[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

SYNTHESIS OF CERTAIN DERIVATIVES OF 2-ETHYLPYRIMIDINE[1]

HENRY R. HENZE AND JAMES L. McPHERSON

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In continuation of our investigation of the synthesis of pyrimidine derivatives through condensation of amidines with malonic esters (1) we have now studied the interaction of propamidine and malonic ester. The 2-ethyl-4,6(1,5)-pyrimidinedione thus obtained was converted into 4,6-dihalo derivatives through interaction with phosphorus oxychloride or oxybromide. The dibromo derivative is less stable and more reactive than is its dichloro analog. Finally, the dibromopyrimidine reacted with ammonia to replace with amino either one or both halo atoms.

EXPERIMENTAL

Phosphorus oxybromide was prepared, in general as outlined by Booth and Seegmiller (2), except that a longer period of digestion (ten hours) on the steam-bath seemed essential to obtain a 75% yield.

Propionitrile was obtained (91% yield) by following the method of Walden (3); d_4^{25} 0.7780.

Preparation of promamidine hydrochloride. A solution was prepared containing 460 g. (10 moles) of ethanol, 550 g. (10 moles) of propionitrile, and 365 g. (10 moles) of dry hydrogen chloride. The securely stoppered flask was shaken for eight hours; after standing for four days imido ester separated. With minimum exposure to the atmosphere, the imido ester was mixed with 300 ml. of ethanol, transferred to a mortar, and ground as fine as possible. The slurry was treated with 1540 ml. of 6.5 *N* alcoholic ammonia (10 moles) and was stirred in a closed vessel for 24 hours. The ammonium chloride which had separated from solution was removed, and from the filtrate 1000 ml. of alcohol was distilled. The residual viscous liquid solidified upon cooling. This propamidine hydrochloride weighed 955 g. (88% yield), and was stored in brown bottles; no signs of decomposition were noted during 18 months of storage. The salt melted at 129° in agreement with the datum recorded by Pinner and Klein (4).

Preparation of 2-ethyl-4,6(1,5)-pyrimidinedione. The procedure utilized followed that of Kenner, *et al.* (5) and of Dox and Yoder (6) for the lower homolog. Thus, 170 g. (3 moles of sodium methoxide) of commercial 95% sodium methoxide[2] was dissolved in 800 ml. of dry methanol. To this solution was added another solution of 103 g. (1 mole) of propamidine hydrochloride in 200 ml. of methanol. To the well-stirred mixture (containing sodium chloride in suspension) 160 g. of diethyl malonate was added dropwise. During a period of one hour, the color of the mixture changed from white to red and finally to a yellow-orange. As much as possible of the alcohol was removed by vacuum distillation, the amorphous solid residue was dissolved in the minimum of water, and with vigorous agitation, the product was precipitated by the addition of concentrated hydrochloric acid.

The product, very small, white platelets, was collected and washed on the funnel with 50 ml. of water. It was then dissolved in concentrated ammonium hydroxide and was reprecipitated with concentrated hydrochloric acid. The purified product was dried in an oven at 105° for 18 hours. Thus there was obtained 123 g. (88% yield) of 2-ethyl-4,6(1,5)-

[1] From the M.A. Thesis of J. L. McPherson, University of Texas, 1949.

[2] Purchased from the Mathison Alkali Company of Niagara Falls, N. Y. If the malonic ester was not added immediately after that of the propamidine hydrochloride, the yield of pyrimidinedione dropped quite rapidly.

pyrimidinedione which decomposed at 298.5° (corr.); Huber and Hölscher (7) reported decomposition at 299°.

Anal. Calc'd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75.
Found: C, 51.00; H, 5.50.

Preparation of 4,6-dichloro-2-ethylpyrimidine. Five grams (0.036 mole) of finely ground 2-ethyl-4,6(1,5)-pyrimidinedione and 32.7 g. (0.216 mole) of phosphorus oxychloride were added to a flask, provided with a stirrer, reflux condenser, and another condenser set for use in distillation. The mixture was heated to refluxing for about 20 minutes, during which time the evolution of hydrogen chloride was evident; the mixture became a light yellow liquid. After refluxing for 15 minutes beyond the point of cessation of gas evolution, most of the excess oxychloride was removed by distillation under diminished pressure. The residual material was allowed to cool before being poured onto a small quantity of ice.[3] After an hour, the yellow liquid was extracted with 80 ml. of ether, the extracts were washed with 10% sodium hydroxide solution (which failed to extract any organic material), de colorized with charcoal (Darco), and dried overnight with sodium sulfate. After removal of solvent, the almost colorless liquid was fractionated *in vacuo*; b.p. 77° (5 mm.);[4] 5.18 g. (82% yield); n_D^{25} 1.5261; d_4^{25} 1.2850; ΣMR 42.20; MR found 42.30.

Anal. Calc'd for $C_6H_6Cl_2N_2$: Cl, 40.10. Found: Cl, 40.00.

Preparation of 4,6-dibromo-2-ethylpyrimidine. As rapidly as possible and with minimum exposure to the air, 10 g. (0.071 mole) of 2-ethyl-4,6(1,5)pyrimidinedione and 61.6 g. (0.214 mole) of phosphorus oxybromide were ground together in a mortar and transferred to a flask provided with a "warm-finger" condenser[5] and connected to a source of vacuum. At a bath temperature of 80° the phosphorus oxybromide began to melt and escape of hydrogen bromide could be demonstrated. Production of hydrogen bromide ceased when the reaction mixture had been warmed to about 99°. At this temperature sublimation began and needle-like crystals formed on the "warm-finger" condenser; sublimation continued until the bath temperature rose to about 160°.

The "warm-finger" was removed, and the white, sublimed, crystalline product,[6] which immediately began to react with moisture in the atmosphere, was added to 20 ml. of water; much heat was evolved, the solution was acidic, and gave a positive test for phosphate ion. The mass of plate-like crystals was removed and dried in a desiccator; m.p. 52°; weight 16 g. This material was resublimed to yield crystalline plates of m.p. 53° (corr.); 15 g. (79% yield).

Anal. Calc'd for $C_6H_6Br_2N_2$: Br, 60.10. Found: Br, 60.02.

When 4,6-dibromo-2-ethylpyrimidine was prepared like its dichloro analog, by ether extraction rather than by sublimation, the yields were much lower, and the purification was much more difficult. This dibromopyrimidine has such a high vapor pressure that upon standing overnight in a closed container, crystals would sublime to the stopper and upper flask walls. As a result of boiling an ether extract of this dibromo product, over 50% by weight of the compound was lost.

Preparation of 6-bromo-2-ethyl-4(3)-pyrimidone. As quickly as possible, 4.2 g. (0.03 mole) of 2-ethyl-4,6(1,5)-pyrimidinedione and 8.61 g. (0.103 mole) of phosphorus oxybromide were ground together in a mortar and transferred to the apparatus used previously

[3] It was found that the yield could be increased as much as 20% by using the minimum of ice in decomposing the excess phosphorus oxychloride. This may account for the improvement over the yield of but 55% reported by Huber and Hölscher (7).

[4] Huber and Hölscher (7) reported b.p. 86–87° (14 mm.).

[5] The "warm-finger" condenser was a small "cold-finger" condenser through which water at 80° was circulated.

[6] There is considerable doubt as to the composition of the first sublimed product which decomposed upon contact with water. The "warm-finger" condenser, with its temperature of 80°, should have prevented any of the phosphorus oxybromide (m.p. 56°) from solidifying with the sublimed dibromopyrimidine.

for preparation of the dibromopyrimidine. The oil bath was heated slowly to 160°. The "warm-finger" was removed with one gram of adhering dibromo derivative. The solid, yellow-brown residue was added to 10 g. of ice and extracted with 60 ml. of ether. The aqueous layer was evaporated to dryness, and this residue extracted with ether. The combined ether extracts were shaken with 10 ml. of 10% sodium hydroxide solution which extracted the color and left a clear ether extract. The latter yielded 0.5 g. of the dibromopyrimidine.

The alkaline extract was acidified with glacial acetic acid; the heavy precipitate which formed was primarily the desired bromopyrimidone. The latter was removed, washed free of alkali, and dissolved in cold benzene (in which the dione is insoluble). By concentration of the solvent, there was obtained 4.38 g. (72%) of 6-bromo-2-ethyl-4(3)-pyrimidone; m.p. 157.8° (corr.). The compound showed signs of decomposition after standing for 12 hours in an oven at 110°.

This monobromo compound was prepared also by refluxing 0.020 mole of the dibromopyrimidine with 0.040 mole of sodium hydroxide in 30 ml. of water for 12 hours, but the yields were below 50%.

Anal. Calc'd for $C_6H_7BrN_2O$: Br, 39.40. Found: Br, 39.30.

Preparation of 4,6-diamino-2-ethylpyrimidine. Freshly sublimed 4,6-dibromo-2-ethylpyrimidine (4 g.) and 50 ml. of concentrated ammonium hydroxide solution were placed in the glass liner of a steel pressure vessel and heated for 24 hours at 150°. After being cooled, the vessel was opened and the clear liquid contents were clarified with Darco, and evaporated to 10 ml. volume. Despite the fact that the concentrated solution was definitely ammoniacal, the salt proved to be the monohydrobromide of 4,6-diamino-2-ethylpyrimidine. This salt was slightly soluble in most organic solvents but was very soluble in absolute alcohol and acetone. It was recrystallized from ethanol and dried; weight, 2.67 g. (81% yield); melting range 168–173° (corr.). In aqueous solution, this hydrobromide salt reacted almost quantitatively with silver nitrate solution.

Anal. Calc'd for $C_6H_{10}N_4 \cdot HBr$: N, 25.59. Found: N, 26.00.

Addition of a 30% potassium hydroxide solution to the saturated aqueous solution of this hydrobromide salt caused precipitation of 4,6-diamino-2-ethylpyrimidine. The latter was filtered off and recrystallized from water to yield 1.21 g. (72% conversion); m.p. 223°.

Anal. Calc'd for $C_6H_{10}N_4$: N, 40.60. Found: N, 40.40.

The diamino derivative was prepared also by interaction of the dibromo compound and sodium amide in liquid ammonia; although removal of bromide was essentially quantitative, the presence of a resinous, orange-red material made purification more difficult, and the yield was lower. The dibromopyrimidine would react with alcoholic (methyl, ethyl, and isopropyl alcohols were used) ammonia at temperatures as low as 70°; however, the products were discolored and purification losses made this procedure less desirable than that initially described.

Preparation of 4-amino-6-bromo-2-ethylpyrimidine. A mixture of 1.2 g. of freshly sublimed 4,6-dibromo-2-ethylpyrimidine and 50 ml. of concentrated ammonium hydroxide solution was heated for 12 hours at 70° in a glass-lined pressure vessel. The container was cooled and opened and its contents diluted with 25 ml. of alcohol. The solution was boiled with charcoal (Darco), filtered, and evaporated to dryness but only ammonium bromide remained. The charcoal was extracted with 25 ml. of benzene; now upon evaporation of this solvent, there remained 1.8 g. (95% yield) of the short, white crystals of 4-amino-6-bromo-2-ethylpyrimidine; m.p. 142.5° (corr.).

Anal. Calc'd for $C_6H_8BrN_3$: Br, 39.60. Found: Br, 39.59.

Attempts failed to prepare this amino-bromo compound by the sodium amide in liquid ammonia treatment; both bromine atoms were removed, as was demonstrated by quantitative conversion into silver bromide. The utilization of alcoholic ammonia solutions at 70°, with periods of warming varied from 2 to 12 hours, resulted in the production of mixtures of the amino-bromo compound and the diamino derivative.

Preparation of 6-amino-2-ethyl-4(3)-pyrimidone. To obtain this derivative, 4 g. of

6-bromo-2-ethyl-4(3)-pyrimidone and 50 ml. of concentrated ammonium hydroxide were warmed at 100° for 24 hours in a glass-lined pressure vessel. After the latter was cooled, it was opened; the liner contained a mass of white, short, needle-like crystals. Upon heating the mixture, the crystals redissolved, the solution was decolorized with charcoal (Darco), and concentrated to regain crystalline material. The latter was filtered off and recrystallized from hot water. Thus was obtained 2.35 g. (86% yield) of the aminopyrimidone, melting with decomposition at 245° (corr.). In another preparation carried out at 110°, the yield was but 20%.

Anal. Calc'd for $C_6H_9N_3O$: N, 30.22. Found: N, 30.60.

SUMMARY

2-Ethyl-4,6(1,5)-pyrimidinedione has been resynthesized and converted into five new bromo and/or amino pyrimidine derivatives.

AUSTIN, TEXAS

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