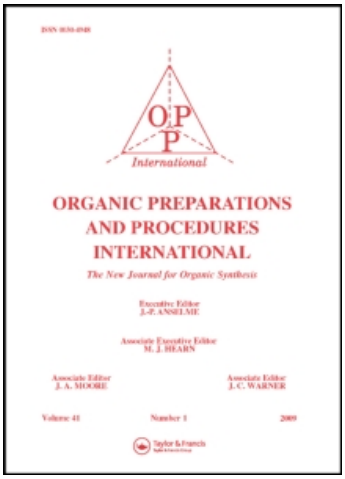

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SOME NEW PYRIMIDINE DERIVATIVES

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SOME NEW PYRIMIDINE DERIVATIVES[1]

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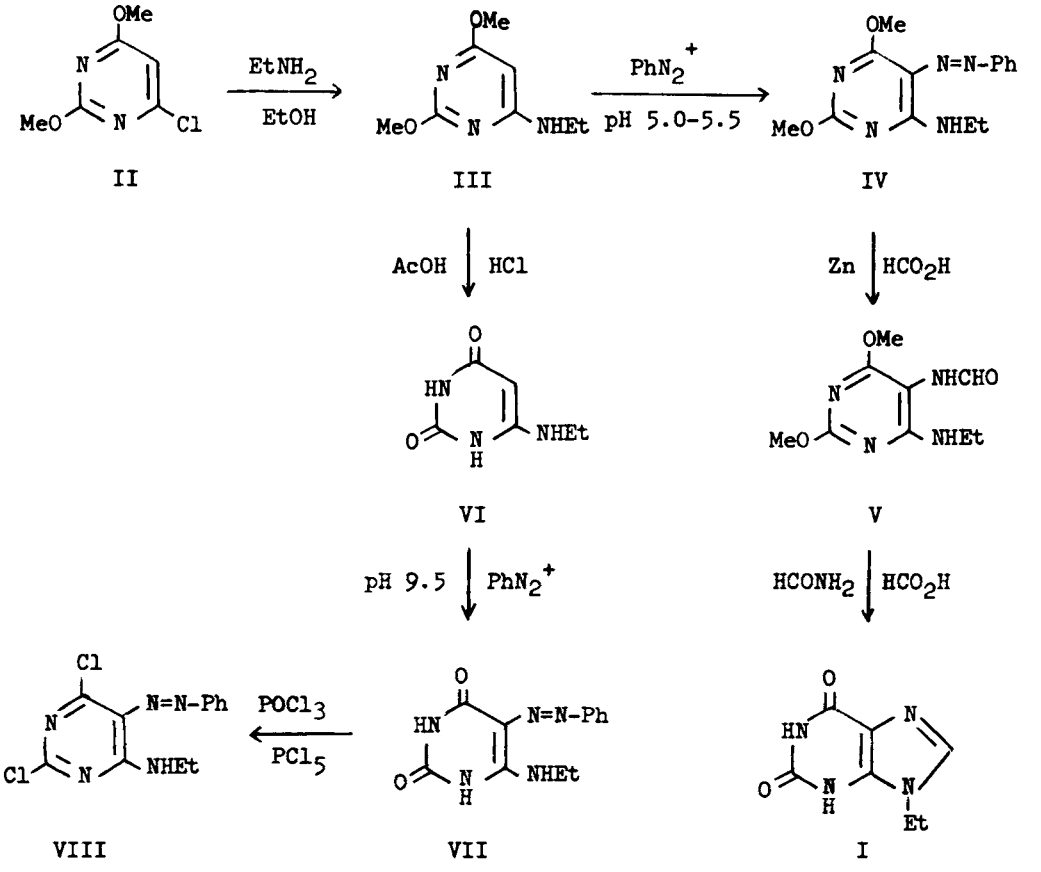

During the course of an unambiguous synthesis of 9-ethylxanthine (I),[2] we prepared several new pyrimidines (III, IV, V, VII, and VIII), as outlined in the scheme. It should be noted that all attempts to reduce 6-ethylamino-5-phenylazouracil (VII) to the corresponding diamine or to

reduce VII and cyclize to I in a single operation were unsuccessful. Also, the dichlorophenylazo compound VIII, prepared from VII, could not be reduced to the diamine or converted into 2,6-dichloro-9-ethylpurine.

EXPERIMENTAL[3]

4-Ethylamino-2,6-dimethoxypyrimidine (III).- Into a stainless steel bomb was added 25 g (0.14 mole) of II,[4] 120 ml of 95% ethanol, and a solution of 17.7 g (0.42 mole) of ethylamine in 100 ml of 95% ethanol. The mixture was heated in the autoclave for 17 hr at 110-120°. The red, slightly fluorescent reaction solution was cooled overnight in the freezer; a small quantity of light brown solid which separated was discarded. The filtrate was concentrated under vacuum and cooled. The pale white solid which precipitated was collected, washed with water, and dried (19.4 g). This material was crystallized twice from 40% aqueous ethanol to give 17.2 g (67%) of product, mp. 96-97°.

Anal. Calcd. for $C_8H_{13}N_3O_2$: C, 52.44; H, 7.15; N, 22.94. Found: C, 52.30; H, 7.14; N, 22.86.

4-Ethylamino-2,6-dimethoxy-5-phenylazopyrimidine (IV).- A solution of 5.0 g (0.027 mole) of III in 500 ml of 20% acetic acid was prepared and cooled to +4°. The pH was adjusted to 4.5 by the addition of solid sodium acetate. To this solution was added a solution of benzenediazonium chloride prepared by the action of 1.97 g (0.029 mole) of sodium nitrite on 2.61 g (0.028 mole) of aniline dissolved in 40 ml of 2 N hydrochloric acid at 0-3°; urea was added to destroy excess nitrous acid. Immediately upon admixture, solid sodium acetate was added to bring the pH back to 5.0-5.5. The bright yellow reaction mixture was allowed to warm gradually to room temperature and was then stirred overnight. The brown precipitate was collected, washed thoroughly with water and dried. The product was purified by precipitation from an ethanolic solution after charcoal treatment

by the addition of water until turbidity. The orange solid was collected and dried (2.78 g, 36%), mp. 109-110°.

Anal. Calcd. for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.97; N, 24.38. Found: C, 58.70; H, 6.03; N, 24.33.

N-(4-Ethylamino-2,6-dimethoxy-5-pyrimidinyl)formamide (V).- A solution of 4.3 g (0.015 mole) of IV in 200 ml of a mixed solvent composed of water, formic acid, and methanol (1 : 2 : 7 by volume) was added dropwise, with vigorous stirring, to 9.7 g (0.15 mole) of zinc dust. Addition required 30 minutes, during which time the temperature was held at 55°. After complete addition, the reaction was stirred at 55° for an additional hr. The supernatant was poured into 200 ml of water and the pH of the resulting solution was adjusted to 8 by the addition of solid sodium carbonate. Methanol was evaporated from the solution (rotary evaporator) and the aqueous solution was extracted several times with 40 ml portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate. Evaporation of the chloroform left an oil, which, upon trituration under ether, hardened to a white solid. When ether was added to a solution of this material in a minimal volume of chloroform there were formed long silky white needles, mp. 145-145.5° (850 mg, 25%); IR: ν max (KCl) 1725 cm^{-1} (carbonyl); NMR ($CDCL_3$): δ 1.20 (3H triplet, J = 15 Hz), 3.47 (2H multiplet, J = 27 Hz), 3.88 and 3.90 (6H, 2 close singlets), 5.42 (1H, broad), 7.13 (1H broad), and 8.28 (1H singlet) ppm.

Anal. Calcd. for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.24; N, 24.76. Found: C, 48.50; H, 6.22; N, 24.86.

9-Ethylxanthine (I).- A mixture of 950 mg (3.8 mmoles) of V, 1.5 ml of formamide, and 0.5 ml of formic acid was heated at reflux with stirring for 4 hr. The still hot reaction mixture was poured into 10 ml of ice water and the resulting solution was evaporated as completely as possible

until only an oily residue remained; ethanol was added during the evaporation to ensure removal of water by azeotropic distillation. The oily residue was taken up in a small volume of ethanol; ether was added and a solid separated. The material was collected, dried, and crystallized from ethanol-ether to give 600 mg (80%) of I. The infrared spectrum showed strong amide carbonyl absorption and the nmr spectrum confirmed the loss of the methoxyl groups; NMR (CD_3OD): δ 1.40 (3H, t, $\underline{J}$ = 15 Hz, $>NCH_2\underline{CH_3}$), 4.06 (2H, q, $\underline{J}$ = 24 Hz, $>N\underline{CH_2}CH_3$), 8.00 (1H, s, purine-8-H) ppm. The quantitative ultraviolet spectrum compared favorably with the values reported for I by Koppel and Robins.[5]

6-Ethylaminouracil (VI).- A solution of 5.0 g (0.03 mole) of III in 450 ml of glacial acetic acid and 58 ml of 2 N hydrochloric acid was maintained at reflux for 1 hr. Evaporation of the reaction solution under reduced pressure left a yellow oil, which was dissolved in 25 ml of warm 60% aqueous ethanol. The resulting solution was cooled overnight in the refrigerator, and the off-white crystalline precipitate was collected. The crude product was washed thoroughly with water, dried, and crystallized from 95% ethanol (1.11 g, 27%), mp. 288-289° (lit.[6] mp. 288°). This material was identical with samples of VI prepared by ethylamination of 6-chlorouracil, as described by Pfleiderer and Nübel.[6]

6-Ethylamino-5-phenylazouracil (VII).- The coupling reaction was achieved at a constant pH of 9.5 in an ammonium hydroxide-ammonium chloride buffer, following a procedure previously described for the preparation of 2,4-diamino-6-mercapto-5-phenylazopyrimidine.[7] Two grams of VI gave 2.4 grams of product (77%) after crystallization from 60% ethanol. The product melted at 262-262.5° with decomposition; IR: ν max (KCl) 1660 cm^{-1} (amide carbonyl).

Anal. Calcd. for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.02.

Found: C, 55.27; H, 5.06; N, 26.82.

2,4-Dichloro-6-ethylamino-5-phenylazopyrimidine (VIII).- A mixture of 200 mg (0.8 mmole) of VII in 20 ml of phosphorus oxychloride containing 2 g of phosphorus pentachloride was heated at reflux for 45 hr with stirring. The deep red colored reaction mixture was cooled to room temperature and the major portion of phosphorus oxychloride was removed under vacuum. The residue was hydrolyzed, with external cooling, by the slow addition of crushed ice. An orange brown precipitate began to appear almost immediately and the resulting suspension was stirred for 1 hr in an ice bath. The solid (218 mg) was collected, washed with cold water, and dried. Two crystallizations from 95% ethanol afforded the product in analytical purity (126 mg, 55%), mp. 135-136°.

Anal. Calcd. for $C_{12}H_{11}Cl_2N_5$: C, 48.66; H, 3.74; Cl, 23.94; N, 23.65. Found: C, 48.37; H, 3.86; Cl, 23.81; N, 23.81.

When freshly distilled phosphorus oxychloride was used in this preparation, it was necessary to add one or two drops of water to the reaction mixture prior to heating in order to obtain good yield of product.

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(1) This investigation was supported in part by research grant C6516 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

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