

THE SYNTHESSES AND REACTIONS OF SOME ISO-THIO-HYDANTOINS.

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By

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October 1st., 1917

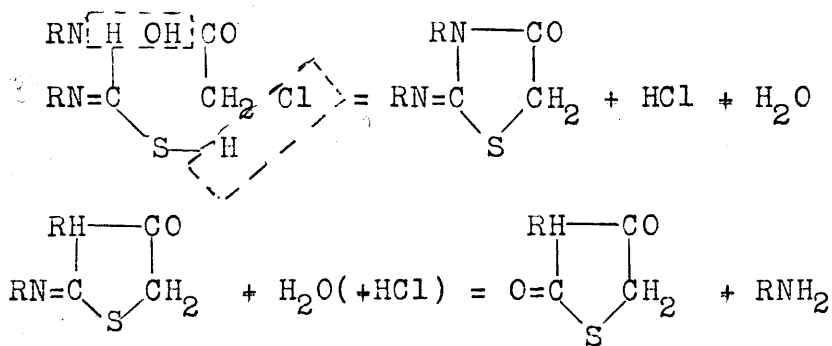
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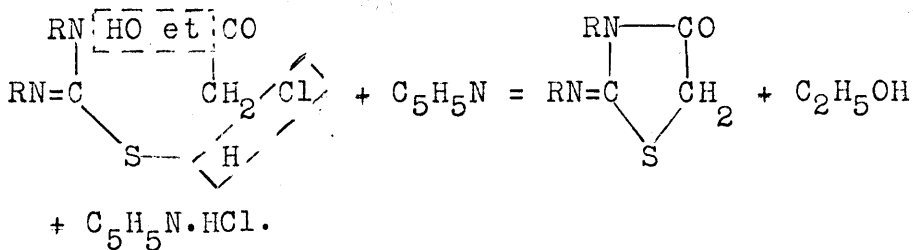
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The general method<sup>(1)</sup> for the preparation of the iso-thio-hydantoins is the warming of molar quantities of chloroacetic acid and aryl thio urea in alcoholic solution. But with this method it was found difficult to prevent the hydrolysis of part of the product, with the formation of a glycollide, due to the presence of free hydrochloric acid.



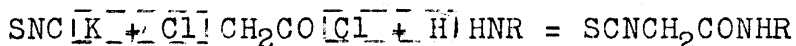
To avoid this last reaction a mole of pyridine was added and the ethyl ester of chloroacetic acid used instead of chloroacetic acid.



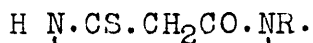
(1) Jr. Am. Chem. Soc. 25, 369(1903).  
 Jr. Am. Chem. Soc. 38, Sept., 1916

With the di-tolyl-thio ureas this reaction gave good yields without the formation of any glycollides. When isothiohydantoin containing halogens were prepared it was found difficult or impossible to obtain pure products unless the latter method was used.

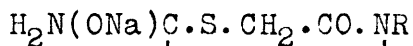
The iso-thio-hydantoin have also been prepared<sup>(1)</sup> by treating potassium thiocyanate with the acid chloride of chloroacetic acid and an amine,



an iso-thio-cyanoacetyl compound being formed which by intramolecular change goes to the normal thio-cyanoacetyl compound,  $\text{NCSCH}_2\text{CONHR}$ . On heating the latter with water or acetic acid, a thio-hydantoin is obtained,



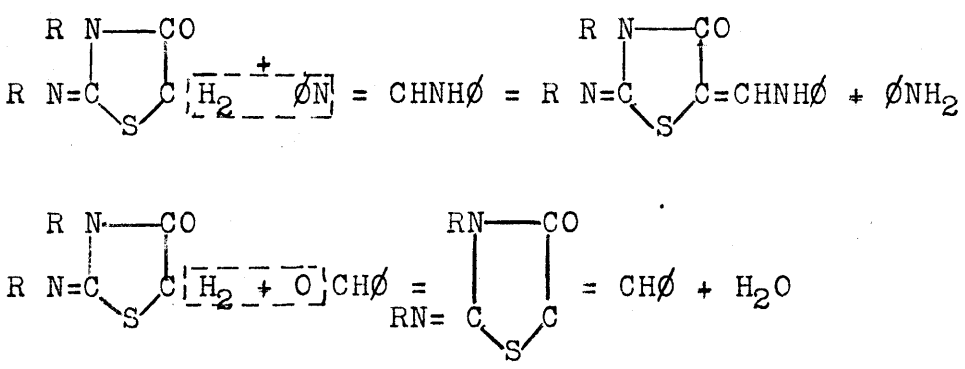
This, with strong sodium hydroxide, gives the pseudo form



It has been found the simpler iso-thio-hydantoin condense with formamidines<sup>(2)</sup> and benzaldehyde. They also yield diketo products on hydrolysis as shown before.

(1) H. Beckurts and G. Frericks. Arch. Pharm. (253) - 233 - 65 (1915).

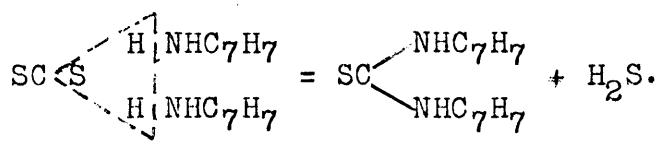
(2) Jr. Am. Chem. Soc. 38, Sept., 1916



But, while condensation with benzaldehyde was easily obtained in this investigation in all cases, it was found impossible to obtain condensation with di-phenyl formamidine in many instances, especially with the tolyl and halogen substituted iso-thio-hydantoins.

p- and m- TOLYL ISO-THIOHYDANTOINS.

Di-m-tolyl-thio urea was prepared by heating under the reflux condenser for eight to twelve hours two moles of m-toluidine and one mole of carbon disulfide in alcoholic solution. A small amount of sulfur was also added to the flask.



Di-p-tolyl-thio urea was prepared in a similar manner.

To make the iso-thio-hydantoins, 75 grams di-m-tolyl-thio urea, 30 grams chloracetic acid and 200 Cc. of alcohol were heated under a reflux condenser for several hours. Two products were obtained - white needles melting

at 90°, and yellow prisms melting at 154° - 155°, both being recrystallized from alcohol.

Some m-toluidine hydrochloride was also obtained by the partial evaporation of the mother liquor.

The first product was suspected to be 3-m-tolyl-2.4 diketo-tetra hydro thiazol. The nitrogen analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub>
I	.2037	25.5	14.75	7.31 %
II	.2525	25.45	13.65	6.95

1 Cc. HCl = .00221 gram N<sub>2</sub>

1 Cc. NaOH = 1.05 Cc. HCl.

Calculated N<sub>2</sub> = 6.75 %

Blank = .8 Cc. HCl.

The other product gave analyses corresponding to the calculated nitrogen percentage of di-m-tolyl iso-thio-hydantoin:

Number	Weight	HCl	NaOH	N <sub>2</sub>
I	.2251	25.4	12.4 Cc.	9.13 %
II	.3116	25.3	9.20	9.54

1 Cc. HCl. = .00221 gram N<sub>2</sub>

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .8 Cc. HCl.

Calculated Nitrogen = 9.45 %

The two products were separated by fractional crystallization. Only a small yield of di-m-tolyl iso-thio-hydantoin was obtained, the hydrolyzed product being in excess of the other.

The diketo product has been obtained by Beckurstand Frericks<sup>(1)</sup> and others who give the melting point as 90° - 91°.

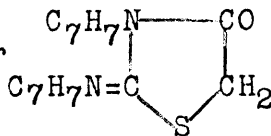
The same method was used to obtain di-p-tolyl isothio-hydantoin, 125 grams of the thio urea, 50 grams of chloroacetic acid and 300 Cc. of alcohol being used. As before, two products were obtained. One, white needles which melted at 162° when recrystallized from hot water, and one, pale yellow flat prisms, which melted at 126.5° - 7° when purified from alcohol. The yield of the unhydrolysed product was again very small. The two substances were separated by fractional crystallization.

The analyses were :

Number	Weight	HCl	NaOH	N <sub>2</sub>
I	.2658 grs.	40.4 Cc.	21.2 Cc.	9.4 %
II	.4716 grs.	40.1 Cc.	7.05 Cc.	9.4 %

HCl and NaOH solutions =  $\frac{1}{10}$  N.

Calculated N<sub>2</sub> = 9.45 % for



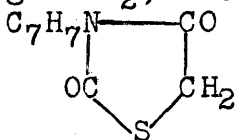
*C<sub>17</sub>H<sub>16</sub>O<sub>2</sub>N<sub>2</sub>S*

(1) Arch. Pharm. (253)-233-65 (1915)

Number	Weight	HCl	NaOH	N <sub>2</sub>
I	.2371	25 Cc.	16.75 Cc.	6.90
II	.2398	25 Cc.	16.9 Cc.	6.68

1 Cc. HCl = .00221 grs. N<sub>2</sub>, 1 Cc. NaOH = 1.05 Cc. HCl.

Calculated N<sub>2</sub> for



= 6.75 %

*C<sub>10</sub>H<sub>9</sub>O<sub>2</sub>N<sub>2</sub>S*

Crystals of p-toluidine were obtained from the mother liquor after it was made basic and concentrated.

It was found that the p-tolyl-iso-thiohydantoin is much more soluble in alcohol than the corresponding meta product, though the contrary might be expected.

The yields obtained by the foregoing method being very unsatisfactory, it was thought best to prevent hydrolysis of the iso-thio-hydantoin by using an alcoholic solution made basic by a mole of pyridine. The ethyl ester of chloracetic acid was used instead of chloracetic acid also.

The quantities used were 25 grams di-p-tolyl thio urea, 15 grams ethyl ester of chloracetic acid, 10 grams of pyridine and 60 Cc. of alcohol. The mixture was heated under a reflux condenser until the solid thio urea disappeared - about one-half to one hour. When the flask was cooled and allowed to stand a mass of light yellow needles separated out. These, purified from



alcohol, melted at  $126^{\circ}$ , which corresponds to the melting point of di-p-tolyl-iso-thio-hydantoin. The yield was 76 per cent. No diketo product was obtained.

Likewise, di-m-tolyl-iso-thio-hydantoin was prepared, a 71 per cent yield being secured and hydrolysis prevented as before.

It has been found<sup>(1)</sup> that di-o-tolyl-iso-thio-hydantoin condenses with di-phenyl-formamidine. In the course of this investigation mono- and di-phenyl iso-thio-hydantoins were prepared and condensation easily obtained with di-phenyl formamidine.

It was expected, therefore, that the same reaction might be obtained with the other two di-tolyl products. Fourteen grams of di-m-tolyl-iso-thio-hydantoin and 9.7 grams of di-phenyl-formamidine were heated together for several hours on an oil bath in a large test-tube. A temperature of  $140^{\circ}$  -  $150^{\circ}$  was maintained. A viscous dark brown substance was obtained which slowly solidified on cooling. It was very soluble in alcohol, benzene, and acetic acid. It was also fairly soluble in gasoline.

It was dissolved in alcohol and precipitated with very dilute hydrochloric acid as a bright yellow

(1) Jr. Am. Chem. Soc., Sept., 1916

amorphous powder. This softened at about  $90^{\circ}$  and was melted at  $105^{\circ}$ . Pure crystals could not be obtained.

This reaction was attempted several times at temperatures varying from  $120^{\circ}$  to  $180^{\circ}$ - $190^{\circ}$ . The periods of heating were varied from thirty minutes to eight to nine hours. Kerosene and Xylene were also tried as solvents in the hope that they might promote the reaction.

Similar negative results were obtained with di-p-tolyl-iso-thio-hydantoin and di-phenylformamide.

Three-methyl-2.4 diketo-tetra-hydrothiazole was heated with molar quantities of di-phenylformamide but this also failed to give a pure crystalline product. A gummy mass was obtained which could not be purified.

In the case of isoxayolons<sup>(1)</sup> it has been found that reaction between the methylene group and di-phenyl formamide is most conveniently obtained by first preparing the benzaldehyde derivatives of the isoxayolon and then treating this with di-phenylformamide.

To see if a similar reaction could be obtained with the iso-thio-hydantoins, di-phenyl-iso-thio-hydantoin was heated with a molar quantity of benzaldehyde and the product thus obtained was heated with di-

(1) Jr. Am. Chem. Soc., August, 1913.

phenylformamidine. No reaction, however, could be obtained and this method was not experimented with further.

To discover if any 2-m-tolyl-imido-3<sup>m</sup>-tolyl-4 keto - 5 anilido-methylene tetra hydrothiazole were formed in the reaction described above, 5 grams of the yellow powder were boiled under the reflux condenser in a solution of 50 Cc of alcohol and 10 Cc of hydrochloric acid for six to eight hours. A portion of the liquid gave a faint test for aniline at the end of the heating period. Twenty Cc. more of hydrochloric acid were then added and boiling continued for four hours longer. A small quantity of white needles separated out from the solution when it was let stand over night. The product, recrystallized from alcohol, melted at 90° which corresponds to the melting point of 3-m-tolyl-2, 4 diketo-tetrahydrothiazole.

Next hydrolysis with alcoholic potash was tried. A portion of the yellow powder was boiled with a strong solution of potassium hydroxide in alcohol for several hours. When the solution was cooled long colorless needles separated out. On recrystallization from alcohol the product melted at 208° - 211°. About 1.2 grams of the purified product were obtained. This gave a nitrogen content corresponding to that of 3-m-tolyl-2,4 diketo-5 anilido methylenetetrahydro-thiazole.

The analyses were:

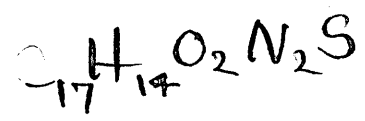
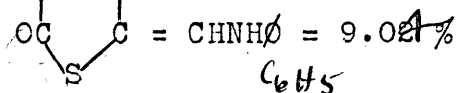
Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.3471 gms.	10 Cc.	4.45 Cc.	9.28 %
II	.5311 gms.	18.5 Cc.	10.27 Cc.	8.88

1 Cc. acid = .00625 grams N<sub>2</sub>

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl.

Calculated N<sub>2</sub> for C<sub>7</sub>H<sub>7</sub>N—CO



Some of the di-p-tolyl-iso-thio-hydantoin di-phenylformamidine product, which was also obtained in the form of a powder of indefinite melting point, was heated with alcoholic potash. In this case no evidence of condensation and the resulting hydrolysed product was found. Instead, colorless needle-like crystals were obtained which when purified melted at 262.5°. The nitrogen content corresponded to that of di<sup>p</sup>-tolyl urea.

Richter gives 256° (263° - 245°) as the melting point of this compound.

The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.3022 gms.	10 Cc.	4.03	11.58
II	.2895 gms.	10 Cc.	4.20	11.70

$$1 \text{ Cc. HCl} = .00625 \text{ N}_2$$

$$1 \text{ Cc. NaOH} = 1.05 \text{ Cc. HCl.}$$

$$\text{Blank} = .17 \text{ Cc. HCl.}$$

$$\text{Calculated N}_2 \text{ for } \text{CO} \begin{array}{l} \text{NHC}_7\text{H}_7 \\ \text{NH}_7\text{H}_7 \end{array} = 11.66 \%$$

The material was purified by first washing with alcohol and draining and then with water and then with boiling alcohol. It was finally recrystallized from hot alcohol. Less than one gram of recrystallized product was obtained.

In both cases when hydrolysis with alcoholic potash was attempted there was obtained a thick gummy substance which seemed to be very slightly soluble, if soluble at all, in alcohol, but readily soluble in water. These were probably potassium compounds.

It was thought that possibly a substituted formamide might give products with the di-tolyl-iso-thiohydantoin which could be isolated and purified.

Three grams of di-m-tolyl-iso-thio-hydantoin and 3.6 grams of di-p-brom-di-phenyl-formamidine were heated together in a large test-tube at 140° for several hours. The temperature rose to 180° for a few minutes.

The resulting gummy substance was dissolved in hot alcohol and a yellow powder precipitated by the addition of very dilute hydrochloric acid. This melted at about 200°.

When this yellow amorphous powder was treated with boiling gasoline a small amount of fine yellow needles remained undissolved. These crystals were washed several times with hot gasoline and then with hot benzene. When so purified they did not melt at 255°.

The above preparation was repeated, molar quantities of the reacting substances being heated at 125° for about one hour and a half. The product obtained was dissolved in hot alcohol and precipitated with dilute hydrochloric acid. It was then dried on porous plate. After rewashing with gasoline and again drying, it melted at 275° - 280°.

Attempts were made to recrystallize the compound from ordinary solvents but without success.

The yields were very small.

The analysis was:

Number	Weight	HCl	NaOH	N <sub>2</sub>
I	.2721	25.4 Cc.	13.00 Cc.	7.25 %

1 Cc. HCl = .0021 grams N<sub>2</sub>

1 Cc. NaOH = 1.2 Cc. HCl

Blank = .4 Cc. HCl

To try further the possibility of condensation between a substituted di-phenyl-formamidine and an isothio-hydantoin, 5.6 grams of di-~~4~~-cummidyl formamidine and 5.4 grams of a substance supposed to be di-phenyl-isothio-hydantoin were heated together in a test-tube on the oil bath for several hours at about  $140^{\circ}$  -  $150^{\circ}$ . Decomposition seemed to have taken place and no crystalline product was isolated.

The same reaction was again attempted at  $120^{\circ}$  -  $130^{\circ}$ , the heating period being limited to one and one-half hours. The dark gummy substance formed was dissolved in hot alcohol and precipitated with dilute hydrochloric acid.

When a portion of the mother liquor was made alkaline with sodium hydroxide a white precipitate formed. This was very soluble in acid solution and was probably  $\Psi$  cumedine.

It was found that after treatment with boiling benzol the product, precipitated with dilute acid, yielded a small amount of white, insoluble, crystalline substance.

The reaction was repeated twice with larger quantities of reacting compounds. The temperature was about  $125^{\circ}$  -  $130^{\circ}$  and the time of heating was limited to ten minutes in one case and thirty minutes in the other.

Each time there was obtained a small amount of a colorless crystalline compound insoluble in benzene. After repeated washing with hot benzene and drying on porous plate the crystals melted at 207°.

(It was discovered afterward that the supposed di-phenyl-iso-thiohydantoin was mono-phenyl thio urea).

The unknown compound gave a positive test for sulphur by the sodium-nitro-prusside method, but no dark coloration when heated with alkaline lead nitrate. These tests indicate a closed ring compound with the sulfur in the ring.

The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.2407 gms.	25.45 Cc.	9.95 Cc.	11.4
II	.3091 gms.	25.25 Cc.	6.30 Cc.	11.4

1 Cc. HCl = .0021 grams N<sub>2</sub>

1 Cc. NaOH = 1.20 Cc. HCl.

Blank = .4 Cc. HCl.

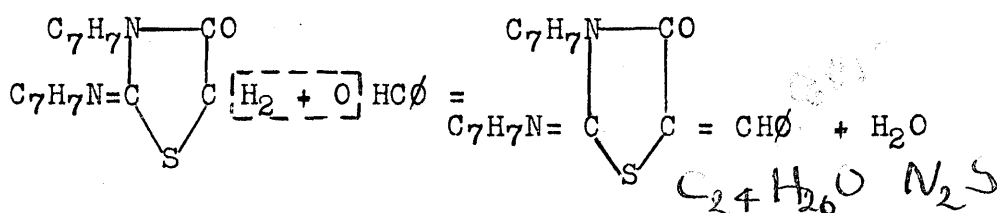
To further test this kind of a reaction molar quantities of di-p-tolyl-thio-urea and di-phenyl formamide were heated together for several hours at 150°. No crystalline product was obtained and the reaction was not tried further.



The attempt to condense the di-tolyl-iso-thio-hydantoins with di-phenyl formamidine having failed, condensation with benzaldehyde was next tried with ready success.

Ten grams of di-m-tolyl-iso-thio-hydantoin and 5 grams of benzaldehyde were heated together at about 150° for five hours. A product was obtained which was almost insoluble in alcohol. The yield, 10.7 grams, was 83 per cent of the theoretical.

The reaction was:



3-m-tolyl-2-m-tolyl imido-4 keto- 5- benzal tetra-hydro-thiazole.

The compound was dissolved in a small amount of hot chloroform and precipitated by the cautious addition of alcohol. Pale yellow, microscopic needles were formed which melted at 175° - 177°.

The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub>
I	.6981	10 Cc.	1.8 Cc.	7.11
II	.6515	10 Cc.	2.25 Cc.	7.16

1 Cc. HCl = .00625 grams N<sub>2</sub>

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl.

Calculated N<sub>2</sub> for  $\begin{array}{c} \text{C}_7\text{H}_7\text{N} \\ | \\ \text{C}_7\text{H}_7\text{N}=\text{C} \\ | \\ \text{S} \end{array} \begin{array}{c} \text{CO} \\ | \\ \text{C} \\ | \\ \text{C} \\ | \\ \text{CH}\emptyset \end{array} = 7.29 \%$

### HALOGEN ISO-THIO-HYDANTOINS.

The results with the <sup>m & p</sup> tolyl iso-thio-hydantoin being far from satisfactory, it was thought best to try new types of substituted iso-thio-hydantoin. Those next investigated contained chlorine and bromine groups. With these compounds many of the condensation products sought for were readily obtained, especially did the chlorine derivatives easily react.

Three-p-brom phenylene - 2 phenyl-imido- 4 - keto-tetra-hydrothiozole was prepared by heating together 12 grams of ethyl ester of chloracetic acid, 30 grams of p-brom-di-phenyl-thio urea, 15 Cc of pyridine and 60 Cc of alcohol under the reflux condenser for one or two hours.

The p-brom-di-phenyl thio urea was prepared by mixing in alcoholic solution molar quantities of phenyl mustard oil and para bromanilin. Gentle heating was used to start the reaction.

From the ethyl ester of chloracetic acid thio-urea reaction, there was obtained a dark, oily substance from which in a few days crystals separated. These were thick colorless prisms. The yield was 49 per cent of the theoretical.

The product seemed to be difficult to purify and when recrystallized melted about  $175^{\circ}$  -  $176^{\circ}$ .

The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.5387 gms.	10 Cc.	2.75 Cc.	8.02
II	.5859 gms.	10.05 Cc.	2.00 Cc.	8.28

1 Cc. HCl = .00625 gram N<sub>2</sub>

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl.

Calculated N<sub>2</sub> for C<sub>15</sub>H<sub>11</sub>N<sub>2</sub>O, Br S = 8.07 % , this being the empirical formula for the mono-brom derivative of di-phenyl iso-thio-hydantoin.

The compound gave a positive halogen test with a hot copper wire.

Chloracetic acid was used in place of the ethyl ester in a second attempt to make the above substance, but, though subsequent tests showed the brom-iso-thio-hydantoin to have been formed, it could not be isolated.

In detail, 40 grams of p-brom-di-phenyl-thio urea, 12.8 grams of chloracetic acid and about 80 Cc of alcohol were heated together for several hours. When the solution was cooled a dark colored, oily substance precipitated but no crystals formed. The thick oil was finally distilled with steam. The distillate contained a small amount of phenyl mustard oil but the main part of the material remained unchanged. It was finally boiled with alcohol containing concentrated hydrochloric acid. This was done on the supposition that if any of brom-iso-thio-hydantoin derivatives were present it would be hydrolysed to the di-keto form. This could possibly then be isolated and purified.

After heating the flask for two hours it was allowed to cool. Long white needles separated out which were readily soluble in alcohol and hot water. Recrystallized they melted at  $124^{\circ}$  -  $125^{\circ}$ . They gave a positive halogen test with a hot copper wire. The mother liquor gave the characteristic test for anilin with bleaching powder.

The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub>
I	.2916 gms	10 Cc.	6.83 Cc	5.69 %
II	.4594 gms	10 Cc.	6.00 Cc	5.12 %

1 Cc HCl = .00625 gram N<sub>2</sub>

1 Cc NaOH = 1.05 Cc. HCl.

Blank = .17 Cc.

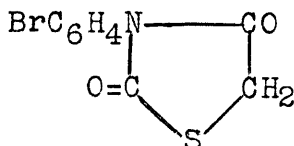
Calculated N<sub>2</sub> for BrC6H4N(CO)C(=O)S = 5.18 %

Bromine (1) : Found 35.2 %  
28.5 %  
Calculated, 29.4 %

*C<sub>9</sub>H<sub>7</sub>O<sub>2</sub>N BrS*

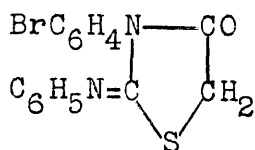
Only a very small amount of the material, a few hundredths of a gram, was available for the halogen analyses. This probably accounts for the variations in the bromine determinations to a large extent.

Now 3-phenyl - 2.4 diketo-tetrahydrathiazole melts at 147° - 148° (Richer - 148°) and contains 7.25 per cent nitrogen. These facts taken in connection with the analyses and melting point given above, together with the positive halogen test obtained, indicate that the formula for the compound obtained is



(1) The Br. determinations were made by Mr. Harly Nelson, K.U., 1917.

the brom-phenyl group being in the -3- position. The formula for the unhydrolysed compound therefore is,



The preparation of 3-p-brom-phenyl -2 phenylimido - 4 - keto-tetrahydrothiazole having been completed and its constitution established, the next step was to try condensation with benzaldehyde and di-phenyl formamidine.

One gram of the mono-brom-<sup>di-phenyl</sup>iso-thio-hydantoin and one gram of benzaldehyde were heated together in a large test-tube fitted with an air condenser for about six hours at 150°.

When alcohol was added to the gummy material in the tube it immediately solidified, fine light yellow crystals being formed. The yield, .9 gram, was 70 per cent of the theoretical.

The compound was recrystallized from acetic acid. It melted at 195° - 196°.

The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.5083 gm.	10 Cc.	4.60 Cc.	6.14
II	.5374 gm.	10 Cc.	4.10 Cc.	6.43

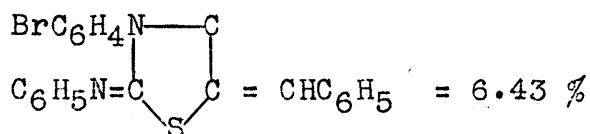
1 Cc. HCl = .00625 gram N<sub>2</sub>

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl.

*C<sub>11</sub>H<sub>15</sub>N<sub>2</sub>BrS*

The calculated nitrogen for BrC<sub>6</sub>H<sub>4</sub>N



It was found that the compound is much more readily soluble in glacial acetic acid than the corresponding chloro-product. It was very soluble in hot chloroform and came down in the form of light yellow plates when precipitated from this solvent by the addition of alcohol. These crystals melted at 197° - 199°.

When 3-p-brom-phenyl - 2 phenyl - imido - 4 keto-tetrahydrothiazole was heated with a molecular amount of di-phenyl formamidine, yellow flaky crystals, quite soluble in alcohol, were obtained. Four and nine-tenths grams of the iso-thio-hydantoin, 2.8 grams of di-phenyl-formamidine were used. The temperature was 140° - 150° and the period of heating, six or seven hours.

A dark viscous material first formed. This was dissolved in hot alcohol and glacial acetic acid. After several days the crystals mentioned above separated out. On recrystallization the compound melted at 204° - 204.5°. The yield was very small, only enough being obtained for

one nitrogen determination.

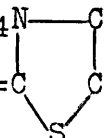
The analysis was:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.1876 gm.	10 Cc.	7.2 Cc.	7.56

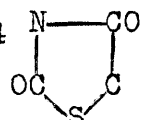
1 Cc. HCl = .00625 gram N<sub>2</sub>.

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl.

Calculated N<sub>2</sub> for  $\text{BrC}_6\text{H}_4\text{N}-\text{C}$   
 $\text{C}_6\text{H}_5\text{N}=\text{C}$   = CHNHC<sub>6</sub>H<sub>5</sub> = 9.33 %

The percentage of nitrogen found corresponds to that of the diketo derivative:

*p* BrC<sub>6</sub>H<sub>4</sub>  = CHNHC<sub>6</sub>H<sub>5</sub> Calculated N<sub>2</sub> = 7.46 %

This compound should be by analogy by fairly soluble in alcohol as was found to be the case.

Three-m-brom phenyl - 2 phenyl imido - 4 keto-tetrahydrothiazole was prepared in the usual manner, 30 grams of m-brom-di-phenyl thio urea, 12 grams of ethyl ester of chloracetic acid, 15 grams of pyridine and 60 Cc. of alcohol being used. The thio urea was made by the same method used in the preparation of the p-brom phenylene, phenyl thio urea.



After the solid thio urea had disappeared, heating was continued for about three quarters of an hour. When the mixture was cooled no crystals formed. The solution was then concentrated on the water bath until it became syrupy. When this material was let stand over night a mass of colorless crystals separated out. They were readily soluble in alcohol. After one recrystallization, they melted at  $171^{\circ}$ , starting to soften at  $164^{\circ}$ .

It might be stated here that all the halogen derivatives of di-phenyl iso-thio-hydantoin gave melting points which were not as sharp as could be desired, even after the second recrystallization.

A 35 per cent yield was obtained of the meta compound. It gave a positive test for bromine with the hot copper wire.

The analyses were:

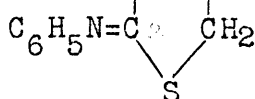
Number	Weight	HCl	NaOH	$N_2$ %
I	.3139 gm	10 Cc.	5.50 Cc.	8.08
II	.3033 gm	10 Cc.	5.75 Cc.	7.83

1 Cc. HCl = .00625 gram  $N_2$ .

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl.

Calculated  $N_2$  for  $BrC_6H_4N$ —CO



= 8.07 %

*C<sub>15</sub>H<sub>11</sub>O<sub>2</sub>N<sub>2</sub>S*

Four grams of the above compound and two and one-half grams of benzaldehyde were heated together in a large test-tube at  $140^{\circ}$  -  $160^{\circ}$  for 8 - 10 hours. On the addition of alcohol, crystals, yellow and of no definite shape, precipitated. The product was purified from a chloroform-alcohol mixture and gave a melting point of  $143^{\circ}$ . Crystallization from this solution started with difficulty, the substance once coming down as a gummy resinous material which later crystallized.

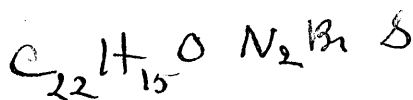
The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.6083 gm.	10 Cc.	3.45 Cc.	6.38
II	.6013 gm.	10 Cc.	3.35 Cc.	6.23

$$1 \text{ Cc. HCl} = .00625 \text{ gram N}_2.$$

$$1 \text{ Cc. NaOH} = 1.05 \text{ Cc. HCl.}$$

$$\text{Blank} = .17 \text{ Cc. HCl.}$$



Calculated N<sub>2</sub> for  $\text{BrC}_6\text{H}_4\text{N}-\text{CO}$

$$\begin{array}{c}
 \text{C}_6\text{H}_5\text{N}=\text{C} \begin{array}{l} \diagup \text{N}-\text{CO} \\ \diagdown \text{S} \end{array} \\
 \text{C} \\
 \text{C} \\
 \text{S}
 \end{array} = \text{CHC}_6\text{H}_5 = 6.43 \%$$

An attempt to condense 3-m-brom phenyl - 2 phenylimido - 4 keto tetra-hydrothiazole with di-phenyl-formamidine was made without success.

Molar quantities of the two compounds were heated together at  $145^{\circ}$  -  $150^{\circ}$  for eight hours. On the addition of alcohol to the resulting pasty mass, part dissolved, the remainder being a reddish, gummy substance which also dissolved when heat was applied. No crystals could be obtained.

Four grams of the m-brom iso-thio-hydantoin were hydrolysed with a solution of 15 Cc. hydrochloric acid in 20 Cc. of alcohol. A small amount of white flocculent crystals was obtained. This product melted at  $142^{\circ}$  -  $144^{\circ}$  after recrystallization from hot water. It gave a positive halogen test with a hot copper wire.

Barely enough of the product was secured for one nitrogen determination.

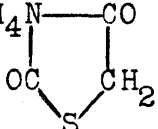
The analysis was:

Number	Weight	HCl	NaOH	$N_2\%$
I	.1886 gm.	10 Cc.	7.6 Cc.	6.13

1 Cc. HCl = .00625 gram  $N_2$

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl.

Calculated  $N_2$  for  $BrC_6H_4N$   = 5.18 %

The theoretical nitrogen percentage in 3-phenyl-2,4 diketo tetra hydrothiazole is 7.25 %. A mixture of equal amounts of these two compounds would give a nitrogen value of 6.21 per cent. Since the substance contained bromine and melted higher than 3-phenyl-2,4 diketotetrahydrothiazole (M.P. ~~125~~<sup>148</sup>), while the pure m-brom derivative might be expected to melt lower than the para, it is possible that a mixture of the di-keto compounds was formed as indicated by the analysis.

The fact that the nitro phenyl group is in the -2- position in the m-nitro phenyl iso-thio-hydantoin lends weight to this theory.

#### CHLORINE DERIVATIVES.

With the chlorine derivatives, on the whole, very satisfactory results were obtained.

About the theoretical yield of p-chlor-, di-phenyl-thio urea was obtained by mixing molar quantities of p-chloranilin and phenyl mustard oil in alcoholic solution. A little heat started crystallization.

Fifty-two and five-tenths grams of this compound, 30 grams of ethyl ester of chloracetic acid, 10 Cc. of pyridine and 90 Cc of alcohol were heated under the reflux condenser for 3/4 hour. Some of the crystals which formed on cooling were removed from the flask and

purified from alcohol. They melted at  $147^{\circ}$  -  $148^{\circ}$ .  
 Pure CS  $\begin{cases} \text{NHC}_6\text{H}_5 \\ \text{NHC}_6\text{H}_4\text{Cl} \end{cases}$  (para) melted at  $152^{\circ}$ . It seemed  
 that the reaction was not complete and heating was  
 therefore continued for several more hours.

When the flask was again allowed to cool thick  
 colorless prisms separated out from the solution. They  
 were sparingly soluble in alcohol and when recrystallized  
 from this solvent melted at  $184^{\circ}$  -  $185^{\circ}$ .

The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.5056 gm.	10.2 Cc.	2.5 Cc.	9.36
II	.6229 gm.	10 Cc.	.53 Cc.	9.44

1 Cc. HCl = .00625 gram N<sub>2</sub>.

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl.

Calculated N<sub>2</sub> for C<sub>15</sub>H<sub>11</sub>N<sub>2</sub>O S Cl = 9.31 %

The yield was 21 per cent (12.5 grams) of the  
 theoretical. There was also obtained from the reaction  
 a small amount of white flaky crystals which did not  
 melt at  $270^{\circ}$ . This product was recrystallized from  
 alcohol for the melting point determination. It was  
 soluble in neither acid or basic solutions.

The analyses were:

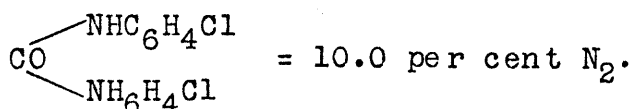
Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.2786 gm.	10.05 Cc.	5.20 Cc.	9.8
II	.2822 gm.	10.00 Cc.	4.80 Cc.	10.6

1 Cc. HCl = .00625 gram N<sub>2</sub>.

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = 0.17 Cc. HCl.

These analyses correspond to the calculated percentage of nitrogen in p-chlor-di-phenyl urea,



This compound melts at 307° (Richard). Both of the preparations obtained above gave a positive test for chlorine with a hot copper wire.

The chloro-iso-thio-hydantoin was also obtained by using chloroacetic acid. In this case a 28 per cent yield was obtained.

It might be stated here that in the preparation of the halogen, nitro, and naphthalene derivatives of di-phenyl-iso-thiohydantoin only small yields were secured and a considerable amount of gummy substance was usually obtained. This often contained a small amount of phenyl-mustard oil, but the main portion could not be purified and identified.

Four grams of the chlor-derivative were hydrolysed with a solution of 20 Cc. of hydrochloric acid in 25 Cc of alcohol. The heating period was four hours. Colorless needles separated from the cooled solution. This product recrystallized from alcohol melted at  $134^{\circ}$  -  $135^{\circ}$  and gave a positive test for chlorine. Mixed with 3-phenyl-2,4 diketo tetra hydro thiazole it melted at  $130^{\circ}$  -  $132^{\circ}$ .

The per-centages of nitrogen found corresponded to the calculated for 3-p-chlor-phenyl - 2,4 diketo tetra hydrothiazole. A good yield was obtained.

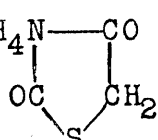
The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.4012 gm.	10 Cc.	5.30 Cc	6.63
II	.3993 gm.	10 Cc.	5.35 Cc	6.58

1 Cc. HCl = .00625 gram N<sub>2</sub>.

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = 0.17 Cc. HCl.

Calculated N<sub>2</sub> for ClC6H4N-CO  = 6.21% <sup>16</sup>

The calculated nitrogen for 3-phenyl-2,4 diketo tetrahydrothiazole is 7.25 per cent.

Thus, as in the bromine derivative, it is evident that the p-chlor-phenyl group is in the -3- position.

The benzaldehyde derivative of -3-p-chlor-phenyl-2-phenyl-imido-4 keto tetra hydrothiazole was readily obtained and a yield of 83 per cent was secured. Three grams of the former and 6 grams of the latter were heated together at  $140^{\circ}$  -  $150^{\circ}$  for five hours. The product solidified upon being cooled. It was ground in a mortar and washed with alcohol. It was found to be sparingly soluble in glacial acetic acid. When recrystallized from this solvent a melting point of  $200^{\circ}$  -  $201\frac{1}{2}^{\circ}$  was obtained. The crystals were microscopic and of a pale yellow color.

The analyses were:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.6935 gm.	10 Cc.	1.95 Cc.	7.30
II	.8254 gm.	10 Cc.	1.10 Cc.	6.83

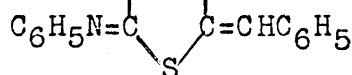
1 Cc. HCl = .00625 gram N<sub>2</sub>

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = 0.17 HCl.

*21 H<sub>2</sub>O N<sub>2</sub> a s*

Calculated N<sub>2</sub> for ClC6H4N-CO = 7.11 %



With di-phenyl formamide condensation was also obtained.

Three grams of the chlor- product and 4.6 grams of di-phenyl formamide were heated together at  $145^{\circ}$  -  $155^{\circ}$



for four hours. Then a small amount of alcohol was added to the flask. A large quantity of gummy material settled to the bottom of the flask together with a very small amount of yellow crystals. The alcohol was evaporated off and the heating continued four hours more. Alcohol and a little acetic acid, to neutralize the aniline set free, were added to the flask. Three grams of yellow crystals were obtained this time when the substance was again cooled and allowed to stand. The yield was 74 per cent of the theoretical. The compound was found to be fairly soluble in alcohol and when recrystallized from this melted at  $176^{\circ} - 180^{\circ}$ .

The analysis was:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.3677 gm.	10 Cc.	3.4 Cc.	10.64

1 Cc. HCl = .00625 gm. N<sub>2</sub>.

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl.

Calculated N<sub>2</sub> for C1C6H4N-CO  
C6H5N=C C=CHNHC6H5 = 10.36%

The melting point and nitrogen determinations indicate that the product was not quite pure.

$C_{22}H_{16}O N_3 Cl$  3

NITRO DERIVATIVES.

Meta-nitro-di-phenyl-thio urea was prepared from phenyl mustard oil and meta-nitronilin by the usual method.

A nitrogen determination (using zinc as a reducing agent) was made upon the purified product. This was done because the melting point,  $160^{\circ}$ , was higher than that given by Richter ( $(155^{\circ}(154^{\circ}))$ ) for this compound.

The di-nitro compound CS  $\begin{matrix} \text{NHC}_6\text{H}_4\text{NO}_2 \\ \text{NHC}_6\text{H}_4\text{NO}_2 \end{matrix}$  (m) melts at  $160^{\circ}$  -  $161^{\circ}$  (Richter).

The analyses were:

Number	Weight	HCl	NaOH	$\text{N}_2$ %
I	.7448 gm.	20 Cc.	1.77 Cc.	15.07
II	.6901 gm.	20 Cc.	3.50 Cc.	14.62

1 Cc. HCl = .00625 gram  $\text{N}_2$ .

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = 0.17 Cc. HCl.

Calculated  $\text{N}_2$  for  $\begin{matrix} \text{NHC}_6\text{H}_4\text{NO}_2 \\ \text{CS} \\ \text{NHC}_6\text{H}_5 \end{matrix}$  = 15.38 %

Though the reduction of the nitro group was evidently not complete, the analyses indicate the mono-nitro- compound. Further experimentation tended to prove that this was the substance obtained.

Seventy and two-tenths grams of m-nitro-di-phenyl thio urea, 23.6 grams of chloracetic acid and 150 Cc. of alcohol were heated together under the reflux condenser for several hours. On the cooling of the flask a dark oily substance precipitated out. This yielded about 5 Cc. of phenyl mustard oil when steam distilled. Sixty-eight grams of a dark colored, very viscous material remained. This could not be purified. It dissolved readily in alcohol but always came down in the original condition.

Twenty grams of the substance were heated with 100 Cc. of alcohol and 40 Cc. of hydrochloric acid for nine hours. The flask was then cooled and allowed to stand. Long, colorless needles formed, which gave a melting point of  $146.5^{\circ}$  -  $147^{\circ}$  when recrystallized from hot water.

The nitrogen determination was:

Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.2618 gm.	15.0 Cc.	11.25 Cc.	7.21

1 Cc. HCl = .00625 gram N<sub>2</sub>.

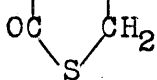
1 Cc. NaOH = 1.05 Cc. HCl.

Blank = .17 Cc. HCl

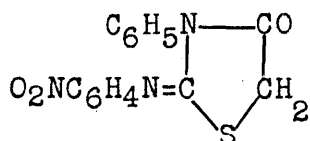
The melting point and percentage of nitrogen obtained correspond to those of 3-phenyl-2,4 diketo-tetra-

hydrothiazole. A mixture of the latter compound and the crystals obtained melted at  $147^{\circ}$  -  $148^{\circ}$ . Pure

$C_6H_5N$ —CO melts at  $148^{\circ}$  (Richter).



The mother liquor was made alkaline and shaken. A yellow precipitate came down which, when recrystallized from hot water, gave a melting point of  $114^{\circ}$  -  $117^{\circ}$ . This was evidently m-nitranilin. Thus, it is evident that the m-nitro-phenylene group is in the -2- position and that the formula for the original compound should be:



Though the above substance could not be obtained in the pure state, its existence in the gummy mixture was indicated when the latter was heated with benzaldehyde. A temperature of  $140^{\circ}$  -  $150^{\circ}$  was maintained for several hours. The resulting material was allowed to stand overnight. Yellow microscopic crystals formed, which were recrystallized from alcohol. They were then recrystallized from a mixture of alcohol and chloroform in which they were much more soluble. The melting point obtained was  $193^{\circ}$ .

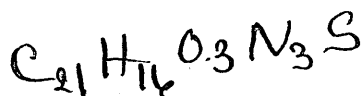
The analyses were:

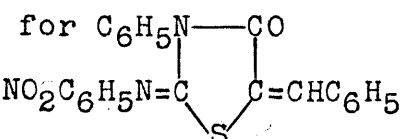
Number	Weight	HCl	NaOH	N <sub>2</sub> %
I	.3996 gm.	15 Cc.	7.7 Cc.	10.55
II	.3852 gm.	15 Cc.	7.85 Cc.	10.69

1 Cc. HCl = .00625 gram N<sub>2</sub>.

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = 0.17 Cc. HCl.



Theoretical N<sub>2</sub> for  = 10.77 %

An attempt was made to obtain pure 3 phenyl-2-m-nitro phenylene-imido - 4 keto-tetra-hydrothiazole by heating molar quantities of the m-nitro-thio urea, chloracetic acid, pyridine and alcohol together. The solid thio urea soon disappeared when heat was applied but nothing precipitated from the solution when it was cooled.

Some of the liquid was boiled with alcohol, acidulated with hydrochloric acid. Colorless needles were obtained. These recrystallized melted at 146°, indicating, as before, the formation of 3-phenyl-2,4 diketotetra-hydrothiazole due to the splitting off of the nitrophenylene-imido group.

NAPHTHALENE DERIVATIVES.

With the naphthalene derivatives of di-phenyl-iso-thio-hydantoin little success was obtained, though, owing to the shortness of time, the experiments were not carried as far as desired.

A 91 % yield of a-naphthylamine-phenyl-thio urea was obtained by mixing molar quantities of a-naphthylamine and phenyl mustard in alcoholic and applying gentle heat. Fifty-six and seven-tenths grams were obtained.

Twenty-five grams of this product and 8.4 grams of chloracetic acid were heated in alcoholic solution until all the thio- urea disappeared - about two and one-half hours.

When the flask was cooled a gummy, oily substance was precipitated. Forty Cc. of concentrated hydrochloric acid was added to the flask and heat applied. No change having taken place, judging from the appearance of the contents of the flask, 25 Cc more of hydrochloric acid were added and boiling was continued. This also was without results as no evidence of hydrolysis was found.

Next an attempt was made to prepare the naphthylamine derivative of phenyl-iso-thio-hydantoin by heating together 27.8 grams of a-naphthylamine-phenyl-thio urea, 13.5 grams ethyl ester of chloracetic acid and 8 grams of

pyridine in alcoholic solution.

As before, a mass of material, very viscous and dark colored, was obtained which could not be purified.

Some of it was heated with benzaldehyde for four to five hours at  $150^{\circ}$ . Examination showed no evidence of reaction at the end of that time. The heating temperature was then raised to  $180^{\circ}$  -  $190^{\circ}$ . After 3 - 4 hours the contents of the flask were cooled and examination showed a dark reddish, almost solid substance. This was dissolved in chloroform. On the addition of alcohol fine yellow needles precipitated. These were washed three times with alcohol, redissolved in chloroform and precipitated with alcohol. They melted then at  $228^{\circ}$  -  $230^{\circ}$ .

The analyses were:

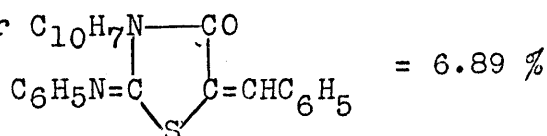
Number	Weight	HCl	NaOH	$N_2$ %
I	.5413 gm.	10 Cc.	3.87 Cc.	6.66
II	.5420 gm.	10 Cc.	3.80 Cc.	6.73

1 Cc. HCl = .00625 gm.  $N_2$ .

1 Cc. NaOH = 1.05 Cc. HCl.

Blank = 0.17 Cc. HCl.

Calculated  $N_2$  for  $C_{10}H_7N$ —CO



I wish to thank Doctor Dains for the assistance and valuable advice given by him in the course of the preparation of this paper.