Attempts were made to prepare the mono- and diphenyl ethers of resorcin and the phenyl ethers of α- and β-naphthols. The work is as yet incomplete.

Summary.

1. Dry distillation of alkali salts of sulfonic acids with alkali phenolates is a convenient method for the preparation of aryl ethers of phenols. Though the yields are considerably less than those obtained by the method of Ullman and Sponagel, the compounds used can, in some cases, be more directly prepared.

2. The reaction probably proceeds according to the equation:

$$RSO_3M + R'OM = R'OR + M_2SO_3,$$

in which equation, the symbol R may represent the phenyl radical and its homologs, provided no long side-chain is present, or a methyl group. The symbol R′ represents a phenyl radical or an aminophenyl radical. The presence of a long side-chain in this radical interferes with the reaction's proceeding normally or causes decomposition of the product.

LEXINGTON, KY.

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

RESEARCHES ON PYRIMIDINES. LXXII. THE SYNTHESIS OF 4-HEXYLURACIL AND ITS RELATIONSHIP TO URACIL-GLUCOSIDE.

BY TREAT B. JOHNSON.

Received June 26, 1914.

CONTENTS.—1. Pyrimidine-Nucleosides: The Structure of Uridine. 2. The Synthesis of Normal 4-Hexyluracil. 3. Experimental Part.

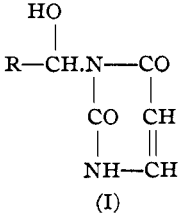
1. Pyrimidine-Nucleosides: The Structure of Uridine.

The elucidation of the structure of nucleic acids obviously involves the determination of the constitution of *nucleosides*. The latter are characteristie purine-carbohydrate and pyrimidine-carbohydrate combinations, which result by partial hydrolysis of these naturally occurring acids. We have practically no knowledge regarding the nature of the carbohydrate linkings in these compounds, and, consequently, we are unable to express structually their exact constitution. One important fact, however, seems to have been very definitely established by the results already obtained, namely, that the two nitrogen cycles—the purines and pyrimidines—are not joined to the carbohydrates in a similar manner. The experimental data, thus far obtained, suggest that the sugar, in the case of the purine-nucleosides, is very probably linked to the purine at a nitrogen atom occupying either the 7- or the 9-position of the purine ring. Such hexose combinations have recently been synthesized by Emil Fischer[1] and it is interesting to note that his synthetical glucosides agree

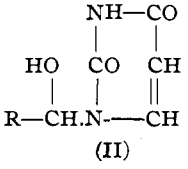
[1] Fischer and Helferich, *Ber.*, **47**, 210 (1914).

very closely, in chemical behavior, with that of the naturally occurring purine-nucleosides. This investigator has not established, however, whether the carbohydrate is joined, in his synthetical products, to the purine ring at positions 7 or 9.

Whether the pyrimidines—uracil, thymine and cytosine—are linked to carbohydrates, in pyrimidine-nucleosides, through one of the nitrogen atoms in positions 1 and 3 of the ring is indeed questionable. Surely the remarkable stability of the natural nucleosides towards hydrolytic agents does not support such an assumption. It has been our experience in this laboratory that such glucosidic combinations, as are represented by the general formulas (I and II), are very unstable and easily undergo hydrolysis



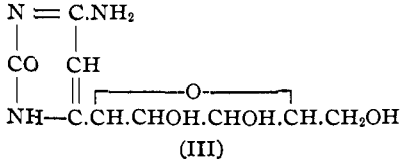
(I)



(II)

in the presence of acids, and even boiling water, giving the original pyrimidine. Several combinations of these types have been synthesized by us, but, in no case which has thus far been carefully examined have we obtained a stable compound. These observations have recently been confirmed by the results obtained by Fischer[1] in his investigations on pyrimidine-glucosides. It seems safe to assume, however, if a nitrogen-carbon linkage is found to be present, that the combination which involves the nitrogen atom in position 3, as represented by Formula II, will be found to be the most resistent to the action of hydrolytic agents. Whether the higher, synthetical, glucosidic combinations of this type will approach in stability that of the pyrimidine-nucleosides remains to be established.

The early observation that pyrimidine-combinations corresponding to Formulas I and II easily break down on hydrolysis with acid, and the interesting conclusion of Levene and La Forge[2] that the constitutions of cytidine and uridine are possibly to be expressed by Formulas III and IV, respectively, led us to turn our attention to the study of simple pyrimi-



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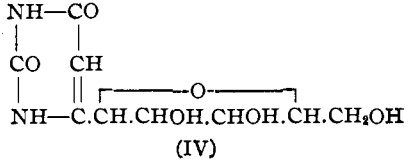
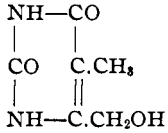


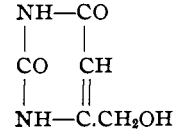
(IV)

[1] *Ber.*, **47**, 1377 (1914).
[2] *Ibid.*, **45**, 608 (1912).

dine-nucleosides containing the glucosidic union R.CH(OH)— in the 4-position of the pyrimidine ring. No representative of this class of pyrimidines had been described in the literature previous to our investigations. This work has proved very fruitful from a synthetical standpoint. A method of synthesizing pyrimidines of this type has now been developed which has enabled us to obtain the simplest nucleosides of thymine (V) and uracil (VI). A description of these interesting compounds has been recorded in papers from this laboratory.[1] The synthesis and properties of a higher homolog of uracil-nucleoside (VI) will be discussed in a future publication.

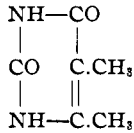


(V)

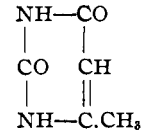


(VI)

Our method of establishing the constitution of these two synthetical nucleosides (V and VI) was to subject them to the action of strong hydriodic acid, when they underwent reduction smoothly giving 4,5-dimethyluracil (VII) and 4-methyluracil[2] (VIII), respectively. The success of this



(VII)



(VIII)

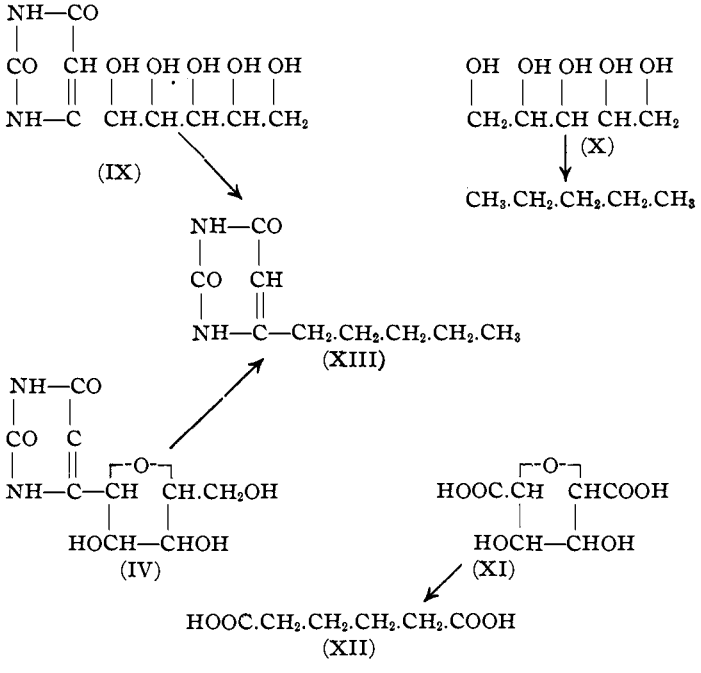
method of identifying hydroxylated derivatives of this type is dependent essentially upon two facts, firstly, that the double bond in uracil compounds is not destroyed by digestion with hydriodic acid, and secondly, that the 4-alkyl substituted uracils, so far as examined, possess such characteristic properties that they can be easily identified, even when working with small amounts of material. Whether the higher homologs of these two nucleosides will be found to interact normally with hydriodic acid remains to be established, but it is certain from what is already known that it should be possible theoretically to accomplish such changes. A knowledge of the properties of the higher homologs of 4-methyluracil and the corresponding thymine compounds is, therefore, very essential.

I find no record, in the papers of other investigators, that any attempts have been made to reduce uridine (IV) or cytidine (III) with hydriodic

[1] Johnson and Chernoff, *J. Biol. Chem.*, **14**, 307 (1913); THIS JOURNAL, **35**, 585 (1913); **36**, 1742 (1914).

[2] Johnson and Chernoff, *loc. cit.*

acid. Reduction of uridine in the presence of palladium[1] leads to the formation of the corresponding hexahydro derivative with destruction of the double bond between the carbons in positions 4 and 5 of the pyrimidine ring. According to Formula (IX) uridine is a monosubstitution product of the alcohol xylite, $C_5H_{12}O_5$ (X), while the relationship between Levene's formula for uridine, and that of isosaccharic acid is apparent by inspection of their respective formulas (IV and XI). Theoretically then, there is no reason to assume that these related compounds should undergo reduction otherwise than in an analogous manner, giving their corresponding alkyl derivatives. Bertrand[2] has shown that xylite is transformed into iodopentane, $CH_3.CHI.CH_2.CH_2.CH_3$, by reduction with hydriodic acid, while isosaccharic acid (XI), which is prepared from chitosamine, by oxidation with nitric acid, and also from chitine,[3] is reduced to adipic acid (XII), when heated with hydriodic acid at 140–150°. The reduction, therefore, of a pyrimidine having either the constitution IV or IX to 4-pentyluracil (XIII) would be a perfectly normal reaction. The forma-



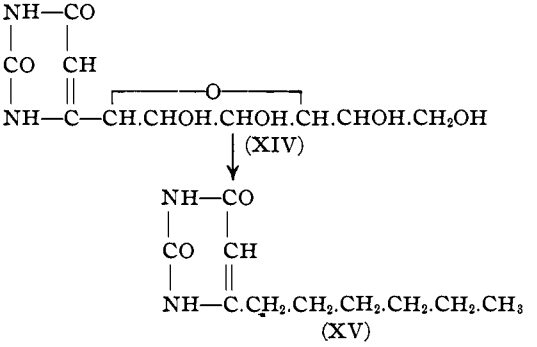
tion of this alkylated uracil from uridine would establish, beyond doubt, the correctness of Levene's Formula (IV). An investigation dealing with

[1] Levene and La Forge, *loc. cit.*

[2] *Bull. soc. chim.*, [3] **5**, 556, 740 (1891).

[3] Tiemann and Haarmann, *Ber.*, **17**, 246 (1884); **19**, 1257 (1886); Tiemann, *Ber.* **27**, 118 (1894).

the synthesis of this unknown uracil derivative (XIII), is now in progress in this laboratory. In the following chapter of this paper is given a description of the synthesis and properties of the next higher homolog of 4-pentyluracil, namely, *4-hexyluracil* (XV), which would be the reduction product of a corresponding hexose uracil-nucleoside represented by Formula XIV.



In Table I, below, is listed a series of some higher polyatomic alcohols and their oxidation products, which have been shown to undergo reduction normally with hydriodic acid.

TABLE I.

Hydroxyl Derivative.		*Reduction Product.*
Xylite,[1] $HOCH_2(CHOH)_3.CH_2OH$	⟶	$CH_3.CHI_2.CH_2.CH_2.CH_3$
Styracite,[2] $C_6H_{12}O_5$	⟶	hexyliodide
Mannite,[3] $HO.CH_2(CHOH)_4.CH_2OH$	⟶	hexyliodide
Sorbit,[4] $C_8H_{14}O_8$	⟶	hexyliodide
Mannoheptite,[5] $C_7H_{16}O_7$	⟶	heptyliodide
Rhamnonic acid,[6] $CH_3(CHOH)_4COOH$	⟶	caproic acid
l-Mannonic acid,[7] $HOCH_2(CHOH)_4COOH$	⟶	caproic acid
d-Galactonic acid[8]	⟶	Lactone of caproic acid
α-Rhamnohexonic acid,[9] $CH_3(CHOH)_5COOH$	⟶	heptylic acid
α-Glucoheptonic acid,[10] $HOCH_2(CHOH)_5COOH$	⟶	heptylic acid
d-Mannoheptonic acid[11]	⟶	heptylic acid

[1] Bertrand, *loc. cit.*

[2] Ashina, *Chem. Zentr.*, **1907**, II, 1431; **1909**,.II, 548; *Ber.*, **45**, 2363 (1912).

[3] Erlenmeyer and Wanklyn, *Ann.*, **111**, 247 (1859); Hecht, *Ber.*, **11**, 1420, 1152 (1878); Schorlemmer, *Ann.*, **199**, 141 (1879).

[4] Vincent and Delachanal, *Compt. rend.*, **108**, 354 (1889); **111**, 51 (1980); Hitzemann and Tollens, *Ber.*, **22**, 1048 (1889).

[5] Maquenne, *Bull. soc. chim.*, [2] **50**, 132, 548 (1888); *Ann. chim. phys.*, [6] **19**, 5 (1890).

[6] Will and Peters, *Ber.*, **21**, 1813 (1888); **22**, 1704 (1889).

[7] Kiliani, *Ber.*, **20**, 339 (1887); **19**, 3034 (1886).

[8] Kiliani, *loc. cit.*

[9] Fischer and Tafel, *Ber.*, **21**, 2175 (1888).

[10] Kiliani, *Ber.*, **19**, 1128 (1886).

[11] Fischer and Hartmann, *Ber.*, **22**, 372 (1889).

TABLE I (*continued*).

Hydroxyl Derivative.		*Reduction Product.*
Laevuloheptonic acid,[1] $HOCH_2(CHOH)_3.C(OH)(COOH)—CH_2OH$	⟶	α-methylhexylic acid
Saccharic acid,[2] $HOOC.(CHOH)_4COOH$	⟶	adipic acid
Mucic acid,[3] $HOOC(CHOH)_4COOH$	⟶	adipic acid
Isosaccharic acid[4]	⟶	adipic acid

2. The Synthesis of Normal 4-Hexyluracil.

It is 31 years since the publication of Behrend's classic paper entitled: "Über die Einwirkung von Harnstoff auf Acetessigäther (Vorläufige Mittheilung),"[5] and 27 years since List[6] showed that 2-thiouracil is formed by condensation of ethyl acetoacetate with thiourea. Since the appearance of these papers a great number of derivatives of ethyl acetoacetate have been shown to undergo condensation with urea compounds forming pyrimidines, but, notwithstanding this activity, no one has shown, thus far, that the higher homologs of ethyl acetoacetate (Table II) functionate

TABLE II.

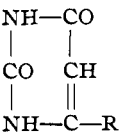
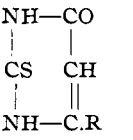
Ethyl propionylacetate,	$CH_3CH_2COCH_2COOC_2H_5$
Ethyl butyrylacetate,	$CH_3CH_2CH_2COCH_2COOC_2H_5$
Ethyl valerianylacetate,	$CH_3.CH_2CH_2CH_2COCH_2COOC_2H_5$
	Etc.

normally and condense with urea and thiourea, giving the corresponding 4-alkyl derivatives of uracil and thiouracil, respectively. We have no knowledge of the higher homologs of 4-methyluracil or 2-thio-4-methyluracil. In fact, no representative of the two homologous series of pyrimidines, represented in Table III below, have been described in the literature except the 4-methyl derivatives. The other members of these two series which are now of immediate biochemical interest, are the lower representatives, and especially the 4-pentyl and 4-hexyl derivatives of uracil, which may be considered as the reduction products of the corresponding pentose and hexose glucosides of this pyrimidine.

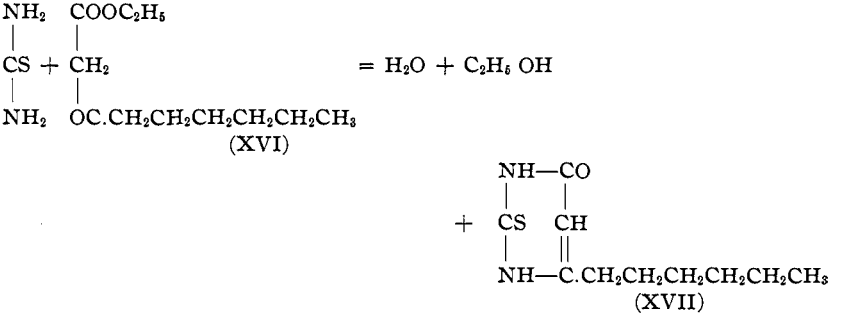
The starting point in our synthesis of 4-hexyluracil (XV) was the β-ketone ester *ethyl heptylylacetate* (XVI), which is now easily obtainable, if ethyl heptylate is available, by condensation of this ester with ethyl acetate.[7] For all the ester, however, which was used in this research, I

[1] Kiliani, *Ber.*, **19**, 224 (1886).
[2] de la Motte, *Ber.*, **12**, 1571 (1879).
[3] Crum-Brown, *Ann.*, **125**, 19 (1863); Heinzelmann, *Ibid.*, **193**, 184 (1878).
[4] Tiemann and Haarmann, *loc. cit.*
[5] *Ber.*, **16**, 3027 (1883).
[6] *Ann.*, **236**, 1 (1887).
[7] Wahl and Doll, *Bull. soc. chim.*, **13**, 265 (1913).

TABLE III.

Pyrimidines.		*Thiopyrimidines.*
	(R = CH_3, C_2H_5, etc)	
1. $C_5H_6O_2N_2$ (Methyluracil)		1. $C_5H_6ON_2S$ (Methylthiouracil)
2. $C_6H_8O_2N_2$ (Ethyluracil)		2. $C_6H_8ON_2S$ (Ethylthiouracil)
3. $C_7H_{10}O_2N_2$ (Propyluracil)		3. $C_7H_{10}ON_2S$ (Propylthiouracil)
4. $C_8H_{12}O_2N_2$ (Amyluracil)		4. $C_8H_{12}ON_2S$ (Amylthiouracil)
5. $C_9H_{14}O_2N_2$ (Pentyluracil)		5. $C_9H_{14}ON_2S$ (Pentylthiouracil)
6. $C_{10}H_{16}O_2N_2$ (Hexyluracil)		6. $C_{10}H_{16}ON_2S$ (Hexylthiouracil)
↓		↓
Etc.		Etc.

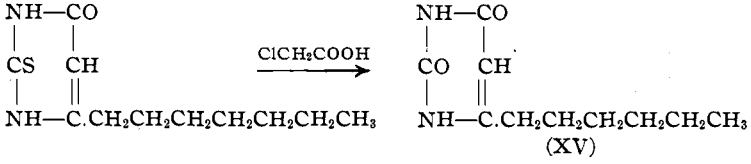
am indebted to Professor André Wahl, of Saint Denis (Seine), France. I take this opportunity to express here my appreciation of his coöperative spirit and kindness in sending me this reagent. When this ketone ester is warmed with thiourea in an alcoholic solution of sodium ethylate there is an immediate reaction with formation of the sodium salt of 2-thio-4-hexyluracil (XVII). The reaction is complete after boiling for a few hours, and, after evaporation of the alcohol, the free pyrimidine is then easily obtained by decomposing its sodium salt with hydrochloric acid. A description of this compound is given in the experimental part of this paper. The reaction may be expressed by the following equation:



(XVI) (XVII)

4-Hexyluracil (XV) is easily obtained by direct desulfurization of this 2-thiopyrimidine (XVII). This is easily accomplished by digesting the

sulfur compound with an excess of chloroacetic acid in aqueous solution. Complete desulfurization is effected within a few hours and the yield of 4-hexyluracil is practically quantitative. This new pyrimidine possesses a sharp, definite melting point (170°), and is especially characterized by its crystalline habit and insolubility in cold water. A complete description of this interesting substance is given in the experimental part of this paper.

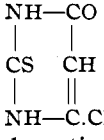


(XV)

The study of pyrimidine-nucleosides and related compounds will be continued.

3. Experimental Part.

The Preparation of 2-Thio-4-hexyluracil,



—This pyrimidine is easily obtained by condensation of thiourea with ethyl heptylacetate.[1] Two molecular proportions of sodium (1.0 g.) were dissolved in 25 cc. of absolute ethyl alcohol, 5 g. of the β-ketone ester dissolved in the solution, and the mixture then heated with 4.0 g. of thiourea (an excess), at the temperature of the steam bath, for 3 hours. A turbid solution was obtained. The alcohol was then removed by heating in an open dish at 100° and the crude reaction product dissolved in about 30 cc. of cold water and the solution filtered. On acidifying this alkaline solution with a slight excess of dilute hydrochloric acid the above 2-thiopyrimidine separated as an oil which very soon solidified. It was nearly colorless and the yield was excellent. This pyrimidine was purified by recrystallization from boiling water. It is difficultly soluble in this solvent and deposits, on cooling, in beautiful, colorless needles which melt at 145° to a clear oil without effervescence. The pyrimidine gave a strong test for sulfur. Nitrogen determination:

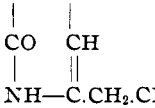
Calc. for $C_{10}H_{16}ON_2S$: N, 13.20; found: N, 13.08.

The above experiment was repeated using the following proportions: 8 g. of the β-ketone ester, 6.4 g. of thiourea, 1.6 g. of sodium and 50 cc. of absolute alcohol. After digesting for 6 hours, the reaction was apparently complete. The alcohol was then removed in the usual manner and the pyrimidine precipitated from its aqueous salt solution by addition of

[1] Wahl and Doll, *loc. cit.*

hydrochloric acid. The crude pyrimidine melted at 140–141° and the yield was about 4.5 g.

Desulfurization of 2-Thio-4-hexyluracil with Formation of 4-hexyluracil,



—The best conditions for the successful conversion of the 2-thiopyrimidine into this pyrimidine are as follows: Equal parts by weight of the thiopyrimidine and monochloroacetic acid are dissolved in about 12–13 times their combined weight of water (4 g. of pyrimidine to 100 cc. of water). While the chloroacetic acid dissolves immediately at ordinary temperature it is necessary to boil for several minutes before solution of the pyrimidine is effected. After complete solution of the pyrimidine, the mixture is then boiled for several hours. After solution of the pyrimidine it is best to add about 10 cc. of dilute hydrochloric acid to aid the reaction. After digesting for about 7–8 hours (working with 4 g. of pyrimidine) the reaction is complete, and, on cooling the solution, hexyluracil separates as an oil which soon solidifies. This pyrimidine is extremely insoluble in boiling water and separates on cooling in beautiful, glistening plates which melt at 170° to a clear oil without effervescence. The yield is practically quantitative. The pyrimidine did not lose weight when heated at 110–120°, and did not respond to a test for sulfur. Nitrogen determination:

Calc. for $C_{10}H_{16}O_2N$: N, 14.28; found: N, 14.15.

This pyrimidine is extremely soluble in alcohol and separates in plates when an alcoholic solution is diluted with water. It dissolves also in sodium hydroxide solution.

NEW HAVEN, CONN.

[CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY.]

THE ACTION OF NITRIC ACID ON IODOANIL.

BY LATHAM CLARKE AND E. K. BOLTON.[1]

Received July 10, 1914.

Owing to the absence from the country of both the authors it has been necessary for me to prepare this work for publication.—C. L. JACKSON.

The object of the work described in this paper was to compare the behavior of iodoanil and chloroanil with nitric acid. Stenhouse[2] obtained from the latter chloropicrine and oxalic acid. As he found that chloroanilic acid behaved in the same way, and that bromoanilic acid gave bromo-

[1] The work described in this paper formed part of a thesis presented to the Faculty of Arts and Sciences of Harvard University for the degree of Doctor of Philosophy by Elmer Keiser Bolton.

[2] *J. Chem. Soc.*, 8, 6 (1870).