Calculated for $C_8H_{14}ON_2$: C, 62.34; H, 9.09
Found: C, 62.27; H, 9.18

(*e*) *Isoamylmalononitrile.*—The nitrile was prepared from isoamylcyanoacetamide (11.5 grams) and phosphorus pentachloride (5.4 grams). These substances were mixed in an Anschütz flask and heated *in vacuo*, in a metal bath at 120°–130°, to start the reaction. When the reaction was practically over, the nitrile was distilled off as a colorless liquid boiling at about 120° under 17 mm. The crude product weighed 7.5 grams, or 74% of the theoretical amount. It was shaken with water and soda solution to remove hydrogen chloride and phosphorus oxychloride, and then extracted with ether. The ether solution was dried with calcium chloride. When the ether was distilled, there remained 6.8 grams of nitrile boiling at 121°–122° under 18 mm. Its specific gravity was 0.899 at 25°. An analysis resulted as follows:

Calculated for $C_8H_{12}N_2$: C, 70.59; H, 8.82; N, 20.59
Found: C, 70.37; H, 9.14; N, 20.87

JAMES MILLIKIN UNIVERSITY, DECATUR, ILL.

[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXIII. A NEW METHOD OF SYNTHESIZING URAMILS AND THIOURAMILS.

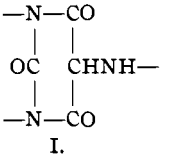
BY TREAT B. JOHNSON AND NORMAN A. SHEPARD.

Received June 10, 1913.

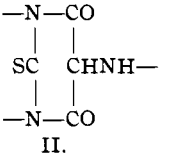
Under the term *uramil* we include in this work only pyrimidines which contain the nucleus (I). The imido derivatives are not considered. Two types of mono thiouramils are theoretically possible, one, in which the sulfur atom has displaced oxygen in position 2 of the pyrimidine ring (II), and the other, where sulfur occupies position 4 or 6 of the ring (III). Two dithiouramils are also possible, IV and V. If we disregard the imido derivatives of 2-thiouramil, which have been prepared by Traube,[1] the only thiouramils which have been described in the literature are 4-thiouramil and 1,3-dimethyl-4-thiouramil. The former was prepared independently by Weidel and Niemilowicz[2] and Fischer and Ach,[3] by heating uric acid with ammonium hydrogen sulfide. This thiouramil can be converted into uramil by oxidation with bromine. Fischer and Ach[4] prepared 1,3-dimethyl-4-thiouramil by the interaction of ammonium hydrogen sulfide with 1,3-dimethyluric acid. The methylether of 2-thiouramil has been prepared by Wheeler and Jamieson[5] and the corresponding

[1] *Ann.*, **331**, 80.
[2] *Monats.*, **16**, 729.
[3] *Ann.*, **288**, 157.
[4] *Loc. cit.*
[5] *Am. Chem. J.*, **32**, 351.

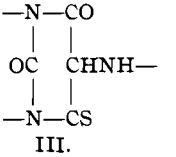
sulfur ethers of 4-thiouramil and 1,3-dimethyl-4-thiouramil were described by Fischer and Ach.



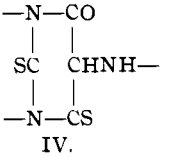
I.



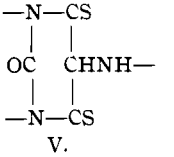
II.



III.



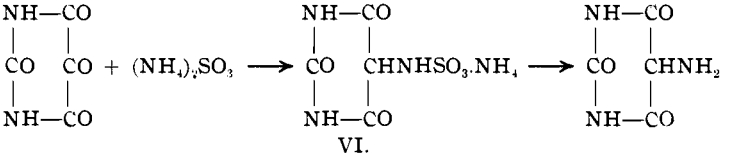
IV.



V.

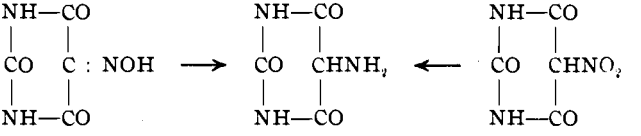
A review of the literature reveals the fact that six different methods of synthesis have been applied for the preparation of uramil and its derivatives. They may be briefly summarized as follows:

1. Alloxan, or its nitrogen substituted derivative, is heated with the sulfite of an amine when a salt of a thionuric acid (VI) is formed. The latter is then hydrolyzed with acids giving the corresponding uramil.[1] This method has received wide application, but Piloty and Finckh[2] have shown that it is not applicable with secondary amines.



VI.

2. By the reduction of violuric (VII) and dilituric acids[3] (VIII).



VII. VIII.

3. By the reduction of the phenylhydrazones of the alloxans with tin and hydrochloric acid.[4]

4. By heating the ammonium salt of dialuric acid (IX).[5] Piloty observed, however, that the reaction could not be applied with secondary amines (dimethyl amine).

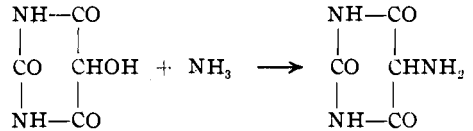
[1] Wöhler and Liebig, *Ann.*, **26**, 274, 310; Techow, *Ber.*, **27**, 3087; Fischer and Clemm, *Ibid.*, **30**, 3091; Fischer, *Ibid.*, **30**, 559.

[2] *Ann.*, **333**, 93.

[3] Baeyer, *Ann.*, **127**, 223; Sembritzki, *Ber.*, **30**, 1821; Whitely, *J. Chem. Soc. (London)*, **91**, 1340; Techow, *loc. cit.*

[4] Kuhling, *Ber.*, **24**, 4140; **31**, 1973.

[5] Piloty and Finckh, *Ann.*, **333**, 71.



IX.

5. By interaction of amines with alloxantine[1] and 6, by heating halogen derivatives of barbituric acids with ammonia. In this manner, Fischer and Dilthey[2] prepared 5,5-aminomethyl- and 5,5-aminoethylbarbituric acids (X) and (XI) from the corresponding bromine derivatives of methyl- and ethylbarbituric acids, respectively.

X. XI.

The only representatives of 7,7-disubstituted uramils are, apparently, the dibarbituryl compounds, which have been described by Mohlau and Litter.[3]

It will readily be seen, from this survey of the methods in use for the preparation of uramils, that every one employs a pyrimidine as the starting point, *viz.*, alloxan and barbituric acid or some derivative of these two compounds. No attempts have been made, so far as the writer is aware, to prepare uramil compounds by condensation of urea, thiourea or guanidine with esters of aminomalonic acids—$RNH.CH(COOC_2H_5)_2$, etc. Esters of this type can be obtained easily in quantity and it seemed very probable that they would interact with ureas giving uramil compounds, which cannot be synthesized easily by any one of the present methods. The data, which we now present, confirms this assumption.[4]

We have now investigated the interaction of urea and thiourea with two derivatives of diethyl aminomalonate, *viz.*: diethyl phthalimidomalonate[5] (XII) and diethyl anilinomalonate[6]—and also one amino acid ester, in which the amino group occupies the γ-position with respect to the ester groupings, *viz.*: diethyl β-phthalimidoethylmalonate.[7]

The action of ethyl phthalimidomalonate (XII) on urea was not in-

[1] Piloty, *Ann.*, **333**, 64; Mohlau and Litter, *J. prakt. chem.*, **73**, 472.

[2] *Ann.*, **335**, 359.

[3] *Loc. cit.*

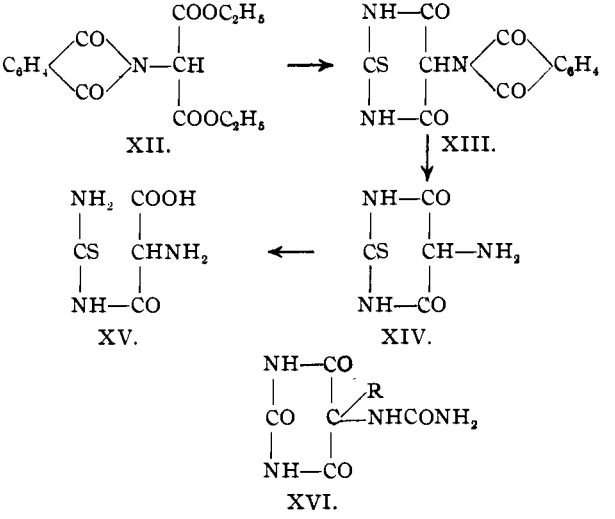
[4] Dr. B. H. Nicolet has recently been able to show that ethyl aminomalonate condenses normally with thiourea forming the hitherto unknown 2-thiouramil. This observation is one of biochemical interest. The results of Dr. Nicolet's investigation will be published in a later paper. (T. B. Johnson.)

[5] Sörensen, *Compt. rend. des travaux du Lab. de Carlsberg*, **6**, 1; *Centrbl.*, **2**, 33 (1903).

[6] Blank, *Ber.*, **31**, 1815; Curtiss, *Am. Chem. J.*, **19**, 693.

[7] Aschan, *Ber.*, **24**, 2449.

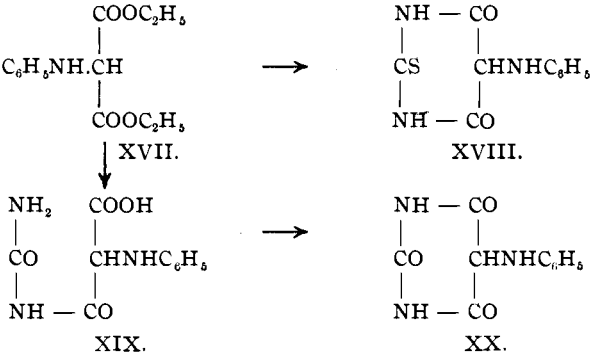
vestigated. This ester, however, condenses smoothly with thiourea, forming a pyrimidine. 2-Thio-5-phthalimidobarbituric acid (XIII) was probably formed, but underwent hydrolysis during the reaction, forming phthalic acid and 2-thiouramil (XIV). This agreed in all its properties with the uramil obtained by interaction of thiourea and diethyl aminomalonate. Since the phthalimido ester (XII) is much more easily prepared than diethyl aminomalonate, this method is to be recommended for the preparation of the thiouramil. The fact, that this phthalimido ester (Sörensen's ester) condenses so smoothly, is of especial interest and suggests that the alkyl substituted derivatives—$C_6H_4(CO)_2N.CR(COOC_2H_5)_2$ will react with thiourea also, thus making possible the synthesis of types of uramils, which have not been investigated. Uramil derivatives of type (X) are of especial interest from a physiological standpoint. Pseudouric acids of type (XVI), apparently have never been prepared.



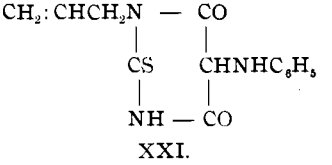
Ethyl anilinomalonate (XVII), which was the next ester examined, condensed smoothly with urea and thiourea in the presence of sodium ethylate. With thiourea, it interacts normally giving nearly a theoretical yield of 2-thio-7-phenyluramil (XVIII). This compound is a strong acid, is insoluble in hydrochloric acid and can be digested with this reagent without removal of the sulfur. Diethylanilinomalonate also condensed with allylthiourea forming 1-allyl-2-thio-7-phenyluramil (XXI). With urea the anilino ester (XVII) reacted abnormally giving an anilino derivative of malonuric acid (XIX). Malonuric acid derivatives have been described by Fischer and Dilthey[1] and also by Conrad and Zalt,[2] but, so

[1] *Ann.*, **335**, 362.
[2] *Ibid.*, **340**, 326.

far as the writer is aware, this is the first amino derivative to be described. We have also obtained evidence that 2-thiouramil undergoes hydrolysis with alkali forming the corresponding amino acid (XV). When the anilinomalonuric acid (XIX) was heated with glacial acetic acid it underwent an inner condensation and was transformed quantitatively into 7-phenyluramil (XX).

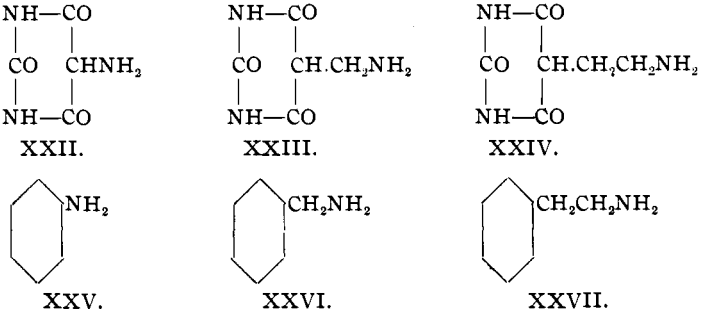


XVII. XVIII. XIX. XX.



XXI.

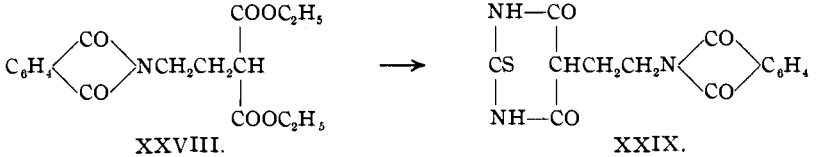
While we are familiar with the chemistry of uramils we have absolutely no knowledge of amino derivatives of barbituric acid, in which the amino group is substituted in a side chain as represented by formulas (XXIII) and (XXIV). Compounds of this type have the same relation (structurally) to uramil (XXII) as that of benzylamine (XXVI) and phenylethylamine (XXVII) to aniline (XXV) in the aromatic series. They would be expected to possess properties similar in character to those of aliphatic amines. It seemed of interest, therefore, to investigate the be-



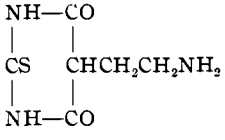
XXII. XXIII. XXIV. XXV. XXVI. XXVII.

havior towards ureas of diethyl β-phthalimidoethylmalonate (XXVIII).

With thiourea this compound interacts normally forming the corresponding barbituric acid derivative (XXIX). This was not, however, the chief product of the reaction. It was unstable in the presence of warm alkali and acids and underwent hydrolysis forming phthalic acid and the amine (XXIV). Both of these pyrimidines possessed distinctly better properties than 2-thiouramil or the 7-phenyluramils. Whereas the latter compounds are very difficultly soluble and do not decompose below 300°, these aliphatic derivatives were more soluble, showed a greater tendency to crystallize, and had sharp melting points.

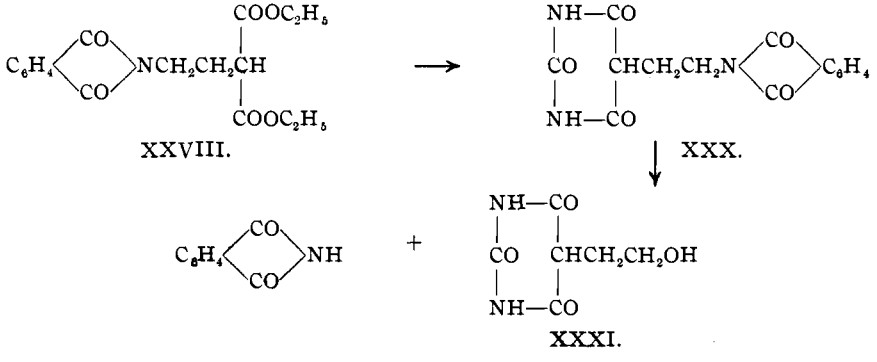


XXVIII. XXIX.



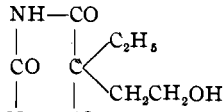
XXIV.

Some interesting results were obtained when this same ester (XXVIII) was condensed with urea in the presence of sodium ethylate. While it reacted with thiourea with formation of an amine (XXIV) and phthalic acid, the condensation product, in this case, underwent hydrolysis in an entirely different manner with formation of phthalimide and an alcohol (XXXI). We did not succeed in isolating the phthalyl compound (XXX). Hydroxyl compounds of this type (XXXI) and that represented by the unknown pyrimidine (XXXII) are of particular interest because of their relationship to veronal. Efforts will be made to synthesize pyrimidines of type (XXXII) in order to investigate their pharmacological action.



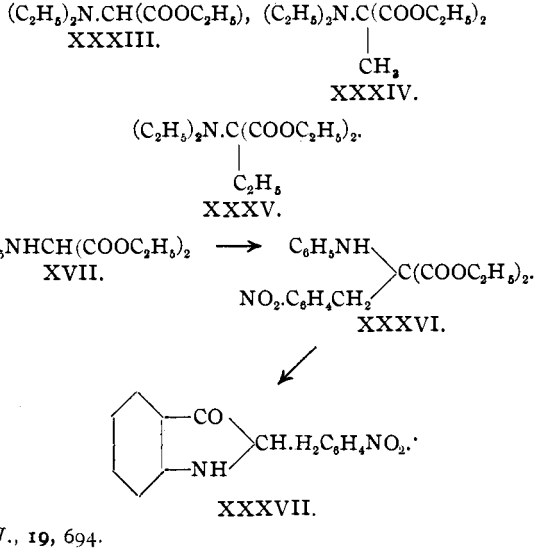
XXVIII. XXX.

XXXI.



XXXII.

Curtiss[1] states that diethyl anilinomalonate (XVII) dissolves in potassium hydroxide solution and also interacts with sodium ethylate in alcohol, at ordinary temperature, giving a sodium salt. Kereszty[2] has recently shown that the aliphatic aminomalonic esters likewise contain an acidic methylene hydrogen and form sodium salts, which react normally with alkyl halides. Diethyl diethylaminomalonate (XXXIII), for example, reacted with methyliodide and ethyliodide, in the presence of sodium ethylate, forming the corresponding alkyl derivatives (XXXIV) and (XXXV), respectively. These interesting results described by Kereszty indicated that diethyl anilinomalonate would also undergo alkylation smoothly. We now find that the sodium salt of this ester reacts immediately with *p*-nitrobenzylchloride forming diethyl *p*-nitrobenzylanilinomalonate (XXXVI). This ester was not, however, the only product of the reaction. We also succeeded in isolating another characteristic, crystallin substance, whose constitution has not been definitely established. A nitrogen determination indicated, however, that we were dealing with an indoxyl derivative and we have provisionally assigned to it the structural formula (XXXVII). The formation of this from the ester (XXXVI) would be perfectly analogous to that of ethyl indoxylcarboxyl-

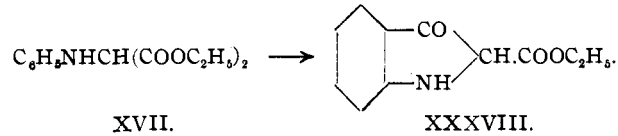


XXXVII.

[1] *Am. Chem. J.*, **19**, 694.

[2] *Chem. Ztg.*, **34**, 373 (1910).

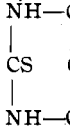
ate (XXXVIII) from diethylanilinomalonate (XVII) by application of heat.[1] Substituted indoxyls of this type apparently have not been prepared and we intend to take up their investigation in the near future.



XVII. XXXVIII.

Esters of aminomalonic ester and related compounds should be of value for further interesting syntheses and their investigation is now in progress in this laboratory.

Experimental Part.

Condensation of Thiourea with Diethyl Phthalimidomalonate. 2-Thiouramil  —Two grams of sodium were dissolved in 75 cc. of absolute alcohol and then 2.5 grams of thiourea (1.5 molecular proportions) dissolved in the solution. Seven grams of the phthalimidomalonate were then added and the mixture heated on the steambath. The ester dissolved at once and the solution assumed a deep orange color, finally becoming turbid. The heating was continued for 10 hours when a yellow, granular sodium salt was obtained in suspension in the alcohol. This was separated, dissolved in water and the solution finally acidified with acetic acid when the thiouramil separated in characteristic lenticular crystals. The yield of crude uramil was 5.5 grams. This product was difficultly soluble in water and alcohol, but was soluble in dilute alkali solution and was reprecipitated by addition of acids. It could not be obtained free from alkali salts, however, by this treatment. In order to obtain the thiouramil pure for analysis it was finally digested with a large volume of hot water. After this treatment it left no residue when burned on a platinum foil and did not melt at 300°. It was dried for analysis at 110°. Nitrogen determination (Kjeldahl):

Calculated for $C_8H_5O_2N_3S$: N, 26.4; found: N, 25.66.

When the aqueous extract above was acidified with hydrochloric acid, concentrated to a small volume, and cooled, phthalic acid separated.

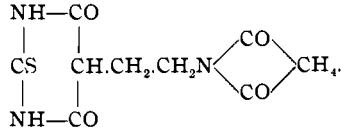
As will be observed, the percentage of nitrogen found was lower than the calculated value for thiouramil. Other methods of purification, however, did not lead to better analytical results. The thiouramil was digested with glacial acetic acid and precipitated from sodium hydroxide solution repeatedly with acetic acid but by both methods the nitrogen determinations were consistently low (N, 25.47, 25.38, 25.66 and 25.65%). It is

[1] Blank, *Ber.*, 31, 1816.

of interest to note that other investigators have observed that the nitrogen in uramil compounds is determined with difficulty. Kuhling[1] writes as follows regarding uramil: "Die volumetrische Stickstoffbestimmung fiel um etwa 2 prozent. zu niedrig aus (27.57 statt 29.3 prozent.), was aber mit den von Liebig und Wohler und von Beilstein bei der Untersuchung des Uramils gemachten Erfahrungen übereinstimmt." Matignon[2] also, in his paper entitled: "Recherches sur les Ureides," writes as follows: "Préparé avec le plus grand soin aet desséchée daus le vide sec ou á 100°, il mà été impossible d'obtenir une uramile qui donne de bous dosages d'azote; j'ai trouvé: Az. Trouvé: 28.65. Calculé: 29.37. Les dosages d'azote effectués par Liebig et Wohler sur l'uramile sout aussi un peu faibles."

Thiouramil apparently undergoes hydrolysis when warmed with sodium hydroxide solution. On acidifying the alkaline solution with acetic acid a powder separated, which had no definit melting point, and gave, on analysis, 23.9% of nitrogen. The calculated value for *aminothiomalonuric acid*, $NH_2CSNHCOCH(NH_2)COOH$, is 23.7%. The same analytical result was also obtained after drying the substance at 130°–140°, showing that the compound was not thiouramil containing water of crystallization.

Condensation of Diethyl β-Phthalimidoethylmalonate with Thiourea.

2-Thio-5-(β-phthalimidoethyl)-barbituric Acid,  .

—The phthalimidoethylmalonic ester, which was used in this work, was prepared according to the method given by Aschan,[3] and finally purified by extraction with ligröin as directed by Fischer.[4] Four and eight-tenths grams of sodium (3 molecular proportions) were dissolved in 90 cc. of absolute alcohol and 8 grams of thiourea dissolved in the solution by warming. Twenty-three grams of the phthalimidomalonate were then added and the solution heated on the steam bath. It assumed at once an orange color and in a short time a bright yellow sodium salt began to deposit. After heating for 2 hours the mixture was cooled and the salt separated. This salt was then dissolved in water, the solution washed with ether to remove a little oil, and finally acidified with hydrochloric acid when this pyrimidine separated as an amorphous solid, which finally assumed a crystallin condition. It was purified for analysis by recrystallization from hot water. It was difficultly soluble in this solvent but exhibited the property of forming supersaturated solutions. Consequently,

[1] *Ber.*, **31**, 1973.

[2] *Ann. chim. phys.*, [6] **28**, 306.

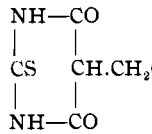
[3] *Loc. cit.*

[4] *Ber.*, **34**, 2901.

in order to effect crystallization, it was necessary to concentrate to a small volume. The pyrimidine crystallized in clusters of small prisms, sometimes corpuscular in appearance, which shriveled at 230° and then decomposed at 265°–270° to a brown oil.

Nitrogen determinations (Kjeldahl):

Calculated for $C_{14}H_{11}O_4N_3S$: N, 13.25; found: N, 13.17, 13.43.

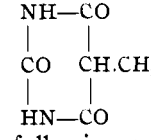
5-Aminoethyl-2-thiobarbituric Acid,  —This pyrimidine is obtained by hydrolysis of the above phthalimido derivative. It was obtained, as a secondary product of the condensation, after separation of the phthalimido derivative and separated from the hydrochloric acid solution as a light yellow powder. It was finally purified by crystallization from hot water after decolorization with bone-coal. It separated from this solvent in cubical prisms, which at times showed distinctly rounded surfaces giving them a barrel-shaped appearance. They shriveled at 270° and then decomposed at 298°–300° with effervescence.

Nitrogen determination (Kjeldahl):

Calculated for $C_6H_9O_2N_3S$: N, 22.46; found: N, 22.26, 22.51.

On further concentration of the original mother liquor, and cooling, phthalic acid finally separated and decomposed from 190°–205°, depending on the rate of heating. It separated in flat prisms, which contained neither sulfur nor nitrogen.

Condensation of Diethyl β-Phthalimidoethylmalonate with Urea.

2,4,6-Trioxy-5-hydroxyethylpyrimidine or 5-Hydroxyethylbarbituric Acid,  —For the preparation of this compound the following proportions were used: 2.1 grams of sodium in 40 cc. of absolute alcohol, 2.7 grams of urea and 10 grams of the β-phthalimidoethyl malonic ester. Upon heating on the steam bath there was an immediate reaction, the solution assumed a deep orange color and after about 15 minutes a magma of sodium salt was obtained. In order to insure complete reaction, the heating was continued for 3 hours and the sodium salt then separated by filtration. This salt was then dissolved in water and the solution acidified with dilute hydrochloric acid. Phthalimide separated immediately and crystallized from hot water in needle-like prisms, which melted at 228°–229° to a clear oil.

Nitrogen determinations (Kjeldahl):

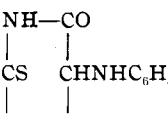
Calculated for $C_8H_5O_2N$: N, 9.52; found: N, 9.46, 9.66.

After the separation of phthalimide the filtrate, above, was acidified strongly with hydrochloric acid and allowed to stand for several hours. The barbituric acid derivative finally deposited mixed with a little phthalimide. This pyrimidine is practically insoluble in boiling water and alcohol but dissolves in sodium hydroxide solution and is recovered by addition of acids. It was purified for analysis by digestion with hot water, in order to remove phthalimide, and was obtained as a light yellow powder, which showed no signs of melting below 300°. It was dried for analysis at 120°–130°.

Nitrogen determinations (Kjeldahl):

Calculated for $C_8H_8O_4N_2$: N, 16.3; found: N, 15.98, 16.33.

Condensation of Diethyl Anilinomalonate with Thiourea.

2-Thio-7-phenyluramil,  —This new uramil is easily prepared by condensing diethyl anilinomalonate with thiourea, in alcohol solution, in the presence of sodium ethylate. When the malonic ester was added to the ethylate solution the mixture assumed a green color, finally turned yellow and a light yellow salt finally deposited. As the heating was continued, this salt underwent a change. It apparently dissolved again and an orange-colored salt separated simultaneously. The heating was continued for 10 hours to complete the reaction and the salt finally separated by filtration. This salt dissolved at once in cold water and on acidifying with hydrochloric acid 2-thio-7-phenyluramil separated immediately as an orange-colored powder. The total yield was 11.5 grams or 90% of the theoretical.

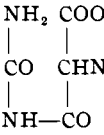
This pyrimidine is very difficultly soluble in water and all the common organic solvents. It was purified by dissolving in dilute sodium hydroxide solution and then reprecipitating with acetic acid. It separated in orange-colored prismatic blocks which showed no definit melting point. The substance began to show signs of decomposition at 250°–260°, charred badly on further heating, and underwent complete decomposition below 300°.

Nitrogen determinations (Kjeldahl):

Calculated for $C_{10}H_6O_2N_2S$; N, 17.87; found: N, 17.76, 17.67, 17.96.

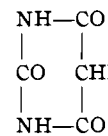
An attempt was made to alkylate this pyrimidine by digesting its sodium salt (suspended in alcohol) with ethylbromide. No 2-ethylmercapto-7-phenyluramil, however, was obtained and the original pyrimidine was recovered unaltered.

Condensation of Diethyl Anilinomalonate with Urea.

Anilinomalonuric Acid,  —This is a representative of a new type of compounds. One and five-tenths molecular proportions of urea were dissolved in a solution of sodium ethylate containing 4 molecular proportions of sodium dissolved in the least possible quantity of absolute alcohol. A molecular proportion of the malonic ester was then added and the mixture heated for 11 hours. The alcohol was then evaporated at 100° and the residue dissolved in water and the solution acidified with dilute hydrochloric acid. The anilinomalonuric acid separated at once in colorless, cubical prisms. The acid was practically insoluble in water and only slightly soluble in boiling alcohol. It assumed a purple color when heated, turned brown at 200°–225°, but did not meet below 300°. It was dried for analysis at 120°–130°.

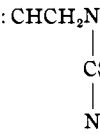
Nitrogen determinations (Kjeldahl):

Calculated for $C_{10}H_{11}O_4N_3$: N, 17.72; found: N, 17.88, 17.82.

Conversion of Anilinomalonuric Acid into 7-Phenyluramil,  —Anilinomalonuric acid was readily converted into this pyrimidine by digestion with glacial acetic acid. The malonuric acid first dissolved in the hot acid and then, as the boiling was continued, the uramil suddenly separated as a granular, crystallin powder. The yield was practically quantitative. This pyrimidine is practically insoluble in water and all the common organic solvents and shows no signs of melting below 300°. It exhibits pyroelectric properties.

Nitrogen determination (Kjeldahl):

Calculated for $C_{10}H_9O_3N_3$: N, 19.18; found: N, 19.07.

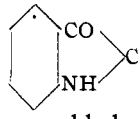
1-Allyl-2-thio-7-Phenyluramil,  —This pyrimidine was formed by condensation of allylthiourea with diethyl anilinomalonate. Its sodium salt was obtained as a fine, brown powder which dissolved immediately in water. On acidifying this aqueous solution, the pyrimidine separated at once as a powder, which was practically insoluble in water. It was purified for analysis by long digestion with hot water and finally dissolving in dilute alkali and reprecipitating

with acid. It melted at 185°–187° to a red oil with slight decomposition. It was dried for analysis at 110°–115°.

Nitrogen determination (Kjeldahl):

Calculated for $C_{13}H_{13}O_2N_3S$: N, 15.27; found: N, 15.01.

The Action of p-Nitrobenzylchloride on the Sodium Salt of Diethyl Anilinomalonate.

α-(p-Nitrobenzyl)-Indoxyl,  — Ten grams of diethyl anilinomalonate were added to an alcoholate solution containing 0.9 gram of metallic sodium (one molecular proportion) and the solution heated gently on the steam bath. The sodium salt separated. Seven grams of *p*-nitrobenzylchloride (one molecular proportion) were then added and the mixture heated at 100°. Sodium chloride began to separate immediately and within 15 minutes the reaction was complete and the solution neutral to turmeric and litmus paper. The excess of alcohol was then evaporated and the residue triturated with cold water to dissolve the sodium chloride. We obtained a semi-solid substance which was triturated with ether, when it partly dissolved, leaving behind a colorless, crystallin solid. This was separated and the ether solution saved (see below). This crystallin product was the indoxyl derivative and was very difficultly soluble in water. It was soluble in alcohol and was purified by crystallization from this solvent. It separated in long needles or prisms, which melted at 180°–182° to a clear oil.

Nitrogen determinations (Kjeldahl):

Calculated for $C_{15}H_{12}O_3N_2$: N, 10.45; found: N, 10.23, 10.41.

p-Nitrobenzyl-anilinomalonic Acid, $NO_2.C_6H_4CH_2C(NHC_6H_5)(COOH)_2$.— The ether extract mentioned above was thoroughly dried over anhydrous potassium carbonate and the ether then removed in the usual manner. We obtained 12.0 grams of a yellow oil. No attempt was made to distil this substance but it was immediately saponified by digestion in 50% alcohol with 3.5 grams of potassium hydroxide. After heating for 5 hours at 100° the alcohol was then evaporated and the oily residue dissolved in water. This solution was then washed with ether to remove a trace of oil and the solution finally acidified with hydrochloric acid. Paranitrobenzylanilinomalonic acid separated at once as a light brown powder. The acid is difficultly soluble in water and separates from a hot solution in clusters of minute prisms resembling in appearance that of chestnut burs. The acid is easily soluble in alcohol and crystallizes from this solvent in glistening leaflets which shriveled at 190° and then decomposed at 205°–210° to a red oil with effervescence. If the bath is heated rapidly the decomposition point is raised to 215°.

Nitrogen determinations (Kjeldahl):

Calculated for $C_{16}H_{14}O_6N_2$: N, 8.5; found: N, 8.59.

NEW HAVEN, CONN.

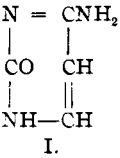
[CONTRIBUTIONS FROM THE SHEFFIELD LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXIV. SYNTHESIS OF 4-METHYL-5-ETHYLCYTOSINE.

BY TREAT B. JOHNSON AND GEORGE C. BAILEY.

Received July 1, 1913.

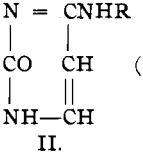
Fourteen alkyl derivatives of cytosine, I, have been described in the



I.

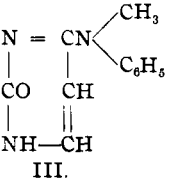
pyrimidine papers published from this laboratory. They may be classed in two groups as follows:

Group One.—This includes all those derivatives of the base I, where a substitution has been made in the amino group of the pyrimidine, namely, 7-phenylcytosine and the corresponding *o*- and *p*-tolyl-, anisyl- and *m*-nitrophenyl compounds,[1] which may be represented by the general formula II, 7,7-methylphenyl- and 3-methyl-7,7-methylphenylcytosines[2]

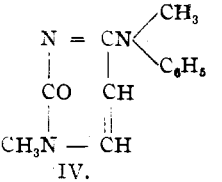


II. ($R = C_6H_5$, $CH_3C_6H_4$–, $CH_3OC_6H_4$– and $NO_2C_6H_4$–)

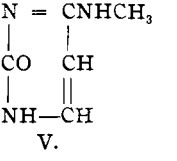
(III and IV), and 7-methyl- and 4,7-dimethylcytosines[3] represented by formulas V and VI, respectively.



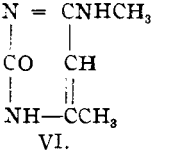
III.



IV.



V.



VI.

[1] Wheeler and Bristol, *Am. Chem. J.*, **33**, 448; Johnson, Johns and Heyl, *Ibid.*, **36**, 160.

[2] Johnson and Clapp, *J. Biol. Chem.*, **5**, 49.

[3] Johns, *Ibid.*, **9**, 161; **11**, 393.