

stituted. After the removal of the aniline, the solution was strongly acidified with hydrochloric acid, and then evaporated to dryness. This manipulation apparently prevented the formation of resinous materials, or at least accomplished their solution, for upon extraction with absolute alcohol, 47 g. of amino-acetanilide hydrochloride was obtained. We have been unable to better this yield, which is approximately 35%.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY.]

RESEARCHES ON THIOCYANATES AND ISOTHIOCYANATES.  
XIV. A NEW METHOD OF SYNTHESIZING  
2-THIOHYDANTOINS.

BY TREAT B. JOHNSON, ARTHUR J. HILL AND ERWIN B. KELSEY.

Received May 24, 1920.

At the present time there exists a difference of opinion with respect to the chemical behavior of potassium and sodium thiocyanates towards the anilide derivatives of chloro-acetic acid, II. It is well known that these salts of thiocyanic acid interact with halides of this



I

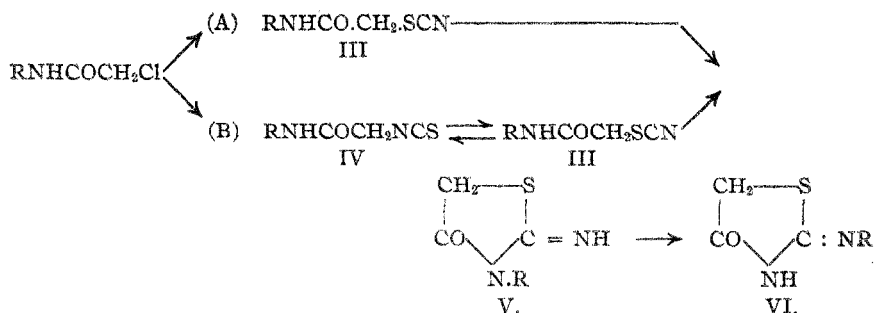


II

type II, to give rhodanide or thiocyanate combinations which easily undergo isomerization to cyclic pseudo-thiohydantoin. One interpretation of the mechanism of this characteristic change is based on the assumption that the primary reaction involves the formation of a normal thiocyanate, III, which then undergoes rearrangement to give labile and stable pseudo-thiohydantoin (V and VI). The other conception is a mechanism of reaction involving the formation of an isothiocyanate IV as the primary product of reaction. This change is then followed by a triple rearrangement giving first the normal thiocyanate III and, finally, the 2 modifications of the pseudo-thiohydantoin. In other words, one group<sup>1</sup> of workers conceives the normal thiocyanate III as the only acyclic product of reaction to be considered, while the other group<sup>2</sup> views this primary change as a tautomeric one giving either a thiocyanate, an isothiocyanate or a mixture of these 2 isomers in unstable equilibrium. In some cases the thiocyanate structure predominates, and in others the mustard oil or iso-thiocyanate, depending on the constitution of the anilide. The two interpretations of the mechanism of reaction may be expressed as follows.

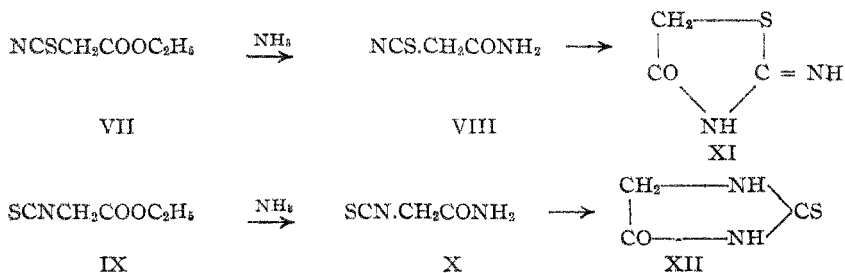
<sup>1</sup> Wheeler and Merriam, *THIS JOURNAL*, 23, 283 (1900); Wheeler and Johnson, *Am. Chem. J.*, 28, 121 (1902); Johnson, *THIS JOURNAL*, 25, 483 (1903); Johnson and Ticknor, *Proc. Nat. Acad. Sci.*, 3, 303 (1917); *THIS JOURNAL*, 40, 636 (1918).

<sup>2</sup> Beckurts and Frerichs, *Arch. Pharm.*, 237, 286, 304 (1899); 238, 9, 329, 615 (1900); Grothe, *ibid.*, 258, 160 (1900); Beckurts and Frerichs, *ibid.*, 253, 233 (1915); Frerichs and Foster, *C. A.*, 4, 2294 (1910).



It was for the purpose of throwing new light on this interesting question that we undertook the work now discussed in this paper. We now present new and very conclusive evidence that these reactions proceed according to Scheme A, or that an isothiocyanate IV is not a product of reaction in these transformations. We have obtained no evidence supporting the assumption that a thiocyanate corresponding to Formula III can undergo rearrangement to its isomeric isothiocyanate IV as expressed in Scheme B.

In a previous paper from the Sheffield Laboratory by Johnson and Hemingway,<sup>1</sup> it was shown that the ethyl ester of iso-thiocyano-acetic acid, IX, interacts with ammonia in benzene solution in a unique manner. Instead of combining as expected to form the corresponding thio-urea derivative,  $\text{NH}_2\text{SCNH.CH}_2\text{COOC}_2\text{H}_5$ , they interact smoothly to give the normal 2-thiohydantoin XII. In other words, the ester grouping is the point of attack by ammonia, giving apparently an amide of iso-thiocyano-acetic acid X as an intermediate product, which immediately condenses at low temperature, giving the 2-thiohydantoin XII. Thus, while the 2 isomeric esters VII and IX react with ammonia in an analogous manner, the products of reaction isomerize in an entirely different manner, giving *pseudo*- and *normal*-thiohydantoin, respectively.<sup>2</sup>



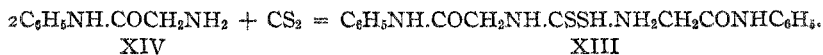
This unique behavior of ethyl iso-thiocyano-acetate in the presence of ammonia suggested to the writer that a substituted amide of iso-thio-

<sup>1</sup> THIS JOURNAL, 38, 1550 (1916).

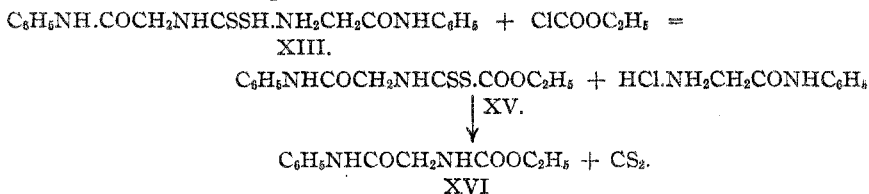
<sup>2</sup> Claesson, *Ber.*, 10, 1349 (1877); Miolati, *Gazz. chim. ital.*, [1] 23, 94 (1893); Johnson and Hemingway, *loc. cit.*

cyano-acetic acid (Formula IV), if once formed, would behave in a manner similar to its prototype X, and would undergo immediate isomerization to a substituted 2-thiohydantoin. In order to decide this point and, furthermore, to obtain experimental evidence in favor of Equations A or B represented above, it only remained, therefore, to synthesize an anilide of this type IV by a method which excludes from consideration the possible formation of an isomeric thiocyanate III and study its chemical behavior. A method of synthesis which permits us to obtain isothiocyanate combinations of this type has now been worked out and applied successfully for the preparation of the anilide of iso-thiocyanacetic acid XVII. The further application of this synthesis is now in progress and the results obtained will be published in a later paper.

The starting point of our synthesis is the anilide of amino-acetic acid XIV, which can be obtained easily and in quantity for synthetical work by the method of preparation recently described by Hill and Kelsey.<sup>1</sup> Interaction of this anilide XIV with carbon disulfide in alcohol solution at ordinary temperature leads to the formation of an almost quantitative yield of the corresponding dithio-carbamate XIII. This change is expressed by the following equation:



The next stage of our synthesis is the treatment of this salt XIII with ethyl chloroformate in ether solution when 2 compounds are formed as products of the reaction, namely, the urethane and the dithio-carbamate corresponding to Formulas XVI and XV, respectively. The dithio-carbamate is the chief product of reaction.



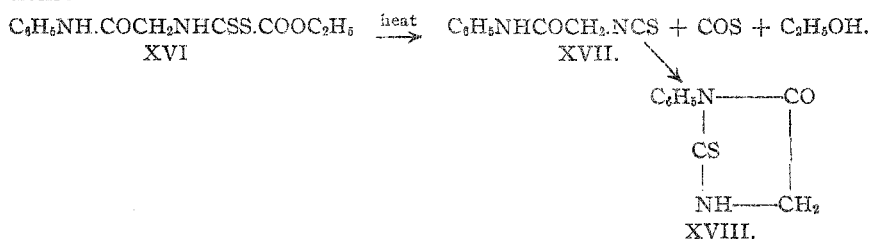
Andreasch<sup>2</sup> has shown that dithio-carbamates corresponding to Formula XV decompose on distillation with formation of iso-thiocyanates. Johnson and Ticknor<sup>3</sup> prepared the dithio-carbamate of ethyl amino-acetate and showed that this compound undergoes an analogous change on heating, giving the corresponding iso-thiocyanate IX. We now find that the ester XV breaks down in a similar manner on distillation, giving the desired anilide of iso-thiocyanacetic acid XVII. This compound, however, was not isolated on account of its great instability. Just as we an-

<sup>1</sup> THIS JOURNAL, 42, 1704 (1920)

<sup>2</sup> Andreasch, *Monatsh.*, 27, 1906 (1211).

<sup>3</sup> *Loc. cit.*

tipicated, it exhibited a unique behavior and underwent an immediate isomerization at the temperature of formation giving quantitatively 1-phenyl-2-thiohydantoin.<sup>1</sup> We obtained no evidence of the formation of the labile or stable forms of phenyl pseudo-thiohydantoin V and VI (R = phenyl), proving that the normal thiocyno-acetanilide III is not formed here in this change by molecular rearrangement of the iso-thio-cyanate XVII. This result again confirms our previous conclusions that the change  $R.SCN \rightarrow R.NCS$  is not a reversible reaction, and that a normal thiocyanate is the primary product of reaction when potassium thiocyanate interacts with an anilide derivative of chloro-acetic acid. These fundamental changes are expressed by the following equations:



The 1-phenyl-2-thiohydantoin is also formed by distillation of the dithiocarbamic acid salt XIII with mercuric chloride. This change involves the primary formation of the iso-thiocyanate XVII and then a molecular rearrangement to the thiohydantoin XVIII.

This new method of synthesizing 2-thiohydantoin will be thoroughly investigated in this laboratory and the results obtained described in a future publication. We shall investigate particularly those cases where it has been interpreted that iso-thiocyanates are the products of reaction when an alkali thiocyanate interacts with an anilide derivative of chloro-acetic acid. For further information regarding the details of our work the reader is referred to the experimental part of this paper.

#### Experimental Part.

**Amino-acetanilide,  $\text{NH}_2\text{CH}_2\text{CONHC}_6\text{H}_5$ .**—All of this reagent used in the following research was prepared according to the method recently described by Hill and Kelsey.<sup>2</sup>

**Interaction of Amino-acetanilide with Carbon Disulfide. The Formation of Amino-acetanilide Dithio-carbamate,  $\text{C}_6\text{H}_5\text{NH.CO.CH}_2\text{NH.CSSH.NH}_2\text{CH}_2\text{CONHC}_6\text{H}_5$ .**—The method of operation which led to the production of a good yield of this new salt was as follows.

Fifty-five g. (1.33 moles) of carbon disulfide was slowly added, with

<sup>1</sup> Aschan, *Ber.*, 17, 420 (1884); Marckwald, Neumark and Stelzner, *ibid.*, 24, 3278 (1891); Wheeler and Brautlecht, *Am. Chem. J.*, 45, 446 (1911).

<sup>2</sup> *Loc. cit.*

frequent agitation, to a well cooled solution of 175 g. of dry amino-acetanilide (2 moles) in 300 cc. of absolute alcohol. A slightly endothermic reaction took place. When approximately  $\frac{2}{3}$  of the carbon disulfide had been added a white solid began to separate from the reaction mixture, and when all had been added, the solution became quite solid from a mass of small colorless needles.

After standing for about one hour, the insoluble dithio-carbamate was filtered off and then triturated very thoroughly with 500 cc. of cold water in order to remove unchanged amino-acetanilide. Following this treatment, it was washed successively with small amounts of alcohol and ether, and then dried at a temperature of  $50^{\circ}$ . The yield was 200 g. or 91%. When the reaction is applied in 95% instead of absolute alcohol the yield of carbamate is reduced considerably.

The salt is rather unstable. When moderately heated, or even when allowed to stand exposed to the air for a few hours, it turns a delicate pink color and the odor of hydrogen sulfide is plainly perceptible. On this account, the salt was always freshly prepared for reactions in which it was to be used.

It is fairly soluble in alcohol, but decomposes rather readily in this solvent with evolution of hydrogen sulfide. It is less soluble in warm water and apparently more stable in this solvent than in alcohol. From water, it crystallizes in thin plates of a light salmon color, which melt at  $145^{\circ}$  with decomposition.

For analysis the salt was crystallized from water, washed with alcohol and ether, and then dried at room temperature.

Calc. for  $C_{17}H_{20}O_2N_4S_2$ : N, 14.89; S, 17.03. Found: N, (I) 14.88; (II) 14.96; S, 16.84.

**Carbethoxyl Amino-acetanilide Dithio-carbamate**,  $C_8H_9NHC(=O)CH_2NHCSS.COOC_2H_5$ .—This interesting anhydride is formed by the action of ethyl chloroformate on amino-acetanilide dithio-carbamate suspended in anhydrous ether.

Two hundred g. of the finely pulverized dithio-carbamate was suspended in one liter of anhydrous ether and 57 g. (one molecule) of ethyl chloroformate added rather rapidly, with thorough agitation. No visible reaction occurred. The mixture was then heated gently on the water bath for 3 hours. During the period of heating it was found desirable to agitate the solution frequently in order to prevent caking. After standing in the cold for 12 hours, the ether solution had assumed a yellow color and the insoluble residue was more granular in appearance than the original material.

The suspension was then filtered, the precipitate was washed repeatedly with fresh ether, and the washings were added to the original filtrate. If the reaction had proceeded quantitatively, the residue should have

weighed 99 g. We obtained 165 g. of a mixture consisting of amino-acetanilide hydrochloride and unchanged dithio-carbamate. The ether solution was found to contain unchanged ethyl chloroformate corresponding to the unaltered dithio-carbamate.

When the ether solution was evaporated, we obtained as a residue a yellow oil which soon solidified partially to a mass of light yellow crystals. The crystalline material weighed 60 g., after it was dried at room temperature, and was identified as a mixture of the dithio-anhydride and the normal urethane of amino-acetanilide. The air-dried product decomposes at 100° with considerable effervescence. It has a pleasant aromatic odor. Owing to its instability in almost all solvents except ether, it is practically impossible to obtain it in a state of purity. Its principle impurity, the urethane described below, can be removed only in part by trituration with ether.

Several attempts were made to improve the yields in this reaction. The best results were obtained by using smaller amounts of the reacting substances and increasing the proportion of ethyl chloroformate to 1.33 moles. Under these conditions a yield of 47% was obtained. A vigorous mechanical agitation of the reaction mixture would undoubtedly increase this yield.

The analyses of the reaction product showed results low for sulfur and high for nitrogen. It was contaminated with small quantities of the urethane,  $C_6H_5NHCOCH_2NHCOOC_2H_5$ , which could not be removed completely owing to the fact that the instability of the dithio-carbamic ester rendered it impossible to utilize a choice of solvents in order to effect the separation.

Calc. for  $C_{12}H_{14}O_2N_2S_2$ : N, 9.4. Calc. for  $C_{11}H_{14}O_2N_2$ : N, 12.6. Found: 10.2, 10.4.

The urethane formed in this process is not a product of reaction between ethyl chloroformate and the hydrochloride of amino-acetanilide. For example, 10 g. of the hydrochloride and ethyl chloroformate, respectively, were suspended in 50 cc. of ether and the solution was boiled for 4 hours. The resulting precipitate remaining after this treatment was then filtered off and was identified as unchanged hydrochloride. Evaporation of the ether left behind a clear oil which was identified as unaltered ethyl chloroformate. The weight of the latter was practically the same as that originally taken (10 g.).

**Behavior of Carbethoxyl Amino-acetanilide Dithio-carbamate on Distillation. Its Conversion into 1 - Phenyl - 2 - thiohydantoin,  $C_6H_5NCSNHCH_2CO$ .**—Sixty g. of the air-dried ester were placed in a

distilling flask which was connected with a small ice-cooled receiver, and this in turn with a bulb containing a strong solution of sodium hydrox-

ide in 50% alcohol. The system was evacuated to a pressure of 55 mm. and the ester heated in an oil bath to a temperature of 120° when decomposition ensued, and soon became so brisk that the vacuum was practically lost. A few cc. of a colorless distillate collected in the receiver. The contents of the flask were liquid at first but soon set to a light brown mass. After the decomposition was over the vacuum was restored and the heating was continued for 15 minutes. The products of the reaction were investigated as follows:

The caustic alkali solution, through which the gases of decomposition were passed during destructive distillation was evaporated nearly to dryness on the steam-bath in order to remove the alcohol. The residual aqueous solution gave a strong positive test for sulfur, indicating that carbon oxysulfide or carbon disulfide had been evolved during distillation.

The distillate collected in the receiver boiled at 80° under atmospheric pressure. It gave iodoform with caustic potash and iodine, and acetaldehyde by oxidation with potassium dichromate and sulfuric acid. The distillate was, therefore, ethyl alcohol and the total amount collected was 6 g. or 66%.

The residue in the flask was of a light brown color and crystal faces could be detected throughout the mass. The customary tests for a mustard oil gave negative results. A small portion, however, when digested with alkaline lead acetate, gave a black precipitate of lead sulfide. The entire residue was warmed with 100 cc. of alcohol in order to disintegrate the cake. The highly colored alcoholic liquors were filtered and the residual solid washed with fresh alcohol. As a result of this treatment a yellow, finely crystalline material was obtained. The total weight of the latter was 30 g. It was sparingly soluble in glacial acetic acid and in alcohol. After crystallization from the latter solvent it melted at 240-242° with slight decomposition. The melting point was identical with that of 1-phenyl-2-thiohydantoin. A mixture of the 2 substances melted also at 240°. That we were dealing with this hydantoin was also established by its behavior towards benzaldehyde and chloro-acetic acid.

**Condensation with Benzaldehyde. 1-Phenyl-2-thio-4-benzalhydantoin,**  $C_6H_5N.CS.NHC : (CHC_6H_5).CO.$ —Five g. of 1-phenyl-2-thiohy-

dantoin was digested in an oil bath with 3 g. of benzaldehyde and 10 g. of sodium acetate in 60 g. of glacial acetic acid. After being heated for 2 hours the mixture was poured into water. A yellow solid immediately separated. This product was filtered and then purified by crystallization from alcohol. The melting point of the compound corresponded to that of 1-phenyl-2-thio-4-benzalhydantoin and a mixture of the two melted unchanged at 204°.<sup>1</sup>

<sup>1</sup> Wheeler and Brautlecht, *loc. cit.*

**Desulfurization of the Thiohydantoin by Digestion with Chloroacetic Acid.** 1-Phenylhydantoin,  $C_6H_5N.CO.NH.CH_2.CO.$ —Five g. of

the thiohydantoin was digested on the water bath for 2.5 hours with a solution of 15 g. of chloro-acetic acid in 75 cc. of water. After filtration, the solution was evaporated to a small volume on the water bath. After trituration with ether to remove oily products, a white solid crystallized from the liquor. This was filtered and then crystallized from a small volume of water. It crystallized from this solvent in glistening needles melting at  $159^\circ$  (corr.).<sup>1</sup> A mixture of this substance with 1-phenylhydantoin melted at the same temperature.

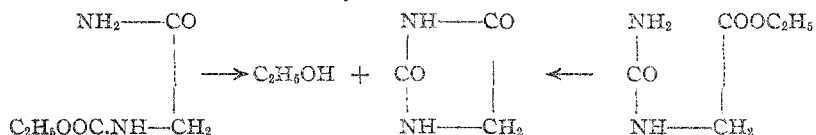
**Carbethoxy Amino-acetanilide**,  $C_6H_5NHC(O)CH_2NHCOOC_2H_5.$ —The alcoholic liquors resulting from the trituration of the crude 1-phenyl-2-thiohydantoin (above) were evaporated to dryness. The residue was then redissolved in a small volume of alcohol and decolorized with a little of the vegetable carbon "Norite." When this solution was diluted with 5 volumes of water and then cooled a colorless compound finally crystallized from the solution in characteristic plates melting at  $137.5^\circ$ . Seven g. of this solid was obtained; it was identified as the urethane derivative.

Calc. for  $C_{11}H_{14}O_5N_2$ : N, 12.61. Found: (Kjeldahl) (I), 12.78, (II), 12.52.

Four g. of ethyl chloroformate was slowly added to a suspension of 10 g. of amino-acetanilide in 75 cc. of dry ether. A fairly vigorous reaction ensued. After the addition of the ester, the solution was warmed for 2 hours on the steam bath. The precipitate was then filtered and triturated with 100 cc. of water in order to remove the hydrochloride of amino-acetanilide and the insoluble material crystallized from dil. alcohol. It melted at  $137.5^\circ$  and proved to be identical with that produced by destructive distillation during the formation of 1-phenyl-2-thiohydantoin. The urethane is quite soluble in alcohol and sparingly soluble in ether and hot water.

**The Conversion of Carbethoxy Amino-acetanilide into 1-Phenylhydantoin**,  $C_6H_5N.CO.NH.CH_2.CO.$ —Fischer and Otto<sup>2</sup> were unable

to convert carbethoxy-glycinamide into hydantoin either by application of heat or by treatment with acid or alkali. In fact they were led to suggest this reaction as a means of differentiation between this type of urethane and the isomeric hydantoic esters.



<sup>1</sup> Mouneyrat, *Ber.*, 33, 2394 (1900).

<sup>2</sup> *Ibid.*, 36, 2109 (1903).



Later, however, Koenig and Mylo<sup>1</sup> were successful in accomplishing this transformation by means of a dil. solution of sodium hydroxide, followed by treatment with dil. hydrochloric acid. Their yield, however, was very poor.

In the light of the above work it seemed of interest to determine whether the introduction of the phenyl group, as in the case of carbethoxy-amino-acetanilide would affect the reactivity of the adjacent hydrogen atom. Five g. of the urethane was added to a warm solution of 2 g. of potassium hydroxide in 50 cc. of alcohol, and the mixture was allowed to stand for 18 hours. The solution was then made strongly acid with alcoholic hydrochloric acid. After filtration of the precipitated potassium chloride, the filtrate was evaporated to a small volume on the steam-bath. A colorless solid was precipitated by the addition of 2 volumes of ether. This material was filtered off and purified by crystallization from hot water, when it was obtained in the form of colorless needles melting at 159°. It proved to be identical with 1-phenylhydantoin and melted at an unchanged temperature when mixed with a known sample of this compound. The yield was 50%. Koenig and Milo obtained a 10% yield in the transformation of carbethoxy-glycinamide into hydantoin. We were unable to accomplish this change either by heat or through the agency of either aqueous or alcoholic hydrochloric acid. In the first case no reaction occurred until the product had been heated to a temperature of 260°. At this temperature decomposition took place and a resin was formed. Two hours heating with alcoholic hydrochloric acid resulted in the decomposition of our urethane into amino-acetanilide. On the other hand, evaporation with aqueous hydrochloric acid had no effect and the hydrochloric acid salt of the urethane was recovered. The latter was transformed into the urethane by treatment with sodium hydrogen carbonate.

**The Action of Mercuric Chloride on Amino-acetanilide Dithio-carbamate,  $C_6H_5NHC(O)CH_2NH.CSSH.NH_2CH_2CONHC_6H_5$ .**—This salt undergoes a normal transformation when digested with mercuric chloride and is converted into the mustard oil  $C_6H_5NH.COCH_2.NCS$ . Since the latter is unstable, it condenses to give the corresponding thiohydantoin.

Thirty g. of the dithio-carbamate was added to a solution of 10 g. of mercuric chloride in 150 cc. of water. A little less than one molecular proportion of mercuric chloride was employed in order to avoid desulfurization of the hydantoin. A white precipitate of the mercury salt soon separated, but this became black when it was gently warmed; at the same time hydrogen sulfide was evolved. Gentle heat was applied until the evolution of hydrogen sulfide had ceased. When the reaction was over, the precipitate was filtered and extracted repeatedly with hot alcohol. When the alcoholic solution was cooled, 1-phenyl-2-thiohydan-

<sup>1</sup> Ber., 41, 4431 (1908).

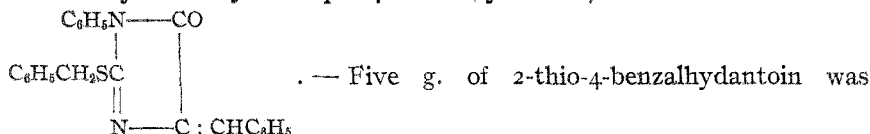
toin crystallized in characteristic prisms which melted at  $240^{\circ}$ . This melted unchanged with a known sample of 1-phenyl-2-thiohydantoin. The yield was 7 g., corresponding to 46%. It is a very significant fact that hydrogen sulfide was evolved freely in this decomposition. According to Anschutz<sup>1</sup> the hydrogen sulfide evolved in such reactions is destroyed at once by interaction with the mustard oil to give a thio-urea combination. This change is expressed as follows,



In our experiment we obtained no evidence of the formation of the thio-urea derivative of amino-acetanilide. Apparently the mustard oil derivative immediately after formation is converted into the thiohydantoin. XVIII



**1-Phenyl-2-benzylmercapto-4-benzalhydantoin,**



dissolved in a solution of sodium ethylate, prepared by dissolving 0.6 g. of sodium in 30 cc. of absolute alcohol. Then 5 g. of benzyl chloride was added slowly to the alkaline solution of the thiohydantoin. There was an immediate reaction and the solution became solid. After standing for 2 hours, the precipitate was filtered and then triturated with hot alcohol in order to separate the benzyl derivative from sodium chloride. This was then purified by crystallization from boiling alcohol and separated in the form of yellow needles melting at  $178^{\circ}$ .

Calc. for  $C_{23}H_{18}ON_2S$ : N, 7.57. Found: (Kjeldahl), 7.46, 7.74.

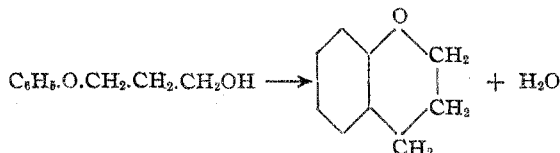
NEW HAVEN, CONN.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS.]  
**HETEROCYCLIC COMPOUNDS OF N-ARYLAMINO ALCOHOLS.**

BY R. E. RINDFUSZ AND V. L. HARNACK.

Received May 28, 1920.

A simple method has recently been published<sup>2</sup> for the preparation of chromanes and coumaranes according to the following reaction



<sup>1</sup> Anschutz, *Ann.*, **371**, 211 (1909).

<sup>2</sup> THIS JOURNAL, **41**, 665 (1919); **42**, 157 (1920).