

lies between P_H 3 and 4, which is very close to the hydrogen-ion concentration of 0.25 *M* phenylhydrazine hydrochloride itself (P_H 3.5).

It seems strange that the addition of saturated sodium chloride retards the rate of formation of this hydrazone, since in all the other hydrazones we prepared the reverse is the case.

One peculiar phenomenon observed in dealing with both the acetophenone and benzophenone phenylhydrazones was that, while both hydrazones are capable of supersaturation to a high degree during formation, nevertheless when they were forced out of solution as soon as they were formed (by constant agitation) the rate of formation was not increased. In the case of the benzophenone phenylhydrazone it even seemed that the longer the elapsed time before the crystals of hydrazone appeared (depending on the menstruum employed), the higher was the final yield.

Summary

1. The conditions requisite for obtaining satisfactory results in the iodimetric determination, more particularly in the presence of ethyl alcohol, have been worked out.

2. The effect of hydrogen-ion concentration upon the minimum time required to secure a high yield of the hydrazones of acetophenone and benzophenone has been determined.

3. Details of a method by which very pure phenylhydrazine hydrochloride can be prepared have been worked out.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

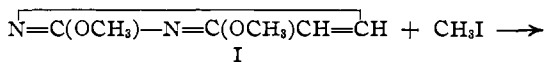
RESEARCHES ON PYRIMIDINES. CXXIII. THE REARRANGEMENT OF 2,6-DIMETHOXY-4-CHLOROPYRIMIDINE AND 2,4,6-TRIMETHOXPYRIMIDINE IN THE PRESENCE OF METHYL IODIDE¹

BY HARRY J. FISHER AND TREAT B. JOHNSON

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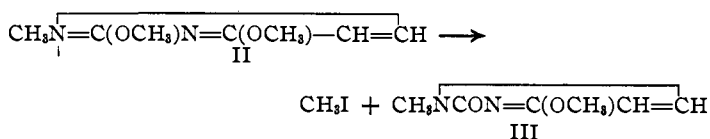
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Hilbert and Johnson² showed that 2,6-dimethoxyypyrimidine I in the presence of methyl iodide was quantitatively rearranged at room temperature to 2-oxy-3-methyl-6-methoxyypyrimidine III.



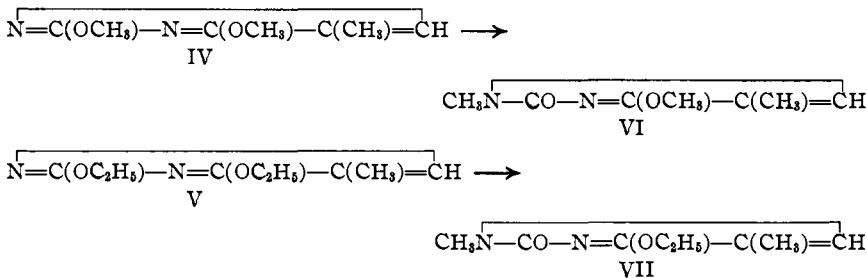
¹ This paper is constructed from a portion of a Dissertation presented by Harry Johnstone Fisher to the Graduate School of Yale University, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1931.

² Hilbert and Johnson, THIS JOURNAL, 52, 2001 (1930); Johnson and Hilbert, Science, 69, 579 (1929).

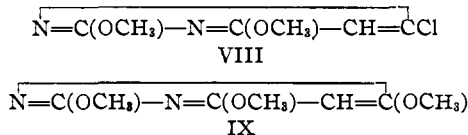


While the intermediate compound II was not isolated, evidence that the above equations represent the mechanism of the reaction was afforded by the behavior of 2,6-diethoxypyrimidine with methyl iodide. In this case the reaction product was 2-oxy-3-methyl-6-ethoxypyrimidine.

When acetobromoglucose was substituted for methyl iodide, it was found possible to prepare a nucleoside derivative of uracil with the sugar attached to the nitrogen in position 3.³ Schmidt-Nickels and Johnson⁴ later showed that 2,6-dimethoxy-5-methylpyrimidine IV and 2,6-diethoxy-5-methylpyrimidine V likewise rearranged quantitatively in the presence of methyl iodide at room temperature, giving, respectively, 2-oxy-3,5-dimethyl-6-methoxypyrimidine VI and 2-oxy-3,5-dimethyl-6-ethoxypyrimidine VII. Analogous transformations were obtained in the presence of ethyl iodide.



The present study was undertaken with the ultimate aim of synthesizing barbituric acid 3-glucoside. With this end in view, the behavior of 2,6-dimethoxy-4-chloropyrimidine VIII and 2,4,6-trimethoxypyrimidine IX toward methyl iodide was investigated.

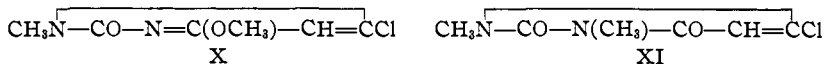


It was found that VIII, in contrast to the behavior of I, IV and V, did not rearrange at all when dissolved in methyl iodide and allowed to stand at room temperature, nor was there any reaction at the boiling point of methyl iodide. When VIII was heated with methyl iodide, in a sealed

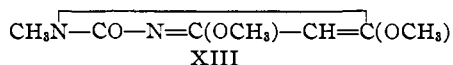
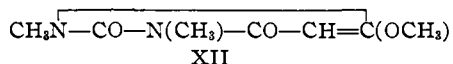
³ Hilbert and Johnson, *THIS JOURNAL*, **52**, 4489 (1930); Johnson and Hilbert, *Science*, **69**, 579 (1929).

⁴ Schmidt-Nickels and Johnson, *THIS JOURNAL*, **52**, 4511 (1930); Johnson, *Ber.*, **63**, 1974 (1930).

tube at 100°, rearrangement did take place, but the change was not quantitative, and the reaction product was not the partially rearranged pyrimidine X, but 1,3-dimethyl-4-chlorouracil XI. In other words, when rearrangement did take place the completely rearranged pyrimidine resulted.



Trimethoxypyrimidine IX did react with methyl iodide at room temperature, and more readily at 60°. Here likewise the completely rearranged 1,3-dimethyl-4-methoxyuracil XII was formed, but also the partially rearranged compound, 2-oxy-3-methyl-4,6-dimethoxypyrimidine, XIII.



The inability of VIII to rearrange at room temperature as did the compounds studied by Hilbert and Johnson and Schmidt-Nickels and Johnson is believed to be due to the decreased basicity caused by the presence of a chlorine atom in position 4 of the pyrimidine cycle with a consequent lessened tendency toward the formation of the intermediate quaternary compound with methyl iodide. That VIII is less basic than IX, which does react with methyl iodide at room temperature, is shown by the fact that IX dissolves readily in dilute hydrochloric acid and forms a compound with gold chloride,⁵ while VIII is apparently no more soluble in hydrochloric acid than in water. Chapman⁶ in his study of the rearrangement of N-arylaminoaryl ethers to acyl diphenylamines noted that the presence of negative substituents in the amino group retarded the change.

The explanation of the formation of the completely rearranged compounds in the reactions of VIII and IX with methyl iodide, instead of the partially rearranged compounds obtained quantitatively from I, IV and V, under the same conditions, probably lies in the difference in the solubility relations of the compounds involved. 2,6-Dimethoxypyrimidine I is a liquid at ordinary temperatures, readily miscible with methyl iodide, while 2-oxy-3-methyl-6-methoxypyrimidine III is a solid melting at 150°, which crystallizes out of the reaction mixture as formed, and so is removed from the action of the methyl iodide before further rearrangement takes place. In the case of the reaction of IX with methyl iodide, the partially rearranged compound XIII has a melting point of only 97°, and at the temperature of the reaction (60°) probably remains largely dissolved in the

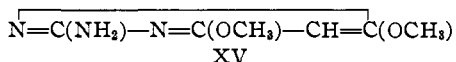
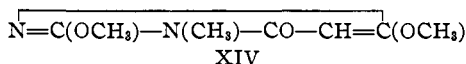
⁵ Büttner, *Ber.*, 36, 2227 (1903).

⁶ Chapman, *J. Chem. Soc.*, 569 (1929).

methyl iodide and so undergoes further rearrangement to XII. As compound X has not been isolated, its melting point is unknown, but it may be speculated that the same explanation holds for the formation of the completely rearranged compound in the reaction of VIII with methyl iodide, particularly as this rearrangement was carried out at the comparatively elevated temperature of 100°.

The constitution of 1,3-dimethyl-4-chlorouracil XI, which has not previously been described, was established by hydrolyzing it to 1,3-dimethylbarbituric acid by evaporation with concentrated hydrochloric acid on the steam-bath.

Of the rearrangement products of IX, 1,3-dimethyl-4-methoxyuracil XII has been prepared by Biltz and Wittek⁷ and by Herzig⁸ by methylating barbituric acid with diazomethane. Its constitution was also proved by hydrolysis to 1,3-dimethylbarbituric acid with hydrochloric acid. 2-Oxy-3-methyl-4-6-dimethoxypyrimidine XIII has not been previously isolated in pure form, although Herzig found in the mother liquors from his preparation of XII a substance analyzing for two methoxyl groups, melting at 75-90°, which he was unable to purify, that may have been this compound. The partially rearranged compound obtained from the reaction of IX with methyl iodide yielded 1-methylbarbituric acid on hydrolysis with hydrochloric acid, and on the basis of this evidence the constitution XIII has been assigned to it. While the compound of structure XIV would likewise give 1-methylbarbituric acid, from the evidence of the work of Hilbert and Johnson and Schmidt-Nickels and Johnson the methyl group shifts first to the 3-position, so formula XIII appears the most reasonable.



In the course of the study of the rearrangement of the alkoxy pyrimidines, 2-amino-4,6-dimethoxypyrimidine XV was prepared. It is a solid melting at 95°.

Experimental Part

2,6-Dimethoxy-4-chloropyrimidine.—This compound was prepared by Büttner⁹ from trichloropyrimidine in two steps. It was found that it could be made directly from trichloropyrimidine.

Twenty-five grams of trichloropyrimidine (prepared from barbituric acid by the method of Gabriel and Colman)⁹ in 360 cc. of absolute methanol was mixed with a solution of 6.4 g. of sodium in 81 cc. of methanol and let stand overnight. The next day the solution was decanted from sodium chloride, cooled in ice and the crystals which

⁷ Biltz and Wittek, *Ber.*, 54, 1035 (1921).

⁸ Herzig, *Z. physiol. Chem.*, 117, 13 (1921).

⁹ Gabriel, *Ber.*, 33, 3666 (1900); Gabriel and Colman, *ibid.*, 37, 3657 (1904).

separated filtered and washed with water. The sodium chloride was dissolved in a little water, the solution cooled and the crystals separating filtered, washed, combined with the first crop and dried *in vacuo*; yield, about 13 g.

Recrystallized from petroleum ether, ethyl alcohol or methyl iodide the substance melts at 76–77°. Slow crystallization from methyl iodide yields perfectly formed prisms several millimeters long.

2,4,6-Trimethoxypyrimidine.—Büttner⁵ prepared this compound by heating trichloropyrimidine in a sealed tube at 100°. It was found that the third chlorine atom could be removed by a less drastic treatment.

Thirty grams of trichloropyrimidine in 240 cc. of absolute methanol was mixed with a solution of 23 g. of sodium in 290 cc. of methanol, the mixture refluxed for one hour and let stand overnight. The solution was decanted from the sodium chloride, mixed with 330 cc. of water and cooled in ice. The colorless needles which crystallized out were filtered, washed with a little water and dried *in vacuo*.

The sodium chloride was dissolved in water, cooled in the ice-box overnight, and the long needles which crystallized out in very pure condition were filtered, washed with water and dried in a desiccator. The total yield was about 19 g. Trimethoxypyrimidine separates in long silky needles which are usually quite pure and melt at 57°. It can be recrystallized best from dilute methanol.

Anal. Calcd. for $C_7H_{10}O_3N_2$: N, 16.47. Found: N, 16.73.

The Action of Methyl Iodide on 2,6-Dimethoxy-4-chloropyrimidine.—When 2,6-dimethoxy-4-chloropyrimidine was refluxed for six and one-half hours with sufficient methyl iodide to dissolve it, the mixture allowed to stand overnight and the methyl iodide evaporated on the water-bath, a crystalline residue was left which melted at 70–75° without purification, and after one recrystallization from petroleum ether melted at 77°. A mixed melting point with the original substance showed no depression.

When the temperature was raised to 100° reaction took place. Five grams of 2,6-dimethoxy-4-chloropyrimidine and 10 g. of methyl iodide were heated at 100° in a sealed tube for thirty hours and the tube allowed to stand without opening for thirty-nine days. The contents of the tube were then evaporated on the water-bath, the pasty residue extracted with a little ether and the light-colored residue recrystallized from alcohol after decolorization by the use of norite. 1,3-Dimethyl-4-chlorouracil crystallized in colorless prisms melting at 111°. The yield was about 3 g.

Anal. Calcd. for $C_8H_7O_2N_2Cl$: N, 16.06. Found: N, 16.21, 15.96.

When this pyrimidine was mixed with concentrated hydrochloric acid and the mixture evaporated to dryness on the steam-bath, the residue on recrystallization from alcohol gave colorless needles melting at 121–122°. A mixed melting point with a sample of 1,3-dimethylbarbituric acid, prepared by the method of Techow¹⁰ from tetramethylalloxantin which had been obtained from caffeine by the procedure of Biltz,¹¹ showed no depression.

Anal. Calcd. for $C_8H_9O_3N_2$: N, 17.95. Found: N, 17.93, 17.93.

The Action of Methyl Iodide on 2,4,6-Trimethoxypyrimidine.—When 2,4,6-trimethoxypyrimidine was dissolved in three times its weight of methyl iodide and allowed to stand at room temperature, there was no visible change in twenty-four hours. Nevertheless, on working up the reaction mixture, some 1,3-dimethyl-4-methoxyuracil XII was found. On standing for a week the mixture, which had gradually grown darker, began to deposit crystals of XII. At the end of a month the reaction mixture was filled with crystals of XII, the amount being about 60% of the original material.

¹⁰ Techow, *Ber.*, 27, 3082 (1894).

¹¹ Biltz, *ibid.*, 45, 3674 (1912).

Ten grams of trimethoxy-pyrimidine and 20 g. of methyl iodide were heated in a sealed tube at 60° for forty-eight hours. On cooling a large amount of crystals was deposited from the dark red liquid. Without separation, the contents of the tube were evaporated on the steam-bath, the residue taken up in 20 cc. of chloroform, 80 cc. of petroleum ether added, the mixture cooled in ice and the dark red precipitate filtered and washed with petroleum ether. Heated for half an hour at 125° the residue became nearly colorless; wt., 5 g. Recrystallized from benzene, the 1,3-dimethyl-4-methoxyuracil was obtained in long colorless needles melting at 164-166°.

Anal. Calcd. for $C_7H_{10}O_3N_2$: N, 16.47. Found: N, 16.68.

A mixed melting point with a sample of XII prepared from barbituric acid and diazomethane by the method of Biltz and Wittek⁷ showed no depression. Hydrolysis with hydrochloric acid yielded 1,3-dimethylbarbituric acid.

The chloroform-petroleum ether solution from which XII had precipitated was evaporated. The light yellow residue after several recrystallizations from ether melted at 95.5-97°.

Anal. Calcd. for $C_7H_{10}O_3N_2$: N, 16.47. Found: N, 16.73.

This substance on evaporation with concentrated hydrochloric acid and recrystallization of the residue from alcohol gave needles melting at 132°, which showed no depression in melting point when mixed with 1-methylbarbituric acid prepared by the method of Biltz and Wittek.⁷

Anal. Calcd. for $C_8H_8O_3N_2$: N, 19.72. Found: N, 20.31.

On the basis of this evidence it was concluded that the substance was 2-oxy-3-methyl-4,6-dimethoxy-pyrimidine.

The Preparation of 2-Amino-4,6-dimethoxy-pyrimidine.—2-Amino-4,6-dichloropyrimidine was prepared by the method of Büttner⁸ from malonylguanidine made from guanidine thiocyanate and malonic ester according to Michael.¹² The dried crude product was used without the purification by vacuum sublimation recommended by Büttner.

Five grams of crude 2-amino-4,6-dichloropyrimidine, 14 cc. of an absolute methyl alcoholic solution of 1.2 g. of sodium and 136 cc. of absolute methanol were heated in a pressure-bottle in steam for four hours, then let stand overnight. The mixture was then distilled in vacuo to a small volume, diluted with water and extracted with ether. The ether extract was dried with calcium chloride, filtered and the ether evaporated. The residue was a light yellow oil which solidified on cooling; wt. about 3 g. Recrystallized from ligroin, it separated in colorless prisms melting at 95°. A test for chlorine was negative.

Anal. Calcd. for $C_8H_8O_2N_3$: N, 27.09. Found: N, 26.93.

Summary

1. 2,6-Dimethoxy-4-chloropyrimidine does not rearrange in the presence of methyl iodide at room temperature. At 100° molecular rearrangement takes place to give the completely rearranged compound, 1,3-dimethyl-4-chlorouracil.

2. 2,4,6-Trimethylpyrimidine rearranges in the presence of methyl iodide at room temperature, and more rapidly at higher temperatures, to give a mixture of the partially rearranged compound 2-oxy-3-methyl-4,6-

¹² Michael, *J. prakt. Chem.*, 49, 35 (1894).

dimethoxypyrimidine and the completely rearranged 1,3-dimethyl-4-methoxyuracil.

3. The preparation of 2-amino-4,6-dimethoxypyrimidine is described.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

2-iodofuran and 2-furylmagnesium iodide

By Henry Gilman, Harvey E. Mallory and George F. Wright

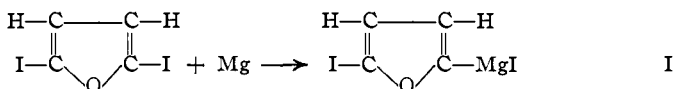
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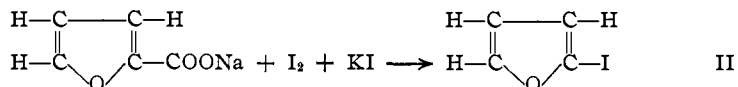
Introduction

The chemistry of furan compounds is markedly circumscribed by present limitations on methods for the introduction of nuclear substituents, and by want of definite information on the positions assumed by substituents together with an inadequate understanding and formulation of rules of orientation. Within recent years, the number of direct nuclear substitution products of furfural and derivatives has been extended significantly. However, such substituents have not as yet lent themselves to widely diversified transformations.

One of several highly reactive key-groupings of this type, through which a miscellany of functions can be introduced indirectly, is the —MgX group attached to carbon. The ready reaction of 2,5-diiodofuran with activated



magnesium-copper alloy leading to the formation of 5-iodo-2-furylmagnesium iodide¹ suggested that the simple mono-iodofurans might react smoothly with magnesium to form the corresponding Grignard reagents. Unfortunately, however, no mono-iodofuran was known although attempts² have been made to prepare them. After a series of studies, we have devised a method for the preparation of pure 2-iodofuran from the accessible furoic acid and iodine.



Despite the fact that the present yield of 2-iodofuran is only 20% it is the most accessible simple halogen-furan which can be prepared conveniently in large quantities. 2-Iodofuran is not of a high order of stability, as might have been predicted from the known relative instabilities of chloro

¹ Gilman and Wright, *Iowa State Coll. J. Sci.*, 5, 85 (1931).

² (a) Shepard, Winslow and Johnson, *This Journal*, 52, 2083 (1930); (b) Ciusa and Grillo, *Gazz. chim. ital.*, 57, 323 (1927).