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PHOSPHORUS OXYBROMIDE AS A BROMINATING AGENT. BROMOPYRIMIDINES[1]

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The introduction of bromine into the 4 or 6 position of the pyrimidine nucleus has been reported in only one case, that of the preparation of 2,4,5,6-tetrabromopyrimidine, by the reaction of a mixture of phosphorus pentabromide and phosphorus oxychloride with 5-hydroxybarbituric acid (1). On the other hand pyrimidines with chlorine in these positions are readily prepared by the use of phosphorus oxychloride (2).

While attempting to synthesize analogs of sulfadiazine brominated in the pyrimidine ring, we found that the required bromopyrimidines could be prepared by the action of phosphorus oxybromide on the corresponding hydroxypyrimidines. Direct fusion of the reactants led to the formation of 2,4,6-tribromopyrimidine, 2-amino-4-bromopyrimidine, 2-amino-4,6-dibromopyrimidine, and 2-amino-4-bromo-6-methylpyrimidine, in moderate yields; a good yield of 2-(*p*-nitrobenzenesulfonamido)-4-bromo-6-methylpyrimidine was obtained when the reaction was carried out employing toluene as a diluent. The desirable physical properties of phosphorus oxybromide and its ease of handling suggest that it might find more general use as a brominating agent.

EXPERIMENTAL[3]

Phosphorus oxybromide. This material was prepared by the method of Berger (3), and was then distilled, b.p. 89–90°/20 mm. It was a colorless, crystalline solid, which could be preserved indefinitely in a desiccator. It was convenient to melt the compound when weighing a portion of it for use.

2,4,6-Tribromopyrimidine. Ten grams of barbituric acid and 143 grams of phosphorus oxybromide were heated at 150–160° for five and one-half hours; the mixture was then cooled and added slowly to an ice-ether mixture which had been cooled to −10°. The precipitate was collected, extracted with ether, and the combined ethereal extracts dried. The ether was removed and the material which remained was distilled, giving 15 grams (61%) of pro duct, b.p. 124°/5 mm., m.p. 113–115°.

Anal. Calc'd for $C_4HBr_3N_2$: C, 15.16; H, 0.31; N, 8.84.
Found: C, 15.34; H, 0.41; N, 8.61.

2-Amino-4-bromopyrimidine.[4] Four grams of isocytosine (4) and 10 g. of phosphorus oxybromide were mixed and heated for two hours, while the temperature was slowly raised from 80° to 135°, and finally held at the higher temperature. The melt was decomposed with

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[3] All melting points reported in this paper are corrected for exposed stem. The microanalyses were carried out by Dr. Gertrude Oppenheimer and her staff, of this institute.

[4] This reaction was carried out by Mr. John T. Maynard.

ice, the solution was brought to *p*H 12, and the product, 1.0 g. (16%), filtered off. It was purified by recrystallization from water, and an analytical sample was prepared by sublimation at 110–120° and atmospheric pressure. The product had no melting point, but decomposed slowly when heated above 130°.

Anal. Calc'd for $C_4H_4BrN_3$: C, 27.61; H, 2.32.
Found: C, 27.28; H, 2.31.

2-Amino-4,6-dibromopyrimidine. A mixture of 1.70 g. of 2-amino-4,6-dihydroxypyrimidine (5) and 6.8 g. of phosphorus oxybromide was heated to 135°, initiating a vigorous reaction, with evolution of hydrogen bromide. When the reaction had subsided the melt was poured over ice, and the solid product was filtered off and recrystallized from ethanol, giving 1.10 g. (32%) of material which melted at 180–186° after sintering from 155°. An analytical sample was sublimed *in vacuo*, and melted at 189.5–192.5°.

Anal. Calc'd for $C_4H_3Br_2N_3$: C, 19.00; H, 1.19.
Found: C, 19.11; H, 1.42.

2-Amino-4-bromo-6-methylpyrimidine. Thirty grams of crude 2-amino-4-hydroxy-6-methylpyrimidine (6) was treated with 135 g. of molten phosphorus oxybromide, whereupon an immediate reaction ensued. After forty-five minutes at 135° the mixture was cooled and added to 600 g. of ice. To the resulting aqueous solution 15 *N* ammonia was added slowly with cooling. The supernate was decanted from a red gummy precipitate which came down while the solution was still strongly acid, and the crude product was precipitated by adding an excess of ammonia. It was partially purified by reprecipitation from acid solution. The crude solid weighed 22 g., from which 10–15 g. of pure product, m.p. 153°, could be isolated by recrystallization from isopropyl ether or from acetone and water.

Anal. Calc'd for $C_5H_6BrN_3$: C, 31.94; H, 3.22; N, 22.35.
Found: C, 31.84; H, 2.98; N, 22.23.

2-(p-Nitrobenzenesulfonamido)-4-bromo-6-methylpyrimidine. Fifteen grams of phosphorus oxybromide was dissolved in 60 ml. of dry toluene, and 6.5 g. of 2-(*p*-nitrobenzenesulfonamido)-4-hydroxy-6-methylpyrimidine (7) was added. The resulting suspension was refluxed for seven hours, cooled, and shaken with ice to decompose unreacted oxybromide. The product was recovered by filtration, and recrystallized from 250 ml. of ethanol and 200 ml. of water to give 6.1 g. (78%) of thin, colorless bars, m.p. 210.5–212.5° (dec.).

Anal. Calc'd for $C_{11}H_9BrN_4O_4$: C, 35.40; H, 2.43; N 15.02.
Found: C, 35.11; H, 2.39; N, 15.12.

SUMMARY

1. The use of phosphorus oxybromide as a reagent for the bromination of hydroxypyrimidines is reported.

2. A number of new bromopyrimidines, with bromine in the 2, 4, and 6-positions are reported.

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