TABLE I

YIELDS OF PIPERAZINE UNDER VARIOUS REACTION CONDITIONS

Reagent	G.	Solvent	Temperature, °C.	Time, hr.	Yield of piperazine, g.	Yield %
Diethylenetriamine	103	None	Reflux	10	46	53
Diethylenetriamine		Tetrahydronaphthalene	Reflux	12	53	62
Diethylenetriamine		None	150, autoclave	8	33	38
Diethylenetriamine		Dipentene	160, autoclave	8	63	73
Diethylenetriamine		Xylene	Reflux	7	15	17
Diethylenetriamine		Dioxane	160, autoclave	7	28	32
Ethylenediamine	60	Tetrahydronaphthalene	150, autoclave	6	17	39

ments were repeated using ethylenediamine instead of diethylenetriamine. The formation of piperazine from ethylenediamine probably resulted through preliminary formation of diethylenetriamine which then condensed to form piperazine as described above.

$$2H_2NCH_2CH_2NH_2 \longrightarrow H{-}N\begin{matrix}CH_2{-}CH_2{-}NH_2\\ \diagdown\\ \diagup\\ CH_2{-}CH_2{-}NH_2\end{matrix} + NH_3$$

The piperazine was isolated as white crystals upon distillation and was identified in each case as the dibenzoyl derivative.

Experimental

The experimental conditions are summarized in Table I. Ethylenediamine and diethylenetriamine were purified by drying the commercial material over potassium hydroxide pellets and subsequent fractional distillation. Ethylenediamine was collected between 117 and 119°, while the diethylenetriamine used distilled from 83 to 86° at 3 mm. pressure. All solvents were dried and purified by distillation with the exception of dioxane which was first refluxed with sodium and aniline and then distilled. In each of the reactions listed in Table I, 10 g. of Raney nickel was used.

The reaction mixture was fractionally distilled in each case to remove solvent and separate the products. The piperazine was isolated as colorless prisms, all samples melting within a few degrees of 100°. In each case the dibenzoyl derivative was prepared. The melting points of the dibenzoyl derivatives of each reaction product ranged from 193 to 195°. In all cases, a mixed melting point with an authentic sample of dibenzoylpiperazine showed no depression.

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Summary

Experimental conditions for the preparation of piperazine by catalytic deamination of diethylenetriamine and of ethylenediamine are described.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Pyrimidine. II. Amino Alcohols Derived from Pyrimidine[1]

BY RAY A. CLARKE AND BERT E. CHRISTENSEN

This laboratory has previously synthesized[2] a number of amino alcohols with this substituent in the 5 position of pyrimidine nucleus, by the application of the Mannich reaction to various 5-acetylpyrimidines.

The usual methods for the preparation of such compounds involve the Mannich reaction on the acetyl derivative or the coupling of the bromomethyl ketone with the desired amine. The bromomethyl ketones are prepared either by direct bromination of the acetyl derivative or by means of the Arndt–Eistert reaction. Whenever possible, this latter method is preferable since it utilizes the acid rather than the less common acetyl derivative of the desired nucleus. Furthermore, there is less possibility of brominating other positions in the molecule and hence fewer separations and characterization problems.

Several 4-pyrimidinecarboxylic acid derivatives have been reported.[3,4,5] In this laboratory, 5-methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid was prepared in 50 to 60% yield from sodio diethyloxalpropionate and benzamidine. The acid in this instance was obtained directly in contrast to the diethyl oxalacetate condensation described by both Pinner[3] and Rappeport.[4]

5 - Methyl - 6 - oxo - 2 - phenyl - 4 - pyrimidinecarboxylic acid I was readily converted through the series of intermediates, 6-chloro-5-methyl-2-phenylpyrimidine-4-carbonyl chloride II → 4-bromoacetyl - 6 - chloro - 5 - methyl - 2 - phenylpyrimidine III → 4-(2-diethylamino-1-oxoethyl)-6-chloro-5-methyl-2-phenylpyrimidine hydrochloride IV to the amino alcohol, 4-(2-diethylamino-

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(2) Bruce Graham, A. M. Griffith, C. S. Pease and B. E. Christensen, THIS JOURNAL, **67**, 1294 (1945).

(3) A. Pinner, *Ber.*, **22**, 2615 (1889).

(4) T. Rappeport, *Ber.*, **34**, 1986 (1901).

(5) T. B. Johnson and K. G. Mackenzie, *Am. Chem. J.*, **42**, 365 (1909).

1 - hydroxyethyl) - 6 - chloro - 5 - methyl - 2-phenylpyrimidine hydrochloride V. These reactions were all straight-forward, giving good yields of crystalline intermediates. The free base of the amino ketone as is frequently the case was rather unstable.

Experimental

5-Methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic Acid (I).—An aqueous solution of sodio diethyloxalpropionate was prepared according to the directions of Johnson and Mackenzie[5] except that benzene was substituted for ether as the solvent. To the aqueous solution was added 34.8 g. (0.22 mole) of benzamidine hydrochloride and a solution containing 21 g. (0.445 mole, assuming 85% purity) of sodium hydroxide. The mixture was allowed to stand for one hour. A small amount of solid material was filtered off. The filtrate was acidified with concentrated hydrochloric acid causing a precipitate to form. After cooling in the refrigerator the white- to tan-colored solid was filtered by suction, washed with water, and dried. The yield of acid was 27 g. (53%). This acid was purified for analysis by dissolving in dilute alkali, decolorizing with charcoal, and reprecipitating with hydrochloric acid. The acid melted at 274° with decomposition.

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.35; N, 12.18; neutral equivalent, 230. Found: C, 62.35; H, 4.24; N, 12.29; neutral equivalent, 228.

6-Chloro-5-methyl-2-phenylpyrimidine-4-carbonyl Chloride (II).—Sixteen grams of I (0.07 mole) and 85.5 g. (0.42 mole) of phosphorus pentachloride were mixed and heated in an oil-bath at 130° for one hour. The mixture on cooling solidified to a solid mass. The acid chloride was extracted from the excess phosphorus pentachloride with warm dry ether. By partial evaporation and cooling of the ether, the acid chloride crystallized and was removed by filtration. The yield of very nearly pure acid chloride was 16 g. (86%). Thirteen and one-half grams of pure product was obtained by recrystallization from 50 ml. of heptane, m. p. 99–101°.

Anal. Calcd. for $C_{12}H_8Cl_2N_2O$: C, 54.0; H, 3.00; N, 10.49; Cl, 26.6. Found: C, 53.5; H, 3.36; N, 10.53; Cl, 26.4.

4-Bromoacetyl-6-chloro-5-methyl-2-phenylpyrimidine (III).—A solution of 12 g. of II (0.045 mole) in 60 ml. of dry benzene was added dropwise with stirring to 200 ml. of a cold benzene solution of diazomethane (0.135 mole). The reaction appeared to take place rapidly as evidenced by the vigorous evolution of nitrogen. The solution was allowed to warm up to room temperature and after standing for about one hour, the benzene was evaporated under reduced pressure. The solid residue was suspended in ether and 25 ml. of 48% hydrobromic acid was added slowly with stirring. The bromomethyl ketone precipitated and nitrogen was evolved. The crude product (13.0 g.) was removed by filtration. Some additional material was obtained by evaporation of the ether. This residue and crude product when combined and recrystallized from heptane, gave 12.6 g. (86% yield) of slightly yellow needles. For analysis a portion of this product was recrystallized twice from heptane after decolorizing with charcoal (m. p. 139–141°).

Anal. Calcd. for $C_{13}H_{10}BrClN_2O$: C, 47.93; H, 3.08; total halogen, 35.4. Found: C, 48.38; H, 3.39; total halogen, 35.4.

6-Chloro-4-chloroacetyl-5-methyl-2-phenylpyrimidine.—The chloromethyl ketone was prepared in a manner similar to the bromomethyl ketone. From 4.00 g. of the acid chloride was obtained 3.48 g. of the crystalline chloromethyl ketone, m. p. 155–156°. This was purified for analysis by recrystallization from heptane.

Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O$: N, 9.96; Cl, 25.2. Found: N, 10.02; Cl, 24.8.

6-Chloro-4-(2-diethylamino-1-oxoethyl)-5-methyl-2-phenylpyrimidine Hydrochloride (IV).—Two grams (0.00615 mole) of III was dissolved in 20 ml. of dry benzene and 1.26 ml. (0.0123 mole) of diethylamine were added dropwise. The formation of crystalline diethylamine hydrobromide was very rapid. After standing for fifteen minutes, the mixture was diluted with dry ether and the crystalline solid (0.82 g.) was filtered with suction and washed with dry ether.

Dry hydrogen chloride was passed into the filtrate to precipitate the condensate as the hydrochloride. The solid was filtered with suction and washed with dry ether. The weight of crude product was 2.15 g. This material after purification by three recrystallizations from isopropyl alcohol gave 0.61 g. of crystalline product, m. p. 170–178° (red melt).

Anal. Calcd. for $C_{17}H_{21}Cl_2N_3O$: N, 11.86; total Cl, 20.0; ionizable Cl, 10.0. Found: N, 12.10; total Cl, 20.0; ionizable Cl, 9.84.

6-Chloro-4-(2-diethylamino-1-hydroxyethyl)-5-methyl-2-phenylpyrimidine Hydrochloride (V).—The amino ketone (0.50 g.) was dissolved in 20 ml. of methanol and reduced in a low pressure hydrogenation apparatus at 34 pounds pressure using 30 mg. of platinum oxide catalyst. After about two hours the catalyst was removed by filtration and the solvent evaporated. The residue was taken up in 10 ml. of warm isopropyl alcohol and upon cooling deposited 0.29 g. of white solid. This product partially melted at 160°, resolidified and finally melted at 170–172°.

Anal. Calcd. for $C_{17}H_{23}Cl_2N_3O$: N, 11.80; total Cl, 19.9; ionizable Cl, 9.82. Found: N, 12.15; total Cl, 19.5; ionizable Cl, 9.95.

6-Chloro-4-(2-di-*n*-propylamino-1-oxoethyl)-5-methyl-2-phenylpyrimidine Hydrochloride.—The condensation of the bromomethyl ketone with di-*n*-propylamine was carried out in the same manner as that with diethylamine. From 2.00 g. (0.00615 mole) of the bromomethyl ketone, 1.85 g. of crude amino ketone hydrochloride was obtained. This was recrystallized twice from a minimum amount of isopropyl alcohol yielding 0.85 g. of product, m. p. 170–178° (red melt).

Anal. Calcd. for $C_{19}H_{25}Cl_2N_3O$: N, 11.00; total Cl, 18.6; ionizable Cl, 9.28. Found: N, 11.06; total Cl, 18.3; ionizable Cl, 9.45.

6-Chloro-4-(2-di-*n*-propylamino-1-hydroxyethyl)-5-methyl-2-phenylpyrimidine Hydrochloride.—The reduction to the di-*n*-propylamino alcohol was carried out in the same way as that given for the preparation of the diethylamino alcohol. This amino alcohol crystallized very slowly with low recovery from a minimum of isopropyl alcohol; from 0.50 g. of the amino ketone was obtained 0.20 g. of solid product, m. p. 180–181°.

Anal. Calcd. for $C_{19}H_{27}Cl_2N_3O$: N, 10.94; total Cl, 18.5; ionizable Cl, 9.23. Found: N, 11.33; total Cl, 18.3; ionizable Cl, 9.18.

Summary

4-Bromo(and chloro)-acetyl-6-chloro-5-methyl-2-phenylpyrimidine were prepared by application of the diazomethane synthesis to the acid chloride prepared from 5-methyl-6-oxo-2-phenyl-4-pyrimidinecarboxylic acid.

The amino alcohols, 6-chloro-4-(2-di-*n*-propylamino-1-hydroxyethyl)-5-methyl-2-phenylpyrimidine hydrochloride, 6-chloro-4-(2-diethylamino-1-hydroxyethyl)-5-methyl-2-phenylpyrimidine hydrochloride, were prepared by coupling the bromoacetylpyrimidine with the appropriate secondary amine and subsequent reducing of the amino ketones.

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