NOTE.

Glauconite or Greensand.—My attention was called to this mineral as a possible source of potash several months since. On examination, I find the grains of marl from Mullica Hill and Sewell, New Jersey, consist of a core which is apparently nearly pure silica and a covering layer of glauconite containing apparently no, or very little, silica. The published analyses show 50% and over silica. If examination of other samples which I am now collecting gives the same result, it becomes apparent that the composition of the mineral has been misrepresented. Analyses so far made, show that the glauconite contains about 41% Fe_2O_3, 3% FeO, 18% Al_2O_3, 2% CaO, 5% MgO, 17% K_2O, 0.5% Na_2O and 13.5% H_2O.

The cleanest sample from Sewell contains 45% green mineral and 55% white insoluble. The best solvent is sulfuric acid diluted with an equal volume of water.

It is well known that the lowest layers contain most potash. Whether this is because the grains have there the heaviest coating I have not yet been able to ascertain.

EDWARD HART.

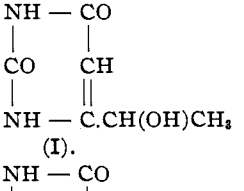
[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXXXV. THE SYNTHESIS OF A SECONDARY NUCLEOSIDE OF THYMINE, AND ITS CONVERSION INTO A DERIVATIVE OF GLYOXALINE BY HYDROLYSIS WITH ACIDS.

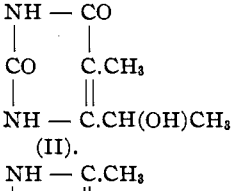
BY TREAT B. JOHNSON AND SIDNEY E. HADLEY.

Received June 21, 1917.

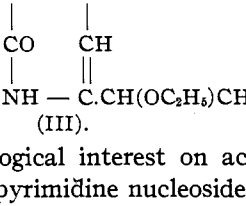
The two pyrimidines, represented by Formulas I and II, are members of a new class of alcohols to which we have assigned the class name—*secondary nucleosides*. Such combinations have recently assumed a chemical and biological interest on account of their possible relationship in structure to pyrimidine nucleosides, which have been shown to be degradation products of the naturally occurring nucleic acids. As far as the writers are aware, no representative of this type of nucleosides has hitherto been described in the literature. Ether derivatives of these alcohols, however, are known and a method of synthesis has been developed whereby



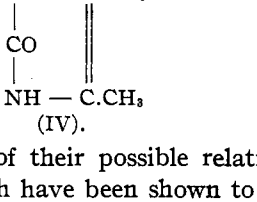
(I).



(II).



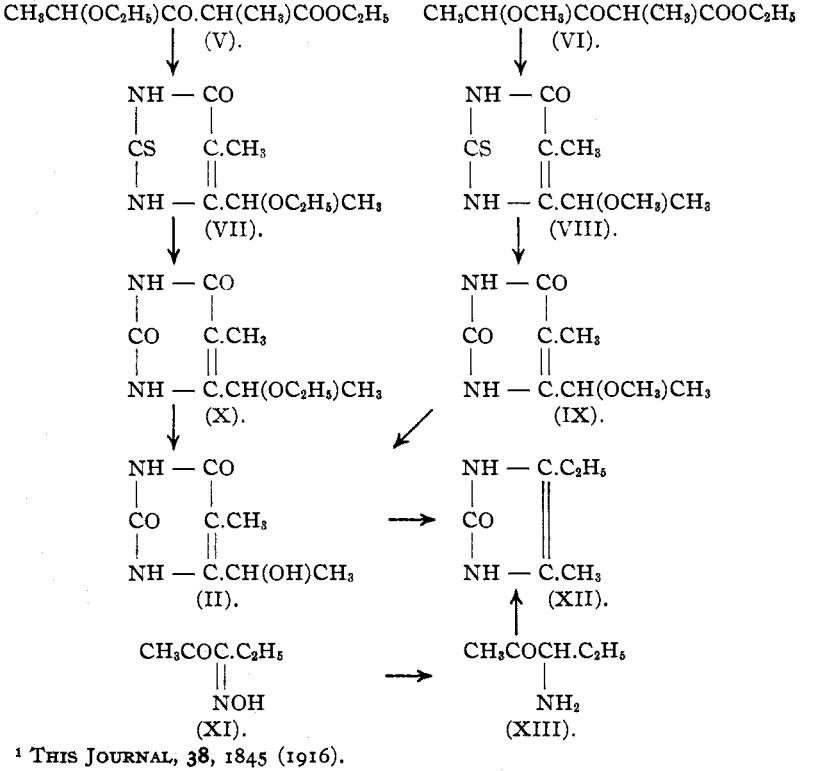
(III).



(IV).

such combinations can be prepared in quantity without difficulty. The ethyl ether of the secondary-uracil nucleoside (III) has been described in a previous publication from this laboratory by Johnson and Hadley,[1] and in this paper we will give a description of our method of synthesizing the corresponding thymine derivative represented by Formula X.

The starting point in this work was the β-ketone ester represented by Formula V. This combination and also its corresponding methyl ether (VI) were described in our previous paper[2] and were synthesized by condensing, according to Claisen's method, ethyl propionate with ethyl α-ethoxy- and α-methoxypropionates, respectively, by means of metallic sodium. Both of the ketone esters react smoothly with thiourea, when digested with this reagent in alcohol solution and in the presence of sodium ethylate, forming the two thiopyrimidines represented by Formulas VII and VIII, respectively. Both of these combinations are crystalline compounds and are produced by application of this reaction in excellent yields. When they are digested with chloroacetic acid in aqueous solution the sulfur is easily removed and the corresponding oxypyrimidines or nucleoside ethers (X) and (IX) are formed almost quantitatively. These transformations are expressed by the following formulas:



[1] THIS JOURNAL, **38**, 1845 (1916).

[2] Johnson and Hadley, *Loc. cit.*; Hadley, Dissertation, Yale University, 1916.

Attempts by Johnson and Hadley[1] to prepare the uracil nucleoside (I) by hydrolysis of its ethyl ether (III) with hydrobromic or hydrochloric acids were unsuccessful. It was observed, much to our surprise, that the pyrimidine behaved abnormally under such conditions and underwent a profound change, being transformed into a glyoxaline combination which we have succeeded in proving to be dimethylglyoxalone represented by Formula IV.[2] In the light of this interesting result it was especially important to investigate the behavior of the ethyl ether of the thymine-nucleoside (X) when heated with halogen acids. This work has now been completed and we find that this pyrimidine (X) also undergoes a similar change as its lower homolog when subjected to hydrolysis. Ethyl bromide and chloride are evolved together with carbon dioxide and the pyrimidine is transformed into a glyoxaline derivative having the formula $C_6H_{10}ON_2$. A preliminary report of this work has already been published in the Proceedings of the National Academy of Sciences.[3]

We now find that this product of hydrolysis $C_6H_{10}ON_2$ is identical with ethylmethylglyoxalone (XII) which has previously been described by Gabriel and Posner.[4] We have prepared this glyoxaline derivative by reducing the oxime of methylpropylketone (XI) to its corresponding amine (XIII) and then treating this base in acid solution with potassium cyanate. The glyoxalone, which was obtained in this manner, melted as stated by Gabriel and Posner at 270° and agreed in all its properties, both chemical and physical, with our hydrolytic product. Furthermore there was no lowering of the melting point when a mixture of the two substances was heated in a capillary tube. In other words, the two pyrimidines (III and X) react in a perfectly analogous manner and are transformed when heated with mineral acids into derivatives of glyoxaline, namely, dimethylglyoxalone and ethylmethylglyoxalone represented by Formulas IV and XII, respectively.

While we did not succeed in obtaining the nucleoside of uracil (I) by hydrolysis of its ethyl ether[5] (III), we were successful in this investigation in isolating the corresponding thymine nucleoside (II). This can be obtained from its ethyl ether (X) if its hydrolysis with acids is applied under special conditions. It is an intermediate product of our pyrimidine-glyoxaline transformation, but even under the most favorable conditions that we have been able to develop, it can be obtained in small amounts only. It is extremely unstable in the presence of hot acids and gradually looses carbon dioxide, being transformed into the glyoxalone (XII). The

[1] *Loc. cit.*

[2] Johnson and Hadley, THIS JOURNAL, **39**, 1715 (1917).

[3] Toluene III, 1917.

[4] *Ber.*, **27**, 1037 (1894).

[5] Johnson and Hadley, *Loc. cit.*

investigation of these interesting transformations is being continued in this laboratory.

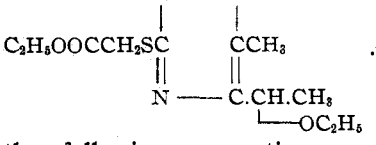
Experimental Part.

Ethyl α-Methyl-γ-methyl-γ-methoxyacetoacetate, $CH_3CH(OCH_3)CO.CH(CH_3)COOC_2H_5$, **and Ethyl α-Methyl-γ-methyl-γ-ethoxyacetoacetate,** $CH_3CH(OC_2H_5)CO.CH(CH_3)COOC_2H_5$.—These two esters, which served as the starting points in this investigation, were first prepared in this laboratory and have already been described in a previous publication.[1] The methoxy compound boils at 105° at 14 mm. pressure and the ethoxy derivative at 114° at 17 mm.

2-Thio-4-(α-ethoxyethyl)-5-methyl-6-oxypyrimidine (VII).—This new pyrimidine is easily prepared by condensation of ethyl α-methyl-γ-methyl-γ-ethoxyacetoacetate with thiourea in the presence of sodium ethylate. A description of one experiment will serve to illustrate the general procedure adopted for preparing the pyrimidine. 6.5 g. of sodium were dissolved in 125 cc. of alcohol and 14 g. of thiourea then dissolved in the ethylate solution. After cooling, 37 g. of the ketone ester were added and the mixture then heated on a water bath for about 10 hours. The fluid assumed a yellow color during this operation and the sodium salt of the 2-thiopyrimidine deposited. After completion of the reaction the alcohol was evaporated by heating at 100° and the residue finally dissolved in a small amount of cold water. On acidifying this solution with hydrochloric acid the 2-thiopyrimidine separated immediately in a crystalline condition. It was purified by crystallization from hot 50% acetic acid and separated, on cooling, in the form of minute, colorless prisms which melted at 222° to a clear oil. The yield of purified material was 25 g. This pyrimidine is difficultly soluble in water and alcohol and extremely soluble in hot glacial acetic acid. Nitrogen determination:

Calc. for $C_9H_{14}O_2N_2S$: N, 13.1. Found: N, 12.87.

4-(α-Ethoxyethyl)-5-methyl-6-oxypyrimidine-2-ethyl-thioglycollate,



.—For the preparation of this pyrimidine the following proportions were taken: 10 g. of 2-thio-4-(α-ethoxyethyl)-5-methyl-6-oxypyrimidine, 5.8 g. of ethyl chloroacetate, 1.1 g. of sodium and 50 cc. of absolute alcohol. The sodium was first dissolved in the alcohol and the thiopyrimidine then dissolved in the ethylate solution by heating on the steam bath for one hour. Finally the ethyl chloroacetate was added and the heating continued for 6 to 8

[1] Hadley, Dissertation, Yale University, 1916; Johnson and Hadley, THIS JOURNAL, 38, 1844 (1916).

hours. A mixture of sodium chloride and the pyrimidine deposited and was separated from the alcohol by filtration. The sodium chloride was separated from the pyrimidine by washing with cold water and the latter then combined with the residue left by evaporating the alcohol filtrate and purified by crystallization from boiling alcohol. It separated in the form of colorless prisms which melted at 119° to an oil. The yield was 9 g. Nitrogen determination:

Calc. for $C_{13}H_{20}O_4N_2S$: N, 9.36. Found: N, 9.35.

2,6-Dioxy-4-(α-ethoxyethyl)-5-methylpyrimidine (X).—This pyrimidine was prepared by digesting 10 g. of the corresponding 2-thiopyrimidine with 6 g. of chloroacetic acid in 150 cc. of water for 8 hours. The solution was then concentrated by evaporation at 100° and the resulting residue triturated with a small amount of cold water when the above pyrimidine was obtained in a crystalline condition. It was purified by crystallization from water and alcohol and separated from both solvents in the form of elongated prisms which melted at 176° to a clear oil. The yield of purified pyrimidine was 7 g. Nitrogen determination:

Calc. for $C_9H_{14}O_3N_2$: N, 14.1. Found: N, 13.94.

2-Thio-4-(α-methoxyethyl)-5-methyl-6-oxypyrimidine (VIII). — This pyrimidine was obtained in the form of its sodium salt by digesting thiourea in sodium ethylate solution with ethyl α-methyl-γ-methyl-γ-methoxyacetoacetate. After completion of the condensation, the excess of alcohol was removed by heating at 100° and the sodium salt of the pyrimidine dissolved in cold water. On acidifying this solution with hydrochloric acid the pyrimidine separated immediately as a colorless powder. It was purified by crystallization from hot alcohol and separated on cooling in the form of plates which melted at 207°. The yield was 20 g. This pyrimidine is difficultly soluble in water. Nitrogen determination:

Calc. for $C_8H_{12}O_2N_2S$: N, 14.0. Found: N, 13.73.

2,6-Dioxy-4-(α-methoxyethyl)-5-methylpyrimidine (IX). — This pyrimidine was obtained in good yield by desulfurization of the above thiopyrimidine with chloroacetic acid. A mixture of 4 g. of the thiopyrimidine 4 g. of chloroacetic acid and 15 cc. of water was boiled under a reflux condenser for 5 hours. The solution was then concentrated to a syrupy consistency and the residue triturated with cold water when the pyrimidine separated in a crystalline condition. It was purified by crystallization from hot alcohol and separated in prisms which melted at 217°. The yield was 2.5 g. Nitrogen determination:

Calc. for $C_8H_{12}O_3N_2$: N, 15.2. Found: N, 14.94.

The Behavior of 2,6-Dioxy-4-(α-ethoxyethyl)-5-methylpyrimidine (X) on Hydrolysis with Mineral Acids. The Formation of the Thymine-nucleoside (II). The Action of Hydrobromic Acid.—This pyrimidine is

easily decomposed by heating with strong hydrobromic acid, but several experiments were made by us before we succeeded in establishing the experimental conditions favorable for the reaction, and consequently to obtain definite and consistent results. Our procedure at first was to take 2 g. of the pyrimidine and 30 cc. of hydrobromic acid (sp. gr. 1.4) and heat in a flask at the boiling point of the solution for 2 to 4 hours. Finally the proportions were changed and for 2 g. of the pyrimidine 6 cc. and 10 cc. of acid were used. The pyrimidine dissolves easily in this acid with formation of ethyl bromide and if the heating is continued carbon dioxide is copiously evolved. If digestions are conducted under the above conditions and the excess of hydrobromic acid then evaporated by heating the mixture at 100° a dark-colored viscous oil is obtained which will show no tendency to crystallize on standing. Trituration with sodium hydroxide will lead to the production of some ammonia and precipitation of a crystalline substance having an indefinite melting point. Attempts to purify this product by crystallization from water or alcohol were not successful. We were apparently dealing here with a mixture of at least three compounds and the melting points of the crystallized material varied from 200° to 250°. The analytical results were also unreliable and determinations of nitrogen varied from 15.0 to 19.5%.

It was evident from the results obtained in our preliminary experiments that we might control the course of the reaction by limiting the time of digestion and regulating more carefully the temperature. After studying the effect of changing these factors we finally worked out conditions under which we were able to obtain a definite product which we identified as the secondary nucleoside of thymine (II). The description of a single experiment will illustrate the procedure finally adopted for the preparation of this compound. Working under these conditions we always succeeded in obtaining the nucleoside. Four grams of the ethoxypyrimidine were dissolved in 20 cc. of hydrobromic acid and the solution heated in an oil bath at 180° for exactly 30 minutes. Under these conditions ethylbromide and carbon dioxide were evolved and a dark red liquid was obtained. The excess of acid was then evaporated on the steam bath when we obtained a thick viscous residue containing hydrobromic acid. This was triturated with a small volume of dilute sodium hydroxide solution when a colorless crystalline substance was obtained. The nucleoside was obtained from this by fractional crystallization from water. The product was a mixture and the nucleoside was separated in the fraction most soluble in water. This usually melted below 200°. In order to obtain it pure for analysis it was digested several times with benzene and finally recrystallized from boiling 95% alcohol. It melted at 219–220°. This compound was analyzed for nitrogen and the results indicated that we were dealing with the nucleoside represented by Formula II.

Calc. for $C_7H_{10}O_3N_2$: N, 16.4. Found: N, 16.4, 16.5.

The yield of this pyrimidine was small and was not increased by hydrolysis of the ethoxypyrimidine with a smaller proportion of acid.

The Action of Hydrochloric Acid.—This same nucleoside, described above, can also be obtained by the action of hydrochloric acid on its ethyl ether. Here again we encountered much difficulty in establishing conditions that were productive of a good yield of this pyrimidine, as it was destroyed by too long heating with hydrochloric acid with production of carbon dioxide. The procedure which proved to be the most successful was as follows: Two grams of the pyrimidine and 10 cc. of concentrated hydrochloric acid were heated in a sealed tube at 110° for 2.5 hours. When the tube was opened there was evidence of great pressure due to the presence of ethylchloride and carbon dioxide and a clear amber-colored fluid was obtained. The solution was transferred to a distilling bulb and the water and hydrochloric acid removed by heating at 100° under reduced pressure, when we obtained a viscous residue which showed no signs of solidifying on standing. This residue was dissolved in 25 cc. of hot water and the solution cooled when the crude nucleoside separated in a crystalline condition. It was very difficult to purify this product by recrystallization alone. Trituration with hot benzene proved to be beneficial and after thorough washing to remove impurities purification was finally effected by several crystallizations from hot alcohol. The compound crystallized from this solvent in the form of rosets melting at 219–220°. The yield of purified material was 0.3 g.

Nitrogen determination (Dumas): 0.1234 g. substance gave 17.1 cc. Nitrogen at 767 mm. and 17.5°.

Calc. for $C_7H_{10}O_3N_2$: N, 16.4. Found: N, 16.10.

Ethylmethyl-glyoxalone, $C_6H_{10}ON_2$ **(XII).**—In order to prepare this glyoxaline combination isonitrosoethylacetone was first synthesized according to the directions of Meyer and Züblin,[1] and this then reduced with tin and hydrochloric acid to aminopropylmethylketone, $CH_3COCH(NH_2)C_2H_5$.[2] The glyoxalone was then prepared by treatment of this aminoketone with potassium cyanate according to the method of Gabriel and Posner.[3] It was purified as directed by crystallization from hot water and melted at 270° with decomposition.

The Transformation of the Ethoxypyrimidine (X) into Ethylmethyl-glyoxalone (XII) by Hydrolysis under Pressure with Strong Hydrochloric Acid.—Several unsuccessful experiments were performed before we succeeded in developing conditions which were favorable for the transformation of the ethoxypyrimidine into this glyoxaline combination. We first

[1] *Ber.*, 11, 323, 695 (1878).

[2] Gabriel and Pinkus, *Ibid.*, **26**, 2197 (1893).

[3] *Loc. cit.*

worked at a temperature of 100° and heated 2 g. of the pyrimidine with 10 cc. of concentrated hydrochloric acid for 2 hours. Under these conditions there was no evidence of hydrolysis and the pyrimidine was recovered unaltered. When 2 g. of the pyrimidine and 10 cc. of acid were heated for the same length of time at 110° there were decisive indications of a change and ethylchloride and carbon dioxide were evolved. The hydrolysis, however, was far from complete and a mixture of compounds was obtained from which we were unable to isolate a definite product. The material melted, after crystallization from hot water, from 125–194°. A repetition of this experiment gave a product melting at 126–176°. Always heating at a constant temperature (110°) the time of heating was then gradually increased to 30 hours when we succeeded in obtaining a hydrolytic mixture from which we were able to isolate the glyoxalone in a state of purity. As the time of hydrolysis was lengthened the melting point of the crude hydrolytic product increased, and in the first experiment when we heated the acid solution for 30 hours, we succeeded in isolating, by fractional crystallization from water and alcohol, two definite products. One of these melted at 220° and possessed all the properties of the nucleoside, while the second and more insoluble substance melted at 262°. The method of operating which was finally adopted and proved successful in every case tried was to heat 4 grams of the pyrimidine with 20 cc. of concentrated hydrochloric acid in a sealed tube at 110° for 30 to 40 hours. After the hydrolysis was complete and the bomb tube was cooled, there was always great pressure due to the presence of carbon dioxide and an amber-colored fluid was obtained. This was then transferred to a distilling bulb and the water and hydrochloric acid evaporated by heating at 100° under a partial vacuum. A gummy residue was obtained by this treatment which dissolved in boiling water. On cooling the aqueous solution the glyoxalone separated in the form of colorless flakes. When crystallized from alcohol it deposited as a fine powder. Both modifications melted at 270° with decomposition. It was observed that this melting point varied by several degrees, depending upon the rate of heating. By rapid heating the thermometer could be forced to register 275° before the compound completely decomposed in the capillary tube. The glyoxalone behaved in every respect like the ethylmethyl-glyoxalone described by Gabriel and Posner,[1] and when our product was mixed with their compound and the mixture heated in a capillary tube there was absolutely no lowering of the melting point, proving that they were identical. The analytical determinations for carbon, hydrogen and nitrogen gave values agreeing with the theoretical in a compound having the formula $C_6H_{10}ON_2$.

[1] *Loc. cit.*

Carbon and hydrogen determinations:

(1) 0.1524 g. substance gave 0.3194 g. CO_2 and 0.1118 g. H_2O.
(2) 0.1544 g. substance gave 0.3214 g. CO_2 and 0.1122 g. H_2O.
(3) 0.1027 g. substance gave 0.2123 g. CO_2 and 0.0742 g. H_2O.

Nitrogen determinations (Dumas):

(1) 0.1330 g. substance gave 26.4 cc. N at 760 mm. and 25°.
(2) 0.998 g. substance gave 19.6 cc. N at 763 mm. and 22°.

Calc. for $C_6H_{10}ON_2$:	C, 57.0; H, 8.0; N, 22.2
Found:	C, 56.78; H, 8.1; N, 21.96
	C, 56.77; H, 8.1; N, 22.3
	C, 56.39; H, 8.0

The Formation of the Glyoxalone (XII) by Hydrolysis of the Methoxypyrimidine (IX) with Hydrobromic Acid.—Four grams of the methoxypyrimidine were heated with 20 cc. of hydrobromic acid at 150° until the evolution of carbon dioxide ceased. After the end of this operation the heating was then continued for about 6 hours and the solution finally evaporated to dryness to remove the excess of hydrobromic acid. The same procedure was then applied at this stage as we have already discussed in the previous experiments involving hydrolysis of the ethoxypyrimidine. The glyoxalone separated in a crystalline condition after trituration with dilute sodium hydroxide solution and was purified by recrystallization from boiling 95% alcohol. It was identical with the product obtained by hydrolysis of the ethoxypyrimidine (X) and melted at 270° with decomposition. The yield of the glyoxalone was 1 g.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF NEBRASKA.]

ACTION OF SODIUM BENZYL CYANIDE WITH *p*-TOLYLCINNAMIC ESTER.[1]

BY MILO REASON DAUGHTERS.

Received June 22, 1917.

The results obtained by Auwers and Köbner,[2] Perkins,[3] and Avery,[4] in analogous reactions in the preparation of alkyl glutaric acids, did not correspond with the result obtained in this reaction. According to Michael's reaction,[5] the following result should have been obtained:

$$C_6H_5CHNaCN + CH_3C_6H_4CH{:}CH.COOR \longrightarrow CH_3C_6H_4 - \underset{\displaystyle C_6H_5 - CH - CN}{\underset{|}{CHNa}} - CH - COOR$$

[1] From the thesis prepared as a part of the work required for the degree of Master of Arts.

[2] *Ber.*, **24**, 1936 (1891).

[3] *J. Chem. Soc.*, **69**, 1472 (1896).

[4] *Am. Chem. J.*, **20**, 509 (1898); **28**, 48 (1902).

[5] *J. prakt. Chem.*, [2] **35**, 352 (1887).