Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.93; H, 12.08. Found: C, 71.98; H, 12.04.

Hydrolysis with a small quantity of sulfuric acid gave 5-decanone, b. p. 106–107° (27 mm.); $n^{25}D$ 1.4225.

Reaction of Thiocyanogen and Iodine Monobromide with Dialkylacetylenes.—A benzene solution of thiocyanogen was prepared according to the method of Söderbäck.[5] To one-half of this solution was added 1.3 g. of diphenylacetylene in 25 ml. of dry benzene, while to the other was added a comparable quantity of dibutylacetylene. The two solutions were placed in the dark for twenty hours. The diphenylacetylene deposited a crystalline product melting at 192–193°, as previously reported by Söderbäck.[5] Dibutylacetylene failed to give a derivative.

Dioctylacetylene (2 g.) was added to an ether solution of iodine monobromide (4 g.). After twenty-four hours at room temperature a brownish-black solid was obtained which decomposed upon heating.

Acknowledgment.—The authors acknowledge the kind assistance of Messrs. H. I. Lipsie and C. J. Kelley in a number of experiments.

Summary

1. The action of hexyl bromide, octyl bromide and decyl bromide on mixtures of sodium acetylide, and sodamide in liquid ammonia is described.

2. Oxidation, hydrogenation, bromination, hydration and the addition of methanol, acetic acid and glycol to dibutylacetylene are described.

3. No solid addition compound of dialkylacetylenes, suitable for identification purposes, has been found to date.

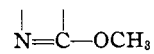
NOTRE DAME, INDIANA RECEIVED MAY 4, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KWANGSI, CHINA]

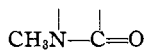
Pyrimidine Research: The Molecular Rearrangement of 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine[1]

BY YUOH FONG CHI, CHI WEI AND NAW SHAUNG PAN

It has long been known that lactim ethers of configuration I will undergo rearrangement to their isomeric and stable lactam form II. These transformations are irreversible and can be brought about by the application of heat with or without the presence of special catalytic agents, and have been observed to take place in both acyclic and cyclic compounds.



I



II

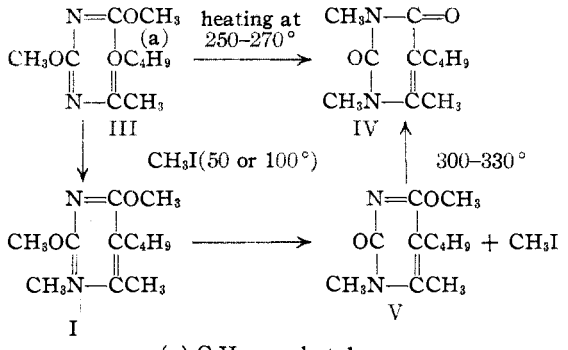
This interesting rearrangement recently has been illustrated by Hilbert and Johnson[2] in the pyrimidine series. They showed that 2,6-dialkoxypyrimidines and 2-oxy-3-alkyl-6-alkoxypyrimidines easily undergo rearrangement on heating without catalytic reagents, at an elevated temperature to form the corresponding 1,3-dialkyl-uracils. Nevertheless, 2,6-dialkoxypyrimidine, containing two lactim configurations within the same pyrimidine molecule, will only undergo partial rearrangement by treatment with methyl iodide at a much lower temperature to form 2-oxy-3-alkyl-6-alkoxypyrimidines.

In this paper, the authors have extended this study and describe the conditions under which 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine III, rearranges to (a) 1,3,4-trimethyl-5-*n*-butyl-uracil IV, and (b) 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine V. Thus far, it has been found that the 2,6-dimethoxypyrimidine III easily undergoes transformation into its isomeric and stable lactam configuration, 1,3,4-trimethyl-5-*n*-butyl-uracil IV, by merely heating at 250–270° for three hours. On the other hand, it was only transformed into 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine V, under the catalytic influence of methyl iodide at 50 or at 100°. Such partially rearranged pyrimidines like 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine V, were only stable, however, at this lower temperature, and undergo further transformation into the isomeric and completely rearranged modification IV by heating. These respective changes are expressed by the formulas.

1,3,4-Trimethyl-5-*n*-butyl-uracil, IV, was identical with the pyrimidine prepared by methylation of 4-methyl-5-*n*-butyluracil. 2-Oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine very easily underwent hydrolysis by treatment with dilute hydrochloric acid yielding 3,4-dimethyl-5-*n*-butyl-uracil. The dimethoxypyrimidine III required for this research was synthesized by the action of

(1) This paper was constructed from a dissertation presented by C. Wei and N. S. Pan to the Faculty of Chemistry at the University of Kwangsi in partial fulfilment of the requirements for the degree of B. Sci. in June, 1937. The authors especially desire to acknowledge the personal assistance of Professor Treat B. Johnson of Yale University in the preparation of the paper for publication.

(2) Hilbert and Johnson, THIS JOURNAL, **52**, 2001 (1930).



sodium methylate upon 4-methyl-5-*n*-butyl-2,6-dichloropyrimidine, which was obtained by treating its corresponding uracil precursor previously described by Chi,[3] with a mixture of phosphorus oxychloride and phosphorus pentachloride.

Experimental Part

4-Methyl-5-*n*-butyl-2,6-dichloropyrimidine.—One hundred and ten grams of 4-methyl-5-*n*-butyluracil was dissolved in a cold mixture of 500 cc. phosphorus oxychloride and 50 g. of phosphorus pentachloride. This was then heated in an oil-bath at 120° until hydrogen chloride gas ceased to be evolved. This required about ten hours. The excess of phosphorus oxychloride was distilled off under diminished pressure at water-bath temperature, when there was left behind a dark brown, resinous residue. In order to decompose any phosphorus compounds, this product was cooled by an ice–salt mixture, and then treated with cracked ice. Care must be taken to add a very small piece of ice at each time and to observe that the temperature does not rise above 20°. This precaution must be observed in order to avoid hydrolysis of the dichloro compound to the corresponding uracil derivative. After this treatment, the mixture was extracted with ether, the ethereal solution washed with water and dried over calcium chloride. After distilling off the solvent there was left an oil which was distilled under diminished pressure whereupon we obtained the pure dichloropyrimidine boiling at 171° at 23 mm. pressure. The yield was 106 g. or 80% of the theoretical.

Anal. Calcd. for $C_9H_{12}N_2Cl_2$: N, 12.79. Found: N, 12.87, 12.84.

4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine.—Four and six-tenths grams of sodium was dissolved in 50 cc. of absolute methyl alcohol. To this cold alcoholic solution of sodium methylate 21.9 g. of 4-methyl-5-*n*-butyl-2,6-dichloropyrimidine dissolved in 50 cc. of absolute methyl alcohol was added slowly. There separated immediately solid sodium chloride. After allowing to stand for one hour to complete the reaction, the sodium chloride was filtered off and washed thoroughly with methyl alcohol. The excess of alcohol was then removed by heating when we obtained an oil. This was shaken with 30 cc. of 30% sodium hydroxide solution, in which the required pyrimidine-2,6-dimethyl ether is insoluble and separated as the upper layer of the solution and was extracted with ether. 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine distilled as a colorless oil, boiling at 159° at 29 mm. The yield was 20 g. or 95% of the theoretical.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 13.28, 13.21.

Further alkoxypyrimidines of this type that we prepared according to this procedure are recorded in Table I.

TABLE I

DIALKOXYPYRIMIDINES

4-Methyl-5-*n*-butyl-2,6-	B. p., °C.	Yield, %	Formula	Analyses, % N Calcd.	Found	
Diethoxy-pyrimidine	174 at 27 mm.	87.6	$C_{13}H_{22}O_2N_2$	11.76	11.80	11.82
Di-*n*-propoxy-pyrimidine	193–4 at 23 mm.	98.8	$C_{15}H_{26}O_2N_2$	10.52	10.56	10.74
Di-*n*-butoxy-pyrimidine	219 at 29 mm.	86.5	$C_{17}H_{30}O_2N_2$	9.52	9.71	9.60
Diallyoxy-pyrimidine	192–3 at 31 mm.	96.0	$C_{14}H_{22}O_2N_2$	10.68	10.74	10.53

The Molecular Rearrangement of 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine, III. A. Rearrangement to 1,3,4-Trimethyl-5-*n*-butyluracil, IV.—Five grams of the pyrimidine III was heated in an oil-bath at 250–270° for three hours. At first there was a vigorous ebullition which gradually subsided and finally ceased as the proportion of the rearranged compound increased. On cooling, the pale brown reaction product completely solidified. This was purified by dissolving in hot benzene, to which petroleum ether was gradually added to turbidity. After cooling a solid amorphous mass separated. After filtering, this reaction product was dissolved in dry benzene, and then petroleum ether added just to turbidity. On cooling, more amorphous material separated. The clear combined filtrates were then heated at 100° to expel the solvents when an oil was obtained which solidified on cooling. It was purified by recrystallization from a benzene–petroleum ether mixture (1:40), whereupon a compound melting at 54–55° separated in colorless needles.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 13.8.

This compound, melting at 54–55°, proved to be identical with 1,3,4-trimethyl-5-*n*-butyluracil, IV, which has not been described previously in the literature. It was prepared as follows.

Synthesis of 1,3,4-Trimethyl-5-*n*-butyluracil, IV.—Five grams of 4-methyl-5-*n*-butyluracil was dissolved in 150 cc. of a sodium hydroxide solution containing 2.6 g. of sodium hydroxide. To this cold solution, 6.9 g. of dimethyl sulfate was then added slowly from a dropping funnel, and during its addition the fluid was stirred vigorously. It was then heated to boiling for one hour. After cooling, the product was extracted with benzene and the solution dried over calcium chloride. After distilling off the benzene we obtained an oil which solidified on cooling. It was purified by crystallization from a mixture of benzene and petroleum ether, from which pure 1,3,4-trimethyl-5-*n*-butyluracil separated. It melted at 54–55° and its melting point was not depressed on mixing with 1,3,4-trimethyl-5-*n*-butyluracil described in the preceding experiment.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 12.86, 13.17.

(3) Chi, THIS JOURNAL, **58**, 1151 (1936).

Rearrangement of 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine, III, to 2-Oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine, V. Method A.—Five grams of 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine, III, was mixed with 14.2 g. of freshly distilled methyl iodide and the solution was heated in a sealed tube at 100° for six hours. The excess of methyl iodide was removed by a blast of air and the residue distilled under a vacuum. Pure 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine boiled at 235–236° at 31 mm. pressure with slight decomposition and at 183–184° at 1 mm. pressure without decomposition. This compound is a light yellow and very viscous oil which showed no signs of solidifying.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 13.48.

Method B.—Five grams of 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine was heated with 14.2 g. of freshly distilled methyl iodide in a sealed tube at 50° for ten hours; from which the partially rearranged pyrimidine 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine was isolated as described above. It boiled at 183–184° at 1 mm. pressure.

Anal. Calcd. for $C_{11}H_{18}O_2N_2$: N, 13.33. Found: N, 13.22.

The structure of this compound was established by its behavior on hydrolysis.

Hydrolysis to 3,4-Dimethyl-5-*n*-butyluracil.—2-Oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine was heated with dilute hydrochloric acid for one hour. The solution was then evaporated to dryness on a water-bath. The residue dissolved in hot water, whereupon 3,4-dimethyl-5-*n*-butyluracil crystallized on cooling in long needles melting at 151–152°.

Anal. Calcd. for $C_{10}H_{16}O_2N_2$: N, 14.28. Found: N, 14.21, 14.75.

In another experiment, 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine was exposed to freshly distilled methyl iodide in the presence of methyl alcohol at room temperature for two weeks, from which a trace of 3,4-dimethyl-5-*n*-butyluracil was isolated. Probably it was produced due to the secondary hydrolytic effect of methyl alcohol upon the partially rearranged product, 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine, first formed in the reaction.

Method C. Rearrangement of the Pyrimidine V into the Uracil Compound IV.—2-Oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine, V, was heated at 300–360° for three to four hours. The above reaction mixture was dissolved in benzene, to which a large volume of petroleum ether was then added. After cooling, the benzene–petroleum ether solution was decanted from the insoluble portion. The solvent being removed from the benzene–petroleum ether solution, there remained an oil which solidified on cooling. It was recrystallized from benzene–petroleum ether and melted at 54–55°. This proved to be identical with 1,3,4-trimethyl-5-*n*-butyluracil, IV, obtained by heating 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine, III.

Summary

1. 4-Methyl-5-*n*-butyl-2,6-dichloropyrimidine has been prepared by the action of phosphorus oxychloride and phosphorus pentachloride upon its corresponding uracil compound.

2. 4-Methyl-5-*n*-butyl-2,6-dialkoxypyrimidines are formed smoothly by interaction of 4-methyl-5-*n*-butyl-2,6-dichloropyrimidine with sodium alcoholates.

3. 4-Methyl-5-*n*-butyl-2,6-dimethoxypyrimidine and 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine are found to undergo a transformation into their isomeric and stable lactam modification, 1,3,4-trimethyl-5-*n*-butyluracil, on heating at an elevated temperature. On the other hand, 4-methyl-5-*n*-butyl-2,6-dimethoxypyrimidine will rearrange only partially on heating with methyl iodide at 50 or 100° giving 2-oxy-3,4-dimethyl-5-*n*-butyl-6-methoxypyrimidine.

KWANGSI, CHINA RECEIVED APRIL 7, 1938

[CONTRIBUTION FROM NATIONAL RESEARCH INSTITUTE OF CHEMISTRY, ACADEMIA SINICA, CHINA]

Pyrimidine Research. Synthesis of 4-Methyl-5-*n*-propylcytosine[1]

BY YUOH FONG CHI AND KOU-JEN CHANG

In this short paper is described a method for synthesizing 4-methyl-5-*n*-propylcytosine III. Starting with 2-thio-4-methyl-5-*n*-propyl-6-oxypyrimidine, which is prepared by condensing ethyl *n*-propylacetoacetate with thiourea, the corresponding 2-ethylmercapto compound I is obtained by alkylation in the usual manner, and the resulting mercapto derivative is then treated with phosphorus oxychloride to give 2-ethylmercapto-4-methyl-5-*n*-propyl-6-chloropyrimidine. This new chloropyrimidine derivative reacts with alcoholic ammonia in a normal manner giving the corresponding 6-amino compound II. On digesting the latter with concentrated hydrobromic acid 4-methyl-5-*n*-propylcytosine hydrobromide is formed. The free cytosine base III is liberated by treatment with a slight excess of ammonia.

(1) The authors wish to express their thanks to Mr. Yao-Tseng Huang for his assistance in making micro-analyses of the compounds described in this paper. They are also indebted to Professor Treat B. Johnson of Yale University for his personal help in the preparation of this report for publication.