[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

RESEARCHES ON PYRIMIDINES. CXIX. DETERMINATION OF THE CONSTITUTION OF ALKYLATION PRODUCTS OF PHENYLURACIL AND PHENYLHYDROURACIL[1]

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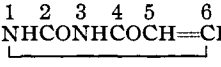
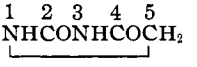
In uracil, as in hydantoin, the hydrogen atoms attached to each nitrogen atom can be replaced with alkyl or substituted alkyl groups by appropriate methods. If only one group is substituted, it enters the hydantoin mole-



Uracil



Hydantoin

cule in the 3-position.[2] This is not always true of the pyrimidine series, mixtures of N-1 and N-3 substitution products being formed in some cases.[3,4] The position of the entering group in hydantoin can be determined directly by identifying the α-amino acids formed when the molecule undergoes complete hydrolysis.[2] On the other hand, the double bond of uracil is not easy to reduce,[5] and hydrouracils are hydrolyzed either only partially with the formation of the ureido acids, or are broken down completely, probably because the β-amino acids which would be formed are more unstable[6] than the α-amino acids which result from the hydrolysis of hydantoins. The present investigation was undertaken with a view to establish some method for the determination of the position of an entering group.

Since uracil and hydantoin are somewhat related and since comparison of the ultraviolet absorption spectra of hydantoin compounds had proved useful in the identification of substituted hydantoins,[7,8] it seemed advisable to prepare a series of substituted uracils and to study their spectra in the ultraviolet. Uracils isomeric with hydantoins, whose spectra[8] had been determined, were chosen so that structural differences between uracils and hydantoins could also be studied. The absorption spectra will be published in a later paper.

Another consideration which led to the choice of this series of uracil

[1] Constructed from a dissertation presented by Janet Evans to the Faculty of the Graduate School of Yale University in June, 1929, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Johnson and Bates, THIS JOURNAL, **38**, 1087 (1916).

[3] Johnson and Hahn, *ibid.*, **39**, 1256 (1917).

[4] Behrend and Dietrich, *Ann.*, **309**, 265 (1899).

[5] Behrend, *ibid.*, **229**, 38 (1885); **251**, 239 (1899).

[6] Rodionow, THIS JOURNAL, **51**, 850 (1929).

[7] Carr and Dobbrow, *ibid.*, **47**, 2961 (1925); Carr, Report at Richmond Meeting of the American Chemical Society, April, 1927; Maclean, Thesis, Mount Holyoke College, **1926**.

[8] Hahn and Evans, THIS JOURNAL, **50**, 806 (1928).

compounds for synthesis was the fact that in the course of the synthesis of methyl N-1-methyl-5-benzalhydantoin-N-3-acetate[9]

$$N(CH_3)CON(CH_2COOCH_3)COC{=}CHC_6H_5$$

it was noted that the two isomeric esters of this constitution (m. p. 66° and 98°) suffer a transformation to the same compound (m. p. 278°) when they are allowed to stand in the light. This new compound is extremely insoluble as well as high melting, and its analysis showed it to have the same empirical formula as the esters from which it was obtained. The acid corresponding to the esters and melting at 198–199.5° was similarly transformed by light to an insoluble substance at 310°.

At the time the possibility of a rearrangement from a five- to a six-membered ring with the formation of the isomeric substituted uracil was considered.[9] Synthesis of the pyrimidine to which the ester and acid might rearrange and comparison of their properties with those of the compounds melting at 278 and 310° would definitely prove whether a change in the number of atoms in the ring had taken place.

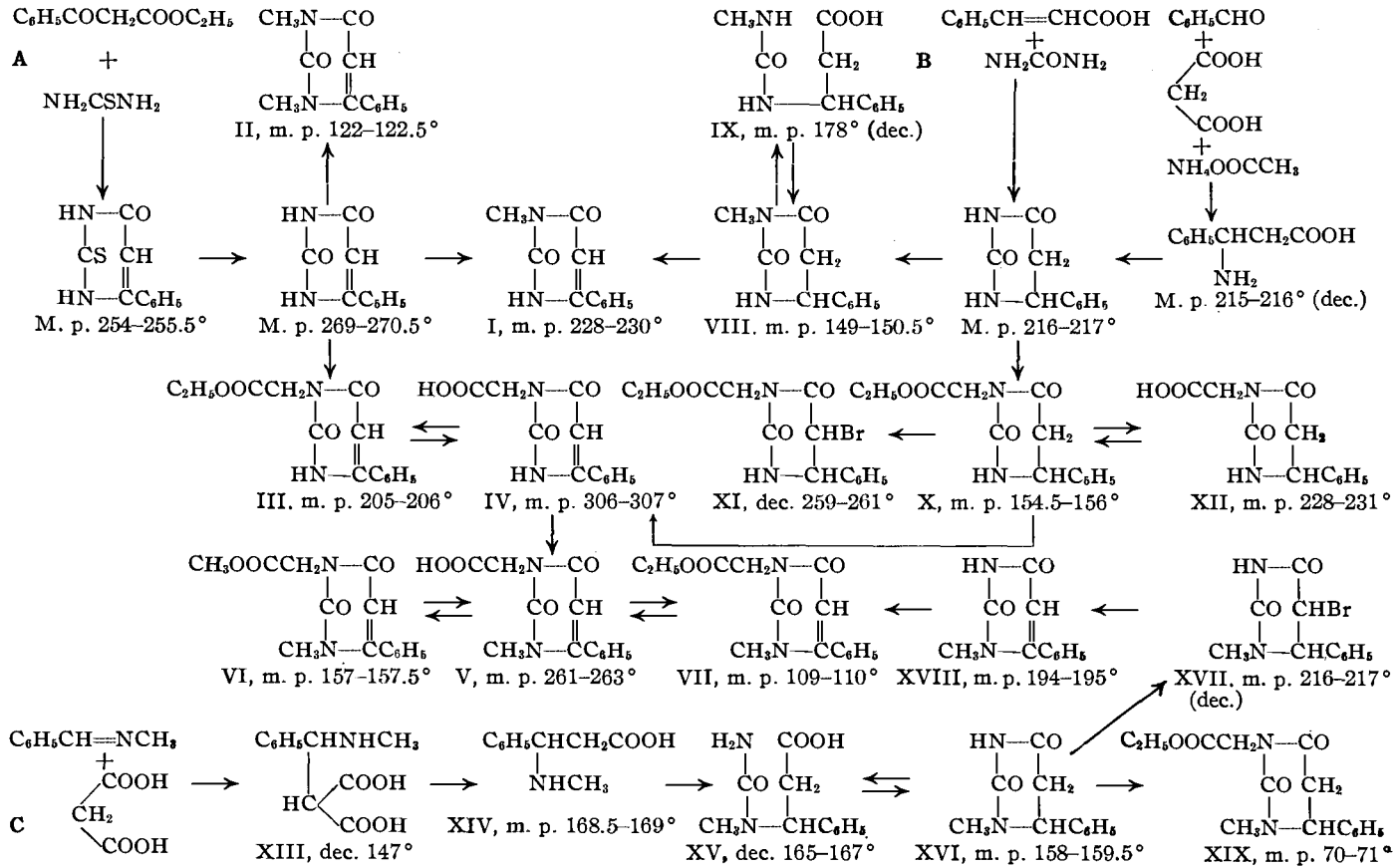
The present experimental evidence can lead us to no such conclusions. The uracil derivative, methyl N-1-methyl-6-phenyl-uracil-N-3-acetate, VI (see chart), has properties differing widely from those of the product formed by the action of light on the isomeric hydantoin. The former has a melting point of 159° and is very soluble in alcohol, whereas the latter melts at 278°, and is practically insoluble. The corresponding acid melts at 261°, in contrast to 310°, and is moderately soluble in alcohol. No evidence of the true structure of the compounds melting at 278 and 310° has as yet been obtained.

The compound methyl N-1-methyl-6-phenyl-uracil-N-3-acetate, VI, was synthesized by three different series of transformations, one of which definitely proves its structure. The course of the transformations and other minor relationships can be visualized by reference to the chart. The methods will be discussed separately.

In carrying out the first series, it was found that alkylation of 6-phenyl-uracil, with either methyl iodide or ethyl chloro-acetate, resulted in the formation of but one monosubstitution product, numbered, respectively, I and III. Another product was isolated from the treatment with methyl iodide, and was proved to be dimethyl-6-phenyluracil, II. That the positive methyl group and the less positive ethyl acetate residue enter the same position in the ring is proved by the following facts.

The methyl derivative, I, prepared by the alkylation of 6-phenyluracil has very different properties from those of the 1-methyl-6-phenyluracil, XVIII, synthesized from benzalmethylamine. The former crystallizes in glistening leaves and melts at 228–230°, whereas the latter occurs in long

[9] Hahn and Evans, THIS JOURNAL, 49, 2877 (1927).


A
B
C
II, m. p. 122–122.5°
IX, m. p. 178° (dec.)
M. p. 254–255.5°
M. p. 269–270.5°
I, m. p. 228–230°
VIII. m. p. 149–150.5°
M. p. 216–217°
M. p. 215–216° (dec.)
III. m. p. 205–206°
IV, m. p. 306–307°
XI, dec. 259–261°
X, m. p. 154.5–156°
XII, m. p. 228–231°
VI, m. p. 157–157.5°
V, m. p. 261–263°
VII, m. p. 109–110°
XVIII, m. p. 194–195°
XVII, m. p. 216–217° (dec.)
XIII, dec. 147°
XIV, m. p. 168.5–169°
XV, dec. 165–167°
XVI, m. p. 158–159.5°
XIX, m. p. 70–71°

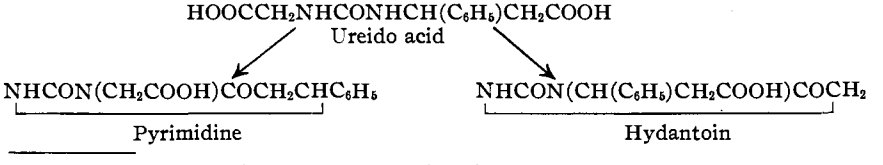
slender needles and melts at 194–195°. The nitrogen content of the two compounds is identical. Since the method of preparation of the latter substance requires that the methyl group must be in the 1-position, it follows that the hydrogen in the 3-position of the former compound must have been replaced by a methyl group.

Similarly, the methyl derivative, V, of ethyl 6-phenyl-uracil-N-3-acetate, III, which was prepared by alkylation of the corresponding acid, IV, with dimethyl sulfate and subsequent esterification, was shown by mixed melting point determinations and analyses to be the same compound as that prepared from 1-methyl-6-phenyluracil, XVIII, by treatment with ethyl chloro-acetate. On saponification, a sample of the ester formed from 1-methyl-6-phenyluracil was transformed into the corresponding acid, which has the same properties as those of the acid prepared by methylation of the 6-phenyl-3-acetic acid, IV. Thus the acetic acid or ester residue is in the 3-position, which is the same position entered by the methyl group.

The yield of substituted 6-phenyl-uracils was very low; moreover, it was found that reduction to the corresponding saturated compounds could not be effected by ordinary means. The saturated compounds were therefore prepared by alkylation of phenyl-hydrouracil. Their relationships to the unsaturated compounds were demonstrated by the substitution of bromine in position 5 of the ring,[10] and subsequent expulsion of hydrogen bromide. The products were identical with those prepared by alkylation of phenyluracil.

The hydrolysis of these saturated compounds cannot be used to determine their constitution. It was found that 3-methyl-6-phenyl-5,6-dihydrouracil VIII is rather readily hydrolyzed to the corresponding ureido acid IX, but prolonged action of boiling barium hydroxide solution at atmospheric pressure failed to complete the hydrolysis. When the compound was heated with barium hydroxide solution in a sealed tube at 150°, complete destruction of the molecule resulted.

Alkylation of 6-phenyl-5,6-dihydrouracil with ethyl chloro-acetate resulted in the formation of a mixture of which the major portion was identified as ethyl-6-phenyl-5,6-dihydrouracil-N-3-acetate. Two acids were obtained by the saponification of this ester in either acid or alkaline solution. Of these, the one, XII, melting at 231°, is that related to the original ester since it reverts to that ester on treatment with absolute alcohol and dry hydrogen chloride. The formation of the other acid may be accounted for by the following mechanism



[10] Fischer and Roeder, *Ber.*, **34**, 3763 (1901).

Hydrouracils can be hydrolyzed to the corresponding ureido acids, and reclosure of the ring effected by heating in acid solution. Two possibilities for ring formation from the ureido acid in question are evident. The validity of this explanation has not been determined.

The synthesis of N-1-methyl-6-phenyl-5,6-dihydrouracil, XVI, which now became essential for the proof of the structure of the whole series, depends on the fact that β-amino acids react with potassium cyanate[11] in water solution and then undergo rearrangement to *β-ureido acids*, which form hydrouracils on the closure of the ring. Accordingly the acid β-N-methylamino-β-phenylpropionic acid, XIV, had to be synthesized.

A modification of the recent method of Rodionow for the synthesis of β-amino acids[12] seemed the most promising for the synthesis of β-N-methyl-β-phenylpropionic acid, especially since it offered a plausible mechanism of his reaction. Rodionow discovered that the reaction of alcoholic solutions of ammonia or amines with aldehydes and malonic acid is more complicated than Knoevenagel[13] supposed and results in the formation of β-amino acids as well as cinnamic acids.

The repetition of Knoevenagel's experiments with acid and neutral ammonium malonate and benzaldehyde in the present investigation shows that besides the cinnamic acid, which was formed in slightly smaller amounts than those reported by him, the corresponding β-amino acid was isolated in yields corresponding to slightly more than 50% of the calculated amount. Ammonium acetate was also used very successfully as a source of ammonia with benzaldehyde and malonic acid in alcoholic solution.

The reaction of malonic acid with benzalmethylamine, the aliphatic analog of Knoevenagel's benzalaniline, proceeds to form β-methylamino-β-phenylpropionic acid, XIV, and cinnamic acid in approximately equal amounts. The intermediate addition product, XIII, of benzalmethylamine and malonic acid was isolated in pure condition. On heating, it undergoes decomposition, giving a mixture of β-amino acid and cinnamic acid.

The isolation of this amine dicarboxylic acid addition product offers some positive evidence in support of Rodionow's postulation[14] that the formation of β-amino acids from an aldehyde, ammonia and malonic acid proceeds in the following order: first, condensation of aldehyde and ammonia to form an imine; second, addition of malonic acid to the double bond; and, finally, loss of carbon dioxide. This mechanism is the most plausible one suggested. The relative yields of β-amino acid and cinnamic acid depend on the stability of the former.

N-1-methyl-6-phenyl-dihydrouracil, XV, was formed without difficulty

[11] Lengfeld and Stieglitz, *Am. Chem. J.*, **15**, 516 (1893).

[12] Rodionow and Malewinskaja, *Ber.*, **59**, 2952 (1926).

[13] Knoevenagel, *ibid.*, **31**, 2596 (1898).

[14] Rodionow and Postovskaja, THIS JOURNAL, **51**, 841 (1929).

from the β-amino acid by the use of potassium cyanate in neutral solution and could be made to condense quantitatively with ethyl chloro-acetate in the presence of sodium ethylate to form the disubstituted saturated uracil, XIX.

N-1-methyl-6-phenyl-hydrouracil, XVI, is converted quantitatively by the action of bromine in chloroform solution under pressure into the 5-bromine substitution product, XVII, which loses hydrogen bromide on heating at its decomposition point and forms the theoretical amount of 1-methyl-6-phenyluracil, XVIII. Condensation of the latter compound with ethyl chloro-acetate in the presence of sodium ethylate results in nearly quantitative formation of ethyl N-1-methyl-6-phenyl-uracil-1-acetate, VII. Saponification of the ester obtained by this method results in the formation of the acid V. Both acid and ester are identical in properties with the products obtained by direct substitution of phenyluracil.

The synthesis from benzalmethylamine in addition to its inherent theoretical interest, and its being absolute proof of the structure of the disubstituted uracils, was also the most efficient method for their preparation, since the yields of each of the intermediate products were extremely good.

Experimental Part

A. Derivatives of 6-Phenyluracil

The 6-phenyluracil, used as a starting point in this investigation was prepared according to the method of Johnson and Hemingway.[15] This method involves the condensation of ethyl benzoylacetate[16] and thiourea to form 6-phenyl-2-thiouracil and the subsequent desulfurization of this compound. The 6-phenyluracil obtained in this way was recrystallized once before using for syntheses.

N-3-methyl-6-phenyluracil, I, (m. p. 228–230°), and **N-1-3-dimethyl-6-phenyluracil**, II, (m. p. 122–122.5°) were prepared simultaneously by treating 6-phenyluracil with methyl iodide in alkaline solution.

The general method is illustrated by the following experiment. Ten grams of 6-phenyluracil (m. p. 269–270.5°) was refluxed on the steam-bath for six hours with a solution of 1.2 g. of sodium in 100 cc. of methyl alcohol. Excess methyl iodide was added and refluxing continued for twenty-four hours or until the sodium salt had disappeared and the solution had become neutral. On evaporation, 5 g. of material melting from 110 to 210° and 4 g. melting from 89 to 125° were obtained. Since it was found that the substituted uracils are much more soluble in boiling chloroform than the unsubstituted phenyluracil, separation of these mixtures could be accomplished with comparative ease. Extraction of these two successive precipitates with boiling chloroform gave in the first case, 2 g. of almost pure mono-methyluracil (m. p. 225–228°); and in the second case, 3 g. of dimethyluracil, m. p. 106–118°. The combined residues, insoluble in chloroform, amounted to 4 g. of unsubstituted phenyluracil (m. p. 265–269°). Evaporation of the mother liquor gave products contaminated with iodine and which could not be further purified. Iodoform separated in several cases and was identified by mixed melting point determinations. Only one monomethyl derivative was ever isolated from the reaction mixture although diligent search was made for another.

[15] Johnson and Hemingway, THIS JOURNAL, **37**, 379 (1915).

[16] Wahl and Doll, *Bull. soc. chim.*, [4] **13**, 265 (1913).

N-3-methyl-6-phenyluracil, I, m. p. 228–230°, was also prepared by treating N-3-methyl-6-phenyl-5,6-dihydrouracil, VIII, with bromine. Equal molecular quantities of bromine and hydrouracil were heated for one hour in a sealed tube with acetic acid as a solvent. Half of the product consisted of N-3-methyl-6-phenyluracil, m. p. 224–229°, which does not lower the melting point of the product obtained by direct methylation of phenyluracil. The rest of the product was a mixture, m. p. 140–155°, which contained the original N-3-methyl-6-phenyl-dihydrouracil.

After four recrystallizations from boiling alcohol, its melting point remained constant at 228–230°. It is soluble in boiling alcohol and precipitates in the form of large glistening leaves. It is also soluble in boiling chloroform.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: N, 13.86. Found: N, 13.80, 13.75.

N-1-3-dimethyl-6-phenyluracil, II, m. p. 122–122.5°, is soluble in chloroform and in boiling alcohol. After four recrystallizations from alcohol, from which it precipitates as small glistening leaves, a sample melting at 122–122.5° was used for analysis.

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: N, 12.96. Found: N, 13.01, 13.17.

Potassium 6-phenyluracil was prepared by boiling 15 g. of 6-phenyluracil with a solution of one equivalent of potassium hydroxide in 150 cc. of water and filtering out the undissolved uracil. Its melting point lies above 300°. After one recrystallization from boiling water the salt was analyzed.

Anal. Calcd. for $C_{10}H_8O_2N_2K$: N, 12.33. Found: N. 12.61, 12.63.

Ethyl-6-phenyluracil-N-3-acetate, III, m. p. 205–206°, was prepared from 6-phenyluracil by treatment with sodium ethylate and ethyl chloro-acetate. In a sample experiment, 25 g. of 6-phenyluracil was refluxed for three-quarters of an hour with a solution of 4 g. of sodium in 300 cc. of absolute alcohol. Twenty-five grams of ethyl chloroacetate was added and the refluxing continued until the solution was practically neutral, which required ten days. Nearly complete precipitation was brought about by the addition of an equal volume of water and a few drops of hydrochloric acid. Boiling chloroform extracted 4.3 g. of ester from this precipitate, leaving 19 g. of unchanged phenyluracil. Although the ester was prepared several times with variations in the length of time of heating, no better yields were obtained. No evidence of the formation of the isomeric N-1 substituted compound was obtained. When two equivalents of sodium was used with 35 g. of phenyluracil, the yield of ester was increased to 8 g., and 19.7 g. of phenyluracil was recovered unchanged. On long standing, additional precipitates were obtained from the mother liquor aggregating 7.6 g., m. p. 75–220°. This gave more ester on extraction with chloroform.

Anal. Calcd. for $C_{14}H_{14}O_4N_2$: N, 10.22. Found: N, 10.19, 10.42, 10.49.

The ester passes quantitatively into the salt of the corresponding acid IV, m. p. 305°, on saponification with potassium hydroxide. The ester is soluble in boiling alcohol from which it can be conveniently recrystallized. It forms as fine colorless needles.

6-Phenyluracil-N-3-acetic, IV, m. p. 304–305°, was obtained in quantitative yield by boiling the corresponding ester with about six equivalents of dilute potassium hydroxide for one and one-half hours and acidifying the resulting solution with hydrochloric acid. It is insoluble in water and only very slightly soluble in boiling alcohol and acetone. It can be recrystallized most conveniently from boiling glacial acetic acid, in the form of tiny clear cubes.

Anal. Calcd. for $C_{12}H_{10}O_4N_2$: N, 11.39. Found: N, 11.12, 11.27.

The acid can be esterified by treatment of its suspension in absolute alcohol with dry hydrogen chloride, when it passes quantitatively to the ester, III, m. p. 205–206°. When treated with dimethyl sulfate it yields the N-1-methyl derivative, V. The acid

is also formed when ethyl 6-phenyl-5,6-dihydrouracil-3-acetate, X, is treated with bromine in a sealed tube.

N-1-methyl-6-phenyluracil-N-3-acetic acid, V, m. p. 261–263°, was readily prepared by treating 6-phenyluracil-N-3-acetic acid, IV, with dimethyl sulfate. For example, 7 g. of acid, m. p. 303–305°, was dissolved in a solution of somewhat more than two equivalents of potassium hydroxide in 100 cc. of alcohol. About 9 moles of dimethyl sulfate (15 cc.) was added dropwise and alternately with a solution of potassium hydroxide to keep the reaction mixture alkaline. The mixture was refluxed for half an hour to destroy any excess dimethyl sulfate, evaporated to small volume, diluted with water and acidified with hydrochloric acid. An immediate precipitate of 7.3 g. of an acid resulted.

Anal. Calcd. for $C_{13}H_{12}O_4N_2$: N, 10.77. Found: N, 10.63, 10.67.

The acid is very slightly soluble in boiling water, but it is soluble in boiling glacial acetic acid and in boiling ethyl alcohol, from which it crystallizes in the form of small clear cubical crystals.

Methyl-N-1-methyl-6-phenyluracil-N-3-acetate, VI, m. p. 157–157.5°, was formed quantitatively by alternately saturating with hydrogen chloride and refluxing a suspension of the corresponding acid, V, in methyl alcohol.

Anal. Calcd. for $C_{14}H_{14}O_4N_2$: N, 10.21. Found: N, 10.06, 10.21.

The ester is very soluble in boiling alcohol, but is much less soluble in cold alcohol. It crystallizes in stout colorless needles. On saponification with concentrated hydrochloric acid the ester reverts quantitatively to the acid V.

Ethyl-N-1-methyl-6-phenyluracil-N-3-acetate, VII, m. p. 109–110, was prepared from the acid, V, by the above method using absolute ethyl alcohol in place of methyl alcohol. The yield was quantitative, 2.9 g. of ester resulting from the esterification of 2.6 g. of acid. Its analysis is given below (a). This ester was also prepared by treating 2.8 g. of N-1-methyl-6-phenyluracil, XVIII, with 0.4 g. of sodium in 40 cc. of absolute alcohol, and 0.8 g. of ethyl chloro-acetate. The sodium salt, which precipitated immediately on the addition of the uracil to the sodium ethylate solution, was refluxed for fifteen minutes before the addition of the ethyl chloro-acetate, and refluxing continued for four hours thereafter, or until the solution had become neutral to litmus. Water was added causing successive precipitates which aggregated 3.1 g. of fairly pure ester. After four recrystallizations it was analyzed (b).

Anal. Calcd. for $C_{15}H_{16}O_4N_2$: N, 9.72. Found: (a) N, 9.85, (b) N, 9.98.

The ester is very soluble in boiling alcohol and in 50% alcohol, from which it crystallizes in clusters of long, very fine silky needles. On saponification with concentrated hydrochloric acid it passes quantitatively into the corresponding acid, V.

Reduction of **N-1-methyl-6-phenyl-N-3-acetic acid** or its methyl ester could not be accomplished by catalytic methods, nor by the use of hydrogen iodide, both of which had proved successful in reducing the isomeric hydantoins.[8] Units of 1.5 g. of acid or ester were used and recovered quantitatively in each of the four experiments. In two cases, one with the acid and one with the ester, hydrogen was used with colloidal palladium as a catalyst.[17] In the third the acid was heated for two hours at 120–130° with 5 cc. of hydrogen iodide, 0.5 g. of red phosphorus and 20 cc. of acetic acid. In the fourth, the acid was heated for five hours at 140–145° with 1.0 g. of red phosphorus and 30 cc. of hydrogen iodide, sp. gr. 1.70.

B. Derivatives of 6-Phenyl-5,6-dihydrouracil

6-Phenyl-5,6-dihydrouracil was prepared by heating cinnamic acid with urea, the general method of Fischer and Roeder.[10] Their procedure was modified by decreasing

[17] Hahn and Gilman, THIS JOURNAL, **47**, 2948 (1925).

the temperature from 250 to 190°, and increasing the length of time of heating from one to six hours, whereby the yields were nearly tripled. From 50 g. of cinnamic acid and 30 g. of urea yields of 22–24 g. of phenyldihydrouracil, m. p. 215–217°, were obtained. This melting point agrees with that given by Posner[18] and by Dakin,[19] 216–217°, rather than that obtained by Fischer,[10] 202–203°.

6-Phenyl-5,6-dihydrouracil was also prepared by treating a solution of β-phenyl-β-aminopropionic acid with potassium cyanate and evaporating to dryness.[11] The product was dissolved in a little water and acidified with hydrochloric acid. The precipitate, m. p. 183–186°, proved to be the ureido acid and passed quantitatively into phenyl-hydrouracil (m. p. 215–217°) on heating with 10% hydrochloric acid. Mixed melting point determinations demonstrated the identity of these compounds with those obtained by Fischer's synthesis.

The β-phenyl-β-aminopropionic acid used in the above synthesis was prepared by treatment of 3 g. of benzaldehyde with 3 g. of malonic acid, 4.5 g. of ammonium acetate and 25 cc. of absolute alcohol. The materials were refluxed for two hours, during which time carbon dioxide was evolved. On cooling, 3.2 g. of amino acid decomposing at 213–215° precipitated, and from the filtrates, 1.2 g. of cinnamic acid, m. p. 128–131°.

In several experiments ammonium malonate was used in place of malonic acid and ammonium acetate. The ammonium malonate was prepared by treating a solution of malonic acid in dry ether with a stream of dry ammonia gas.[20]

From 10 g. of the mono-ammonium malonate refluxed for two hours with 10 g. of benzaldehyde and 25 cc. of absolute alcohol, 6 g. of amino acid and 3.2 g. of cinnamic acid were obtained; from 6 g. of the mixture of mono and di-ammonium malonate refluxed for three and one-half hours with 4.6 g. of benzaldehyde and 25 cc. of absolute alcohol, 3.2 g. of amino acid and 2.8 g. of cinnamic acid were obtained. After recrystallization from boiling alcohol, the amino acid melted at 215–216°. Since the melting point does not agree with that given by Posner,[18] 231°, or Rodionow,[12] 228°, the identity of the compound was established by an analysis.

Anal. Calcd. for $C_9H_{11}O_2N$: N, 8.49. Found: N, 8.48.

N-3-methyl-6-phenyl-5,6-dihydrouracil, VIII, m. p. 149–150.5°, was prepared by the following method. The sodium salt of 6-phenyl-5,6-dihydrouracil was formed by refluxing 17.5 g. of the hydrouracil with a solution of 2.3 g. of sodium in 300 cc. of absolute alcohol for one hour. The addition of 20 g. of methyl iodide caused almost immediate solution of the salt. Refluxing was continued for one-half hour. On standing for twenty-four hours and further evaporation, 14 g., m. p. 145–149°, precipitated and a small amount of unchanged hydrouracil was recovered. The methylated compound was purified by recrystallization from boiling water and alcohol, from which it precipitates in the form of needles.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: N, 13.73. Found: N, 13.88, 13.86.

On treatment with bromine, in sealed tubes, N-3-methyl-6-phenyl-5,6-dihydrouracil can be transformed into the corresponding unsaturated compound, I. On hydrolysis at atmospheric pressure the corresponding ureido acid IX is formed.

Hydrolysis of N-3-methyl-6-phenyl-5,6-dihydrouracil, VIII.—The hydrolysis was conducted both at atmospheric pressure and at elevated pressures. In the first case, 6.4 g. of hydrouracil was digested with 50 g. of barium hydroxide, 100 cc. of water and 100 cc. of methyl alcohol for one hundred hours. After removing the solid barium

[18] Posner, *Ber.*, **38**, 2316 (1905).

[19] Dakin, *J. Biol. Chem.*, **8**, 39 (1910).

[20] McMaster, *Am. Chem. J.*, **49**, 295 (1913).

hydroxide by filtration, the solution was distilled into weak hydrochloric acid. A very small amount of methylamine hydrochloride contaminated with ammonium chloride was isolated from the distillate. The residue in the flask was exactly neutralized with sulfuric acid and filtered from the barium sulfate. A precipitate of 2.6 g. of coarse needles which decompose at 178° resulted after further evaporation. This compound reverted quantitatively to the original hydrouracil on treatment with 10% hydrochloric acid. This result and the following analysis of the product decomposing at 178° established the fact that the hydrouracil is hydrolyzed with the formation of the ureido acid IX, on prolonged treatment with barium hydroxide and that complete hydrolysis cannot be effected by this means.

Anal. Calcd. for $C_{11}H_{14}O_3N_2$: N, 12.61. Found: N, 12.70, 12.74.

The molecule degenerated completely when N-3-methyl-6-phenyl-5,6-dihydrouracil (3.5 g.) was heated at 150° for seventy-two hours in a sealed tube with excess barium hydroxide and a little water and subsequently treated as described above. The acid distillate yielded 1.5 g. of solid which was extracted with absolute butyl alcohol and found to consist of nearly the theoretical quantities of ammonium chloride and methylamine hydrochloride. After the barium had been removed from the reaction mixture and the filtrate evaporated to dryness only 0.5 g. of a substance, m. p. 115–120°, remained. This was found to be neither benzoic acid nor cinnamic acid. The peculiar odor and lachrymal effect of the vapors indicate that the other products of this profound decomposition are volatile with steam. It is evident that this method cannot be used for the determination of the position of the methyl group.

Ethyl-6-phenyl-5,6-dihydrouracil-N-3-acetate, X, m. p. 154.5–156°, is the major product formed when the sodium salt of phenyl-dihydrouracil is treated with ethyl chloro-acetate. Twenty grams of phenyl-dihydrouracil was refluxed for four hours with two equivalents of sodium (4.8 g.) in 250 cc. of absolute alcohol; 40 g. of ethyl chloro-acetate was added and refluxing continued for nine hours or until the solution was neutral. The addition of an equal volume of water caused the precipitation of 10.4 g., m. p. 135–170°. The filtrate was evaporated to dryness and extracted with chloroform and then alcohol. From the chloroform solution 2.7 g. of a mixture, m. p. 110–128°, was obtained. This mixture was never resolved, though several attempts with chloroform, water and alcohol were made. The alcohol extraction yielded 3,4 g. of original hydrouracil. The ester was obtained by extraction of the first precipitate with chloroform, leaving a residue of 1.7 g. of the original hydrouracil. The extract was recrystallized from boiling alcohol, giving 5.1 g., m. p. 148–151°. After several recrystallizations from boiling alcohol, from which it precipitates as fine white needles, its melting point remained constant at 154.5–156°.

Anal. Calcd. for $C_{14}H_{16}O_4N_2$: N, 10.15. Found: N, 10.15, 10.17.

On hydrolysis the ester is converted into a mixture from which the acid, XI, m. p. 228–231°, can be isolated. Treatment with bromine also results in the formation of a mixture from which a bromine compound, XII, and the corresponding unsaturated acid, IV, were isolated.

Bromination of **ethyl-6-phenyl-5,6-dihydrouracil-N-3-acetate** was carried out at 100° in a sealed tube. Three grams of the hydrouracil was heated with 1.5 moles of bromine in glacial acetic acid for three hours. After neutralization, a precipitate of 2.8 g. which decomposed at 212–235° was obtained. This was recrystallized from boiling alcohol, giving 0.8 g. of a bromine compound, XI, which forms in spongy balls and melts at 259–261° with decomposition.

Anal. Calcd. for $C_{14}H_{15}O_4N_2Br$: N, 7.89. Found: N, 7.61, 7.63.

From the filtrate, 0.35 g. of original ester and 1.3 g. of a mixture melting from 80° to above 267° were obtained.

In a second experiment the heating at 100° was continued for seven hours and resulted in the formation of another mixture. In this case, however, no pure bromine compound could be isolated but a small amount (0.8 g.) of material melting at 350° was obtained by recrystallization. It was proved to be 6-phenyluracil-N-3-acetic acid, IV, by a mixed melting point determination. The remainder of the material consisted of a mixture melting from 180 to 275° with decomposition. Although this method is not feasible for the preparation of the acid, IV, the relationship between the two compounds has been definitely established.

6-Phenyl-5,6-dihydrouracil-N-3-acetic acid, XII, m. p. 228–231°, can be isolated from the mixture formed when the corresponding ester, X, is hydrolyzed in either acid or alkaline solution. The proportion of it is practically the same in either case. When 0.5 g. of pure ester was boiled with 30 cc. of concentrated hydrochloric acid for two hours, 0.2 g., m. p. 228–231°, and 0.2 g., m. p. 165–215°, were obtained. The product melting at 228–231° passed quantitatively to the ester, m. p. 154.5–156°, on treatment with absolute ethyl alcohol and dry hydrogen chloride. On esterification of the mixture, both the original ester, m. p. 148–152°, and a new ester, m. p. 132–135°, were obtained. This latter ester was not obtained in large enough quantities for analysis.

When 5 g. of ester, m. p. 154.5–156°, was refluxed with potassium hydroxide for one and one-half hours and the resulting solution acidified, 4.2 g., m. p. 180–220°, precipitated. This was resolved into two products, 2.6 g., m. p. 228–231°, and 1.0 g., m. p. 170–180°, by one recrystallization from boiling alcohol. Further recrystallization from boiling alcohol failed to alter the melting point.

Anal. Calcd. for $C_{12}H_{12}O_4N_2$: N, 11.29. Found: N, 11.07, 11.19.

C. Derivatives of Benzalmethylamine

β-N-methyl-benzylmalonic acid, XIII, decomposition point 147°, is the primary product of the action of malonic acid on benzalmethylamine. It is formed with the evolution of heat and begins to precipitate from the reaction mixture almost immediately. On further heating it loses carbon dioxide to form the corresponding β-aminopropionic acid, XIV, and cinnamic acid. It was recrystallized once from boiling alcohol.

Anal. Calcd. for $C_{11}H_{13}O_4N$: N, 6.28. Found: N, 6.53.

β-N-methyl-β-phenylpropionic Acid, XIV, m. p. 168.5–169°.—Benzalmethylamine (20 g.), malonic acid (16.7 g.) and absolute alcohol (80 cc.) were mixed and warmed gently on the steam-bath. After five to ten minutes the solution was filled with the feathery white crystals of the malonic acid addition product and carbon dioxide was being given off. The refluxing was continued, causing the gradual disappearance of the precipitate. At the end of three hours solution was complete and evolution of carbon dioxide had ceased. The solution was cooled in a freezing mixture and the product precipitated slowly as a white powder by addition of ether or by seeding. The precipitate obtained by seeding always contained some cinnamic acid. The yield of β-amino acid was 12 g., and of cinnamic acid obtained from the ether solution, 9 g. Small amounts of benzaldehyde and benzoic acid were also detected.

Anal. Calcd. for $C_{10}H_{13}O_2N$: N, 7.82. Found: N, 7.72, 7.71.

The acid precipitates as feathery crystals from pure boiling alcohol, in which it is less soluble than it is in the reaction mixture. It is extremely soluble in hydrochloric acid. From the latter, the hydrochloride crystallizes in clusters of needles.

β-Phenyl-β-N-1-methyl-ureido-propionic acid, XV, m. p. 165–167°, could be prepared in good yield by the treatment of β-phenyl-β-N-methylpropionic acid with the calculated amount of potassium cyanate in a small quantity of water. Thus, 2.5 g. of the amino acid dissolved in 15 cc. of water was treated with 2 g. of potassium cyanate. The solution was heated on the steam-bath for one and one-half hours, cooled, acidified

and filtered immediately. The yield was 2.0 g., m. p. 165–167°. When the hydrochloride of the amino acid was used the product of the reaction was a mixture of the ureido acid, the corresponding hydrouracil, and a little cinnamic acid. The mixture melts from 130–150° with decomposition.

The ureido acid can also be prepared by the partial hydrolysis of the corresponding hydrouracil with dilute alkali.

N-1-methyl-6-phenyl-5,6-dihydrouracil, XVI, m. p. 158–159.5°.—Closure of the ring was brought about quantitatively by heating either the pure ureido acid, XV, or the mixture with 10% hydrochloric acid. The product is soluble in boiling water, from which it crystallizes in long fine needles, and in alcohol, from which it crystallizes in short heavy needles.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: N, 13.73. Found: N, 13.72, 13.56.

N-1-methyl-6-phenyl-5,6-dihydrouracil can be transformed readily into the corresponding unsaturated compound by treatment with bromine and subsequent expulsion of hydrogen bromide. An ethyl acetate residue can be readily substituted for hydrogen in the N-3-position.

N-1-methyl-6-phenyl-5-bromo-5,6-dihydrouracil, XVII, m. p. 214–215°.—Bromination of N-1-methyl-6-phenyl-5,6-dihydrouracil was brought about in sealed tubes at 100°. When acetic acid was used as solvent, the major product was the 5-bromo compound, but a small quantity of another mono-bromo compound which crystallizes in long needles, m. p. 240–242° without decomposition, was also formed. It was found more convenient to brominate in chloroform solution by the following method. Bromine (4.5 g.) in 40 cc. of alcohol-free chloroform and 5 g. of dihydrouracil were sealed in a Carius tube and heated at 100° for one and one-half hours. After cooling, the solution was diluted to 200 cc. and extracted with a solution of sodium bicarbonate until free from acid. The chloroform was evaporated and the product (6.9 g.) recrystallized several times from boiling alcohol. It precipitates as glistening leaflets which decompose at 214–215°. None of the compound melting at 240–242° was formed.

Anal. Calcd. for $C_{11}H_{11}O_2N_2Br$: N, 9.93. Found: 214–216°, N, 9.92, 10.19; 240–242°, N, 9.95, 10.18.

Boiling the bromine compound for four hours with an equivalent of pyridine in absolute alcohol produced no change. Hydrogen bromide could, however, be driven off by heating, as described below.

N-1-methyl-6-phenyluracil, XVIII, m. p. 194–195°, was prepared by heating the bromine derivative, XVII, at its decomposition point, 215°. Hydrogen bromide is given off, the reaction being complete in fifteen minutes. The yield is quantitative, 3 g. of bromine derivative giving 2.1 g. of uracil. The product was purified by recrystallization from boiling alcohol and from water. No test for bromine could be obtained by fusion with sodium.

Anal. Calcd. for $C_{11}H_{10}O_2N_2$: N, 13.86. Found: N, 13.79, 13.84.

On treatment with sodium and ethyl chloro-acetate the N-3-ethyl acetate derivative, VII, is formed.

Ethyl N-1-methyl-6-phenyl-5,6-dihydrouracil-N-3-acetate, XIX, m. p. 70–71°, resulted in good yield from the treatment of N-1-methyl-6-phenyl-5,6-dihydrouracil with sodium and ethyl acetate in the usual manner. The reaction is complete half an hour after the addition of ethyl chloro-acetate. The ester could not be induced to crystallize from the reaction mixture. It was therefore evaporated to dryness and extracted with ether, leaving behind sodium chloride and unchanged N-1-methyl-6-phenyl-5,6-dihydrouracil. The ester was obtained in crystalline form after evaporation of the ether and stirring. From 7.8 g. of N-1-methyl-6-phenyl-5,6-dihydrouracil, 6.6 g. of ester was obtained. The ester is exceedingly soluble in boiling alcohol, but it was puri-

fied for analysis by recrystallizations from slightly more dilute solutions in this solvent. Water can be added to precipitate the remainder of the ester.

Anal. Calcd. for $C_{16}H_{18}O_4N_2$: N, 9.66. Found: N, 9.52, 9.42.

Summary

1. The pyrimidine methyl N-1-methyl-6-phenyluracil-N-3-acetate has been synthesized by three series of transformations using 6-phenyluracil, 6-phenyl-5,6-dihydrouracil and benzalmethylamine as starting points.

2. The structure of methyl N-1-methyl-6-phenyluracil-N-3-acetate has been definitely established by its synthesis from benzalmethylamine. The structures of the other uracils and hydrouracils have also been proved by relationships to this ester.

3. β-Phenyl-β-aminopropionic acid has been prepared by the reaction of benzaldehyde, malonic acid and ammonium acetate.

4. The preparation of β-phenyl-β-methylaminopropionic acid from benzalmethylamine is evidence that the formation of β-amino acids from ammonia or amines with aldehydes and malonic acid may take place with the intermediate formation of an imine.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MARYLAND]

THE DECOMPOSITION OF ETHYL NORMAL-BUTYLACETOACETATE INTO CAPROIC ACID AND METHYL NORMAL-AMYL KETONE

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A number of methods for the preparation of *n*-caproic acid have appeared in the literature from time to time.[2] Of the various schemes which have been suggested, the synthetic method described in the article mentioned,[2] starting from ethyl malonate, is the most useful. By use of this method, yields of 74% of the theoretical were obtained.

A synthesis of caproic acid from ethyl *n*-butylacetoacetate is possible and, inasmuch as ethyl malonate has a molecular weight of 160 compared to 130 for ethyl acetoacetate, the acetoacetic ester method appears at first sight attractive. Prices of raw materials are also much in favor of this method.[3] Consequently, if satisfactory yields can be obtained, the de-

[1] From a thesis submitted to the Graduate School of the University of Maryland by R. W. Riemenschneider in partial fulfilment of the requirements for the degree of Master of Science.

[2] See Adams and Marvel, THIS JOURNAL, **42**, 317–319 (1920), for a brief summary of these methods.

[3] Eastman's "List No. 21" quotes the following: ethyl acetoacetate $7.00 per kg.; ethyl acetoacetate (pract.) $3.00 per kg.; ethyl malonate, $12.00 per kg.; ethyl malonate (techn.) $10.00 per kg.