

THE PREPARATION AND REACTION OF SOME IMIDAZOLES

by

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requirements for the
MASTER'S DEGREE.

1921

Department of Chemistry

Signed-----



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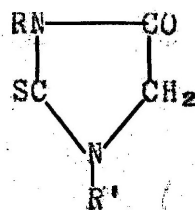
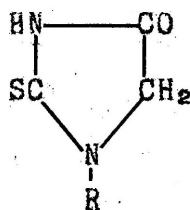
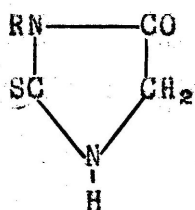
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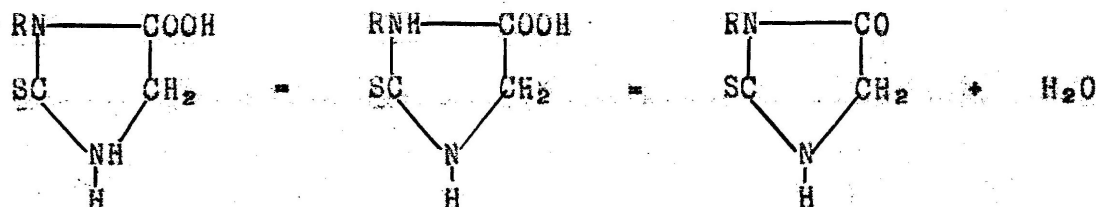
REACTIONS AND PREPARATIONS OF SOME IMIDAZOLES

The thio-hydantoin, or more correctly called the thio-imidazole, was first described in literature in 1890, by a chemist named Peter Klason*. He obtained it by heating together at 150°, a mixture of the hydrochloride of ethyl amino-acetate and potassium thiocyanide. This gave him the 2-thio-5-keto-tetrahydro-imidazole.

There are three possible substituted 2-thio-5-keto-tetrahydro-imidazoles in which one or both of the hydrogens on the nitrogen are replaced by some radicle,



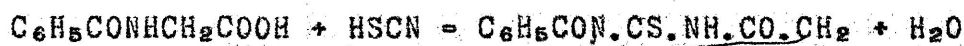
These substituted thio-imidazoles can be prepared in a very simple manner and the yield is usually very good*. The 1-R-2-thio-5-keto-tetrahydro-imidazole can be prepared by heating a mixture of a mustard oil with amino acetic acid in an alkaline solution. On acidulating the reaction mixture the imidazole is precipitated. This reaction can be represented by the equation:-



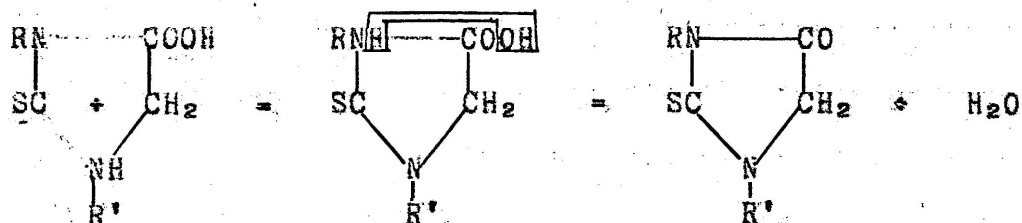
* T. B. Johnson, J.A.C.S. Vol. 35, p 780

* Wheeler and Brautlecht, A.C.J. Vol. 45, p 447

In preparing the 2-thio-3-R-5-keto-tetrahydro-imidazole, corresponding to formula II, a mixture of molal proportions of ammonium thiocyanide and a substituted glycine are heated together in a solution of glacial acetic acid and acetic anhydride. To obtain the best results, nine volumes of acetic anhydride to one of glacial acetic acid are used. On pouring the reaction mixture in cold water, the thio-imidazole separates out as an oil that soon solidifies. The following equation represents the reaction:-



When a mustard oil and a substituted glycine are heated together for some time, until the crystals are all dissolved, a reaction occurs, producing the 1-R-2-thio-3-R'-5-keto-tetrahydro-imidazole as represented by formula III. The reaction proceeds very rapidly and when the solution is cooled, the thionydantoin separates out. The reaction takes place in accordance with the following equation:-



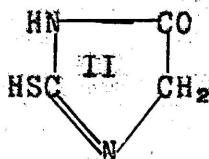
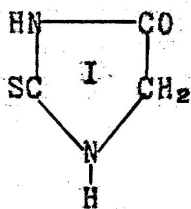
In this case the reaction proceeds readily and, as a rule, the yield is very good.

During the last few years, considerable work has been done on the thio-imidazoles and the reaction of various reagents on them. One particular phase of this work was started in this laboratory a year ago, and it is the purpose of

this investigation to study the compounds more in detail. The experimental possibilities have been no means been exhausted and in this paper only a small portion of the field will be discussed.

One peculiar behavior of this class of compounds is the action of the methylene hydrogen. It has long been known that when a $-\text{CH}_2-$ group is found in an arrangement like $-\text{NH}-\text{CH}_2-\text{CO}-$, the $-\text{CH}_2-$ radicle readily condensed with aldehydes*. In this laboratory, the action of formamidines upon the $-\text{CH}_2-$ group of the thio-imidazole has been studied, and it was found to condense very readily giving the grouping $-\text{C}-\text{CHNHR}^*$. When the imidazole $-\text{CH}_2-$ group had been condensed the reactivity of the other groups in the molecule were very materially changed.

In the case of the 1-phenyl-2-thio-5-keto-tetrahydro-imidazole, where the phenyl is in the 1-position, the solubility is due to the formation of the tautomer 1-phenyl-2-hydro-thio-5-keto-tetrahydro-imidazole, as shown by formulas I and II.

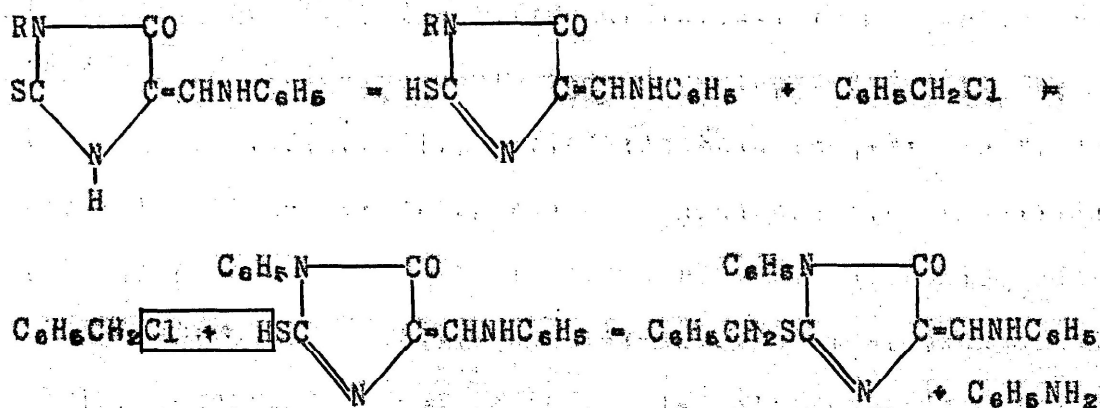


The second modification is known as the thio-mercaptan base. In the case where the $-\text{CH}_2-$ has been condensed with a formamidine or an aldehyde, the solubility of the compound in potassium hydroxide solution is not materially affected.

* Wheeler and Brautlecht, A.C.J. Vol 45, p 450.

* Miss Ruth Thompson, University of Kansas, 1920.

It has been shown by Wheeler and Brautlecht* that if the thio-hydantoin is dissolved in potassium hydroxide and benzyl chloride allowed to react with it, a thio ether is formed. In the same way, the previous work done at the University of Kansas under the direction of Dr. Dains, has proven that when the $-\text{CH}_2-$ group is condensed with a formamidine, a similar reaction takes place and a thio ether results. The reaction goes very smoothly and in accordance with the following equation.



One of the problems of this work was to determine if, by leaving the methylene hydrogens active, the thio ether could be formed. In preparing these, the same general method was employed as that previously mentioned. And if they could be made, to what extent the methylene group favored or hindered the formation of these thio ethers.

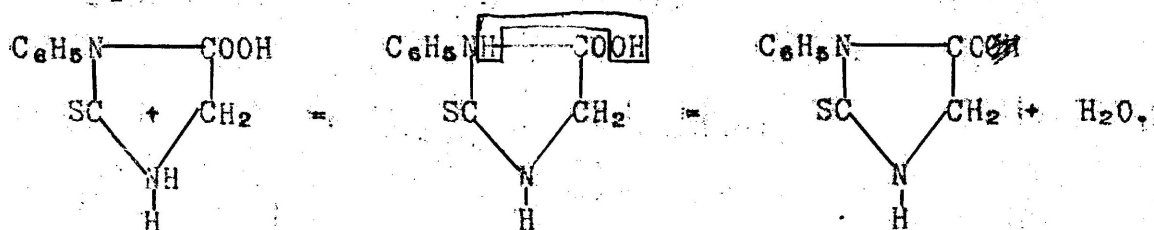
The action of hydrochloric acid and sodium hydroxide on the stability of the ring was finally taken up. The object of this was to determine if the ring was very stable to these reagents, or if not, how the ring split and what the resulting products were.

* Wheeler and Brautlecht, A.C.J. Vol 45, p 450.

1-Phenyl-2-Thio-5-Keto-Tetrahydro-Imidazole

1-phenyl-2-thio-5-keto-tetrahydro-imidazole was prepared by heating amino-acetic acid in an alkaline solution with phenyl mustard oil*. This was heated for some time on a sand bath and the alcohol evaporated off on a water bath. The solution was then cooled, neutralized with hydrochloric acid and evaporated to dryness on a water bath. The precipitate which formed was washed several times with water to remove the sodium chloride and excess acid, and then recrystallized from boiling alcohol. After several recrystallizations, small yellow needles were obtained which melted at 214°. They were easily soluble in alcohol and glacial acetic acid.

Equation:-



The above equation represents the typical reaction that takes place in preparing this type of mono-substituted imidazoles.

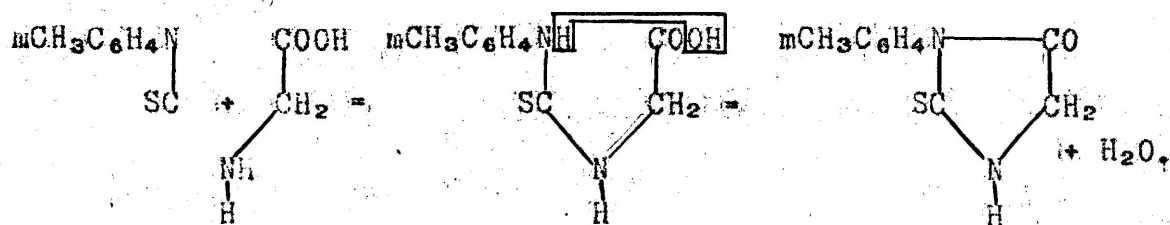
1-m-Tolyl-2-Thio-5-Keto-Tetrahydro-Imidazole.

In preparing the 1-m-tolyl-2-thio-5-keto-tetrahydro-imidazole, the following method was used:- 8 grams of sodium hydroxide, 10 grams of ^{tolyl}phenyl mustard oil, 5.5 grams of glycine, 10 cc of water, and 25 cc of alcohol was heated together at

*Wheeler and Brautlecht, A. C. J. Vol. 45, p 447.

100° for three hours in a flask fitted with a reflux condenser. After heating, the solution was concentrated on a water bath to one half of its original volume and made acid with hydrochloric acid. This was then evaporated to dryness, the sodium chloride and excess acid removed by washing with water, and the product recrystallized from alcohol. Fine yellow needles were obtained which melted at 167°. A yield of 13.7 grams was obtained which is 90 percent of the theoretical.

Equation:-



Analysis for $\text{C}_{10}\text{H}_{10}\text{ON}_2\text{S}$.

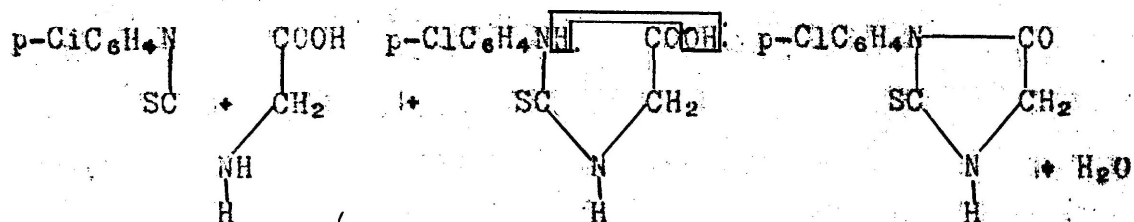
Weight of the sample	.4148	.4487
cc Acid used	26.52	25.52
Normality of acid	.3240	
cc NaOH used	12.57	10.87
Acid / Base ratio	1.124	
Percent N found	13.57	13.66
Calculated	13.58	13.58

1p-Chlor-Phenyl-2-Thio-5-Keto-Tetrahydro-Imidazole.

The 1-p-chlor-phenyl-2-thio-5-keto-tetrahydro-imidazole was prepared by heating together on a sand bath at 100° for three hours 10 grams of p-chlor-phenyl mustard oil, 4.5 grams

of glycine, 8 grams of sodium hydroxide, 10 cc of water and 25 cc of alcohol, or until the solution was clear. The reaction mixture was heated on a water bath to remove the alcohol, cooled, acidified with hydrochloric acid and again heated on a water bath until dry. The crystals that formed were titrated with cold water to remove the sodium chloride and excess hydrochloric acid. The product recrystallized from alcohol in the form of very fine yellow needles. These melted at 234-5° and were easily soluble in alcohol.

Equation:-



Analysis for $\text{C}_9\text{H}_7\text{ON}_2\text{SCl}$

Weight of sample	.2510	.1658
cc Acid used	25.13	25.34
Normality of acid	.3240	
cc NaOH used	16.30	18.52
Acid / Base ratio	1.124	
Percent N found	12.32	12.41
Calculated	12.36	12.36

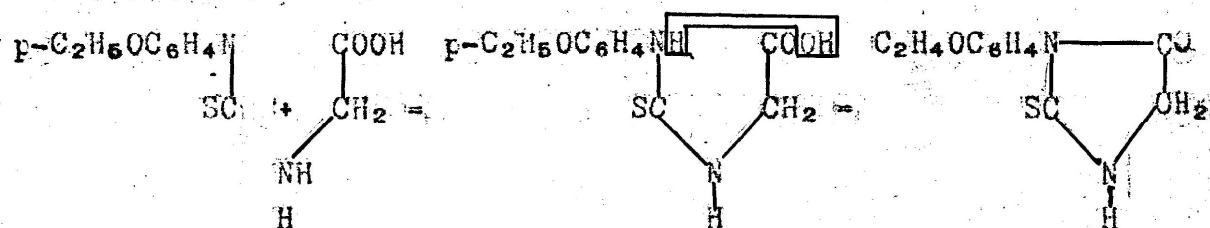
Chlorine determination:

Weight of sample	.3485	.2420
Weight of AgCl	.2213	.1527
Percent of Cl found	15.71	15.60
Calculated	15.65	15.65

1-p-Phenetol-2-Thio-5-Keto-Tetrahydro-Imidazole.

The 1-p-phenetol-2-thio-5-keto-tetrahydro-imidazole was made by heating together on a sand bath at 100° , 10 grams of p-phenetol mustard oil, 4.2 grams glycine, 4 grams of sodium hydroxide, 25 cc of alcohol and 10 cc of water in a flask provided with a reflux condenser until the solution became clear. The resultant solution was heated on a water bath to drive off the alcohol, cooled, and hydrochloric added to acid the reaction. It was then evaporated to dryness on a water bath, and the crystals obtained, washed with water to remove the sodium chloride and excess acid. When the crude product was recrystallized from alcohol, pale yellow crystals were obtained. These melted to a pale yellow oil at 198° . They are soluble in alcohol and glacial acetic acid.

Equations:-



+ H₂O

Analysis for C₁₁H₁₂O₂N₂S.

Weight of sample	.5491	.3409
cc Acid used	26.15	25.19
Normality of acid used	.3240	
cc of NaOH used	10.41	14.61
Acid / Base ratio	1.124	
Percent of S found	11.95	11.95

Calculated.

11.75.

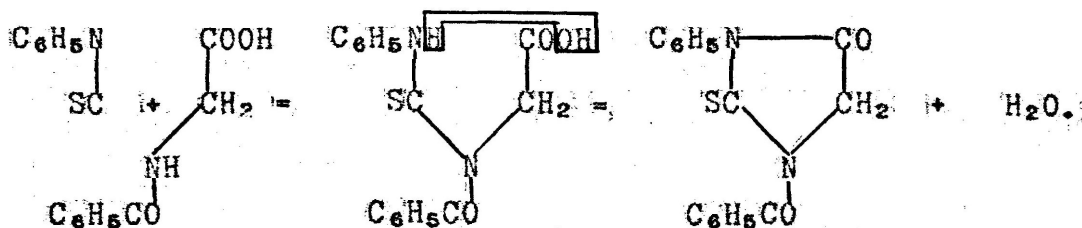
11.75.

1-Phenyl-2-Thio-3-Benzoyl-5-Hydro-Tetrahydro-
Imidazole.

The above compound represents the second type of imidazole in which the hydrogens in the 1 and 3 positions are replaced by some other radicles, in this case, the phenyl and benzoyl. These are prepared by heating together at 150°, a mixture of a mustard oil and a substituted glycine, a hydrogen of the NH₂ group being replaced by some other radicle.

In preparing the above imidazole, 10 grams of phenyl mustard oil, and 13.2 grams of hippuric acid were heated together in a flask provided with an air condenser for some time at 150 degrees*. The reaction mixture assumed a deep red color, and solidified to a solid mass on cooling. The entire mass was dissolved in hot alcohol, forming a deep red solution from which white needles were deposited on cooling. The crystalline meal was treated with hot water to remove any unchanged hippuric acid, and then recrystallized from alcohol. Small lustrous white needles were obtained with a melting point of 177-9°.

Equation:-

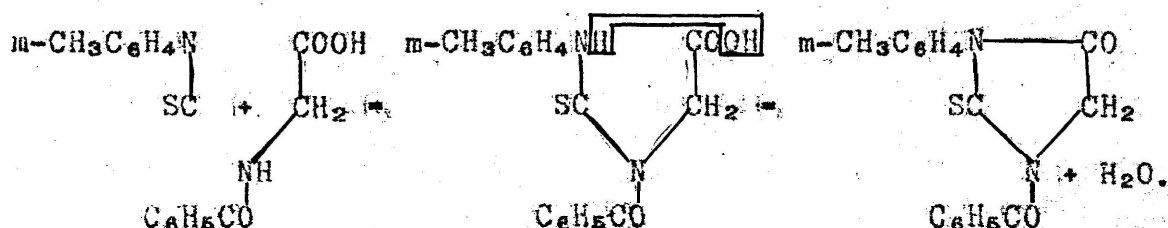


* Wheeler and Brautlecht, *J.A.C.S.*, Vol. 45, p 457. (1911)

1-m-Tolyl-2-Thio-3-Benzoyl-5-Keto-Tetrahydro-
Imidazole

1-m-tolyl-2-thio-3-benzoyl-5-keto-tetrahydro-imidazole was prepared by combining 3.2 grams of hippuric acid with 12 grams of m-tolyl mustard oil at a temperature of 150°. The reaction mixture was heated for several hours when it changed to a deep red colored solution. This solution on cooling deposited needle like crystals. These were titrated with hot water to remove any of the unchanged hippuric acid and again recrystallized from alcohol. Small white crystals separated out which melted at 187°. These were easily soluble in alcohol.

Equation:-



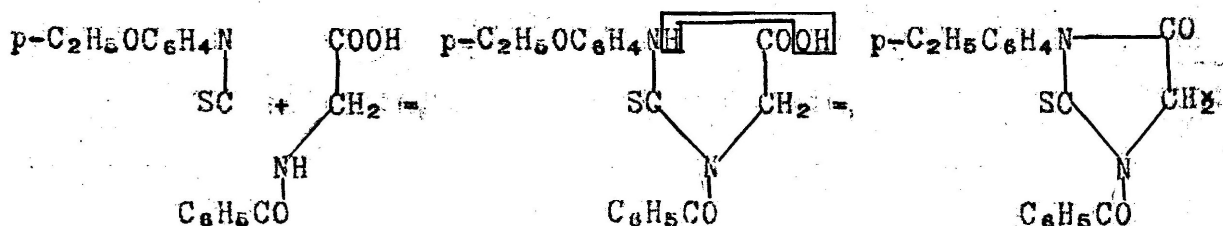
Analysis for $\text{C}_{17}\text{H}_{14}\text{O}_2\text{N}_2\text{S}$

Weight of the sample	.3334	.3134
cc of acid used	15.28	15.13
Normality of acid	.3240	
cc of NaOH used	7.68	7.92
Acid / Base ratio	1.124	
Percent of N found	9.07	9.03
Calculated	9.04	9.04

1-p-Phenetol-2-Thio-3-Benzoyl-5-Keto-Tetrahydro-
Imidazole

The 1-p-phenetol-2-thio-3-benzoyl-5-keto-tetrahydro-imidazole was obtained when 25 grams of p-phenetol mustard oil, 30 grams of hippuric acid, 10 grams of sodium hydroxide, 50 cc of alcohol and 25 cc of water were heated together in a flask fitted with a reflux condenser. The heating was continued until the entire mass dissolved. The excess alcohol was then evaporated off on a water bath, the solution neutralized with hydrochloric acid and the evaporation to dryness continued. The resulting crystals were washed with hot water to remove the excess hydrochloric acid and hippuric acid. After several recrystallizations from alcohol pale green crystals were obtained; these melted at 168°.

Equation:-



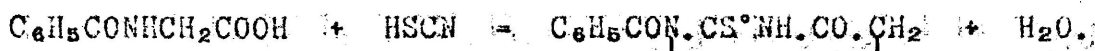
Analysis for $\text{C}_{18}\text{H}_{18}\text{O}_3\text{N}_2\text{S}$.

Weight of the sample	.4868	.2367
cc of acid used	25.15	25.55
Normality of acid used	.2472	
cc of NaOH used	12.99	18.94
Acid / Base ratio	1.049	
Percent N found	8.21	8.35
Calculated	8.24	8.24

2-Thio-3-Benzoyl-5-Keto-Tetrahydro-Imidazole.

Twenty grams of hippuric acid, 20 grams of ammonium thiocyanate, 10 cc of glacial acetic acid, and 90 cc of acetic anhydride were heated* together at 110° in a flask fitted with a reflux condenser until a deep red colored solution resulted. All of the crystals dissolved after the mixture had been heated for a few minutes. The solution was then cooled and poured into cold water, when the imidazole separated out as a an oil which soon crystallized to yellowish red crystals. The yield was 39 percent of the theoretical. After several recrystallizations from alcohol, square plates of yellowish red color were obtained. These melted at 167°.

Equation:-



2-Thio-5-Keto-Tetrahydro-Imidazole.

Twenty-five grams of 2-thio-3-benzoyl-5-keto-tetrahydro-imidazole was dissolved in 100 cc of alcohol to which 10 cc of concentrated hydrochloric acid was added, and the mixture heated for some time (1). After heating for some time, the odor of benzoic acid was noticeable. The solution was then evaporated to dryness, the crystals ²titrated with ether and the undissolved portion recrystallized from alcohol. Prismatic dark red crystals were obtained, melting at 225-7°. The

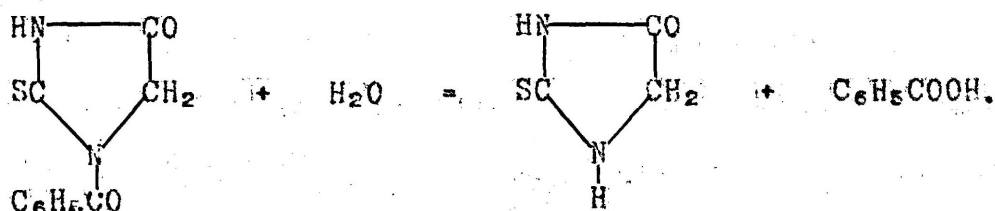
1 Treat B. Johnson and Ben H. Nicolet, J. A. C. S. Vol 33 p1977.

1 Treat B. Johnson and Ben H. Nicolet, J. A. C. S. Vol 33 p1978.

yield of the imidazole was 85 percent of the theoretical.

The portion insoluble in ether was purified by recrystallizing from water. These gave a melting point of 121° which corresponds to that of benzoic acid.

Equation:-



2-Thio-3-phenyl-5-keto-Tetrahydro-Imidazole.

Ten grams of ammonium thiocyanate, 5.1 grams of phenyl-glycine, 45cc of acetic anhydride, and 5 cc of glacial acetic acid were heated for some time until the solution was complete.

This showed no sign of crystallizing out after standing for a long time. Similar negative results were obtained in an attempt to make 2-thio-3-phenetol-5-keto-tetrahydro-imidazole.

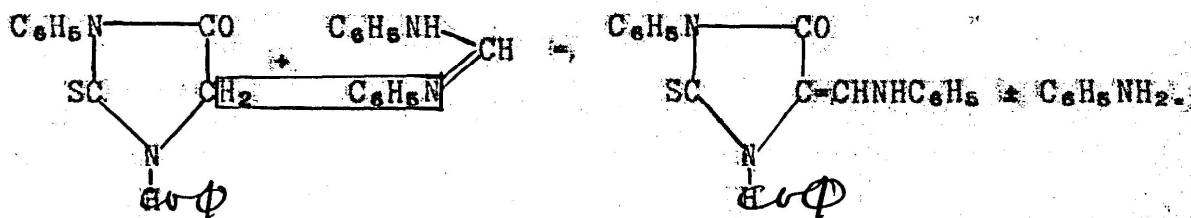
1-Phenyl-2-Thio-3-Benzoyl-4-Anilino-Methylene-5-Keto-Tetrahydro-Imidazole.

Molar proportions of 1-phenyl-2-thio-3-benzoyl-5-keto-tetrahydro-imidazole and diphenyl formamidine were combined by heating the mixture to 135° for thirty minutes*. After heating for a short time, the crystalline mass fused to a dark red liquid. On cooling, this solidified to a semi-tarry mass which was then treated with cold alcohol to remove the aniline formed in the reaction. The substance insoluble in cold alcohol was

* Miss Ruth Thompson, University of Kansas, 1920.

recrystallized from boiling alcohol. White crystals separated out, which melted at 184-6°. These were easily soluble in glacial acetic acid and alcohol.

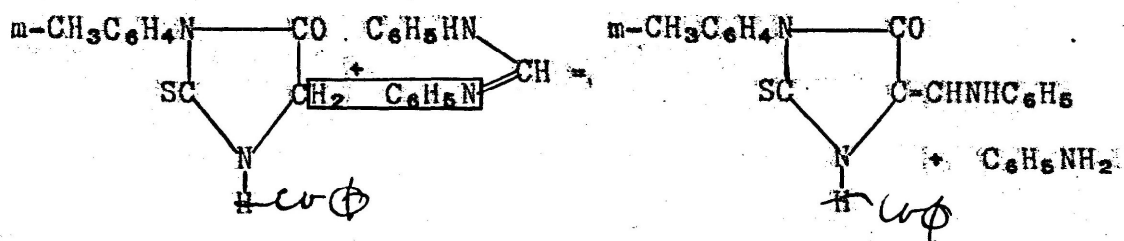
Equation:-



1-m-Tolyl-2-Thio-3-Benzoyl-4-Anilino-Methylene-5-Keto-Tetrahydro-Imidazole.

In making this compound, quantities proportional to their molar weights were heated for some time at 140°. The crystals fused to a deep red liquid, which on cooling solidified to a semi-solid mass. Alcohol was added to remove the aniline and the remaining portion was recrystallized from alcohol. Small lustrous white needles formed which melted at 187°.

Equation:..



Analysis for $\text{C}_{24}\text{H}_{19}\text{O}_2\text{N}_3\text{S}$

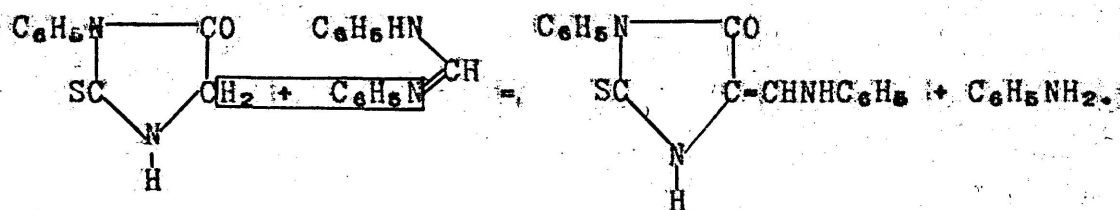
Weight of sample	.2364	.2936
cc of acid used	25.32	25.19
Normality of acid used	.2472	
cc of NaOH used	17.63	14.78

Acid / Base ratio	1.049	
Percent, of N found	10.01	10.26
Calculated	10.15	10.15

1-Phenyl-2-Thio-4-Anilino-Methylene-5-Keto-Tetrahydro-
Imidazole.*

Molal proportions of 1-phenyl-2-thio-5-keto-tetrahydro-imidazole and diphenyl fromamidine were heated together in a flask provided with an air condenser, to a temperature of 136° for about thirty minutes. The mixture soon fused to a dark red liquid and on cooling, solidified to a red tarry mass. The tarry substance was titrated with cold alcohol to remove the aniline. The remaining yellow mass was recrystallized from glacial acetic acid in which it is readily soluble. To obtain the pure substance, the compound was recrystallized from alcohol. Pale yellow needles were obtained, having a melting point of 252°.

Equation:.



Made and analyzed by Miss Ruth Thompson.

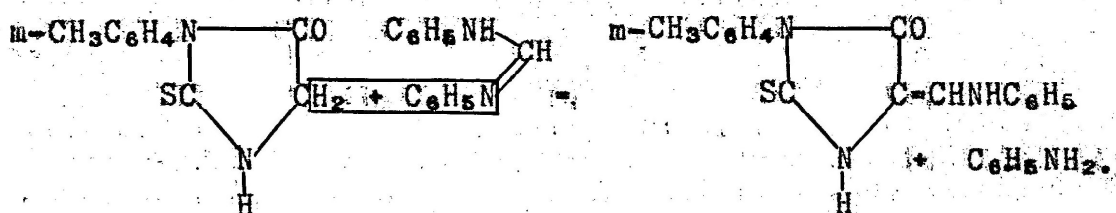
1-m-Tolyl-2-Thio-4-Anilino-Methylene-5-Keto-Tetra-
hydro-Imidazole.

1-m-tolyl-2-thio-4-anilino-methylene-5-keto-tetrahydro-imidazole was prepared by heating together molal proportions of the

* Miss Ruth Thompson, University of Kansas.

imidazole and diphenyl formamidine at 135° until the crystals had all fused. On cooling, the solution solidified to a semi-tarry mass. Alcohol was added to dissolve out the aniline which formed in the reaction. The remaining yellow substance was recrystallized from alcohol and after standing for some time, pale yellow crystals separated out. These melted to a yellow oil at 207-8°. The product was soluble in glacial acetic acid and in sodium hydroxide, forming a deep red solution. On acidulating the alkaline solution the compound was again precipitated.

Equation:-



Analysis for $\text{C}_{17}\text{H}_{15}\text{ON}_3\text{S}$

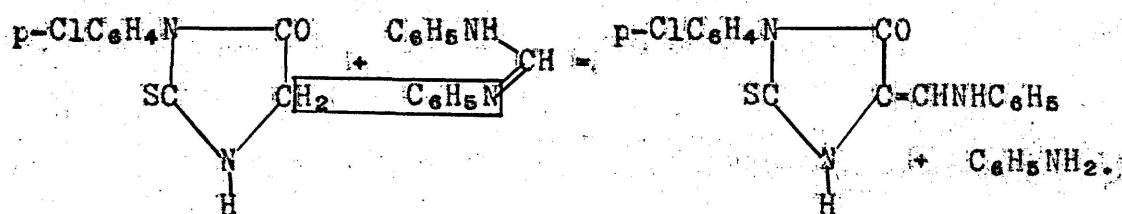
Weight of sample	.4862	.3422
cc acid used	26.31	25.15
Normality of acid used	.2472	
cc NaOH used	7.16	11.06
Acid / Base ratio	1.049	
Percent of N found	13.40	13.72
Calculated	13.60	13.60

1-p-Chlor-Phenyl-2-Thio-4-Anilino-Methylene-5-Keto-
Tetrahydro-Imidazole.

In preparing this compound, molar proportions of 1-p-chlor-phenyl-2-thio-5-keto-tetrahydro-imidazole and diphenyl formami-

dine were heated together at 135° until a dark tarry liquid resulted. On cooling, alcohol was added to dissolve out the aniline and the resulting mass recrystallized from glacial acetic acid and finally from alcohol. A fine light brown crystalline substance separated out. This was dried and the melting point found to be $274-6^{\circ}$. This product, was found to be soluble in sodium hydroxide solution from which it was reprecipitated on the addition of hydrochloric acid. It is not readily soluble in alcohol as are many of the other diphenyl-formamidine condensation products.

Equation:-



Analysis for $\text{C}_{16}\text{H}_{12}\text{ON}_3\text{SCl}$

Weight of the sample	.2446	.3892
cc of acid used	26.14	25.14
Normality of the acid	.2472	
cc of NaOH used	16.40	10.31
Acid / Base ratio	1.049	
Percent of N found	12.66	12.76
Calculated	12.75	12.75

Chlorine analysis for $\text{C}_{16}\text{H}_{12}\text{ON}_3\text{SCl}$

Weight of the sample	.2081	.6742
Weight of AgCl	.0909	.3033
Percent of Cl found	10.81	11.38

Calculated for Cl

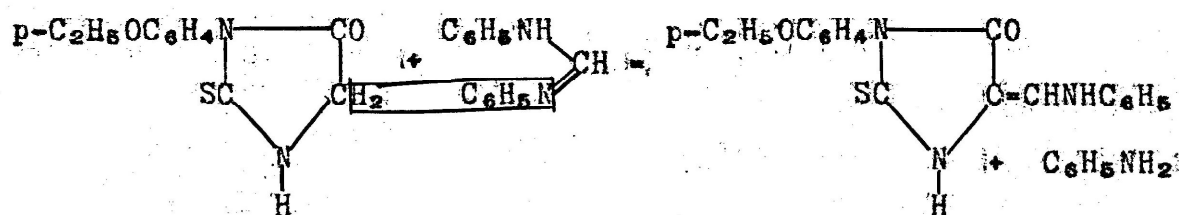
11.06

11.06

~~1-p-Phenetol-2-Thio-4-Anilino-Methylens-5-Keto-~~
~~Tetrahydro-Imidazole.~~

To prepare this compound, molal proportions of 1-p-phenetol-tetrahydro-imidazole and diphenyl formamidine were heated together in an oil bath at 135° for some time until the mixture assumed a dark red color. When cool, alcohol was added to remove the aniline formed in the reaction. The remaining product was recrystallized from alcohol. After standing for some time, pale yellow needles separated out which melted to a dark yellow oil at 227° . The product is soluble in sodium hydroxide from which it is precipitated on the addition of hydrochloric acid.

Equation:-

Analysis for $\text{C}_{18}\text{H}_{17}\text{O}_2\text{N}_3\text{S}$

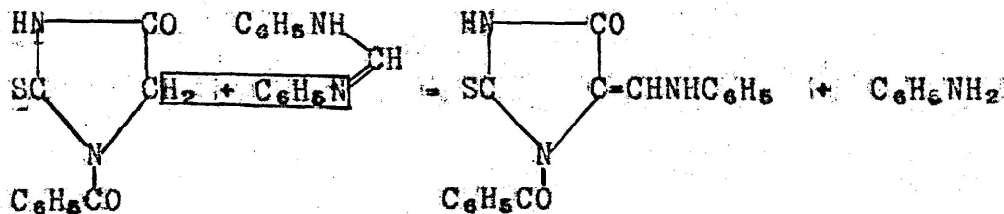
Weight of sample	.2486	.2742
cc of acid used	25.36	25.18
Normality of the acid	.2472	
cc of NaOH used	15.73	14.53
Acid / Base ratio	1.049	
Percent of N found	12.38	12.56
Calculated	12.39	12.39

2-Thio-3-Benzoyl-4-Anilino-Methylene-5-Keto-

Tetrahydro-Imidazole:

By heating molar proportions of 2-thio-3-benzoyl-5-keto tetrahydro-imidazole and diphenyl formamidine at 135° on an oil bath for about 30 minutes, a deep red colored liquid was obtained which changed to a semi-tarry mass on cooling. Cold alcohol was added to remove the aniline formed in the reaction and the remaining substance recrystallized from boiling alcohol. On standing for a short time, dark red needles separated out. These melted at 164-5°, forming a dark oil. This substance is readily soluble in sodium hydroxide solution. When the alkaline solution is acidified with hydrochloric acid, the product is reprecipitated.

Equation: -



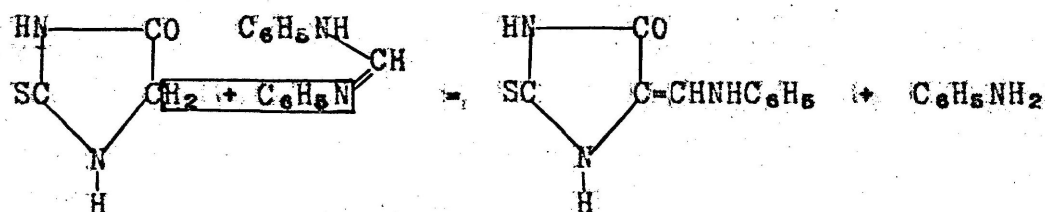
Analysis for $C_{18}H_{13}O_2N_3S$

Weight of sample	.7058	.3620
cc of acid used	35.00	36.40
Normality of acid	.2472	
cc of NaOH used	8.12	21.68
Acid / Base ratio	1.049	
Percent. of N found	13.15	13.17
Calculated	13.00	13.00

2-Thio-4-Anilino-Methylene-5-Keto-Tetrahydro-
Imidazole.

The above condensation product was obtained by heating molar proportions of 2-thio-5-keto-tetrahydro-imidazole and diphenyl formamidine on an oil bath at 135° for thirty minutes. A tarry deep red colored liquid was obtained which solidified on cooling. The solid substance was titrated with cold alcohol to remove the aniline. The insoluble portion was dissolved in hot alcohol and on standing for some time, deep red colored crystals were obtained. These melted at 264° and were easily soluble in alcohol and glacial acetic acid. In sodium hydroxide, they dissolved, forming a deep red solution and on acidulating with hydrochloric acid the compound was reprecipitated.

Equation:



Analysis for $\text{C}_{10}\text{H}_9\text{ON}_3\text{S}$

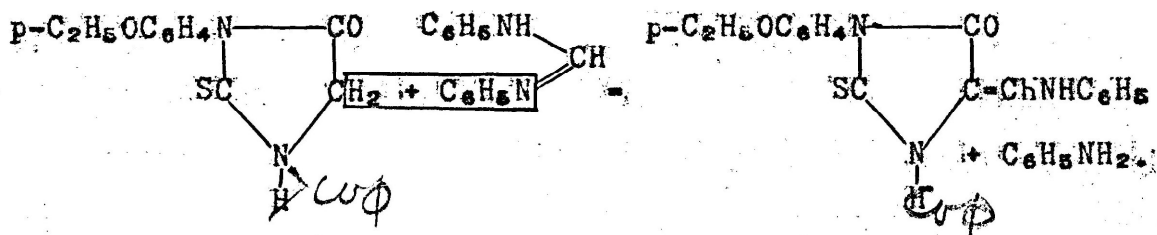
Weight of the sample	.2977	.3154
cc of acid used	35.30	35.00
Normality of the acid	.2472	
cc of NaOH used	17.92	16.40
Acid / Base ratio	1.049	
Percent of N found	19.22	18.91
Calculated	19.19	19.19

-3-Benzoyl-

1-p-Phenetol-2-Thio-4-Anilino-Methylene-5-Keto-
Tetrahydro-Imidazole.

This compound was prepared by heating molar proportions of 1-p-phenetol-2-thio-^{3-Benzoyl}5-keto-tetrahydro-imidazole and diphenyl formamidine in an oil bath of 135° for thirty minutes. After heating for a little while, the crystals fused to a dark colored oil, and on cooling a semi-tarry mass was obtained. This was extracted with cold alcohol to remove the aniline formed in the reaction. After several recrystallizations, yellowish white crystals were obtained. These melted at 151-3°. They dissolved in alcohol and glacial acetic acid, but not in sodium hydroxide.

Equation:-



Analysis for $\text{C}_{25}\text{H}_{21}\text{O}_3\text{N}_3$

Weight of the sample	.3690	.7269
cc of acid used	25.12	26.22
Normality of the acid	.2472	
cc of NaOH used	14.36	5.82
Acid & Base ratio	1.049	
Percent of N found	9.45	9.59
Calculated	9.48	9.48

III THIO-ETHERS

Wheeler and Brautlecht, on their previous work with imidazoles, have prepared the benzyl thio-ethers of 1-phenyl 2-thio-4-benzal-5-keto-tetrahydro-imidazole by shaking the thio-imidazole in a 20 percent sodium hydroxide solution with benzyl chloride*. They washed the precipitate that was formed with water and recrystallized it from alcohol.

In later work done by Miss Ruth Thompson at the University of Kansas under the direction of Dr. Dains, the thio ethers of the imidazoles condensed with diphenyl formamidine were prepared (1). The same general method was carried out as that used in making the benzal derivatives. The diphenyl formamidine condensation product of the thionhydantoin was dissolved in a 20 percent sodium hydroxide solution and benzyl chloride added. The precipitate that formed was washed with cold water and recrystallized from hot alcohol. In every case the reaction proceeded very smoothly, and in no case was negative results obtained.

Since the thio ethers formed very readily when the methylene group was condensed with an aldehyde or a formamidine, attempts were made to see if the corresponding thio ethers of the uncondensed imidazoles could be made. Several attempts were made to prepare this class of compounds, but with no results.

* Wheeler and Brautlecht, A.C.J., Vol 45, p 450.

1 Miss Ruth Thompson, University of Kansas, 1920.

1-Phenyl-2-Benzylmercapto-5-Keto-Tetrahydro-
Imidazole.

Ten grams of 1-phenyl-2-thio-5-keto-tetrahydro-imidazole was dissolved in a 20 percent sodium hydroxide solution at ordinary temperature and a molar proportion of benzyl chloride added. The mixture was thoroughly shaken and allowed to stand over night. There was an oily substance present with no evidence of the formation of crystals. The entire solution was then acidified with hydrochloric acid, when a heavy dark oil separated out, having a very disagreeable odor. This was allowed to stand for some time. After several days, the oily substance was dissolved in sodium hydroxide and the alkaline solution extracted with ether. The portion that dissolved in ether had a very disagreeable odor, much like that of a mercaptan. The alkaline solution was then acidified with hydrochloric acid, and the original substance was again recovered.

A similar experiment was carried out at a higher temperature. The solution was warmed to about 80° to see if the reaction would occur. In this case again negative results were obtained.

Having made several attempts of making the thio ether of 1-phenyl-2-thiohydantoin at a higher temperature, another attempt was made by keeping the mixture in ice. Ten grams of 1-phenyl-2-thio-5-keto-tetrahydro-imidazole was dissolved in a 20 percent solution of sodium hydroxide, and a molar por-

tion of benzyl chloride added, drop by drop. The solution was thoroughly stirred for several hours, and then allowed to stand until the substance that formed separated out. After standing for several weeks, white glistening crystals separated out of the oily mother liquor. These were recrystallized from alcohol, giving silvery white crystals which melted at 67°. These gave a negative test for nitrogen and a positive for sulphur.

The mother liquor was diluted with water and made acid with hydrochloric acid. A yellowish amorphous substance separated out. This was recrystallized from hot alcohol forming pale yellow needles, melting at 197°. These showed a negative test for sulphur and a positive one for nitrogen.

Analysis of the portion melting at 197°.

Weight of the sample	.1874	.3894
cc of acid used	26.15	29.10
Normality of the acid	.2472	
cc of NaOH used	17.47	12.45
Acid / Base ratio	1.049	
Percent of N found	14.48	14.27
Calculated for $C_6H_5NHCONHCH_2COOH$,	14.41 percent.	

The substance that separated out on standing was found to contain 21.64 percent of sulphur. $(GH_2)_2 S_2$ in P 70°

1-Phenyl-2-Ethyl-Thio-5-Keto-Tetrahydro-Imidazole.

Ten grams of 1-phenyl-2-thio-5-keto-tetrahydro-imidazole was dissolved in sodium ethylate and ethyl iodide added. The

solution was thoroughly stirred for some time and finally refluxed for two hours. The alcohol was evaporated off and the precipitate titrated with water. The substance was then dissolved in hot alcohol and allowed to stand for some time. There was no evidence of crystals, but a dark tarry substance separated out. This was dissolved in sodium hydroxide, filtered and acidulated with hydrochloric acid. The original substance was recovered and identified by its melting point. During the reaction, a disagreeable odor was noticeable with no evidence of a thio ether being formed.

Since the reaction did not proceed at a higher temperature, it was carried out in an ice bath with similar negative results.

As a rule, the methylene thio ether has a higher melting point, so attempts were made to prepare this compound. In all cases negative results were obtained.

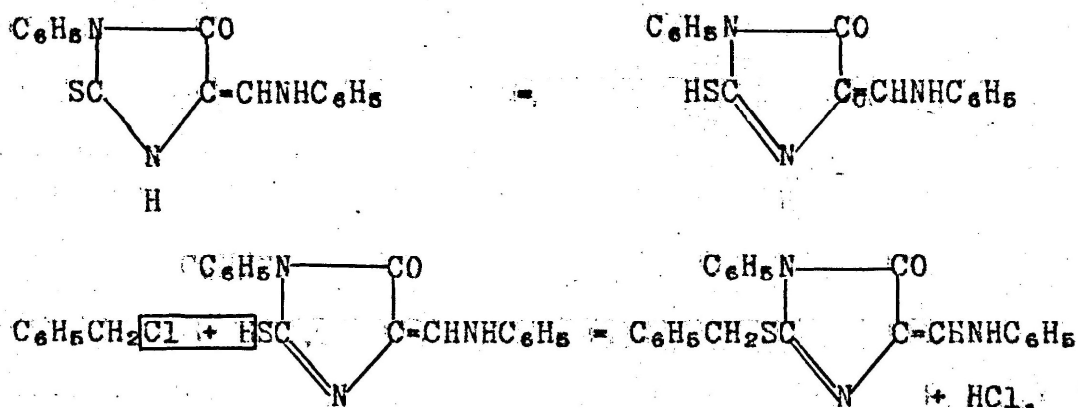
After spending considerable time in attempting to make the thio ether of the uncondensed hydantoins, the experimental work on the thio ether of the formamidine condensation products was continued as started by Miss Thompson.

1-Phenyl-2-Benzyl-Thio-4-Anilino-Methylene-5-Keto-
Tetrahydro-Imidazole.

Six grams of 1-phenyl-2-thio-4-anilino-methylene-5-keto-tetrahydro-imidazole was dissolved in a 20 percent sodium hydroxide solution and 3 grams of benzyl chloride added. During

the addition of the chloride, the solution was thoroughly shaken. A precipitate soon formed and after standing for a day, it was washed with cold water. The substance was recrystallized from boiling alcohol. Fine yellow needles separated out which melted to a clear yellow oil at 145-7°. These crystals were easily soluble in alcohol and glacial acetic acid.

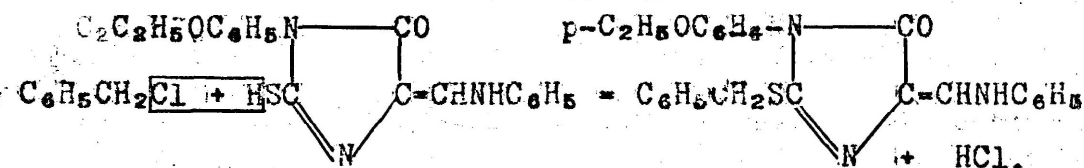
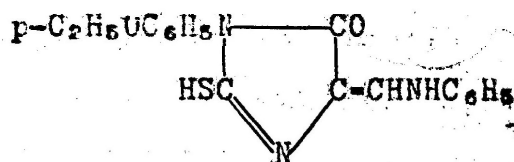
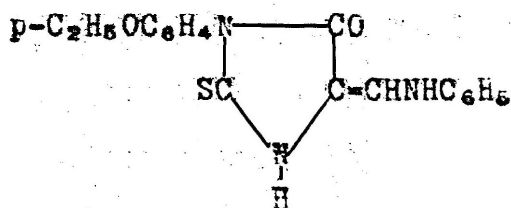
Equation:;



**1-p-Phenetol-2-Benzyl-Thio-4-Anilino-Methylene-
5-Keto-Tetrahydro-Imidazole**

Five grams of 1-p-phenetol-hydantoin was dissolved in a 20 percent sodium hydroxide solution and an excess of benzyl chloride added. After shaking the mixture thoroughly, for a some time, it was allowed to stand for several days. The crystals that formed were washed with cold water and recrystallized from alcohol. Fine yellow needles separated out, that were easily soluble in alcohol and glacial acetic acid. These melted at 169-7°.

Equation:~



Analysis for $\text{C}_{25}\text{H}_{13}\text{O}_2\text{N}_3\text{S}$

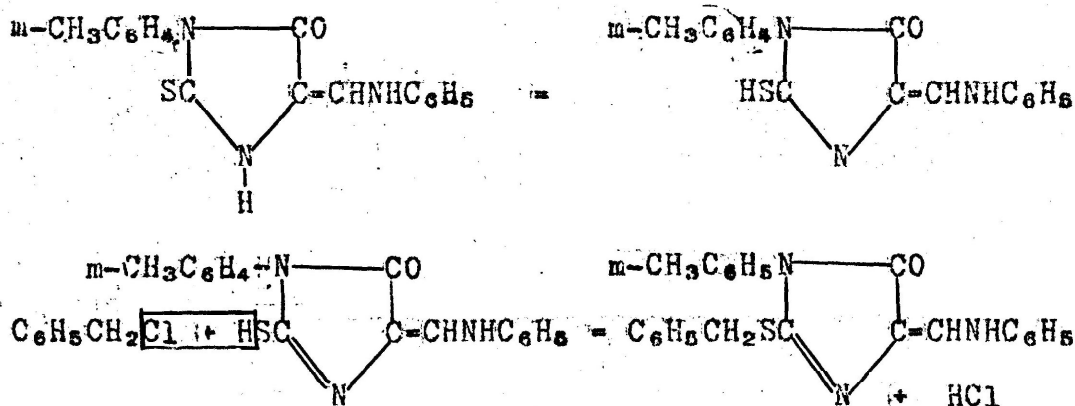
Weight of the sample	.1868	.5401
cc of acid used	40.70	40.25
Normality of the acid	.2472	
cc of NaOH used	32.98	23.80
Acid / Base ratio	1.049	
Percent of N found	9.48	9.81
Calculated	9.58	9.58

1-m-Tolyl-2-Benzyl-Thio-4-Anilino-Methylene-
5-Keto-Tetrahydro-Imidazole.

In preparing this compound, 5 grams of 1-m-tolyl-2-thio-4-anilino-methylene-5-keto-tetrahydro-imidazole was dissolved in a 20 percent sodium hydroxide solution and a molal portion of benzyl chloride added. After shaking for a little while, a white precipitate was formed. The reaction mixture was allowed to stand over night when the crystals that formed were washed with cold water. After several recrystallizations from alcohol, small pale yellow needle like crystals were obtained. These melted at $153-4^\circ$, and were easily soluble in

alcohol and glacial acetic acid.

Equation:-



Analysis for $\text{C}_{24}\text{H}_{21}\text{ON}_3\text{S}$

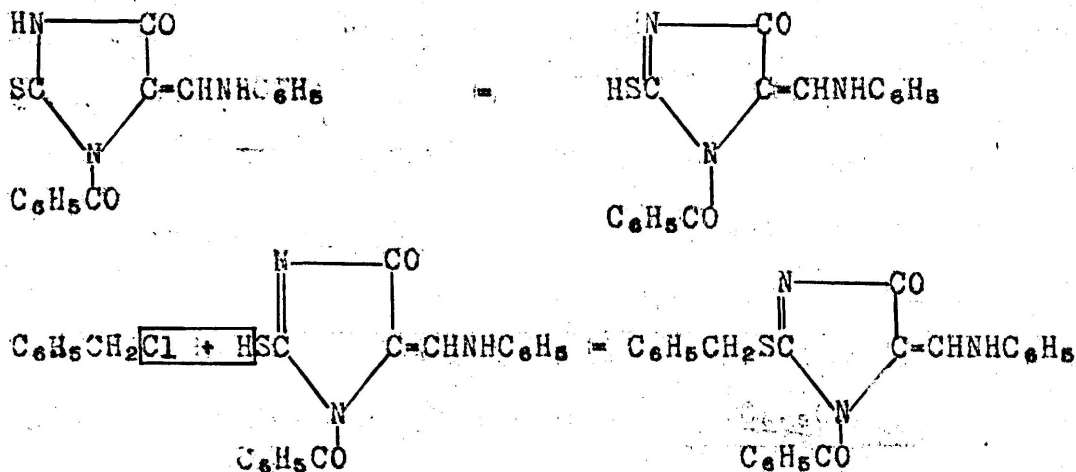
Weight of the sample	.3410	.2648
cc of acid used	25.45	25.70
Normality of the acid	.2472	
cc of NaOH used	14.20	16.30
Acid / Base ratio	1.049	
Percent of N found	10.73	10.57
Calculated	10.51	10.51

2-Benzyl-Thio-3-Benzoyl-4-Anilino-Methylene-5-
Keto-Tetrahydro-Imidazole

Four grams of 2-thio-3-benzoyl-4-anilino-methylene-5-keto-tetrahydro-imidazole was dissolved in a 20 percent of sodium hydroxide solution and 2 grams of benzyl chloride added. After shaking for some time, a precipitate formed. This was allowed to stand over night. The substance that separated out was washed with cold water and recrystallized several times from alcohol. Fine yellow needles separated.

out that melted at, 164-5°. They dissolved in alcohol and glacial acetic acid.

Equation:-



Analysis for $\text{C}_{24}\text{H}_{19}\text{O}_2\text{N}_3\text{S}$

Weight of sample	.3386	.2336
cc of acid used	25.40	25.00
Normality of acid	.2472	
cc of NaOH used	14.90	17.50
Acid/Base Ratio	1.049	
Percent of N found	9.99	9.87
Calculated	10.14	10.14

Reaction of Benzyl Chloride on 2-Thio-4-Anilino-
Methylene-5-Keto-Tetrahydro-Imidazole

Three grams of 2-thiohydantoin was dissolved in a 20 percent sodium hydroxide solution and benzyl chloride added, with thorough shaking. A precipitate did not form immediately, so the solution was allowed to stand for some time. Finally an amorphous substance separated out. This was

washed with cold water and dissolved in hot alcohol. After standing for a while, a semi-tarry substance settled down. This was dried and the melting point determined. It had no definite melting point, even after being recrystallized from alcohol several times.

This particular part is of interest, to see if the benzyl group will react with the hydrogen of the one or three position of the ring. Owing to the fact that no definite crystalline substance was formed as in the case of other thio ethers, would lead one to believe that there might be two different isomers. Lack of time made it impossible to determine definitely the reaction that occurred in this case. However this particular reaction will again be investigated in the near future.

Hydrolysis of Imidazoles

In the work of Joahson and Nicolet,* on the hydrolysis of 2-thio-3-benzoyl-5-keto-tetrahydro-imidazole, they have shown that when this compound is heated with hydrochloric acid, hydrolysis takes place in which the benzoyl group is converted into benzoic acid, giving the 2-thio-hydantoin. The same reaction was tried in this laboratory with the same results. The hydrolysis proceeded very smoothly with about an 80 percent yield.

Since in this case the benzoyl group was split off, it was thought that the 1-phenyl-2thio-5-ketp-tetrahydro-imidazole could be prepared by heating hippuric acid with phenyl mustard oil and hydrolizing off the benzoyl group.

Five grams of 1-phenyl-2-thio-3-benzoyl-5-keto-tetrahydro-imidazole was dissolved in 75 cc of alcohol and 10 cc of hydrochloric acid added. The solution was refluxed for six hours and during the hydrolysis, the odor of benzoic acid was clearly noticeable. The solution was then tested for aniline and a positive test obtained. After the heating was complete, the alcohol was evaporated off and the remaining substance recrystallized from alcohol. Fine white needles separated out, which melted at 191°, corresponding to that of hippuric acid. On taking a mixed melting point with hippuric acid, it was found to melt at the same temperature. This seems to favor the possibility of a rupture in

* Johnson and Nicolet, J.A.C.S. Vol. 33, p 1978.

the ring with the formation of aniline and hippuric acid.

In order to form hippuric acid and aniline, the ring would have to break between the N and the C in the 1 and 5 position and also between the C and the N in the 2 and 3 position. The phenyl mustard oil would react with water to give the aniline. In order to further establish the identity of this compound, an analysis was made of it.

Weight of the sample	.3071	.2829
cc of acid used	26.58	25.00
Normality of the acid	.2472	
cc of NaOH used	18.65	117.60
Acid / Base ratio	1.049	
Percent of N found	7.92	8.01
Calculated for $C_6H_5CONHCH_2COOH$	7.82	

Since in the case of 1-phenyl-2-thio-3-benzoyl-5-keto-tetrahydro-imidazole, the hippuric acid was formed, it was decided to find out what the effect of the methylene group condensed with diphenyl formamidine might be.

Five grams of 1-phenyl-2-thio-3-benzoyl-4-anilino-methylene-5-keto-tetrahydro-imidazole was dissolved in alcohol and 10 cc of concentrated hydrochloric acid added. After refluxing the solution for six hours, it gave a strong positive test for aniline. The alcohol was then evaporated off and the precipitate recrystallized from boiling water. Small white crystals formed that melted at 191° . A mixed melting point with hippuric acid produced no change in the

melting point.

Analysis of the substance:-

Weight of the sample	.2490	.1991
cc of acid used	26.60	25.00
Normality of the acid	.2472	
cc of NaOH used	20.05	19.45
Acid / Base ratio	1.049	
Percent of N found	7.75	7.98

Hydrolysis of 2-Thio-3-Benzoyl-4-Anilino-Methylene-
5-Keto-Tetrahydro-Imidazole.

Five grams of 2-thio-3-benzoyl-4-anilino-methylene-5-keto-tetrahydro-imidazole was dissolved in alcohol and 10 cc of concentrated hydrochloric added. The entire solution was heated for six hours and tested for aniline. Negative tests for aniline were obtained. The alcohol was then evaporated off and the substance recrystallized from alcohol. The crystals melted at 164° which is the same as that of the original substance.

Hydrolysis of 1-Phenyl-2-Thio-5-Keto-Tetrahydro-
Imidazole.

Three grams of 1-phenyl-2-thio-hydantoin was dissolved in alcohol and refluxed with 10 cc of concentrated hydrochloric acid, for six hours. After examining the crystals, the original product was again obtained. A 20 percent of sodium hydroxide solution was used with similar negative results.

Hydrolysis of 1-Phenyl-2-Thio-4-Anilino-Methylene-
5-Keto-Tetrahydro-Imidazole.

Three grams of 1-phenyl-2-thio-4-anilino-methylene-5-keto tetrahydro-imidazole was dissolved in alcohol and 10 cc of concentrated hydrochloric acid added. After refluxing for six hours, the test for aniline gave negative results. On recovering the crystals, they were found to have a melting point identical with the original substance. On heating with a 20 percent sodium hydroxide solution, no change was observed, as the original substance was recovered.

From the foregoing experimental evidence, one would be led to think that the group substituted for the H in the 1 position has a great effect on the action of hydrochloric acid on the ring. When this substance was condensed with diphenyl formamidine, the experimental evidence showed no hydrolysis whatever.

When the 1-phenyl-2-thio-3-benzoyl-5-keto-tetrahydro-imidazole was treated with hydrochloric, the entire ring was broken down. Similarly, when the 1-phenyl-2-thio-3-benzoyl-4-anilino-methylene-5-keto-tetrahydro-imidazole was heated with hydrochloric acid, an identical breaking of the ring occurred. This would lead one to believe that the groups substituted for the H in the 1 position and the 3 position materially affect the stability of the ring.

This work will be continued in the near future and a more detailed study of the general behavior of hydrochloric acid on

and other hydrolyzing agents on this class of compounds will be made.

In concluding this paper, the writer wishes to acknowledge his appreciation to Dr. Dains for his many helpful suggestions and kindly interest, which have made this paper possible.

Chemical Laboratories

University of Kansas

July 25, 1921.