when positive, are to be added to the calculated pressures, and subtracted when negative. Table II gives the normal boiling point, the latent heats of vaporization, and $L/T$, or the "entropy of vaporization." All pressure readings are in mm. of mercury at 0°, and all temperatures are corrected.

## Summary and Conclusions

1. The vapor pressures of all the polymethylbenzenes containing four or more methyl groups have been determined over a considerable range of temperatures, and the results are given in the form of tables and curves.

2. From these data, the latent heats of vaporization have been calculated.

MINNEAPOLIS, MINNESOTA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

# RESEARCHES ON PYRIMIDINES. CXV. ALKYLATION ON NITROGEN OF THE PYRIMIDINE CYCLE BY APPLICATION OF A NEW TECHNIQUE INVOLVING MOLECULAR REARRANGEMENTS

BY GUIDO E. HILBERT[1] AND TREAT B. JOHNSON

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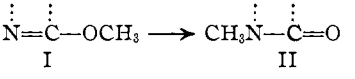
That the *lactim* ethers **I** will undergo rearrangements to their isomeric and stable *lactam* configurations **II** has been known for a long time. These transformations are not reversible and are brought about by the application of heat or through the influence of special catalytic agents, and have been observed to take place in both the acyclic and cyclic series of organic compounds.[2]



I II

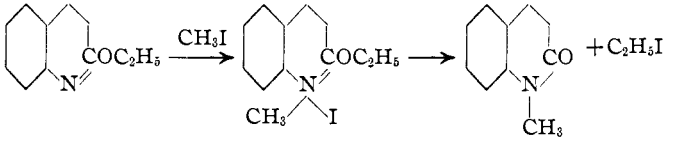
The interesting data obtained by Knorr as a result of his study of molecular transformations in the pyrazolone and quinoline series suggested that corresponding changes might be brought about in pyrimidine combinations containing *lactim* ether groupings.[3] Knorr showed that certain $\alpha$- and $\gamma$-alkoxyquinolines interact with methyl iodide with formation of addition products IV which are unstable and break down on heating to form N-alkylquinolones V. The transformation of the ethoxyquinoline

[1] Sterling Research Fellow, 1928–1930.

[2] A review of the literature on imido-ester rearrangements has been recorded in the following publications: Johnson and Hahn, "Theories of Organic Chemistry (Henrich)," John Wiley and Sons, Inc., New York, **1922,** and in "Molecular Rearrangements," by C. W. Porter, American Chemical Society Monograph No. 45, The Chemical Catalog Company, Inc., New York, **1929.** See also Chapman, *J. Chem. Soc.*, 569 (1929).

[3] Knorr, *Ann.*, **293,** 5 (1896); *Ber.*, **30,** 922, 927, 937 (1897); see also Lieben and Haitinger, *Monatsh.*, **6,** 315 (1885), for rearrangement of alkoxypyridines.

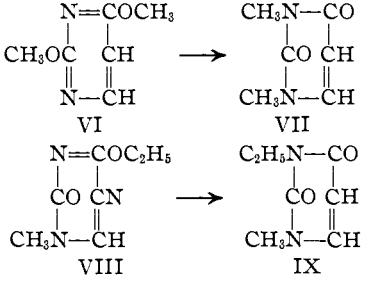
III into the corresponding N-methyl derivative (lactam construction) is expressed by the following formulas. Knorr also found that the *lactim*



III IV V

constructions III are rearranged by heating, forming the isomeric *lactams* in good yield.

Substituted pyrimidines of the type represented by the 2,6-dialkoxypyrimidines are analogous in constitution to the quinoline *lactim* compounds studied by Knorr. Several pyrimidine ether constructions of this type have been prepared,[4] but in no case has any tendency to undergo molecular rearrangements been observed, nor has the behavior of these compounds toward alkyl iodides been investigated. We have had occasion to investigate the properties of certain representatives of this series and we find that the 2,6-dialkoxypyrimidines and constructions like 2-oxy-3-alkyl-6-alkoxypyrimidines easily undergo rearrangement on heating to form the 1,3-dialkyluracils in excellent yields. The respective changes are expressed by the following formulas.



VI VII

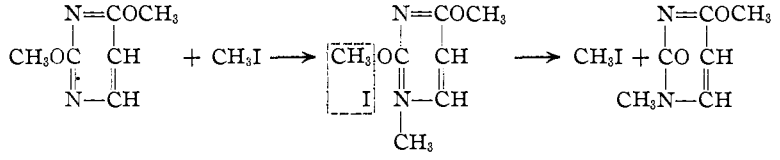
VIII IX

These rearrangements open up a new technique for synthesizing N-alkylated uracils of known structure which hitherto have been very difficult to obtain in a pure condition. Thus far it has been impossible to produce a partial rearrangement by heating a 2,6-dialkoxypyrimidine leading to the formation of derivatives in which only one *lactim* grouping has been destroyed. 1,3-Dialkylpyrimidines are always the end-products of pyrolysis.

Pyrimidines representing the partially rearranged forms are obtained by the action of alkyl halides. The interaction of methyl iodide with 2,6-dimethoxypyrimidine VI at room temperature, for example, yields smoothly 2-oxy-3-methyl-6-methoxypyrimidine. In other words, the two

[4] Schlenker, *Ber.*, **34**, 2812 (1901); St. Augerstein, *ibid.*, **34**, 3956 (1901); Büttner, *ibid.*, **36**, 2227 (1903); Gabriel and Colman, *ibid.*, **36**, 3379 (1903); Johnson and Joyce, THIS JOURNAL, **37**, 215 (1915); Johnson and Moran, *ibid.*, **37**, 2591 (1915).

*lactim* configurations within the same pyrimidine molecule differ in their stability, and the nitrogen atom which is alkylated during the molecular changes is that one which is the most basic, or the nitrogen in position 3 of the pyrimidine ring. The mechanism of the reaction, which is practically quantitative, is easily explained by assuming the primary formation of an addition product with methyl iodide. This intermediate pentavalent nitrogen compound X being unstable, dissociates with the production of the 3-nitrogen derivative XI and a new alkyl halide by coupling of the *lactim* alkyl group with iodine. These changes are expressed by the formulas



VI X XI

That an intermediate addition product as expressed by formula X represents one stage of our reaction is supported by the behavior of 2,6-diethoxypyrimidine toward methyl iodide. In this case the product of the reaction was 2-oxy-3-methyl-6-ethoxypyrimidine, but we were unable to identify any substance corresponding to an addition compound. That such addition compounds, are exceedingly unstable was shown by the behavior of 2,6-dimethoxypyrimidine toward methyl iodide at ordinary temperature in quantities very much less than molecular proportions of the halide. Under these experimental conditions the dimethoxy compound was completely transformed into 2-oxy-3-methyl-6-methoxypyrimidine XI in a few days. This interesting result is direct evidence that the addition product is an unstable configuration, breaking down as soon as formed and continually regenerating the halide, thus allowing the reaction to go to completion.

In the above reactions methyl iodide was found to be much more reactive than ethyl iodide, and the use of benzene as a solvent decreased the rate of reactivity very appreciably, which is in accord with the recent work of Norris and Prentiss.[5] It is also a well-known fact that alkyl halides show a much greater tendency to add to basic nitrogen groupings than the corresponding alkyl bromides or chlorides. In the case of 2,6-diethoxypyrimidine, for every molecule of methyl iodide interacting with this compound, one molecule of ethyl iodide is liberated. However, since methyl iodide is in excess and is also the more reactive halide, the main product formed is 2-oxy-3-methyl-6-ethoxypyrimidine with the practical exclusion of 2-oxy-3-ethyl-6-ethoxypyrimidine.

The 2-oxy-3-alkyl-6-alkoxypyrimidines very easily undergo hydrolysis

[5] Norris and Prentiss, THIS JOURNAL, **50**, 3042 (1928).

by treatment with hydrochloric acid, yielding mono alkylated uracils quantitatively. This new reaction, which makes possible the application of a new technique for the preparation of 2,6-dioxypyrimidine compounds alkylated in position 3, promises to assume an important biochemical significance. By application of this new procedure it should be possible to synthesize sugar derivatives of pyrimidines related structurally to the nucleosides found in nucleic acids. In fact, we have already found that the hexose derivative—bromotetra-acetylglucose—interacts smoothly with 2,6-dimethoxypyrimidine giving a crystalline compound exhibiting the properties of a true nucleoside derivative.[6] This special reaction is now under investigation and the results of our research will be reported in a future paper from this Laboratory.

## Experimental Part

**The Preparation of 2,6-Dialkoxypyrimidines.**—The chlorine atoms occupying the 2- and 6-positions in the pyrimidine ring are very reactive and interact practically instantaneously with sodium alcoholates to give the corresponding 2,6-dialkoxypyrimidines in excellent yields.

**2,6-Dimethoxypyrimidine,** $\overline{N{=}C(OCH_3)N{=}C(OCH_3)CH{=}CH}$.—This compound has been described previously by Gabriel and Colman,[7] who prepared it by reduction of 2,6-dimethoxy-4-chloropyrimidine. They report a boiling point of 204.5–205° and a melting point at about 10°. Their method, however, is an impractical one for quantity production and we recommend the following. Forty grams of 2,6-dichloropyrimidine[8] are dissolved in 200 cc. of absolute methyl alcohol[9] and added slowly to a solution of 12.5 g. of sodium in 200 cc. of dry methyl alcohol. A vigorous reaction immediately takes place, sodium chloride precipitating and the mixture generating sufficient heat to raise the temperature of the solution to its boiling point. The reaction is complete within a few minutes. After filtering off the sodium chloride, the excess of alcohol is then expelled by distillation under reduced pressure and the residual oil treated with 100 cc. of 30% sodium hydroxide solution. The dimethoxypyrimidine separates as the upper layer and is extracted by ether, dried over sodium sulfate and finally purified by distillation. Our product distilled as a colorless oil boiling at 202°, and solidified on cooling. The compound melts at 17.5° and the yield is 35 g. or 93% of the theoretical.

*Anal.* Calcd. for $C_6H_8O_2N_2$: N, 20.00. Found: N, 19.72, 19.85.

**2,6,-Diethoxypyrimidine,** $\overline{N{=}C(OC_2H_5)N{=}C(OC_2H_5)CH{=}CH}$.—The procedure for obtaining this pyrimidine was similar to that described above. It was produced as a colorless oil boiling at 224–225° and melting at 19–20°. The yield was 85% of the theoretical.

*Anal.* Calcd. for $C_8H_{12}O_2N_2$: N, 16.67; H, 7.14; C, 57.14. Found: N, 16.27, 16.67; H, 7.21; C, 56.92.

[6] Johnson and Hilbert, *Science*, **69**, 579 (1929).

[7] Gabriel and Colman, *Ber.*, **36**, 3379 (1903).

[8] Hilbert and Johnson, THIS JOURNAL, **52**, 1152 (1930).

[9] On dissolving 2,6-dichloropyrimidine in methyl alcohol heat should not be applied as this initiates a reaction with replacement of halogen and formation of the dialkoxypyrimidine. The latter compound undergoes hydrolysis in the presence of the generated hydrochloric acid and is changed immediately into uracil.

## Rearrangement of Alkoxypyrimidines

**Rearrangement of 2,6-Dimethoxypyrimidine to 1,3-Dimethyluracil.**—Four and one-half grams of the dimethoxypyrimidine is heated in an oil-bath at 220–240° for four hours. At first there is vigorous ebullition which gradually subsides and finally ceases as the proportion of rearranged compound increases. On cooling, the pale brown reaction product completely solidified. This was purified by dissolving in a mixture of alcohol and ether and allowing to cool after decolorization with norite. The yield of rearranged pyrimidine was 4 g. and it crystallized in colorless prisms melting at 123–124°. A mixture of this substance with a sample of 1,3-dimethyluracil prepared by a known method[10] melted at the same temperature.

**Rearrangement of 2-Oxy-3-methyl-6-methoxypyrimidine to 1,3-Dimethyluracil.**—This change is accomplished by heating under the same conditions that were employed for the molecular rearrangement of 2,6-dimethoxypyrimidine to dimethyluracil. The purified 1,3-dimethyluracil melted at 123–124° and the yield was excellent.

**Rearrangement of 2-Oxy-3-methyl-6-ethoxypyrimidine to 1-Ethyl-3-methyluracil,** $CH_3\overline{N—CO—N(C_2H_5)COCH=CH}$.—After heating 5 g. of the above ethoxypyrimidine in an oil-bath at 250° for eight hours, the resulting dark brown reaction product was extracted with ether, dried and purified by distillation under diminished pressure. The rearranged pyrimidine was obtained as a colorless oil boiling at 140–141° at 4 mm. which solidified on cooling. It melted at 60–61°. The yield was 4 g. This pyrimidine is very soluble in water, alcohol and ether and sparingly soluble in ligroin. It gives a negative Wheeler and Johnson color test.[11]

*Anal.* Calcd. for $C_7H_{10}O_2N_2$: N, 18.18; H, 6.49; C, 54.55. Found: N, 18.26, 18.43; H, 6.67; C, 54.64.

## The Action of Alkyl Iodides on Alkoxypyrimidines from Uracil

**2-Oxy-3-methyl-6-methoxypyrimidine,** $CH_3\overline{NCON=C(OCH_3)CH=CH}$.—Five grams of 2,6-dimethoxypyrimidine was mixed with 10 g. of freshly distilled methyl iodide and the solution allowed to stand at room temperature.[12] Within two to three hours large colorless crystals started to deposit in the solution, and in twelve hours the reaction was complete. The reaction product was separated by filtration and washed with ether. It was purified by recrystallization from warm alcohol and separated, on cooling, in the form of colorless prisms which melted at 149–150°. The yield of rearranged pyrimidine was quantitative. The compound is very soluble in alcohol and water and insoluble in benzene and ether.

*Anal.* Calcd. for $C_6H_8O_2N_2$: N, 20.00; H, 5.71; C, 51.43. Found: N, 19.98, 20.13; H, 5.82; C, 51.40.

The structure of this compound was established by its behavior on hydrolysis. When dissolved in dilute hydrochloric acid and the solution evaporated on a steam-bath it was converted quantitatively into 3-methyluracil melting at 237–238°.[13]

*Anal.* Calcd. for $C_5H_6O_2N_2$: N, 22.22. Found: N, 22.21, 22.19.

An experiment was carried out using the same quantities of 2,6-dimethoxypyrimidine and methyl iodide as given above. The solution, however, was diluted with

[10] Davidson and Baudisch, THIS JOURNAL, **48**, 2379 (1926).

[11] Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907).

[12] It is preferable to carry out this reaction in the dark and thereby reduce to a minimum the quantity of colored products formed during the reaction.

[13] Wheeler and Johnson, *Am. Chem. J.*, **42**, 30 (1909).

benzene. The effect of this was to decrease the rate of reaction enormously, as the rearrangement required several weeks to go to completion. The reaction was furthermore highly colored.

In a second experiment 5 g. of 2,6-dimethoxypyrimidine was mixed with two droplets of methyl iodide and the solution sealed in a tube. In two days the rearrangement was complete, giving a quantitative yield of 2-oxy-3-methyl-6-methoxypyrimidine. If two drops of ethyl iodide are substituted for the methyl iodide, similar results are obtained except that in this case the reaction requires several weeks for completion.

**2-Oxy-3-Methyl-6-Ethoxypyrimidine,** $CH_3\overline{NCON{=}C(OC_2H_5)CH{=}CH}$.—Five grams of 2,6-diethoxypyrimidine dissolved in 10 g. of methyl iodide was converted completely at room temperature and within ten hours into the above pyrimidine. It was purified by recrystallization from a mixture of alcohol and ether and separated as colorless plates melting at 136°. This pyrimidine is very soluble in alcohol and water and insoluble in ether. The yield was excellent and no trace of a pyrimidine containing an ethyl group substituted on nitrogen of the pyrimidine cycle was detected.

*Anal.* Calcd. for $C_7H_{10}O_2N_2$: N, 18.18; C, 54.5; H, 6.49. Found: N, 18.33, 18.20; C, 54.68; H, 6.33.

When this compound was warmed in hydrochloric acid solution it was converted quantitatively into 3-methyluracil.

**1,3-Diethyluracil,** $C_2H_5\overline{NCON(C_2H_5)COCH{=}CH}$.—This was formed by refluxing 2,6-diethoxypyrimidine (5 g.) with ethyl iodide (10 g.) for one week. The excess of the iodide was then removed with a blast of air and the residue distilled under diminished pressure. It boiled at 135° at 4 mm. and the yield of pyrimidine was 4 g. 1,3-Diethyluracil is a colorless, odorless oil which solidifies on cooling and melts at 14–15°. It gives a negative Wheeler and Johnson color test.[11]

*Anal.* Calcd. for $C_8H_{12}O_2N_2$: N, 16.67; C, 57.14; H, 7.14. Found: N, 16.27, 16.67; C, 56.86; H, 7.48.

This rearrangement to diethyluracil is also brought about by heating the 2,6-diethoxypyrimidine in a bomb tube at 260° for twenty-four hours. The product of the reaction was a dark brown viscous oil. This was dissolved in ether, dried over sodium sulfate and purified by distillation. The yield was 4 g. of a colorless oil boiling at 290–295°.

*Anal.* Calcd. for $C_8H_{12}O_2N_2$: N, 16.67. Found: N, 16.55, 16.33.

1,3-Diethyluracil has not been described previously in the literature and as we wished to compare the properties of our new compound with a sample prepared by a different method, an alkaline solution of uracil was alkylated by interaction with diethyl sulfate according to the technique employed by Davidson and Baudisch[10] for the preparation of 1,3-dimethyluracil. Twenty grams of uracil and 17 g. of sodium hydroxide were dissolved in 100 cc. of water, warmed to 30° and 45 cc. of diethyl sulfate was added slowly with constant agitation. The reaction mixture, after standing for one hour, was finally heated to boiling and then cooled. This solution was then repeatedly extracted with chloroform to remove 1,3-diethyluracil. This was purified by distillation as described above and agreed in all its properties with the pyrimidine obtained by rearrangement of the 2,6-diethoxypyrimidine. The yield was 10 g.

**1,3-Diethyl-5-bromo-uracil,** $C_2H_5\overline{NCON(C_2H_5)COBr{=}CH}$.—This is formed by dissolving the 1,3-diethyluracil in absolute alcohol and then adding to the solution the required amount of bromine. The alcohol was evaporated on a steam-bath and the bromopyrimidine left behind purified by crystallization from water. It separated in prisms melting at 80–81°. Depending on the conditions of crystallization it sometimes

separates as colorless needles and at other times as colorless rhombic blocks. In one experiment a modification was obtained which melted at 71°; after resolidifying the melting point rose to 80–81°.

*Anal.* Calcd. for $C_8H_{11}O_2N_2Br$: N, 11.34. Found: N, 11.45, 11.38.

## Summary

1. 2,6-Dialkoxypyrimidines are formed smoothly by interaction of 2,6-dichloropyrimidine with sodium alcoholates.

2. The 2,6-dialkoxypyrimidines and the 2-oxy-3-alkyl-6-alkoxypyrimidines rearrange on heating to form 1,3-dialkyluracils. This method of operating makes possible the synthesis of uracil derivatives which hitherto have not been available for the development of pyrimidine chemistry.

3. A new method for the alkylation of pyrimidines of the uracil type in position 3 has been developed.

4. This new reaction will be applied for the synthesis of hexose and pentose derivatives of pyrimidines. It is possible that some of these sugar derivatives will be found to be identical with the naturally occurring nucleosides. This same technique will also be applied in the purine series.

NEW HAVEN, CONNECTICUT

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# PIPERIDINE DERIVATIVES. IX. METHYLPIPERIDINO-ALKYL CINNAMATES

BY C. F. BAILEY AND S. M. MCELVAIN

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It has been pointed out in two previous communications[1] from this Laboratory, that those piperidino-alkyl benzoates containing a methyl group as a substituent in the piperidine nucleus were much more effective as local anesthetics than the corresponding compounds in which the piperidine nucleus was unsubstituted or was substituted by certain other aliphatic groups. In two very interesting papers concerned with the correlation of aromatic properties with physiological action, Gilman and co-workers[2] have shown that in the amino-alkyl ester type of anesthetic a distinct local anesthetic effect is found associated with those structures in which the carbonyl group of the ester is attached to an unsaturated carbon atom. Of all such types of compounds that have been investigated, the cinnamates are by far the most effective. Apothesine, γ-diethylaminopropyl cinnamate, is a well-known example of this type of ester.

Since the methylpiperidino-alkyl nucleus has been found to be so efficient

[1] McElvain, THIS JOURNAL, **49**, 2835 (1927); Bailey and McElvain, *ibid.*, **52**, 1633 (1930).

[2] Gilman and co-workers, *ibid.*, **47**, 245 (1925); *ibid.*, **50**, 437 (1928).