

Midwest Research Institute

## Pyrimidines. XIII. 2- and 6-Substituted 4-Pyrimidinecarboxylic Acids (1a)

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The "abnormal" behavior of 4,6-dimethyl-2-pyrimidinol towards nitrous acid has been clarified. The reaction between 4-methyl-2-pyrimidinol and nitrous acid has been utilized as a new synthetic procedure for the preparation of several 2-substituted 4-pyrimidinecarboxylic acids. 2-Hydroxy-4-pyrimidinecarboxylic acid has also been prepared from 4-chloro-2-methylthiopyrimidine *via* the trimethylammonium intermediate. 6-Amino- and 6-thio-4-pyrimidinecarboxylic acids have been readily prepared from the previously reported 6-hydroxy-4-pyrimidinecarboxylic acid.

More than 70 years ago, Evans (2) reported the production of a red, rather unstable substance on treating 4,6-dimethyl-2-pyrimidinol (I) with diazotized aniline in the presence of sodium acetate; no structure was assigned to this substance. At the turn of this century, Majima (3) noticed that when compound I was allowed to react with nitrous acid, and the intermediate boiled with water, a nitroso compound was obtained. This "abnormal" reaction of compound I toward nitrous acid also puzzled Lythgoe, Todd, and Topham (4) since it is well known that, in general, nitrosation will only occur at position 5 in pyrimidines which possess at least one hydroxyl or amino group at position 4 or 6 (5). Lythgoe *et al.* (4) also tried to repeat Evans' coupling reaction, but failed to react compound I with diazotized *p*-nitroaniline.

Behrend (6) reported the preparation of "diazois-nitroso methyluracil" (III) by the reaction of nitrous acid with 5-amino-6-methyluracil (II). Similar reactions involving the treatment of a properly substituted methyl group on a pyrimidine ring with nitrous acid to form oxime derivatives of pyrimidine-carboxaldehydes have also been reported by King and King (7) and Pfeleiderer and Mosthaf (8). This interesting reaction is by no means limited to the pyrimidine compounds. Ostrogovich *et al.*, (9) and more recently Grundmann and Mini, (10) have converted methyl-*s*-triazines into *s*-triazine aldoximes (11).

It is now obvious that the "red" or "deep red" products derived from 4,6-dimethyl-2-pyrimidinol (I) which had perplexed Evans (2), Majima (3) and Lythgoe *et al.* (4) are either the dioxime of 2-hydroxy-4,6-pyrimidinedicarboxaldehyde (12), or, under less vigorous conditions, the oxime of 2-hydroxy-6-methyl-4-pyrimidinecarboxaldehyde (IV). The position 5 of I, therefore, has not been affected by nitrous acid, which explains the failure of the attempted diazo-coupling (13) of I at position 5, as reported by Lythgoe *et al.* (4).

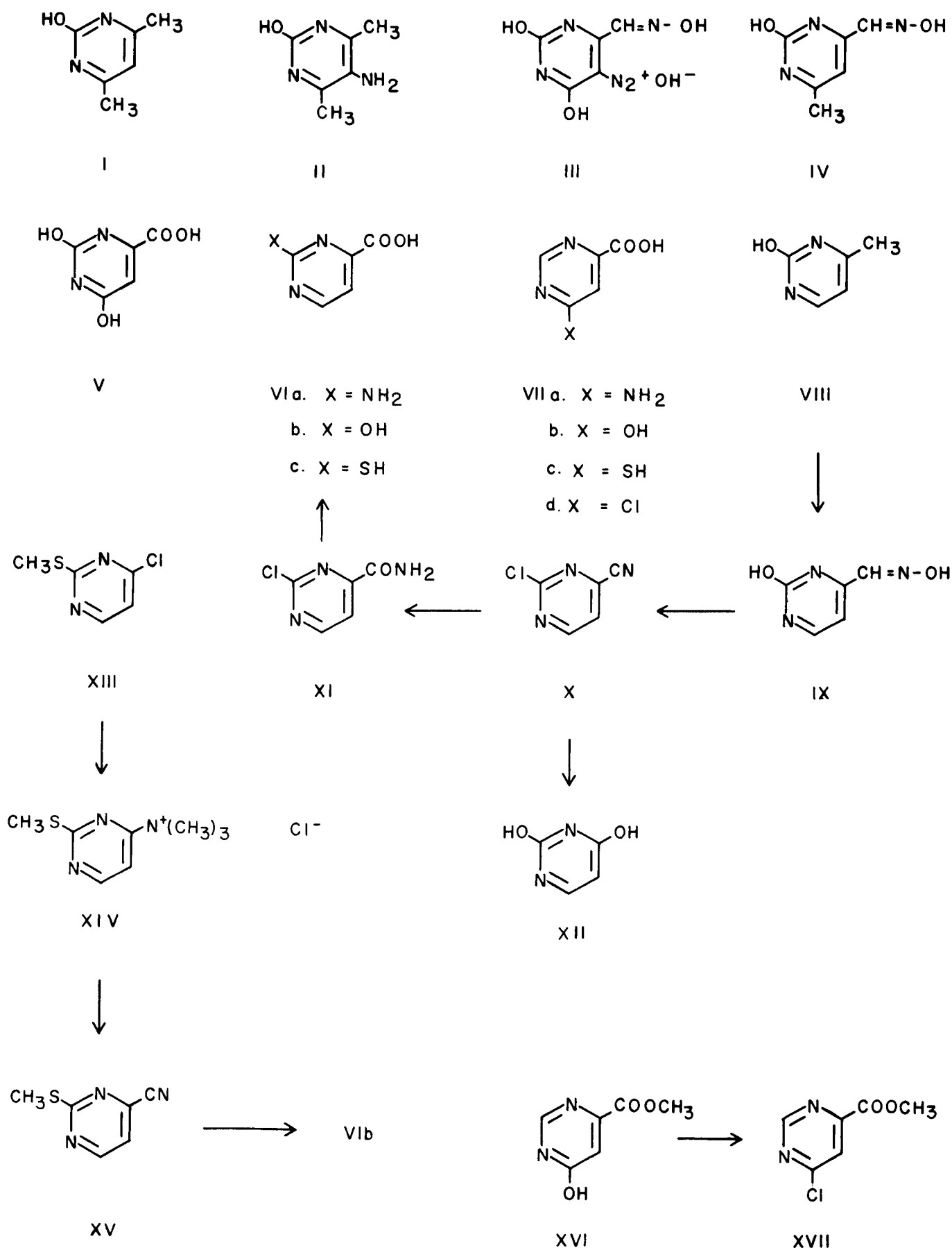
In connection with our investigation of orotic acid (V) analogs and other pyrimidinecarboxylic acids, (14, 15) closely related 4-pyrimidinecarboxylic acids with common hydrogen-bonding groups substituted at

either position 2 (VI) or position 6 (VII) of the pyrimidine ring were studied.

One of the frequently employed procedures for the preparation of pyrimidinecarboxylic acids is the direct oxidation of methyl or other alkyl substituted pyrimidines with potassium permanganate (16). Matsukawa and Shirakawa (17), for instance, prepared 2-amino-4-pyrimidinecarboxylic acid (VIa) from 2-amino-4-methylpyrimidine by oxidizing the styryl derivative of the latter. As permanganate oxidation often gave variable results, different synthetic approaches have been investigated in our laboratories. It has now been found that the reaction  $-\text{CH}_3 \rightarrow -\text{CH}=\text{N}-\text{OH}$  can be conveniently extended for the preparation of carboxylic acids. Treatment of 4-methyl-2-pyrimidinol (VIII) (18) with nitrous acid produced the oxime of 2-hydroxy-4-pyrimidine-carboxaldehyde (IX) which underwent simultaneous chlorination and dehydration with phosphorus oxychloride to give 2-chloro-4-pyrimidinecarbonitrile (X). Cold, concentrated sulfuric acid then smoothly converted X into 2-chloro-4-pyrimidinecarboxamide (XI). It is of interest to note that vigorous hydrolysis of X gave uracil (XII) as a by-product. Treatment of XI with appropriate nucleophilic agents followed by basic hydrolysis of the amide group readily yielded the corresponding 2-substituted-4-pyrimidinecarboxylic acids (VIa-c).

The preparation of several pyrimidinyl trimethylammonium salts from chloropyrimidines (19) and the subsequent conversion to pyrimidinecarbonitriles (20) have been reported by Klötzer. Utilizing this synthetic approach 2-hydroxy-4-pyrimidinecarboxylic acid (VIb) can also be conveniently prepared by basic hydrolysis of 2-methylthio-4-pyrimidinecarbonitrile (XV), which was obtained from 4-chloro-2-methylthiopyrimidine (21) *via* the reaction sequence XIII  $\rightarrow$  XV. The product prepared by this method was found to be identical with compound VIb prepared by the nitrous acid synthetic route (22).

The preparation of the isomeric 6-hydroxy-4-pyrimidinecarboxylic acid (VIIb) has already been reported from our laboratories (14). Chlorination of VIIb with phosphorus oxychloride failed to give



pure 6-chloro-4-pyrimidinecarboxylic acid (VIIId). Esterification of VIIb and subsequent chlorination of the product XVI readily yielded methyl 6-chloro-4-pyrimidinecarboxylate (XVII). Treatment of XVII with aqueous ammonia at 130° followed by basic hydrolysis afforded 6-amino-4-pyrimidinecarboxylic acid (VIIa). The corresponding 6-thio analog, VIIc, was prepared by hydrolysis of the product of XVII and thiourea.

## EXPERIMENTAL

### 2-Hydroxy-6-methyl-4-pyrimidinecarboxaldehyde, oxime (IV).

To a suspension of 10.0 g. (0.062 mole) of 4,6-dimethyl-2-pyrimidinol hydrochloride (2, 3, 4) in 25 ml. of water was slowly added 4.0 g. (0.058 mole) of sodium nitrite dissolved in a small amount of water. The dark reaction mixture was stirred at room temperature for 3 hr. and the precipitated product separated by filtration. It was recrystallized from water to give 6.3 g. (66% yield) of tan solid, which decomposed rapidly at 286°.  $\lambda$  max (pH 1) 260 m $\mu$  ( $\epsilon$ , 8,600); 342 m $\mu$  ( $\epsilon$ , 10,300).  $\lambda$  max (pH 11) 244 (sh) ( $\epsilon$ , 9,200); 275 ( $\epsilon$ , 13,700); 334 m $\mu$  ( $\epsilon$ , 8,900).

*Anal.* Calcd. for C<sub>8</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>: C, 47.0; H, 4.6; N, 27.5. Found: C, 46.5; H, 4.5; N, 27.9.

### 2-Hydroxy-4-pyrimidinecarboxaldehyde, oxime (IX).

To a solution of 14.7 g. (0.1 mole) of 4-methyl-2-pyrimidinol hydrochloride (18) in 100 ml. of 50% acetic acid cooled at 15° was added 10.4 g. (0.15 mole) of sodium nitrite all at once, with vigorous stirring. An exothermic reaction occurred (temperature rose to ca. 40°) and a pale yellow solid precipitated. The reaction mixture was stirred at room temperature for 3 hr. after which the solid product was separated by filtration, washed with ice water and dried at 80°. Recrystallization from water gave 11.0 g. (79% yield) of analytically pure product which melted with rapid decomposition at 226°.  $\lambda$  max (pH 1) 220 ( $\epsilon$ , 9,900); 251 ( $\epsilon$ , 8,500); 330 m $\mu$  ( $\epsilon$ , 5,800);  $\lambda$  max (pH 11) 239 ( $\epsilon$ , 7,400); 274 ( $\epsilon$ , 11,100); 324 m $\mu$  ( $\epsilon$ , 8,600).

*Anal.* Calcd. for C<sub>8</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>: C, 43.2; H, 3.6; N, 30.2. Found: C, 43.2; H, 3.8; N, 29.8.

### 2-Chloro-4-pyrimidinecarbonitrile (X).

A mixture of 50 g. (0.36 mole) of IX in 200 ml. of cold phosphorus oxychloride was carefully warmed until a vigorous reaction commenced. Heating was quickly discontinued and soon a complete solution resulted. To this solution was added 25 ml. of N,N-dimethylaniline and the resulting dark solution was refluxed for 30 min. It was then cooled and added slowly to 1.5 kg. of crushed ice. The aqueous solution was extracted with ether (4 x 300 ml.). The combined extracts were washed successively with water (2 x 150 ml.), saturated sodium bicarbonate solution (2 x 100 ml.) and water (2 x 100 ml.), then dried over anhydrous sodium sulfate. Evaporation of the ethereal extract gave 36 g. (77% yield) of the crude product. Recrystallization from a mixture of ethyl acetate and heptane afforded 30 g. (60% yield) of analytically pure X, m.p. 50-51°.  $\lambda$  max (ethanol) 269 m $\mu$  ( $\epsilon$ , 4,200). The product failed to show a characteristic nitrile absorption at 2250 cm<sup>-1</sup> (24).

*Anal.* Calcd. for C<sub>5</sub>H<sub>2</sub>ClN<sub>2</sub>: C, 43.1; H, 1.4; N, 30.1. Found: C, 43.3; H, 1.9; N, 30.0.

### Reaction of 2-chloro-4-pyrimidinecarbonitrile with boiling alkali.

A suspension of 5.0 g. of X and 100 ml. of 2 N sodium hydroxide was heated under reflux for 1 hr. The resulting solution (25) was treated with charcoal, filtered, concentrated to 50 ml., and acidified to pH 4 with dilute hydrochloric acid to yield 1.7 g. (43% yield) of uracil (XII).

### 2-Chloro-4-pyrimidinecarboxamide (XI).

To 50 ml. of concentrated sulfuric acid cooled to 15° was slowly added 14.0 g. of X. After the addition was complete the mixture was allowed to stir at room temperature for 4 hr. The resulting solution was then added, with vigorous stirring, to 300 g. of crushed ice. The white precipitate was filtered and washed well with ice water. Recrystallization of the product from water gave 7.5 g. (47% yield) of white needles, m.p. 151-153°.  $\lambda$  max (pH 1) 267 m $\mu$  ( $\epsilon$ , 4,300);  $\lambda$  max (pH 11) 268 m $\mu$  ( $\epsilon$ , 4,300).

*Anal.* Calcd. for C<sub>5</sub>H<sub>4</sub>ClN<sub>2</sub>O: C 38.2; H, 2.5; N, 26.7. Found: C, 38.3; H, 2.8; N, 26.6.

### 2-Amino-4-pyrimidinecarboxylic acid (VIa).

A mixture of 15.8 g. of XI and 200 ml. of concentrated aqueous ammonia was treated in an autoclave at 130° for 5 hr. The cooled reaction mixture was evaporated to dryness and the residue dissolved in 100 ml. of 4 N sodium hydroxide solution. The solution was then refluxed for 1 hr., decolorized with charcoal and filtered. The filtrate was acidified to pH 4 with dilute hydrochloric acid. On cooling, the acid solution deposited 9.8 g. (70% yield) of analytically pure VIa, m.p. 275° (subl.).  $\lambda$  max (pH 1) 320 m $\mu$  ( $\epsilon$ , 4,200);  $\lambda$  max (pH 11) 306 m $\mu$  ( $\epsilon$ , 3,600). The product was found to be identical with that prepared by the oxidation method (17).

### 2-Thio-4-pyrimidinecarboxylic acid (VIc).

A mixture of 7.9 g. of XI, 7.9 g. of thiourea and 250 ml. of absolute ethanol was refluxed for 3 hr. The resulting solution was evaporated to dryness and the solid residue dissolved in 100 ml. of 4 N sodium hydroxide. The solution was boiled for 1 hr., treated with charcoal, and filtered. The filtrate was acidified to pH 1 with dilute hydrochloric acid. On cooling, an orange solid separated, which was isolated by filtration and recrystallized from water to give 2.9 g. (37% yield) of VIc.  $\lambda$  max (pH 1) 284 m $\mu$  ( $\epsilon$ , 17,000);  $\lambda$  max (pH 11) 230 ( $\epsilon$ , 5,800); 272 m $\mu$  ( $\epsilon$ , 15,800).

*Anal.* Calcd. for C<sub>5</sub>H<sub>4</sub>N<sub>2</sub>O<sub>2</sub>S: C, 38.4; H, 2.6; N, 17.8. Found: C, 38.1; H, 2.7; N, 17.6.

### (2-Methylthio-4-pyrimidinyl)trimethylammonium chloride (XIV).

To a solution of 20.0 g. of 4-chloro-2-methylthiopyrimidine (XIII) (21) in 100 ml. of anhydrous benzene was added 6 ml. of anhydrous trimethylamine. The mixture was shaken well and allowed to stand in a stoppered flask at room temperature for 24 hr. The resulting solid product was filtered, dissolved in ethanol, and reprecipitated with ether to give 24.9 g. (91% yield) of XIV. The product melted at 150-151° followed by resolidification, and then remelted at 205-206°.  $\lambda$  max (pH 1) 257 m $\mu$  ( $\epsilon$ , 16,000);  $\lambda$  max (pH 11) 257 m $\mu$  ( $\epsilon$ , 15,100).

*Anal.* Calcd. for C<sub>8</sub>H<sub>14</sub>ClN<sub>3</sub>S: C, 43.7; H, 6.4; N, 19.1. Found: C, 43.8; H, 6.4; N, 19.0.

### 2-Methylthio-4-pyrimidinecarbonitrile (XV).

A mixture of 20.0 g. of potassium cyanide and 35 g. of acetamide was heated at 80-90° in a hood. To the resulting melt was added 10 g. of XIV in small portions over a period of 30 min. After the addition was complete, the mixture was heated for an additional 30 min. at 80-90°. The flask was cooled to room temperature. The solidified mass was dissolved by adding a mixture of 100 ml. of water and 100 ml. of ether. The mixture was stirred for a few min. and the ether layer separated. The aqueous layer was then extracted with 5 x 100 ml. of ether. The combined ethereal extract was dried over anhydrous sodium sulfate, treated with decolorizing charcoal, and filtered. The solvent was evaporated *in vacuo* and the residue recrystallized from petroleum ether (b.p. 30-60°) to give 3.0 g. (44% yield) of XV, m.p. 81-82°.  $\lambda$  max (pH 1 and 11) 258 m $\mu$  ( $\epsilon$ , 5,400). The product gave a characteristic nitrile absorption at 2250 cm<sup>-1</sup> (in KBr pellets only).

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>3</sub>S: C, 47.7; H, 3.3; N, 27.7. Found: C, 47.5; H, 3.3; N, 27.4.

### 2-Hydroxy-4-pyrimidinecarboxylic acid (VIb). Method A.

A mixture of 15.8 g. of 2-chloro-4-pyrimidinecarboxamide (XI) and 500 ml. of 2 N sodium hydroxide was refluxed for 3 hr. The clear solution was treated with charcoal and filtered. The filtrate was acidified to pH 1 with dilute hydrochloric acid. On cooling, the precipitated product was separated by filtration. Recrystallization of the crude product from dilute ethanol gave 7.3 g. (52% yield) of analytically pure VIb, which slowly decomposed without melting above 180°.  $\lambda$  max (pH 1) 325 m $\mu$  ( $\epsilon$ , 6,000);  $\lambda$  max (pH 11) 224 ( $\epsilon$ , 8,100); 306 m $\mu$  ( $\epsilon$ , 4,600).

*Anal.* Calcd. for C<sub>5</sub>H<sub>4</sub>N<sub>2</sub>O<sub>3</sub>: C, 42.8; H, 2.9; N, 20.0. Found: C, 42.6; H, 2.9; N, 20.0.

### Method B.

Three grams of 2-methylthio-4-pyrimidinecarbonitrile (XV) were refluxed with 2 N sodium hydroxide for 4 hr. The solution was then mixed with ca. 1 g. of filter-aid and filtered. The filtrate was heated to boiling and acidified with hydrochloric acid. The solution was cooled and the light pink crystals filtered and recrystallized from dilute acetic acid to give 1.6 g. (58% yield) of off-white solid which slowly decomposed without melting above 180°. The product was found to be identical with that prepared by method A. No uracil was detected from the reaction mixture.

### Methyl 6-hydroxy-4-pyrimidinecarboxylate (XVI).

A stream of dry hydrogen chloride was bubbled through a stirred refluxing mixture of 50 g. of 6-hydroxy-4-pyrimidinecarboxylic acid (14) and 500 ml. of anhydrous methanol for 4 hr. The resulting solution was evaporated to ca. 250 ml. and cooled. The resulting

precipitate was filtered and the crude product recrystallized from a small amount of methanol to give 17 g. (31% yield) of XVI, m.p. 226-228°.  $\lambda$  max (pH 1) 285  $\mu$  ( $\epsilon$ , 4,200);  $\lambda$  max (pH 11) 294  $\mu$  ( $\epsilon$ , 3,500).

*Anal.* Calcd. for  $C_8H_8N_2O_3$ : C, 46.7; H, 3.9; N, 18.2. Found: C, 46.2; H, 4.0; N, 18.6.

Methyl 6-chloro-4-pyrimidinecarboxylate (XVII).

A mixture of 44 g. of XVI and 300 ml. of phosphorus oxychloride was refluxed for 3 hr. Excess solvent was removed *in vacuo* and the residual syrup added slowly to 1 kg. of crushed ice. The resulting cold, aqueous solution was extracted with ether (4 x 500 ml.) and the ethereal extract washed successively with water (2 x 250 ml.), saturated sodium bicarbonate solution (2 x 100 ml.) and water (2 x 250 ml.). After drying over anhydrous sodium sulfate the ethereal solution was evaporated to yield 35 g. of crude product, m.p. 56-60°. Recrystallization from petroleum ether (b.p. 40-60°) afforded 30 g. (61% yield) of analytically pure product, m.p. 60-61°.  $\lambda$  max (ethanol) 265  $\mu$  ( $\epsilon$ , 3,400).

*Anal.* Calcd. for  $C_8H_7ClN_2O_2$ : C, 41.7; H, 2.9; N, 16.3. Found: C, 41.5; H, 3.1; N, 16.3.

6-Amino-4-pyrimidinecarboxylic acid (VIIa).

A mixture of 17.3 g. of XVII and 200 ml. of concentrated aqueous ammonia was heated in an autoclave at 130° for 5 hr. The cooled solution was evaporated to dryness and the residue was dissolved in 100 ml. of 10% sodium hydroxide. The solution was boiled for 30 min., treated with charcoal, and filtered. The filtrate was acidified to pH 4 with dilute hydrochloric acid. On cooling, the acid solution deposited 5.9 g. (37% yield) of VIIa, m.p. 256-257°. Recrystallization from water gave a product with the same melting point.  $\lambda$  max (pH 1) 224 ( $\epsilon$ , 9,500); 280  $\mu$  ( $\epsilon$ , 3,800);  $\lambda$  max (pH 11) 230 ( $\epsilon$ , 11,500); 284  $\mu$  ( $\epsilon$ , 3,600).

*Anal.* Calcd. for  $C_5H_6N_2O_2 \cdot H_2O$ : C, 38.3; H, 4.5; N, 26.7. Found: C, 38.7; H, 4.5; N, 26.6.

6-Thio-4-pyrimidinecarboxylic acid (VIIc).

A mixture of 8.6 g. of XVII and 8.6 g. of thiourea in 150 ml. of absolute ethanol was refluxed for 2 hr. The product was isolated by a procedure similar to the preparation for IIc. Three and one-half grams (40% yield) of analytically pure VIIc was obtained as red-orange crystals, m.p. 247-248°.  $\lambda$  max (pH 1) 285 ( $\epsilon$ , 10,900); 363  $\mu$  ( $\epsilon$ , 7,200);  $\lambda$  max (pH 11) 280 ( $\epsilon$ , 10,000); (sh) 312  $\mu$  ( $\epsilon$ , 7,200).

*Anal.* Calcd. for  $C_5H_4N_2O_2S$ : C, 38.4; H, 2.6; N, 17.8. Found: C, 38.6; H, 2.7; N, 17.4.

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- (24) The fact that 2-chloro-4-pyrimidinecarbonitrile (VI) failed to show the characteristic nitrile absorption at 2250  $\text{cm}^{-1}$  is not without precedent. Sensi and Gallo (26) have reported that the presence of electron-withdrawing groups *ortho* or *para* to an aromatic nitrile group tends to reduce or diminish the intensity of nitrile bands.
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