH_3$$

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

$$CRR':N\cdot NH\cdot CO\cdot NHR'' + HCl + H_2O = RR'C:O + NH_2NH\cdot CO\cdot NH_2HCl$$

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

Wilson and co-workers (loc. cit.) have extended the above reaction to include amines in which the amino group occurs in the side chain, and also to include aliphatic amines. Moreover, these workers suggested that optically active semicarbazides might be useful in the resolution of certain racemic aldehydes and ketones, and later accomplished a resolution of benzoin using d- δ - (α-phenyl ethyl) semicarbazide. (The discussion on the use of active semicarbazides for resolving racemic aldehydes and ketones is withheld until Part 2 page 59).

No work has been published dealing with the reactions of amines on aminocarbocarbazones and since these compounds, like semicarbazones, may be regarded as/

as derivatives of hydrazine, we expected the reaction to take the following course;-

$$RR'C{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NH_2 + R''NH_2 = RR'C{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NHR'' + NH_3 \qquad (A)$$

The substituted aminocarbocarbazone (A) could not be isolated however, although the products obtained, appeared to show that (A) was probably formed initially and reacted with more amine with production mainly of a δ- substituted semicarbazone and a di-substituted carbamyl hydrazine according to the following scheme;-

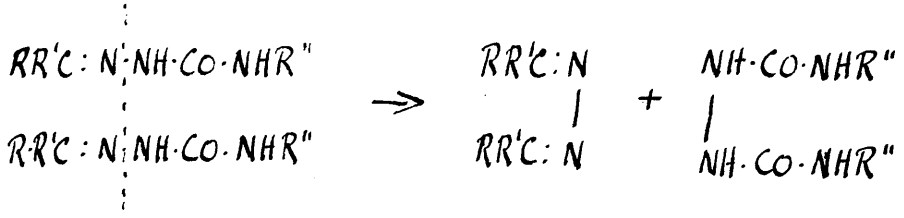
$$2(RR'C{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NHR'') + 2R''NH_2 \longrightarrow 2(RR'C{:}N{\cdot}NH{\cdot}CO{\cdot}NHR'') + NH_2{\cdot}NH_2 + \begin{matrix} NH{\cdot}CO{\cdot}NHR'' \\ | \\ NH{\cdot}CO{\cdot}NHR'' \end{matrix}$$

In addition to hydrazine being obtained as a product of the reaction, azines $RR'C{:}N{\cdot}N{:}C{\cdot}RR'$, symmetrical disubstituted ureas, and 4 - amino urazole were also isolated.

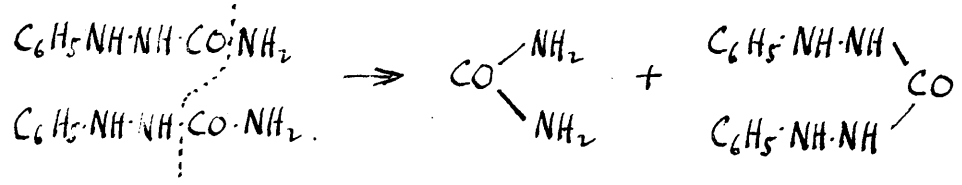
The variety of decomposition products obtained led to a search of the literature being made to ascertain the nature of the decomposition products of semicarbazones. Curtius (Ber. 26, 405, 27, 57) has shown that semicarbazones on heating may decompose to give an azine and hydrazodicarbonamide;-

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

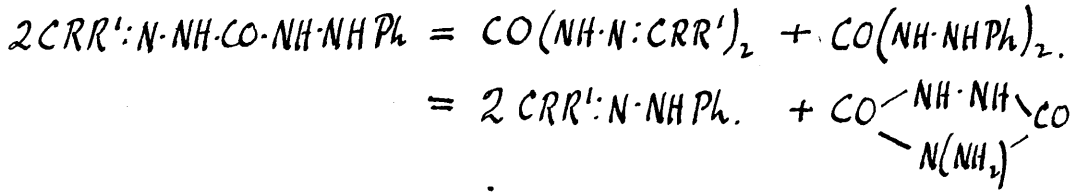
The above case is exactly analogous to that described, in that if we assume compound A to be decomposed with formation of a δ- substituted semicarbazone, the latter may then decompose according to the scheme outlined by Curtius, viz;-



Other types of decomposition may also take place. Poth and Bailey (J. Am. C. S. 45, 3008) have shown that α phenyl semicarbazide may decompose to give urea and diphenyl carbazide.



Again, Baird and Wilson (J.C.S. 1927, 2114) have shown that acetophenone δ- anil semicarbazone on thermal decomposition yields the phenyl hydrazone and 4-amino urazole.



A similar decomposition is possible in the cases described in the following pages where 4-amino urazole was isolated.

The reactions were carried out employing acetophenone aminocarbocarbazone with benzylamine, aniline and naphthylamine as typical representative of primary amines, and also with piperidine, monomethylaniline and dibenzylamine as representative of secondary amines.

Benzylamine reacted with acetophenone aminocarbocarbazone when reagents were heated together to a temperature of 140°C without solvent. Had it been possible to carry out the reaction at a lower temperature, it seems likely that the expected product formed by elimination of ammonia, viz;- $\begin{matrix} CH_3 \\ C_6H_5 \end{matrix}\!\!>\!C:N\cdot NH\cdot CO\cdot NH\cdot NH\,CO\cdot NH\,CH_2C_6H_5$ --(A)

could have been isolated. In this particular reaction however, as in the others described, it was found necessary to heat to a comparatively high temperature in order to bring about a reaction. (No reaction was observed to take place after heating for a period of 8 hours in toluene suspension). Consequently instead of obtaining compound/

compound A as a product of the reaction, thermal decomposition products of A were obtained, the main product being acetophenone δ- benzyl semicarbazone.

Aniline also reacted with acetophenone aminocarbozone at a high temperature, the chief product being acetophenone δ- phenyl semicarbazone.

Naphthylamine behaved exactly like aniline and benzylamine with formation of acetophenone δ- naphthyl semicarbazone.

With secondary amines the reaction appeared to be much more sluggish, although piperidine appeared to follow the normal course with formation of acetophenone piperidinoformylhydrazone. This is in agreement with the observations of Stratton and Wilson (J.C.S. 1931, 1157) who found that whereas secondary amines in general react but slightly or not at all, with semicarbazones, piperidine reacted vigorously behaving in this respect like a primary amine.

Monomethylaniline appeared to react with acetophenone aminocarbocarbazone but the product could not be identified.

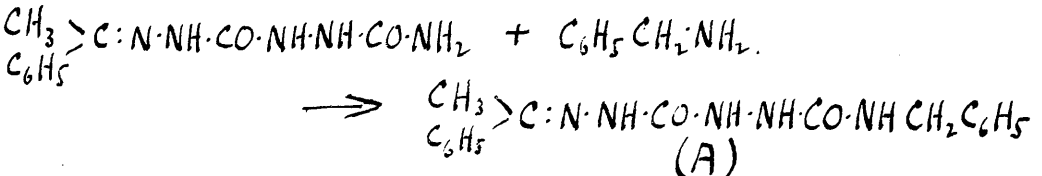
Dibenzylamine reacted to give a thick viscous oil which could not be identified.

BENZYLAMINE AND ACETOPHENONE AMINOCARBOCARBAZONE.

THE ACTION OF BENZYLAMINE ON ACETOPHENONE AMINOCARBOCARBAZONE.

THEORETICAL.

It was expected the acetophenone amino-carbocarbazone would react with benzylamine with evolution of ammonia as indicated by the equation;-



The reaction was carried out at 140° C and compound (A) was not isolated. The main product, which was isolated in a pure state, was a crystalline solid, M.Pt. 141° C. This compound was analysed and a molecular formula $C_{16}H_{17}N_3O$ obtained. This clearly showed that it was not the expected derivative, the molecular formula of which is $C_{17}H_{19}N_5O$..
The compound obtained was then examined. Hydrolysis was accomplished with concentrated hydrochloric acid and the products were identified as acetophenone, hydrazine dihydrochloride, and benzylamine hydrochloride. A quantitative hydrolysis showed that these substances were present in the following ratio by weight.
Acetophenone /

Acetophenone; hydrazine dihydrochloride; benzylamine hydrochloride : 1.5; 1.2; 1.9.

Assuming single molecules of these substances are in combination, the ratio by weight would be 1.2: 1.0: 1.4. These facts led to the conclusion that the unknown compound was acetophenone δ- benzyl semicarbazone which undergoes hydrolysis with concentrated acid according to the equation;-

$$\begin{matrix} CH_3 \\ C_6H_5 \end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CO{\cdot}NHCH_2C_6H_5 + 2H_2O + 3HCl \longrightarrow \begin{matrix} CH_3 \\ C_6H_5 \end{matrix}\!\!>\!C{:}O + NH_2{\cdot}NH_2{\cdot}2HCl + C_6H_5CH_2{\cdot}NH_2{\cdot}HCl + CO_2.$$

The nature of the compound was proved conclusively by combining acetophenone with δ-benzyl semicarbazide when acetophenone δ-benzyl semicarbazone was obtained, identical in all respects with the reaction product.

In addition to acetophenone δ-benzyl semicarbazone, the reaction also yielded acetophenone azine, symmetrical dibenzyl urea, and dibenzyl carbamyl hydrazine. The acetophenone azine and the dibenzyl carbamyl hydrazine were, presumably, derived from the partial decomposition of acetophenone δ benzyl semicarbazone according to the scheme outlined by Curtius (page 7), viz;-

$$2\ \begin{matrix} CH_3 \\ C_6H_5 \end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CO{\cdot}NHCH_2C_6H_5 \longrightarrow \begin{matrix} CH_3 \\ C_6H_5 \end{matrix}\!\!>\!C{:}N{\cdot}N{:}C\!<\!\begin{matrix} CH_3 \\ C_6H_5 \end{matrix}$$

$$+\ \begin{matrix} NH{\cdot}CO{\cdot}NHCH_2{\cdot}C_6H_5 \\ | \\ NH{\cdot}CO{\cdot}NHCH_2{\cdot}C_6H_5 \end{matrix}.$$

The presence of symmetrical dibenzyl urea as a product of the reaction can not be explained. Poth and Bailey (page 7) have shown that semicarbazides may decompose to give urea, but there is no mention of semicarbazones decomposing in this manner.

ACETOPHENONE AMINOCARBOCARBAZONE AND BENZYLAMINE.

EXPERIMENTAL.

ACETOPHENONE AMINOCARBOCARBAZONE.

Carbohydrazide was prepared from diethyl carbonate and hydrazine hydrate after the method of Kesting (Ber. 1924, 57, 1324), and by treating this substance with potassium cyanate in presence of acid, aminocarbocarbazide was formed. (Pellizzari and Roncagliolo G. 1907, 37, 440).

Aminocarbocarbazide (6gm.) was dissolved in the minimum quantity of dilute hydrochloric acid and acetophenone (6gm.) added, the solution being kept cold. Sufficient alcohol was added to form a homogeneous solution and, on standing and shaking, crystals of acetophenone aminocarbocarbazone separated.

These were recrystallised from hot water. M.Pt. 214° C.

ACETOPHENONE AMINOCARBOCARBAZONE AND BENZYLAMINE.

It was found that by refluxing the reactants in xylene or tolnene suspension for a period of 8 hours, very little change took place, and accordingly it was decided to carry out the reaction without solvent.

Acetophenone aminocarbocarbazone (3gm.) and benzylamine (4gm.) were mixed and heated in a glycerine bath /

bath to a temperature of 180° C for half an hour. The solid dissolved in the amine and reacted with it, ammonia being evolved. After half an hour the melt solidified and the evolution of ammonia slackened, this being taken as a sign that the reaction was complete. Heating was discontinued and the solid product was refluxed for a period of 5 minutes with alcohol, and filtered from a solid residue, which was quite insoluble in hot alcohol. The alcoholic filtrate, on addition of a little water, deposited crystals of symmetrical dibenzyl urea. These were recrystallised from benzene. M.Pt. 171° C. Nitrogen content. Found 11.81%. 11.78%.

Theory 11.7%.

The dibenzyl urea was identical with a specimen prepared from urea and benzylamine.

The benzene mother liquors resulting from the recrystallisation of the dibenzyl urea were evaporated to small bulk, when a yellow crystalline solid was obtained, which was identified as acetophenone azine. M.Pt. 122° C.

The alcoholic filtrate from which dibenzyl urea had been removed was further diluted with water when precipitation of a solid took place, which melted between 130° C- 140° C. This solid was thoroughly dried, and recrystallised from benzene containing petroleum ether, when a pure compound was obtained. M.Pt.141°C.

The nature of this compound presented considerable difficulty, and consequently it was found necessary to examine the products which it yielded on hydrolysis with concentrated hydrochloric acid.

5gm. of compound, melting point 141° C, was heated under reflux for 4 hours with concentrated hydrochloric acid, small oily globules separating. The oil was extracted with successive small quantities of petroleum ether, and the petroleum ether extract evaporated, when acetophenone remained.

On distilling the acid solution under reduced pressure to small bulk, crystals separated which were identified as hydrazine dihydrochloride by (a) melting point 199° C, (b) the reduction of Fehling's solution without heating and (c) by the formation of benzal azine, melting point 93° C. On further evaporation of the acid liquor, a compound was obtained which was identified as benzylamine hydrochloride by (1) its melting point 258° C and (2) by the formation of benzylamine on treatment with alkali.

A quantitative estimation of these

hydrolysis/

hydrolysis products was carried out and it was found that they were present in the following proportions by weight. Acetophenone; hydrazine dihydrochloride; benzylamine hydrochloride= 1.5; 1.2; 1.9 (Appendix page 163). Assuming the molecular ratio of these substances to be as 1;1;1, the gravimetric ratio should be 1.2; 1.0; 1.4. It was thus assumed that 1 molecule of each of these substances was combined in the parent substance, and, on the strength of these facts, the parent substance was believed to be acetophenone δ-benzyl semicarbazone. This view was confirmed by synthesis.

Nitrogen content. Found 15.72%. 15.77%.

Theory 15.73%.

SYNTHESIS OF ACETOPHENONE δ-BENZYL SEMICARBAZONE.

Acetone δ-benzyl semicarbazone was prepared by heating acetone semicarbazone with benzylamine. Hydrolysis of this compound was then effected by heating with dilute hydrochloric acid (2N) when δ-benzyl semicarbazide hydrochloride was obtained. 1gm. δ-benzyl semicarbazide hydrochloride was dissolved in a small quantity of warm water, sodium acetate (1gm.) was added, followed by (0.8gm.) acetophenone and sufficient alcohol to form/

form a homogeneous solution. On standing, crystals of acetophenone δ-benzyl semicarbazone separated, identical with the product obtained above.

The residue which remained on digesting the melt with alcohol was found to be insoluble in all the common solvents with the exception of glacial acetic acid. Accordingly the substance was purified by recrystallisation from this solvent, when it was obtained in the form of glistening plates. M.Pt. 248° C. This compound was identified as symmetrical dibenzyl carbamyl hydrazine. Nitrogen content. Found 18.90%. 18.92%.

Theory 18.8%.

The synthesis of dibenzyl carbamyl hydrazine was carried out as follows;-

δ-benzyl semicarbazide (1gm.) was dissolved in warm water and treated with iodine (1.5gm;) in potassium iodide. (Hopper. Journal.Royal Tech. Coll. 1927, 4, 48). Formation of a white precipitate took place, and the solid which separated was washed with sodium thiosulphate to remove any adhering iodine, and then recrystallised from glacial acetic acid. Dibenzyl carbamyl hydrazine was obtained identical with the specimen obtained above.

ANILINE AND ACETOPHENONE AMINOCARBOCARBAZONE.

THE ACTION OF ANILINE ON ACETOPHENONE AMINOCARBOCARBAZONE.

THEORETICAL.

While it was expected that aniline would react with acetophenone aminocarbocarbazone to yield a phenyl substituted aminocarbocarbazone with elimination of ammonia, the findings of the previous experiment with benzylamine, suggested thermal decomposition might occur with formation of acetophenone δ phenyl semicarbazone, diphenyl urea and symmetrical diphenyl carbamyl hydrazine. These products were actually formed and isolated, and in addition 4-amino urazole was isolated. The formation of 4-amino urazole as a decomposition product of δ substituted semicarbazones has already been cited. (page 7).
(Baird and Wilson J.C.S. 1927, 2114).

THE ACTION OF ANILINE ON ACETOPHENONE AMINOCARBOCARBAZONE.

EXPERIMENTAL.

It was found that no reaction took place when the reactants were refluxed in toluene or xylene suspension for a period of 8 hours; accordingly the experiment was carried out without solvent.

Acetophenone aminocarbocarbazone (5gm.) was added to aniline (6gm.) and the mixture heated in a glycerine bath to a temperature of 180° C. Ammonia was evolved freely, and after heating 1 hour, the reaction appeared to be over as the evolution of ammonia slackened. The melt was filtered hot to remove a small quantity of insoluble matter, melting point 270° C. This substance was recrystallised from hot water and identified as 4-amino urazole by comparison.

Nitrogen content. Found 47.9%.

Theory 48.3%.

The filtered melt was allowed to cool when it solidified completely, and then digested with hot benzene. Continued refluxing with benzene failed to dissolve a portion of the solid melt. This unsoluble portion was filtered off and found to possess a high

melting/

melting point, viz;- 247° C, and moreover it was insoluble in the common organic solvents. These properties indicated that the substance was possibly symmetrical diphenyl carbamyl hydrazone, as it behaved exactly like the dibenzylcarbamyl hydrazine obtained in the previous experiment. The substance was purified by recrystallisation from glacial acetic acid, when it was obtained in the form of glistening plates, melting point 247° C. This agrees with the melting point of diphenyl carbamyl hydrazine as given in the literature.

Nitrogen content. Found 20.8%. 21.0%.

Theory 20.8%.

The benzene extract, from which the diphenyl carbamyl hydrazine had been filtered, deposited crystals on cooling. One crop, melting at 230° C- 235° C which was not readily soluble in cold benzene; and a second crop melting at 180° C- 190° C. Addition of petroleum ether to the benzene solution caused separation of a further quantity of material, melting at 180°C- 190°C. The benzene-petroleum ether residues were examined further. (Below).

The first crop of crystals was recrystallised from benzene and yielded a quantity of symmetrical diphenyl/

diphenyl urea, melting point 235° C.

Nitrogen content. Found 13.15%. 13.22%.

Theory 13.2%.

The second crop (melting point between 180 and 190° C) was found to recrystallise well from absolute alcohol, when a pure product was obtained melting at 188° C. A further quantity of this substance was obtained by addition of water to the alcoholic solution. This compound was identified as acetophenone δ phenyl semicarbazone (C. 1921, 111, 636).

Nitrogen content. Found 16.74%. 16.88%.

Theory 16.9%.

The benzene-petroleum ether residues from which acetophenone δ-phenyl semicarbazone and diphenyl urea had been separated, were examined for further products, as they were decidedly yellow in colour, and it was felt that the coloration was due to presence of acetophenone azine. The method of treatment employed, consisted in evaporating the liquors to small bulk, followed by digestion of the residue with petroleum ether. It was found that the yellow substance was dissolved out of the residue in this way leaving behind an oil which was immiscible with petroleum ether. The petroleum ether extract on evaporation yielded a small quantity of acetophenone azine/

azine, melting point 122° C, which was shown to be identical with an authentic specimen by determining the melting point of the mixture.

The oil which was immiscible with petroleum ether was identified as aniline, and resulted from an excess of aniline being used in the reaction.

B-NAPHTHYLAMINE AND ACETOPHENONE AMINOCARBOCARBAZONE.

THE ACTION OF B-NAPHTHYLAMINE ON ACETOPHENONE AMINOCARBOCARBAZONE.

THEORETICAL.

As a result of the experiments already described, it was expected that B-naphthylamine would react with acetophenone aminocarbocarbazone to give mainly acetophenone δ-naphthyl semicarbazone and dinaphthyl carbamyl hydrazine. It is difficult to write an equation to meet the demands of these experiments as the thermal decomposition in each case appears to be extensive. However, it was decided that the equation given on page 6 , viz;-

$$2(RR'C{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH{\cdot}CO{\cdot}NHR'') + 2R''NH_2 \rightarrow 2(RR'C{:}N{\cdot}NH{\cdot}CO{\cdot}NHR'') + NH_2{\cdot}NH_2 + \begin{matrix} NH{\cdot}CO{\cdot}NHR'' \\ | \\ NH{\cdot}CO{\cdot}NHR'' \end{matrix}$$

best suited the case, and it was decided to look for hydrazine as a product of this reaction, not forgetting that hydrazine may decompose to give ammonia ($N_2H_4 \rightarrow NH_3 + N_2$) at elevated temperatures. The procedure was varied slightly in that the reaction was carried out in a distilling flask, and a few drops of distillate were obtained which undoubtedly contained hydrazine. It was this fact which led to the adoption of the general equation, above.

THE ACTION OF B-NAPHTHYLAMINE ON ACETOPHENONE AMINOCARBOCARBAZONE.

EXPERIMENTAL.

B-naphthylamine (7gm.) was mixed with acetophenone aminocarbocarbazone (4gm.) and the mixture heated in a distilling flask to a temperature of 190° C for 1 hour. During the course of the reaction a liquid distillate was collected from the side arm of the flask and ammonia was freely evolved. The melt became pasty, without ever liquefying completely, and on cooling, solidified.

The distillate was shown to contain hydrazine by reducing Fehling's solution in the cold, and by forming hydrazine dihydrochloride, melting point 199° C, when treated with hydrochloric acid.

The solid reaction product was refluxed with alcohol, and a considerable portion of the solid remained undissolved. The undissolved matter was filtered off, and the filtrate, on cooling, deposited a small quantity of crystalline material, melting point 202° C. This was identified as acetophenone δ-naphthyl semicarbazone. (Borsche, Ber. 38, 836).

Nitrogen content. Found 14.03%. 14.01%.

Theory 13.9%.

The residue obtained on extraction with alcohol was found to be sparingly soluble in all the commoner solvents, although repeated extractions with alcohol continued to remove small quantities of acetophenone δ-naphthyl semicarbazone. Dekalin was found to be more suitable for the purpose than alcohol, and on digestion of the insoluble matter with this solvent, followed by filtration, acetophenone δ naphthyl semicarbazone crystallised from the filtrate on cooling.

There was, however, still a residue which was insoluble in dekalin and other solvents. The method of purification adopted for this substance, was repeated refluxing with dekalin, until the melting point of the substance did not rise on further washing. When this stage was reached the substance was refluxed with alcohol to remove any adhering dekalin, and symmetrical dinaphthyl carbamyl hydrazine was obtained, melting point 270° C.

Nitrogen content. Found 15.40%. 15.36%.

Theory 15.2%.

Some dinaphthyl carbamyl hydrazine was prepared according to the method used by Hopper (Jour. Roy. Tech. College 1927, 4) for the corresponding dibenzyl compound. Acetophenone δ-naphthyl semicarbazone (1gm.) was hydrolysed in an open beaker with dilute hydrochloric acid/

acid by heating for an hour on the water bath. On cooling, crystals of δ-naphthyl semicarbazide hydrochloride separated. These were dissolved in hot water and a solution of iodine in potassium iodide added, when an amorphous solid separated -- dinaphthyl carbamyl hydrazine, melting point 270° C. Like the specimen prepared above, this compound was insoluble in all solvents.

Nitrogen content. Found 15.1%.

Theory 15.2%.

PIPERIDINE AND ACETOPHENONE AMINOCARBOCARBAZONE.

THE ACTION OF PIPERIDINE ON ACETOPHENONE AMINOCARBOCARBAZONE.

THEORETICAL.

Piperidine was expected to react in the same manner as the primary amines already considered, since it reacts with acetophenone semioxamazone to yield acetophenone piperidino-oxalyl hydrazone and ammonia. (Wilson and Pickering, J.C.S. 1924, 125, 1152); and with acetone semicarbazone under special conditions to give acetone piperidino-formyl-hydrazone (Stratton and Wilson J.C.S. 1931, 1154).

In both reactions cited above, piperidine is behaving in the same manner as a primary amine, and consequently we expected it to react with acetophenone aminocarbocarbazone to give acetophenone piperidino formyl hydrazone. This product was obtained along with acetophenone azine and an oil which could not be identified.

THE ACTION OF PIPERIDINE ON ACETOPHENONE AMINOCARBOCARBAZONE.

EXPERIMENTAL.

Acetophenone aminocarbocarbazone (5gm.) was mixed with piperidine (4gm.) and heated to a temperature of 180° C, until evolution of ammonia slackened. The melt was cooled, extracted with alcohol and filtered from a small quantity of insoluble matter. The filtrate on cooling yielded a crystalline solid, which was identified as acetophenone piperidino formyl hydrazone, melting point 169° C.

Nitrogen content. Found 17.1%.

Theory 17.1%.

The acetophenone piperidino formyl hydrazone was identical with a specimen prepared from acetophenone semicarbazone and piperidine (Stratton and Wilson. loc, cit.).

The alcoholic mother liquor, from which the acetophenone piperidino formyl hydrazone had crystallised, was deep yellow in colour and on addition of water yielded acetophenone azine, and on further addition of water, an oil was obtained which did not solidify when left in a vacuum, and decomposed on vacuum distillation.

METHYLANILINE AND ACETOPHENONE AMINOCARBOCARBAZONE.

THE ACTION OF METHYLANILINE ON ACETOPHENONE AMINOCARBOCARBAZONE.

Borsche states in his first publication concerning the action of amines on semicarbazones, that the action of methyl aniline, which he had attempted, proceeded much less smoothly than that of aniline. In fact, he expressed some doubt as to whether any reaction took place.

In the first reaction carried out between methyl aniline and acetophenone amino carbocarbazone, no special precautions were taken to ensure freedom from small amounts of aniline, and accordingly acetophenone δ phenyl semicarbazone was isolated as a reaction product, a fact which indicated that aniline reacted more smoothly than methyl-aniline.

A quantity of methyl aniline was purified according to the method described by Hepp (Ber. 10, 328) and the purified amine (7gm.) heated with acetophenone aminocarbocarbazone (5gm.) to a temperature of 180° C without solvent. The cooled melt, on extraction with alcohol, yielded a considerable quantity (about 3gm.) of acetophenone azine, which seemed to indicate that decomposition/

decomposition had been extensive. On evaporating the alcoholic extract to small bulk, a small quantity of material, melting point 196° C, was obtained, but this could not be identified. In addition an oily residue remained, which resisted all attempts at purification.

The action of dibenzylamine on acetophenone aminocarbocarbazone resembled the foregoing experiment with piperidine, in that the products consisted of acetophenone azine and a thick viscous oil which could not be identified. It was felt that the oil may have consisted of a solution of solid matter in excess of dibenzylamine, and consequently excess amine was removed by vigorously agitating the oil with dilute hydrochloric acid and subsequent removal of the dibenzylamine hydrochloride. This treatment, however, did not cause the oily residue to solidify, and when purification of the oil by vacuum distillation was attempted, decomposition took place to a marked degree.

PART 1 (B).

THE ACTION OF PYRIDYL HYDRAZINE ON SEMICARBAZONES.

THE ACTION OF PYRIDYL HYDRAZINE ON SEMICARBAZONES.

INTRODUCTION.

The preparation of 2-pyridyl hydrazine is given by Fargher and Furness (J.C.S. 1915, 688). These authors describe the preparation of several pyridyl hydrazones obtained by combining the base with aldehydes and ketones, but no mention is made of the reaction of the substance with compounds containing the $-CO-NH_2$ grouping. It has been shown by Pinner (Ber. 1887, 20, 2358) that carbamide and phenyl hydrazine react with elimination of ammonia and formation of α phenyl semicarbazide. Skinner and Ruhemam (J.C.S. 1888, 53, 550) extended the reaction to carbamide derivatives. Sutherland and Wilson (J.C.S. 1924, 125, 2145) have studied the action of phenyl hydrazine on semicarbazones, and found that the reaction proceeded according to one of two schemes.

(1) $CRR':N\cdot NH\cdot CO\cdot NH_2 + NH_2\cdot NHPh = NH_3 + CRR':N\cdot NH\,CO\cdot NH\cdot NHPh.$

(2) $CRR':N\cdot NH\cdot CO\cdot NH_2 + NH_2\cdot NHPh = CRR':N\cdot NHPh + NH_2\cdot NH\cdot CO\cdot NH_2.$

Baird and Wilson (J.C.S. 1926, 2369) continuing the above work, have shown that aldehydic semicarbazones react almost exclusively according to reaction (2) above, with the exception of semicarbazones derived from aldehydes of high molecular weight and containing straight chains, which react/

react according to equation (1) with formation of δ-anilino semicarbazones. Moreover, they showed that ketonic semicarbazones varied in their reactions with phenyl hydrazine, depending upon the nature of the semicarbazone. If in the compounds $CRR'{:}N{\cdot}NHCO{\cdot}NH_2$, R and R' are bulky groups of high molecular weight, the formation of the hydrazone was inhibited, and the δ-anilino-semicarbazone was formed according to scheme (1). With other ketonic semicarbazones, where R and R' were not heavy groups, the hydrazone and the δ-anilino semicarbazone were formed in varying amounts.

No work had been carried out on the action of pyridyl hydrazine on semicarbazones, and it was decided to investigate the action with a number of semicarbazones.

The semicarbazones of benzaldehyde, acetophenone, benzophenone and benzoin were employed for the experiments, in which the procedure was to heat the reactants to a sufficiently high temperature to cause evolution of ammonia, the heating being conducted in an inert atmosphere to prevent oxidation of the pyridyl hydrazine. (Fargher and Furness loc. cit.).

The reaction was expected to occur with formation of δ 2-pyridyl semicarbazones and elimination of ammonia as in the following general equation ;-

$$CRR'{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + H_2N{\cdot}NHC_5H_4N \Rightarrow CRR'{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NHC_5H_4N$$

the case being analogous to that described by Wilson and Sutherland (loc. cit.). In addition to δ 2-pyridyl semicarbazones/

semicarbazones, however, pyridyl hydrazones and 4 amino-urazole were also isolated, which would indicate that the δ 2-pyridyl semicarbazone underwent decomposition, after the manner of acetophenone δ anilino semicarbazone (Baird and Wilson J.C.S. 1927, 2114). viz;-

$$2(CRR':N\cdot NH\cdot CO\cdot NH\cdot NHPh) = 2(CRR':N\cdot NH\cdot Ph) + CO\begin{matrix}NH\cdot NH\\ N(NH_2)\end{matrix}CO$$

or, in the case of the δ pyridyl semicarbazone as follows ;-

$$2(CRR':N\cdot NH\cdot CO\cdot NH\cdot NHC_5H_4N) = 2(CRR':N\cdot NH\cdot C_5H_4N) + CO\begin{matrix}NH\cdot NH\\ N(NH_2)\end{matrix}CO.$$

In the reactions between pyridyl hydrazine and the semicarbazones of benzophenone and benzoin, the corresponding δ 2-pyridyl semicarbazones were isolated. With acetophenone semicarbazone the reaction product could not be identified.

In all cases the yield of solid product obtained was poor, and this fact, combined with the unstable nature of pyridyl hydrazine, (in that it is very susceptible to atmospheric oxidation), led to the investigations being discontinued.

Since the 2-pyridyl semicarbazones, produced in the above experiments, contained the basic pyridyl residue, we felt that they might form salts with acids, and in the case of benzoin δ 2-pyridyl semicarbazone, which contains an asymmetric carbon, it should be possible on/

on combining with an active acid (say dextro- rotatory) to form the isomeric salts, d-benzoin δ 2-pyridyl semicarbazone-d-acid, and ℓ-benzoin δ 2-pyridyl semicarbazone-d-acid. If such salts could be formed, the possibility of resolving benzoin into its optical enantiomorphs was apparent. This possibility was investigated using d-tartaric acid and also d-camphor sulphonic acid, but salts of these acids could not be isolated.

The foregoing experiment on the resolution of benzoin, suggested the possibility of resolving racemic aldehydes and ketones via the pyridyl hydrazones of these compounds, by combination with an active acid. In this way we hoped to effect a separation into d-ketone pyridyl hydrazone d-acid, and ℓ-ketone pyridyl hydrazone d-acid, both of which compounds should yield the active ketone on hydrolysis.

No mention is made in the literature of the pyridyl hydrazones of racemic aldehydes or ketones, and accordingly the preparation of some of these was undertaken, namely, the pyridyl hydrazones of benzoin, menthone, 1-3 methyl cyclohexanone and p-methoxyhydratropaldehyde (Bougault, Ann. Chim. Phys. 1902. (7) 25. 43). In all cases the pyridyl hydrazones were isolated, those of menthone and methyl cyclohexanone as thick, almost immobile, oils, which could be distilled under reduced pressure. The pyridyl hydrazones/

hydrazones so prepared were combined with tartaric acid and camphor sulphonic acid.

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p-Methoxyhydratropaldehyde formed a stable tartrate, which, however, did not show any rotation when examined in the potarimeter. This suggested that the tartaric acid had racemised, or else the rotatory power of the tartrate was so small as to be negligible. The latter view was shown to be correct by recovering the tartaric acid from the tartrate as sodium tartrate, which exhibited its normal rotatory power. Separation of the enantiomorphs could not be effected.

Menthone pyridyl hydrazone formed a less stable tartrate, which is readily hydrolysed with liberation of menthone, on dissolving in hot water. The instability of the tartrate rendered recrystallisation difficult, although a small quantity of material was obtained, which yielded a specimen of active menthone on hydrolysis, this indicating that a partial separation of the isomers had occurred. The loose union of the pyridyl hydrazone with tartaric acid did not justify the continuance of the investigation.

Benzoin pyridyl hydrazone and methyl

cyclohexanone/

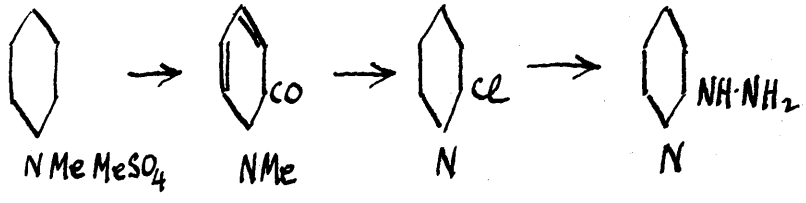
cyclohexanone pyridyl hydrazone did not form tartrates.

In no case was a solid camphor sulphonate of the pyridyl hydrazones isolated.

2-PYRIDYL HYDRAZINE.

(Fargher and Furness J.C.S. 1915, 688).

The preparation of pyridyl hydrazine is difficult and lengthy. Starting from pyridine, pyridine methosulphate is prepared by interaction with dimethyl sulphate. The pyridine methosulphate is oxidised to methyl pyridone with potassium ferricyanide, the methyl pyridone being salted out by saturating the aqueous solution with potassium hydroxide. By treating the methyl pyridone with a mixture of phosphoryl chloride and phosphorus pentachloride, 2-chloro-pyridine is obtained by steam distillation, after removal of excess phosphorus halides. The 2-chloro-pyridine on refluxing with hydrazine hydrate, yields 2-pyridyl hydrazine, which when pure is a thick viscous oil boiling at 140°C under a pressure of 20mms.



BENZOPHENONE SEMICARBAZONE AND PYRIDYL HYDRAZINE.

BENZOPHENONE SEMICARBAZONE AND PYRIDYL HYDRAZINE.

THEORETICAL.

From the findings of Wilson and co-workers on the action of hydrazines on semicarbazones, we expected benzophenone semicarbazone to react with pyridyl hydrazine with formation of benzophenone δ 2-pyridyl semicarbazone. The possibility of this compound undergoing thermal decomposition was also taken into account, and, if this secondary change took place, it would probably follow the lines suggested by Baird and Wilson (J.C.S. 1926, 2369) for the thermal decomposition of benzophenone δ anilino semicarbazone, with formation of benzophenone pyridyl hydrazone and 4-amino urazole.

$$C_6H_5(C_6H_5)C{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + H_2N{\cdot}NH{\cdot}C_5H_4N \rightarrow C_6H_5(C_6H_5)C{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NHC_5H_4N + NH_3$$

$$2\left(C_6H_5{\cdot}C_6H_5{\cdot}C{:}N{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NHC_5H_4N\right) \rightarrow 2\left(C_6H_5{\cdot}C_6H_5{\cdot}C{:}N{\cdot}NH{\cdot}C_5H_4N\right) + CO\begin{matrix}NH{\cdot}NH\\ N(NH_2)\end{matrix}CO.$$

In the experiment described on the following page, these products were actually identified and, in addition, a resinous substance was obtained which could not be identified. The yield of solid products was poor in all cases, never exceeding 15% -17% of the theoretical.

BENZOPHENONE SEMICARBAZONE AND PYRIDYL HYDRAZINE.

EXPERIMENTAL.

The reactants were mixed in molecular proportions and heated in an atmosphere of nitrogen to 135 C, at which temperature ammonia was evolved. The heating was conducted in a flask fitted with a ground glass condenser, nitrogen being carried down the inner condenser tube to fill the flask, a slow stream of the gas being continually passed, during the heating period. The temperature was maintained at 135° C for three hours, and the reaction was then stopped as the mixture appeared to be decomposing. The melt was allowed to cool and digested with a small quantity of hot water. The aqueous extract was filtered from resinous matter, and the filtrate on cooling deposited 4-amino urazole. Melting point 270° C.

Nitrogen content. Found 48.41%.

Theory 48.3%.

The resinous matter which was insoluble in water was taken up in methyl alcohol and by careful addition of water to the alcoholic solution, a crystalline solid was deposited which, when recrystallised from aqueous alcohol, yielded benzophenone pyridyl hydrazone, melting point 206° C, identical with a specimen prepared from benzophenone and pyridyl hydrazine.

Nitrogen content. Found 15.53%. 15.45%.

Theory 15.38%.

The alcoholic liquor, from which benzophenone pyridyl hydrazone had separated, was added with stirring, to a large volume of water, when a semi solid mass separated. This was removed by filtration, dried, and dissolved in a small quantity of benzene. The benzene solution was poured slowly with stirring into a large volume of petroleum ether when a colourless solid separated in small amount. Melting point 64-66° C. Attempts to recrystallise the solid from alcohol and water mixtures gave an oily product, and the only suitable method of purification was to pour the benzene solution of the solid into a large bulk of low boiling petroleum ether. This procedure still gave a solid of melting point 64-66° C.

Nitrogen content 21.44%. 21.50%.

Theory for benzophenone δ 2-pyridyl semicarbazone is 21.1%.

Hydrolysis of this compound with dilute hydrochloric acid produced benzophenone and a black gummy product which could not be identified.

The reaction was also carried out in toluene suspension, the mixture being refluxed for 20 hours, during which time ammonia was evolved. The toluene was distilled off under reduced pressure, when a thick viscous mass remained, which did not solidify. This was dissolved in benzene and added to a large excess of petroleum ether when a white flocculent/

flocculent precipitate was obtained melting point 64-66° C, corresponding to the compound obtained above.

BENZALDEHYDE SEMICARBAZONE AND PYRIDYL HYDRAZINE.

EXPERIMENTAL.

Benzaldehyde semicarbazone (8gm.) and pyridyl hydrazine (5gm.) were mixed and heated without solvent, in an atmosphere of nitrogen. There was no perceptible reaction until 145° C was reached, when ammonia was evolved and a yellowish liquid formed in the flask. The reaction was continued for 18 hours after which time ammonia ceased to be evolved. The melt was extracted with a small quantity of hot water, and on cooling the aqueous extract, 4-amino urazole was obtained. The resinous portion which was insoluble in water, was dissolved in a small quantity of methyl alcohol and, on cooling, crystals of benzaldehyde pyridyl hydrazone were obtained, melting point 148° C. (Fargher and Furness J.C.S. 1915, 692).

Nitrogen content. Found 21.47%. 21.49%.

Theory 21.37%.

Concentration of the alcoholic mother liquor produced a resinous substance, which could not be obtained in a solid form.

ACETOPHENONE SEMICARBAZONE AND PYRIDYL HYDRAZINE.

EXPERIMENTAL.

The product from this reaction appeared to be anomalous, in that it could not be identified, according to the scheme outlined for similar reactions.

Molecular quantities of acetophenone semicarbazone and pyridyl hydrazine were heated to a temperature of 140° C., when a reaction took place with evolution of ammonia. The melt was extracted with hot methyl alcohol, in which it dissolved completely, and on cooling a small amount of a crystalline solid separated, melting point 214-220° C. This material was further purified by recrystallisation from chloroform, when clear needle shaped crystals were obtained, melting point 226° C. Nitrogen content 30.5%. 30.7%.

This product was not identified. On hydrolysis with dilute hydrochloric acid, acetophenone was obtained and a dark coloured tarry resin.

Acetophenone pyridyl hydrazone requires nitrogen 19.9%.

Acetophenone δ 2-pyridyl semicarbazone requires nitrogen 24.3%.

On account of the small quantity of solid obtainable and the unattractive nature of the product, the reaction was abandoned.

BENZOIN SEMICARBAZONE AND PYRIDYL HYDRAZINE.

Benzoin semicarbazone (10gm.) and pyridyl hydrazine (4gm.) were added to 40cc. xylene. On heating to the boil, solution took place and ammonia was evolved, The temperature was maintained at 130 - 135° C, and heating continued until ammonia was no longer evolved (about 3 hours). The xylene was removed under reduced pressure, and the residue, on recrystallisation from alcohol, yielded long, clear, needle shaped crystals, melting point 179-180° C. These consisted of benzoin δ 2-pyridyl semicarbazone.

Nitrogen content. Found 19.49%. 19.39%.
Theory 19.39%.

Benzoin δ 2-pyridyl semicarbazone was dissolved in alcohol and a solution of tartaric acid in alcohol was added to this. There was no indication of salt formation as the temperature did not rise on mixing. On concentrating the mixed solutions under reduced pressure, unchanged semicarbazone was recovered.

Salt formation using camphor sulphonic acid was also attempted without success.

THE PYRIDYL HYDRAZONES OF SOME RACEMIC ALDEHYDES AND KETONES.

Some pyridyl hydrazones have been described by Fargher and Furness (loc. cit.), and since these contain the basic pyridyl residue, it was felt that salt formation would take place with acids. Using a pyridyl hydrazone derived from a racemic aldehyde or ketone, and combining this with an active acid, separation into isomers should be possible.

The pyridyl hydrazones of benzoin, 1-3-methylcyclohexanone, p-methoxyhydratropaldehyde and menthone are described.

While the tartrates of p-methoxyhydratropaldehyde and menthone pyridyl hydrazones were isolated, they did not prove suitable as a means of resolving these compounds.

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p-METHOXYHYDRATROPALDEHYDE PYRIDYL HYDRAZONE.

p-Methoxyhydratropaldehyde was prepared after the method of Bougault(Ann. Chim. Phys. 1902 (7), 25, 483) by the oxidation of anethole with mercuric oxide and iodine.

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

The aldehyde (8.5gm.) was added to a solution of pyridyl hydrazine (5.5gm.) in alcohol. The solution warmed considerably and the reaction was completed by refluxing for 15 mins. On cooling p-methoxhydratropaldehyde pyridyl hydrazone separated in the form of long silky needles. The compound was recrystallised from alcohol. Melting point 105° C. The yield of hydrazone was about 60% of the theoretical.

Nitrogen content. Found 16.4%.

Theory 16.4%.

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p-METHOXYHYDRATROPALDEHYDE PYRIDYL HYDRAZONE TARTRATE.

The hydrazone (6.5gm.) was dissolved in alcohol and added to a solution of tartaric acid (2gm.) in alcohol. The solution warmed and the crystalline tartrate separated almost immediately. The tartrate was recrystallised from alcohol, and melted at 164° C.

Nitrogen content. Found 12.6%.

Theory for tartrate 12.7%.

The tartrate was readily soluble in dioxan and chloroform, but was insoluble in water.

No rotation was observed when the tartrate was examined in alcoholic solution, and a concentrated solution in chloroform also failed to show a rotation. This may have been due to the fact that the natural rotatory power of the tartrate was so slight as to be immeasurable, or to the racemisation of the tartaric acid. The latter view was shown to be incorrect by decomposing the tartrate with the requisite quantity of sodium carbonate in aqueous alcoholic solution, when the free pyridyl hydrazone was recovered, in an inactive form and removed by filtration. The filtrate was decolourised with animal charcoal and on examination was found to be active, thereby indicating that the tartaric acid had not racemised.

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p-Methoxyhydratropaldehyde was also combined with d-camphor sulphonic acid in alcoholic solution. On removing the alcohol under reduced pressure, a resin remained which could not be crystallised.

BENZOIN PYRIDYL HYDRAZONE.

Benzoin (4gm.) was heated with pyridyl hydrazine (2gm.) in 50cc. alcohol. The solution was refluxed for 7 hours and evaporated to half bulk. On cooling a small quantity/

quantity of unchanged benzoin was precipitated. This was removed by filtration and on allowing the filtrate to stand, benzoin pyridyl hydrazone separated. The yield of hydrazone obtained was poor, about 15% of the theoretical value. Benzoin pyridyl hydrazone crystallises from aqueous alcohol in small colourless crystals, melting point 189° C. The crystals become yellow on exposure. Nitrogen Found 13.9%
Theory 13.86%

Benzoin pyridyl hydrazone does not form a tartrate. The hydrazone was dissolved in alcohol and added to the requisite amount of tartaric acid also dissolved in alcohol. On standing, benzoin pyridyl hydrazone was recovered unchanged.

An attempt was made to obtain the camphor sulphonate by combining the reagents in alcoholic solution. Precipitation of the camphor sulphonate was expected to take place on addition of water to the alcoholic solution, but this procedure resulted in the formation of benzoin, hydrolysis of the pyridyl hydrazone taking place. The benzoin was identified by melting point and by the production of a blue colour with alcoholic potassium hydroxide.

1.3 METHYL CYCLOHEXANONE PYRIDYL HYDRAZONE.

1.3 Methyl cyclohexanone (8gm.) was added to 20cc. alcohol, and mixed with a solution of pyridyl hydrazine (4gm.) in 10cc. alcohol. The solutions warmed on mixing and the reaction was completed by refluxing for 15 mins. No solid matter separated on cooling or on standing, and the alcohol was evaporated off under reduced pressure when a very viscous oil remained. This oil could be distilled under reduced pressure without decomposition when methyl cyclohexanone pyridyl hydrazone was obtained. The boiling point of the hydrazone was ~~obtained~~ 168-170° C under a pressure of 3mm. of mercury.

Nitrogen content. Found 20.3%.

Theory 20.6%.

Neither the tartrate nor the camphor sulphonate could be isolated.

MENTHONE PYRIDYL HYDRAZONE.

Menthone (6gm.) and pyridyl hydrazine (4gm.) were heated under reflux in alcoholic solution for a period of 5 hours. No solid matter separated on standing and the alcohol was removed under reduced pressure, when a thick immobile oil remained which did not solidify on/

on freezing. The oil, however, could be distilled under reduced pressure when menthone pyridyl hydrazone was obtained as a viscous oil, boiling point 184° C. under a pressure of 4mms.

Nitrogen content. Found 16.9%.

Theory 17.1%.

MENTHONE PYRIDYL HYDRAZONE TARTRATE.

The tartrate of the hydrazone was prepared by mixing a solution of menthone pyridyl hydrazone (6gm.) in alcohol, with a solution of tartaric acid (2gm.) in alcohol. On allowing to stand for a short time, crystals of menthone pyridyl hydrazone tartrate separated, melting point 136° C, the yield being theoretical. The tartrate is unstable in that it is readily hydrolysed in presence of water or aqueous alcohol with liberation of menthone. 1gm. of the tartrate in 25cc. of chloroform showed a laevo rotation of 3.03° when examined in a 1 decimetre tube.

The tartrate was recrystallised several times from small quantities of methyl alcohol and a sample of thrice recrystallised tartrate was hydrolysed by warming with dilute hydrochloric acid for a minute. The liquid was cooled and the liberated menthone extracted with ether.

On distilling off the ether, 0.3gm. of menthone was obtained which showed a very slight rotation when examined in the polarimeter.

0.3gm. in 10cc. alcohol gave $[\alpha]_D^{12} +3.3$.

This indicated that a partial separation of the isomers had occurred although the method is not likely to prove successful for the resolution of menthone.

PART 2.

THE RESOLUTION OF RACEMIC ALDEHYDES AND KETONES VIA ACTIVE SEMICARBAZIDES.

THE RESOLUTION OF RACEMIC ALDEHYDES AND KETONES VIA ACTIVE SEMICARBAZIDES.

The use of optically active semicarbazides for the resolution of racemic carbonyl compounds has been suggested by various workers. Forster and Fierz (J.C.S. 1905, 87, 722) prepared camphoryl ψ semicarbazide, but do not appear to have used it for this purpose . Hopper and Wilson (J.C.S. 1922, 121, 866) prepared active δα(phenylethyl)semicarbazide and in a later paper (J.C.S. 1928. 2483) were successful in resolving benzoin by this method.

Goodson (J.C.S. 1927, 1997) attempted a resolution of 1-3 methyl cyclohexanone using active δ -bornyl semicarbazide, and although well defined crystalline compounds were obtained, they did not separate into optical antipodes on fractional crystallisation.

Crawford and Wilson (J.C.S. 1934. 1122) effected a resolution of benzoin using laevo δ-menthyl semicarbazide. The separation of the isomers, however, proved to be exceedingly difficult, as the gummy matrix formed on condensing benzoin with l-δ-menthyl semicarbazide, could be induced to crystallise only after a period of years.

Stratton and Wilson (private communication) attempted to resolve benzoin and p-methoxyhydratropaldehyde/

aldehyde making use of d-nor ψ ephedrinoformylhydrazide, which they obtained by condensing benzaldehyde semicarbazone with d-nor ψ ephedrine (a primary amine), followed by removal of benzaldehyde by hydrolysis. The products obtained however, on combining the hydrazide with benzoin and p-methoxyhydratropaldehyde, were gummy and could not be induced to crystallise.

The work described in the following pages was undertaken in the knowledge that gummy products are to be regarded as the rule, rather than the exception, and if any of the gums obtained in these experiments show signs of crystallising during storage, the investigations will be reopened, and the solid matter used for seeding purposes.

Two methods were employed in the preparation of the active semicarbazones.

(1) The racemic aldehyde or ketone was combined with an active δ-substituted semicarbazide —

$$RR'HC{\cdot}CHO + H_2N{\cdot}NH{\cdot}CO{\cdot}NHX = RR'HC{\cdot}CH{:}N{\cdot}NH{\cdot}CO{\cdot}NHX + H_2O$$

(where X is an active grouping).

and

(2) The semicarbazone of the aldehyde or ketone was heated with an active amine till evolution of ammonia ceased.

$$R'RHC{\cdot}CH{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + NH_2X = R'RHC{\cdot}CH{:}N{\cdot}NH{\cdot}CO{\cdot}NHX + NH_3.$$

The second method is quicker, in that the semicarbazones are more easily prepared than the δ- semicarbazides, but it has the disadvantage of requiring a fairly high temperature to bring about the reaction.

As active amines, we employed α-phenyl ethylamine, camphylamine, and d-nor ψ ephedrine, while the ketones consisted of 1-3 methylcyclohexanone, camphor (d-l) benzoin and menthone (d-l).

1-3 Methylcyclohexanone formed crystalline δ-(α phenylethyl)semicarbazones, and while partial separation of the optical antipodes was affected by fractional recrystallisation extending over a period of three months, the process was much too laborious to be of practical use. Goodson (loc. Cit.) had the same difficulty using the δ-bornyl semicarbazone of 1-3 methylcyclohexanone.

An attempt was made to resolve 1-3 methylcyclohexanone using d-camphylamine (method (2) above) but a gum was obtained.

Another attempt using 1-3 methylcyclohexanone thiosemicarbazone and active α phenyl ethylamine resulted in complete decomposition taking place with evolution of much hydrogen sulphide. This difficulty could be overcome by using method (1).

Camphor semicarbazone combined with active α phenylethylamine, but again, a separation into the antipodes could not be effected. It seems strange that the melting point of (d-l)camphor l-δ(α phenylethyl)semicarbazone (A) should be higher than that of isomers, d-camphor l-δ(α phenylethyl)semicarbazone (B) and l-camphor l-δ(α phenyl ethyl)semicarbazones (C). From these findings, it would appear that (A) is an eutectic compound. This view is supported by the fact that when equal quantities of (B) and (C) are mixed in solution, compound (A) crystallises.

Camphor semicarbazone was also condensed with d-camphylamine when solid δ- camphyl semicarbazones were obtained. Separation of these by fractional crystallisation could not be carried out.

Camphor semicarbazone condensed with d-nor ψ ephedrine gave a gummy product.

Benzoin semicarbazone reacted with inactive camphylamine to give benzoin δ- camphyl semicarbazone. Using active camphylamine a resin was produced which is slowly depositing a crystalline solid,

Benzoin thiosemicarbazone condensed with active α phenylethylamine to give a crystalline solid,/

solid, the analysis of which agrees with that required for benzoin δ (α phenylethyl) thiosemicarbazone. Benzoin however, has not yet been obtained by hydrolysis of this compound.

The preparations of the thiosemicarbazones of benzoin, 1-3 methylcyclohexanone and camphor have not previously been described, and accordingly, the methods employed for their preparation are given.

ATTEMPT TO RESOLVE 1.3 METHYL CYCLOHEXANONE.

EXPERIMENTAL.

The following compounds are described;-

r-1.3 Methyl cyclohexanone rδ (α phenyl ethyl) semicarbazone.

* r-1.3 Methyl cyclohexanone l-δ (α phenyl ethyl) semicarbazone.

* r-1.3 Methyl cyclohexanone d-δ (α phenyl ethyl) semicarbazone.

d-1.3 Methyl cyclohexanone dδ (α phenyl ethyl)semicarbazone.

r-1.3 Methyl cyclohexanone rδ (α phenyl ethyl) thiosemicarbazone.

These substances marked with the astertisk are, of course, mixtures of the d-and l-forms of the ketone combined with the active semicarbazide.

1.3 METHYL CYCLOHEXANONE.

1.3 Methyl cyclohexanone (Knoevenagel A 297, 154) was prepared by the oxidation of the corresponding alcohol (methyl cyclohexanol) with chromic acid, the reaction being carried out in acetic acid. When oxidation was complete, the acetic acid was neutralised with excess caustic soda and the methyl cyclohexanone extracted with ether. The ketone was purified by forming the bisulphite compound, and on treating this with potassium carbonate, methyl cyclohaxanone was obtained, boiling point 169° C.

Neutralisation of the acid oxidising medium with caustic soda may be advantageously omitted, as this procedure leads to the formation of a fairly stable emulsion on extracting the ketone with ether. It was found to be more convenient to dilute the acid liquor with water after oxidation was complete, and then to extract with ether.

δ - α - (PHENYLETHYL) SEMICARBAZIDE.

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

α Phenylethylamine was prepared by the reduction of acetophenone oxime. 13gm. of the amine were heated with 12gm. of acetone semicarbazone at 135-138° C for an hour. The product (acetone δ αphenylethyl semicarbazone)/

semicarbazone) was hydrolysed with 5% hydrochloric acid, when δ (α phenylethyl) semicarbazide hydrochloride was obtained.

Active δ (α phenylethyl) semicarbazide hydrochloride was prepared in a similar manner using active amine. (Active α phenylethylamine was obtained by a combination of the methods of Lovén and Betti; see Hopper and Ritchie (Journal Roy. Tech. College 1926, 3, 65)).

---

r-1.3 METHYL CYCLOHEXANONE r- δ (α PHENYLETHYL)SEMICARBAZONE.

It was decided to experiment with the racemic semicarbazide, in order to gain some experience of the nature of the semicarbazones involved. The reaction between the ketone and the semicarbazide hydrochloride was carried out in alcohol and in pyridine.

REACTION IN PYRIDINE.

4gm. Racemic δ(α phenylethyl) semicarbazide hydrochloride was dissolved in about 60cc. pyridine and 4gm. methyl cyclohexanone added. The solution became warm on mixing, and after standing for three days at room temperature, it was poured into half a litre of ice water. A plastic solid separated, which was washed free of pyridine with water and dried in vacuo. The amber coloured solid which remained was dissolved in benzene and by careful addition of petroleum ether to this solution/

solution r-methyl cyclohexanone r.δ-(α phenylethyl) semicarbazone was obtained as a crystalline solid, melting point 130° C. The solid was readily recrystallised from benzene-petroleum ether mixtures.

Nitrogen content. Found 15.37%. 15.40%.

Theory 15.38%.

REACTION IN ALCOHOL:-

4gm. Racemic δ(α phenylethyl) semicarbazide hydrochloride was dissolved in about 10cc. hot water, and a solution of 1.9gm. anhydrous potassium acetate in 30cc. alcohol added. The precipitated potassium chloride was filtered off and 4gm. r-methyl cyclohexanone added to the filtrate. The solution was refluxed for 3 hours and, on cooling, poured into half a litre of ice water. A plastic solid separated as before, which was dissolved in benzene. On adding petroleum ether to the benzene solution r-1.3 methyl cyclohexanone r δ(α phenylethyl) semicarbazone was obtained, exactly similar to the compound prepared in pyridine solution.

---

r-1.3 METHYL CYCLOHEXANONE AND l-δ(α PHENYLETHYL) SEMICARBAZIDE.

l-δ (α phenylethyl) semicarbazide hydrochloride (22gm.) was dissolved in pyridine and 10gm. 1.3 methyl cyclohexanone added. The solution was allowed to stand for a week and then poured into ice water, when a plastic/

plastic solid separated which largely solidified on standing for some time. The semi solid mass was washed by decantation to remove pyridine, and then dissolved in a small quantity of alcohol. On immersion of the alcoholic solution in ice, crystals of isomeric semicarbazones were deposited showing a melting range of 95°-100° C. Continued recrystallisation caused elevation of the melting point to 101°-104° C, but a sharp melting point could not be obtained.

Nitrogen content of material melting 101-104° C.

Found 15.39%.

Theory 15.38%.

2gm. of the less soluble fraction (melting 101-104° C) was hydrolysed by heating with 2N hydrochloric acid, and the liberated ketone extracted with ether. On evaporating off the ether, a small quantity of ketone remained which was distilled from a 5cc. distilling flask. 2 drops of ketone were obtained which showed a dextro rotation when examined in the polarimeter in ethereal solution. The quantity did not justify an accurate determination of the rotation, but it seemed that the crop melting 101-104° C contained a preponderance of d-ketone l-semicarbazone.

It was hoped that the experience

gained/

gained in the first attempt to resolve 1.3-methyl cyclohexanone, would prove of value in a second effort. In the second case, however, d-δ-(α phenylethyl) semi-carbazide hydrochloride was employed.

---

r-1.3-METHYL CYCLOHEXANONE AND d-δ-(α PHENYLETHYL) SEMICARBAZIDE.

The recation was carried out exactly as before in pyridine solution, and on pouring the latter into ice water a semi solid mass separated, which deposited needle shaped crystals from benzene petroleum ether mixture, melting point 97-99° C. This material was readily soluble in organic solvents, but could be recrystallised from aqueous alcohol and from petroleum ether. Aqueous alcohol was employed and the melting point of the recrystallised substance raised to 101-104° C. An extensive fractional recrystallisation of this was then attempted using petroleum ether as solvent, and after many recrystallisations the melting point of the less soluble fraction was raised to 106-110° C.

Nitrogen content 15.40%.

This material was believed to be mainly l-ketone d-semicarbazone, and the belief was confirmed by a synthesis of d-ketone d-semicarbazone, which was found to melt at 86° C, whereas the above recrystallisations are producing a progressively higher melting product.

Rotation of 106-110° C fraction $[\alpha]_D^{14}$ -49.9. (c = 4.000)

d-1.3-METHYL CYCLOHEXANONE d- δ-(α PHENYLETHYL) SEMICARBAZONE.

Active 1.3-methyl cyclohexanone was prepared from pulegon by treating the latter with sulphuric acid (Knoevanagel loc.cit.), the liberated ketone being purified via the bisulphite compound. The active ketone (dextro-rotatory) was combined with d- δ-(α phenylethyl) semicarbazide in pyridine as above, and the plastic solid obtained on pouring the pyridine solution into water was dried and recrystallised from petroleum ether, when d-1.3 methyl cyclohexanone d- δ-(α phenylethyl) semicarbazone was obtained, melting point 86° C.

Nitrogen content Found 15.42%.

Theory 15.38%.

Like the *l*-ketone d-semicarbazone (106-110° C) obtained previously, this compound was readily soluble in organic solvents and insoluble in water, but it appeared to be rather more soluble in petroleum ether than the 106-110° C mixture, thus indicating that petroleum ether would be a likely solvent to affect a separation by recrystallisation. This, however, could not be accomplished after many recrystallisations.

The optical rotation of d-ketone d-semicarbazone was determined and the value $[\alpha]_D^{15} = -100.7$ obtained. ($c = 3.974$).

r-1.3 METHYL CYCLOHEXANONE AND r-δ (α PHENYLETHYL) THIOSEMICARBAZIDE.

2.6gm. r δ (α phenylethyl) thiosemicarbazide (Burns, Baird and Wilson J.C.S. 1927, 2533) was combined with 1.5gm. methyl cyclohexanone by heating the reagents in alcoholic solution for six hours on the water bath. The alcohol was removed under reduced pressure leaving an amber coloured resin which was dissolved in a small quantity of benzene. Addition of petroleum ether and immersion in a freezing mixture caused separation of r-1.3 methyl cyclohexanone r δ (α phenylethyl) thiosemicarbazone, melting point 62° C - 63° C. Recrystallisation was carried out by dissolving in benzene and adding petroleum ether till a haze appeared. A drop or two of benzene was then added to clear the solution, and on immersion in a freezing mixture the thiosemicarbazone separated.

Nitrogen content. Found 14.6%. 14.6%.

Theory 14.5%.

The above compound was also prepared in pyridine solution.

---

r 1.3 METHYL CYCLOHEXANONE AND ACTIVE δ (α PHENYLETHYL) THIOSEMICARBAZIDE.

An attempt was made to prepare active δ (α phenylethyl) thiosemicarbazide from acetone thiosemicarbazone and l-α phenylethylamine but the laevo δ (α phenylethyl) thiosemicarbazide obtained was a thick syrup and could not be purified. In view of this difficulty it was decided to adopt method (2) (page 60) in preparing the active semicarbazones, viz;- r-1.3 methyl cyclohexanone thiosemicarbazone (below) was heated with l α phenylethylamine in toluene suspension. Decomposition, however, was extensive, much hydrogen sulphide being evolved, and the reaction was discontinued. [It was found later (page 93) that the syrupy l-δ (α phenylethyl) thiosemicarbazide could be employed in the preparation of l-δ (α phenylethyl) thiosemicarbazones without purification.]

PREPARATION OF 1.3 METHYL CYCLOHEXANONE THIOSEMICARBAZONE.

6.5gm. Thiosemicarbazide was dissolved in about 60cc. hot water and 8gm. 1.3 methyl cyclohexanone added. Sufficient alcohol was then added to form a homogeneous solution and the mixture was refluxed for 24 hours. An oil separated during refluxing but this was redissolved by/

by addition of a further small quantity of alcohol. On cooling the solution in ice, an oil separated which soon solidified, the solid matter being removed by filtration. Recrystallisation of the solid from dilute alcohol gave 1.3 methyl cyclohexanone thiosemicarbazone, melting point 117° C.

Nitrogen content. Found 22.7%. 22.8%.

Theory 22.7%.

AN ATTEMPT TO RESOLVE CAMPHOR VIA ACTIVE δ (∝PHENYLETHYL) SEMICARBAZIDE.

The following compounds are described;-

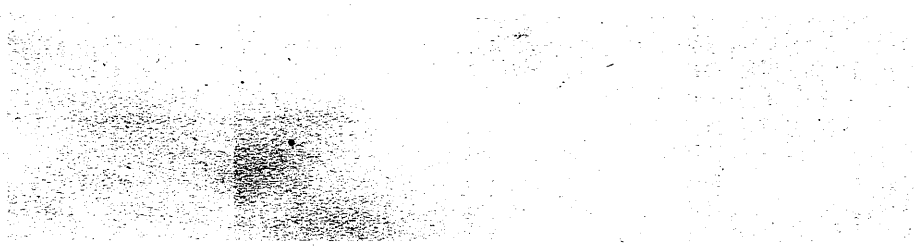
r-Camphor r δ(∝phenylethyl) semicarbazone.

* d-l Camphor l-δ-(∝ phenylethyl) semicarbazone.

d-Camphor l-δ-(∝phenylethyl) semicarbazone.

l-Camphor l-δ-(∝ phenylethyl) semicarbazone.

* This substance is a mixture of the dextro and laevo forms of the ketone combined with active δ(∝ phenylethyl) semicarbazide.



ATTEMPT TO RESOLVE CAMPHOR VIA LAEVO δ- (α PHENYLETHYL) SEMICARBAZIDE.

Instead of isolating *l*-δ-(α phenylethyl) semicarbazide as was done in the previous experiments with 1.3-methyl cyclohexanone, it was decided to prepare the δ-substituted semicarbazones by interaction of laevo α phenylethylamine with camphor semicarbazone. [Method (2) page 60]. This procedure was successfully carried out but the isomers, namely *l*-camphor *l*-semicarbazone and d-camphor *l*- semicarbazone could not be separated. The results are rather surprising, in that the melting point of the semicarbazone obtained from r-camphor semicarbazone and *l*- amine namely (d-*l*) camphor *l*-δ-(α phenylethyl) semicarbazone, was higher than that of the isomers d-camphor *l*- semicarbazone and *l* camphor *l*- semicarbazone. This would point to (d-*l*) camphor *l*- semicarbazone having the nature of a eutectic compound, and this view was supported by the fact that it could be prepared by mixing equal quantities of d-camphor *l*-semicarbazone and *l*- camphor *l*-semicarbazone.

In order to gain some knowledge of the semicarbazones involved, we again experimented with racemic compounds first.

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r-CAMPHOR r- δ-(α PHENYLETHYL) SEMICARBAZONE.

7gm. r-camphor semicarbazone and 4gm. r- α phenylethylamine were heated together for 1hour/

1 hour at a temperature of 180° C, during which time ammonia was evolved. The melt liquefied completely to give an almost clear coloured liquid, and, on cooling, this was dissolved in alcohol. The alcoholic solution deposited beautiful crystals, which, when recrystallised from alcohol, showed a melting point of 144° C. An analysis showed this compound to contain 14.4% nitrogen, whereas theory requires 13.4%. This discrepancy was traced to the presence of methane in the nitrogen, the latter being examined in the Haldane gas analysis apparatus and found to contain 6.24% methane. Applying the necessary correction, a nitrogen content of 13.5% was obtained.

The following data was obtained from the Haldane apparatus;-

Initial vol. of gas (18.50cc) was diluted with air to 41.55cc.

Volume of sample : 18.030cc.

Volume after combustion : 16.970cc.

∴ Contraction after combustion : 1.060cc.

Volume after absorption of CO_2 : 16.528cc.

∴ Contraction after absorption of CO_2 : 0.442cc.

Volume of methane : ⅓ total contraction
: ⅓ x 0,442. : 0.501cc.

% CH_4 in original gas : $\frac{0.501 \times 41.55 \times 100}{18.03 \times 18.5}$

: 6.24%.

As the analysis of the gas in the Haldane apparatus takes a considerable time in unskilled hands, it was decided to employ copper oxide containing cuprous chloride in carrying out the combustion. In the presence of cuprous chloride as catalyst, methane is said to be completely oxidised. The catalyst, prepared as follows, was found to be entirely suitable. Cuprous chloride (40gm.) was suspended in water and copper oxide (200gm.) added to the suspension. The mixture was taken to dryness with continual stirring and then ignited at a dull red heat. The mixture was found to burn methane completely.

---

r-CAMPHOR SEMICARBAZONE AND l-α-PHENYLETHYLAMINE.

r-Camphor semicarbazone (8gm.) and l-α phenylethylamine (4.6gm.) were heated as before and alcohol added to the melt. Crystallisation did not take place, however, and addition of water caused precipitation of an oil. The oil was readily soluble in organic solvents and was dissolved in petroleum ether and filtered from a small quantity of insoluble matter. The filtrate did not deposit crystals, however, and was taken to dryness when a sticky solid remained. This was again dissolved in alcohol and water added in just/

just sufficient quantity to prevent precipitation of oil. On allowing the aqueous alcoholic solution to evaporate slowly in a conical flask, crystals were deposited, which were recrystallised from alcoholic water mixtures with ease, scratching of the glass promoting crystallisation. After two recrystallisations, compound melted at 122-123° C.

Nitrogen content. Found 13.6%. 13.5%.

Theory 13.4%.

2gm. of compound, melting point 122-123°C, was hydrolysed by boiling for an hour with 3N hydrochloric acid, and the liberated camphor steam distilled. The camphor which collected in the distillate was found to be inactive, so that the compound formed above appeared to be d-l camphor l-δ-(α phenylethyl) semicarbazone and showed a rotation $[\alpha]_D^{15} = +68.9$ in alcohol. This rotation was found to be intermediate to that obtained from d-camphor l-semicarbazone and l-camphor l-semicarbazone.

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d-CAMPHOR l-δ-(α PHENYLETHYL) SEMICARBAZONE.

8gm. d-camphor semicarbazone and 4.6gm. l-α phenylethylamine were heated together as above and oily substance obtained was recrystallised by allowing aqueous alcoholic solutions to evaporate slowly, when d-camphor l-δ-(α phenylethyl) semicarbazone was/

was obtained, melting point 112° C.

Nitrogen content. Found 13.5%.

Theory 13.4%.

Rotation in alcoholic solution $[\alpha]_D^{15}$: + 41.3.. (C=4.01)

---

l-CAMPHOR l-δ-(α PHENYLETHYL) SEMICARBAZONE.

l-Camphor was prepared by the oxidation of l-borneol with concentrated nitric acid. (Pope and Harvey J.C.S. 1901, 76) and the corresponding semicarbazone prepared. The l-camphor semicarbazone was combined with active amine, and the melt taken up in alcohol. On cooling the alcoholic extract, fine needles of l-camphor l-δ(α phenylethyl) semicarbazone separated, which were recrystallised from alcohol, melting point 112° C.

Nitrogen content. Found 13.5%.

Theory 13.4%.

Rotation in alcohol $[\alpha]_D^{14}$: + 102.4. (C = 4.00)

While the melting points of d-camphor l-semicarbazone and l-camphor l-semicarbazone were the same, the former appeared to be more soluble in alcohol and it was surprising that a separation could not be affected. 1gm. of each was combined and dissolved in 10cc. alcohol, Freezing did not cause separation of l-camphor l-semicarbazone as was expected, and addition of water caused separation/

separation of (d-l)-camphor l-δ(α phenylethyl) semicarbazone, melting point 123-124° C.

CAMPHOR THIOSEMICARBAZONE AND l-αPHENYLETHYLAMINE.

Camphor thiosemicarbazone has not been described. It was prepared by heating equimolecular quantities of camphor and thiosemicarbazide in aqueous alcoholic solution for 30 hours. Thiosemicarbazide (5gm.) was dissolved in about 30cc. water and camphor (7.5gm.) added along with sufficient alcohol to form a homogeneous solution. After refluxing for 30 hours the solution was cooled when an oil separated, which solidified on standing. The solid was recrystallised from alcohol when camphor thiosemicarbazone was obtained, melting point 156° C.

Nitrogen content. Found 18.8%.

Theory 18.7%.

It was necessary to use copper oxide-cuprous chloride mixture in the nitrogen estimation.

When camphor thiosemicarbazone was heated to 160° C with l-α-phenylethylamine, ammonia was evolved. The melt solidified to a resin and all attempts at recrystallisation failed.

AN ATTEMPT TO RESOLVE CAMPHOR VIA ACTIVE δ-CAMPHYL SEMICARBAZIDE.

The following compounds are described;-

r-Camphor r δ-camphyl semicarbazone.

(d-l)-Camphor d δ-camphyl semicarbazone.

d-Camphor d δ-camphyl semicarbazone.

l-Camphor d δ-camphyl semicarbazone.

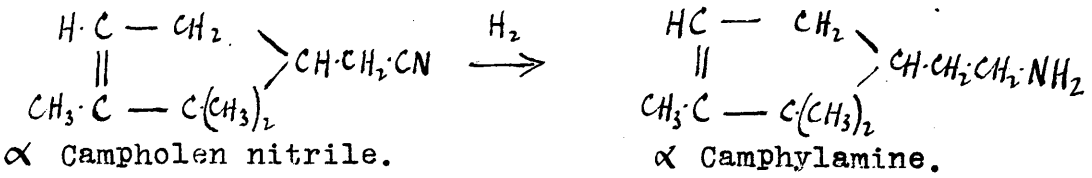
Inactive δ-camphyl semicarbazide hydrochloride.

ISOMERIC CAMPHOR δ CAMPHYL SEMICARBAZONES.

The camphor δ-camphyl semicarbazones were prepared by heating camphor semicarbazone with camphylamine to a sufficiently high temperature to cause interaction with liberation of ammonia. It was found that while r-ketone r- semicarbazone was sparingly soluble, r-ketone active-semicarbazones were, in all cases, readily soluble in organic solvents, but could be recrystallised from alcohol-water mixtures. A separation of the isomers, however, could not be effected.

The preparation of camphylamine is interesting in that, by slightly varying the method, active or inactive amine can be obtained. The methods which were employed are described;-

PREPARATION OF d-CAMPHYLAMINE.



∝ Campholen nitrile. ∝ Camphylamine.

d-Campholen nitrile (Tiemann B 29, 3008) was prepared by digesting camphor oxime with 25% H_2SO_4 . The nitrile so obtained was dissolved in 4 to 5 times its volume of absolute alcohol and sodium added until the reaction was sluggish at the boil. Much water was added to the reduction mixture to decompose the ethoxide, and the amine/

amine separated as an oil. After separating the oil, the aqueous layer was shaken with ether to increase the yield of amine. The amine together with the ethereal extract, was washed with water, dried with anhydrous sodium sulphate and distilled. The fraction boiling from 200-210° C was collected, higher boiling material being mainly unchanged nitrile. Redistillation of the 200-210° C fraction, gave d-camphylamine, boiling point 204-206° C. Rotation + 6.02 in a 1 decimetre tube.

INACTIVE CAMPHYLAMINE.

d-Campholen nitrile was reduced as above with sodium in alcohol, and hydrochloric acid added to neutralise the reduction mixture. The unchanged nitrile was extracted with ether and the aqueous layer concentrated on the water bath to quarter bulk. During concentration, a slimy skin formed on the surface of the solution and was probably amine hydrochloride. Excess sodium hydroxide was added to the concentrated solution and the liberated amine steam distilled. The amine so obtained was redistilled, boiling point 194-196°C and found to be inactive.

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r-CAMPHOR r δ-CAMPHYL SEMICARBAZONE.

5gm. r-camphor semicarbazone and 3.5gm. inactive camphylamine were heated together for 1 hour at a temperature of 175° C, ammonia being evolved freely. The melt was extracted with hot methyl alcohol and, on cooling, the alcoholic solution, r-camphor r-δ-camphyl semicarbazone separated readily, melting point 175° C.

Nitrogen content. Found 12.3%. 12.4%.

Theory 12.2%.

(Copper oxide-cuprous chloride mixture was used in nitrogen determinations).

(d-l)-CAMPHOR d- δ- CAMPHYL SEMICARBAZONE.

Camphor semicarbazone (10gm.) and d-camphylamine were heated together as above for 1 hour at 160° C to 165° C. The melt was dissolved in methyl alcohol and the alcoholic solution deposited crystals on cooling and scratching after the addition of a little water. It was found most convenient to recrystallise the product from alcohol and water mixtures, but repeated recrystallisation did not raise the melting point of the material above 110° C- 113° C.

Nitrogen content. Found 12.3%.

Theory 12.2%.

3gm. of the substance melting at 110-113° C was hydrolysed by refluxing with hydrochloric acid, sufficient alcohol being present to retain the substance in solution. The product was steam distilled when inactive camphor was obtained, thus indicating that the original substance was a mixture of the d and l forms of camphor combined with the active semicarbazide. This view was supported by the fact that the specific rotation of the compound was approximately the mean of that of d-camphor d- δ camphyl semicarbazone, and l-camphor dδcamphyl semicarbazone.
Rd- δ camphyl semicarbazone, and l-camphor dδcamphyl semicarbazone

Rotation of (d-l)-camphor d- δ-camphyl semicarbazone.

$[\alpha]_D^{14}$ (in alcohol) : + 2.9. (c = 3·98)

d-CAMPHOR d- δ- CAMPHYL SEMICARBAZONE.

d-Camphor d- δ camphyl semicarbazone was prepared as above from d-camphor semicarbazone and d-camphylamine. The melt obtained was readily soluble in organic solvents but could be crystallised from alcohol water mixtures, when d-camphor d- δ camphyl semicarbazone was obtained, melting point 105° C.

Nitrogen content. Found 12.25%.

Theory 12.2%.

Rotation in alcohol $[\alpha]_D^{14}$: − 23.1. (c = 3·84)

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l-CAMPHOR d-δ CAMPHYL SEMICARBAZONE.

l-Camphor d-δ camphyl semicarbazone was prepared as above from l-camphor semicarbazone and d-camphylamine. The melt was dissolved in petroleum ether and a small amount of unchanged l-camphor semicarbazone removed by filtration. The petroleum ether solution was taken to dryness and the residue was recrystallised from 90% alcohol, freezing being necessary to cause separation of crystals. In this way l-camphor d-δ-camphyl semicarbazone was obtained, melting point 117-118° C.

Rotation in alcoholic solution $[\alpha]_D^{14}$: + 26.9. (c = 3·66)

Nitrogen content. Found 12.2%.

Theory 12.2%.

AN ATTEMPT TO RESOLVE BENZOIN VIA THE ACTIVE δ-CAMPHYL SEMICARBAZONE.

An attempt was made to prepare d-δ-camphyl semicarbazide hydrochloride by heating acetone semicarbazone with d-camphylamine. The acetone d-δ-camphyl semicarbazone obtained was resinous, and a hydrolysis of the resin yielded inactive δ-camphyl semicarbazide hydrochloride. It seems reasonable to assume that during the hydrolysis, racemisation had occurred, for while the resinous acetone d-δ camphyl semicarbazone was not examined in the polarimeter, the corresponding compound from r-camphor had already been shown to be active. Consequently, for resolutions involving d-camphylamine, method (1) page 60, namely the combination of ketone with active semicarbazide, is not applicable.

r-Benzoin was combined with inactive δ-camphyl semicarbazide, in alcoholic and in pyridine solution and the corresponding r-benzoin r-δ- camphyl semicarbazone isolated.

The combination of r-benzoin semicarbazone with d-camphylamine yielded a resin which is slowly depositing solid matter.

AN ATTEMPT TO PREPARE d-δ-CAMPHYL SEMICARBAZIDE HYDROCHLORIDE.

Acetone semicarbazone and d-camphylamine

in/

d-camphylamine, in equimolecular quantities, were heated together for half an hour to a temperature of 150-155° C when ammonia was evolved. The melt obtained was syrupy, and could not be obtained in the solid form. The syrup(9gm.) was dissolved in aqueous alcohol(60cc.) and hydrolysed by boiling with hydrochloric acid for an hour. (15cc. of concentrated acid were added to the alcoholic solution). The solution was then evaporated under reduced pressure until solid matter separated, when it was cooled and filtered. The filtrate was again evaporated under reduced pressure till solid matter separated, and again filtered, the process being repeated until evaporation was complete. This procedure was adopted to prevent unnecessary heating of concentrated solutions. The combined residues were recrystallised from absolute alcohol, when δ camphyl semicarbazide hydrochloride was obtained, melting point 179-180° C.

Nitrogen content. Found 17.2%.

Theory 17.04%.

The δ camphyl semicarbazide hydrochloride was inactive.

---

r-BENZOIN r-δ CAMPHYL SEMICARBAZONE.

Inactive δ camphyl semicarbazide hydrochloride (6gm.) was dissolved in 40cc. alcohol and added to a solution/

solution of potassium acetate (2.5gm.) in alcohol. The mixed solution was cooled and potassium chloride removed by filtration. Benzoin (5.2gm.) was added to the filtrate and the solution was refluxed for 5 hours. On cooling, a small quantity of benzoin separated and was filtered off. The filtrate on evaporation yielded a resin which solidified on standing. All attempts at crystallisation failed until a crystal of r-benzoin r- δ camphyl semicarbazone (obtained below) was introduced into an aqueous alcoholic solution of the resin. When this was done, a good yield of crystalline matter was obtained overnight. r-benzoin r- δ camphyl semicarbazone crystallises from methyl alcohol in fine needles, melting point 100° C.

Nitrogen content. Found 10.34%.

Theory 10.45%.

REACTION IN PYRIDINE.

The reaction between r-benzoin and r- δ-camphyl semicarbazide hydrochloride was also carried out in pyridine solution, by allowing the reactants to stand at the ordinary temperature for a week. After that time the pyridine solution was poured into water when a sticky, semi solid mass separated. This was washed free of pyridine and allowed to stand in an open flask, and after 4 months a few crystals appeared. These were used to seed the alcoholic solution above/

above, when r-benzoin r-δ camphyl semicarbazone was obtained.

HYDROLYSIS OF r-BENZOIN r-δ CAMPHYL SEMICARBAZONE.

r-Benzoin r-δ camphyl semicarbazone (1gm.) was dissolved in 15cc. of alcohol, and 15cc. hydrochloric acid (5N) added to the solution. Refluxing was carried out for 10 minutes and the solution cooled. Crystals separated which were identified as benzoin, and after a short time a further crop of a crystalline solid separated which was identified as r-δ camphyl semicarbazide hydrochloride.

BENZOIN SEMICARBAZONE AND ACTIVE CAMPHYLAMINE.

Equimolecular quantities of benzoin semicarbazone and d-camphylamine were heated together for 1 hour at a temperature of 160° C. The cooled product was resinous in nature and was soluble in all the common organic solvents with the exception of petroleum ether. A solution of the resin was left standing in a conical flask for several months, but evaporation of the alcohol took place without crystallisation occurring. (The resin has now been standing for about 3 years and is slowly depositing solid matter, melting point 82-84° C. This substance will be investigated.).

AN ATTEMPT TO RESOLVE BENZOIN VIA ACTIVE δ (α PHENYLETHYL) THIOSEMICARBAZIDE.

The preparation of l- δ (α phenylethyl) thiosemicarbazide hydrochloride described on page 72, resulted in the formation of a syrup. It has now been shown that this syrup may be used for the preparation of r-benzoin l- δ-(α phenylethyl) thiosemicarbazone.

The possibility of preparing the substituted thiosemicarbazone from benzoin thiosemicarbazone and active α phenylethylamine was also considered. (Benzoin thiosemicarbazone has not previously been described and its method of preparation is given). It was found that both methods;viz;-

(1) Benzoin + l-δ-(α phenylethyl) thiosemicarbazide.

(2) Benzoin thiosemicarbazone + l α phenylethylamine.

gave a product, which on complete analysis indicated that it was a benzoin l-δ-(α phenylethyl) thiosemicarbazone, but so far, attempts to liberate benzoin from this compound by hydrolysis have been unsuccessful.

EXPERIMENTAL

BENZOIN THIOSEMICARBAZONE.

Thiosemicarbazide (3gm.) was dissolved in about 20cc. hot water, and 50cc. alcohol added to the/

the solution. Benzoin (7gm.) was added and a few drops glacial acetic acid, and the solution refluxed for 15 hours. The presence of acetic acid was found to catalyse the condensation. (This has been confirmed quantitatively by Conant and Bartlett J.Am.C.S. 1932, 2881, with regard to the condensation of ketones with semicarbazide). After refluxing, the solution was cooled, when benzoin thiosemicarbazone crystallised in the form of minute needles. The product was purified by heating an alcoholic solution with animal charcoal, melting point 182° C.

Nitrogen content: Found 14.5%.

Theory 14.7%.

BENZOIN THIOSEMICARBAZONE AND l∝ PHENYLETHYLAMINE

Benzoin thiosemicarbazone (4gm.) and l-∝ phenylethylamine (2gm.) were heated together in xylene solution for 7 hours during which time ammonia was evolved. The xylene was removed under reduced pressure and the resin which remained as residue was taken up in a small quantity of benzene. Petroleum ether was added to the benzene solution in just sufficient quantity to prevent separation of an oil. On standing for some time crystals separated which were readily recrystallised from benzene-petroleum ether mixtures or from aqueous alcohol in the form of long colourless needles, melting point 171° C.
analysis of this compound indicated that it was a benzoin l-δ-(∝ phenylethyl) thiosemicarbazone.

Nitrogen	Found	10.73%.	Nitrogen	Theory	10.78%.
Sulphur	Found	8.01%.	Sulphur	Theory	8.22%.
Carbon	Found	71.01%.	Carbon	Theory	70.9%.
Hydrogen	Found	5.96%.	Hydrogen	Theory	5.91%.

So far, benzoin has not been obtained by hydrolysis of the above compound.

BENZOIN AND l-δ-(∝PHENYLETHYL) THIOSEMICARBAZIDE.

l-δ-(∝ Phenylethyl) thiosemicarbazide has

not/

been described. It was prepared by heating acetone thiosemicarbazone with l α phenylethylamine in xylene solution for 6 hours, when on removal of the xylene, acetone l-δ-(α phenyethyl) thiosemicarbazone remained as a syrup. The syrup was hydrolysed by refluxing with hydrochloric acid in aqueous alcohol. On removing the alcohol a syrup remained which could not be obtained in the solid form, and was suspected to be l-δ-(α phenylethyl) thiosemicarbazide hydrochloride.

The above syrup (2gm.) was dissolved in alcohol and a solution of potassium acetate in alcohol added. The precipitated potassium chloride was filtered off and benzoin (2gm.) dissolved in the filtrate. The solution was refluxed for 10 hours and on cooling and removal of most of the solvent, a benzoin l-δ-(α phenylethyl) thiosemicarbazone was obtained, identical with that obtained above. This was recrystallised from aqueous alcohol and had a melting point of 171° C.

EXPERIMENTS EMPLOYING d nor ψ EPHEDRINE.

Stratton and Wilson (loc. cit.) attempted to combine racemic benzoin and p-methoxyhydratropaldehyde with d nor ψ ephedrino formyl hydrazide with a view to resolving these carbonyl compounds but the products in

both/

both cases were oily.

Camphor semicarbazone and camphor thiosemicarbazone on heating with d nor ψ ephedrine have also been found to yield resinous products, which have not solidified on standing for 3 years.

PART 3:

THIAZOLE FORMATION FROM THIOSEMICARBAZONES.

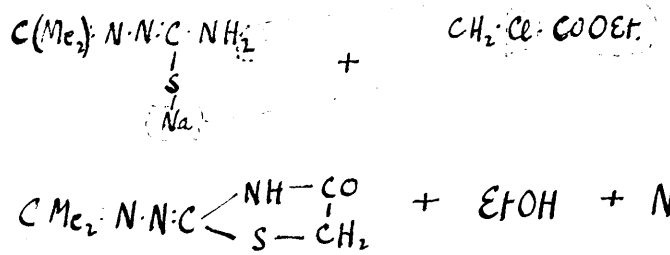
PREPARATION OF OPTICALLY ACTIVE THIAZOLES.

THIAZOLE FORMATION FROM THIOSEMICARBAZONES.

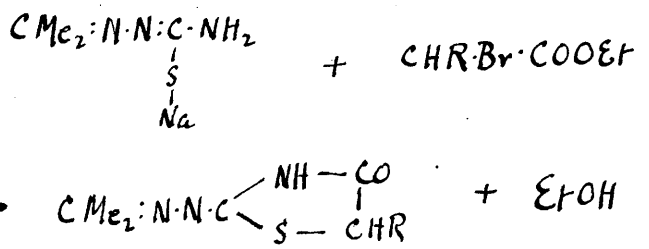
PREPARATION OF OPTICALLY ACTIVE THIAZOLES.

INTRODUCTION.

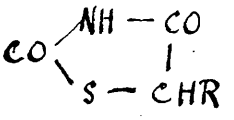
Wilson and Burns (J.C.S. 1922; 121, 870) found that the sodium derivative of acetone thiosemicarbazone reacted with esters of chloracetic acid with ~~chloride~~ formation of a ψ thio hydantoin of a new type, viz;- ethyl chloracetate and the sodium salt of acetone thiosemicarbazone gave 2.4 diketo-tetrahydrothiazole 2-isopropylidene hydrazone.



In a later paper (J.C.S. 1923, 123, 799) these authors extended the above reaction to the esters of other α halogenated acids and found the reaction proceeded according to the general scheme.



Hydrolysis of these compounds by boiling with concentrated hydrochloric acid gave[a] 2.4 diketo/

diketo tetrahydrothiazole:— 

These 2.4 diketo tetrahydrothiazoles contain an asymmetric carbon atom and it was hoped to effect a synthesis of an optically active one, by employing an ester of an active ∝ halogenated acid. Accordingly the ethyl ester of active phenyl chloracetic acid was combined with the sodium salt of acetone thiosemicarbazone, but the thiazole obtained was inactive, probably due to enolisation occurring;-

To overcome this difficulty, esters of acids containing no ∝ hydrogen were employed viz;-

Ethyl ∝bromo methyl ethyl acetate. $CH_3(C_2H_5)CBr\cdot COOEt.$

Ethyl ∝bromo iso butyrate , $CH_3(CH_3)CBr\cdot COOEt.$

Diethyl brom acetic ester , $(C_2H_5)_2CBr\cdot COOEt.$

Diphenyl chlor acetic ester, $(Ph)_2CCl\cdot COOEt.$

Using these esters no reaction was found to occur, the thiosemicarbazone being recovered in each case. This can only be attributed to steric hindrance, and in this connection Cohen (Vol.1 Reactions p.357) cites a parallel example of steric hindrance in that ∝ brom isobutyric ester does not react with sodio-ethyl malonate,

It was felt that by employing an ester

in/

in which the halogen atom was in close proximity to two carbonyl groups a reaction might occur due to the enhanced activity of the halogen and the following esters were employed;-

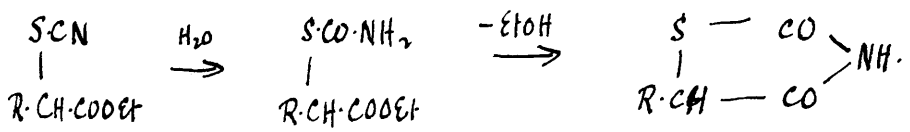
Methyl brom malonic ester — $CH_3 \cdot C \cdot Br(COOEt)_2$.

Isopropyl brom malonic ester — $C_3H_7 \cdot C \cdot Br \cdot (COOEt)_2$.

Benzyl brom malonic ester — $C_6H_5CH_2 \cdot C \cdot Br \cdot (COOMe)_2$

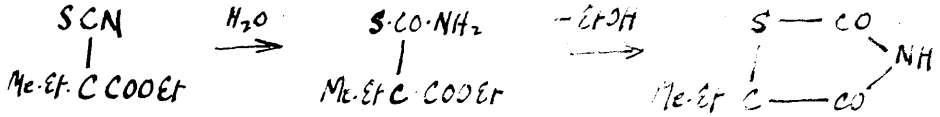
With methyl brom malonic ester and benzyl brom malonic ester a reaction seemed to take place but the oily products could not be identified. With isopropyl brom malonic ester no reaction took place and the acetone thiosemicarbazone was recovered. While the products obtained using benzyl brom malonic ester and methyl brom malonic ester were oily, it was felt that by employing a thiosemicarbazone of higher molecular weight, a solid product might be obtained and accordingly camphor thiosemicarbazone was used in place of acetone thiosemicarbazone but the resinous solids obtained could not be identified.

Other methods of preparing racemic thiazols were investigated. Wheeler and Barnes (Amer. Chem. Jour. 1900, 24, 60) describe the preparation of thiazole derivatives from ∝ sulphocyanic esters, by boiling these with hydrochloric acid when ring closure takes place, viz;-



Moreover, these authors found that while sulphocyanic esters of the type, $CH_2(SCN)COOAlk$ reacted smoothly, to give thiazole derivatives, the replacement of one of the hydrogen atoms in the α position by alkyl groups inhibited the reaction. They did not, however, employ esters containing the grouping $CRR'(SCN)COOAlk$ in which both hydrogen atoms in the α position are replaced by heavier groups.

The possibility of adopting this method for the preparation of a thiazole derivative containing an asymmetric carbon atom was investigated. Methyl ethyl sulphocyanic acetic ester was synthesised from methyl ethyl brom acetic ester, and if ring closure occurred on boiling with hydrochloric acid, a thiazole derivative should be formed in which enolisation is not possible with destruction of asymmetry.

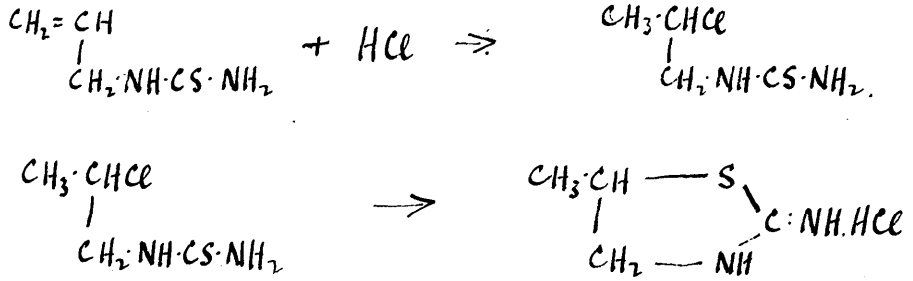


This ester, however, did not undergo ring closure, which confirmed our previous finding that steric hindrance does not allow the reaction to occur when both α hydrogen atoms are replaced by bulkier groups.

Again, Andreasch (Ber. 1898, 31, 137) describes the preparation of thiazole derivatives by condensing thiocarbamide with ethyl chloracetate and ethyl α bromo propionate in alcoholic solution.

He did not employ esters of the type $CRR'Cl \cdot COOEt$ which should yield a thiazole derivative containing an asymmetric carbon atom. The possibility of employing esters of this type was investigated but unchanged starting materials were recovered, again confirming our findings that the ester must contain hydrogen attached to the carbon atom adjacent to the carbethoxy group.

Gabriel and Ohle (Ber. 22, 2985,) describe the preparation of a thiazole derivative, 2-imino - 5-methyl thiazolidine hydrochloride, by heating allyl thio urea with concentrated hydrochloric acid under pressure.



This thiazolidine was prepared and successfully resolved into the dextro and laevo forms by means of *d*- and *l*- camphor sulphonic acids. The resolution of a thiazole has not previously been described.

THIAZOLE FORMATION FROM THIOSEMICARBAZONES.

PREPARATION OF OPTICALLY ACTIVE THIAZOLES.

EXPERIMENTAL.

ACETONE THIOSEMICARBAZONE AND l-ETHYL PHENYL CHLOR-ACETATE.

l-Ethyl phenyl chlor acetate was prepared from ethyl l-mandelate and thionyl chloride (McKenzie and Barrow J.C.S. 1911, 1910) and had a specific rotation of $[\alpha]_D^{17} -64$.

Acetone thiosemicarbazone (5gm.) was dissolved in 60cc. hot absolute alcohol and sodium ethoxide (2.6gm.) added in alcoholic solution. The mixture was refluxed for 5 minutes to complete the formation of the sodium salt of acetone thiosemicarbazone, and allowed to cool.

$$CMe_2{:}N{\cdot}N{:}C(SH)NH_2 + NaOEt \Rightarrow CMe_2{:}N{\cdot}N{:}C(SNa)NH_2.$$

l-Ethyl phenyl chloracetate (8gm.) was added to the cold solution, which was allowed to stand at the ordinary temperature for 3 days then heated to boiling and filtered from sodium chloride. On cooling, the filtrate, crystals of 2.4 diketo tetrahydrothiazole 2-isopropylidene hydrazone were obtained, melting point 198-199° C (Burns and Wilson J.C.S. 1923, 803). This compound showed no rotation in chloroform solution, as enolisation had probably occurred (page 98).

ACETONE THIOSEMICARBAZONE AND ETHYL ∝ BROM METHYL ETHYL ACETATE.

ETHYL ∝BROM METHYL ETHYL ACETATE.

Methyl ethyl acetic acid was prepared from secondary butyl bromide (Organic Synthesis V, 75) by forming the Grignard compound with magnesium, treating this with carbon dioxide, and decomposing the product with water. The following equations indicate the course of the reaction:-

$$C_2H_5CHBr\cdot CH_3 + Mg \rightarrow C_2H_5CH\cdot(MgBr)CH_3.$$
$$C_2H_5\cdot CH(MgBr)CH_3 + CO_2 \rightarrow C_2H_5\cdot CH\cdot(MgBrCO_2)CH_3$$
$$C_2H_5\cdot CH(MgBrCO_2)CH_3 + H_2O \rightarrow C_2H_5CH(CO_2H)CH_3 + Mg(OH)Br.$$

The acid was then brominated with phosphorus and bromine and converted to the ester with alcohol (Auwers Ann. 297, 167). It was found to be more convenient to form the acid chloride with thionyl chloride, brominate this, and treat with alcohol when ethyl ∝ brom methyl ethyl acetate was obtained.

Acetone thiosemicarbazone(5gm.) was dissolved in 60cc. boiling alcohol and sodium ethoxide added (0.9gm. sodium in 15cc. absolute alcohol). The solution was refluxed for 10 minutes, cooled, and ethyl ∝ bromo methyl ethyl acetate (7.8gm.) added to the cold/

cold solution. Separation of sodium bromide did not occur and the solution was refluxed for 2 hours, during which time the sodium bromide had separated. The solution was filtered hot, and the filtrate, on standing, deposited crystals, melting at 180° C. These were identified as acetone thiosemicarbazone.

Nitrogen content. Found 32.9%.

Theory 32.6%.

Apparently the sodium had reacted as sodium ethoxide, and to overcome this difficulty, it was decided to isolate the sodium salt of acetone thiosemicarbazone and carry out the reaction in benzene suspension. This was done by precipitating the sodium salt of the thiosemicarbazone from alcoholic solution by the addition of excess dry ether. (Burns and Wilson J.C.S. 1922, 870). The dry sodium acetone thiosemicarbazone was suspended in benzene and the bromo ester added. (No heat was evolved on mixing, whereas with bromo esters containing hydrogen in the α position considerable warming occurs when the reaction is conducted in benzene suspension). The suspension was refluxed for 6 hours but no reaction occurred.

Another attempt was made to bring about a reaction by mixing acetone thiosemicarbazone and the bromo ester in pyridine solution. This was also unsuccessful. Wilson and Burns (loc. cit.) found/

found the reaction could be carried out in pyridine using ethyl chlor acetate without the necessity of preparing the sodium salt of the thiosemicarbazone.

ACETONE THIOSEMICARBAZONE AND ETHYL ∝ BROM ISOBUTYRATE.

Ethyl ∝ brom isobutyrate was prepared by converting isobutyric acid to the acid chloride with thionyl chloride, the reaction being completed on the water bath. The acid chloride was then brominated, and when the reaction was complete, sufficient alcohol was added to form the bromo ester, boiling point 164° C. (This agrees with the boiling point given by Volhard A 242, 161, but the method of preparation is different).

0.75gm. Sodium was dissolved in 15cc. absolute alcohol and added to a boiling solution of 4.1gm. acetone thiosemicarbazone in absolute alcohol, boiling being continued for 10 minutes. The solution was then cooled and 6.1gm. of ethyl ∝ brom isobutyrate added. No sodium bromide separated until the solution was refluxed, the refluxing being conducted for 1 hour. The solution was filtered hot from sodium bromide, and, on cooling the filtrate, crystals of acetone thiosemicarbazone separated. Here again the sodium apparently reacts as sodium ethoxide.

ACETONE THIOSEMICARBAZONE AND DI-ETHYL BROM ACETIC ESTER.

Di-ethyl brom acetic ester was prepared by converting diethyl acetic acid (25gm.) to the acid chloride with thionyl chloride (33gm.) the reaction being completed on the water bath. Bromine (45gm.) was added to the acid chloride and bromination conducted in sunlight, the reaction being completed on the water bath. When the colour of the bromine had disappeared, the reaction mixture was allowed to cool and 20cc. absolute alcohol added gradually. The mixture was again heated to complete the conversion to ester, cooled, and treated with a saturated solution of potassium bicarbonate to remove any free acid. The ester separated as an oil, boiling point 195-197° C. This agrees with boiling point given by Rosenmund B. 42, 4472, but his method of preparation was different, in that he prepared diethyl brom acetic acid from diethyl malonic acid and bromine, and then esterified the bromo acid.

The reaction between the sodium salt of acetone thiosemicarbazone and diethyl brom acetic ester was conducted in alcoholic solution as before, and acetone thiosemicarbazone recovered.

Diphenyl chlor acetic ester (Bickel B. 22, 1537) was also employed and again the acetone/

acetone thiosemicarbazone was recovered.

ACETONE THIOSEMICARBAZONE AND METHYL BROM MALONIC ESTER.

In methyl brom malonic ester $CCH_3Br(COOEt)_2$ the bromine atom is adjacent to two carbonyl groups, and consequently will probably exhibit pronounced activity. It was in this belief that the ester was employed.

Methyl malonic ester was prepared from ethyl malonate and brominated in presence of a crystal of iodine.

The methyl brom malonic ester so prepared was combined with the sodium salt of acetone thiosemicarbazone in alcohol solution, and sodium bromide separated almost immediately. The reaction was completed by refluxing for half an hour and the liberated sodium bromide removed by filtration, The filtrate did not deposit solid matter on cooling and was taken to dryness under reduced pressure when an oil remained which was contaminated with sodium bromide. The bromide was removed by washing with water and the oily residue left in a vacuum desiccator, but it did not solidify: An attempt to distil it under reduced pressure resulted in decomposition taking place.

In view of the fact that a reaction of some kind took place with methyl brom malonic ester, it was decided to vary the nature of the malonic ester with a view to producing a solid product. Accordingly esters of higher molecular weight were employed namely isopropyl brom malonic ester and benzyl brom malonic ester.

Isopropyl brom malonic ester (Koetz J.pr.(2) 75, 495) behaved like the esters of monobasic acids in that a reaction did not appear to take place in alcoholic solution, the acetone thiosemicarbazone being recovered.

Benzyl brom malonic ester (Conrad B, 35, 1821) on the other behaved like methyl brom malonic ester. On bringing the reactants together in alcoholic solution, heat was evolved with separation of sodium bromide. The filtrate,after removal of sodium bromide, yielded a viscous glue on removal of solvent. Camphor thiosemicarbazone was combined with benzyl brom malonic ester with the same result, the viscous material which was obtained could not be obtained in the solid form.

THIAZOLE FORMATION FROM SULPHOCYANIC ESTERS.

Wheeler and Barnes (loc. cit.) describe the/

the preparation of thiazoles from sulphocyanic esters (page 99). With a view to preparing a thiazole containing an asymmetric carbon, the possibilities of this method were investigated, and a preparation of methyl ethyl sulphocyanic acetic ester was undertaken.

METHYL ETHYL SULPHOCYANIC ACETIC ESTER.

Methyl ethyl brom acetic ester (14gm.) was refluxed for 30 hours with potassium sulphocyanide (7gm.) in 30cc. alcohol. After that time the precipitated potassium bromide was filtered off and the alcohol removed under reduced pressure. The residue was oily and distilled at 90-92° C under 2mm. pressure, to give a colourless oil with a strong, penetrating odour.
Nitrogen content. Found 8.1%.
Theory for methyl ethyl brom acetic ester 7.9%.

The methyl ethyl brom acetic ester (3gm.) was heated with 4cc. concentrated hydrochloric acid for 6 hours on the water bath, and during that time the two layers (oil and aqueous hydrochloric acid) persisted. In the cases reported by Wheeler and Barnes (page 99) using methyl sulphocyan acetic ester, $CH(CH_3)(SCN)COOEt$. and ethyl sulphocyan acetic ester, $CH(C_2H_5)(SCN)COOEt$. the oily layer disappeared after heating for a short time. It is interesting to note that these authors were not/

not successful in forming thiazoles from the sulphocyanic esters of the higher members of the fatty acid series, which confirms our suspicion that steric hindrance is preventing these reactions from taking place.

Andreasch (Ber. 1898, 31, 137 and Monatshefte 1928, 49, 122) prepared thiazole derivatives by heating brom esters with thiocarbamide in alcoholic solution (page 100). As further support for the present argument we attempted to combine thiocarbamide with esters which did not contain hydrogen in the α position to the carbethoxy group.

When methyl ethyl brom acetic ester was refluxed with thiocarbamide in alcoholic solution for 6 hours, no reaction took place, the thiocarbamide being recovered unchanged. Refluxing for a further period of 6 hours did not bring about a reaction.

Again, thiocarbamide did not condense with ethyl α brom isobutyrate when the reagents were heated in alcoholic solution for 6 hours.

RESOLUTION OF 2-IMINO 5-METHYL THIAZOLIDENE.

Gabriel and Ohle (Ber. 22, 2985) describe the preparation of a reduced thiazole derivative containing an asymmetric carbon atom, namely 2-imino 5-methyl thiazolidene (page 101) The resolution of this compound is described.

INACTIVE 2-IMINO 5-METHYL THIAZOLIDENE.

Allyl thiourea (20gm.) was heated in a pressure flask with 40cc. concentrated hydrochloric acid on a boiling water bath, the flask being stoppered. In this way the reaction was conducted under increased pressure. After heating for an hour, the solution which had formed was evaporated on a water bath to a syrup, the latter solidifying readily when rubbed with a glass rod. The solid which consisted of 2-imino 5-methyl thiazolidene hydrochloride was decomposed by addition of potassium hydroxide (33gm. in 100cc. of water) when the free base separated as a thick oil. The oil was removed and aqueous layer extracted with benzene, the benzene extract being added to the oil. On evaporating off the benzene 2-imino 5-methyl thiazolidene was obtained as a thick oil which was dried at 90° C. The oil could not be distilled as it decomposed readily at high temperature.

L-2-IMINO 5-METHYL THIAZOLIDENE d-CAMPHOR SULPHONATE.

2-Imino 5-methyl thiazolidene (18gm.) was added to a solution of d-camphor 10 sulphonic acid (30gm.) in 70cc. of absolute alcohol. On allowing the mixture to stand overnight, a crop of crystals (m.p. 180-183°) were obtained which were filtered off and washed with a little ice cold alcohol. After 2 crystallisations from small quantities of absolute alcohol, the melting point rose to 182-184° C and further recrystallisation did not alter the optical rotation.

1gm. of l-thiazolidene d-camphor sulphonate in 25cc. water showed a specific rotation $[\alpha]_D^{15}$ — 19.63.

The mother liquors obtained during the recrystallisation were mixed and evaporated to half bulk when a further small quantity of l-thiazolidene d-camphor sulphonate was obtained and filtered off.

---

l-2-IMINO 5-METHYL THIAZOLIDENE HYDROCHLORIDE.

15gm. of the l-thiazolidene d-camphor sulphonate were dissolved in 70cc. water and a 50% solution of caustic potash added in excess. The free thiazolidene remained in solution and was separated

by/

by repeated extractions with benzene. It was found to be advantageous to extract the hot solution with benzene, otherwise the potassium salt of camphor sulphonic acid separates and chokes the separating funnel. In all, 7 extractions were made, and the combined benzene extracts evaporated under reduced pressure, when the *l*-base remained as a syrup. The syrup was dissolved in dilute hydrochloric acid and evaporated to dryness when about 5gm. of *l*-thiazolidene hydrochloride was obtained, which was recrystallised by addition of dry ether to an alcoholic solution, melting point 175° C.

Nitrogen content. Found 10.1%. 10.2%.

Theory 10.10%.

Rotation (1gm. in 25cc. water) α : -3.06.

$[\alpha]_D^{14}$: -76.5.

---

d-THIAZOLIDENE *l*-CAMPHOR SULPHONATE.

The alcoholic mother liquors obtained on recrystallisation of the *l*-base d-camphor sulphonate, were taken to small bulk, when a syrup remained which did not crystallise on cooling. This syrup was treated with excess of 50% potassium hydroxide and the liberated base extracted repeatedly with/

with benzene. In all 6 extractions were made, 8gm. of the base being obtained. A further 6 extractions yielded an additional 1.5gm. of base, on removal of benzene under diminished pressure. The liberated base (9.5gm.) was added to a solution of *l*-camphor 10 sulphonic acid (19gm.) in absolute alcohol (40cc.). On standing overnight the solution deposited crystals of d-thiazolidene *l*-camphor sulphonate which were filtered off and washed with a little ice cold alcohol. These were optically pure after 2 crystallisations from absolute alcohol, melting point 182-184° C. Concentration of the mother liquors to half bulk yielded a further crop of the salt.

Rotation (1gm. in 25cc. water) $[\alpha]_D^{15} = +20.10$.

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d-2-IMINO 5-METHYL THIAZOLIDENE HYDROCHLORIDE.

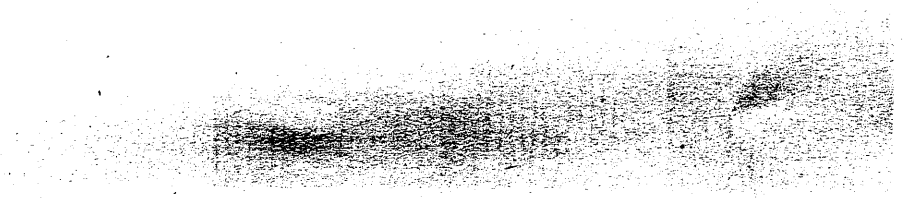
The d-base was separated from the d-base *l*-camphor sulphonate, by dissolving the latter in water and adding excess potassium hydroxide. The base was extracted from the aqueous solution with benzene (6 extractions), and the benzene removed under reduced pressure. The resulting syrup was dissolved in dilute hydrochloric acid and evaporated to dryness on the water bath, when 4gm. of the d-base hydrochloride were/

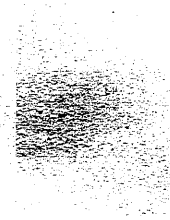
were obtained, melting point 171-173° C. This was recrystallised by dissolving in absolute alcohol and adding dry ether till crystals separated.

Nitrogen content. Found 10.2%. 10.2%.

Theory 10.1%.

Rotation (1gm. in 25cc. water) $[\alpha]_D^{15}$: + 77.5.





PART 4

REACTIONS OF THIOSEMICARBAZONES WITH THE ANHYDRIDES OF UNSATURATED ACIDS.

REACTIONS OF THIOSEMICARBAZONES WITH THE ANHYDRIDES OF UNSATURATED ACIDS.

INTRODUCTION.

The action of thiosemicarbazones on the anhydrides of unsaturated acids does not appear to have been investigated previously. With anhydrides of saturated acids, thiosemicarbazide forms α - substituted thiosemicarbazides (Freund and Meinecke B 1896, 29, 2515) acetic anhydride, for example, gives α - acetyl thiosemicarbazide.

$$CH_3\cdot CO\diagdown \atop CH_3\cdot CO\diagup O + H_2N\cdot NH\cdot CS\cdot NH_2 \rightarrow CH_3\cdot CO\cdot NH\cdot NH\,CS\cdot NH_2.$$

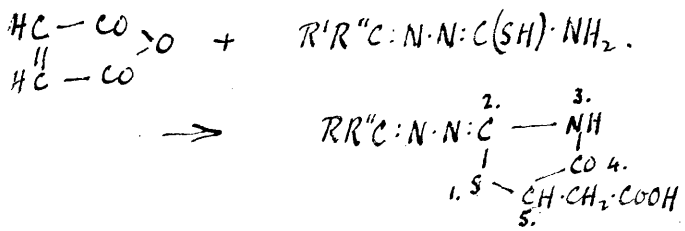
Andreasch (Monatshefte 16, 790) investigated the reaction which occurred between thiocarbamide and the anhydrides of unsaturated acids and concluded that there was no reaction using the anhydride of a monobasic unsaturated acid (crotonic, cinnamic, and oleic anhydrides were employed); while the anhydrides of unsaturated dibasic acids condensed with thiocarbamide to give Ψ thiohydantoins, according to the following scheme;-

$$NH{:}C(SH)\cdot NH_2 + \begin{matrix} RC-CO\diagdown \\ \| \\ R'C-CO\diagup \end{matrix} O \rightarrow \begin{matrix} NH{:}C & \text{---} & S \\ | & & | \\ NH\diagdown & CO\diagup & CR\cdot CHR'\cdot COOH \end{matrix}$$

Thiosemicarbazide and thiosemi-

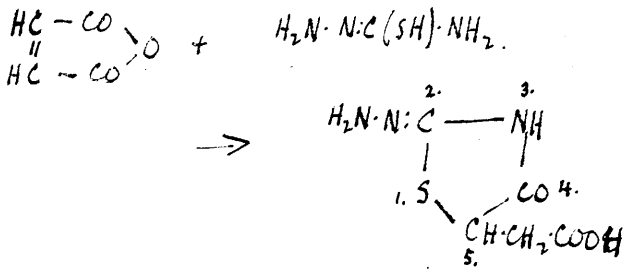
carbazones/

thiosemicarbazones have been found to behave in a similar manner. With maleic anhydride and a semicarbazone the reaction proceeds with formation of a derivative of diketo tetrahydrothiazole acetic acid viz;-



The product is a monobasic acid which forms salts with organic bases and insoluble precipitates with many metallic salts.

With thiosemicarbazide and maleic anhydride the free hydrazone presumably is formed if the reaction is conducted in neutral solvent. Using glacial acetic acid as solvent, the corresponding acetate is produced.



2.4-diketo tetrahydrothiazole-

-2-hydrazine 5- acetic acid.

When water or aqueous alcohol was employed as solvent for the above condensation, the product/

product was obtained in a resinous form but could be purified(in the case of citraconic anhydride) by dissolving the resin in alkali followed by precipitation with acid. This method of purification was not entirely satisfactory as the precipitated solid occluded alkali, and it was found to be much more convenient to conduct the condensation in amyl alcohol solution, thiosemicarbazide being appreciably soluble in this solvent.

It was found that if thiosemicarbazide and maleic anhydride were heated together for a short time in water, fumaric acid was produced and thiosemicarbazide recovered. This change may have been due to the presence of traces of free sulphur in the thiosemicarbazide (Skraup J.C.S. 1930, 213) on the other hand it may have been due to the weak acidic nature of thiosemicarbazide.

Whereas maleic and citraconic anhydrides react with thiosemicarbazide and thiosemicarbazones according to the scheme outlined above, the anhydrides of the unsaturated monobasic acids, crotonic and cinnamic, do not react with thiosemicarbazones at all, and with thiosemicarbazide they form the corresponding α substituted thiosemicarbazide, in this respect behaving like the anhydrides of saturated acids.

The nature of the condensation products was confirmed by the synthesis of 2-4 diketo-tetrahydrothiazole 2-acetophenone hydrazone 5-acetic acid using the method of Wilson and Burns (loc. cit.) namely from acetophenone thiosemicarbazone and monochlorsuccinic acid. At the present time, this reaction constitutes the only experimental evidence in support of our theory regarding the condensation of thiosemicarbazones with the anhydrides of unsaturated dibasic acids.

The following condensations are described;-

Maleic anhydride and thiosemicarbazide.

Citraconic anhydride and thiosemicarbazide.

Maleic anhydride and acetophenone thiosemicarbazone.

Maleic anhydride and methyl cyclohexanone thiosemicarbazone.

Citraconic anhydride and benzal thiosemicarbazone.

Cinnamic anhydride and thiosemicarbazide.

Crotonic anhydride and thiosemicarbazide.

MALEIC ANHYDRIDE AND THIOSEMICARBAZIDE.

EXPERIMENTAL.

REACTION IN AQUEOUS SOLUTION.

Maleic anhydride (4.9gm.) was dissolved in about 50cc. water and the solution heated to 60° C. Thiosemicarbazide (4.5gm.) was added and dissolved immediately with liberation of heat. In a few minutes a product separated, which was recrystallised from water, melting point 288° C in a sealed capillary tube. This substance contained no nitrogen and was identified as fumaric acid. The mother liquor from which the fumaric acid had crystallised deposited thiosemicarbazide on standing, the only change which had taken place under the conditions specified being the transformation of maleic acid to fumaric acid.

The above reaction was repeated but the time of heating was extended to 8 hours, during which the solution was boiled. On cooling, an oil separated which solidified to a hard resin on drying. The resin was readily soluble in caustic soda and in ammonia and was precipitated from alkaline solution as an amorphous powder which became sticky on exposure for a short time to the atmosphere, thereby rendering analysis impossible.

REACTION WITHOUT SOLVENT.

Maleic anhydride and thiosemicarbazide in equimolecular quantities were heated together for 5 minutes at a temperature of 120° C. The melt liquefied completely and, on cooling, was dissolved in ammonia. Precipitation of the ammoniacal solution with acid resulted again in the formation of a sticky solid.

REACTION IN NON AQUEOUS SOLVENTS.

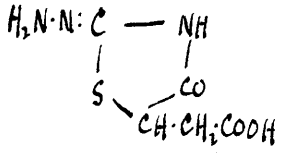
IN AMYL ALCOHOL.

Thiosemicarbazide (4.5gm.) was dissolved in about 100cc. of hot amyl alcohol. Maleic anhydride (4.9gm.) was then added and after a short time a sticky solid separated from the hot solution and adhered to the walls of the reaction vessel. The liquid was decanted from the solid and, on cooling, a very fine, colourless, amorphous powder separated. This was purified by refluxing with alcohol until the melting point did not rise on further washing.

Melting point 203° C.

Nitrogen content. Found 22.00%. 22.19%.

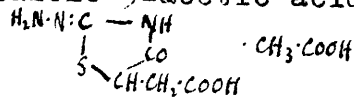
Theory for 2.4-diketo 2-hydrazine tetrahydrothiazole. 5-acetic acid is 22.22%.



IN GLACIAL ACETIC ACID.

4.5gm. Thiosemicarbazide was dissolved in 100cc. of hot glacial acetic acid and (4.9gm.) maleic anhydride added to the hot solution. The mixture was allowed to stand overnight when an amorphous solid separated, which was filtered off and washed with alcohol. The powder was not soluble in alcohol, benzene, petroleum ether or any of the usual organic solvents, but was soluble in alkali. Boiling water dissolved it but decomposition appeared to take place. The most satisfactory method of purification was found to be digestion with boiling absolute alcohol until the melting point did not rise on further treatment. The purified powder decomposed at 225° C and from the alcoholic extract an amorphous substance separated on addition of petroleum ether. This substance was not identified as it liquefied on standing in the air for a short time and then solidified to a hard resin. The insoluble substance melting point 225° C gave a nitrogen content of 16.90%. 16.92%.

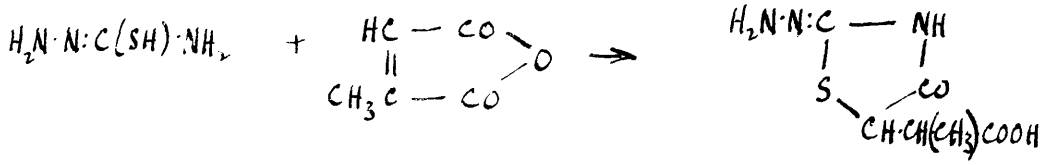
Theory for the acetate of 2.4 diketo 2 hydrazino tetrahydrothiazole 5-acetic acid is 16.87%.



The insoluble nature of this compound did not allow it to be condensed with aldehydes or ketones.

CITRACONIC ANHYDRIDE AND THIOSEMICARBAZIDE.

In view of the results obtained with maleic anhydride in conjunction with the work of Andreasch (page 117) it was expected that citraconic anhydride would react with thiosemicarbazide to give 2.4-diketo 2-hydrazone tetrahydrothiazole 5 ∝ propionic acid as follows;-



The reaction was conducted in aqueous solution and the solid resin which was obtained was found on purification to give a compound which was very insoluble but the analysis agreed with that demanded by the above theory. The constitution of the compound has not been proved and its insoluble nature does not permit of the preparation of a ketonic derivative. In view of the reactions of the thiosemicarbazones with unsaturated anhydrides however, it seems likely that the reaction takes the above course.

EXPERIMENTAL.

REACTION WITHOUT SOLVENT. Citraconic anhydride (5.6gm.) was mixed with thiosemicarbazide (4.5gm.) and the solid mixture/

mixture heated to 170° C for an hour. The melt liquefied and on cooling set to a hard transparent resin. Two methods of purifying the resin were adopted;-

(1) A portion of the resin was dissolved in caustic soda and reprecipitated by neutralising the alkaline solution with dilute acid. The precipitated amorphous solid was washed with water, alcohol, and finally ether, and melted with decomposition at 225° C.

Nitrogen content. Found 19.1%.

Theory for condensation product is 20.68%.

It was felt that the low nitrogen result was due to occlusion of caustic soda in the precipitated powder and ammonia was substituted for caustic soda;-

A portion of the resin was dissolved in ammonia and the ammoniacal solution neutralised with dilute acid. The amorphous powder which separated was washed as above and an analysis revealed a high nitrogen content, namely 21.2% (Theory 20.68%) which may be due to occlusion of ammonia.

(2) Another method of purification was carried out. A portion of the resin was ground to a fine powder in an agate mortar, and the powder refluxed with absolute alcohol for two hours. The alcohol was removed by filtration and the colourless solid which remained decomposed sharply at 225° C.

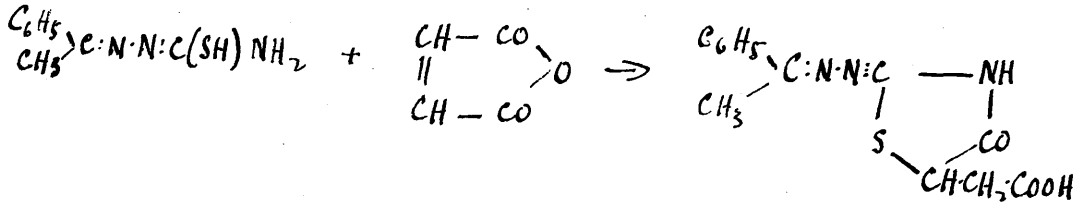
Nitrogen content. Found 20.59%. 20.61%.

Theory 20.68%.

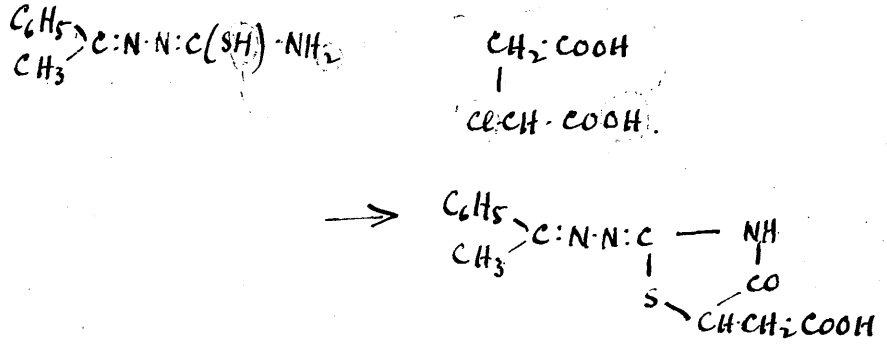
ACETOPHENONE THIOSEMICARBAZONE AND MALEIC ANHYDRIDE.

EXPERIMENTAL.

Acetophenone thiosemicarbazone reacted with maleic anhydride to give 2.4-diketo tetrahydrothiazole 2-acetophenone hydrazone 5-acetic acid.



The structure of the compound formed was confirmed by its synthesis from acetophenone thiosemicarbazone and mono-chlorsuccinic acid.



3.3gm. Maleic anhydride was dissolved in about 50cc. hot benzene and 6.3gm. acetophenone thiosemicarbazone was added to the hot solution. The thiosemicarbazone dissolved immediately, the solution becoming yellow in colour, and on heating to the boil for/

for a few minutes an amorphous solid separated. The solution set to a solid mass on cooling, but gentle warming rendered it sufficiently fluid to allow of its filtration. The residue obtained on filtration was washed with hot benzene in which it was very sparingly soluble, and then purified by dissolving in acetone and precipitating the solid by addition of petroleum ether, when 2.4-diketo tetrahydro-thiazole 2-acetophenone hydrazone 5-acetic acid was obtained as a colourless amorphous powder, melting point 244° C. This compound was soluble in acetone and alcohol and sparingly soluble in hot water. Like the other condensation products it was readily soluble in alkali.

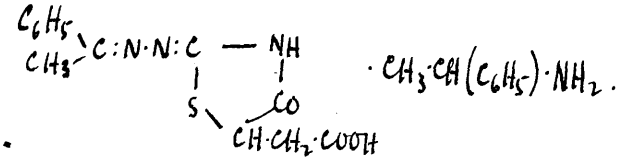
Nitrogen content. Found 14.51%. 14.48%.

Theory 14.43%.

THE ∝ PHENYL ETHYLAMINE SALT OF 2.4-DIKETO TETRAHYDRO-THIAZOLE 2-ACETOPHENONE HYDRAZONE 5-ACETIC ACID.

2.5gm. of the condensation product above was dissolved in a small quantity of boiling absolute alcohol and 1.2gm. of ∝ phenyl ethylamine added to the solution. On cooling, the ∝ phenyl ethyl-amine salt of the acid separated and was recrystallised from absolute/

absolute alcohol, melting point 194° C.

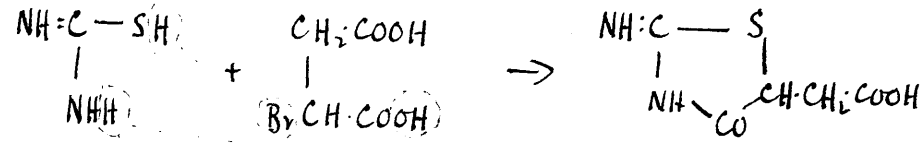


Nitrogen content. Found 13.61%. 13.68%.

Theory 13.59%.

ACETOPHENONE THIOSEMICARBAZONE AND MONOCHLORSUCCINIC ACID.

The reactions of thiosemicarbazones with halogenated dibasic acids does not appear to have been studied, but Tambach (J.C.S. Abs. 1895, 1, 13) prepared thiohydantoin acetic acid from thiocarbamide and monobromsuccinic acid, viz;-



If acetophenone thiosemicarbazone reacts in a similar manner with monohalogenated succinic acid it should yield the 2.4-diketo tetrahydrothiazole 2-acetophenone hydrazone 5-acetic acid described above.

Molecular quantities of acetophenone thiosemicarbazone and monochlorsuccinic acid were mixed and heated to a temperature of 120° C for a few minutes when liquefaction took place. The melt was dissolved in a small quantity of hot alcohol and filtered/

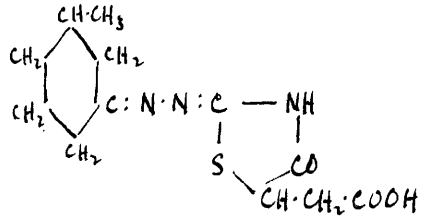
filtered, the filtrate depositing 2.4-diketo tetrahydrothiazole 2-acetophenone hydrazone 5-acetic acid, identical with the compound obtained above, melting point 244° C. This was confirmed by forming the ∝ phenylethylamine salt which had melting point 194°C.

1.3-METHYL CYCLOHEXANONE THIOSEMICARBAZONE AND MALEIC ANHYDRIDE.

EXPERIMENTAL.

4.6gm. 1.3-methyl cyclohexanone thiosemicarbazone was dissolved in about 20cc. of hot benzene. To the hot solution 2.5gm. of maleic anhydride was added and on boiling for a few minutes the solution became turbid due to the separation of a fine amorphous powder. This was filtered off, and by addition of petroleum ether to the mother liquor a further quantity of the solid was obtained. Purification of the solid was effected by dissolving it in acetone and precipitating by addition of petroleum ether, when 2.4-diketo tetrahydrothiazole 2(3'-methyl cyclohexanone hydrazone)5-acetic acid was obtained as a colourless amorphous powder, melting point 208° C.

Nitrogen Found 14.75%. 14.80%.
Theory 14.85%.



This compound dissolved readily in caustic soda solution and was precipitated on addition of acid.

Since methyl cyclohexanone contains an asymmetric carbon atom, the possibility of utilising the acidic properties of the condensation product as a means of resolving the ketone was considered. The condensation product however, when combined with active α phenylethylamine formed a sticky resin which could not be crystallised. The resin remained sticky after standing for a year.

BENZALDEHYDE THIOSEMICARBAZONE AND CITRACONIC ANHYDRIDE.

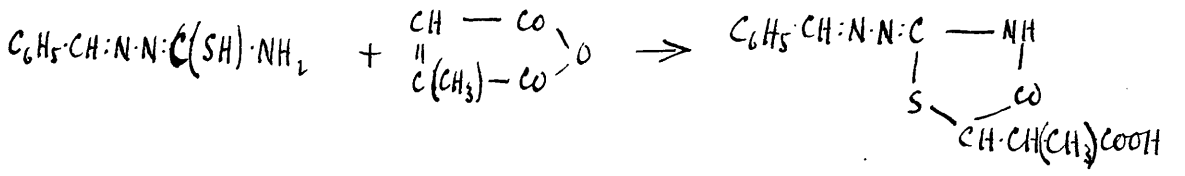
Benzaldehyde thiosemicarbazone is very sparingly soluble in benzene and accordingly amyl alcohol was chosen as the solvent. Molecular quantities of the reactants were heated for 5 minutes in boiling amyl alcohol solution, and on cooling, benzaldehyde thiosemicarbazone was recovered unchanged. Refluxing was then prolonged for a period of 3 hours, but again no reaction took place.

REACTION WITHOUT SOLVENT.

5.3gm. Benzaldehyde thiosemicarbazone was mixed with 3.3gm. of citraconic anhydride and the mixture heated in a glycerine bath to a temperature of 140-150° C. After some time liquefaction took place and on cooling, the melt set to a solid mass. The solid was dissolved in a small quantity of alcohol, and was readily deposited in a crystalline form on cooling, melting point 245-248° C. On further recrystallisation from a small quantity of alcohol 2.4-diketo tetrahydro-thiazole 2-benzal hydrazone 5 α propionic acid was obtained, melting point 252° C.

Nitrogen content. Found 14.31%. 14.40%.

Theory 14.43%.



α PHENYLETHYLAMINE SALT OF 2.4-DIKETO TETRAHYDRO-THIAZOLE 2-BENZAL HYDRAZONE 5 α PROPIONIC ACID.

1.4gm. of the acid was dissolved in a small quantity of absolute alcohol and 0.6gm. α phenyethylamine added. On standing for a short time colourless needles of the α phenylethylamine salt of the acid separated, melting point 213° C.

Nitrogen content. Found 13.61%. 13.54%.

Theory 13.60%.

THIOSEMICARBAZIDE AND ANHYDRIDES OF UNSATURATED MONOBASIC ACIDS.

Thiosemicarbazide was found to react with cinnamic and crotonic anhydrides to give the corresponding α substituted thiosemicarbazides. With cinnamic anhydride the reaction may be represented as follows:-

$$(C_6H_5\cdot CH:CH\cdot CO)_2O + H_2N\cdot NH\cdot CS\cdot NH_2 .$$

$$\rightarrow C_6H_5CH:CHCOHN\cdot NHCS\,NH_2 + C_6H_5CH:CH\cdot COOH .$$

The α cinnamyl thiosemicarbazide formed was hydrolysed when cinnamic acid and thiosemicarbazide were obtained.

THIOSEMICARBAZIDE AND CINNAMIC ANHYDRIDE.

EXPERIMENTAL.

Thiosemicarbazide (2.2gm.) was dissolved in warm amyl alcohol and cinnamic anhydride (3.5gm.) added to the hot solution, which was refluxed for 1 hour. After refluxing for about 5 minutes the solution became opalescent due to the separation of a solid in a finely divided state, but in spite of this, heating was continued for an hour, the suspension then being filtered hot, when a colourless insoluble powder was obtained. The filtrate on cooling, deposited a further quantity of solid which was combined with that already obtained. The combined solids were digested with boiling water to remove any unchanged thiosemicarbazide, which is soluble in hot water, and the residue was recrystallised from boiling absolute alcohol in which it was sparingly soluble, when α cinnamyl thiosemicarbazide was obtained, melting point 221° C.

Nitrogen content. Found 19.03%. 19.20%.

Theory 19.00%.

About 1gm. of cinnamic acid (melting point 133° C) was obtained from the amyl alcohol mother liquor on evaporating to small bulk under reduced pressure.

HYDROLYSIS OF α-CINNAMYL THIOSEMICARBAZIDE.

As there was some doubt as to the nature of the compound obtained above, it was hydrolysed with dilute hydrochloric acid (5N) sufficient alcohol being added to 'wet' the solid. After refluxing for half an hour the substance went into solution and the odour of ethyl cinnamate became apparent. The solution was evaporated and the solid which was obtained, recrystallised from a small quantity of water, when cinnamic acid crystallised, melting point 133° C. After removal of the cinnamic acid, a second crop of crystals was obtained on evaporating the solvent to reduced bulk. This solid was washed with alcohol to remove any cinnamic acid and a solid remained, melting point 175-180° C. On recrystallising this from a small quantity of water thiosemicarbazide was obtained, melting point 179° C, identical with an authentic specimen of this substance.

THIOSEMICARBAZIDE AND CROTONIC ANHYDRIDE.

Thiosemicarbazide (3gm.) was suspended in about 60cc. hot amyl alcohol and crotonic anhydride (5gm.) added to the suspension. On boiling under reflux for a few minutes solution became complete, and on cooling, a little oily matter separated, followed by/

by a solid. The suspension was filtered after standing for several hours and the residue washed with alcohol, in which it was very sparingly soluble. Recrystallisation from alcohol, gave ∝ crotonyl thiosemicarbazide, melting point 201° C.

Nitrogen content. Found 26.13%. 26.31%.

Theory 26.41%.

∝ Crotonyl thiosemicarbazide is readily soluble in water and in hot alcohol. It is insoluble in benzene, chloroform and petroleum ether.

THIOSEMICARBAZONES AND THE ANHYDRIDES OF UNSATURATED MONOBASIC ACIDS.

Acetophenone thiosemicarbazone did not react with crotonic anhydride or with cinnamic anhydride, when the reactants were heated for six hours in benzene solution, the starting materials being recovered.

Benzaldehyde thiosemicarbazone behaved like acetophenone thiosemicarbazone in that no reaction occurred with cinnamic or crotonic anhydrides.

PART 5.

THE ACTION OF THIOSEMICARBAZONES ON HALOGENO-ALDEHYDES AND KETONES.

The following reactions are described:-

Benzaldehyde thiosemicarbazone and chlor-acetone.

Acetone thiosemicarbazone and chlor-acetone.

Acetophenone thiosemicarbazone and chlor-acetone.

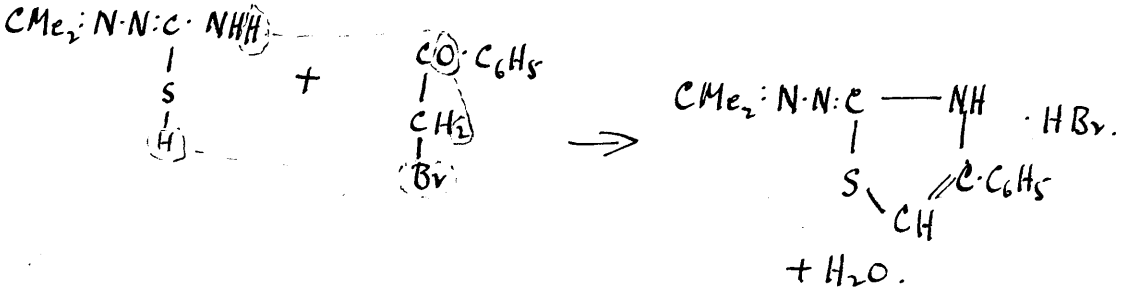
Acetone thiosemicarbazone and chlor-acetaldehyde.

Benzaldehyde thiosemicarbazone and chlor-acetaldehyde.

THE ACTION OF THIOSEMICARBAZONES ON HALOGENO-ALDEHYDES AND KETONES.

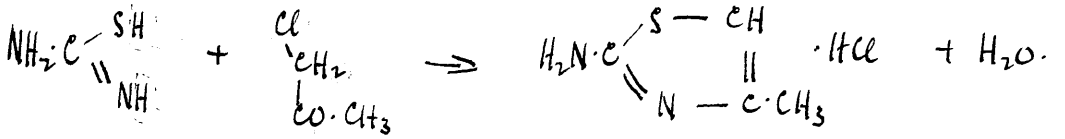
INTRODUCTION

The action of halogeno-aldehydes and ketones on thiosemicarbazones has not been investigated, but in a paper on the condensation of thiosemicarbazide with ω-brom acetophenone, Bose (J.Ind.C.S. 1924, 1, 51) studied the action of acetone thiosemicarbazone on ω-brom acetophenone and found that condensation occurred with formation of 2-keto 4-phenyl 2-3-dihydrothiazole 2-isopropylinene hydrazone hydrobromide.

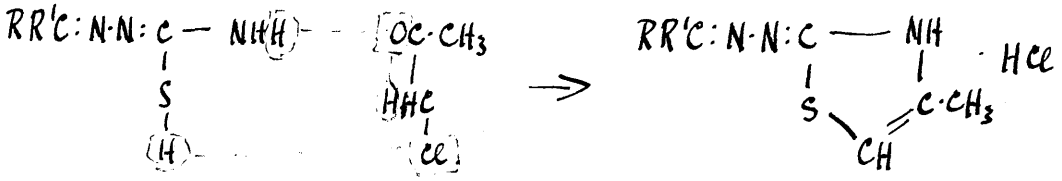


The free base could be obtained by treatment of the hydrobromide with dilute alkali.

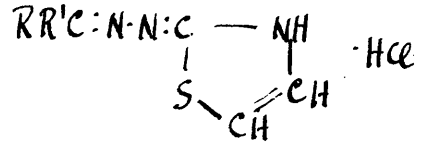
A similar type of ring closure is reported by Traumann (Ann. 249, 36, 37) by the condensation of chlor-acetone with thiourea, amino methyl thiazole being formed;-



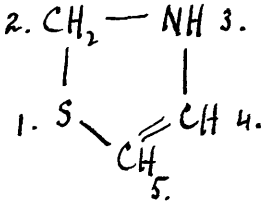
In the following pages the reactions of chloracetone and chloracetaldehyde on thiosemicarbazones are reported and the reaction appears in all cases to conform to the following general equation;-



or when chloracetaldehyde is employed the product becomes;-



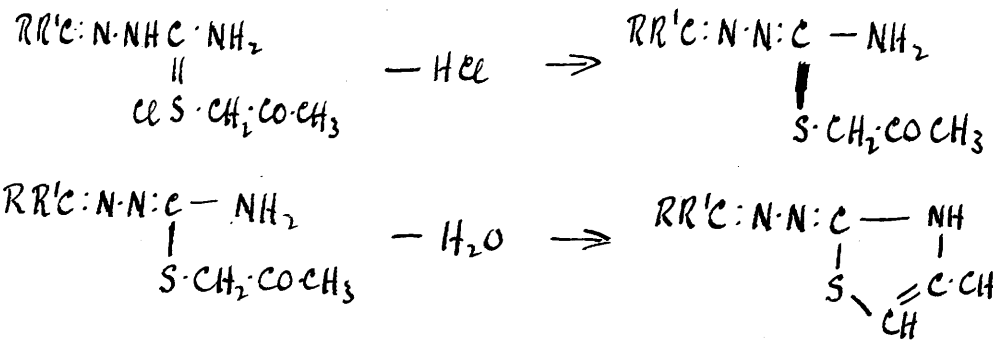
In both cases the product is a derivative of 2.3 dihydrothiazole viz;-



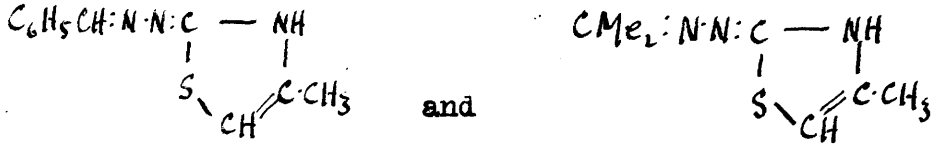
The condensations were carried out in absolute alcohol solution, and it was not usual to isolate the hydrochloride.

In the case of acetophophenone thiosemicarbazone and chloracetone, an addition product appeared to be formed when the reaction was carried out in benzene solution. The addition compound however on treatment with dilute alkali formed the ring compound This was confirmed by synthesising the ring compound in alcoholic solution.

The fact that the addition compound was isolated in one case, would suggest that the mechanism of thiazole formation from thiosemicarbazones and chloracetone, depends first of all on the production of an addition compound, which is probably a sulphonium derivative. The sulphonium compound then loses hydrogen chloride and water to form a thiazole according to the following scheme;-



The experimental work on the hydrolysis of these thiazole products is still in progress. The condensation products obtained from (1) benzal thiosemicarbazone and chloracetone and (2) from acetone thiosemicarbazone and chloracetone, namely;-



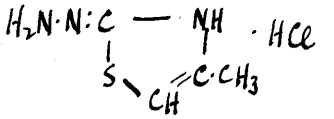
(A) and (B)

have been found to give similar products on hydrolysis with (5N) hydrochloric acid.

(A) on hydrolysis has given benzaldehyde, a solid melting at 229-222° C and an oil.

(B) has given acetone, a solid melting at 220-222° C and an oil.

The solid (melting point 220-222° C) has been analysed in both cases and the analysis agrees with that of the free hydrazone hydrochloride;-



Condensation of the free hydrazone with benzaldehyde has, however, not yet proved successful.

BENZALDEHYDE THIOSEMICARBAZONE AND CHLOR-ACETONE.

EXPERIMENTAL.

Benzaldehyde thiosemicarbazone (8gm.) was dissolved in absolute alcohol (100cc.) and chloracetone (4.5gm.) added to the solution; The mixture was refluxed for 15 minutes, (during which time a light reddish colour developed,), and then cooled. As no solid matter separated on cooling, the alcohol was taken to small bulk and the residue dissolved in water. On treating the aqueous solution with sodium carbonate, a dark yellow powder was precipitated, and was purified by dissolving in dilute hydrochloric acid followed by reprecipitation with sodium carbonate. On purification the powder had a light yellow colour and when/

when heated blackening occurred at 185° C, fusion being complete at 190° C.

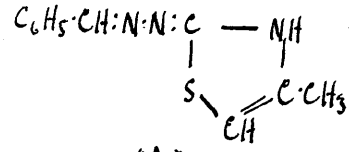
Nitrogen Found 19.37%.

Sulphur Found 14.70%. 14.40%.

2-keto 4-methyl 2.3-dihydrothiazole 2-benzal-hydrazone requires;-

Nitrogen 19.35%.

Sulphur 14.74%.



(A.)

The substance was dissolved in normal hydrochloric acid and the solution evaporated to dryness under vacuum. A solid remained which was soluble in chloroform and could be precipitated from that solvent by addition of petroleum ether, when an almost colourless amorphous powder was obtained, melting point 130° C.

Nitrogen content 16.5%. 16.4%.

The hydrochloride of (A) requires;-

Nitrogen 16.69%.

HYDROLYSIS OF COMPOUND (A).

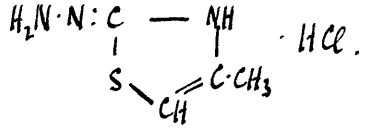
Substance (A) above was refluxed for an hour with hydrochloric acid (5N), and after that time/

time the refluxed liquid did not give a precipitate when a portion was neutralised with sodium carbonate solution, thus indicating that decomposition of (A) had occurred. The hydrochloric acid solution was filtered from a negligible quantity of solid matter and the filtrate evaporated, when a reddish yellow residue remained containing some solid matter associated with oil. The oily matter was removed with cold absolute alcohol, and the remaining solid purified by dissolving it in hot absolute alcohol and precipitating with petroleum ether. The purified substance darkened about 215° C and fused from 220-222° C.

Nitrogen content. Found 25.3%. 25.2%.

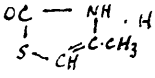
The substance (melting point 220-222°C) was a hydrochloride giving a precipitate with silver nitrate, the precipitate being insoluble in nitric acid.

The theoretical nitrogen content of 2-keto 4-methyl 2.3-dihydrothiazole 2-hydrazone hydrochloride is 25.4%.



So far the above substance has not been induced to form a benzaldehyde derivative, and with the $:N\cdot NH_2$ group present one would expect it to do so.

The oil which was also obtained as a hydrolysis/

hydrolysis product was shown to be a hydrochloride but attempts to purify it have not been successful. It may be the completely hydrolysed product:- 

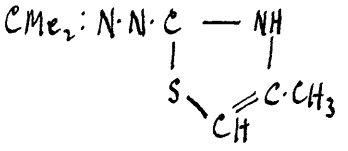
ACETONE THIOSEMICARBAZONE AND CHLORACETONE.

This condensation was carried out in alcoholic and in chloroform solution.

Acetone thiosemicarbazone (9.8gm.) was suspended in about 60cc. chloroform and chloracetone (6.9gm.) added to the suspension. The mixture was refluxed when complete solution of the thiosemicarbazone took place, and after refluxing for 10-15 minutes, the odour of chloracetone had disappeared and a small amount of solid matter had separated. This was removed by filtration and the chloroform solution extracted with several small quantities of water. The aqueous extracts were combined and neutralised with dilute sodium carbonate, when a light yellow coloured precipitate was obtained. This substance was readily soluble in organic solvents, and could be purified by recrystallisation from aqueous alcohol. It was found to be more convenient however, to purify it by dissolving in dilute hydrochloric acid followed by precipitation with alkali. The pure substance obtained melted at 90° C if heated quickly, but on slow heating it did not melt until 115° C was reached.

Nitrogen content. Found 25.04%. Sulphur content: Found 19.3%.

For 2-keto 4-methyl 2.3-dihydrothiazole 2-isopropylidene hydrazone viz;-



(B)

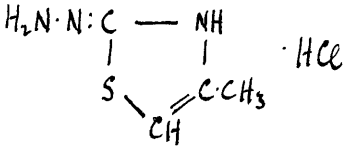
Theory requires Nitrogen 24.84%.

Sulphur 18.9%.

HYDROLYSIS OF (B).

Compound (B) was refluxed with hydrochloric acid (5N) until no precipitate was formed on neutralising a portion of the acid solution with sodium carbonate, this state being attained after refluxing for an hour. On removal of the acid under reduced pressure, the same products were formed as were obtained from the benzaldehyde compound, namely, an oil which was definitely a hydrochloride and a solid which melted at 220-222° C. The solid product had a nitrogen content of 25.6%.

Theory for the free hydrazone hydrochloride ;-



is 25.4%.

The condensation of chloracetone with acetone thiosemicarbazone was also conducted in absolute alcohol. After refluxing for 15 minutes, most of the alcohol was removed on the water bath and the residue diluted with water. On adding sodium carbonate, compound (B) separated, identical with the product obtained when the reaction was conducted in chloroform.

ACETOPHENONE THIOSEMICARBAZONE AND CHLORACETONE.

Acetophenone thiosemicarbazone was found to combine with chloracetone in benzene solution forming an addition compound (page 138) which could be recrystallised from absolute alcohol, melting point 152° C. Presumably the addition compound has the structure of a sulphonium compound;-

$$\begin{matrix} CH_3 \\ C_6H_5 \end{matrix}\!\!>\!C\!:\!N\cdot NH\cdot CS\cdot NH_2 \;+\; Cl\cdot CH_2\cdot CO\cdot CH_3$$

$$\longrightarrow \begin{matrix} CH_3 \\ C_6H_5 \end{matrix}\!\!>\!C\!:\!N\cdot NH\,\underset{\underset{Cl\cdot S\cdot CH_2\cdot CO\cdot CH_3}{\|}}{C}\cdot NH_2 \qquad (C)$$

The addition compound (C) however on recrystallisation from aqueous alcohol, or on treatment with sodium carbonate yielded a compound, melting point 134° C. It appeared that ring closure had been effected by this means as compound melting point 134° C was obtained/

obtained when the reaction was carried out in alcohol according to the usual plan. The addition compound is interesting in that it serves to indicate a possible mechanism of the reaction (page 139).

ACETOPHENONE THIOSEMICARBAZONE AND CHLOR-ACETONE.

EXPERIMENTAL.

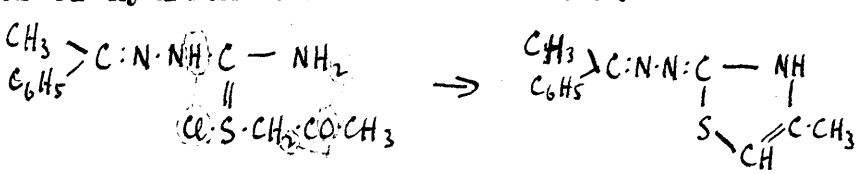
REACTION CONDUCTED IN BENZENE SOLUTION.

Acetophenone thiosemicarbazone (6gm.) was dissolved in about 100cc. hot benzene and chloracetone (3gm.) added to the solution. On cooling a cream coloured crystalline solid separated, melting point 150-151° C which on recrystallisation from absolute alcohol showed a melting point of 152° C. The pure substance quickly turned brown on standing in the air.

Nitrogen content. Found 14.74%. 14.78%.

Theory for addition compound 14.72%.

When the above substance was dissolved in aqueous alcohol and treated with sodium carbonate it yielded a substance, melting point 134° C. Moreover recrystallisation of compound, melting point 152° C from aqueous alcohol, also gave the substance melting at 134° C, ring closure appearing to take place with loss of hydrochloric acid and water.



Analysis of compound, melting point 134° C would indicate that it is 2-keto 4-methyl 2.3-dihydrothiazole/

2.3-dihydrothiazole 2-acetophenone hydrazone.

Nitrogen content. Found 18.45%. 18.34%.

Theory 18.2%.

REACTION IN ALCOHOL.

Acetophenone thiosemicarbazone and chloracetone in equimolecular proportions were heated in absolute alcohol solution for 15 minutes, after which time most of the alcohol was removed on the water bath. The residue was diluted with water and sodium carbonate solution added when compound melting point 134° C was obtained identical with that obtained above.

Hydrolysis of this compound will be carried out.

ACETONE THIOSEMICARBAZONE AND CHLORACETALDEHYDE.

Acetone thiosemicarbazone (2gm.) was dissolved in 20cc. absolute alcohol and chloracetaldehyde (1gm.) added to the solution, which was then refluxed for 10 minutes. The solution was cooled and diluted to 100cc. with water and dilute sodium carbonate added till just alkaline, when a light yellow coloured solid was precipitated. The solid was purified by dissolving it in dilute hydrochloric acid followed by reprecipitation with sodium carbonate, when a cream coloured amorphous solid was obtained, melting point 140° C.

Nitrogen content. Found 27.20%. 27.14%.

Theory for condensation product 27.09%.

$$CMe_2:C:N\cdot N:C(SH)\cdot NH_2 + CH_2Cl\cdot CHO$$

$$\rightarrow CMe_2:C:N\cdot N\cdot C(-S-CH=CH-)-NH$$

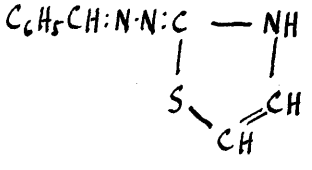
2-keto 2.3-dihydrothiazole 2-isopropylidene hydrazone is readily soluble in organic solvents and may be recrystallised from aqueous alcohol.

BENZALDEHYDE THIOSEMICARBAZONE AND CHLORACETALDEHYDE.

Benzaldehyde thiosemicarbazone (1.8gm.) was refluxed with chloracetaldehyde (0.8gm.) in absolute alcohol solution for half an hour. The alcohol was then reduced to small bulk on a water bath and the residue diluted considerably with water. The acid solution was neutralised with sodium carbonate and on standing and scratching, an amorphous solid of yellow colour was precipitated, which was purified by dissolving in dilute hydrochloric acid followed by precipitation with sodium carbonate, when a cream coloured amorphous solid separated, melting point 169° C.

Nitrogen content. Found 20.6%. 20.6%.

Theory for 2-keto 2.3-dihydrothiazole 2-benzal-hydrazone requires 20.7%.



PART 6.

THE ACTION OF HALOGENS ON THIOSEMICARBAZONES.

The following compounds are described;-

Acetophenone thiosemicarbazone mono-bromide.

Acetophenone thiosemicarbazone tri-bromide.

Acetophenone thiosemicarbazone mono-iodide.

Acetophenone thiosemicarbazone tri-iodide.

Benzal thiosemicarbazone di-iodide.

Benzal thiosemicarbazone tetra-iodide.

Acetone thiosemicarbazone mono-iodide.

Acetophenone δ benzyl thiosemicarbazone mono-iodide.

Benzal semicarbazone di-iodide.

THE ACTION OF HALOGENS ON THIOSEMICARBAZONES.

Wilson, Heilbron and Sutherland (J.C.S. 1914, 105, 2901) describe the preparation of a dibromide of cinnamaldehyde phenyl semicarbazone by the interaction of the semicarbazone with bromine in chloroform solution, and apart from this there does not appear to be any reference in the literature to other halides of semicarbazones or thiosemicarbazones.

From the work described in the following pages it would appear to be the rule that thiosemicarbazones react with the halogens, bromine and iodine, to form addition compounds, when the reaction is carried out in non polar solvents.

The bromides described, namely the monobromide and the tribromide of acetophenone thiosemicarbazone were found to be unstable, but the corresponding iodides form well defined solid compounds of characteristic colour. The union of iodine with thiosemicarbazone is however easily ruptured as the iodine may be removed quantitatively with sodium thiosulphate.

Acetophenone thiosemicarbazone was found to form a monobromide and a tribromide but as great difficulty was experienced with the analysis of these compounds, due to their unstable nature, it was/

was decided to concentrate on the formation of iodides.

Acetophenone thiosemicarbazone formed a mono and a tri-iodide. The former having a bright scarlet colour, while the latter was brown.

In every case the deepening of colour with increasing iodine content was observed.

Benzal thiosemicarbazone formed a di-iodide which was green in colour, and a tetra-iodide which was a very dark green, in fact, almost black.

Acetone thiosemicarbazone formed a mono-iodide of a maroon colour. The tri-iodide was a dark oil.

Acetophenone δ benzyl thiosemicarbazone formed a mono-iodide of scarlet colour, and an oily tri-iodide.

Attempts were made to form iodides of the corresponding semicarbazones, but these do not appear to form so readily. Only benzal semicarbazone was found to give a solid di-iodide,

---

ACETOPHENONE THIOSEMICARBAZONE AND BROMINE.

EXPERIMENTAL.

Acetophenone thiosemicarbazone (1gm.) was dissolved in 60cc. cold glacial acetic acid and a solution of bromine (0.4gm.) in glacial acetic acid added, the mixture being kept cold. The addition of bromine caused immediate precipitation to take place. The precipitated bromide was filtered off, washed free of glacial acetic acid with petroleum ether, and dried. The dry substance melted at 147° C with decomposition.

Nitrogen content. Found 15.1%. 15.3%.

Theory for monobromide 15.4%.

ACETOPHENONE THIOSEMICARBAZONE TRI-BROMIDE.

Acetophenone thiosemicarbazone (0.5gm.) was dissolved in 10cc. cold glacial acetic acid and a solution of bromine (3gm.) in glacial acetic acid added. With the first few drops of bromine a precipitate appeared, but this dissolved on further addition of bromine. When all the bromine had been added the liquid was decanted from a small amount of undissolved substance and almost immediately the decanted liquid deposited deep red coloured prisms. These were filtered off, washed/

washed with a little petroleum ether and dried. The dried substance had an odour of bromine and acetophenone, and melted at 87 ° C with decomposition.

Nitrogen Found 8.7%. 9.3%.

Bromine Found 57.6%.

Acetophenone thiosemicarbazone tri-bromide requires;-

Nitrogen 9.7%.

Bromine 55.4%.

Acetophenone thiosemicarbazone tri-bromide was also prepared from the thiosemicarbazone and bromine in cold chloroform solution. The unstable nature of the tri-bromide however rendered the analysis of doubtful value, and it was decided to investigate the nature of the corresponding iodine compounds.

ACETOPHENONE THIOSEMICARBAZONE MONO-IODIDE.

Acetophenone thiosemicarbazone (0.9gm.) was dissolved in benzene (20cc.) and iodine (0.6gm.) added to the solution, which was heated until the iodine dissolved. On allowing the mixture to stand overnight, beautiful scarlet coloured crystals separated melting point 88-89° C. These were readily soluble in alcohol, acetone and chloroform and could be recrystallised from benzene. Addition of petroleum ether to the benzene/

benzene solution increased the yield of pure material. Nitrogen content. Found 12.9%. 13.0%. (using copper oxide-cuprous chloride mixture for the combustion).

Iodine:- Found. 38.2%. 38.5%.

Theory for acetophenone thiosemicarbazone mono-iodide requires;- Nitrogen 13.1%.

Iodine 38.7%.

The estimation of iodine was performed by dissolving the substance in chloroform, and titrating the coloured solution with deci-normal sodium thiosulphate, shaking vigorously after each addition of thiosulphate. Acetophenone thiosemicarbazone (melting point 118° C) separated at the interface during the titration.

ACETOPHENONE THIOSEMICARBAZONE TRI-IODIDE.

Acetophenone thiosemicarbazone (1gm.) and iodine (2gm.) were added to a small quantity of glacial acetic acid (about 20cc.), and the mixture was heated on the water bath for 10 minutes, when the iodine had gone into solution. On allowing the dark coloured solution to stand for a short time, a crystalline precipitate formed, which was filtered off, and/

and recrystallised from chloroform. The pure material was brown in colour and melted at 115° C.

Nitrogen Found 7.2%. Iodine Found 65.8%.

Theory 7.3%. Theory 66.3%.

BENZAL THIOSEMICARBAZONE DI-IODIDE.

In the expectation of preparing a mono-iodide, 0.5gm. of benzal thiosemicarbazone was dissolved in about 100cc. chloroform and a solution of 0.32gm. iodine in chloroform added. The chloroform solution of iodine was violet before mixing but when mixed with the thiosemicarbazone, the solution became dark red. On allowing to stand for several days the dark red solution deposited a spongy mass of minute dark green needles. These were filtered off, and melted at 144° C.

Nitrogen content. Found 9.6%.

Theory for di-iodide 9.7%.

In view of the fact that a di-iodide was formed, the experiment was repeated, the quantity of iodine being doubled. Again the reaction took the same course with formation of benzal thiosemicarbazone di-iodide, melting point 144° C.

Iodine. Found 58.9%. Theory 58.6%.

BENZAL THIOSEMICARBAZONE TETRA-IODIDE.

An attempt was made to form the tri-iodide of benzal thiosemicarbazone by combining iodine (0.96gm.) with the thiosemicarbazone (0.45gm.) in chloroform solution. On standing for several days a compound separated in the form of dark green (almost black) crystals, melting point 136° C. On analysis the compound was shown to be a tetra-iodide.

Iodine Found 72.5%. Theory 73.9%.

Accordingly the experiment was repeated using the necessary quantities for formation of this compound. 0.45gm. of thiosemicarbazone was dissolved in about 80cc. of chloroform and added to a solution of iodine (1.26gm) in chloroform. On standing for a short time, benzal thiosemicarbazone tetra-iodide separated, melting point 136° C,

The crystals were washed with chloroform and analysed.

Iodine. Found 73.1%. Theory 73.9%.

ACETONE THIOSEMICARBAZONE MONO-IODIDE.

Acetone thiosemicarbazone is not soluble in benzene or chloroform, and the iodide was formed in benzene suspension. The thiosemicarbazone (2.5gm.) was suspended in 40cc. benzene and iodine (2.5gm.) added.

The mixture was then heated to boiling for 5 minutes when solution became almost complete, the small quantity of undissolved matter being removed by filtration. The filtrate on cooling deposited beautiful maroon coloured crystals of acetone thiosemicarbazone mono-iodide, melting point 87° C.

Iodine content. Found 49.1%. 49.1%.

Theory 49.2%.

An attempt to form the tri-iodide of acetone thiosemicarbazone by the above method resulted in the formation of a dark red oil which was unstable, readily losing iodine on warming.

ACETOPHENONE δ-BENZYL THIOSEMICARBAZONE MONO-IODIDE.

Acetophenone δ-benzyl thiosemicarbazone (Burns, Baird and Wilson J.C.S. 1927, 2537) was prepared by heating acetophenone thiosemicarbazone with benzylamine at a temperature of 150° C until the evolution of ammonia slackened (about 1½ hours). The melt was extracted with benzene when acetophenone δ benzyl thiosemicarbazone was obtained, melting point 161° C.

Acetophenone δ- benzyl thiosemicarbazone (0.56gm.) was dissolved in 20cc. benzene and iodine (0.27gm.) added, the mixture being warmed on the/

the water bath until solution was complete. On allowing to cool beautiful scarlet prisms separated, melting point 137° C. A further crop was obtained by addition of petroleum ether to the benzene solution.

Iodine content. Found 31.3%. 31.2%.

Theory 31.0%.

An attempt to prepare the tri-iodide using the above method resulted in the formation of a dark red oil.

SEMICARBAZONES AND IODINE.

In view of the ready formation of well defined iodides from thiosemicarbazones, the possibility of semicarbazones combining with iodine was investigated, but only in one case was a solid iodide isolated, namely benzal semicarbazone di-iodide. This compound was less stable than the corresponding benzal thiosemicarbazone di-iodide, as it lost iodine on heating in a capillary tube before the melting point was reached.

Attempts to prepare iodides of acetone semicarbazone and acetophenone semicarbazone resulted in/

in the formation of dark red tarry oils which were very unstable to heat.

BENZAL SEMICARBAZONE DI-IODIDE.

Benzal semicarbazone (0.58gm.) was dissolved in about 10cc. glacial acetic acid, and a solution of iodine (0.84gm.) in chloroform added. No precipitation took place until petroleum ether was added to the solution, when long, dark green, needle shaped crystals separated on standing. These decomposed with evolution of iodine at 120° C but fusion did not take place till 145° C was reached.

Iodine content. Found 60.8%. 59.8%.

Theory for di-iodide 60.8%.

APPENDIX.

HYDROLYSIS OF ACETOPHENONE δ-BENZYL SEMICARBAZONE.

(See page 18).

While the hydrolysis has been styled quantitative, the method employed was somewhat crude, but it proved to be sufficiently accurate to indicate the nature of acetophenone δ-benzyl semicarbazone.

A weighed amount of the semicarbazone was hydrolysed by boiling under reflux with dilute hydrochloric acid and the liberated acetophenone extracted with successive small quantities of petroleum ether. The petroleum ether extracts were combined and evaporated, leaving a residue of acetophenone which was weighed.

$$\begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C{:}N{\cdot}NH{\cdot}CO{\cdot}NHCH_2C_6H_5 + H_2O \rightarrow \begin{matrix} C_6H_5 \\ CH_3 \end{matrix}\!\!>\!C{:}O + NH_2{\cdot}NH{\cdot}CO{\cdot}NHCH_2C_6H_5$$

The δ-benzyl semicarbazide remained in the aqueous layer as the hydrochloride. After removal of acetophenone the aqueous layer was concentrated and refluxed further, some concentrated hydrochloric acid being added. In this way the δ-benzyl semicarbazide was broken up as follows;-

$$NH_2{\cdot}NH{\cdot}CO{\cdot}NHCH_2C_6H_5 \xleftrightarrow[H\ O\ H]{} N_2H_4 + C_6H_5CH_2NH_2 + CO_2.$$

the hydrazine and benzylamine being present in solution as the hydrochloride. The amount of these present was ascertained/

ascertained by evaporation, and the total quantity of hydrazine dihydrochloride and benzylamine hydrochloride estimated by weighing the residue.

The amount of hydrazine dihydrochloride present was obtained by dissolving an aliquot portion of the residue in water and introducing this solution into a nitrometer containing Fehling's solution. The volume of liberated nitrogen was read, corrected to standard temperature and pressure, and estimated as hydrazine dihydrochloride,

using the fact that 1cc.N : .0047gm. hydrazine dihydrochloride.

$$N_2H_4 + 4CuO = N_2 + 2Cu_2O + 2H_2O$$

Wt. of acetophenone δ benzyl semicarbazone : 5gm.

Wt. of acetophenone : 1.5gm.

Wt. of hydrazine dihydrochloride + benzylamine hydrochloride : 3.1gm.

Wt. of hydrazine dihydrochloride : 1.2gm.

Wt. of benzylamine hydrochloride : 1.9gm.

CHLORO-METHYL-*l*-MENTHYL ETHER.

Chloro-methyl-*l*-menthyl ether has been described by Wedekind (Ber. 1901, 34, 813) and as this compound contains a reactive chlorine atom, it seemed that it might be of value in bringing about a resolution of benzoin, provided combination with benzoin took place. The ether was prepared according to Wedekind's method, but exhibited a marked difference in boiling point from that given by him. Wedekind describes the ether as an oil, boiling at 160-162° C under 16mms. pressure, whereas the specimen prepared by us boiled at 120-123° C under 20 mms. pressure.

In attempting to combine the ether with benzoin in pyridine solution, immediate separation of glistening plates took place which were found to be a quaternary compound of pyridine with the ether.

The preparation of the ether is described and also its compounds with pyridine and quinoline.

PREPARATION OF CHLORO-METHYL *l*- MENTHYL ETHER.

l -Menthol (50gm.) was heated on a water bath till it liquefied and 30gm. formalin (40%) added. The mixture, which contained two layers was saturated with dry hydrogen chloride, the gas being passed for a period of 6 hours. With the first bubbles of gas considerable warming of the mixture occurred and it was essential to surround the reaction vessel with ice. When the gas had passed for 6 hours, the reaction was discontinued and the upper layer, which contained the ether, was separated from the aqueous layer, which consisted of hydrochloric acid. The ethereal layer was dried with anhydrous sodium sulphate and distilled under a pressure of 20 mms., the distillation being conducted as quickly as possible. Several fractions were collected, much hydrogen chloride being evolved with the first fraction.

1st. Fraction 100° C - 120° C.

2nd. Fraction 120° C - 123° C.

3rd. Fraction 123° C - 150° C.

The residue which remained was completely charred, while the third fraction solidified on cooling and consisted mainly of *l*- menthol

The second fraction was the largest (about 35gm.) and was redistilled under a pressure of 8 mm., when further decomposition took place with elimination of hydrogen chloride, the main portion distilling at 101-102° C.

The analysis of this fraction was difficult firstly because of the difficulty experienced in purifying it, and secondly because of its unstable nature, moisture causing rapid decomposition.

The analysis of the fraction (101-102°C) was carried out and its rotation and refractive index determined. These figures are contrasted with those obtained by Wedekind.

		Wedekind's Values:
Boiling Point	120-123° C / 20 mm.	160-162° C / 16mm.
Chlorine content	16.8%.	15.03%.
Rotation	$[\alpha]_D^{20}$ -116.8 (c : 6.16).	$[\alpha]_D^{21}$ -172.6. (c=6.78)
Refractive index (18° C)	1.468.	1.465.

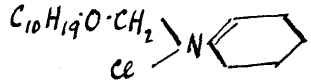
The theoretical chlorine content is 17.3%.

PYRIDINE AND CHLORO-METHYL *l*-MENTHYL ETHER.

When chloro-methyl *l*-menthyl ether (4cc.) was added to pyridine (5cc.), crystals, having appearance of white plates, separated. These were filtered off and washed with benzene and had a melting point 103° C. Purification of this solid was carried out by dissolving it in dry chloroform and precipitating from solution with dry benzene.

Nitrogen content. Found 5.05%.

Theory for quaternary compound 4.96%.



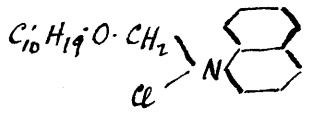
A solution of the compound in dry chloroform exhibited a rotation $[\alpha]_D^{19}$: -102 (c : 2.01)

QUINOLINE AND CHLORO-METHYL *l*-MENTHYL ETHER.

The quinoline derivative of chloro-methyl *l*-menthyl ether was prepared by adding the ether (4cc.) to quinoline (5cc.), the crystalline precipitate being filtered off. The solid was purified by dissolving it in dry chloroform and precipitating from solution with dry benzene, when clusters of small needle shaped crystals were obtained, melting point 80° C.

Nitrogen content. Found 4.26%. 4.29%.

Theory for quaternary compound 4.21%.



Rotation (in chloroform) $[\alpha]_D^{20}$ - 163 (c : 2.15).
