cinnamalhydantoin were heated with 30 cc. of acetic anhydride for 4 hours at 140–150°. There was no apparent reaction at first but after heating for about an hour most of the hydantoin had disappeared and a new product began to deposit in the form of needles. On continued heating all the cinnamalhydantoin changed to this modification. This was identified as the acetyl derivative of cinnamalhydantoin and crystallized from glacial acetic acid as yellow prisms, which melted at 241–242° without any apparent decomposition. This hydantoin was less soluble in glacial acetic acid than cinnamalhydantoin.

Calc. for $C_{14}H_{12}O_3N_2$: N, 10.94. Found: N, 10.96, 10.94.

This hydantoin easily underwent hydrolysis when warmed with hydrochloric acid was changed into cinnamalhydantoin. This was crystallized from glacial acetic acid and melted at 272–273° with decomposition.

In order to determine whether the acetyl group in this new hydantoin was linked to the 1- or 3-position of the ring 3-acetylhydantoin[1] (XVI) was condensed with cinnamic aldehyde by heating in the presence of sodium acetate, acetic acid and acetic anhydride. After heating for 3.5 hours at 130–135° the fused mass was cooled and then triturated with 500 cc. of cold water when the above acetylhydantoin separated in a crystalline condition. The yield was excellent. It was purified by crystallization from acetic acid and melted at 241–242°. A mixture of this substance with some of the acetyl compound described above melted at the same temperature.

Calc. for $C_{14}H_{12}O_3N_2$: N, 10.94. Found: N, 10.9.

NEW HAVEN, CONN.

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

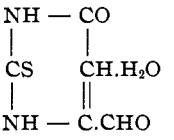
RESEARCHES ON PYRIMIDINES. LXXV. PYRIMIDINE ALDEHYDES AND THEIR BIOCHEMICAL INTEREST (THIOURACILALDEHYDE).

BY TREAT B. JOHNSON AND LEONARD H. CRETCHER, JR.

Received July 5, 1915.

So far as the writers are aware, no cyclic aldehydes of the pyrimidine series have been described in the literature. Such unsaturated combinations should manifest great reactivity and consequently a knowledge of their chemistry is especially desirable, because of the probability that they will prove of value for the future synthesis of new pyrimidine combinations of great biochemical interest. A description of three aldehydes of this series of cyclic compounds will be given in this paper. One of these, *2-thiouracil-4-aldehyde* (I), can be obtained easily in quantity for synthetical work.

[1] Siemonsen, *Loc. cit.*



(I).

Our pyrimidine-nucleoside investigations have, so far, been practically confined to the study of uracil combinations containing simple monoatomic, alcohol groupings in the 4-position of the pyrimidine ring.[1] Our method of synthesizing such combinations is somewhat limited in its utility, because it is dependent on the use of characteristic β-ketone esters of definite structure. Most of these esters required for our work are unknown and many of them would be extremely difficult to synthesize in quantity.[2] It became necessary, therefore, as our work developed, to obtain, if possible, uracil combinations (or thiouracil) containing a grouping in the 4-position, which could be utilized for side-chain construction. A grouping was desired which would render possible the synthesis indirectly of glycol and higher alcohol combinations. Such a radical is the aldehyde group —CHO, which we have now been able to introduce into the pyrimidine ring according to the method described below.

Among the aliphatic esters which have been observed to condense with ethyl acetate, in the presence of sodium, to form β-ketone esters (Claisen's condensation), is the ethyl ester of diethoxyacetic acid $(C_2H_5O)_2CH.COOC_2H_5$. Dakin and Dudley[3] have shown that these two aliphatic esters interact smoothly under specific conditions, forming the new β-ketone ester (II). This compound and its α-carbon substituted derivatives are characterized by their behavior on hydrolysis. They exhibit the normal behavior of β-ketone esters and can be transformed into ketone acetals. The latter on hydrolysis with acids are easily transformed into glyoxals. The complete hydrolysis of ethyl γ-diethoxyacetoacetate (II) may be expressed in the following manner:

$$(C_2H_5O)_2CH.COCH_2COOC_2H_5 \longrightarrow CH_3CO.CH(OC_2H_5)_2 \longrightarrow CH_3CO.CHO$$

(II).

We have now incorporated this characteristic β-ketone ester into our nucleoside work[4] and find that it condenses normally with thiourea in

[1] See our pyrimidine papers.

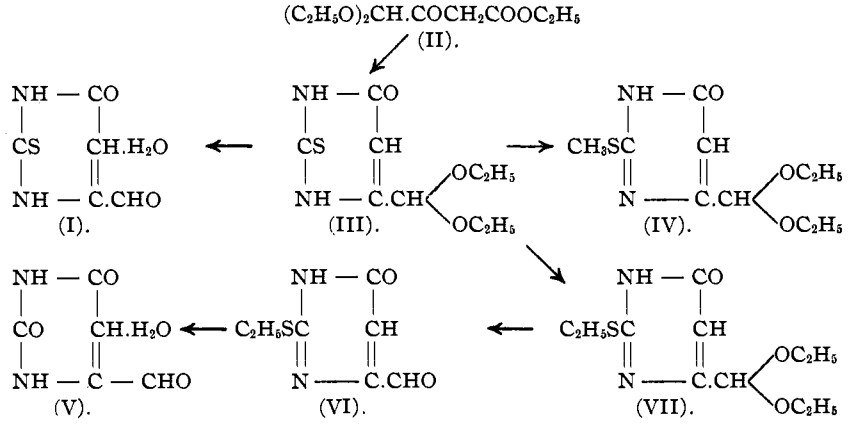
[2] Work is now in progress, in this laboratory, dealing with the synthesis of various representatives of new types of β-ketone esters. This investigation involves the application of Claisen's reaction with types of esters, which hitherto have not been studied, and new combinations have been obtained which are of great value for future syntheses. (T. B. J.)

[3] *J. Chem. Soc.*, **105**, 2453 (1914).

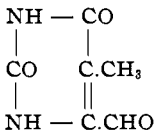
[4] So far as we are aware the behavior of ethyl triethoxyacetate $(C_2H_5O)_3C.COOC_2H_5$ towards ethylacetate in the presence of sodium has not been investigated. (T. B. J.)

alcohol solution, and in the presence of sodium ethylate, forming the pyrimidine-acetal represented by Formula III. The acetal grouping in this pyrimidine exhibits a normal behavior. It is stable in the presence of alkali, but undergoes hydrolysis with mineral acids, and is transformed quantitatively into the aldehyde of 2-thiouracil represented by Formula I. The sodium salt of the thiopyrimidine (III) behaves in a regular manner when allowed to interact with alkylhalides. Alkylation takes place with substitution upon the sulfur atom and the corresponding mercaptopyrimidines are formed quantitatively. We have prepared by the action of methyliodide and ethylbromide the two mercaptopyrimidines represented by Formula IV and VII, respectively.

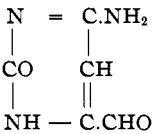
The mercaptopyrimidine (VII) behaves in an interesting manner when subjected to hydrolysis with hydrochloric acid. If the action is not allowed to become too vigorous, only the acetal grouping is destroyed, and the corresponding mercaptopyrimidinealdehyde (VI) is formed. If, however, the pyrimidine (VII) is subjected to very vigorous treatment with strong hydrochloric acid, the reaction proceeds further. Mercaptan is then also evolved and the final product of the reaction is uracilaldehyde represented by Formula V. Attempts to prepare this aldehyde (V) by desulfurization of the corresponding thiouracilaldehyde (I) have, thus far, been unsuccessful. Very little attention has been paid to the chemistry of uracilaldehyde (V), but a careful study of its properties and reactions will be taken up the coming year. The various changes, which have been discussed above, are expressed by the following structural formulas:



We ask that the investigation of pyrimidine aldehydes be reserved for this laboratory. Attempts will be made to synthesize the two unknown aldehyde derivatives of thymine and cytosine, which are represented by Formulas VIII and IX, respectively.



(VIII).



(IX).

Experimental Part.

Preparation of Dichloroacetic Acid, $Cl_2.CH.COOH$.—All the dichloroacetic acid which was used in this investigation was made from chloral hydrate. The procedure was to convert the chloral into the potassium salt of the halogen acid by digesting it with potassium ferrocyanide according to Wallach's[1] directions, and then decompose the potassium salt with hydrochloric acid.

Our method of obtaining the free acid from its potassium salt is illustrated by a description of one experiment: 180 g. of the potassium salt were suspeneed in 600 cc. of dry benzene and the salt decomposed by passing a stream of dry hydrochloric acid gas through the mixture until completely saturated. It was thoroughly shaken at times in order to produce a thorough decomposition. After the salt was completely decomposed the insoluble potassium chloride was filtered off by suction and the benzene removed by heating the mixture finally up to 150° in an oil bath. The dichloroacetic acid was then distilled at ordinary pressure, when we obtained 105 g. of the acid boiling at 188–192°. This was a yield of 76% of the theoretical. In another experiment we obtained 67 g. of the acid from 100 g. of the potassium salt, which is a yield of 87% of the theoretical.

Ethyl Diethoxyacetate, $(C_2H_5O)_2CH.COOC_2H_5$.[2]—A description of one experiment will illustrate our procedure for making this ester: Three molecular proportions of sodium (56.2 g.) were dissolved in 800 cc. of ethyl alcohol, which had previously been desiccated by distillation over metallic sodium. The flask containing the ethylate solution was then connected with a reflux condenser and the solution heated to 80° in a water bath. While maintaining the temperature at 80°, 105 g. of dichloroacetic acid were added slowly by means of a dropping funnel. There was an immediate reaction with formation of sodium chloride and the sodium salt of diethoxyacetic acid. After the reaction was complete the solution was then cooled and exactly 35 g. of hydrochloric acid, in absolute alcohol solution, added cautiously while holding the temperature of the solution below 10°. This is approximately 0.2 of a mol in excess of the amount of acid required to liberate the diethoxyacetic acid, or 5.8 g. of hydrochloric acid. The alcoholic solution was then allowed to stand for 15–18 hours at room temperature to effect a thorough esterification.

[1] *Ber.*, **10**, 1525 (1877).

[2] Wohl and Lange, *Ber.*, **41**, 3612 (1908).

The hydrochloric acid was then exactly neutralized cold by adding the required amount of sodium ethylate in alcohol solution and the undissolved sodium chloride separated by filtration. We obtained a clear, yellow solution which was heated at 30–35° under diminished pressure to remove all the alcohol. The red syrupy liquid which was obtained, was then diluted with 20 cc. of cold water and a large volume of ether added, when we obtained 75 cc. of material immiscible with the solvent. The ether extract was saved and the immiscible liquid extracted repeatedly with fresh ether until the volume finally remained constant at 55 cc. (see below).

The ethereal solution was dried over sodium sulfate and, after removal of the ether, the oil was distilled under diminished pressure. We obtained 48 g. of the ester boiling from 94.5–98° at 19 mm. pressure and about 10 g. boiling somewhat higher, 98–103° at 20–21 mm. pressure. There were about 12 g. of a higher fraction with indefinite boiling point.

The immiscible liquid (55 cc.) mentioned above was dark red in color and very viscous. It was covered with ether and hydrochloric acid cautiously added, when the red color disappeared and an oil dissolved in the ether. This was thoroughly extracted and the ether dried over calcium chloride for 24 hours. On evaporating the solvent we obtained 48 g. of crude diethoxyacetic acid. This was esterified by dissolving it in 72 g. of absolute alcohol containing 2.5 g. of hydrochloric acid and allowing the solution to stand for several hours. The hydrochloric acid was then neutralized with the required amount of sodium ethylate and the ester separated in the usual way. We recovered here 12 g. of pure ester boiling at 83–85° under a pressure of 13 mm. The total yield of ester was 70 g. or 50% of the theoretical.

Ethyl γ-Diethoxyacetoacetate (II).—This ester has previously been described by Dakin and Dudley[1] who have assigned to it a boiling point of 112° at 4–6 mm. pressure. We prepared the ester according to their method with slight modifications. These changes were made after we found it was not necessary to obtain the pure β-ketone ester for our work. We proceeded as follows: The following proportions were taken: 65 g. of ethyl diethoxyacetate, 26 g. of metallic sodium in wire form and 100 g. of ethyl acetate. The ethoxy ester and one-half of the acetate were mixed in an Erlenmeyer flask, connected to a reflux condenser, and the mixture heated to 80°. One-half of the sodium was then introduced in small portions at a time. Heating was continued, and in about 3 hours the sodium had completely dissolved. The remainder of the ethylacetate was then added and finally, in small amounts at a time, the rest of the sodium. Heating was then continued for 4 hours, when the sodium had practically all disappeared and then reaction was apparently complete.

[1] Dakin and Dudley, *Loc. cit.*

The resulting mixture was then cooled and carefully mixed with ice water. The unaltered esters were first removed by extraction with ether and the clear aqueous solution acidified cold with hydrochloric acid to liberate the β-ketone ester from its sodium salt. This ester was extracted with ether and the solution desiccated by allowing it to stand over anhydrous sodium sulfate. After removal of the ether the β-ketone ester was obtained as a red oil. This was not distilled but was heated in an oil bath at 145° under a pressure of 23 mm. in order to expel any ethyl acetoacetate that was present. The product left behind after this treatment weighed 65 g. From 86 g. of $(C_2H_5O)_2CHCOOC_2H_5$ Dakin and Dudley obtained 76 g. of the pure β-ketone ester.

The Diethylacetal of 2-Thio-4-uracilaldehyde (III.)—For the preparation of this new pyrimidine the following proportions were taken:

65 g. of the undistilled β-ketone ester described above, 10.5 g. of sodium, 40 g. of thiourea and 200 cc. of absolute alcohol. The sodium was first dissolved in the alcohol and the thiourea then dissolved in the resulting solution. Finally the β-ketone ester was added and then 50 cc. more of alcohol. The mixture was then heated on a steam bath for 7 hours after which the mixture was transferred to a casserole and the alcohol evaporated by heating at 100°. The residue, which remained behind, was black and very viscous. This was dissolved in 275 cc. of water, and the solution digested with bone coal, when a clear, dark red solution was obtained. This was cooled and acidified cautiously with dilute hydrochloric acid. At first the pyrimidine separated as a thick oil, but soon assumed a granular condition on stirring. The product was dried in a desiccator over sulfuric acid and weighed 52 g. The crude material melted at 150°. The acetal was purified by crystallization from 95% alcohol and separated in thick, rhombic blocks which melted at 160°. The compound is sparingly soluble in water and soluble in cold hydrochloric acid.

Calc. for $C_9H_{14}O_3N_2S$: N, 12.17. Found: N, 12.16, 12.12.

This pyrimidine was not desulfurized by digesting in alcohol solution with mercuric oxide. Freshly precipitated lead hydroxide was also used, but here also there was only slight evidence of the formation of lead sulfide. Attempts to desulfurize the pyrimidine by warming with chloroacetic acid were unsuccessful.

2-Thio-4-uracilaldehyde (I).—A quantitative yield of this interesting pyrimidine is obtained by hydrolysis of its acetal with hydrochloric acid. Three grams of the thioacetal (above) were dissolved in about 100 cc. of dilute hydrochloric acid and the solution finally heated to boiling. On cooling, the aldehyde separated in the form of golden-yellow, glistening plates, which darkened at about 230° and then decomposed at 250°. The melting point was not altered by further crystallization from dilute

hydrochloric acid. The aldehyde reduces silver nitrate in ammoniacal solution and also Fehling's solution. It dissolves easily in alcohol and glacial acetic acid. It behaves peculiarly when warmed with water. It dissolves in this solvent, but on cooling separates as a tarry product. The addition of water to an acetic acid solution of the aldehyde produces the same tarry precipitate. The aldehyde contained one molecule of water of crystallization, which was not completely expelled until the pyrimidine was heated to 160–170°.

Calc. for $C_5H_4O_2N_2S.H_2O$: N, 16.08; H_2O, 10.36. Found: N, 16.04; H_2O, 10.17.

Phenylhydrazone of the Thiouracil Aldehyde.—A small quantity of the aldehyde was dissolved in dilute hydrochloric acid and sodium acetate and phenylhydrazine added to the solution. The hydrazone separated at once as yellow needles which did not melt below 300°. This compound is insoluble in alcohol, benzene, petroleum ether and only slightly soluble in water. Analysis (Dumas' method):

Calc. for $C_{11}H_{10}ON_4S$: N, 22.7. Found: N, 22.33.

Diethyl Acetal of 2-Ethylmercapto-6-oxy-4-aldehydopyrimidine (VII).—For the preparation of this new pyrimidine the following reagents were used: 10 g. of the corresponding 2-thiopyrimidine (above), 1 g. of sodium, 1.2 g. of ethyl bromide and 250 cc. of alcohol. The sodium was first converted into sodium ethylate by dissolving in the alcohol and the thiopyrimidine then dissolved in this solution. The ethyl bromide was then added and the solution heated on the steam bath for 1 hour when the alkylation was complete. The alcohol was then evaporated and the residue triturated with water to remove the salt when the pyrimidine was obtained in a crystalline condition. It was purified by crystallization from hot water and separated in the form of colorless, slender needles, which melted at 128° to an oil. The yield of pyrimidine was 11 g. The compound is very soluble in alcohol and benzene.

Calc. for $C_{11}H_{18}O_3N_2S$: N, 10.85. Found: N, 10.65.

Diethyl Acetal of 2-Methylmercapto-6-oxy-4-aldehydopyrimidine (IV).—Obtained by alkylation of the corresponding 2-thiopyrimidine with methyliodide. The yield was practically quantitative. The pyrimidine was purified for analysis by recrystallization from alcohol and separated in the form of needles which melted at 133° to a clear oil.

Calc. for $C_{10}H_{16}O_3N_2S$: N, 11.4. Found: N, 11.20.

2-Ethylmercapto-6-oxy-4-aldehydopyrimidine (VI).—This is formed by careful hydrolysis of its corresponding acetal. Two grams of the latter were dissolved in 100 cc. of hydrochloric acid (equivalent parts of water and concentrated acid) and the solution evaporated on the steam bath until crystals made their appearance on the surface of the liquid. This condition was reached at a volume of

about 20 cc. On cooling more of the same material separated. This was identified as the mercaptoaldehyde and melted at 145°. It crystallized in elongated prisms which were soluble in hot water and dilute hydrochloric acid and sparingly soluble in alcohol. The aldehyde reduced silver nitrate in ammoniacal solution and gave a crystalline hydrazone. Analysis:

Calc. for $C_7H_8O_2N_2S$: N, 15.16. Found: N, 15.06.

Uracil-4-aldehyde (V).—This aldehyde has not been subjected to investigation and consequently we shall only mention here a single experiment in which the pyrimidine was obtained. One gram of the above 2-ethylmercaptopyrimidineacetal was heated with boiling hydrochloric acid for one-half hour and the solution then evaporated practically to dryness. On cooling the remaining liquid, this pyrimidine separated as a white powder which was crystallized from dilute hydrochloric acid. It separated in small distorted prisms arranged in rosets which did not melt at 300°. It did not respond to a test for sulfur and contained a molecule of water of crystallization, which was removed by heating the pyrimidine at 130°.

Calc. for $C_5H_4O_2N_2$: N, 17.7; H_2O, 11.39. Found: N, 17.45; H_2O, 11.30.

This pyrimidine will be subjected to a thorough investigation.

NEW HAVEN, CONN.

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

RESEARCHES ON PYRIMIDINES. LXXVI. NEW METHODS OF SYNTHESIZING 2-KETOPYRIMIDINES AND THEIR SULFUR ANALOGS.

BY TREAT B. JOHNSON AND A. WILLARD JOYCE.

Received July 5, 1915.

Although the chemistry of the 2,6-dioxypyrimidines, of which uracil (I), is the prototype, has been the subject of extended investigation largely on account of the ready accessibility of such substances and their biochemical interest, that of the *mono*-ketopyrimidines and the simple pyrimidine compounds has received comparatively little attention, and it was with the view of filling this gap and partly with definite synthetical aims that the preliminary work discussed in this paper was instituted.

The 2,6-dioxypyrimidines (I) are easily transformed into their corresponding dichloropyrimidines (II) by interaction with phosphorus pentachloride and phosphorus oxychloride. The yields of these dihalides are good and consequently they are available in quantity for synthetical purposes. When such halogenated pyrimidines are subjected to reduction, different intermediate products can theoretically be formed before complete removal of the halogen is effected. For example, reduction