THE PREPARATION AND REACTIONS OF SOME IMIDAZOLES.

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A thesis submitted to the Department of Chemistry, and the Faculty of the Graduate School, in partial fulfillment of the requirements for the MASTER'S DEGREE.

Department of Chemistry.

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This investigation has been undertaken for the purpose of studying the action of certain reagents upon some of the mono- and di- substituted imidazoles. No attempt has been made to exhaust the experimental possibilities of the few imidazoles investigated, it being the plan to continue these studies in the future, when time and opportunity permit.

A series of investigations upon the imidazoles or, as they are often called, this hydantoins has been carried out by other experimenters. The behavior of the -CH<sub>2</sub>-, which acts like a methylene group with aldehydes<sup>1</sup>; the formation of mercapto derivatives or thisethers in the case of monosubstituted imidazoles<sup>2</sup>; the desulphurization of these compounds<sup>3</sup>; and their hydrolysis<sup>4</sup>:- all these, and more, have been experimented upon - yet by no means has the limit of investigation been reached.

The experimental work described in this paper is concerned with two general types of reactions:- (1) the condensation product obtained when the imidazoles are treated with substituted formamidines; and (2) the treatment of these condensation products with alkyl and aryl halides.

The first depends upon the reactivity of the methylene hydrogen of the  $-CH_2$ -group. It has been shown in previous papers that the hydrogen of the  $-CH_2$ - group can be replaced

1 Am. Chem. Jour. Vol. 45, p. 446. 2Am. Chem. Jour. Vol. 45. p. 448. 3J. A. C. S. Vol. 34. p. 1047, (1912) 4Am. Chem. Jour. Vol. 45. p. 456. by the complex = OHNHR in such types of methylene compounds as the following:-

| 2) | Aceto acetic ester   |                                                                         |
|----|----------------------|-------------------------------------------------------------------------|
| Ъ) | Bencoly acetic estor | 2 -00-CH2-00-grouping1                                                  |
| c) | Acetyl scetone       | \$                                                                      |
| ā) | Cyanacetic ester     | CH-CH2-CO grouping <sup>2</sup>                                         |
| 0) | Bonsyl cynnide       | C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -CH grouping <sup>3</sup> |
| £) | Pyrazolones          | =C-CH2-CO-grouping4                                                     |
| g) | Thiazoles            | -CO-CH <sub>2</sub> -S-grouping <sup>5</sup>                            |

The inidezolos with a grouping -N-CO-CH2-N- possess a different grouping but one that reacts with aldehydes like the true mothylene type. It has seemed therefore of interest to see whether the formamidine reaction could be extended to this type of complex.

Ehree different formanidines have been used in the preparation of these condensation products:- diphenyl and di-parabromformamidines, each giving methylone amilino groups attached to the carbon atom by a double bonding, and di-alpha-mapthyl formamidine which gives a methylone nepthylino group, also attached to the carbon by a double bonding. Condensation takes place according to the follow-

| -Be: | Co i | 35, | 294                | 16.  |     |    |       |        |
|------|------|-----|--------------------|------|-----|----|-------|--------|
| 000  | 20   | C.  | 3a                 | Vol. | 31, | p. | 1151  | (1909) |
| 3J.  | A.   | C.  | s.                 | Vol. | 31, | p. | 1151  | (1909) |
| 230  | 3.0  | C.  |                    | Vol. | 31, | De | 1155  | (1909) |
| DJ.  | ź.   | C,  | ्र<br>धन <b>्य</b> | Vol. | 38, | p. | 1841. |        |

an Bea





-3.

In the preparation of these condensation products it has been found that heating at high temperatures or a continuation of heating for some time at lower temperatures decomposes the condensation products. This decomposition was evidenced in each case by the formation of a dark tarry substance from which it was impossible to obtain any crystalline product whatever. In one instance after prolonged heating the product was let stand in alcoholic solution for about two weeks and the substance separating out was purified by treatment with alcohol. However, a melting point identical with that of the same compound whose analysis for the nitrogen content showed a relatively pure product, could not be obtained. Therefore, in these preparations high temperatures and prolonged heating were avoided.

The second type of reaction investigated was concerned with the fact that in the mono-substituted imidazoles the -HN-CS-NR group may also exist in the tautomeric form  $-N = CSH-NN^{-}$ . Due to this interchanging of the hydrogen atom between nitrogen and sulphur, it is possible to prepare mercapto derivatives of the following general formula:-



Most of the experimental work was carried out upon the l-phenyl-2-thio-5-keto-tetrahydroimidazole, this one being selected as the typical mono-substituted imidazole. Since most of the experiments with this imidazole were successful it may be assumed that the same reactions will take place with the other mono-substituted imidazoles whose method of preparation is recorded in this thesis.

All the imidazoles used in this work were prepared by the action of aminoacetic acid or its derivatives, upon mustard oils.

# I. FREPARATION OF IMIDAZOLES.

A. Di-substituted Imidazoles.

#### 1.-3-Diphenyl-2-Thio-5-Keto-Tetrahydro Imidazole.

Wheeler and Brautlecht have prepared 1-3-diphenyl tetrahydro imidazole by heating phenylglycine (phenyl amino acetic acid) or its ethyl estor, with phenyl mustard oil.<sup>1</sup>

This same method of preparation was used. Proportions corresponding to the molar weights of phenyl mustard oil and phenyl glycine were heated in an oil bath at a temperature of 150° as long as water was evolved. The mixture at first foamed up, then soon solidified to a hard mass of yellow color and remained in this condition during the remainder of the reaction. The imidazole was crystallized from alcohol from which it separated in flat yellow prisms that melted to a clear liquid at 208°.

1Am. Chem. Jour. Vol. 45, p. 457.



lp-Tolyl-3-phenyl-2-thio-tetrahydro imidazole, another type of di-substituted imidazole, was prepared in a manner similar to that of the diphenyl compound. Molar proportions of p-tolyl mustard oil and phenyl amino acetic acid were heated together in a flask provided with a short air condenser, at a temperature of 156° as long as water was evolued. The mixture solidified before the reaction was complete. It crystallized from boiling alcohol in yellow crystals which melted to a clear liquid at 190° - 195°.

Equations:-



B. Monosubstituted Imidazoles. 1-p-Toly1-2-Thio-5-Keto-Tetrahydro Imidazole.

The p-Tolyl thio tetrahydroimidazole was prepared by taking the reagents in the following proportions:- 4 grams of potassium hydroxide, 5.5 grams aminoacetic acid, 10 cc.

- 5-

of water, 25 cc. of alcohol, and 10 grams of p-tolylmustard oil.<sup>1</sup> These were mixed in a flask to which an air condenser was attached, and boiled on a sand bath for one hour. The alcohol was then evaporated off on a water bath and the residue made acid with hydrochloric acid. It was evaporated to dryness, washed with water to dissolve potassium chloride and excess acid, and crystallized from alcohol. The crystals were small yellow plates which melted with slight decomposition at 220°.

Equations:-



1-O-Toly1-2-Thio-5-Keto-Tetrahydro Imidazole.

For the preparation of the 1-O-tolyl-2-thio-tetrahydro imidazole, 8 grams of potassium hydroxide, 5.4 grams of amino acetic acid, 10 cc. of water, 10 grams of O-tolyl mustard oil, and alcohol to form a solution were heated together at  $100^{\circ}$  for three hours, in a flask provided with a reflux condenser.<sup>1</sup> After heating, it was concentrated to one-half-its bulk and hydrochloric acid added to acid reaction. This was then evaporated to dryness and the potassium chloride and excess acid were extracted with water, the imidazole crystallized from alcohol in small yellow crystals which melted to  $l_{Johnson}$ , J.A.C.S. vol. 34, p. 1047 (1912) a clear oil at 147°.

Equations :-



#### 1-Phenyl-2-Thip-5-Keto-Tetrahydro Imidazole.

1-phenyl-2-Thio-tetrahydro imidazole was prepared by combining amino acetic acid in alkaline solution with phenyl mustard oil.<sup>1</sup> This was boiled for some length of time on a sand bath, then cooled and acidified with hydrochloric acid. The precipitate which formed was washed with water until the washings were clear, and then crystallized from boiling alcohol. Several pecrystallizations were made and the recrystallized product melted at 215°. Small yellow crystals were obtained.

Equations:-

The above compound was taken as the typical monosubstituted imidazole and was used for most of the experimenting upon this type of imidazole.

> <sup>1</sup>Wheeler and Brantlecht. Am. Chem. Jour. Vol.45 p. 447.

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# II. CONDENSATION WITH THE FORMAMIDINES. 1-3-Diphenyl-2-Thio-4-Anilino Methylene-5-Keto-

# Tetrahydro Imidazole.

Holar proportions of the 1-3-diphenyl-2-thio-tetrahydro imidazole and diphenyl formamidine were heated together in a flask provided with a short air condenser, at 135°-140° for fifteen to twenty minutes. The mixture became dark red and solidified to a semi-tarry mass upon cooling. Alcohol was added and the condensation product separated out as a yellow solid. It was recrystallized from hot alcohol. Small orange yellow crystals which melted at 175° were formed. These were insoluble in potassium hydroxide, readily soluble in glacial acetic acid and very soluble in hot alcohol.

Equations:-

| Analysis for $C_{22}H_{17}ON_{3}S$ . | (Kjeldahl). | TT     |
|--------------------------------------|-------------|--------|
| Weight of sample                     | 0.5674      | 0.2374 |
| CC. of NaOH used                     | 65.4        | 35.3   |
| Normality of NaOH                    | 0,5145      | 0.5145 |
| cc. of HCl used                      | 94.7        | 52.0   |
| Normality of HCl                     | 0,3853      | 0,3853 |
| Per cont of N found                  | 10.79       | 11.0   |
| Calculated                           | 11.39_      | 11.34  |

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## 1-p-Toly1-5-Pheny1-2-Thio-4-Anilino Methylene-5-Keto-

#### Tetrahydro Imidazole.

Molar proportions of 1-p-toly1-5-pheny1-2-thio-tetrahydro imidazole and diphenyl formamidine were heated togother in a flask at a temperature of  $135^{\circ}-140^{\circ}$  until the mixture became homogenous. After cooling, the aniline was removed from the semi-tarry mass with cold alcohol. This left the condensation product as a yellow residue. This was crystallized from boiling alcohol in which it was very soluble. It separated out in small needlelike yellow crystals which melted to a yellowish red liquid at  $197^{\circ}-198^{\circ}$ . It is insoluble in potassium hydroxide, and soluble in glacial acetic acid.

Equation:-

Analysis for C<sub>23</sub>H<sub>19</sub>ON<sub>3</sub>S (Ejeldahl)

| Veight of sample    | ,3031 |
|---------------------|-------|
| cc. NaOH used       | 36.35 |
| Normality of NeOH   | .5145 |
| cc. HCl used        | 50.25 |
| Normality of HCl    | ,4198 |
| Per cent of N found | 11.08 |
| Calculated          | 10.93 |

There was only sufficient of this compound for one analysis.

# 1-p-Toly1-2-Thio-4-Anilino Methylene-5-Keto-

# Tetrahydro Imidazole.

To prepare this compound molar proportions of p-tolyl tetrahydroimidazole and diphenyl formamidine were heated together in an oil bath at  $135^{\circ}-140^{\circ}$  until the mass became liquid and turned a dark red. After cooling, cold alcohol was added to dissolve out the aniline and the condensation product was crystallized from boiling alcohol. On long standing in dilute alcoholic solution, clear yellow plates separated out. These gave a melting point of  $248^{\circ}-250^{\circ}$ . This condensation product is soluble in potassium hydroxide from which it is reprecipitated by hydrochloric acid.

Equation :-

$$\begin{array}{c} CH_{3}C_{6}H_{4}H - CO & C_{6}H_{5}HH \\ SC & CH_{2} & C_{6}H_{5}H \\ SC & CH_{2} & C_{6}H_{5}H \\ H & H \end{array} \right) = CH = \begin{array}{c} CH_{3}C_{6}H_{4}H - CO & + C_{6}H_{5}HH_{2} \\ SC & C & CH_{2}H_{5}H_{5} \\ SC & C & CH_{2}H_{5}H_{5} \\ SC & C & CH_{2}H_{5}H_{5} \\ H & H \end{array} \right)$$

Analysis for C17H150H3S (Kjeldahl)

|                   | 1                     | 1.1    |
|-------------------|-----------------------|--------|
| Weight of sample  | <b>.</b> 49 <b>73</b> | . 5263 |
| cc. HaOH          | 15.                   | 19.2   |
| Normality of NaOH | <b>•</b> 6674         | ,6674  |
| cc. HOl vsed      | 35.                   | 42.5   |
| Normality of HCl  | •4198                 | ,4198  |
| Percent N found   | 13.45                 | 13.40  |
| Calculated        | 13.61                 | 13.61  |

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# 1-O-Tolyl-2-Thio-4-Anilino Methylene-5-Keto-

# Tetrahydro Imidazole.

This condensation product of o-tolyl thio tetrahydro imidazole and diphenyl formamidine was prepared by heating together molar proportions of the imidazole and diphenyl formamidine in an oil bath at a temperature of  $140^{\circ}-145^{\circ}$ . After cooling alcohol was added and the product washed free from aniline. It was purified by crystallization from boiling alcohol. Yellow crystals separated out. These melted at  $215^{\circ}$  to a reddish yellow liquid. They were soluble in potassium hydroxide and the original compound was reprecipitated by hydrochlorid acid.

Equation:-

Analysis for C<sub>17</sub>H<sub>15</sub>ON<sub>3</sub>S (Kjeldahl)

|                   | 1      | TT     |
|-------------------|--------|--------|
| Weight of sample  | . 3075 | .2495  |
| cc. HaOH used     | 33.9   | 33.6   |
| Normality of NaOh | .5145  | ,5145  |
| cc. HCl used      | 52.7   | 51.00  |
| Normality of HCl  | .3583  | , 3583 |
| Per cont 1 found  | 13,03  | 13.24  |
| Calculated        | 13.61  | 13.61  |

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## 1-Phenyl-2-Thio-4-Anilino Methylene-5-Keto-

### Tetrahydro Imidazole.

Condensation of 1-phenyl tetrahydro imidazole with diphenyl formamidine was brought about by heating together molecular proportions of each at 1350-1400 for a short time. The mixture fused and formed a semi-tarry mass of a dark red color. When cool, alcohol was added to discolve out the aniline. The crude product obtained was slightly soluble in alcohol but readily soluble in glacial acetic acid from which it separated in small flaky yellow crystals. This product from glacial acetic acid was used in the following experiments. To obtain a melting point, the crystals deposited from glacial acetic were dissolved in alcohol and after long standing clear yellow crystals separated out. The melting point obtained was 250°-253°. This product is soluble in potassium hydroxide from which it is representated by hydrochloric acid. It is elso soluble to some extent in benzene, chloroform, nitrobenzene and very slightly in acetone.

Equation: -

 $C_{G}H_{5}H - C_{0} + C_{G}H_{5}HH = C_{G}H_{5}H - C_{0} + C_{G}H_{5}HH_{2}$ SC  $C_{H_{2}} + C_{G}H_{5}HH = C_{H_{5}}H + C_{G}H_{5}HH_{2}$ H H H

| Analysis for C16H13 <sup>0H</sup> 3 <sup>S</sup> | (Kjeldahl) |        |  |
|--------------------------------------------------|------------|--------|--|
|                                                  | I          | II     |  |
| Weight of sample                                 | .2071      | .2128  |  |
| cc. NaOH used                                    | 33, 55     | 33.35  |  |
| Normality of MaOH                                | .5145      | .5145  |  |
| cc. HCl usea                                     | 50.        | 50.    |  |
| Normelity of HOl                                 | . 3855     | . 3853 |  |
| Per cent of N found                              | 14.17      | 15.94  |  |
| Calculated                                       | 14,23      | 14,23  |  |
|                                                  |            |        |  |

#### 1-Ihenyl-2-Thio-4-p-bromaniline Methylene-5-Keto-

#### Totrahydro Imidazole.

This condensation and the following one were carried out with the monophonyl imidazole in order to compare the reaction of other formamidines with that of the diphenyl formamidine. Condensation with the di-p-brom phenyl formamidine was brought about readily but not with the case of the unsubstituted diphenyl formamidine, neither was the product obtained a definite crystalline compound.

To condense mono phenyl tetrahydro imidazole with di-p-bromphenyl formamidine molar portions of each were heated together in an oil bath at a temperature of 200<sup>0</sup>-220<sup>°</sup> for one and one-half to two hours. The mixture fused and turned to a hard mass during the heating. Alcohol was added and the entire product discolved. The condensation product was precipitated from this by the addition of water. The crude product was of a light reddish brown color, slightly soluble in carbon tetrachloride, chloroform

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and benzene, and readily soluble in glacial acetic acid and alcohol. It melted to a dark liquid at 189<sup>0</sup>-190<sup>0</sup>.

Analysis for C<sub>13</sub>H<sub>2</sub>H<sub>3</sub>SOBr I 11 Weight of sample .5984 - .2381 cc. of HaOH 17.3 20.4 Normality of NaOH .6674 .6674 cc. of HCl 35. 36.9 Normality of HCl . 41.98 .4198 Per cent of N found 11.09 11.05 Calculated. 11,25 11.25

# <u>1-Phenyl-2-Thio-4-Alpha Napthylino Methylene-5-Keto-</u> <u>Tetrahydro Imidasole.</u>

For the condensation of 1-pheny1-2-thio-5-keto-tetrahydro imidazole with di-alpha-naphthyl formamidine, quantities propertional to their molecular weights were heated in an oil bath at a temperature of 200°-220° for about an hour. The cooled product was washed with alcohol, and the condensation product which remained was not very soluble in any of the organic solvents. Glacial acetic acid, benzone, carbon tetrachloride, and chloroform dissolved it slightly. It was slightly soluble in alcohol and the melting point obtained from this purification was 160°. It melted to a dark red liquid. It was quite soluble in nitrobenzenc. The product which separated from all the organic solvents used was not crystalline.

Equation:-

 $C_{6}H_{5}H - C_{0} \qquad C_{10}H_{7}H \qquad C_{6}H_{5}H - C_{0} \qquad + C_{10}H_{7}H_{2}$ SC  $C_{12}C_{10}H_{7}H \qquad SC \qquad C = CHNHC_{0}H_{7} \qquad + C_{10}H_{7}H_{2}$ H H H

Analysis for C20H150N3C (Kjeldahl)

|                   | Ŧ             | II    |
|-------------------|---------------|-------|
| Weight of sample  | .4087         | .4294 |
| cc. NeOH used     | 18.75         | 17.1  |
| Normality of NaOH | .6674         | .6674 |
| cc. NO1 used      | 38,25         | 36.3  |
| Normality of HOL  | <b>~</b> 4198 | .4198 |
| Per cent & found  | 12.17         | 12.49 |
| Calculated        | 12.19         | 18.19 |

#### III. THIO ETEERS.

#### 1-Phenyl-2-Ethyl Phio-4-Anilino Methylene-5-Keto-

#### Tetrahydro Inidazole.

5.5 grams of 1-phenyl-2-thio-4-anilino methylene-5 ketp tetrahydro imidazole were treated with alcohol in which 0.5 grams of sodium was dissolved, and alcohol sufficient for solution was added. This was heated on a water bath until solution took place. 3 grams of ethyl iodide were then added and the mixture was refluxed until it became neutral. On cooling, crystallization took place. The entire product

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was treated with water, filtered and the residue was washed repeatedly with water until the washings were clear. The residue was crystallized from boiling alcohol in which it was very soluble. It crystallized out in slender white needles of exceedingly light weight, which turned to a cream on exposure to the air. They melted to a colorless liquid at  $164^{\circ}-165^{\circ}$ .

Equations:-

# 1-Phenyl-2-Methylthio-4-Anilino Methylene-5-Keto-

#### Tetrahydro Imidazole.

The reaction for the preparation of the above compound is analogous to that of the ethyl thic derivative and was carried out under the same general conditions.

5.5 grams of 1-phenyl-2-thio-4-anilino methylene-5-keto tetrahydro imidazole were treated with 0.5 gram of sodium in alcoholic solution and 2.64 grams of methyl iodide were added. This was refluxed on a water bath until the solution became neutral. After being cooled, the product was washed with water until the washings were clear. The crude product was crystallized from boiling alcohol in which it was very soluble. The crystels strongly resembled those of the analagous ethyl compound. They melted to a clear liquid at 172°-175°.

Equations :-

 $\frac{C_{6}E_{5}H - CO}{NE_{2}H_{5} + H_{3}C} = C_{6}H_{5}H - CO} = C_{6}H_{5}H - CO} + C_{2}H_{5}OH + C_{2}H_{5}OH$ 

| Analysis for C <sub>17</sub> H <sub>15</sub> OH S | (Kjeldahl)    |        |
|---------------------------------------------------|---------------|--------|
|                                                   | I             | II     |
| Weight of sample                                  | .5298         | . 6039 |
| cc NaON used                                      | 17.5          | 24,36  |
| Normality of NaOH                                 | <b>.</b> 6674 | .6674  |
| cc. HCl used                                      | 52.94         | 52,94  |
| Normality of HCl                                  | .4198         | .4198  |
| Per Cent of N found                               | 13.60         | 13,87  |
| Calculated                                        | 13.61         | 13.61  |

#### 1-Phenyl-2-Allyl Thio-4-Anilino Methylene-5-Keto-

## Tetrahydro Imidazole.

The method of preparing the allyl thio derivative of the mono phenyl tetrahydro imidazole differs from that of the ethyl and methyl derivatives, since it is carried out in alcoholic potassium hydroxide solution, and no intermediate sodium compound was prepared.

To prepare this allyl derivative, 5 grams of 1-phenyl-2-thio-4-anilino methylene-tetrahydro imidazole were refluxed for about two hours with 2.6 grams of allyl iodide in alcoholic twenty per cent potassium hydroxide solution. After standing over night, brown crystals separated from the dark reddish brown solution. These crystals were separated from the solution and purified by recrystallization from alcohol. They separated yellowish green crystals which melted to a dark liquid at 215°-218°. Repeated crystallization gave the same product.

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Equations:-

$$C_{6}H_{5}N - CO \qquad C_{6}H_{5}N - CO \qquad + HI$$

$$C_{3}H_{5}\overline{I} + \underline{H}SC \qquad C = C N C_{6}H_{5} \qquad C_{3}H_{5}SC \qquad C = C N C_{6}H_{5} \qquad + HI$$

$$N \qquad N$$

Analysis for C19H170H3S (Kjeldahl)

|                  | I     | II    |
|------------------|-------|-------|
| Weight of sample | .1475 | .1526 |
| cc NaOH          | 29.5  | 28.6  |
| Normality NaOH   | .6674 | .6674 |
| CC HCl           | 50.   | 50.   |
| Normality of HCl | ,4198 | .4198 |
| Per Cent N found | 12.58 | 12.45 |
| Calculated       | 12.56 | 12.56 |
|                  |       |       |

#### 1-Phenyl-2-Benzyl Thio-4-Anilino Methylene-5-Keto

# Tetrahydro Imidazole.

Wheeler and Brantlecht have prepared the 2-benzyl-1phenyl benzal thiohydantoin by shaking the thio hydantoin in 20 per cent potassium hydrozide solution with benzyl chloride washing with water and crystallizing from alcohol.<sup>1</sup>

This same method was tried with 1-phenyl-2-thio-4-anilino methylenc-tetrahydro imidazole to see whether or not its benzyl derivative might be prepared in the same way. 3 grams of the phenyl-thio-anilino methylene tetrahydroimidazole

<sup>1</sup>Am. Chem. Jour. Vol. 45, p. 450.

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in 20 per cent potassium hydroxide solution were shaken with 1.5grams of benzyl chloride. A precipitate soon formed and after standing over night it was washed with water and crystallized from alcohol. It crystallized in fine needles of a yellow color, which melted to a light yellow liquid at 145<sup>0</sup>.

Equations:-

 $\begin{array}{ccccccc} c_{6}H_{5}N - c_{0} & c_{6}H_{5}N - c_{0} \\ c_{6}H_{5}CH_{2}CIHBC & c = c N c_{6}H_{5} & c_{6}H_{5}CH_{2}SC & c = c N c_{6}H_{5} + HC1 \\ N & N & N \end{array}$ 

| Analysis for C <sub>25</sub> H19CN3S | (Kjoldahl) | тТ     |
|--------------------------------------|------------|--------|
| Weight of sample                     | .3945      | .3127  |
| cc. of NaOH                          | 34.8       | 37.9   |
| Normality of NaOH                    | .5145      | .5145  |
| cc. of HCl                           | 50.1       | 52.0   |
| Normality of HCl                     | .3853      | . 3853 |
| Per cent N found                     | 11.11      | 10.91  |
| Calculated                           | 10.93      | 10,93  |

# <u>l-Phenyl-2-Normal Butyl Thio-4-Anilino Methylene-5-</u> <u>Keto-Tetrahydro Imidazole.</u>

5.5 grams of 1-phenyl-2-thio-4-anilino methylene-5-keto tetrahydro imidazole, .5 gram of sodium and the molar proportion of normal butyl iodide in alcoholic solution, were refluxed on a water bath until the solution became neutral. It was cooled and the precipitate which separated out was washed with water and recrystallized from boiling alcohol. It crystallized in slender light yellow needles, which melted to a clear yellow oil at 122°-124°.

Equations:-

 $\begin{array}{cccc} C_{6}H_{5}N & -& CO \\ SC & +& C \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\$  $\frac{{}^{C}_{6}{}^{H}_{5}{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{5}{}^{H}_{1} - {}^{H}_{1}} = \frac{{}^{C}_{6}{}^{H}_{5}{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{5}{}^{H}_{1} - {}^{H}_{1}} + {}^{C}_{6}{}^{H}_{5}{}^{OH}_{1}$   $= \frac{{}^{C}_{6}{}^{H}_{5}{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{5}{}^{H}_{1} - {}^{H}_{1}} + {}^{C}_{6}{}^{H}_{5}{}^{OH}_{1}$   $= \frac{{}^{H}_{6}{}^{H}_{5}{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{5}{}^{H}_{1} - {}^{C}_{0}} + {}^{C}_{6}{}^{H}_{5}{}^{OH}_{1}$   $= \frac{{}^{H}_{6}{}^{H}_{5}{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{5}{}^{H}_{1} - {}^{C}_{0}} + {}^{C}_{6}{}^{H}_{5}{}^{OH}_{1}$   $= \frac{{}^{H}_{6}{}^{H}_{5}{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{1} - {}^{C}_{0}{{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{1} - {}^{C}_{0}{{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{1} - {}^{C}_{0}}{{}^{H}_{1}$  $C_{6}H_{5}N - CO = C_{6}H_{5}N - CO = C_{6}H_{5}N$ + NaI Analysis for C20H210H S I II .7861 .5558 Weight of sample 35.35 32.67 cc. of NaOH .5145 . 5145 Normality of NaOH

 cc. of HCl
 50.8
 58.85

 Normality of HCl
 .4198
 .4198

 Per cent N found
 11.58
 11.69

 Calculated
 11.95
 11.95

 <u>1-o-Tolyl-2-Benzyl Thio-4-Anilino Methylene-5-Keto</u>

Tetrahydro Imidazole.

2-Benzyl mercapto-l-phenylbenzalhydantoin has been made by

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shaking the thiohydantoin in 20 per cent potashium hydroxide solution with benzyl chloride.<sup>1</sup> This same method was tried for the formation of the corresponding this compound. 3 gram of -1-O-toyl-2-thio-4-anilino methylene tetrahydroimidazole were shaken and stirred at room temperature with the requisite amount of benzyl chloride in 20 per cent potassium hydroxide solution, a flaky yellow solid separated out after standing

for sometime. This was washed with water, and crystallized from alcohol. Soft silky, flocculent needles of a creamy color separated out and gave a melting point of 146<sup>0</sup>-148<sup>0</sup>, melting to a light colored liquid.

Equations:-

I

II

 $C_{6}H_{5}C_{H_{2}C_{1}} + H_{5}C_{1} = C_{HNHC_{6}H_{5}} = C_{6}H_{5}C_{6}H_{4}N - C_{0} + H_{1}C_{1} + H_$ 

Analysis for C24H210N3S (Ijeldahl)

| Veight of sample           | ,1705                     | . 3642             |
|----------------------------|---------------------------|--------------------|
| cc NaOH used               | 31.1                      | 25,45              |
| Normality of NaOH          | .6674                     | .6674              |
| cc. HC1 used               | 52.5                      | 46.9               |
| Normality of HCl           | .4198                     | ,4198              |
| Per cent of 1 found        | 10.57                     | 10.42              |
| Calculated<br>IWheeler and | 10.54<br>Braublecht. Am.C | 10.54<br>hem.Jour. |

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The above compound represents a type of di-substituted imidazole which differs from those discussed previously in this work, in that the amino acid used in its preparation contains a benzoyl radical, whereas the others prepared contained a phenyl radical.

For the preparation of this imidazole, 10 grams of phenyl mustard oil and 3.2 grams of hippuric acid were heated together in an oil bath for one and one-half hours at a temperature of 150°. After cooling it solidified to a red tarry mass. Alcohol was added and the entire mass dissolved forming a red solution from which white crystals were deposited. This crystalline meal was troated with boiling water to dissolve out any unchanged hippuric acid, and then recrystallized from boiling alcohol. Small lustrous white crystals separated out. Melting point 177°-179°.

Equations:-

Analysis for C<sub>16</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>S (Kjeldahl) I II Weight of sample .5916 .3112 cc. NaOH used 25.4 28.3 Normality of NaOH .6674 .6674 cc. MC1 used 50. 50. Normality of HCl .4198 .4198 Per cent N founa 9,58 9.42 9.47 9.47 Calculated

# 1-Pheny1-2-Thip-3-Benzoy1-4-Anilino Methylene-5-Keto-

Tetrahydro Imidazole.

The condensation of 1-phenyl-2-thio-3-benzoyl-5-keto tetrahydro imidazole with diphenyl formamidine takes place readily. To bring about this condensation molar proportions of the two substances were heated in an oil bath at  $160^{\circ}-180^{\circ}$  for an hour. The mixture fused, became homogenous and turned to a dark red tarry mass. It was cooled and treated with alcohol in which it was bery soluble. The product which separated out was crystallized from boiling alcohol. The crystals formed were creamy white flakes which melted to a bright red liquid at  $184^{\circ}-186^{\circ}$ .

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Analysis for C23H17N3SO2

| I             | II                                                            |
|---------------|---------------------------------------------------------------|
| .5814         | <b>.</b> 5436                                                 |
| 16.5          | 17.53                                                         |
| .6674         | .6674                                                         |
| 40.           | 38.                                                           |
| <b>.</b> 4198 | .4198                                                         |
| 10,73         | 11.01                                                         |
| 10,88         | 10.88                                                         |
|               | I<br>.5814<br>18.5<br>.6674<br>40.<br>.4198<br>10.73<br>10.88 |

# Action of Mono-Chlor-Acetic acid upon 1-Fheny1-2-Thio-

5-Keto-Tetrahydro Imidazole.

The thic hydantoins may be desulphurised by the action of mono chloracetic acid upon them.<sup>1</sup> To deSulphurize the 1-phenyl-2-thic-5-keto-tetrahydroimidazole, 6 grams of it were taken, and reFluxed on a sand bath with 13.2 grams of mono chloracetic acid and 24 cc. of water for 2 and onehalf hours. A clear yellow solution was formed. This was concentrated until a sirupy liquid was obtained. After this stood for several days, water was added until a dark colored oil began to collect in the bottom of the flask. After standing for a short time, slender white needles separated out and the oil solidified. The crystals were dried and a melting point of 148°-150° obtained from them. The solidified oil was crystallized from boiling watwe and gave the same melting point as the other crystals.

1 J.A.C.S. vol. 34, p. 1047 (1912)

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Equations:-

|                |     | C <sub>6</sub> H <sub>5</sub> M −<br>OC<br>N<br>H | CO<br>CH2<br>CH2 | ಕ್ಕಲ  | H <sub>2</sub> S |
|----------------|-----|---------------------------------------------------|------------------|-------|------------------|
| Analysis       | for | C9H802N2                                          | (Kj              | ielās | hl)              |
| Weight of samp | le  | . 38                                              | 508              |       |                  |

cc. NaOH used 25.7 Normality of NaOH .6674 cc. HCl used 50. Normality of HCl .4198 Per cent N found 15.06 Calculated 15.08

There was only sufficient material for one analysis.

1-Phenyl-2-Thio-5-Keto-Tetrahydroimidagole with Benzal-

#### dehyde:

Wheeler and Brautlecht, prepare the 1-phenyl-2-thiobenzal hydantoin by the interaction of monophenyl tetrahydro imidazole and benzaldehyde in the pressage of sodium acetate and glacial acetic acid. The product obtained was a yellow crystalline substance with a mething point of 204°. It was thought that this same condensation product of the imidazole and benzaldehyde ought to be obtained without the intervention of sodium acetate and glacial acetic acid. To determine whether or not this method would be successful, three grams of mono phenyl tetrahydroimidazole were heated with a slight excess of benzaldehyde at a temperature ranging from 150° to 170° for some length of time. It was cooled and alcohol was added. The excess benzaldehyde was dissolved and the crude product which remained was purified by several crystallizations from boiling alcohol. Yellow crystals separated out and melted at 204°. There is no doubt that this compound is identical with the one described by Wheeler and Bautlecht.<sup>1</sup> No estimate of percentage yield was made. The only purpose of the experiment being to determine whether or not condensation could be brought about without the aid of sodium acetate and glacial acetic acid.

Hydrolysis of some Imidazole Condensation Products.

Wheeler and Brautlecht desulphurize 2-ethyl mercapto -3-phenylbenzalhydantoin by boiling it with a mixture of alcohol and concentrated hydrochloric acid, digesting on a steam bath for a number of hours, evaporating to dryness, washing the residue with ether and crystallizing from alcohol.<sup>2</sup>

This same method was tried with the ethyl-and methylmercapto derivatives of 1-phenyl2-thio-4-anilino methylene-5 5 keto tetrahydroimidazole but no product was obtained in either case.

The hydrolygis of the ethyl mercapto compound was attempted as follows:- 2 grams of the ethyl-mercapto compound in alcoholic solution were refluxed with an excess of con-

> 1 Am. Jour. Chem. Vol. 45, p. 448. 2 Am. Jour. Chem. Vol. 45, p. 456.

centrated hydrochloric acid about two hours. The odor of mercaptan was apparent in a very short time. At the end of about ten minutes aniline was tested for with bleaching powder solution, but none was found, showing the the =CH- $\rm NHC_6H_5$  chaft had not been acted upon. Tests for aniline were made from time to time in the course of the reaction but none was detected. This was evaporated down and a gummy substance obtained. This was washed with ether and treated with alcohol, but only negative results were obtained.

The methyl mercapto derivative was also tried wn the same way, but no positive results were obtained.

This same method was tried upon the 1-phenyl-2-thio-3-benzoyl-5-keto-tetrahydroimidazole and its condensation product with diphenyl formamidine. In each case the odor of ethyl benzoate was noticeable, but again there was a failure to bbtain any substance capable of being crystallized and analyzed.

The time available was not of sufficient length for a repetition of the experiment.

Appreciation:-

In conclusion I wish to express my appreciation to Dr. F. B. Dains whose many helpful suggestions and kindly interest have made this work possible.

Chemical Laboratories,

University of Kansas.

July 31, 1920.