settled in a few minutes. The blue mother liquor was decanted and the blue precipitate was pressed between cotton cloth and filter paper. It was dissolved in 150 cc. of 1:1 hydrochloric acid and precipitated by the addition of one liter of 95% alcohol. The precipitate was allowed to settle and the alcoholic liquor was then decanted. The precipitate was washed with three successive portions of alcohol. It was redissolved in 100 cc. of water and again precipitated by alcohol. The product was washed and dried for several hours in vacuum at 70°. The samples weighed 51 g. and contained only traces of copper. $\alpha = -2.85°$ where $l = 2$ and $C = 3.94$; $(\alpha)_D$ $-36.2°$.

Anal. Subs., 0.982: CO_2 (Lefèvre method), 0.0435. Found: 4.43% CO_2, equivalent to 19.5% uronic acid. Subs., 0.491: mucic acid, 0.134. Found: galactose, 41.1. Subs., 0.491: alcohol-soluble furfural phloroglucid, 0.033; alcohol insoluble furfural phloroglucid, 0.155. From the latter figure was deducted 0.032 g. to allow for the phloroglucid due to uronic acid.[8] Found: methyl pentose (as rhamnose hydrate), 12.7; pentose (as arabinose), 28.8.

Summary

The araban of Salkowski has been shown not to be a simple polymer of arabinose but to contain arabinose, galactose, rhamnose and glucuronic acid in about the same proportion as they are present in ash-free gum arabic.

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RESEARCHES ON PYRIMIDINES. CXVIII. MOLECULAR REARRANGEMENTS IN THE THYMINE SERIES

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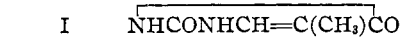
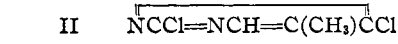
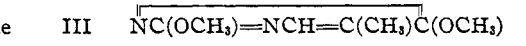
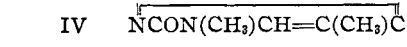
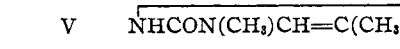
Hilbert and Johnson discovered that 2,6-dimethoxypyrimidine interacts with bromo-acetoglucose giving an acetyl derivative which is converted by hydrolysis into a 3-glucoside of uracil,[2] namely, "*glucuridine.*" This fact was the incentive to develop the present paper, which deals with new rearrangements in the thymine series.

Thymine	I	
2,6-Dichloro-5-methylpyrimidine	II	
2,6-Dimethoxy-5-methylpyrimidine	III	
2-Oxy-3,5-dimethyl-6-methoxypyrimidine	IV	
2,6-Dioxy-3,5-dimethylpyrimidine	V	

[8] Ref. 5, p. 75.

[1] Chemical Foundation Research Fellow, 1929–1930.

[2] Hilbert and Johnson, *Science*, **69**, 579 (1929); THIS JOURNAL, **52**, 200 (1930).

2,6-Dioxy-1,3,5-trimethylpyrimidine	VI	$N(CH_3)CON(CH_3)CH{=}C(CH_3)CO$
2,6-Diethoxy-5-methylpyrimidine	VII	$NC(OC_2H_5){=}NCH{=}C(CH_3)C(OC_2H_5)$
2-Oxy-3,5-dimethyl-6-ethoxypyrimidine	VIII	$NCON(CH_3)CH{=}C(CH_3)C(OC_2H_5)$
2-Oxy-3-ethyl-5-methyl-6-ethoxy-pyrimidine	IX	$NCON(C_2H_5)CH{=}C(CH_3)C(OC_2H_5)$
2,6-Dioxy-3-ethyl-5-methylpyrimidine	X	$NHCON(C_2H_5)CH{=}C(CH_3)CO$

The work was started with the investigation of 2,6-dimethoxy-5-methylpyrimidine, III, which is described by Gerngross,[3] who made it by reduction of 2,6-dimethoxy-4-chloro-5-methylpyrimidine with zinc dust and hydrochloric acid. The same compound was, however, prepared for our work by another method. Starting with thymine I, 2,6-dichloro-5-methylpyrimidine II was made by treatment with phosphorus oxychloride as described by Steudel and Kossel[4] and the latter then converted into 2,6-dimethoxy-5-methylpyrimidine III by the action of sodium methylate. We now find that the imido ester linkages in this compound are very susceptible to change, and the methyl groups show a great tendency to migrate to the adjacent nitrogen atoms of the pyrimidine ring. By heating at 200° for forty-eight hours a quantitative rearrangement to 1,3-dimethyl-thymine VI is obtained. Interaction with methyl iodide led to the formation of 2-oxy-3,5-dimethyl-6-methoxypyrimidine IV. The structure of this compound follows from the fact that it gives 3-methylthymine V quantitatively when the methoxy group is destroyed by hydrolysis with hydrochloric acid.

After having discovered this characteristic behavior of 2.6-dimethoxy-5-methylpyrimidine III, we hoped to obtain a nucleoside of thymine by treatment of this pyrimidine with bromo-acetoglucose according to the technique of Hilbert and Johnson. The result was, however, the formation of 3-methylthymine V. It was assumed that by addition of bromo-acetoglucose to the pyrimidine nitrogen in the 3-position a small amount of the nucleoside was probably formed, the bromine and the adjacent methyl attached to oxygen in the 2-position then combining to form methyl bromide. This methyl bromide adds to the 3-nitrogen, whereupon more methyl bromide is formed and the process is continued until the rearrangement is complete and a 3-methylated compound is formed instead of the desired glucoside of thymine.

Guided by the above conception of reaction mechanism, it was thought that by replacing the methyl bromide by the less active methyl chloride, the addition of the alkyl halide might be depressed, affording a better chance for the addition of the sugar. So chloro-acetoglucose was used instead of bromo-acetoglucose; but here, also, no reaction product of the

[3] Gerngross, *Ber.*, **38**, 3408 (1905).

[4] Steudel and Kossel, *Z. phys.ol. Chem.*, **29**, 303 (1900).

desired constitution was obtained. When the temperature of reaction was raised from 50 to 100° the mixture underwent decomposition.

Keeping in mind the synthesis of a thymine nucleoside, the methyl group was next replaced by the ethyl group and this led to the synthesis and investigation of 2,6-diethoxy-5-methylpyrimidine VII. This compound, prepared from 2,6-dichloro-5-methylpyrimidine II and sodium ethylate, had a lower melting point (36°) than 2,6-dimethoxy-5-methylpyrimidine III, which fact made the compound useful for attempts to melt it together with bromo-acetoglucose or chloro-acetoglucose.

Our first observation was that 2,6-diethoxy-5-methylpyrimidine VII differed considerably from 2,6-dimethoxy-5-methylpyrimidine III in so far as its behavior at high temperatures was concerned. While the methyl compound was completely rearranged at 200° in forty-eight hours, the corresponding ethyl compound was stable under the same conditions. It was, however, observed that methyl iodide acted in the same way as in the case of 2,6-dimethoxy-5-methylpyrimidine III: 2-oxy-3,5-dimethyl-6-ethoxypyrimidine VIII was formed. Its structure follows from the fact that 3-methyl-thymine V was formed by digesting the pyrimidine with hydrochloric acid. The action of ethyl iodide was also studied and the expected substance, 2-oxy-3-ethyl-5-methyl-6-ethoxypyrimidine IX was obtained. This was converted by hydrolysis with hydrochloric acid into 3-ethyl-thymine X.

Since ethyl bromide would be the probable by-product of a reaction between 2,6-diethoxy-5-methylpyrimidine VII and bromo-acetoglucose, and since it was found by experimentation that ethyl bromide does not react with 2,6-diethoxy-5-methylpyrimidine, it was concluded that the reaction between this pyrimidine and bromo-acetoglucose might be of promise for the formation of the desired nucleoside of thymine. By heating the compound with the sugar derivative at 50° for seven days, we obtained a very small amount of a crystalline substance which melted at 316° after recrystallization from alcohol. The amount was, however, too small for investigation. Chloro-acetoglucose did not react with 2,6-diethoxy-5-methylpyrimidine VII, as might have been expected from the experiment with the corresponding methyl compound.

All the pyrimidines prepared in the course of this work are easily obtained in a high state of purity. Three of the compounds described (III, V, VI) were already known but prepared by other methods. In each of these cases our compounds showed a higher melting point. With the exception of 1,3-dimethyl-thymine VI, which can be prepared more easily and just as pure by methylation of thymine with methyl sulfate, we believe that we have shown the easiest way for the preparation of absolutely pure alkyl derivatives of thymine. The study of pyrimidine rearrangements will be continued in this Laboratory.

Experimental Part

Preparation of Thymine, I.—Thymine, from which all the compounds described in this paper were prepared, was synthesized by the method of Wheeler and Merriam[5] by condensing ethyl pseudothiourea with the sodium salt of ethyl formylpropionate in aqueous solution, and hydrolysis of the resulting 2-ethylmercapto-5-methyl-6-oxypyrimidine with hydrochloric acid. It was observed, however, that the yield of thymine was best when the mixture of ethyl formate and ethyl propionate was added to the suspension of sodium in dry ether immediately and not added slowly as stated in the original directions for carrying out the ester condensation. Thirty-seven grams of thymine was obtained in one operation by using 46 g. of sodium in 1 liter of ether, 229.5 cc. of ethyl propionate, 240.5 cc. ethyl formate and 92 g. of ethyl pseudothiourea hydrobromide. The same proportions of reagents gave only 27 g. of thymine when the original directions were followed.

2,6-Dichloro-5-methylpyrimidine, II.—The method employed for the preparation of this compound was essentially that of Steudel and Kossel[6] with slight variations in technique. Twenty grams of thymine was heated with 80 cc. of phosphorus oxychloride at 110–120° for five hours, whereafter the excess of phosphorus halide was removed by heating at 80° under vacuum. The cooled residue was then dissolved in ether, the ethereal solution washed with water and dilute sodium carbonate solution and finally dried over sodium sulfate. The pyrimidine was finally purified by distillation and boiled at 108–109° at 11 mm. It melted at 25–26° and the yield was 21.5 g.

2,6-Dimethoxy-5-methylpyrimidine, III.—Twenty grams of the dichloropyrimidine II was dissolved in 100 cc. of methyl alcohol and the liquid poured into a solution of 7 g. of sodium in 100 cc. of methyl alcohol, whereupon sodium chloride separated immediately, the mixture becoming warm. The reaction was complete after heating for five minutes and after filtering from sodium chloride and distilling off excess of alcohol, the resulting oil was dissolved in ether, washed with sodium hydroxide solution and then dried over anhydrous sodium sulfate. On evaporating the solvent the pyrimidine separated in crystalline form. It was purified further by crystallization from petroleum ether and melted at 61°. The yield was 15.5 g.

Anal. Calcd. for $C_7H_{10}O_2N_2$: C, 54.51; H, 6.54; N, 18.17. Found: C, 54.33; H, 6.50; N, 18.14, 18.04.

Rearrangement of the Pyrimidine III into its Isomer 1,3-Dimethylthymine, VI.—Five grams of the pyrimidine III were heated in a sealed tube at 200° for forty-eight hours, when the rearrangement into the alkylated thymine was complete. The pyrimidine was purified by recrystallization from alcohol and melted at 155°.[7] The absence of methoxy groups was proved by recovering the unchanged pyrimidine melting at 155° after evaporation with strong hydrochloric acid.

Anal. Calcd. for $C_7H_{10}O_2N_2$: C, 54.51; H, 6.54; N, 18.17. Found: C, 54.60; H, 6.54; N, 18.06, 18.27.

2-Oxy-3,5-dimethyl-6-methoxypyrimidine, IV.—This compound is easily obtained by allowing 2,6-dimethoxy-5-methylpyrimidine to interact with methyl iodide at ordinary temperature. Solution of the pyrimidine takes place immediately and within fifteen minutes crystals of the rearranged pyrimidine begin to separate. The reaction was complete after fifteen hours. This pyrimidine crystallized from a mixture of alcohol and ether in the form of needles melting at 144°.

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[5] Wheeler and Merriam, *Am. Chem. J.*, **29**, 478 (1903); see also Harkins and Johnson, THIS JOURNAL, **51**, 1237 (1929).

[6] Steudel and Kossel, *Z. physiol. Chem.*, **29**, 393 (1900).

[7] Johnson and Clapp, *J. Biol. Chem.*, **5**, 60 (1908).

Anal. Calcd. for $C_7H_{10}O_2N_2$: C, 54.51; H, 6.54; N, 18.17. Found: C, 54.53; H, 6.63; N, 18.04, 18.09.

When this compound was warmed in aqueous hydrochloric acid solution it was converted quantitatively into 3-methyl-thymine V. The latter crystallized from hot water in the form of needles melting at 291°. Johnson and Clapp[8] reported a melting point of 280–282°.

Anal. Calcd. for $C_6H_8O_2N_2$: C, 51.40; H, 5.76; N, 20.00. Found: C, 51.39; H, 5.69; N, 20.00, 19.96.

2,6-Diethoxy-5-methylpyrimidine, VII.—From 21.5 g. of 2,6-dichloro-5-methyl-pyrimidine II and sodium ethylate (7.5 g. Na) by interaction in alcohol solution. The pyrimidine crystallizes from alcohol and melts at 36° to an oil. The yield was 16.5 g.

Anal. Calcd. for $C_9H_{14}O_2N_2$: C, 59.30; H, 7.75; N, 15.38. Found: C, 59.39; H, 7.80; N, 15.24, 15.55.

An attempt was made to rearrange this pyrimidine into its corresponding nitrogen substituted derivative by heating at 200° for forty-eight hours. Slight decomposition resulted from this treatment, but the greater part of the pyrimidine was recovered, melting at 35°. There was no evidence of any molecular rearrangement having taken place.

2-Oxy-3,5-dimethyl-6-ethoxypyrimidine, VIII.—A solution of 3. g. of the pyrimidine VII in 2.1 cc. of methyl iodide was allowed to stand at room temperature for four days. The crystalline substance which separated in excellent yield was purified by crystallization from a mixture of alcohol and ether and melted at 111° to an oil. The structure of this compound was established by the fact that it was converted into 3-methyl-thymine by hydrolysis with boiling hydrochloric acid solution.

Anal. Calcd. for $C_8H_{12}O_2N_2$: C, 57.10; H, 7.20; N, 16.67. Found: C, 57.02; H, 7.18; N, 16.62.

2-Oxy-3-ethyl-5-methyl-6-ethoxypyrimidine, IX.—This compound is formed by molecular rearrangement when 2,6-diethoxy-5-methyl-pyrimidine VII is dissolved in ethyl iodide and the solution allowed to stand for seven days. The pyrimidine was obtained in the form of colorless needles when crystallized from ether, and melted at 78°. Attempts to bring about this same rearrangement of the pyrimidine VII by the use of ethyl bromide were unsuccessful. No change was observed after remaining in contact with an excess of ethyl bromide for two weeks.

Anal. Calcd. for $C_9H_{14}O_2N_2$: C, 59.30; H, 7.75; N, 15.38. Found: C, 59.46; H, 7.81; N, 15.54.

2,6-Dioxy-3-ethyl-5-methylpyrimidine or 3-Ethyl-thymine, X.—This pyrimidine was formed when the compound IX was dissolved in hydrochloric acid and the solution evaporated to dryness. It crystallized from hot water in needles which melted at 223°.

Anal. Calcd. for $C_7H_{10}O_2N_2$: C, 54.51; H, 6.54; N, 18.17. Found: C, 54.42; H, 6.53; N, 18.36.

Attempts to Prepare Glucosidic Derivatives of the Pyrimidine Thymine

1.—A mixture of 2 g. of 2,6-dimethoxy-5-methylpyrimidine and 2 g. of bromo-acetoglucose was heated at 60° for forty-eight hours. The resulting product was then extracted three times with 5 cc. of water and then with ether at room temperature. A small quantity of crystalline material did not dissolve and was identified as 3-methyl-thymine. A large quantity of this same pyrimidine also deposited as the aqueous extract was allowed to stand. In other words, a rearrangement of methyl from oxygen

[8] Johnson and Clapp, *J. Biol. Chem.*, **5**, 57 (1908).

to nitrogen in the pyrimidine ring had been effected by the action of the halogenated glucose compounds.

2.—A second experiment was carried out with chloro-acetoglucose by heating this with the pyrimidine at 50° for eight days and then for one week at 100°. The mixture darkened considerably during this treatment and only a very small amount of an undefined product was left after the extraction with ether.

3.—Experiments 1 and 2 were repeated with 2,6-diethoxy-5-methylpyrimidine using both bromo- and chloro-acetoglucose, respectively. The mixtures were heated at 50° for seven days and in the case of the bromo-acetoglucose experiment a small amount of material was finally separated which crystallized from alcohol and melted at 316° but the quantity obtained was too small for further investigation. The second experiment with chloro-acetoglucose did not lead to the formation of any product which could be identified.

Summary

1. 2,6-Dimethoxy-5-methylpyrimidine and 2,6-diethoxy-5-methylpyrimidine were synthesized.

2. 2,6-Dimethoxy-5-methylpyrimidine rearranged quantitatively to 1,3-dimethyl-thymine at 200° in forty-eight hours. 2,6-Diethoxy-5-methyl pyrimidine was stable under these conditions.

3. 2,6-Dimethoxy-5-methylpyrimidine gave with methyl iodide 2-oxy-3,5-dimethyl-6-methoxypyrimidine. 2,6-Diethoxy-5-methylpyrimidine gave with methyl iodide 2-oxy-3,5-dimethyl-6-ethoxypyrimidine and with ethyl iodide 2-oxy-3-ethyl-5-methyl-6-ethoxypyrimidine. Ethyl bromide did not react.

4. 3-Methyl-thymine was obtained from 2-oxy-3,5-dimethyl-6-methoxypyrimidine and from 2-oxy-3,5-dimethyl-6-ethoxypyrimidine by treatment with hydrochloric acid. 3-Ethyl-thymine was obtained from 2-oxy-3-ethyl-5-methyl-6-ethoxypyrimidine and hydrochloric acid.

5. 2,6-Dimethoxy-5-methylpyrimidine and bromo-acetoglucose gave 3-methyl-thymine. Chloro-acetoglucose did not react. 2,6-Diethoxy-5-methylpyrimidine and bromo-acetoglucose gave a substance, m. p. 316°, the quantity of which was too small for investigation. Chloro-acetoglucose did not react.

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