42. 1906 Ullmann and Sponagel, *Ann.*, **350**, 84 (92, 1, 38).
A study of the yields obtained with various halogen benzene and alkaline phenolates in the presence of finely divided copper.
43. 1906 Ullmann and Stein, *Ber.*, **39**, 622 (90, 1, 258).
Made various methoxy and hydroxy phenyl ethers.
44. 1910 Cook, *THIS JOURNAL*, **32**, 1285 (98, 1, 731).
A study of the bromination of phenyl and tolyl ethers.
45. 1910 Sabatier and Mailhe, *Compt. rend.*, **151**, 492 (98, 1, 669).
Manufactured phenyl ether and its homologs by the use of thorium oxide as a catalytic agent.
46. 1910 Bonneaud, *Bull. soc. chim.*, [IV] **7**, 776 (98, 1, 669).
A study of the action of bromine in the presence of aluminum bromide, on the phenyl ethers and their homologs.
47. 1910 Farb. v. Friedr. Bayer & Co. (98, 1, 312, 373).
A description of the preparation of dyes from some diazotized aromatic amino ethers.
48. 1911 Cook, *THIS JOURNAL*, **33**, 254.
An addenda to No. (44) containing omitted material.
49. 1911 Borsche and Rautschef, *Ann.*, **379**, 152 (100, 1, 329).
A study of the reaction of chloronitro benzene in which they prepared 2:6-dinitrophenyl ether.
50. 1912 Mailhe and Murat, *Bull. soc. chim.*, **154**, 122-3 (1912, 1-183).
Made a study of the decomposition of phenyl ether by hydrogen in the presence of heated nickel.
51. 1912 Mailhe and Murat, *Compt. rend.*, **154**, 601 and *Bull. soc. chim.*, [IV] **11**, 288 (102, 1, 254).
A study of the halogen derivatives of phenyl and ditolyl ethers.
52. 1912 Mailhe and Murat, *Compt. rend.*, **154**, 715 (102, 1, 346).
A study of the nitration of phenyl ether.
53. 1912 Mailhe, *Compt. rend.*, **154**, 1240 (102, 1, 548).
A description of the dyes obtained by treating diazotized *p*-amino phenyl ether with various compounds.
54. 1912 Sabatier and Mailhe, *Compt. rend.*, **155**, 260 (102, 1, 767).
An extension of previous studies, several new compounds being produced.
55. 1914 Nollau and Daniels, *THIS JOURNAL*, **36**, 1885 (106, 1, 1129).
A study of the reaction of the alkaline salts of sulfonic acids with the alkaline phenolates resulting in the preparation of various aromatic ethers.
56. 1915 Cook and Sherwood, *THIS JOURNAL*, **37**, 1835 (108, 1, 877).
Made a number of new derivatives of phenyl ether.

MITCHELL, S. DAKOTA.

[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON THIOCYANATES AND ISOTHIOCYANATES.¹

IX. ETHYL ISOTHIOCYANACETATE.

BY TREAT B. JOHNSON AND E. HEATON HEMINGWAY.

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Organic combinations containing the primary halide grouping ClCH_2 -

¹ *Am. Chem. J.*, **26**, 345 (1901); **28**, 121 (1902); **33**, 448 (1905); **38**, 456 (1907); **40**, 132 (1908); last paper, *Ibid.*, **41**, 337 (1909); *THIS JOURNAL*, **23**, 283 (1901); **24**, 439, 680, 743 (1902); **25**, 483 (1903); **28**, 1454 (1906).

CO— are characterized by their behavior towards potassium thiocyanate. They interact with this salt with formation of normal thiocyanates, and in no case, which has been carefully investigated, has it been demonstrated that mustard oils are products of the reaction. Furthermore, it has never been shown, so far as the writers are aware, that thiocyanates of the type $\text{NCS.CH}_2\text{CO.R}$ can be rearranged by heat into the isomeric mustard oils $\text{SCNCH}_2\text{CO.R}$. Such transformations have been assumed to take place by different investigators and also the reverse change, $\text{SCN.CH}_2\text{COR} \rightarrow \text{NCS.CH}_2\text{COR}$, but a careful reëxamination of their work has been productive of evidence, in every case investigated, that such conclusions are incorrect. Changes of an entirely different nature have been observed to take place, and they do not involve a migration of the polyketide group $-\text{CH}_2\text{CO.R}$ from sulfur to nitrogen of the SCN radical.¹

Recent developments in this laboratory² have now directed our attention again to the chemistry of these polyketide mustard oils. In connection with our work on polypeptide-hydantoins we have foreseen the possibility of utilizing certain combinations of this type for coupling with α -aminoacids and consequently it was necessary to have available a practical method whereby they can be obtained in quantity for synthetical purposes. Such a method of synthesis has now been developed and in this paper we shall give a description of its application for the preparation of ethyl isothiocyanacetate, $\text{SCN.CH}_2\text{COOC}_2\text{H}_5$. So far as we are aware, this is the first polyketide isothiocyanate (mustard oil) to be described in the literature whose constitution has been definitely established.

In 1890, P. Klason published an interesting paper entitled, "Ueber Senfölessigsäure und Thiohydantoin," in which he described the preparation of ethyl isothiocyanacetate. He states that it is formed by the action of thiophosgene or ethyl aminoacetate in ether solution and expressed the transformation by the following equation:

The reaction apparently was a smooth one and the ester was obtained in good yield, but from what we can learn from abstracts of his original publication nothing was done by him to establish its constitution. While the results of this work are recorded, to our knowledge, in three different journals,³ the mustard oil is not listed in Richter's *Lexikon der Kohlenstoff Verbindungen* nor described in Beilstein's *Handbuch*. It was undoubtedly due to this omission that Wheeler, in 1901, was led to insert, in one

¹ See previous papers from this laboratory.

² Unpublished results.

³ *Ofv. kongl. Vet.-Ak.*, 87 (1890); *Chem. Ztg.*, 14, Rep. 200; *Chem. Zentr.*, 2, 344 (1890).

of his earlier papers on alkylthiocyanates,¹ the following statement: "The results, now at hand, show that neither isothiocyanacetic acid nor any of its derivatives have yet been prepared."

During this same year (1901), E. Fischer investigated the action of phosgene on ethyl aminoacetate and showed that they interact in toluene to form the urea (I).² Apparently he obtained no evidence of the formation of the isocyanate (II) corresponding to ethylisothiocyanacetate.

He did not take up the study of the action of thiophosgene on ethyl aminoacetate and furthermore makes no reference, in his paper, to the previous work of Klason. On the other hand, he attempted to convert the amino ester into ethyl isothiocyanacetate by combining it with carbon bisulfide and then breaking down the resulting dithiocarbamic acid salt (III) in the usual manner by digestion in aqueous solution with metallic salts. Fischer found that the salt (III) is formed smoothly, but the only evidence given in the paper indicating that an isothiocyanate was formed by its decomposition is the statement that the odor of mustard oil was apparent after digesting with mercury salts. Ethyl isothiocyanacetate was not isolated.

While ethyl aminoacetate interacts with phosgene to give the corresponding urea (I), the hydrochloride of this ester reacts with phosgene in an entirely different manner. Morel and Gautier³ made the observation that they interact, when warmed in toluene, with evolution of hydrochloric acid and formation of the isocyanate (II). This reactive substance was obtained as an oil which could be distilled without decomposition, but was transformed by the action of water into the urea, $\text{CO}(\text{NH}.\text{CH}_2\text{COOH})_2$, originally obtained by Fischer.⁴

In the light of these developments it was of especial interest to investigate the behavior of thiophosgene towards the hydrochloride of ethyl aminoacetate. We now find that these substances interact at the temperature of boiling toluene giving Klason's ethyl isothiocyanacetate. In fact the yield is excellent and the ester can be synthesized in quantity without difficulty. We obtained no evidence of the formation of the thio-urea, $\text{CS}(\text{NHCH}_2\text{COOC}_2\text{H}_5)_2$. The reaction is expressed by the following equation:

¹ Wheeler and Merriam, *THIS JOURNAL*, **23**, 183 (1901).

² *Ber.*, **34**, 440 (1901).

³ *Compt. rend.*, **143**, 119 (1906).

⁴ *Loc. cit.*

From this result it is apparent that the equation formulated by Klason¹ to express the behavior of thiophosgene towards ethyl aminoacetate applies only when one molecular proportion of thiophosgene is used. The incorporation of an excess of thiophosgene would lead to a complete transformation of the aminoacetate into the corresponding isothiocyanate. Under these conditions the reaction would conform to the following expression:

Ethyl isothiocyanacetate boils at practically the same temperature as ethyl thiocyanacetate without undergoing a molecular rearrangement. It exhibits the properties of a true mustard oil and interacts with amines giving thiourea combinations or thiohydantoates. For example, it interacts with aniline giving the same thiohydantoate as was obtained by Fischer¹ by the action of phenylisothiocyanate on ethylaminoacetate.

Especially interesting was the behavior of this ester towards anhydrous ammonia. The isomeric ethyl rhodan acetate reacts with this reagent to form the corresponding amide²— $\text{NSC} \cdot \text{CH}_2\text{CO} \cdot \text{NH}_2$. When a benzene solution of the ethyl isothiocyanacetate was saturated with ammonia gas at ordinary temperature the corresponding thiohydantoate (IV) was not formed as expected, but the mustard oil was converted practically quantitatively into 2-thiohydantoin (VI). This is a new method of entering the hydantoin series and the ease with which the hydantoin is formed at such a low temperature suggests that the thiohydantoate (IV) is not an intermediate product of the reaction. Harries and Weiss³ were unable to convert this hydantoate into 2-thiohydantoin by hydrolysis. Klason¹ accomplished the transformation by heating the hydantoate at $140\text{--}150^\circ$. Johnson⁴ recently confirmed this observation of Klason's but showed that the reaction is of no practical importance for the preparation of the thiohydantoin. It is not improbable that the ethyl isothiocyanacetate interacts with ammonia in a similar manner as its isomer (ethyl thiocyanacetate) with formation of the amide (V). If such a combination were formed it would be expected to undergo an inner condensation with formation of the 2-thiohydantoin (VI). A substituted acid amide (VII) on condensation would lead to the forma-

¹ *Loc. cit.*

² Claesson, *Ber.*, **10**, 1346 (1877).

³ *Ber.*, **33**, 3418 (1900); *Ann.*, **327**, 355.

⁴ *THIS JOURNAL*, **35**, 780 (1913).

tion 1-phenyl-2-thiohydantoin (VIII). It has been shown in a paper from this laboratory¹ that the corresponding anilides of rhodanacetic acid (IX) condense in an entirely different manner, giving pseudothiohydantoin combinations (X).

It is our intention to investigate the action of thiophosgene on other α -aminoacids and to develop new reactions which will serve to distinguish polyketidethiocyanates (XI) from polyketideisothiocyanates (XII).

Experimental Part.

The Preparation of Thiophosgene, CSCl_2 .—All the thiophosgene used in our work was manufactured by reduction of tetrachloromethylmercaptan with stannous chloride according to the method of Kern and Sandoz.² The tetrachloromethylmercaptan was prepared by chlorination of carbon bisulfide.³ We have prepared several thousand grams of this reagent this year, and have in progress several researches dealing with its application for synthetical purposes. The operation is carried on in the following manner: Five pounds of carbon bisulfide, to which is added about 5 g. of iodine as a catalyzer, are placed in a large bottle and cooled with ice-water. This bottle is connected with a condenser and the operation conducted in a hood. Chlorine gas from a bomb is then passed rapidly into the bisulfide until the increase in weight corresponds to 5 atomic

¹ Wheeler and Johnson, *Am. Chem. J.*, **28**, 121 (1902).

² *Jahresbr.*, **1887**, 2545; *Monit. scientif.*, [4] **1**, 1328.

³ P. Klason, *Ber.*, **20**, 2376 (1887).

proportions of the halogen. The crude reaction product is then washed by pouring into a tall, cylindrical glass retort and allowing water to circulate through the oil from the bottom. By running a constant stream of cold water beneath the oil and allowing to rise through it the sulfur halides are slowly decomposed and the soluble material gradually carried away. The tetrachloromethylmercaptan is thus obtained as a heavy oil and can be tapped off and distilled with steam to remove the last traces of sulfur halides. This last operation was applied twice and the mercaptan derivative then heated at 142° in an oil bath to remove carbon tetrachloride. This crude tetrachloromethylmercaptan was then used for the preparation of thiophosgene. From 5 pounds of carbon bisulfide we obtained 4.5 pounds of the tetrachloride. In order to prepare thiophosgene, 1.5 pounds of this tetrachloride were reduced at a time when we obtained from the 4.5 pounds of mercaptan 2.33 pounds of thiophosgene, corresponding to 84% of a theoretical yield. This was then bottled and used as needed in our research.

Preparation of the Hydrochloride of Ethyl Aminoacetate, $\text{HCl} \cdot \text{NH}_2 \cdot \text{CH}_2\text{COOC}_2\text{H}_5$.—All the ester used was prepared by esterification of methylene-aminoacetonitrile according to the directions of Klages.¹ Since potassium cyanide was not available we utilized commercial sodium cyanide for the manufacture of the nitrile. The modified procedure was not productive of as good yields as those obtained by Klages when potassium cyanide was used. The sodium cyanide seemed to favor the formation of the lower melting modification of methyleneaminoacetonitrile (m. $86-87^{\circ}$). From 6000 g. of commercial 40% formaldehyde we obtained 853 g. of methyleneaminoacetonitrile melting at $127-128^{\circ}$ and 328 g. of the lower melting modification. By hydrolysis of the 853 g. of methyleneaminoacetonitrile with alcohol and hydrochloric acid we obtained 1004 g. of the hydrochloride of ethyl aminoacetate.

The Action of Thiophosgene on the Hydrochloride of Ethyl Aminoacetate. The Formation of Ethyl Isothiocyanacetate, $\text{SCN} \cdot \text{CH}_2\text{COOC}_2\text{H}_5$.—This mustard oil is formed by the action of thiophosgene on the hydrochloride in either benzene or toluene solution. The yield is about 20 per cent. of theory when benzene is used and 50–60% when toluene is employed. Four hundred and twenty-five grams of the hydrochloride of ethylaminoacetate suspended in 600 cc. of toluene were heated in an oil bath at $110-115^{\circ}$, and 405 g. of thiophosgene (slightly more than one molecular proportion) added in small quantities during the course of eight hours. This mixture was then boiled gently for about one day in order to complete the reaction. There was still unaltered hydrochloride present after this treatment. This was separated by filtration and dried in the

¹ *Ber.*, 36, 1507 (1903).

air. It weighed 68 g. This was suspended again in fresh toluene and heated with an excess of thiophosgene in order to convert it completely into the mustard oil. After the reaction was complete the toluene was removed by heating at 100° under diminished pressure, when the isothiocyanate was obtained as a dark-colored oil. This new mustard oil was purified by distillation under diminished pressure. It boiled at $112-113^{\circ}$ at 12 mm. and the yield corresponded to 60% of theory. In two other experiments our product boiled at 110° at 10 mm. and 113° at 15 mm. From 874 g. of the hydrochloride and 2.3 pounds of thiophosgene we obtained in all 642 g. of pure distilled isothiocyanate. This is a yield of 70% of the theoretical calculating from the weight of the hydrochloride used. In other words, from 5 pounds of carbon bisulfide, 11.6 pounds of chlorine and 6000 g. of 40% formaldehyde were produced 642 g. of mustard oil. This oil is colorless when first distilled, but turns red on standing. Under atmospheric pressure it boils at 215° with partial decomposition. Its density is 1.1710 at 20° (Westphal) and its refractive index is $N_D^{20} = 1.5038$ (Abbe) and 1.5028 (Pulfrich).

Calc. for $C_8H_7O_2NS$: N, 9.67%. Found: N, 9.73, 9.41.

The Action of Ammonia on Ethyl Isothiocyanacetate. The Formation of 2-Thiohydantoin.—Five grams of ethyl isothiocyanacetate were dissolved in 50 cc. of benzene and dry ammonia gas passed through the solution for one hour. There was an immediate reaction and during the operation a crystalline product separated from the benzene. This was identified as 2-thiohydantoin. It was purified by crystallization from alcohol and melted at 227° with decomposition. To further establish its identity it was mixed with 2-thiohydantoin prepared according to the method described by Johnson and Nicolet¹ and a melting point taken. The mixture and the pure hydantoin melted at exactly the same temperature.

Behavior of Ethyl Isothiocyanacetate towards Aromatic Amides.

Action of Aniline: Ethyl 1-Phenylthiohydantoate, $C_6H_5.NH.CS.NH.CH_2COOC_2H_5$.—Two and two-tenths grams of ethyl isothiocyanacetate and 1.4 grams of aniline were dissolved in 60 cc. of ether and the mixture digested on the water bath for several hours. On allowing the ether to evaporate spontaneously the above hydantoate was obtained in a crystalline condition. It crystallized from ether in the form of plates and melted at 89° to an oil. Fischer² prepared this same compound by the action of phenylisothiocyanate on ethyl aminoacetate and assigned to it a melting point of 85° .

Calc. for $C_{11}H_{14}O_2N_2S$: N, 11.74%. Found: N, 11.58, 11.51.

Ethyl *p*-Tolylthiohydantoate, $CH_3C_6H_4NHCSNHCH_2COOC_2H_5$.—This

¹ THIS JOURNAL, 33, 1974 (1911).

² *Loc. cit.*

was easily obtained by action of *p*-toluidine on ethyl isothiocyanacetate. It was purified by crystallization from ether and alcohol and separated in long needles which melted at 96°. The hydantoate is soluble in benzene, ether and alcohol and insoluble in water.

Calc. for $C_{12}H_{16}O_2N_2S$: N, 11.13%. Found: N, 11.01, 10.96.

Ethyl *o*-Tolylthiohydantoate, $CH_3C_6H_4NHCSNHCH_2COOC_2H_5$.—From *o*-toluidine and ethyl isothiocyanacetate. The compound is soluble in alcohol and ether and insoluble in water. It melts at 90°.

Calc. for $C_{12}H_{16}O_2N_2S$: N, 11.13%. Found: N, 11.00, 10.97.

Ethyl *m*-Tolylthiohydantoate, $CH_3C_6H_4NHCSNHCH_2COOC_2H_5$.—From *m*-toluidine and ethyl isothiocyanacetate. It crystallizes from alcohol or ether in the form of prismatic needles and melts at 97°.

Calc. for $C_{12}H_{16}O_2N_2S$: N, 11.13%. Found: N, 11.25, 11.21.

Ethyl *p*-Nitrophenylthiohydantoate, $NO_2.C_6H_4NHCSNHCH_2COOC_2H_5$.—This ester crystallizes from alcohol in the form of light yellow needles arranged in rosets. It melts at 191.5°.

Calc. for $C_{11}H_{13}O_4N_3S$: N, 14.87%. Found: N, 14.82, 15.00.

The Action of Thiophosgene on the Hydrochloride of Glycocoll.—Twenty grams of the hydrochloride of glycocoll were suspended in 60 cc. of toluene and 22 g. of thiophosgene added to the toluene. The mixture was then digested for two days at 110–115°. The unaltered hydrochloride was then separated by filtration and dried. Practically the whole amount taken was recovered unaltered.

NEW HAVEN, CONN.

[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXXX. THE MECHANISM OF THE ACTION OF BROMINE ON 2-MERCAPTOPYRIMIDINES.

BY TREAT B. JOHNSON AND A. WILLARD JOYCE.

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It is known that 6-oxypyrimidines of the three types represented by uracil (I), 2-methylmercapto-6-oxypyrimidine (II), and isocytosine or 2-amino-6-oxypyrimidine (III), interact, respectively, with chlorine, bromine and iodine with substitution of one hydrogen atom of the pyrimidine ring by halogen. Wheeler and Bristol¹ showed that the 5-position of the pyrimidine ring is the point of attack in such reactions leading to the formation of the corresponding 5-halogenated pyrimidines (VII, VIII and IX). These transformations, when bromine is used, are represented by the following formulas:

¹ *Am. Chem. J.*, **33**, 437 (1905); Johnson and Johns, *Ibid.*, **34**, 175 (1905); *J. Biol. Chem.*, **1**, 305 (1905).