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

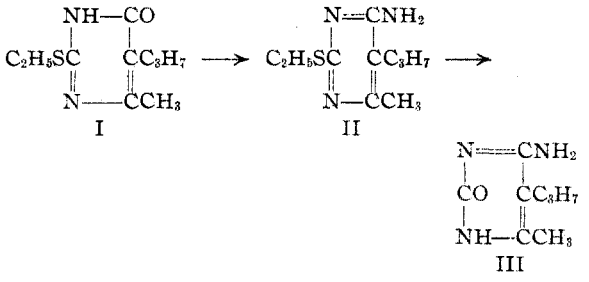
[CONTRIBUTION FROM NATIONAL RESEARCH INSTITUTE OF CHEMISTRY, ACADEMIA SINICA, CHINA]

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.



I II III

Experimental Part

2-Thio-4-methyl-5-*n*-propyl-6-oxypyrimidine.—Twenty-three grams of metallic sodium was dissolved in 400 cc. of absolute alcohol. One hundred and seventy-two grams of ethyl *n*-propylacetoacetate and 84 g. of thiourea were then added to the solution. The mixture was heated on a water-bath for four hours. After distilling off the solvent the residue remaining behind was dissolved in cold water. This was acidified with dilute acetic acid, when the desired thiopyrimidine separated. After being recrystallized from boiling water, it separated in needles and melted at 209–209.5°. The yield was 103 g. For analysis, the compound was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_8H_{12}ON_2S$: N, 15.21. Found: N, 15.5, 15.5.

2-Methylmercapto-4-methyl-5-*n*-propyl-6-oxypyrimidine.—Twenty-three hundredths gram of sodium was dissolved in 20 cc. of absolute alcohol. To this solution, 1.84 g. of the above thiopyrimidine and 1.55 g. of methyl iodide were added and the mixture heated on a water-bath for four hours. On cooling, the methylmercapto compound separated in needles. It was recrystallized from absolute alcohol and melted at 180–181° to a clear oil. The yield was 1.2 g. The substance was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_9H_{14}ON_2S$: N, 14.14. Found: N, 14.5, 14.1.

2-Ethylmercapto-4-methyl-5-*n*-propyl-6-oxypyrimidine I.—One hundred and fifteen grams of sodium was dissolved in 1 liter of absolute alcohol and 92 g. of the thiopyrimidine and 60 g. of ethyl bromide were added to the solution. The mixture was heated on a water-bath for four hours and the solution then filtered from the insoluble sodium chloride. After distilling off the excess of alcohol the residue was triturated with cold water and filtered. The pyrimidine was recrystallized from dilute alcohol, and melted at 92–93°. The yield was 87.5 g. The substance was dried for analysis over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_{10}H_{16}ON_2S$: C, 56.55; H, 7.60. Found: C, 56.55; H, 7.68.

2-*n*-Propylmercapto-4-methyl-5-*n*-propyl-6-oxypyrimidine.—Twenty-three hundredths gram of sodium was dissolved in 20 cc. of absolute alcohol, to which 1.84 g. of thiopyrimidine and 1.55 g. of *n*-propyl bromide were then added. The experiment was carried out as described above, whereby the *n*-propylmercaptopyrimidine was obtained melting at 89–90°. It was recrystallized from dilute alcohol and separated in needles. The substance was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_{11}H_{18}ON_2S$: N, 12.39. Found: N, 12.6, 12.2.

$NHCONHC(CH_3)=C(C_3H_7)CO$, **4-Methyl-5-*n*-propyluracil.**—This pyrimidine is formed quantitatively by digesting any one of the preceding mercaptopyrimidines with hydrobromic or hydrochloric acid. It is also easily prepared by digesting the corresponding 2-thiopyrimidine described above with chloroacetic acid in aqueous solution. The uracil derivative crystallizes from hot water in the form of needles melting at 247–248°.

Anal. Calcd. for $C_8H_{12}O_2N_2$: C, 57.10; H, 7.20. Found: C, 57.36, 57.04; H, 7.17, 7.26.

Ethyl 4-Methyl-5-*n*-propyl-6-oxypyrimidine-2-thioglycolate was obtained easily by alkylation of the above 2-thiouracil derivative in alcohol solution with ethyl chloroacetate. It was purified by crystallization from dilute alcohol and melted at 100–101°.

Anal. Calcd. for $C_{12}H_{18}O_3N_2S$: C, 53.29; H, 6.71. Found: C, 53.40; H, 7.04.

4-Methyl-5-*n*-propyl-6-oxypyrimidine-2-thioglycolic Acid was prepared by saponification of the above ethyl ester with alcoholic potash solution. The acid crystallized from hot water as plates melting at 105–106°. The compound contained water of crystallization.

Anal. Calcd. for $C_{10}H_{14}O_3N_2S$: N, 11.57; H_2O, 6.92. Found: N, 11.4, 11.45; H_2O, 6.74.

2-Ethylmercapto-4-methyl-5-*n*-propyl-6-chloropyrimidine.—Twenty-one and two-tenths grams of 2-ethylmercapto-4-methyl-5-*n*-propyl-6-oxypyrimidine was dissolved in cold phosphorus oxychloride. The solution was heated for twelve hours at 120–130°. After the excess of phosphorus oxychloride was removed, the residue was then treated with cracked ice, the solution extracted with ether and the ether solution dried over calcium chloride. After distilling off the ether the pyrimidine chloride distilled at 165–166° at 11 mm. pressure.

Anal. Calcd. for $C_{10}H_{15}N_2SCl$: C, 52.02; H, 6.56. Found: C, 52.26; H, 6.47.

2-Ethylmercapto-4-methyl-5-*n*-propyl-6-aminopyrimidine II.—Six grams of the above 6-chloropyrimidine was heated with alcoholic ammonia at 160–170° for three hours. The solution was evaporated to dryness and the residue triturated with cold water. The crude pyrimidine dissolved in petroleum ether, from which the 6-amino compound separated in needles, melting at 86–87°.

Anal. Calcd. for $C_{10}H_{17}N_3S$: N, 19.90. Found: N, 20.01, 19.9.

4-Methyl-5-*n*-propylcytosine, III.—The above 6-aminopyrimidine was digested with concentrated hydrobromic acid for sixteen hours, and the solution then evaporated to dryness. After dissolving the residue in boiling water and cooling, the hydrobromide of 4-methyl-5-*n*-propylcytosine separated in prisms. It melted at 253–254°. The salt was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_8H_{13}ON_3 \cdot HBr$: C, 38.70; H, 5.69. Found: C, 38.90; H, 5.79.

The free base was obtained by treating the aqueous solution of the above hydrobromide with ammonia. It was recrystallized from water and melted at 317–318° with

decomposition. The substance was dried over phosphorus pentoxide in a vacuum at 80°.

Anal. Calcd. for $C_8H_{13}ON_3$: C, 57.44; H, 7.84. Found: C, 57.81; H, 7.92.

Hydrochloride.—The above cytosine derivative dissolved in dilute hydrochloric acid, and on cooling the hydrochloride separated in prisms, melting at 235°.

Anal. Calcd. for $C_8H_{13}ON_3 \cdot HCl$: C, 47.15; H, 6.93. Found: C, 46.78; H, 6.65.

Summary

1. Ethyl *n*-propylacetoacetate condenses with thiourea in alcohol solution in the presence of sodium ethylate to give 2-thio-4-methyl-5-*n*-propyl-6-oxypyrimidine.

2. 2-Thio-4-methyl-5-*n*-propyl-6-oxypyrimidine is alkylated on sulfur by treatment with methyl iodide, ethyl bromide, *n*-propyl bromide and ethyl monochloroacetate to form the corresponding 2-mercaptopyrimidine derivatives, respectively.

3. 2-Ethylmercapto-4-methyl-5-*n*-propyl-6-chloropyrimidine is obtained from its corresponding 6-oxypyrimidine compound by heating the latter with phosphorus oxychloride.

4. This chloropyrimidine interacts with alcoholic ammonia to form 2-ethylmercapto-4-methyl-5-*n*-propyl-6-aminopyrimidine.

5. Treatment with concentrated hydrobromic acid converts 2-ethylmercapto-4-methyl-5-*n*-propyl-6-aminopyrimidine into 4-methyl-5-*n*-propylcytosine hydrobromide, from which the free base is obtained by neutralization with ammonia.

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

The Alkaloids of Chinese Gelsemium, Kou Wen[1]

BY YUOH FONG CHI, YEE-SHENG KAO AND YAO-TSENG HUANG

Chou[2] has isolated the following alkaloids from the plant Kou Wen: (A) koumine $C_{20}H_{22}N_2O$, m. p. 170°, (B) kouminine, (C) kouminicine and (D) kouminidine. Of these four alkaloids, koumine only was obtained in a good crystalline state and kouminidine was probably not very pure on account of small traces of impurity present, while kouminine and kouminicine were only obtained in an amorphous condition. Recently, Chou[3] isolated the following alkaloids from Ta-Cha-Yeh: (Z) koumine $C_{20}H_{22}N_2O$, m. p. 170°; (B) kouminine in the form of its hydrochloride; (C) gelsemine, $C_{20}H_{22}N_2O_2$, m. p. 178°; and kounidine $C_{21}H_{24}N_2O_5$. In this short paper the authors give a report of their investigation of the alkaloids of Kou Wen. Besides koumine, m. p. 168°, they succeeded in separating Chou's kouminine into gelsemine and other impure bases. From the kouminidine fraction, they isolated a base, m. p. 299° (instead of 200°), to which the original name, kouminidine, was assigned.

Experimental Part

Twenty-two and seven-tenths kilograms of Kou Wen in the form of stems, roots and leaves was powdered and percolated with cold 95% alcohol. The alcoholic extract was evaporated under diminished pressure, and the resin left over was taken up with a sufficient quantity of 2% hydrochloric acid. When the insoluble resinous matter was filtered off the acid extract was allowed to stand for about two weeks, when there deposited a further quantity of neutral resinous material. The clear solution, obtained after removing the insoluble non-basic resinous matter, was finally neutralized with sodium carbonate and extracted thoroughly, first with ether several times (A), and then with chloroform (B).

Isolation of Koumine.—After removing the solvent from the ethereal solution (A), the crude basic residue weighed 38 g. This was dissolved in a small quantity of acetone, and the solution allowed to stand in an ice-box for several days; whereupon koumine deposited in the form of colorless prisms. This was recrystallized from acetone several times or until the melting point became constant at 168°. It was readily soluble in alcohol, chloroform and benzene and slightly soluble in hot water.

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.38, H, 7.24; N, 9.15. Found: C, 78.52, 78.37; H, 7.31, 7.39; N, 9.37, 9.35.

Acetylation of Koumine.—When Koumine was treated with acetic anhydride, the original alkaloid melting at 168° was recovered.

Isolation of Gelsemine.—The acetone mother liquid, from which the base, koumine, had been separated, was evaporated to dryness. The residue was dissolved in ethyl alcohol and acidified with the desired amount of alcoholic hydrochloric acid. The solution was then allowed to stand for several days, whereupon the mixed hydrochlorides separated in the form of a crystalline pow-

(1) The authors desire to express their thanks to Professor Treat B. Johnson of Yale University for his personal help in arranging this report for publication in THIS JOURNAL.

(2) Chou, *Chinese J. Physiol.*, **5**, 345–352 (1931).

(3) Chou, *ibid.*, **10**, 79–84 (1936).