ON THE CONSTITUTION OF CERTAIN
THIAZOLIDONES DERIVATED FROM THE
2-p-TOLYL THIAZOLIDONE.

By

Carrol O. Holmberg
B. S. Bethany College, 1925.

Submitted to the Department of
Chemistry and the Faculty of the
Graduate School of the University
of Kansas in partial fulfillment of
the requirements for the degree of
MASTER OF SCIENCE.

Approved by: 

[Signature]
Instructor in Charge.

[Signature]
Chairman of Department.

June, 1927.
TABLE OF CONTENTS

Chapter I. Constitution of Mono-substituted thiazolidones ........................................... I.
Chapter II. Purpose of investigation .................................................................................... 7.
Chapter III. Reactions of the thiazolidones ........................................................................... 8.
Chapter IV. Experimental work ............................................................................................. 9.

2-p-tolyl-4-thiazolidone ........................................................................................................ 9.
Sodium salt of 2-p-tolyl-4-thiazolidone ............................................................................... 11.
2-p-tolyl-2-ethyl-amino-4-thiazolidone ............................................................................... 12.
α-ethyl α-p-tolyl β-phenyl urea .......................................................................................... 14.
2-p-tolyl-2-benzyl-amino-4-thiazolidone .............................................................................. 14.
β-benzyl α-p-tolyl β-phenyl urea ....................................................................................... 17.
2-p-tolyl-2-p-nitro benzyl-amino-4-thiazolidone ................................................................ 17.
p-nitro benzyl p-toluidine ..................................................................................................... 18.
2-p-tolyl-2-ethyl-amino-5-benzal-4-thiazolidone ................................................................ 20.
2-α-di-keto-5-benzal thiazolidone ....................................................................................... 21.
5-benzal-4-thiazolidone ......................................................................................................... 23.
α-p-tolyl β-ethyl thio urea .................................................................................................. 25.
2-p-tolyl-3-ethyl-4-thiazolidone ........................................................................................... 26.
3-ethyl-2-4-di-keto-thiazolidone .......................................................................................... 28.
2-p-tolyl-3-ethyl-5-benzal-4-thiazolidone ............................................................................ 28.
Comparison of the isomeric thiazolidones ........................................................................ 29.
2-p-tolyl-3-ethyl-5-benzal-4-thiazolidone ............................................................................ 31.
2-o-tolyl-4-thiazolidone ........................................................................................................ 31.
MOH0chlor acet o-toluidine ................................................................................................. 32.
Sodium salt of 2-o-tolyl-4-thiazolidone ............................................................................... 34.
2-o-tolyl-2-benzyl-amino-4-thiazolidone

HCl salt of 2-o-tolyl-2-benzyl-amino-4-thiazolidone

2-o-tolyl-2-ethyl-amino-4-thiazolidone

α-o-tolyl α benzyl β phenyl urea

HCl salt of 2-o-tolyl-2-ethyl-amino-4-thiazolidone

α-o-tolyl α ethyl β phenyl urea

2-o-tolyl-2-methyl-amino-4-thiazolidone

α-o-tolyl α methyl β phenyl urea

2-p-anisidin-4-thiazolidone

Mono chlor acetyl p-anisidin

Sodium salt of 2-p-anisidin-4-thiazolidone

2-p-anisidin-2-ethyl-amino-4-thiazolidone

2-p-anisidin-2-benzyl-amino-4-thiazolidone
The writer wishes to express his sincere appreciation and thanks to Dr. F. B. Dains whose direction and help made this work possible.
Nearly fifty years ago it was found by F. Meyer and others that the thio ureas reacted with chloracetic acid or its derivatives, such as acid chlorides, esters or anilides, to give a thasol ring compound. The unsubstituted ring exists in two tautomeric forms.

\[ \text{H} \quad \text{S} \quad \text{H} \quad \text{O} \quad \text{II} \]

\[ \text{H} \quad \text{H} \quad \text{S} \quad \text{H} \quad \text{O} \quad \text{I} \]

While the three possible mono phenyl derivatives could be

\[ \text{H} \quad \text{S} \quad \text{H} \quad \text{O} \quad \text{III} \]

\[ \text{H} \quad \text{H} \quad \text{S} \quad \text{H} \quad \text{O} \quad \text{IV} \]

\[ \text{H} \quad \text{H} \quad \text{S} \quad \text{H} \quad \text{O} \quad \text{V} \]

The synthesis from thio urea and chloracetenilide would seem to give V

\[ \text{H} \quad \text{S} \quad \text{H} \quad \text{O} \quad \text{V} \]

While the synthesis from mono phenyl thio urea and ethyl chloracetate could be formulated as forming not only V but also III and IV.
Since Meyer obtained the 2-4 diketo 3-phenyl thiasolidone from mono
phenyl thiasolidone, he concluded that formula V was the correct one, and
that the action might be formulated as taking place.

Lieberman and Lange thought that mono alkyl pseudo-thiohydantoin may
occur in two isomeric forms, IV and V above.

Andreasch \(^3\) after having prepared the same thiasolidone as Meyer;

3. Andreasch, Berichte. 15, 325 (1862)
from phenylcyanamide and thioglycollic acid, concluded that formula 3 was the only formula by which the structure of the mono substituted thiasolidones could be represented.

Several years later, in 1897, Dixon(4) heated the mono phenyl thiasolidone with carbon disulphide at a high temperature and obtained phenyl mustard oil and rhodanic acid. He therefore concluded that the following reaction took place.

\[
\text{CS}_3 + \text{C}_6\text{H}_5\text{N}=\text{SCH}_3 \rightarrow \text{HC}=\text{S} + \text{C}_6\text{H}_5\text{NCS}
\]

He further established the structure of this compound by showing that the sulphur atom is attached to the Carbon No 2 group, because on boiling mono ortho tolyl thiasolidone with baryta he obtained thioglycollic acid and O-toluidine.

\[
\begin{array}{c}
\text{CO} \\
\text{C}_6\text{H}_4\text{N} = \text{SCH}_3
\end{array} + 3 \text{H}_2\text{O} \rightarrow \text{CH}_3\text{SH} + \text{C}_6\text{H}_7\text{N} + 2 \text{H}_2\text{O}
\]

While Dixon admitted that the compound might behave in a tautomeric manner he nevertheless preferred the formula just used above.

Dixon's method of preparing the thiasolidone was by using the halogen substitutionary derivatives of the acid thiocarbamides, and combining these with organic bases to form closed ring compounds. This method of preparation did not prove satisfactory as the reaction must be stopped at the exact time that the reaction is complete, and there is no sure means of determining this stage of the reaction.

4. Dixon, A. E. J. C. S. 71, 617 (1897)
If the reaction is stopped too soon the product is contaminated with unchanged acid chloride, and if the reaction is allowed to continue too long there is a tendency toward the formation of the thiocarbinic product.

The reaction would take place in the following form:

\[
\text{\( p\text{-C}_{6}\text{H}_{5}\text{CH}_{2} \)} + \text{\( \text{CO} \)} \quad \text{HCl} \quad \text{\( \text{o-C}_{6}\text{H}_{5}\text{CH}_{2} \)}
\]

Dixon, from his investigations, concluded that the same thiasolidone is the product of each of the following reactions:

1. Monosubstituted thiourea and ethyl chloracetate.
2. Thiourea and chloracetanilide.
3. Chlorinated acidic thiocarbinide and an organic base.

Wheeler and Johnson\(^5\) have shown that phenyl thiohydantoin

\[
\text{C}_{6}\text{H}_{5}\text{NH} \\
\text{H} \quad \text{OSCH}_{3}\text{COOH}
\]

behaves in a tautomeric manner, with the double bond shifting from one nitrogen atom to another. They have also shown that the unsymmetrical acetyl-phenyl-pseudo-thioureas will undergo the following tautomeric change:

5. Wheeler and Johnson, A. C. J. 28, 3 (Aug. 1903)
This suggested that the thiasolidones might behave in a similar manner. They set to work to determine if this were the case.

By the action of chlor-acetanilide upon KCNS, Wheeler and Johnson prepared the normal thio-cyan-acetanilide. When this was melted on the water bath for 15 minutes, they obtained what they thought was the 2-imino-3-phenyl thiasolidone. This form is termed the "labile" form.

\[
\begin{align*}
\text{C}_6\text{H}_5&\text{S} \quad \text{C} \quad \text{O} \\
\text{H} & \text{N} \quad \text{C} \quad \text{H}_2
\end{align*}
\]

When this was treated with thio acetic acid they obtained H_2S and an acetyl derivative. When the 2-imino-3 phenyl thiasolidone is heated on the water bath for a few minutes it is converted into the stable form or 2-phenyl imino thiasolidone.

\[
\begin{align*}
\text{C}_6\text{H}_5&\text{S} \quad \text{C} \quad \text{O} \\
\text{H} & \text{N} \quad \text{C} \quad \text{H}_2
\end{align*}
\]

This is in agreement with the structure assigned to the same compound by both Meyer and Dixon.

This work was not accepted by Beckurth and Frerich who regard V as the true constitution, and do not think that the stable form as represented by Wheeler and Johnson exists. They synthesised a number of alkyl derivatives of the aryl thiasolidones to which they gave the formula 2-alkyl imino 3 aryl thiasolidone. When KCNS reacted on C\_2H\_5C\_6H\_4NO\_2C\_7H\_7--m they secured a product to which they assigned the formula

\[
\begin{align*}
\text{m-C}_7\text{H}_7&\text{S} \quad \text{C} \quad \text{O} \\
\text{H} & \text{N} \quad \text{C} \quad \text{H}_2
\end{align*}
\]
When this was dissolved in NaOH solution the sodium salt of the above thiazolidones crystallised with four mols of water of crystallisation. This was then boiled with ethyl iodide, when Hal was split off and a compound melting at 106° was also secured. The course of the above reactions was represented as taking place as follows:

\[
\text{m-C}_7\text{H}_7\text{H} - \text{CO} + \text{NaOH} \rightarrow \text{m-C}_7\text{H}_7\text{H} - \text{CO} \]

\[
\text{HO-N} - \text{C} - \text{CH}_2 \]

\[
\text{C}_2\text{H}_5\text{I} + \]

\[
\text{m-C}_7\text{H}_7\text{H} - \text{CO} \]

This last formula was the one assigned to the disubstituted thiazolidones by Beckurth and Frerich.

When these compounds were hydrolysed with several times their weight of 25% HCl, they secured in all cases, a diketo derivative and an alkyl amine. The aryl group in all cases remaining on the ring. This would seem to justify their conclusion that the above formula was the correct one.
PURPOSE OF THIS INVESTIGATION.

The purpose of this investigation was to secure further evidence of the constitution of the disubstituted thiazolidones, and to show, if possible, that the work of Beckarts and Frericks(6) which was in direct contradiction of the careful work of Wheeler and Johnson was erroneous.

The general plan for proving the structure of this group of compounds was to prepare the compound in a pure form, and by analysis determine the empirical formula of the compound. The compound was then subjected to hydrolysis either in alcoholic solution of dilute HCl on the water bath for several hours or with dilute HCl in sealed tube at 130° - 140° for several hours.

The products of hydrolysis were then examined, and in the cases of the disubstituted thiazolidones, the secondary amine which split from the original compound was treated with phenyl isocyanate to form a substituted urea, giving a compound that was rather easily crystallised and purified for subsequent analysis. The urea was also compared, whenever possible with the corresponding urea of known constitution.

\[
\begin{array}{c}
R' \\
N\text{ON} \\
R \\
O \\
N\text{ON} \\
R''
\end{array}
\]

6. Beckarts and Frericks. Archives der Pharmacie, 238, 615 (1900)
REATIONS OF THE THIAZOLIDONES.

From the fact that the thiazolidones undergo only a limited number of reactions, the work of determining the constitution of them is increased. There are, however, at least two reactions which were found to be perfectly general.

1. All the mono-substituted thiazolidones form addition products with sodium hydroxide.

\[
\begin{align*}
\text{HN-CO} & \quad + \quad \text{NaOH} \quad \rightarrow \quad \text{Na} & \quad \text{HN-CO} \\
\text{HN-O} & \quad \text{OH}_{3} & \quad \text{OH}_{2}
\end{align*}
\]

2. By means of the methylene group the thiazolidones form condensation products with benzaldehyde.

This reaction was especially valuable in the case of certain thiazolidones which were oils. The benzaldehyde condensation products in all cases investigated had a much higher melting point than the original thiazolidone, and were usually easily prepared and recrystallized.

The thiazolidones can be hydrolyzed when heated in a sealed tube with dilute HCl for several hours at 130°-140°. The resulting products can be identified and from these the constitution of the original compound determined.
EXPERIMENTAL WORK.

2-p-tolyl-4-thiazolidone.

To prepare the 2-p-tolyl-4-thiazolidone, it was first necessary to prepare p-tolyl thio urea. This was made by heating together one mol p-toluidine, one mol HCl, and 1.35 mol ammonium thio cyanate on a water bath to dryness. The product was then washed with water to remove the soluble ammonia salts, but very little of the thio urea was lost in this process, since it is very slightly soluble in water. The thio urea was purified by recrystallisation from hot alcohol, in which it is moderately soluble.

\[
\text{NH}_4\text{SCN} + \text{C}_6\text{H}_5\text{C}_6\text{H}_4\text{NH}_2 + \text{HCl} \rightarrow \text{C}_7\text{H}_5\text{C}_6\text{H}_4\text{NH}_2 + \text{NH}_4\text{Cl}
\]

M. P. = 187º

Yield = 90 %

The 2-p-tolyl-4-thiazolidone was next prepared by refluxing one mol of p-tolyl thio urea, one mol mono chlor acetic acid and two mols pyridine in alcohol solution. When this mixture was first heated, it became a thick cream colored mass, but with continued heating the entire mass dissolved to a clear brown solution from which the yellow needles of the thiazolidone separated out on cooling. These crystals were filtered from the excess alcoholic solution which was then concentrated to one-third its original volume and poured into water to precipitate the remaining thiazolidone. This was purified by recrystallisation from hot alcohol in which it is moderately soluble. It is almost insoluble in water.
\[
\text{p- C}_7\text{H}_5\text{NH}_{3}\text{H}_2 + \text{CH}_3\text{C}_{6}\text{H}_4\text{COOH} \rightarrow \text{p- C}_7\text{H}_5\text{NH}_{3}\text{H}_2 + \text{H}_2\text{O} + \text{HCl}
\]

\[
\text{M. P.} = 163^\circ
\]
\[
\text{Yield} = 80\%
\]

This compound was purified and analyzed to determine the percent of nitrogen in the compound. As the acid was standardized by using a pure, known compound and as portions of the same sulphuric acid and potassium sulphate were used in succeeding determinations, there was no correction necessary for the blank.

**Analysis of 2- p- tolyl-4-thiazolidone.**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.4916 gm</td>
<td>.5405 gm</td>
</tr>
<tr>
<td>C, Cl acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C, C. alkali used</td>
<td>24 cc</td>
<td>20 cc</td>
</tr>
</tbody>
</table>

1 cc alkali = .839 cc acid

\[
1 \text{ cc acid} = .002201 \text{ gm nitrogen}
\]

Percent nitrogen found

<table>
<thead>
<tr>
<th></th>
<th>13.39 %</th>
<th>13.51 %</th>
</tr>
</thead>
</table>

Percent nitrogen calculated from the formula 0.10H_{10}O_{25} = 13.59 %
Sodium salt of 2- tolyl-4-thiazolidone

In order to prepare the disubstituted thiazolidones of 2- tolyl-4-thiazolidone, it was first necessary to prepare the sodium salt of 2- tolyl-4-thiazolidone in which different radicals could be substituted for the hydrogen at carbon No. 2 in the original compound.

The sodium salt was prepared by heating one mol of p-tolyl thiazolidone with one mol 10% NaOH solution. The solution becomes clear and dark brown, from which the sodium salt crystallizes in colorless plates on cooling. The sodium salt is very soluble in hot water, much less soluble in cold water, and rather soluble in alcohol.

It is thought that the NaOH adds to the nitrogen outside the ring, making it pentavalent. The sodium salt crystallizes with four mols of water.

\[
\begin{align*}
\text{M. P.} & \quad = \quad 107^\circ \\
\text{Yield} & \quad = \quad \text{almost theoretical}
\end{align*}
\]

Almost immediately after melting, this compound again becomes solid; melting again at 132°. This is evidently the melting point of the anhydrous salt.
2- p-tolyl-2-ethyl-amino-4-thiasolidone

One mol of the sodium salt of 2-p-tolyl thiasolidone and one mol ethyl iodide were refluxed in absolute alcohol for four hours. The solution was then distilled with steam to remove the excess alcohol and ethyl iodide. The ethyl derivative remained as a brown oil which solidified after standing several hours. After being repeatedly recrystallized from alcohol the crystals became colorless.

This compound easily forms a supersaturated solution, especially when impure, when it crystallizes very slowly. It is almost insoluble in water and soluble in almost all organic solvents.

\[
\begin{align*}
\text{M. P.} & \quad 124^\circ - 125^\circ \\
\text{Yield} & \quad 65\%
\end{align*}
\]

Analysis of 2- p- tolyl-2-ethyl-amino-4-thiasolidone

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>0.5176 gm</td>
<td>0.4650 gm</td>
</tr>
<tr>
<td>C.C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C.C. alkali used</td>
<td>25.2 cc</td>
<td>29.7 cc</td>
</tr>
</tbody>
</table>

1 cc alkali = 0.838 cc acid
1 cc acid = 0.002201 gm nitrogen

Percent nitrogen found. 11.92% 11.83%
Percent nitrogen calculated from the formula C₂₃H₂₄N₂O₂S = 11.97%
Hydrolysis of 2-p-tolyl-2-ethyl-amino-4-thiazolidone

Ten grams of the above compound were heated with dilute HCl in a bomb tube at 130° - 140° for four hours. When cool, the tube was opened. There was a considerable pressure, due probably to the presence of CO₂ formed during the hydrolysis of the compound. The odor of ethyl mercaptan was very noticeable. The liquid in the tube was made alkaline with NaOH and extracted with ether, dried over solid KOH, the excess ether evaporated. The oil-like residue was then dissolved in dry benzene and one mol of phenyl isocyanate added. On cooling, a crystalline substance separated out.

This compound agreed in melting point and mixed melting point with the urea made by the interaction of ethyl p-toluidine and phenyl isocyanate.

The probable course of the reaction may be represented by the reaction below. The presence of this glycollic acid was shown by adding ferric chlorides to the residue from the ether extraction, when a purple color indicated the presence of this glycollic acid.

\[
\begin{align*}
\text{C}_2\text{H}_5\text{NH} + \text{C}_6\text{H}_5\text{CO} & \rightarrow \text{C}_2\text{H}_5\text{NH} + \text{C}_6\text{H}_5\text{COH} \\
\text{p-C}_7\text{H}_7 + \text{C}_6\text{H}_5\text{NH} & \rightarrow \text{p-C}_7\text{H}_7 + \text{C}_6\text{H}_5\text{NH}
\end{align*}
\]

The reaction of phenyl isocyanate and p-toluidine may be represented as taking place in the manner below to give the urea.

\[
\begin{align*}
\text{C}_2\text{H}_5\text{NH} + \text{C}_6\text{H}_5\text{CO} & \rightarrow \text{C}_2\text{H}_5\text{NH} + \text{C}_6\text{H}_5\text{COH} \\
p-\text{C}_7\text{H}_7 + \text{C}_6\text{H}_5\text{NH} & \rightarrow p-\text{C}_7\text{H}_7 + \text{C}_6\text{H}_5\text{NH}
\end{align*}
\]

M. P. = 67°
In order to further establish the proof of the constitution of this urea it was analyzed for the nitrogen content.

**Analysis of d ethyl d p-tolyl d phenyl urea**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>0.4646 gm</td>
<td>0.5375 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>32.2 cc</td>
<td>27.6 cc</td>
</tr>
</tbody>
</table>

One cc alkali = 0.838 cc acid

One cc acid = 0.00301 gm nitrogen

Percent nitrogen found: 10.90% 10.99%

Percent nitrogen calculated from the formula C₆H₁₈ON₂ = 11.02%

This proves rather conclusively that both the ethyl and the p-tolyl groups are attached to the same nitrogen. It would also show that the methylene group is between the carbonyl and sulphur groups, as that is the only configuration that would satisfactorily explain the formation of this glycollic acid on hydrolysis.

**2-p-tolyl-2-benzyl-amino-4-thiasolidone.**

In order to prepare the above compound, the sodium salt of 2-p tolyl thiasolidone was refluxed with the molecular quantity of benzyl chloride for several hours in absolute alcohol. At the end of this time the solution was distilled with steam to remove the excess benzyl chloride and the alcohol. The remaining oily residue was dissolved in alcohol from which it slowly crystallised in colorless rhombic crystals. It is interesting to note that these crystals are almost
This compound is very soluble in hot alcohol and only slightly soluble in cold alcohol. It is almost insoluble in either hot or cold water.

\[
\text{M. P. } = 121^\circ - 120^\circ \\
\text{Yield } = 50\%
\]

---

**Analysis of 2- p-toly-2-benzyl-amino-4-thiazolidone**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.4808 gm</td>
<td>.4334 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>35.3 cc</td>
<td>37.4 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .338 cc acid

One cc acid = .00201 gm nitrogen

Percent nitrogen found | 9.34% | 9.47%

Percent nitrogen calculated from the formula 617H160N2S-9.46%
Hydrolysis of 2-p-tolyl-2-benzyl-amino-4-thiazolidone

Ten grams of this compound were placed in a bomb tube together with seven cc dilute HCl and heated at 130°–140° for four hours. When cool, the tube was opened. There was considerable pressure, due probably to the presence of CO₂ formed during the hydrolysis of the compound. The odor of a mercaptide was very noticeable. The liquid in the tube was made alkaline with NaOH and extracted with ether, and dried over solid NaOH. The excess ether was evaporated and a light brown oil remained.

A portion of this was dissolved in dry benzene and the molecular quantity of phenyl isocyanate added. After standing for several hours white crystals separated out. These agreed in melting point and mixed melting point with the compound prepared by the interaction of phenyl isocyanate and benzyl p-toluidine.

The reaction for the hydrolysis is the same as the one for the hydrolysis of the ethyl compound, with the exception that the benzyl group is in place of the ethyl group.

\[
\begin{align*}
\text{C₆H₅CH₂NH + C₆H₅NCO} & \quad \rightarrow \quad \text{C₆H₅CH₂} & \quad \text{O} & \quad \text{C₆H₅} \\
\text{p-CH₃} & \quad \text{H} & \quad \text{p-CH₃} & \quad \text{H}
\end{align*}
\]

This urea is easily crystallized from hot alcohol, in which it is rather soluble. On cooling, the crystals of \( \alpha \) p-tolyl \( \alpha \) benzyl \( \beta \) phenyl urea separate from the solution.
Analysis of d benzyl d p-tolyl p phenyl urea

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>0.5742 gm</td>
<td>0.6338 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>32.6 cc</td>
<td>28.3 cc</td>
</tr>
</tbody>
</table>

One cc alkali = 0.833 cc acid

One cc acid = 0.002201 gm nitrogen

Percent nitrogen found     8.69% 7\% 8.46%
Percent nitrogen calculated from the formula C_{21}H_{20}O_{2} 8.54% 8\%

This compound thus evidently had both the benzyl and p-tolyl groups on the same nitrogen.

2-p-tolyl-3-p-nitro benzyl-amino-4-thiazolidone.

This compound was prepared by refluxing molecular quantities of p-nitro benzyl chloride and the sodium salt of 2 p-tolyl-4-thiazolidone in alcohol for several hours. Upon cooling, yellow needle shaped crystals of 2-p-tolyl nitro benzyl-amino thiazolidone separated out. This compound crystallizes from alcohol in light yellow crystals. It is almost insoluble in water.

M. P. = 142°
Yield = 50%
### Analysis of 2-p-tolyl-2-p-nitro benzyl-amino-4-thiazolidone

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.5438 gm</td>
<td>.5015 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>59 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>23.1 cc</td>
<td>28.3 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .336 cc acid
One cc acid = .003201 gm nitrogen

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent nitrogen found</td>
<td>13.40%</td>
<td>12.26%</td>
</tr>
<tr>
<td>Percent nitrogen calculated from the formula C₁₇H₁₆NO₃S</td>
<td>13.33%</td>
<td></td>
</tr>
</tbody>
</table>

### Hydrolysis of 2-p-tolyl-2-p-nitro benzyl-amino-4-thiazolidone

This compound was hydrolysed by heating it in a bomb tube with dilute HCl for four hours. When cool the tube was opened. There was considerable pressure; due to the CO₂ formed during the hydrolysis. The liquid was removed from the bomb tube and allowed to stand over night. A small quantity of yellow crystals separated from this solution. Since it was thought that these were crystals of p-nitro benzyl p-toluidine, some of this compound was made for comparison.

This was prepared by heating one mol p-nitro benzyl chloride and two mols p-toluidine for a half hour on a water bath. The mixture was made alkaline with NaOH and distilled with steam to remove the excess mol of p-toluidine. The residue in the flask was dissolved in alcohol, from which the crystals of nitro benzyl p-toluidine separate on cooling. This compound is rather soluble in hot alcohol and rather insoluble in cold alcohol. It is almost insoluble in water.
p-NO_2C₆H₄CH₂Cl + p-C₇H₇

\[
\text{H. P. } = 630 \text{ -- } 670 \\
\text{Yield } = 20\%
\]

The crystalline compound secured by the hydrolysis of 2-p-tolyl-nitro benzyl-amine thiazolidone agreed in melting point and mixed melting point with the one prepared from p-toluidine and p-nitro benzyl chloride.

This amine was also analyzed to determine the percent nitrogen in it.

**Analysis of p-nitro benzyl p-toluidine**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.4156 gm</td>
<td>.4604 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>32.7 cc</td>
<td>30.9 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .838 cc acid

One cc acid = .002201 gm nitrogen

Percent nitrogen found | 11.43% | 11.53%

Percent nitrogen calculated from the formula C₁₄H₁₄N₂O₂ 11.57%
Molecular quantities of 2-p-tolyl-2-ethyl-amino-4-thiazolidone and benzaldehyde were heated together at 200° - 230° for thirty minutes. As the liquid cooled, crystals of the benzaldehyde derivative separated out. This was recrystallized from hot alcohol. It is only slightly soluble in hot alcohol, and practically insoluble in cold alcohol. It crystallizes from alcohol in very light, colorless, leaf like crystals.

Benzaldehyde was found to condense with the methylene group of all the thiazolidones tested. The benzaldehyde condensation product was always found to have a higher melting point than the original thiazolidone.

It was also found that the benzaldehyde group serves to protect the ring during hydrolysis so that it remains intact after being boiled with dilute acid, or even after being heated in a sealed tube with dilute HCl for several hours at 140°.

The condensation may be represented as taking place in the manner formulated below:

\[
\begin{align*}
\text{p-CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{CO} + \text{CHCC}_6\text{H}_5 & \rightarrow \text{p-CH}_3\text{C}_6\text{H}_4\text{NCO} + \text{CHCC}_6\text{H}_5 \\
\text{C}_2\text{H}_5 & \rightarrow \text{CHCC}_6\text{H}_5
\end{align*}
\]

M. P. = 179°
Yield = 85%
Analysis of 2-p-tolyl-2-ethyl-amino-5-benzal-4-thiazolidone

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.4905 gm</td>
<td>.5310 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>36.4 cc</td>
<td>31.7 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .338 cc acid
One cc acid = .002301 gm nitrogen

Percent nitrogen found | 8.74% | 8.37%

Percent nitrogen calculated from the formula C_{19}H_{20}N_{2}S 8.65%

This compound was hydrolyzed by heating it in a sealed tube with dilute HCl at 130° - 140° for several hours. When cool, the tube was opened. There was considerably less pressure in this case than in the preceding ones, indicating that there had not been as much decomposition of the thiazolidone to give CO_{2}. Later tests showed this to be true. There was considerable quantity of rather heavy yellow crystals that had separated out in the tube. These were re-crystallized from hot alcohol, and later analyzed for nitrogen.

Analysis of hydrolysis product of 2-p-tolyl-2-ethylamino-5-benzal-4-thiazolidone

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.6210 gm</td>
<td>.6345 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>25 cc</td>
<td>25 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>7.2 cc</td>
<td>7.6 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .838 acid
One cc acid = .00231 gm nitrogen

Percent nitrogen found | 6.72% | 6.78%

Percent nitrogen calculated from the formula C_{10}H_{7}O_{2}S 6.32%
The only possible compound having this composition and derived from 2-p-tolyl-ethyl-amine-6-benzal thiazolidone is the following one:

\[
\begin{align*}
\text{H} & \quad \text{CO} \\
\text{O=C} & \quad \text{CHCC}_6\text{H}_5 \\
\text{S} &
\end{align*}
\]

M. P. = 242°

This also accounts for the ethyl p-toluidine which was found to have been split from the original thiazolidone during hydrolysis.

This compound is fairly soluble in hot alcohol and much less soluble in cold alcohol.

The liquid remaining from the solution in the bomb tube was made alkaline with NaOH and extracted with ether. When the ether was evaporated, ethyl p-toluidine remained as an oil. This was proved by adding phenyl isocyanate to the dry amine in dry benzene. After a short time crystals of \( \alpha \)-p-tolyl \( \alpha \)-ethyl \( \beta \)-phenyl urea separated from the solution. These were not analyzed as they had a melting point and mixed melting point with the urea prepared from ethyl p-toluidine and phenyl isocyanide.

It was also desired to prepare the \( 2 \)-4 di keto thiazolidones directly by the hydrolysis of the benzal derivative of the unsubstituted thiazolidone. The unsubstituted thiazolidone was prepared by refluxing one mol thio urea, one mol ethyl mono chlor acetic acid and two mols pyridine in alcohol solution. The pyridine combines with the HCl formed. The excess pyridine was distilled from the solution, and on cooling, the thiazolidone crystallizes in light yellow
needles. This is fairly soluble in hot alcohol, and much less soluble in cold alcohol.

\[
\begin{array}{c}
\text{\(\text{H}_2\text{N} - \text{CO}\text{NHCO}_2\text{H}_3\text{S}\)}
\end{array}
\]

Preparation of the bensal derivative of the unsubstituted thiazolidone

One mol of the unsubstituted thiazolidone and one mol benaldehyde were heated together at 230° - 350° for fifteen minutes. The melted solution in the tube became darker in color, and when cool became solid again. This compound was so slightly soluble in hot alcohol that after being boiled with alcohol for 20 minutes less than one gram dissolved in 500 cc alcohol. The remainder of the compound was not recrystallized but hydrolyzed. It is very probable, however, that most of the impurities were dissolved in the alcohol.

\[
\begin{array}{c}
\text{\(\text{H}_2\text{N} - \text{CO}\text{NHCO}_2\text{H}_3\text{S}\)}
\end{array}
\]

M. P. = decomposes at 250°

Yield = 85%
Hydrolysis of 5-benzal-4-thiazolidone

The above compound was hydrolyzed with dilute HCl in a bomb tube at 130°-140° for five hours. When cool the tube was opened. A small quantity of gas escaped, indicating that there had been a slight amount of decomposition. There remained in the tube a crystalline compound, together with the HCl solution. The crystals were removed and recrystallized from hot alcohol. This compound was fairly soluble in hot alcohol and much less soluble in cold alcohol.

The HCl solution was made alkaline with NaOH, when the odor of ammonia was very noticeable, the fumes also turned moist litmus paper blue, almost immediately.

From the fact that this compound had the same melting point—
as the compound prepared by the hydrolysis of 2-p-tolyl 2 ethyl 5 benzal thiazolidone, and the mixed melting point of the two compounds was the same as the melting point of either of the compounds, and as ammonia was split from the compound during hydrolysis, it was concluded that one and the same compound is the product of the hydrolysis of 5 benzal-4-thiazolidone and 2-p-tolyl-2-ethyl-5-benzal-4-thiazolidone. The reaction being considered as proceeding according to

\[
\text{H}_2\text{N} - \text{S} - \text{CHCOCH} \quad \text{H} \quad \text{H} - \text{SO} \quad + \text{NH}_3
\]

\[\text{H}_2\text{N} - \text{S} - \text{CHCOCH} \quad \text{H} \quad \text{H} - \text{SO} + \text{NH}_3\]

P. = 242°
Preparation of isomeric thiazolidones.

Having the two substituting groups on different nitrogen atoms.

\[ \alpha \text{p-tolyl } \beta \text{ ethyl thio urea.} \]

It was first necessary to prepare p-tolyl mustard oil. This was prepared according to Olander(7). A yield of about 80% was secured.

One mol of ethyl amine was slowly added to one mol of p-tolyl mustard oil in alcohol solution. The solution became warm due to the heat of reaction. The reaction proceeds to completion without any further warming, and as it cools, crystals of p-tolyl 3 ethyl thio urea separate from the solution in pure white flat crystals.

\[
p-\text{C}_7\text{H}_7 + \text{C}_2\text{H}_5\text{NH}_2 \rightarrow p-\text{C}_7\text{H}_7\text{SHC}_2\text{H}_5
\]

M. P. = 96° -- 97°

Yield = 85%
2-p-toly1-3-ethyl-4-thiazolidone

To prepare this thiazolidone one mol d p-toly1 β ethyl thiourea, one mol ethyl mono chlor acetate were refluxed in alcohol with one - two moles pyridine which acts as an acid remover. This solution was refluxed for several hours. The solution was distilled with steam to remove the pyridine and excess alcohol. The thiazolidone was left as a brown oil. This was extracted with ether, dried with solid KOH, and attempts were made to crystallize it from ether, alcohol, benzene and gasoline. But in all cases the solvent evaporated, leaving the thiazolidone as a brown oil. Probably this is an extremely supersaturated solution, but after several months no evidence of crystallization was visible. This oil was dried at 100° and an analysis made to determine if it were the thiazolidone and not a mixture of several impurities.

\[ \text{Analysis of 2-p-toly1-3-ethyl-4-thiazolidone} \]

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>0.4103 gm</td>
<td>0.3915 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>32.7 cc</td>
<td>34.1 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .833 cc acid
One cc acid = .002301 gm nitrogen

Percent nitrogen found 12.12% 12.04%

Percent nitrogen calculated from the formula C₂₅H₃₄O₂S 11.97%
Hydrolysis of 2-p-tolyl-3-ethyl-4-thiazolidone

This compound was refluxed for 20 hours with HCl in dilute alcohol. When cool, a small quantity of grey crystals separated out. These were separated from the solution and recrystallized from hot water, from which they crystallize as colorless crystals. This compound is rather soluble in hot water and almost insoluble in cold water.

The solution from the hydrolysis was made alkaline with NaOH and distilled with steam. An oil, which solidified when cool in water was found to distill from the solution with the steam. From the fact that this compound was a primary amine, and that its melting point agreed with the melting point of p-toluidine, and like p-toluidine it was volatile in steam, it was concluded that this compound was p-toluidine.

The white crystalline compound which crystallized from the original solution was analyzed to determine the nitrogen content.

Analysis of hydrolysis compound of 2-p-tolyl 3 ethyl-4-thiazolidone

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>(0.4347) gm</td>
<td>(0.5196) gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>37.1 cc</td>
<td>22.5 cc</td>
</tr>
</tbody>
</table>

One cc alkali = \(0.333\) cc acid

One cc acid = \(0.502201\) gm nitrogen

Percent nitrogen found | \(9.57\%\) | \(9.54\%\)
Percent nitrogen calculated from the formula \(0.5170\) | 9.83%
There is only one compound that may be derived from the hydrolysis of 2-p-tolyl 3 ethyl-4-thiazolidone that has the above constitution as determined from the nitrogen analysis.

\[ \text{C}_2\text{H}_5\text{N} - \text{SO} \]

\[ \text{O} - \text{S} - \text{CH}_2 \]

\[ \text{H. P.} = 140^\circ \]

This indicates that the ethyl group is more firmly bound to the ring than is the p-tolyl group or that the p-tolyl group is the one that is attached to the nitrogen outside the ring.

As this compound, like the thiazolidones having the two substituting groups on the same nitrogen, contains a methylene group, it was possible to prepare the benzaldehyde derivative of the thiazolidone having the two groups on different nitrogen atoms.

Preparation of the 2-p-tolyl 3 ethyl 5 benzal-4-thiazolidone

One mol of 2-p-tolyl-3-ethyl-4-thiazolidone and one mol benzaldehyde were heated to 200° — 230°, for 15 minutes. When cool the benzal derivative separated from the solution in yellow needles. It is rather soluble in hot alcohol from which it crystallizes in light yellow needles. Almost insoluble in cold alcohol.
Weigh a sample

C. C. acid used
C. C. alkali used

One cc alkali = 0.338 cc acid
One cc acid = 0.002201 gm nitrogen

Percent nitrogen found
Percent nitrogen calculated from the formula C<sub>19</sub>H<sub>18</sub>ON<sub>2</sub>S = 8.60%
8.74%
8.70%

It has thus been possible to prepare two solid isomeric thiazolidones having separate melting points and being two separate and distinct compounds but differing only in the position of the ethyl and p-tolyl groups.

These compounds behave differently on hydrolysis, 2-p-tolyl 3 ethyl 5 benzal-4-thiazolidone losing only the p-tolyl group while the 2-p-tolyl 2-ethyl 5 benzal thiazolidone loses both the p-tolyl and the ethyl groups. Both however, lose only the group or groups bound
to the nitrogen outside the ring.

**Hydrolysis of 2-p-tolyl 3 ethyl 5 benzol-4-thiosolidone**

This compound was hydrolysed by boiling with dilute HCl in alcohol for twenty hours. During the time of boiling the form of the crystals changed from an almost flat plate-like crystal to light yellow needles. At no time was the entire compound dissolved, but the shape of the crystals was observed to change, and when this change was complete the heating was discontinued. On cooling, more of the needle-like crystals separated from the solution. These were re-crystallised from hot alcohol.

When the remaining solution was made alkaline and distilled with steam, p-toluidine was found in the distillate.

**Analysis of the above hydrolysis product.**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.8387 gm</td>
<td>.7589 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>31.5 cc</td>
<td>35.1 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .838 cc acid

One cc acid = .002201 gm nitrogen

Percent nitrogen found               | 6.19%  | 6.10%
Percent nitrogen calculated from the formula | 6.01%  |
From the manner in which this compound was prepared from the hydrolysis of 2-p-tolyl 3 ethyl 5 benzo thiasolidone, and from the fact that the analysis agrees closely with the empirical formula given in the analysis the following constitution was assigned to this compound.

![Chemical Structure](attachment:image.png)

M.P. = 860° -- 870°

2-p-tolyl-4-thiasolidone

In order to study a few of the thiasolidones containing the o-tolyl group it was necessary to prepare the 2-o-tolyl-4-thiasolidone.

This compound was prepared by refluxing one mol o-tolyl thio urea, one mol mono chlor acetic acid, and two mols pyridin in alcohol solution. The pyridin combines with the acid formed. The mixture first becomes a cream colored past-like mass, but on continued heating it changed to a light brown clear solution. After heating this two hours longer, the excess alcohol and pyridin was distilled off on the water bath and the cooled solution was poured into cold water with constant stirring, a portion of the thiasolidone separated as a yellow tar, but this quickly became granular. After a few minutes a mass of almost colorless crystals separated from the main portion of the solution.
After filtering, the thiazolidone was washed with water until free from pyridin. A small portion was recrystallized from alcohol and the melting point determined.

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{C}_7\text{H}_5 & \quad \text{CH}_3 \\
\text{S} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{C}_7\text{H}_5 & \quad \text{CO} \\
\text{S} & \quad \text{OH}
\end{align*}
\]

\[+ \text{HCl}
\]

M. P. = 144°

Yield = 80%

The 2-o-tolyl-4-thiazolidone was prepared in another manner; by heating molecular quantities of mono chlor acet o-toluidine and KCl in alcohol.

**Mono chlor acet o-toluidine**

It was first necessary to prepare the mono chlor acet o-toluidine. One mol of o-toluidine was dissolved in dry benzene and two mols of pyridin added to remove the HCl which was formed during the reaction. To this solution was slowly added one mol mono chlor acetyl chloride. The solution became hot. When most of the mono chlor acetyl chloride had been added, the solution was allowed to stand for thirty minutes. The oily layer was separated from the benzene solution and slowly added to cold water with constant stirring. The oil immediately solidified.
to an almost white solid. This can very readily be recrystallized from dilute alcohol, but for the preparation of the thiazolidones the compound need not be purified. A portion was purified and the melting point determined.

\[ \text{C}_7\text{H}_7\text{NH}_2 + \text{CR}_2\text{C}_6\text{H}_5\text{COCl} \rightarrow \text{C}_7\text{H}_7\text{NH}_{\text{CO}}\text{C}_2\text{H}_5 + \text{HCl} \]

M. P. = 109°

2-o-tolyl-4-thiazolidone

To prepare this compound from mono chlor acet o-toluidine, one mol of mono chlor acet o-toluidine was refluxed with one mol KCNS in alcohol for several hours. During the heating the KCl which was formed could be seen to separate from the solution.

The solution was filtered from the crystals of KCl and distilled with steam to remove the alcohol. The thiazolidone remained as a brown oil which slowly solidified. This was recrystallized from alcohol and the melting point determined, and an analysis made.

M. P. = 144° - 145°
Analysis of 2-o-tolyl-4-thiiazolidone

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.3601 gm</td>
<td>.4849 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>37.45 cc</td>
<td>27.14 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .724 cc acid
One cc acid = .00311 gm nitrogen

Percent nitrogen found 13.41% 13.21%
Percent nitrogen calculated from the formula C\(_{10}\)H\(_4\)ON\(_2\)S 13.59%

Sodium salt of 2-o-tolyl-4-thiiazolidone

The main portion of this thiiazolidone was converted to the Na salt by heating it with the molecular quantity of NaOH. The solution became light brown, but as it cooled, almost colorless crystals of the sodium salt separated out. The sodium salt loses the water of crystallization when it is exposed to the air. From this salt, as from the sodium salt of 2-p-tolyl thiazolidone, the disubstituted thiiazolidones can be prepared.

\[ 
\text{M. P. } = 105^\circ 
\]
The sodium salt of 2-o-tolyl thiazolidone solidifies almost immediately after melting and again melts at 250° without any apparent decomposition.

It is very soluble in hot water, slightly soluble in cold water, and somewhat soluble in cold alcohol. It crystallizes from dilute solutions in needle shaped crystals.

\[ 2-o\text{-tolyl}-2\text{-benzyl-amino-4-thiazolidone} \]

One mol of the sodium salt of 2-o-tolyl-4-thiazolidine and one mol benzyl chloride were refluxed in absolute alcohol for four hours. During the time that this was being heated, crystals of NaCl were seen to separate from the solution. The light brown solution was decanted from the NaCl and distilled with steam to remove the alcohol and excess benzyl chloride. The 2-o-tolyl-2-benzyl-amino-4-thiazolidone remained as a dark brown oil, which after standing several months slowly solidified, from which the pure compound was secured after repeated recrystallizations. This compound very easily forms a supersaturated solution, making it more difficult to crystallize.

\[ \text{M. P.} = 95^\circ \]

\[ \text{Yield} = 40\% \]
Analysis of 2-o-tolyl-benzyl-amino-4-thiazolidone

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>0.4405 gm</td>
<td>0.4939 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>25 cc</td>
<td>25 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>6.90 cc</td>
<td>2.35 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .724 cc acid
One cc acid = .00211 gm nitrogen

Percent nitrogen found 9.58% 9.70%

Percent nitrogen calculated from the formula C_{17}H_{18}O_{2}S = 9.48%

HCl salt of 2-o-tolyl-2-benzyl-amino-4-thiazolidone

Some of the 2-o-tolyl-2-benzyl-amino-4-thiazolidone was dissolved in ether and carefully dried. Dry HCl was passed through the solution until no more crystals separated from the solution. These were filtered from the liquid, washed with a little ether and dried as quickly as possible, as the HCl salt decomposes when exposed to the air. As this compound decomposes when warmed it was impossible to further purify it by recrystallization. As it appeared rather pure it was later analyzed by titrating with NaOH to determine the amount of HCl united with the compound.

H. P. = 179.5°

Yield = 90%
Analysis of HCl salt of 2- tollyl-benzy1-amino thiasolidone.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.5409 gm</td>
<td>.5082 gm</td>
</tr>
<tr>
<td>C. G. acid used</td>
<td>14.9 cc</td>
<td>16.74 cc</td>
</tr>
<tr>
<td>C. G. alkali used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .724 cc acid
One cc acid = .00211 gm nitrogen

Percent HCl found  
Percent HCl calculated from the formula C_{17}H_{17}N_{2}O_{5}Cl = 8.43%  

2- tolyl-2-ethyl-amino-4-thiasolidone

This was prepared by refluxing one mol of the sodium salt of 2- tolyl thiasolidone with one mol ethyl iodide in absolute alcohol for several hours. In order to reduce the loss of ethyl iodide to a minimum, ice water was circulated through the condenser. A good yield of a light brown oil was secured. This was dissolved in alcohol, benzene and ether, but in all cases the solvent evaporated, leaving the oil as before. Finally a small sample crystallized, and this was further purified by recrystallization from alcohol. Attempts were made to use these as "seed" crystals to crystallize the other portion of the same preparation, but this was not successful. Enough of the crystals were not obtained for an analysis, but the melting point was determined, and an analysis was made of the HCl salt of this thiasolidone.

\[ \text{H. P.} = 98^\circ \]
\[ \text{Yield} = 85\% \text{ (on the basis of the oil secured)} \]
Hydrolysis of 2-o-tolyl-2-benzy1-amino-4-thiasolidone.

Ten grams of the above compound were hydrolyzed with dilute HCl in a bomb tube at 130° - 140° for several hours. When the tube was opened there was considerable pressure due to the formation of CO₂ from the hydrolysis of the thiasolidone. There was also a very noticeable odor of mercaptan.

The solution in the bomb tube was made alkaline with NaOH and extracted with ether, dried and the ether evaporated, leaving a dark oil which did not crystallize. A portion of this was treated with phenyl isocyanate to give the urea. The treatment of this oil gives urea which is identical in melting point and mixed melting point with the one prepared by the interaction of benzyl o-toluidine and phenyl isocyanate.

The mechanism of hydrolysis is the same as the hydrolysis of the p-tolyl di substituted thiasolidones.

\[
\text{C}_6\text{H}_5\text{CH}_3 + \text{C}_6\text{H}_5\text{HCO} \rightarrow \text{C}_6\text{H}_5\text{CH}_3\text{N} = \text{C}_6\text{H}_5\text{CH}_3
\]

Melting point = 111°

Analysis of o-tolyl benzyl phenyl urea

<table>
<thead>
<tr>
<th>Weight of sample used</th>
<th>.4683 gm</th>
<th>.4390 gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. C. acid used</td>
<td>25 cc</td>
<td>25 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>8.25 cc</td>
<td>10.25 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .724 cc acid

One cc acid = .00311 gm nitrogen

Percent nitrogen calculated from the formula C₆H₅.H₂O = 8.51%
Percent nitrogen found = 8.68% 8.73%
HCL salt of 2-o-tolyl-2-ethyl-amino-4-thiazolidone

Some of the thiazolidone in the form of the oil was dissolved in dry ether and dry HCl was passed thru the solution until no more of the HCl salt was precipitated. The crystals were separated from the solution, washed with ether and dried as quickly as possible, as the HCl salt decomposes when exposed to the air. This compound crystallizes in almost colorless crystals.

This was analyzed by titrating with standard alkali.

\[
\text{M. F.} = 165^\circ - 168^\circ
\]
\[
\text{Yield} = 90\%
\]

Analysis of HCl salt of 2-o-tolyl-2-ethyl-amino-4-thiazolidone

<table>
<thead>
<tr>
<th>Weight of sample used</th>
<th>.5503 gm</th>
<th>.5050 gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. C. acid used</td>
<td>9.86 cc</td>
<td>11.75 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .724 cc acid
One cc alkali = .001527 gm nitrogen

Percent HCl found

<table>
<thead>
<tr>
<th>Percent HCl found</th>
<th>10.09%</th>
<th>10.21%</th>
</tr>
</thead>
</table>

Percent HCl calculated from the formula C_{12}H_{15}NSO_{2}Cl --- 10.35%
Hydrolysis of 2-α-tolyl-2-ethyl-αmino-4-thiasolidone

A portion of the oil like product which did not crystallize was hydrolyzed with dilute HCl in a sealed tube at 130°--140° for several hours. When the tube was opened there was a considerable pressure and the odor of mercaptan. The solution was made alkaline with NaOH and extracted with ether, dried over solid I0H. When the ether evaporated there was an oil left. This was treated with phenyl isocyanate in benzene. After a few minutes crystals separated from the solution. These agreed in melting point and mixed melting point with the urea prepared from ethyl α-toluidine and phenyl isocyanate.

\[
\begin{align*}
\text{o-C}_7\text{H}_5\text{NH} & + \text{C}_6\text{H}_5\text{NCO} \rightarrow \text{o-C}_7\text{H}_5\text{N} & \text{H} & \text{C}_2\text{H}_5 & \text{C}_6\text{H}_5
\end{align*}
\]

Melting point = 89°

Analysis of α-tolyl-ethyl phenyl urea.

<table>
<thead>
<tr>
<th>Weight of sample used</th>
<th>.6488 gm</th>
<th>.5419 gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>21.5 cc</td>
<td>23.73 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .724 cc acid

One cc acid = .00311 gm nitrogen

Percent nitrogen found: 11.30% 11.37%

Percent nitrogen calculated from the formula C₁₆H₁₈N₂O = 11.20%
2-o-tolyl-2-methyl-amino-4-thiazolidone

This compound was prepared by heating molecular quantities of the sodium salt of 2-o-tolyl-4-thiazolidone and methyl iodide dissolved in methyl alcohol in a sealed tube at 100° for several hours. The dark brown solution was distilled with steam to remove the excess methyl iodide and alcohol. Dissolved in alcohol from which on long standing a small quantity of yellowish crystals separated. On purification they became almost colorless.

![Chemical Structure]

M. P. = 107°

Yield of crystals was very small but if the oil which remained from the crystallization and which was hydrolyzed is considered, the yield was about 50%.

**Analysis of 2-o-tolyl-2-methyl-amino-4-thiazolidone**

Weight of sample used

<table>
<thead>
<tr>
<th></th>
<th>.5601 gm</th>
<th>.5337 gm</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>21.35 cc</td>
<td>24.53 cc</td>
</tr>
</tbody>
</table>

One cc alkali = .724 cc acid

One cc acid = .00311 gm nitrogen

Percent nitrogen calculated from the formula C\(_{11}\)H\(_{12}\)N\(_2\)S\(_2\) = 12.24%

Percent nitrogen found

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13.01%</td>
</tr>
<tr>
<td></td>
<td>13.75%</td>
</tr>
</tbody>
</table>
Hydrolysis of 2-o-tolyl-2-methyl-amino-4-thiazolidone

The oil which failed to crystallize was placed in a bomb tube and heated to 130° - 140° for several hours with dilute HCl. When the tube was opened there was considerable pressure and the odor of mercaptan was very noticeable. The solution was made alkaline with NaOH extracted with ether. The ether solution was dried with solid KOH. When the ether evaporated an oil remained. This was treated with phenyl isocyanate in benzene solution. Colorless crystals almost immediately began to separate from the solution. These agreed in melting point and mixed melting point with the urea prepared from methyl o-toluidine and phenyl isocyanate.

\[
\begin{align*}
\text{o-C}_7\text{H}_5\text{H} + \text{C}_6\text{H}_5\text{CO} & \rightarrow \text{o-C}_7\text{H}_5\text{H} \text{N} \equiv \text{C}_6\text{H}_5 \\
\text{CH}_3 & \text{NH} & \text{CH}_3 & \text{O} & \text{C}_6\text{H}_5
\end{align*}
\]

\[
\text{M. P.} = 82°
\]

\[
\text{Yield} = 85\%
\]

Analysis of \( \alpha \) o-tolyl \( \alpha \) methyl \( \beta \) phenyl urea.

<table>
<thead>
<tr>
<th>Weight of sample used</th>
<th>0.5460 g</th>
<th>0.4301 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>27.5 cc</td>
<td>35.85 cc</td>
</tr>
</tbody>
</table>

One cc alkali = 0.724 cc acid

One cc acid = 0.00211 gm nitrogen

Percent nitrogen found

| 11.63% | 11.80% |

Percent nitrogen calculated from the formula \( \text{C}_{15}\text{H}_{16}\text{O}_2\text{N} = 11.67\% \).
Preparation of thiasolidones containing the p-anisidin group

In order to prepare the 2-p-anisidin thiasolidone it was necessary to prepare mono chlor acetyl p-anisidin.

This was prepared by adding the molecular quantity of mono chlor acetyl chloride to p-anisidin dissolved in benzene to which one to two mols pyridin was added to remove the HCl which was freed during the reaction. The mixture was allowed to stand over night, and the excess benzene decanted from the oil like layer on the bottom of the beaker. The oil was poured into water when it solidified to a slightly yellow solid. The excess benzene was distilled from the solution and the residue poured into water and another portion of yellow solid secured.

A portion of the mono chlor acetyl p-anisidin was recrystallized from dilute alcohol from which it crystallizes in almost colorless plate like crystals.

\[
\text{C}_8\text{H}_8\text{O}_2\text{H} + \text{C}_8\text{H}_8\text{O}_2\text{Cl} \rightarrow \text{C}_8\text{H}_8\text{O}_2\text{H}_2\text{NCOCH}_2\text{Cl} + \text{HCl}
\]

M. P. = 123°

Yield = 80%

2-p-anisidin-4-thiasolidone

In order to prepare this thiasolidone one mol mono chlor acetyl chloride and one mol KCNS were refluxed in alcohol solution for several hours. When cold, the solution was poured into water, when the thiasolidone separated out as a dirty brown appearing solid product. A portion of this was recrystallized for analysis and the melting point determinations.
Analysis of 2-p-anisidin-4-thiazolidone

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>4.962 gm</td>
<td>4.591 gm</td>
</tr>
<tr>
<td>C. C. Acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>14.75 cc</td>
<td>20.25 cc</td>
</tr>
<tr>
<td>One cc alkali</td>
<td>= 0.752 cc acid</td>
<td></td>
</tr>
<tr>
<td>One cc acid</td>
<td>= 0.0023 gm nitrogen</td>
<td></td>
</tr>
<tr>
<td>Percent nitrogen found</td>
<td>16.03 %</td>
<td>17.42 %</td>
</tr>
</tbody>
</table>
| Percent nitrogen calculated from the formula C$_6$H$_{11}$N$_2$O$_2$S = 17.72 %

Sodium salt of 2-p-anisidin-4-thiazolidone

Molecular quantities of 2-p-anisidin-4-thiazolidone and 10% NaOH were heated until all the thiazolidones had dissolved to form a dark brown solution. On cooling, light brown crystals of the Na salt separated out. These were washed with a small quantity of water and alcohol, dried and used in the preparation of the disubstituted thiazolidones.

H. P. = 101°

Yield almost theoretical
Although this compound melted at 101° it solidified almost immediately and melted again at 145°. There was no visible evidence of decomposition. This is evidently the melting point of the anhydrous salt.

2-p-anisidin-2-ethyl-amine-4-thiazolidone

One mol of the sodium salt of 2-p-anisidin-4-thiazolidone and one mol ethyl iodide were refluxed in absolute alcohol for several hours. The product was distilled with steam to remove the excess ethyl iodide and alcohol. The oil like residum was dissolved in alcohol from which yellow rhombic crystals slowly separated.

\[
\text{CH}_3\text{COCH}_2\text{H}_2\text{N}\text{Si}\text{CH}_2\text{CH}_3\text{SO}\text{CH}_3
\]

M. P. = 184°
Yield = 25%

Analysis of 2-p-anisidin-2-ethyl-amine-4-thiazolidone

<table>
<thead>
<tr>
<th>Weight of sample used</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4916 gm.</td>
<td></td>
<td>0.4365 gm.</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>22.65 cc</td>
<td>27.35 cc</td>
</tr>
</tbody>
</table>

One cc alkali = 0.752 cc acid
One cc acid = 0.0023 gm. nitrogen

Percent nitrogen found 15.44 % 15.51 %

Percent nitrogen calculated from the formula \( \text{C}_12\text{H}_{16}\text{O}_2\text{N}_3\text{S} \) = 15.79 %
Molecular quantities of the Na salt of 2-panisidin-4-thiazolidone and benzyl chloride were refluxed for several hours in absolute alcohol. The product was distilled with steam to remove the excess benzyl chloride and alcohol. The oil which remained was dissolved in alcohol, and when the alcohol had evaporated, the oil which remained slowly solidified. This was redissolved in benzene from which the thiazolidone separated as small colorless crystals.

![Chemical structure of 2-panisidin-2-benzyl-amino-4-thiazolidone](attachment:image)

M. P. = 165° -- 167°
Yield = 35%

**Analysis of 2-panisidin-2-benzyl-amino-4-thiazolidone**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of sample used</td>
<td>.5586 gm</td>
<td>.4610 gm</td>
</tr>
<tr>
<td>C. C. acid used</td>
<td>50 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>C. C. alkali used</td>
<td>23.15 cc</td>
<td>31.25 cc</td>
</tr>
</tbody>
</table>

One cc alkali = 752 cc acid
One cc acid = .9923 gm nitrogen

Percent nitrogen found 13.41 %
Percent nitrogen calculated from the formula C₁₇H₁₆O₂N₃S = 12.80 %
It was not possible to prove the constitution of any of the thiazolidones derived from 2-p-anisidin-4-thiazolidone. On hydrolysis these compounds always yielded a small quantity of p-anisidin, which was the only product isolated.

It was also impossible to prepare any derivatives of p-anisidin, such as ethyl or benzyl p-anisidin. The preparation of these derivatives was tried in several ways. When ethyl iodide or benzyl chloride was refluxed with p-anisidin no reaction seemed to take place. Neither was there any reaction when either of these were heated with p-anisidin in a sealed tube at 120°.

Several attempts were made to prepare ethyl p-anisidin by treating the sodium salt of the formic acid derivative of p-anisidin when on hydrolysis the ethyl p-anisidin would be expected to be present in the solution. In all cases only p-anisidin was isolated.

The formulas assigned to these thiazolidones are analogous to the formulas for the other mono and di substituted thiazolidones prepared in the same manner.