

Synthesis of Thiohydantoin. III.

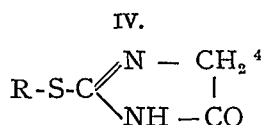
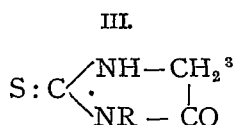
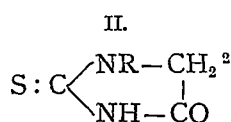
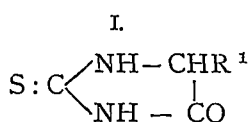
By

Shigeru Komatsu.

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1. Formation of the Substituted Thiohydantoins.

For the alkyl or aryl derivatives of thiohydantoin the following 4 kinds of structural isomers have already been pointed out to be formed:



By the action of thiocyanic acid upon the α -amino-acids such as leucine, phenylaminoacetic acid, α -aminoisobutyric acid, α -aminoisovaleric acid, etc., in presence of acetic anhydride, it has been noticed that there are formed the corresponding acetyl α -substituted thiohydantoins which yield respective α -substituted thiohydantoins (I) by the action of hydrochloric acid under the separation of the acetyl group.

When α -aminoisobutylic acid was used, the yield of the α -substituted thiohydantoin was found to be only about 4 percent, which, as the author believe, may be dependent upon the chemical nature of acid. It is also possible that the β -substituted thiohydantoin corresponding to the formula II, would be formed from thiocyanic acid and sarcosine or phenylglycocolle in the similar manner.

¹ Mem. Coll. Sci. Engin, Kyoto, 3, 11 (1911).

² Wheeler and Brantlecht, Amer. Chem. J., 45, 446 (1911).

³ Marckwald, Ber. D. chem. Ges., 24, 3285 (1891); Aschan, *Ibid.*, 17, 424 (1884) Brantlecht, J. Biol. Chem., 10, 139 (1911).

⁴ Mem. Coll. Sci. Engin. Kyoto, 3, 9 (1911).

Infering from the analogous behaviours of phenylglycocolle and sarcosine toward urea¹ or phenylthiocyanic acid,² it was anticipated that sarcosine may react with thiocyanic acid similarly as phenylglycocolle under the same condition.

When sarcosine and potassium thiocyanate mixed in equimolecular quantities were heated over a water bath with acetic anhydride, neither thiohydantoin nor methylamine was found to be formed, sarcosine remaining in solution, as Johnson and Scott³ have observed in their experiment on phenylglycocolle. When, however, the hydrochloride of sarcosine ethylester prepared by Fischer's method,⁴ was heated with potassium thiocyanate in an alcoholic solution, β -methylthiohydantoin (II.) was obtained just as in the case of phenylglycocolle.⁵

Hence, it is evident that *n*-substituted monobasic α -amino-acid has no capability to condense with thiocyanic acid in presence of acetic anhydride, like aspartic and glutamic acids.⁶

Johnson and Guest, having determined the quantities of ammonium chloride formed in the reaction, have to ascribe such a non-formation of thiohydantoin to the deamidation of amino-acids. As amino-acids, however, do not deamidize so easily the author has been led to raise a suspicion with regard to their view. On repeating their experiment precisely following the description, with pure potassium thiocyanate, acetic anhydride and aspartic acid, the following results were obtained:

- I. 0.8 gm. ammonium chloride from 2 grms. aspartic acid, 1.5 grms. potassium thiocyanate and 9 c.c. acetic anhydride.
- II. 0.75 gm. ammonium chloride from 2 grms. aspartic acid, 1.5 grms. potassium thiocyanate and 9 c.c. acetic anhydride.
- III. 1.2 grms. ammonium chloride from 2 grms. aspartic acid, 3 grms. potassium thiocyanate and 1.8 c.c. acetic anhydride.

As seen from the above experimental results, the quantity of ammonium chloride seems to have no relation to that of aspartic acid, but to be dependent upon that of potassium thiocyanate. Hence, it may be concluded that the source of nitrogen recovered in the form

¹ Schwebel, Ber. D. chem. Ges., 10, 204a (1777); Huppert, *Ibid.*, 6, 1278 (1873).

² Wheeler and Brantleht, Amer. Chem. J., 45, 446 (1911).

³ J. Amer. Chem. Soc., 35, 1142 (1913).

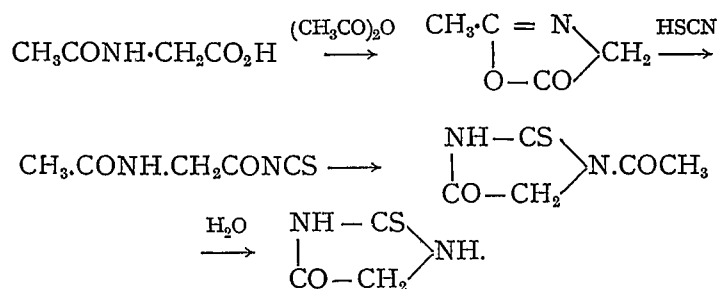
⁴ Über Aminosäure, Polypeptide u. Proteine, p. 193 (1906).

⁵ Wheeler and Brantleht, *Loc. cit.*

⁶ Amer. Chem. J., 47, 242; 48, 160 (1912).

of ammonium chloride would be attributed to potassium thiocyanate but not to aspartic acid.

With regard to the mechanism of the formation of substituted thiohydantoin from monobasic α -amino-acid and thiocyanic acid in presence of acetic anhydride, Johnson and Guest¹ have proposed the following scheme for explanation :



Such a view, as above, may apply only to the case of n -substituted α -amino-acid, but not to the dibasic α -amino-acid and pyrrolidon carboxylic acid.

II. Mechanism of the Desulphurisation of the Thiohydantoins.

The thiohydantoins, when heated in neutral or alkaline solution with metallic oxide², such as mercury or lead oxide or with potassium permanganate³, are transformed into the corresponding hydantoins, and also the latter compounds can be prepared by digesting the thio-compounds with chloracetic acid⁴ or bromine water⁵. In the case of β - γ -disubstituted thiohydantoins desulphurization may be more conveniently effected by the use of 5% nitric acid⁶.

Based upon those facts, the author put forward an explanation for the desulphurization of the thiohydantoins upon the assumption that at first addition of a molecule of water may take place under the disruption of a double bond, between carbon and sulphur atoms or

¹ *Loc. cit.*

² Baily and Randolph, Ber. D. chem. Ges., 41, 2494 (1908); Komatsu, Mem. Coll. Sci. Engin. Kyoto, 3, 1. (1911).

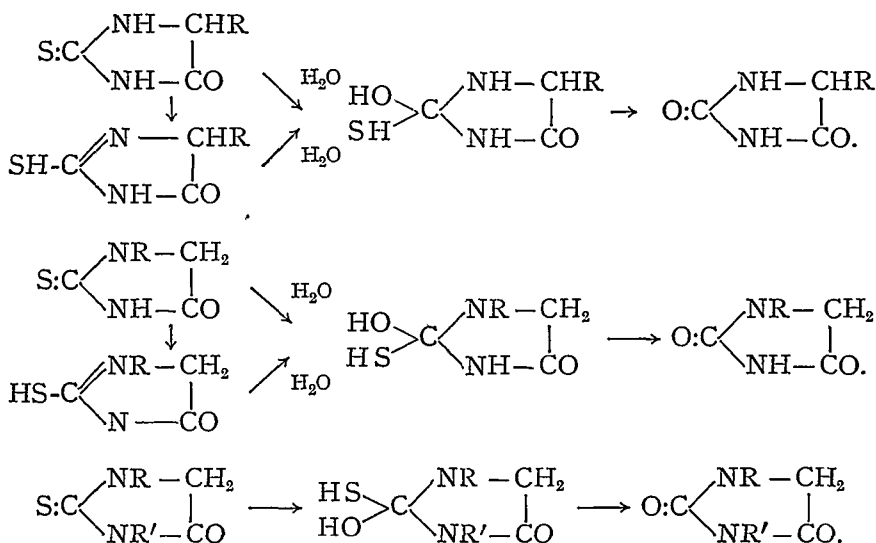
³ H. Biltz, Ber. D. chem. Ges., 42, 1792 (1909).

⁴ Johnson and Guest, Amer. Chem. J., 47, 245 (1912); Komatsu, Mem. Coll. Sci. Engin. Kyoto, 5, 13 (1912).

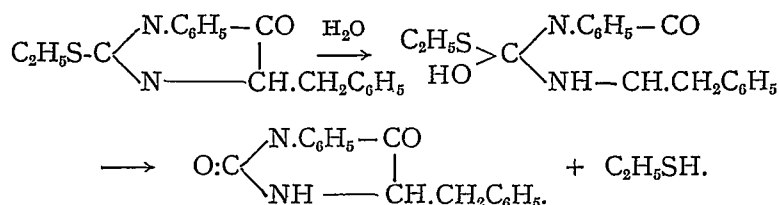
⁵ Baily and Randolph, *Loc. cit.*

⁶ Biltz, Ber. D. chem. Ges., 42, 1792 (1909).

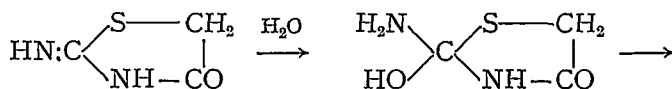
between carbon and nitrogen atoms, and secondarily metallic oxide or other reagents used for desulphurization may simply act to remove hydrogen sulphide from the hydrated compounds, as will be seen in the following representations :



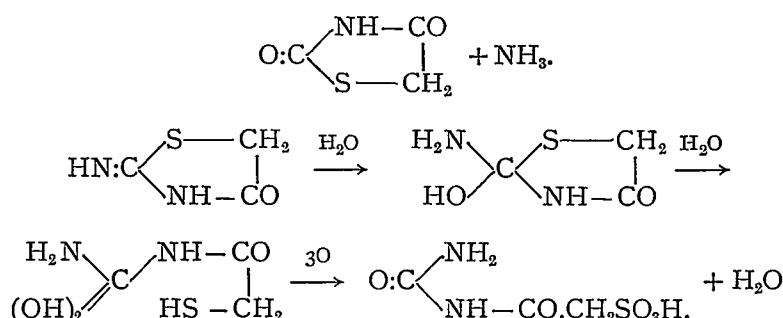
By the similar manner the author has to explain the production of thioalcohol and hydantoin from *s*-alkylthiohydantoin by the action of hydrochloric acid or alcoholic potash¹.



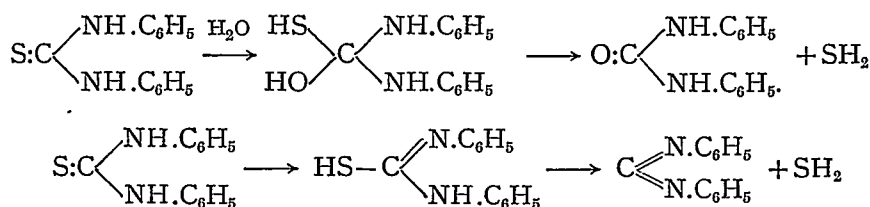
Moreover, the formation of thiocarbamidacetic acid¹ and carbamido-sulphoacetic acid² from isothiohydantoin, can be explained by the author's view, as will be indicated by the following schemes :



¹ Wheeler and Brantlecht, Amer. Chem. J., 45, 45, 446 (1911); Komatsu, Mem. Coll. Sci. Engin. Kyoto, 3, 9 (1912).



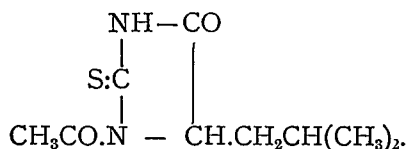
On referring the literatures we find the reactions³ regarding the transformation of thio-carbanilide to the carbanilide and to carbodiimide, which should be parallel with the author's view of desulphurization. Thus, thiocarbanilide in alcoholic solution, when boiled with mercuric oxide, yields carbanilide, but in the benzene solution carbodiimide; so the author dares to interpret the mechanism of the reactions by the following schemes :



EXPERIMENTAL PART.

I. Condensation of Leucine with Thiocyanic Acid.

1. β -Acetyl- α -isobutylthiohydantoin.



When the equimolecular mixture of potassium thiocyanate and leucine from Merck, was heated with acetic anhydride over a water

¹ Volhard, J. prak. Chem., [2], 9, 6 (1874); May, Lieb. Ann., 168, 133 (1873).

² Andreasch, Monatsh. Chem., 1, 446 (1880); 6, 131 (1883); Ber. D. chem. Ges., 13, 1423 (1880).

³ Sidgwick, The Organic Chemistry of Nitrogen, p. 191 (1910).

bath for 15 minutes there was obtained a yellow-coloured solution, which on pouring into cold water, deposited the crystals of β -acetyl- α -isobutyl thiohydantoin.

It crystallizes from hot water in colourless scales with silky luster and melts at 112–113°.

The substance is difficultly soluble in cold water, but easily in hot water and alcohol. Its analysis gave the following value for sulphur:

0.1362 grm. substance gave 0.1528 grm. BaSO₄.

Calc. for C₉H₁₄O₂N₂S. Found.

Sulphur. 14.95 15.38



It was prepared by heating acetylisobutylthiohydantoin with conc. hydrochloric acid, and then by evaporating the solution to dryness. The substance was purified by recrystallization from hot water. It crystallizes in colourless scales with silky luster melting at 169–170°. The substance dried over sulphuric acid gave the following value for sulphur by analysis:

0.176 grm. substance gave 0.2352 grm. BaSO₄.

Calc. for C₇H₁₂ON₂S. Found.

Sulphur. 18.60 18.31

II. Condensation of α -Amino isobutyric Acid with Thiocyanic Acid.



β -Acetyl- α -dimethylthiohydantoin prepared from potassium thiocyanate, α -aminoisobutyric acid and acetic anhydride, as usual, by treating with hydrochloric acid, was converted into α -dimethylthiohydantoin, but its yield was found to be only about 4%.

The substance crystallizes in colourless needles, melting at 163–164°.

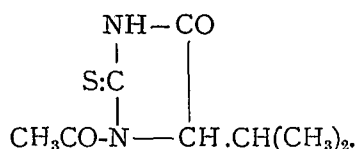
0.1314 grm. of the substance gave 0.2113 grm. BaSO₄.

Calc. for C₅H₈ON₂S. Found.

Sulphur. 22.22 22.26

III. *Condensation of α-Aminoisovaleric Acid with Thiocyanic Acid.*

I. *α-Isopropyl-β-acetylthiohydantoin,*



By heating potassium thiocyanate and α-aminoisovaleric acid mixed in molecular proportions with acetic anhydride for an hour, acetylthiohydantoin was obtained in the form of light-yellow oil which by treating with hot water was transformed into a crystalline state. It crystallizes in fine needles from hot water and alcohol, and melts at 98–99°.

0.1351 grm. of the substance gave 0.1564 grm. BaSO₄.

Calc. for C₈H₁₂O₂N₂S. Found.

Sulphur 16.00 15.86



This compound was prepared by heating acetylthiohydantoin with conc. hydrochloric acid.

It was purified by recrystallisation from hot water, and crystallizes in colourless plates melting at 129–130°.

0.1717 grm. substance gave 0.2634 grm. BaSO₄.

Calc. for C₆H₁₀ON₂S. Found.

Sulphur 20.30 21.00

IV. *Condensation of Phenylaminoacetic Acid with Thiocyanic Acid.*



When the reaction product of potassium thiocyanate, phenylaminoacetic acid and acetic anhydride was poured into cold water, a yellow syrupy substance produced was found to solidify on standing.

It crystallizes in colourless needles from hot water, and melts at 185–186°. Its analysis gave the following value for sulphur :

0.1782 grm. substance gave 0.1913 grm. BaSO ₄ .	
Calc. for C ₁₁ H ₁₀ O ₂ N ₂ S.	Found.
Sulphur	13.70
	14.75



By treating acetylphenylthiohydantoin with hydrochloric acid, α -phenylthiohydantoin was obtained in colourless needle-shaped crystals which melt at 211–212° with decomposition.

It is difficultly soluble in cold water, but readily in hot water and alcohol.

0.0918 grm. substance gave 0.1150 grm. BaSO ₄ .	
Calc. for C ₉ H ₈ ON ₂ S.	Found.
Sulphur	16.60
	17.20

v. *The Action of Thiocyanic Acid upon Aspartic Acid.*

For this purpose the author repeated Johnson and Guest's experiments exactly following their statement, but has reached the different results. 2 grms aspartic acid from Kahlbaum, 1.5 grms. potassium thiocyanate and 9 c.c. acetic anhydride from Merck were mixed together in an Erlenmeyer flask and heated for half an hour, and 0.8 grm. ammonium chloride was obtained in the first experiment and 0.75 grm. in

the second, instead of 1.3 grms. ammonium chloride which ought to be formed from 2 grms. aspartic acid according to two chemists.

To the reaction product a solution of copper acetate was added, and after a while green crystals were found to separate out. The salt recrystallized from hot water was confirmed to be copper aspartate by analysis.

0.2052 grm. substance gave 0.0618 grm. CuO on ignition.

Calc. for $C_4H_5O_4NCu_4\frac{1}{2}H_2O$. Found.

Copper	23.19	24.09
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This shows that the most part of aspartic acid remains unchanged. In the third experiment, 2 grms. aspartic acid, 3 grms. potassium thiocyanate and 1.8 c.c. acetic anhydride having been used, the author has obtained 1.2 grms. ammonium chloride, corresponding to 75% of its quantity equivalent to nitrogen contained in potassium thiocyanate used. The results of experiments as has been shown, point out that aspartic acid is not the source of ammonium chloride, i.e., that it is not deamidized.

VI. The Action of Thiocyanic Acid upon Sarcosine.



Hydrochloride of sarcosine ethylester prepared by Fischer's method¹ was heated in a flask together with potassium thiocyanate and alcohol over a water bath for 5 hours, and then alcohol distilled off. On adding cold water to the residue, there separated out orange yellow crystals. The substance was recrystallized several times from hot water, and finally obtained in yellow scaly crystals which melt at 214–215°. It is soluble in hot water and alcohol. The substance dried by heating at 100° for 2 hours gave the following value for sulphur by analysis:

0.121 grm. of the substance gave 0.2222 grm. BaSO₄.

Calc. for $C_4H_6ON_2S$. Found.

Sulphur	24.62	25.12
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¹ *Loc. cit.*

2. Equivalent mixture of sarcosine and potassium thiocyanate was heated with acetic anhydride over a water bath; there was noticed brisk evolution of a gas, with the formation of a brownish yellow solution. The latter was poured into cold water but no separation of methylthiohydantoin was observed; then the solution was distilled. The distillate was found to contain nothing but acetic acid.

The residue made alkaline with caustic potash was subjected to distillation, and the distillate was found to contain ammonium chloride. Analysis of the platinum double salt gave the following value for platinum.

0.23 grm. platinum double salt gave 0.1006 grm. Pt on ignition.

	Calc. for $(\text{NH}_4\text{Cl})_2\text{PtCl}_4$	Found.
Platinum	44.61	43.74

VII. *Condensation of Phenylthioisocyanate with Sarcosine.*



The substance was prepared according to Aschan's method from phenylthioisocyanate and sarcosine. It consists of light-yellow platy crystals which melt at 150–151°.

The substance dried by heating at 100° for 2 hours was analysed :

0.1734 grm. substance gave 0.198 grm. BaSO_4 .

	Calc. for $\text{C}_{10}\text{H}_{10}\text{ON}_2\text{S}$	Found.
Sulphur	15.54	15.66

VIII. *Condensation of Phenylthioisocyanate with Phenylaminoacetic Acid.*



When the equimolecular quantities of phenylthiocyanate and phenylaminoacetic acid in an alcoholic solution was heated with potas-

sium hydroxide for 3 hours, the reaction took place, the colour of solution changing orange; then the solution was diluted with water, by which treatment an orange precipitate separated out. The precipitate was washed with cold water, and then treated with hot water. The residue dissolved in hot alcohol deposited reddish brown fine needles which melt at 155–156°. The properties of the compound are now going to be studied by the author, and the results will be communicated in a near future.

A part of the precipitate soluble in hot water, crystallizes in fine needles which melt at 223–224°. On analysing the substance dried at 100°, it was confirmed to be α -phenyl- γ -phenylthiohydantoin.

0.235 grm. of the substance gave 0.2021 grm. BaSO₄.

	Calc. for C ₁₅ H ₁₂ ON ₂ S.	Found.
Sulphur	11.93	11.81



This substance was prepared by boiling α -phenyl- γ -phenylthiohydantoin with chloracetic acid in aqueous solution for 5 hours.

It crystallizes in colourless fine needles which melt at 184–185° (not corrected), while Ehrlich¹ states its melting point to be 191°.

Wondering if the substance may be something else rather than α - γ -diphenylhydantoin, it was analysed:

0.2603 grm. of the silver salt gave 0.087 grm. Ag on ignition.

	Calc. for C ₁₅ H ₁₁ O ₂ N ₂ Ag.	Found.
Silver	30.08	29.92

¹ Biochem. Zs., 8, 453, (1908).