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

# PYRIMIDINES. IV. THE SYNTHESIS OF SEVERAL NEW CHLORO SUBSTITUTED PYRIMIDINES[1]

ROLAND K. ROBINS, K. L. DILLE, AND BERT E. CHRISTENSEN

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Interest in a source of chloropurines led this laboratory to apply chlorination procedures to the purinones in the presence of tertiary amines; however, dialkylamine substituted purines were (1) obtained in place of the desired product. For this reason the investigation turned to a study of the 4,5-diaminochloropyrimidines as possible intermediates for the preparation of the chloropurines.

The preparation of the necessary chloropyrimidines (2–4) has been described in the literature with the exception of 2,4,6-trichloro-5-nitropyrimidine (I) which for unknown reasons (3) cannot be obtained from 5-nitrobarbituric acid even by chlorination in the presence of dimethylaniline. In this laboratory, however, it was found that chlorinations at room temperature in the presence of diethylaniline gave yields of up to 20% of the desired product (See Fig. 1.)

Amination of I at 0° in absolute ether saturated with dry ammonia yielded exclusively 2,6-dichloro-4-amino-5-nitropyrimidine (II), while amination at 20° in ethanol gave 2-chloro-4,6-diamino-5-nitropyrimidine (III). These reactions demonstrate the marked influence of the 5-nitrosubstituent on the reactivity of the 4-, and 6- as contrasted with the 2- position.

The influence of the nitro substituent was again demonstrated during the amination of 2,4-dichloro-5-nitropyrimidine which yields a 4-amino derivative. In the case of 2,4,6-trichloropyrimidine it is the 2-chloro which is the more reactive and is replaced upon treatment with alcoholic ammonia at room temperature.

Reduction of I using Raney nickel gave 2,4,6-trichloro-5-aminopyrimidine (IV) in good yield. The reactivity of the 4- and 6- positions was markedly altered by the conversion of the 5-nitro to the 5-amino substituent. This was indicated when IV boiled with aqueous ammonia resulted in the replacement of the 2-chloro substituent to yield 2,5-diamino-4,6-dichloropyrimidine (V). That it was the 2-chloro that reacted was indicated when a mixture melting point test with an authentic sample of 2,6-dichloro-4,5-diaminopyrimidine (2) was depressed over 30°. The relative unreactivity of the chlorine atoms adjacent to the 5-amino group was again demonstrated when 4,6-dichloro-5-aminopyrimidine prepared by the reduction of 4,6-dichloro-5-nitropyrimidine was recovered almost quantitatively after boiling with 15% aqueous ammonia for 30 minutes.

The 2-chloro-(4), the 2,6-dichloro-4,5-diaminopyrimidine, and 2-chloro-4,5,6-triaminopyrimidines (2) were prepared and subjected to formylation and

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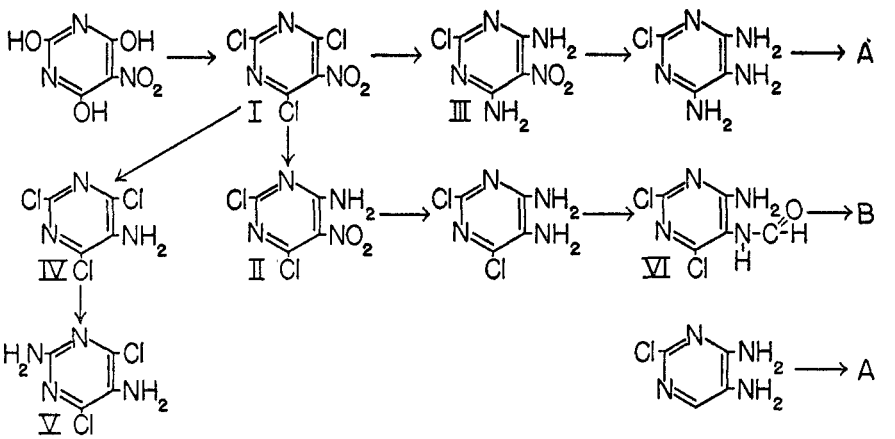


FIGURE ONE

cyclization procedures. Some time ago this laboratory noted that 4,5-diamino-6-chloropyrimidine loses its chlorine on formylation, and on cyclization yields hypoxanthine (5). In the case of the monochlorosubstituted pyrimidines mentioned the chloro substituent did not survive either the formylation or the direct cyclization of its sulfate salt. In contrast to this behavior a 2,6-dichloro-4,5-diaminopyrimidine was sufficiently stable so that it yielded the 2,6-dichloroformyl derivative (VI). Cyclization of the formyl derivative, however, resulted in a mixture containing an appreciable amount of xanthine as judged by u.v. absorption data and chlorine analysis.

## EXPERIMENTAL

*2,4,6-Trichloro-5-nitropyrimidine* (I). In a one-liter round bottom flask was placed 100 ml. of redistilled phosphorus oxychloride and 25 g. of anhydrous 5-nitrobarbituric acid (6). The flask was then cooled in an ice-bath and 65 g. of diethylaniline (free from mono) was added dropwise to the stirred reaction mixture at such a rate that the temperature was maintained between 25–30°. This addition required about 30 minutes, after which the ice-bath was removed and replaced by a water-bath. The water-bath was warmed slowly so that the temperature of the reaction mixture was maintained between 45–50° for 25 minutes. The crude reaction mixture was then poured onto 1000 g. of chopped ice and the resulting aqueous solution was extracted four times with 300 ml. of ether each time. The combined ethereal solution was washed with 300 ml. of water and dried with sodium sulfate. Distillation of the ether gave 8.0 g. of crude 2,4,6-trichloro-5-nitropyrimidine. This crude material was extracted three times with 50 ml. of boiling heptane per extraction. The combined heptane solution was boiled with a little Norit and filtered and evaporation of the heptane left 6.6 g. of a slightly yellow crystalline solid m.p. 55–57°, yield 20.2%. This product was

readily purified further by sublimation under reduced pressure, to give colorless needles, m.p. 57–58°.

*Anal.* Calc'd for $C_4Cl_3N_3O_2$: Cl, 46.5; N, 18.38.

Found: Cl, 46.4; N, 18.29.

*2,6-Dichloro-4-amino-5-nitropyrimidine* (II). A solution of 1.0 g. of 2,4,6-trichloro-5-nitropyrimidine in 100 ml. of dry ether was cooled to 0° and added slowly to 100 ml. of a dry saturated ammonical solution maintained at 0°. The ethereal solution was kept at 0° for one hour and the excess ether and ammonia were evaporated from the cooled solution. The residue was then extracted with 40 ml. of boiling benzene. The cooled benzene solution yielded 0.3 g. of a yellow crystalline solid m.p. 162–164°; a second recrystallization from benzene gave a product m.p. 164–165°. Bitterli and Erlenmeyer (2) give 152° as the m.p. of this compound. A sample prepared by the method of Bitterli and Erlenmeyer and purified by soxhlet extraction with $CCl_4$, followed by recrystallization from benzene gave a product, m.p. 164–165°. No depression on mixture melting point.

*Anal.* Calc'd for $C_4H_2Cl_2N_4O_2$: N, 26.8. Found: N, 26.7.

*2-Chloro-4,6-diamino-5-nitropyrimidine*[2] (III). 2,4,6-Trichloro-5-nitropyrimidine (4 g.) dissolved in 20 ml. of absolute ethanol was added to 20 ml. of absolute ethanol saturated with dry ammonia. The solution was allowed to stand for one hour at room temperature and then filtered and washed with a little water to dissolve all the ammonium chloride. The yield was 3.0 g. of a white amorphous powder m.p. dec. gradually above 300°. A small amount was recrystallized from acetic acid for analysis.

*Anal.* Calc'd for $C_4H_4ClN_3O_2$: N, 36.95. Found: N, 37.06.

*2,4,6-Trichloro-5-aminopyrimidine* (IV). To 40 ml. of 95% ethanol was added 3.0 g. of sublimed 2,4,6-trichloro-5-nitropyrimidine and 0.5 g. of Raney nickel catalyst. The solution was hydrogenated under a pressure of 10 lbs./sq. in. and allowed to shake for two hours. The Raney nickel was filtered from the solution while hot and the excess ethanol was evaporated with the aid of a hot-air fan. The slightly darkened residue was extracted with three 50-ml. portions of boiling *n*-heptane. The combined heptane solution was placed overnight in the refrigerator. The yield of slightly tan-colored needles was 2.8 g., m.p. 114–115°. A small amount was recrystallized from heptane again, m.p. 116–117°. (Colorless needles.)

*Anal.* Calc'd for $C_4H_2Cl_3N_3$: N, 21.16. Found: N, 21.4.

*2,5-Diamino-4,6-dichloropyrimidine* (V). To 50 ml. of concentrated ammonium hydroxide and 180 ml. of water was added 4.0 g. of 2,4,6-trichloro-5-aminopyrimidine. The solution was slowly heated to reflux and a slow stream of gaseous ammonia was bubbled into the solution. The temperature of the refluxing solution was 90–95°. The 2,4,6-trichloropyrimidine went into solution and the reaction mixture was refluxed for 30 minutes. The solution was then boiled with Norit and filtered. The colorless filtrate deposited upon cooling 2.1 g. of white needles, m.p. 260–261°. Recrystallization from water did not raise the m.p. The mixture m.p. with 2,6-dichloro-4,5-diaminopyrimidine (2) was below 230°.

*Anal.* Calc'd for $C_4H_4Cl_2N_4$: N, 31.3. Found: N, 31.15.

*4,6-Dichloro-5-aminopyrimidine.* 4,6-Dichloro-5-nitropyrimidine (7), m.p. 102° (3 g.) was dissolved in 40 ml. of 95% ethanol and approximately two g. (wet) of Raney nickel catalyst was added and the solution was shaken under a pressure of 10 lbs/sq. in. of hydrogen for three hours. The solution was then heated to boiling and the catalyst was filtered from the hot solution. The filtrate was then evaporated to dryness with the aid of a hot-air fan. The residue, which had a slightly brown color, was recrystallized from *n*-heptane. A yield of 2.1 g. of slightly colored needles, m.p. 146–147°, was isolated. A second recrystallization from *n*-heptane gave a m.p. of 147–148°.

*Anal.* Calc'd for $C_4H_3Cl_2N_3$: C, 29.3; H, 1.83; N, 25.6.

Found: C, 29.7; H, 2.04; N, 25.6.

It was noted that this compound did not react with hot 15% aqueous ammonia, but was recovered unchanged even after 30 minutes.

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[2] This compound was recently prepared by Bitterli and Erlenmeyer (2), from 5-nitro-2,6-dichloro-4-aminopyrimidine.

*2,6-Dichloro-4-amino-5-formylaminopyrimidine* (VI). A solution of 0.63 g. of 2,6-dichloro-4,5-diaminopyrimidine (2) in 5 cc. of formic acid (98–100%) was gently refluxed 15 minutes. The excess formic acid was evaporated and the residue was recrystallized from a hot ammonical solution (*p*H 8) to give 0.3 g. (41%) of tan powder, m.p. 213–215°. This was recrystallized from water to give material of m.p. 216–217°.

*Anal.* Calc'd for $C_5H_4Cl_2N_4O$: N, 27.05; Cl, 34.3.
Found: N, 27.1; Cl, 34.0.

*2-Chloro-4,5-diaminopyrimidine sulfate.* 2-Chloro-4,5-diaminopyrimidine (4) was dissolved in 20 cc. of 5% $H_2SO_4$ and cooled and filtered. Yield, 0.6 g. (45%).

*Anal.* Calc'd for $C_8H_{12}Cl_2N_8O_4S$: N, 28.94; Cl, 18.3.
Found: N, 28.7; Cl, 18.2.

SUMMARY

Procedures for the preparation of several amino-chloropyrimidines together with chlorination of 5-nitrobarbituric acid are given. The cyclization of the chloro substituted-4,5-diaminopyrimidines to the corresponding purines was unsuccessful. The 2,6-dichloro-4,5-diaminopyrimidine was the only chlorinated-4,5-diaminopyrimidine which yielded a formyl derivative containing the original chlorine content.

CORVALLIS, OREGON

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