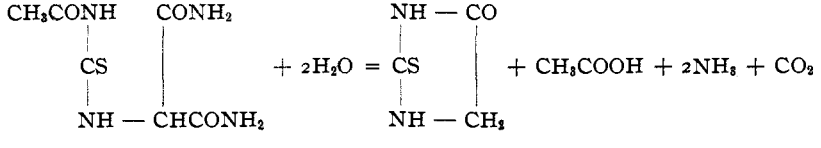
and the mixture warmed gently on the steam bath for 24 hours. On cooling, the thiourea separated. The yield was 2.3 grams. The compound is difficultly soluble in both water and alcohol and crystallizes in fine, colorless, hair-like needles. They turned dark when heated above 220°, finally melting at about 254° with strong effervescence.

Calculated for $C_6H_{10}O_3N_4S$: N, 25.64. Found: N, 25.83, 25.14.

Five-tenths of a gram of the above compound was digested for a few hours with an excess of 20% hydrochloric acid. The acid was then evaporated and the residue crystallized from water. Brown prisms separated which melted at 228° with decomposition. This contained sulfur and was identified as 2-thiohydantoin. The hydrolysis of the thioureidomalonamide may therefore be expressed by the following equation:



Benzoylpseudoethylureidomalonamide, $C_6H_5CONH.C(OC_2H_5)=N.CH(CONH_2)$.—One and five-tenths grams of aminomalonamide were warmed for 15 minutes, at 100°, with an equivalent amount of ethyl benzoylthioncarbamate, $C_6H_5CONH.CSOC_2H_5$ in 20 cc. of alcohol. Hydrogen sulfide was evolved, and the pseudourea separated. The compound is difficultly soluble in hot alcohol, from which it separates on cooling in colorless hair-like needles. The compound darkens when heated above 200° and melts at 230–240° with strong effervescence. The compound is very difficultly soluble in water. The yield was 3.0 grams, or 82% of the theoretical.

Calculated for $C_{13}H_{16}O_4N_4$: N, 19.15. Found: N, 19.4, 19.3.

NEW HAVEN, CONN.

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

RESEARCHES ON PYRIMIDINES. LXVII. THE CONDENSATION OF THIOUREA WITH ETHYL ALLYLACETOACETATE.

BY TREAT B. JOHNSON AND ARTHUR J. HILL.

Received December 20, 1913.

The behavior of thiourea, urea and guanidine towards diethyl allylmalonate (I), diethyl diallylmalonate (II), and diethyl allylbenzylmalonate (III), has been investigated by Johnson and Hill.[1] With thiourea, no one of the three malonic esters condensed normally, in alcohol solution

[1] *Am. Chem. J.*, 45, 356; 46, 537.

$CH_2 : CHCH_2CH(COOC_2H_5)_2$ I.

$(CH_2 : CHCH_2)_2C(COOC_2H_5)_2$ II.

$CH_2 : CHCH_2$
$C_6H_6CH_2$ $C(COOC_2H_5)_2$ III.

and in the presence of sodium ethylate, giving a thiobarbituric acid compound. The diallylester (II), and the benzylallyl ester (III), condensed, in the presence of sodium ethylate, forming sodium salts of malonuric acids (VI and VII, respectively). When the latter were decomposed by acids, the free malonuric acids immediately underwent isomerization and were transformed smoothly into their corresponding lactones (VIII and IX, respectively). Diethyl allylmalonate, on the other hand, reacted with thiourea in an unique manner giving an excellent yield of an interesting cyclic compound, namely, μ-amino-α-keto-β-carbethoxy-d-methyltetrahydrohexathiazole (V). The latter is a representative of a new class of cyclic compounds of which the mother substance would be hexathiazole (IV).

IV.

V.

VI.

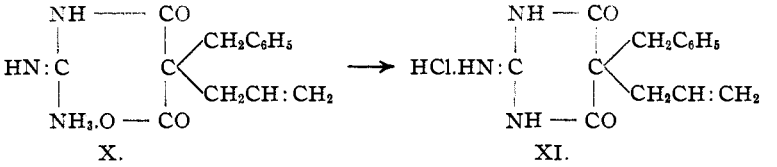
VII.

VIII.

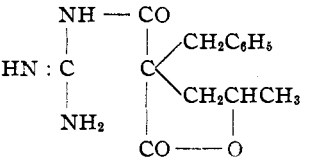
IX.

While thiourea condensed abnormally in every case, on the other hand, urea condensed normally with all three of the malonic esters, forming barbituric acid compounds. Guanidine also interacted normally with diethyl allylmalonate (I), and diethyl diallylmalonate (II), forming the corresponding pyrimidines. Diethyl allylbenzylmalonate (III), on the other hand, interacted with guanidine giving an inner cyclic salt of a

malonuric acid (X). The latter, when treated with acids, was transformed into the hydrochloride of benzylallylmalonylguanidine (XI), with formation of water. There was no tendency, apparently, for the malonuric acid, in this case, to undergo isomerization into the lactone (XII).



X. XI.



XII.

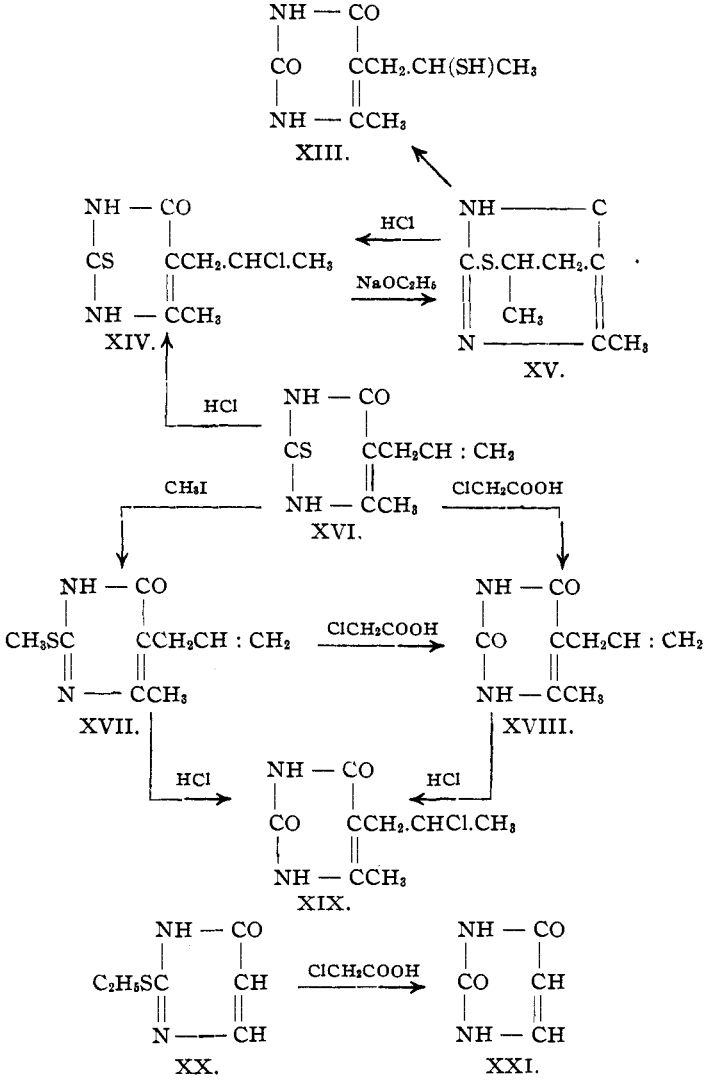
The unique results obtained by interaction of the three allylmalonic esters, I, II, and III, with thiourea were an incentive to examine the behavior of other allyl esters towards this reagent in the presence of sodium ethylate. It was of especial interest to determine, whether the presence of this unsaturated group in β-ketone esters would alter, in any way, the normal behavior of such esters when allowed to interact with thiourea. Ethyl allylacetoacetate is an ester of this type and we, therefore, selected it for this investigation.

We now find that this β-ketone ester reacts smoothly when heated with thiourea, in the presence of sodium ethylate, forming 2-thio-4-methyl-5-allyl-6-oxypyrimidine (XVI). The yield was excellent and we did not obtain evidence of any secondary and abnormal reactions. The sodium salt of this pyrimidine interacted smoothly with methyliodide, forming the corresponding mercaptopyrimidine represented by formula XVII. Both the thio- and mercaptopyrimidines (XVI and XVII, respectively) are converted smoothly into the corresponding oxygen derivative (XVIII), by digestion with chloroacetic acid. This action of chloroacetic acid on mercaptopyrimidines, leading to the formation of oxypyrimidines, is a new reaction and apparently one of general application in the pyrimidine series. 2-Ethylmercapto-6-oxypyrimidine[1] (XX), for example, is converted almost quantitatively, by interaction with this reagent, into uracil (XXI).

2-Methylmercapto-4-methyl-5-allyl-6-oxypyrimidine (XVII) can also be desulfurized by digestion with hydrochloric acid. The oxypyrimidine (XVIII), however, is not the product of the reaction, but the corresponding saturated chloropyrimidine (XIX), which results by addition of the halo-

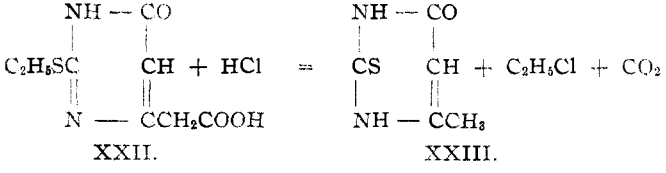
[1] Wheeler and Merriam, *Am. Chem. J.*, **29**, 478.

gen acid at the double bond of the allyl group. The same chloropyrimidine (XIX) is also formed by addition of hydrochloric acid to 2-oxy-4-methyl-5-allyl-6-oxypyrimidine. When 2-thio-4-methyl-5-allyl-6-oxypyrimidine was digested with hydrochloric acid the sulfur was not removed, but the acid added at the double bond in the allyl group, forming the 2-thiochloropyrimidine represented by formula XIV. These various transformations are represented by the following structural formulas:



Especially interesting was the behavior of the thiochloropyrimidine (XIV) when dissolved in alcohol in the presence of sodium ethylate. We were

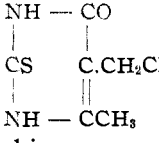
able, in this manner, to bridge across from the 2-position to the 5-position of the pyrimidine ring and obtained in excellent yield the cyclopyrimidine represented by formula XV. This interesting compound is the first representative of a new class of pyrimidines and it is our intention to continue their investigation. The cyclopyrimidine reacts in an unique manner when warmed with concentrated hydrochloric acid. They do not interact normally, as might be expected, with formation of an oxypyrimidine containing the mercapto radical in the propyl group as represented in formula XIII, but the bridge dissociates, with cleavage between sulfur and carbon, giving almost quantitatively 2-thio-4-methyl-5-chloropropyl-6-oxypyrimidine (XIV). This is our first observation, in our pyrimidine researches, that a 2-mercaptopyrimidine can be converted directly in its corresponding 2-thio-derivative, by action of hydrochloric acid, at such a low temperature. Wheeler and Liddle[1] were able to convert 2-ethylmercapto-6-oxypyrimidine-4-acetic acid (XXII), into 2-thio-4-methyluracil (XXIII), by the action of hydrochloric acid, but in order to effect the transformation it was necessary to melt the pyrimidine in a stream of dry hydrochloric acid gas, when ethyl chloride and carbon dioxide were evolved.



XXII. XXIII.

Experimental Part.

2-Thio-4-methyl-5-allyl-6-oxypyrimidine,



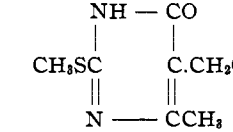
.—Six and seven-tenths grams of sodium were dissolved in 125 cc. of absolute alcohol, and 25 grams of ethyl allylacetoacetate and 13 grams of thiourea were then added. The mixture was heated on the steam bath for ten hours. The reaction was very smooth and the sodium salt of the pyrimidine began to separate within a few minutes' heating. When the reaction was complete, the alcohol was evaporated on the steam bath and the residue dissolved in a small volume of water and the solution acidified with cold, dilute sulfuric acid. Hydrogen sulfide was evolved and the pyrimidine separated as a granular powder. It was soluble in water and alcohol and insoluble in benzene. It was purified for analysis by crystallization from 95% alcohol and separated in flat prisms or rosettes which melted at 187° to an oil without effervescence The compound

[1] THIS JOURNAL, 30, 1156 (1908).

responded to a test for sulfur and was not desulfurized by digestion with mercury oxide in alcoholic solution. The yield of pure pyrimidine was 15.4 grams.

Calc. for $C_8H_{10}ON_2S$: N, 15.38%; found, 15.40, 15.25, 15.30%. Calc. for $C_8H_{10}ON_2S$: S, 17.58%; found, S, 17.8%.

2-Methylmercapto-4-methyl-5-allyl-6-oxypyrimidine,



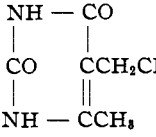
CH_3SC $C.CH_2CH : CH_2$.—Five grams of the preceding 2-thiopyrimidine

N —— CCH_3

were dissolved in absolute alcohol containing a molecular proportion of sodium ethylate, and 4.5 grams of methyliodide were then added. The solution was heated on the steam bath until neutral in reaction towards turmeric. The alcohol was then evaporated and the pyrimidine washed with water and finally purified by crystallization from alcohol or benzene. It deposited from both solvents in colorless, flat prisms which melted at 189–191° to an oil without effervescence. The pyrimidine is insoluble in water.

Calc. for $C_9H_{12}ON_2S$: N, 14.28%; found, N, 14.30, 14.15, 14.10%.

Action of $ClCH_2COOH$ on 2-Methylmercapto-4-methyl-5-allyl-6-oxypyrimidine.



2,6-Dioxy-4-methyl-5-allylpyrimidine, CO $CCH_2CH : CH_2$.—One gram of

NH — CCH_3

the mercaptopyrimidine was digested with 5 grams of chloroacetic acid in aqueous solution for 2 hours. The pyrimidine dissolved immediately and methylmercaptan was given off. After the reaction was complete, the solution was cooled, when the above oxypyrimidine separated in a crystalline condition. It was purified by crystallization from alcohol and melted at 218° without effervescence. It gave no test for sulfur.

Calc. for $C_8H_{10}O_2N_2$: N, 16.86%; found, N, 16.65%.

This same pyrimidine was also obtained by desulfurization of 2-thio-4-methyl-5-allyl-6-oxypyrimidine. Five grams of the 2-thio compound and 2 molecular proportions of chloroacetic acid (2.8 grams) were dissolved in water and the solution boiled for one hour. The thiopyrimidine dissolved quickly, upon warming, and after three-quarters of an hour the desulfurization was nearly complete, and the oxypyrimidine began to separate from the hot solution. If more than two molecular proportions of the halogen acid were used for desulfurization, the reaction was not as smooth and secondary products were formed, due apparently to further decomposition of the allylpyrimidine. The pyrimidine crystallized from

alcohol in characteristic, barrel-shaped prisms which melted at 218° without effervescence. The pyrimidine did not give tests for sulfur and chlorine.

Calc. for $C_8H_{10}O_2N_2$: N, 16.86%; found, N, 16.8%.

Action of Hydrochloric Acid on 2,6-Dioxy-4-methyl-5-allylpyrimidine.

2,6-Dioxy-4-methyl-5-(β-chloropropyl)pyrimidine, $\begin{matrix} NH-CO \\ | \quad | \\ CO \quad C \\ | \quad \| \\ NH-C \end{matrix}$ $\begin{matrix} \\ | \\ CCH_2CHClCH_3. \\ | \\ CH_3 \end{matrix}$—Five grams of the allyl pyrimidine were added to 40 cc. of concentrated hydrochloric acid. It dissolved immediately on warming After heating a short time on the steam bath, the addition of hydrochloric acid at the double bond was apparently complete and the chlorine derivative began to separate from the acid solution. The excess of acid was then removed by evaporation at 100° and the pyrimidine purified by crystallization from water or alcohol. It separated from both solvents in characteristic rosettes of minute prisms. They gave a strong test for chlorine and melted at 233° with decomposition. The pyrimidine is soluble in cold potassium hydroxide solution and is precipitated unaltered by addition of acids. It is insoluble in benzene.

Calc. for $C_8H_{11}O_2N_2Cl$: N, 13.86%; Cl, 17.32%; found, N, 13.8, 13.87%; Cl, 17.01%.

This same pyrimidine was also formed by digestion of 2-methylmercapto-4-methyl-5-allyl-6-oxypyrimidine with hydrochloric acid. Six grams of the mercapto pyrimidine were dissolved in 40 cc. of concentrated hydrochloric acid and the solution boiled for one hour, when the evolution of methylmercaptan ceased. The excess of acid was then evaporated and the pyrimidine purified by crystallization from alcohol. It melted at 233° with effervescence. A mixture of this substance and that from the previous experiment melted at the same temperature.

Action of Hydrochloric Acid on 2-Thio-4-methyl-5-allyl-6-oxypyrimidine.

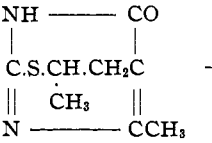
2-Thio-4-methyl-6-oxy-5-(β-chloropropyl)pyrimidine, $\begin{matrix} NH-CO \\ | \quad | \\ CS \quad C \\ | \quad \| \\ NH-CCH_3 \end{matrix}$ $\begin{matrix} \\ | \\ .CH_2CHCl.CH_3. \\ | \\ \end{matrix}$—This pyrimidine was prepared by dissolving 5 grams of the thiopyrimidine in 40 cc. of concentrated hydrochloric acid and evaporating to dryness. After repeating the operation twice, the product was recrystallized from 95% alcohol, when it separated, on cooling, in characteristic ovated prisms which melted at 218–220° with effervescence. The pyrimidine is soluble in alcohol, and difficultly soluble in water and benzene. It dissolved in cold sodium hydroxide solution and was reprecipitated unchanged

upon acidifying with hydrochloric acid. The compound gave tests for sulfur and chlorine.

Calc. for $C_8H_{11}ON_2SCl$: N, 12.84%; Cl, 16.0%; found, N, 12.75, 12.70, 12.80%; Cl, 15.74%.

The Action of Sodium Ethylate on 2-Thio-4-methyl-5-(β-chloropropyl)-6-oxypyrimidine.

2,5-Cyclopropylmercapto-4-methyl-6-oxypyrimidine,

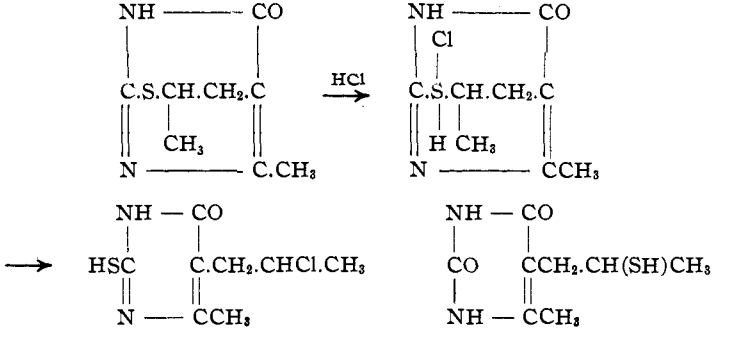


Three grams of the 2-thio-5-chloropropylpyrimidine were dissolved in absolute alcohol containing in solution a molecular proportion of sodium (0.31 gram). Upon heating on the steam bath there was an immediate reaction with separation of sodium chloride. After digestion until the reaction was complete (5 hours) the sodium chloride was separated and the alcohol solution cooled, when the above pyrimidine separated in a crystalline condition. It was purified by crystallization from water or alcohol and separated in characteristic sheaves of needles which melted at 225–227° to an oil. When mixed with the original 2-thiopyrimidine the melting point was lowered to 160°. The cyclopyrimidine is insoluble in cold benzene. It contained sulfur but was absolutely free from chlorine. The yield was excellent.

Calc. for $C_8H_{10}ON_2S$: N, 15.38%; S, 17.58%; found, N, 15.29, 15.10%; S, 17.69%.

Hydrolysis of the Cyclopyrimidine with Hydrochloric Acid.

One gram of the cyclopyrimidine was suspended in 40 cc. of concentrated hydrochloric acid. On gentle heating the pyrimidine dissolved completely. In a short time a crystalline substance began to deposit from the hot acid solution and there was no evidence of loss of volatile material. After evaporating to dryness, to remove the excess of hydrochloric acid, the substance was purified by recrystallization from 95% alcohol. It separated in the form of ovated prisms, which melted at 218–



220° with effervescence. It gave strong tests for sulfur and chlorine and was identified as 2-thio-4-methyl-5-(β-chloropropyl)-6-oxypyrimidine. A mixture of the hydrolytic product and this 2-thiopyrimidine melted at exactly the same temperature. The mechanism of the reaction may be represented by the preceding formulas. We obtained no evidence of the formation of 2,6-dioxy-4-methyl-5-(β-mercaptopropyl)pyrimidine.

The Conversion of 2-Ethylmercapto-6-oxypyrimidine into Uracil by Digestion with Chloroacetic Acid,

Five grams of the 2-mercaptopyrimidine (m. 152°) and two molecular proportions of chloroacetic acid (5 grams) were dissolved in water and the mixture boiled for one hour. Ethylmercaptan was evolved. After concentration and cooling of the solution 3.0 grams of pure uracil separated while a theoretical yield would have been 3.6 grams. The uracil was absolutely free from sulfur and crystallized in characteristic corpuscular crystals which showed no signs of melting below 300°.

NEW HAVEN, CONN.

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

RESEARCHES ON AMINES. IV.[1] THE ALKYLATION AND HYDROLYSIS OF ALIPHATIC SULFONAMIDES. A NEW SYNTHESIS OF SARCOSINE.[2]

BY TREAT B. JOHNSON AND JOSEPH A. AMBLER.

Received December 20, 1913.

CONTENTS: 1. Hinsberg's Method of Alkylation and its Practical Application. 2. The Application of Hinsberg's Reaction with Aliphatic Sulfonamides. 3. Experimental Work.

1. Hinsberg's Method of Alkylation and its Practical Application.

That sulfonamides possess acidic properties was apparently first observed by Gerhardt and his co-worker Chiozza. The announcement of this characteristic property was made in their paper entitled, "Untersuchungen über die Amide," which was published in 1853.[3] These investigators showed that acid amides are formed by the interaction of amines and acid chlorides. They not only applied this reaction successfully with chlorides of carboxylic acids, but also effected an analogous

[1] Johnson and Guest, *Am. Chem. J.*, 42, 340; 43, 310; THIS JOURNAL, 32, 761

[2] The Chairman's address, Organic Chemistry Section, 48th meeting A. C. S., Rochester, September 8–12, 1913, comprised the historical and theoretical parts of this paper.

[3] *Ann.*, 87, 299.