We wish to thank Mr. C. C. Stephenson for assisting with the experimental work.

Summary

The heat capacity of ice has been measured between 15 and 273°K.

It has previously been shown by Giauque and Ashley that a discrepancy exists between the spectroscopic value of the entropy and the $\int_0^T C_p \, d \ln T$ for water.

The purpose of the present investigation was to make an accurate determination of the discrepancy.

With the assistance of the well-known values for the heats of fusion and vaporization of water we find that the $\int_0^T C_p \, d \ln T = 44.28 \pm 0.05$ cal./deg./mole for H_2O (g.) at one atmosphere and 298.1°K. The spectroscopic value is 45.10 leading to a discrepancy of 0.82 cal./deg./mole. This is in excellent agreement with the theoretical discrepancy 0.806 calculated by Pauling on the assumption of random orientation of hydrogen bond directions in ice.

Experiments have been described in which ice was cooled slowly or rapidly to low temperatures or was allowed to stand for long periods of time at low temperatures. No difference in the thermal properties of ice was observed in these experiments.

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

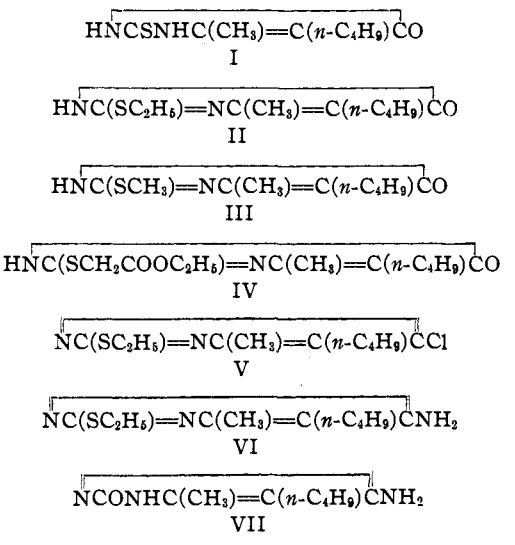
Pyrimidine Research. Synthesis of 4-Methyl-5-*n*-butylcytosine

BY YUOH-FONG CHI

In this paper is described a method of synthesizing 4-methyl-5-*n*-butylcytosine (VII), which is prepared as its hydrobromide from 2-ethylmercapto-4-methyl-5-*n*-butylcytosine (VI) by hydrolysis with concentrated hydrobromic acid. The free base (VII) is liberated from its hydrobromide by neutralizing with ammonia. For the preparation of 2-ethylmercapto-4-methyl-5-*n*-butylcytosine (VI), the starting point is the corresponding 6-oxypyrimidine, 2-ethylmercapto-4-methyl-5-*n*-butyl-6-oxypyrimidine (II). This is treated with phosphorus oxychloride to form the corresponding 6-chloropyrimidine (V), and the latter then heated with alcoholic ammonia at 170–180° to give the desired 2-mercapto-6-amino derivative (VI).

2 - Ethylmercapto - 4 - methyl - 5 - *n* - butyl-6-oxypyrimidine was prepared according to the general method of Wheeler and Liddle.[1] Ethyl *n*-butylacetoacetate is first condensed with thiourea in the presence of sodium ethylate to give 2-thio-4-methyl-5-*n*-butyl-6-oxypyrimidine (I), which is then treated in the presence of sodium ethylate with ethyl bromide to give 2-ethylmercaptopyrimidine (II). Alkylation of the latter with methyl iodide gives the corresponding 2-methylmercapto compound (III), and with ethyl chloroacetate to give ethyl 4-methyl-5-*n*-butyl-6-oxypyrimidine-2-thioglycolate (IV).

(1) Wheeler and Liddle, *Am. Chem. J.*, **40**, 547 (1908).



Experimental Part

2 - Thio - 4 - methyl - 5 - *n* - butyl - 6 - oxypyrimidine I.—Twenty-six grams of sodium was dissolved in 500 cc. of absolute alcohol and 210 g. of ethyl *n*-butylacetoacetate and 94 g. of thiourea added to the solution. This was then heated on a water-bath for ten hours and the excess of alcohol removed by heating under diminished pressure. The crude sodium salt of the desired pyrimidine was dissolved in water and the solution acidified with acetic acid, when the thiopyrimidine separated. It crystallized from hot water in needles, melting at 197–198°. The yield was 144 g.

Anal. Calcd. for $C_9H_{14}ON_2S$: N, 14.14. Found: N, 14.03, 13.98, 14.00.

2 - Ethylmercapto - 4 - methyl - 5 - *n* - butyl - 6 - oxypyrimidine II.—Eight and one-tenth grams of sodium was dissolved in 200 cc. of absolute alcohol and 70 g. of the above thiopyrimidine and 42.5 g. of ethyl bromide were added to the solution. This was then heated on a water-bath until the solution became neutral. The excess alcohol was then distilled off under diminished pressure, and the mercaptopyrimidine washed with water and recrystallized from dilute alcohol. It separated in long needles, melting at 92–93° to a clear oil.

Anal. Calcd. for $C_{11}H_{18}ON_2S$: N, 12.39. Found: N, 12.8, 12.6, 12.5.

4-Methyl-5-*n*-butyluracil. A.—This is easily prepared by digestion of the above 2-thiopyrimidine with chloroacetic acid in aqueous solution. This pyrimidine separated in the form of needles and was purified by recrystallization from hot water. It melted at 245°.

Anal. Calcd. for $C_9H_{14}O_2N_2$: N, 15.38. Found: N, 15.22, 15.10.

B.—This same pyrimidine is also formed from 2-ethylmercapto-4-methyl-5-*n*-butyl-6-oxypyrimidine by digestion with concentrated hydrobromic acid for several hours. It melted at 245°.

2 - Methylmercapto - 4 - methyl - 5 - *n* - butyl - 6 - oxypyrimidine III.—This is formed by alkylation of the 2-thiopyrimidine with methyl iodide. It was purified by crystallization from alcohol and it separated as needles, melting at 158–159° to a clear oil.

Anal. Calcd. for $C_{10}H_{16}ON_2S$: C, 56.55; H, 7.60; N, 13.20. Found: C, 56.33; H, 7.94; N, 13.0, 13.1.

Ethyl - 4 - methyl - 5 - *n* - butyl - 6 - oxypyrimidine - 2 - thioglycolate IV.—This was prepared by the action of ethyl chloroacetate on the sodium salt of the 2-thiopyrimidine. The ester was purified by crystallization from dilute alcohol, whereupon it separated in needles, melting at 110–111°.

Anal. Calcd. for $C_{13}H_{20}O_3N_2S$: N, 9.86. Found: N, 9.94, 10.00.

4 - Methyl - 5 - *n* - butyluracil - 2 - thioglycolic Acid.—Two grams of the thioglycolate was warmed with aqueous potassium hydroxide on a water-bath for half an hour. After cooling, the solution was acidified with dilute hydrochloric acid, when the thioglycolic acid separated in a crystalline condition. The yield was nearly quantitative. It was purified by recrystallizing from dilute alcohol, and melted at 117–118°.

Anal. Calcd. for $C_{11}H_{16}O_3N_2S$: C, 51.52; H, 6.29; N, 10.94. Found: C, 51.55; H, 6.63; N, 11.3, 11.5.

2 - Ethylmercapto - 4 - methyl - 5 - *n* - butyl - 6 - chloropyrimidine V.—Twenty-two and six-tenths grams of the oxypyrimidine was dissolved in 80 cc. of cold phosphorus oxychloride and the solution heated on an oil-bath at 110–120° for seven hours. The excess of phosphorus oxychloride was then removed under diminished pressure. A sirup was obtained which was treated with cold water to decompose phosphorus compounds and then extracted with ether. The ethereal solution was separated and dried, and the solvent removed, leaving behind the desired pyrimidine as an oil. It was distilled under diminished pressure and boiled at 160° at 2 mm. The yield was 19 g.

Anal. Calcd. for $C_{11}H_{17}N_2ClS$: C, 53.95; H, 7.00. Found: C, 54.11; H, 7.33.

2 - Ethylmercapto - 4 - methyl - 5 - *n* - butyl - 6 - aminopyrimidine. VI.—The corresponding 6-chloropyrimidine was heated with alcoholic ammonia under pressure for three hours at 170–180°. The solution was filtered from the insoluble ammonium chloride, and then evaporated to dryness on a water-bath, yielding the desired compound. The aminopyridine crystallized from a benzene–petroleum ether mixture and melted at 104–105°. The yield was 1.7 g. from 5 g. of the chloropyrimidine.

Anal. Calcd. for $C_{11}H_{19}N_3S$: C, 58.60; H, 8.50. Found: C, 59.06, 59.15; H, 8.87, 8.90.

4-Methyl-5-*n*-butylcytosine Hydrobromide.—The above 2 - ethylmercapto - 4 - methyl - 5 - *n* - butyl - 6 - aminopyrimidine was boiled with concentrated hydrobromic acid (48%) for sixteen hours. On evaporating this solution to dryness, cytosine hydrobromide was obtained and crystallized in prisms from hot water, melting at 222° with decomposition.

Anal. Calcd. for $C_9H_{15}ON_3 \cdot HBr$: C, 41.21; H, 6.15. Found: C, 41.15; H, 6.06.

4-Methyl-5-*n*-butylcytosine VII.—An aqueous solution of the above cytosine hydrobromide was treated with ammonia. The free base separated and after purification by recrystallizing from very dilute alcohol (about 10%) it separated in prisms, melting at 299–300° with decomposition.

Anal. Calcd. for $C_9H_{15}ON_3 \cdot {}^3/_4(H_2O)$: C, 55.48; H, 8.55; N, 21.59. Found: C, 55.97, 55.88; H, 8.03, 8.37; N, 21.20, 21.42.

Hydrochloride.—The cytosine was treated with a small quantity of hydrochloric acid, when the cytosine hydrochloride separated in prisms, melting at 235° to a clear oil. It was purified by recrystallizing from hot water.

Anal. Calcd. for $C_9H_{15}ON_3 \cdot HCl$: C, 49.63; H, 7.41. Found: C, 49.41; H, 7.36.

Summary

1. Ethyl *n*-butylacetoacetate condenses with thiourea in the presence of sodium ethylate to form 2-thio-4-methyl-5-*n*-butyl-6-oxypyrimidine.

2. This 2-thiopyrimidine reacts in presence of sodium ethylate with ethyl bromide and methyl iodide to give 2-ethylmercapto-4-methyl-5-*n*-butyl-6-oxypyrimidine and 2-methylmercapto-4-methyl-5-*n*-butyl-6-oxypyrimidine, respectively.

3. Ethylmercapto - 4 - methyl - 5 - *n* - butyl - 6-oxypyrimidine when treated with phosphorus oxychloride gives the corresponding chloropyrimidine which reacts with ammonia to form 2-ethylmercapto - 4 - methyl - 5 - *n* - butyl - 6 - aminopyrimidine. This pyrimidine is converted by boiling with concentrated hydrobromic acid into 4 - methyl - 5 - *n*-butylcytosine.

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