Potassium carbonate was added until the solution became turbid and 2.5 g. of hydroxylamine hydrochloride was then added. The mixture was heated on the steam bath for 20 min., cooled, and filtered to yield 1.20 g. (84%) of oxime XII, m.p. 169–171°. When mixed with the sample obtained from XI above, the melting point was not depressed. The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.71; H, 8.75; N, 15.21; mol. wt., 184.2. Found: C, 58.69; H, 8.71; N, 15.22; mol. wt., 186.

The Synthesis of 2,4,6-Trisubstituted Pyrido[2,3-*d*]pyrimidines from 2-Amino-3,5-Dicyanopyridine[1]

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Reductive dehalogenation of 2-amino-3,5-dicyano-6-chloropyridine gave 2-amino-3,5-dicyanopyridine in good yield. This pyridine has been converted to 2-amino-5-cyano-3-pyridinecarboxamide, 2-amino-3,5-pyridinedicarboxamide, and 2-amino-3-carbethoxy-5-pyridinecarboxylic acid which were excellent precursors to 2,4,6-trisubstituted pyrido[2,3-*d*]pyrimidines. 2,4-Dihydroxy-6-cyanopyrido[2,3-*d*]pyrimidine, 2-amino-4-hydroxy-6-carbethoxypyrido[2,3-*d*]pyrimidine, and several related pyridopyrimidines have been prepared by these routes. Catalytic hydrogenation of 2-amino-5-cyano-3-pyridinecarboxamide gave 2-amino-5-aminomethyl-3-pyridinecarboxamide. The formation of several 2,4,6,7-tetrasubstituted pyrido[2,3-*d*]pyrimidines from 2,3,5,6-tetrasubstituted pyridine precursors is reported.

The availability of 2,3,5,6-tetra functionally substituted pyridines *via* 1,3-dinitrile cyclizations[3] has led us to the consideration of these substrates as intermediates for the synthesis of fused heterocyclic systems. This article reports the synthesis of several pyrido[2,3-*d*]pyrimidines *via* routes having advantages over those previously reported.

Although pyrido[2,3-*d*]pyrimidines are well known,[4–6] 6 functionally substituted pyrido[2,3-*d*]pyrimidines are comparatively rare. Oakes and Rydon have prepared 2,4-dihydroxy-6-methylpyrido[2,3-*d*]pyrimidine and the corresponding 2,4-dichloro compound, but were unable to convert the 6-methyl group to one of greater synthetic utility.[4] Recently, Bernetti, Mancini, and Price have synthesized a series of 2-amino-4-hydroxy-6 functionally substituted pyrido[2,3-*d*]pyrimidines from 2,4-diamino-6-hydroxypyrimidine.[5]

2-Amino-3,5-dicyano-6-alkylthiopyridines[7] and 2-amino-3,5-dicyano-6-chloropyridine (**2**)[8] were considered as potential precursors to 2-amino-3,5-dicyanopyridine (**1**),[8] a useful intermediate for the preparation of 6-substituted pyrido[2,3-*d*]pyrimidines (Scheme I). Conventional reductive desulfurization techniques involving Raney nickel had no effect on the alkylthiopyridines and attempted hydrolytic desulfurization of 2-amino-3,5-dicyano-6-ethylthiopyridine (**3**)[7] gave 2-hydroxy-5-cyano-6-ethylthio-3-pyridinecarboxamide (**4**).

Reductive dehalogenation of **2**, however, gave **1** in good yield. The choice of acid scavenger employed in this reaction was found to be important, since compound **2** reacted readily with pyridine to form N-(2-amino-3,5-dicyano-6-pyridyl)pyridinium chloride (**5**).

The behavior of **1** in aqueous base differed appreciably from that of similar pyridines. Under conditions where 6-substituted 2-amino-3,5-dicyanopyridines are hydrolyzed to the corresponding 5-cyano-3-pyridinecarboxamides (refluxing 0.1 *N* potassium hydroxide),[7] **1** gave the corresponding diamide **6**. Further, conditions under which 6-substituted 2-amino-3,5-dicyanopyridines were converted to the corresponding dicarboxylic acids (10 *N* potassium hydroxide) led to extensive tar formation with **1**. 2-Amino-3,5-pyridinedicarboxylic acid (**7**) was prepared under milder hydrolytic conditions (2.5 *N* sodium hydroxide).

Recent work,[9,10] dealing with strong solvation of nitrile groups in dimethyl sulfoxide suggested that selective hydrolysis of the 3-cyano group of **1** could be achieved. In **1**, preferred solvation of the 5-cyano group (more sterically free) can occur in dimethyl sulfoxide, leaving the 3-cyano group relatively less "protected" and more susceptible to hydrolysis. The reaction was observed to follow the predicted course in dimethyl sulfoxide–aqueous sodium hydroxide mixtures at room temperature, although yields of 2-amino-5-cyano-3-pyridinecarboxamide (**8**) were dependent upon base concentration. That the dimethyl sulfoxide plays a role is indicated by failure to observe monoamide formation in aqueous ethanol. The structure of **8** was established by condensation with diethyl carbonate to give 2,4-dihydroxy-6-cyanopyrido[2,3-*d*]pyrimidine (**9**).

Dicarboxylic acid (**7**) was readily converted to the diethyl ester **10**. Smaller amounts of the corresponding 3-monoester **11** and the 5-monoester **12** were also formed. The structures of the monoesters were determined by condensation with guanidine. Monoester **11** gave 2-amino-4-hydroxy-6-pyrido[2,3-*d*]pyrimidine carboxylic acid (**13**),[5] whereas monoester **12** gave a lower melting colorless solid which was clearly different. Mild saponification of diester **10** gave monoester **12** in excel-

(1) This investigation was supported by Public Health Service Research Grant No. CA-02857-08 from the National Cancer Institute.

(2) National Science Foundation Cooperative Fellow, 1962–1964.

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(4) V. Oakes and H. N. Rydon, *J. Chem. Soc.*, 4433 (1956).

(5) R. Bernetti, F. Mancini, and C. C. Price, *J. Org. Chem.*, **27**, 2863 (1962).

(6) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **77**, 2256 (1955).

(7) S. G. Cottis and H. Tieckelmann, *J. Org. Chem.*, **26**, 79 (1961).

(8) This compound has been reported recently; 3-amino-2-cyanoacrylonitrile was hydrogenated in the presence of 10% palladium on charcoal at 1000–1500 p.s.i. to give 2-amino-3,5-dicyanopyridine. See S. Trofimenko, *ibid.*, **28**, 2755 (1963).

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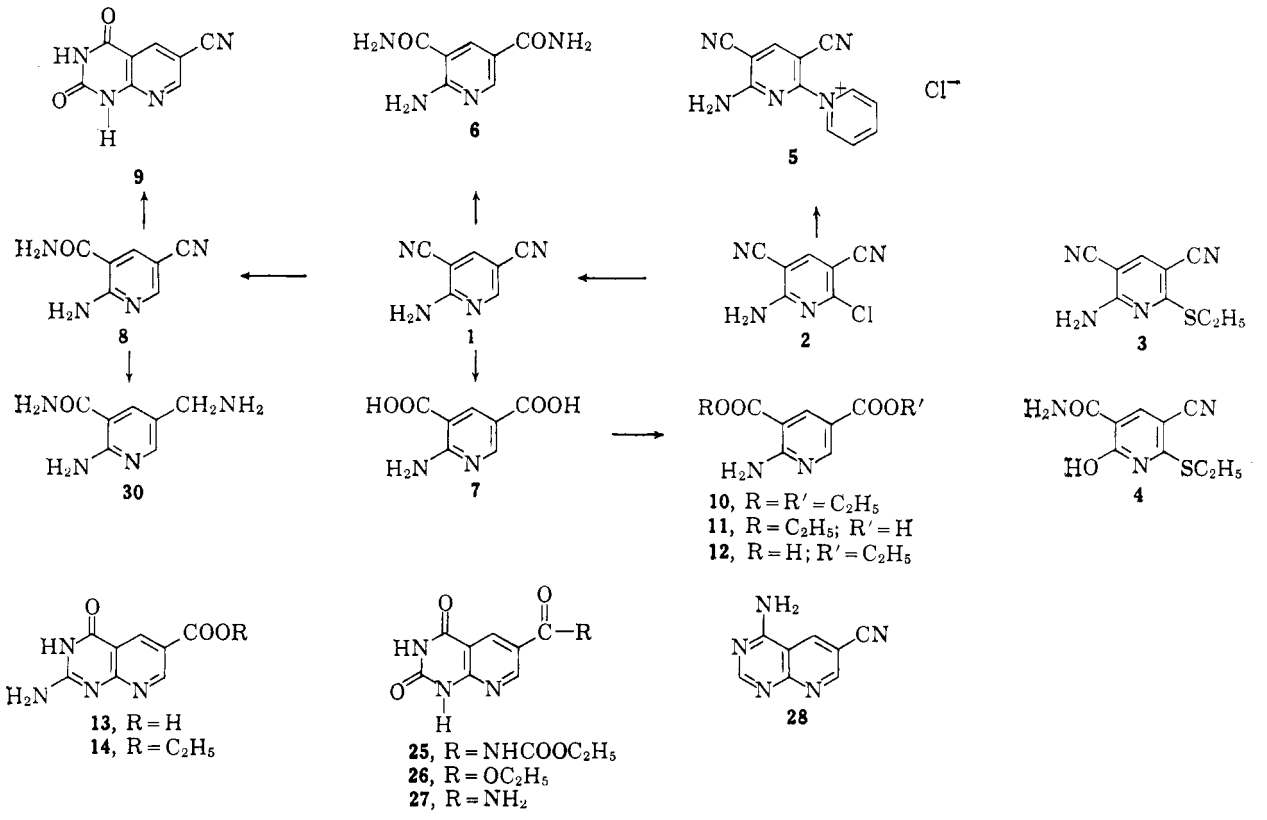
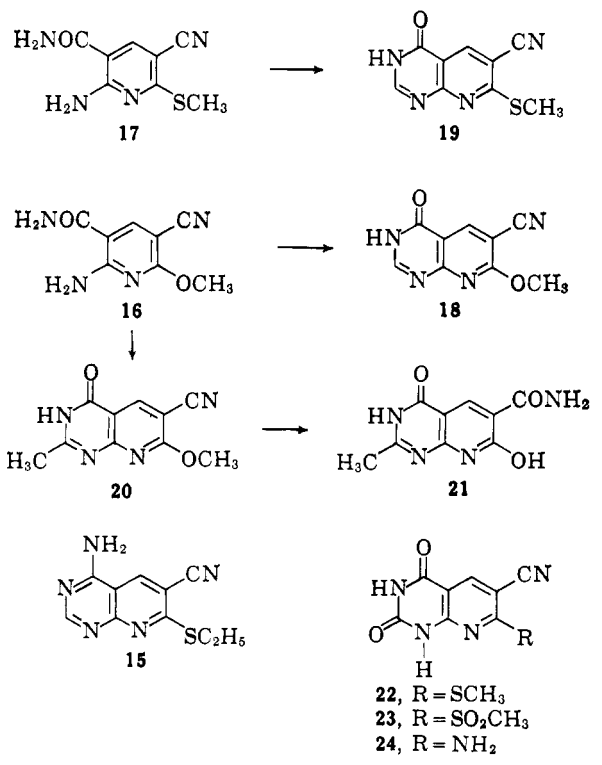
SCHEME I



lent yield. Carboxylic acid **3** gave the corresponding ethyl ester **14**[5] when treated with ethanol and sulfuric acid.

In model experiments when **3**[7] was heated with formamide, 4-amino-6-cyano-7-ethylthiopyrido[2,3-*d*]pyrimidine (**15**) was formed. 6-Methoxy- (**16**) and 6-methylthio-2-amino-5-cyano-3-pyridinecarboxamide (**17**)[7] reacted with triethyl orthoformate in acetic anhydride to give the corresponding 4-hydroxy-6-cyano-7-substituted pyrido[2,3-*d*]pyrimidines (**18** and **19**, Scheme II). Basic hydrolysis of 2-methyl-4-hydroxy-6-cyano-7-methoxypyrido[2,3-*d*]pyrimidine (**20**, prepared from **16** and triethyl orthoacetate) gave 2-methyl-4,7-dihydroxy-6-pyrido[2,3-*d*]pyrimidinecarboxamide (**21**). Thio ether **17** reacted with diethyl carbonate in the presence of sodium ethoxide to give 2,4-dihydroxy-6-cyano-7-methylthiopyrido[2,3-*d*]pyrimidine (**22**).

SCHEME II



In general, the 7-methylthiopyrido[2,3-*d*]pyrimidines with a cyano group in the 6-position were readily oxidized to the corresponding methyl sulfones. Compound **22**, for example, gave 2,4-dihydroxy-6-cyano-7-methylsulfonylpyrido[2,3-*d*]pyrimidine (**23**). These 7-methylsulfonylpyrido[2,3-*d*]pyrimidines readily reacted with ammonia yielding the corresponding 7-aminopyrido[2,3-*d*]pyrimidines. In this manner, 2,4-dihydroxy-6-cyano-7-aminopyrido[2,3-*d*]pyrimidine (**24**) was obtained from **23**.

Treatment of diamide **6** with diethyl carbonate gave 2,4-dihydroxy-6-(N-carbethoxycarboxamido)pyrido-[2,3-*d*]pyrimidine (**25**). The 6-N-carbethoxy structure is supported by the following: (1) resistance to hydrolysis in hot 1.0 *N* potassium hydroxide, (2) variations in the ultraviolet spectra with pH gave evidence for three ionizable hydrogens having approximate pK_a values of 7.5, 12.2, and 13.0. Ethanol and **25** in the presence of sulfuric acid gave 2,4-dihydroxy-6-carbethoxypyrido[2,3-*d*]pyrimidine (**26**). Treatment of **25** with hot acetic acid or refluxing wet dimethylformamide apparently gave 2,4-dihydroxy-6-pyrido-[2,3-*d*]pyrimidinecarboxamide (**27**). Although a satisfactory nitrogen analysis was not obtained for **27**, it was easily dehydrated to the corresponding nitrile with phosphorus oxychloride. This nitrile was identical with **9** prepared by treatment of monoamide **8** with diethyl carbonate. Hydrolysis of **9** regenerated the

TABLE I

Product	Yield, g. (%)	Recrystn. solvent	M.p., °C.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
10	14.0 (43.5)	Heptane	99–100	55.45	55.06	5.93	6.12	11.76	11.49
11	6.25 (22.2)	Dioxane–water	>300 dec.	51.44	51.42	4.79	5.14	13.33	13.09
12	3.0 (10.7)	Dioxane–water	248.5–250.0	51.44	51.25	4.79	4.82	13.33	13.07

amide **27** in good yield. Formamide and **1** gave 4-amino-6-cyanopyrido[2,3-*d*]pyrimidine (**28**).

Several methods were employed in attempts to convert the above pyridines to 5-aminomethyl or 5-formyl derivatives. Dinitrile **1** with lithium triethoxyaluminohydride[11] gave urea, resulting most likely from ring cleavage of a dihydro derivative of **1**. Bohlman and Bohlman have shown that 3,5-dicyanopyridine is reduced to 1,4-dihydro-3,5-dicyanopyridine with lithium aluminum hydride.[12] Reduction of diester **10** with lithium borohydride in diglyme under mild conditions[13] gave diethyl 1,2-dihydro-2-amino-3,5-pyridinedicarboxylate (**29**).

Structure **29** is supported by its n.m.r. spectrum: a triplet at τ 8.85 (intensity 6), methyl groups; two sharp singlets at 2.95 and 3.22 (intensity 2.1), ring protons at positions 4 and 6; singlet at 7.05 (intensity 1.7), primary amino group at position 2; complex multiplet at 6.03 (intensity 4.8), methylene groups and proton in 2-position. The secondary N–H proton (position 1) could not be discerned. Infrared and ultraviolet spectra were in accord with the dihydropyridine structure.

Catalytic hydrogenation of monoamide **8** over Raney nickel gave good yields of 2-amino-5-aminomethyl-3-pyridinecarboxamide (**30**). The chemistry of **30** as well as its applicability to the synthesis of pyrido[2,3-*d*]-pyrimidines is currently under investigation and will be discussed in the future.

Experimental[14]

2-Hydroxy-5-cyano-6-ethylthio-3-pyridinecarboxamide (4).—Two grams (9.8 mmoles) of **3**[7] in 50 ml. of concentrated hydrochloric acid was refluxed for 4 hr. Water (75 ml.) was added and the mixture was cooled in the refrigerator overnight. The solid which formed was collected and dissolved in about 100 ml. of 1.0 *N* potassium hydroxide. The solution was filtered and acidified with glacial acetic acid to give a yellow solid, 1.2 g. (56%).

An analytical sample was obtained by recrystallization from water–dimethylformamide, yielding long, yellow needles which melted at 256.5–258.5°.

Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.41; H, 4.05; N, 18.82. Found: C, 48.07; H, 3.97; N, 18.74.

N-(2-Amino-3,5-dicyano-6-pyridyl)pyridinium Chloride (5).—Five grams (28 mmoles) of **2**[3] in 75 ml. of pyridine was heated to 100°. The black solution was cooled overnight to give 5.0 g. (69.4%) of crude **5** which was washed well with acetone and ether. The crude salt was recrystallized several times from aqueous ethanol to give an analytical sample which melted with decomposition at 237–247°. The compound gave a positive ionizable halide test and was readily water soluble, but essentially insoluble in common organic solvents.

Anal. Calcd. for $C_{12}H_8ClN_5$: C, 55.92; H, 3.12; N, 27.18. Found: C, 55.71; H, 3.16; N, 27.36.

2-Amino-3,5-dicyanopyridine (1).—Triethylamine (40 ml.) and 0.5 g. of palladium chloride were added to a solution of 25.0 g. (140 mmoles) of **2** in 250 ml. of dimethylformamide. The mixture was then hydrogenated at a pressure of 45 p.s.i. for 1.5 hr. The catalyst and triethylamine hydrochloride were filtered off and washed well with acetone. The filtrate and acetone washings were then poured into 700 ml. of cold water and chilled overnight. Collection of the precipitate gave 16.0 g. (78%) of crude **1**. An analytical sample was recrystallized from toluene and decomposed above 221°. The infrared and ultraviolet absorption spectra agreed well with reported values[8]; $\lambda_{max}^{95\%\ EtOH}$ 269.4 mμ (ε 28,100).

Anal. Calcd. for $C_7H_4N_4$: C, 58.33; H, 2.80; N, 38.87. Found: C, 58.58; H, 2.37; N, 39.22.

2-Amino-3,5-pyridinedicarboxamide (6).—Compound **1** (2.5 g., 18.5 mmoles) was added to 150 ml. of 0.1 *N* potassium hydroxide and the mixture refluxed with stirring for 1.5 hr. The slightly turbid reaction mixture was filtered hot and slowly cooled. The resulting precipitate was isolated and dried to give 1.95 g. (62%) of **6**.

The analytical sample was obtained by recrystallization from water and melted at 290.5–292.0°.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.67; H, 4.47; N, 31.10. Found: C, 47.08; H, 4.35; N, 30.99.

2-Amino-3,5-pyridinedicarboxylic Acid (7).—Compound **1** (3 g., 22.2 mmoles) was refluxed with 150 ml. of 2.5 *N* sodium hydroxide for 1 hr. and filtered while hot. The pale yellow filtrate was acidified with dilute hydrochloric acid, giving a flocculent, colorless precipitate which was washed with water, ethanol, and ether, to give 3.0 g. (79%) of **7**. The diacid was reprecipitated several times from alkaline solution and the analytical sample was washed well with hot water, alcohol, and ether. Purified in this manner, **7** melted at 344.5–346.5° dec.

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.15; H, 3.33; N, 15.39. Found: C, 46.11; H, 3.42; N, 15.14.

2-Amino-5-cyano-3-pyridinecarboxamide (8).—Compound **1** (5.5 g., 40.7 mmoles) was dissolved in a mixture of 80 ml. of dimethyl sulfoxide and 40 ml. of 1.0 *N* sodium hydroxide and the mixture was stirred 1.5 hr. at 25°. The clear orange solution was poured into 400 ml. of cold water and the resulting precipitate was isolated and dried to give 6.05 g. (96%) of a pale yellow solid. An analytical sample was obtained by recrystallization from aqueous ethanol and decomposed above 256°.

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 52.14, 52.28; H, 3.59, 3.89; N, 34.19.

Esterification of 7.—A mixture of 40 ml. of concentrated sulfuric acid, 100 ml. of absolute ethanol, and 24.5 g. (134 mmoles) of **7** was refluxed with occasional agitation for 10 hr. and poured onto cracked ice. After addition of sodium bicarbonate to pH 6 the precipitate was isolated and extracted with hot acetone and then with chloroform. The aqueous filtrate was extracted with chloroform. Evaporation of the combined dried extracts gave a gummy yellow solid, which was triturated with boiling heptane until the insoluble residues appeared to be solid. Colorless needles of diester **10** precipitated from the heptane on cooling. The residue from the heptane extractions was then extracted with warm chloroform several times, leaving the 3-monoester **11** as the residue. Evaporation of the chloroform extract gave crude 5-monoester **12**. Purification and yield data are summarized in Table I.

Selective Saponification of 10.——One gram (4.1 mmoles) of **10** was dissolved in a mixture of 75 ml. of ethanol plus 50 ml. of 0.1 *N* potassium hydroxide and stirred at room temperature for 1.5 hr. The clear solution was filtered and acidified, followed by concentration to one-half its volume to give 0.8 g. (91%) of **12** after cooling.

2-Amino-4-hydroxy-6-pyrido[2,3-*d*]pyrimidinecarboxylic Acid (13).[5]—Guanidine hydrochloride (0.9 g.) was added to a solution of 1.0 g. of sodium in 100 ml. of absolute ethanol and the mixture was shaken well. One gram of **11** was added and the mixture refluxed with occasional agitation for 6 hr. The mixture was then poured into 300 ml. of water and filtered. The filtrate was acidified to give a gelatinous solid which was collected and washed with acetone and ether and dried. This gave 1.0 g. of a yellow solid, m.p. >350° dec.

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(12) F. Bohlman and M. Bohlman, *Chem. Ber.*, **86**, 1419 (1953).

(13) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

(14) Melting points were determined in capillary tubes and are corrected.

The ultraviolet spectrum was obtained in 0.1 *N* sodium hydroxide and compared with the data reported by Bernetti, Mancini, and Price[5] for the hydrochloride dissolved in 0.1 *N* sodium hydroxide. Absorption was as follows: λ_{max} 330, 288, and 246 mμ, λ_{min} 307 and 268 mμ; lit.[5] λ_{max} 330.7, 283.7, and 242 mμ, λ_{min} 307 and 367.3 mμ.

2-Amino-4-hydroxy-6-carbethoxypyrido[2,3-*d*]pyrimidine (14).—One gram (4.8 mmoles) of **13** was added to a mixture of 100 ml. of absolute ethanol and 15 ml. of concentrated sulfuric acid and the mixture was refluxed 10 hr. The reaction mixture was then poured onto cracked ice and brought to neutrality with potassium bicarbonate. The resulting precipitate was washed with water, acetone, and ether. This crude solid was recrystallized from glacial acetic acid to give 0.85 g. (75%) of a colorless solid, m.p. 329.5–333.5°, lit.[5] m.p. 328–331°. In 0.1 *N* sodium hydroxide, observed values were λ_{max} 244.5, 287.5, and 330.8 mμ, λ_{min} 268 and 306 mμ; lit.[5] λ_{max} 246, 287, and 330.7 mμ, λ_{min} 267 and 306.1 mμ.

4-Amino-6-cyano-7-ethylthiopyrido[2,3-*d*]pyrimidine (15).—A mixture of 0.8 g. (3.9 mmoles) of **3** and 50 ml. of formamide was heated at 180° for 40 min. under nitrogen. The mixture was cooled to room temperature and 50 ml. of water was introduced. After cooling overnight, precipitated **15** was collected by filtration and washed with water. After drying, 0.72 g. (80%) was obtained. Recrystallization from dimethylformamide–water gave a pale yellow powder which decomposed at 280–285°.

Anal. Calcd. for $C_{10}H_9N_5S$: C, 51.92; H, 3.93; N, 30.29. Found: C, 51.74; H, 3.89; N, 30.11.

2-Amino-5-cyano-6-methoxy-3-pyridinecarboxamide (16).—Ten grams (58 mmoles) of 2-amino-6-methoxy-3,5-dicyanopyridine[7] in 500 ml. of 0.1 *N* potassium hydroxide solution was boiled for 0.5 hr. The mixture was allowed to cool overnight in a refrigerator. The precipitate which formed was washed with water and dried to give 7 g. (64%) of **16**. The analytical sample was recrystallized from anhydrous methanol, m.p. 279–285°.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 50.10; H, 4.14; N, 29.15.

2-Methyl-4-hydroxy-6-cyano-7-methoxypyrido[2,3-*d*]pyridine (20). Method A.—A mixture of 20 ml. of triethyl orthoacetate, 20 ml. of acetic anhydride, and 0.5 g. (2.6 mmoles) of **16** was refluxed for 2 hr. The mixture was cooled to room temperature and 50% aqueous ethyl alcohol was added. The precipitate was washed with water and dissolved in 20 ml. of 1 *N* potassium hydroxide. The solution was filtered and acidified with acetic acid to give 0.4 g. (72%) of a white solid. The analytical sample was recrystallized from dimethylformamide which gave colorless flakes which decomposed at 276–281°. Pertinent infrared bands were at 4.49, 5.99, and 7.20 μ.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.38; H, 3.66; N, 25.71.

Method B.—A mixture of 4.0 g. (21 mmoles) of **16** and 50 ml. of acetic anhydride was refluxed for 8 hr. The precipitate which formed on standing overnight in a refrigerator was collected and washed with aqueous methanol. Further treatment as described in method A gave 2.2 g. (49%). The infrared spectra of products from methods A and B were identical.

4-Hydroxy-6-cyano-7-methoxypyrido[2,3-*d*]pyrimidine (18).—Following method A for the preparation of **20**, 2.5 g. of **18** was prepared from 2.5 g. of **16**, and 30 ml. each of triethyl orthoformate and acetic anhydride employing a reflux period of 35 min. Colorless flakes which melted with decomposition at 272–273° were isolated from dimethylformamide. Pertinent infrared bands were at 4.43, 5.92, and 7.18 μ.

Anal. Calcd. for $C_9H_6N_4O_2$: C, 53.46; H, 3.00; N, 27.71. Found: C, 53.60; H, 3.39; N, 27.53.

2-Methyl-4,7-dihydroxy-6-pyrido[2,3-*d*]pyrimidinecarboxamide (21).—A solution of 2.2 g. (10 mmole) of **20** in 70 ml. of 1 *N* potassium hydroxide was refluxed for 50 min. The solution was cooled to −5° and acidified with acetic acid. After standing overnight in the refrigerator, the solid was collected and washed with water and with methanol. This gave 1.2 g. (54%) of a brown powder. The analytical sample was recrystallized from dimethylformamide to give a yellow-brown powder which decomposed above 315°. Pertinent infrared bands were at 2.95, 3.15, 5.85, and 6.02 μ.

Anal. Calcd. for $C_9H_8N_4O_3$: C, 49.09; H, 3.67; N, 25.45. Found: C, 49.29; H, 3.83; N, 25.26.

4-Hydroxy-6-cyano-7-methylthiopyrido[2,3-*d*]pyrimidine (19).—With the method used for **18**, **19** was formed in 88% yield from **17**,[7] triethyl orthoformate, and acetic anhydride employing a reflux period of 1.5 hr. Recrystallization from dimethylformamide gave colorless flakes which decomposed above 330°. Pertinent infrared bands were at 3.00, 4.48, and 5.92 μ.

Anal. Calcd. for $C_9H_6N_4OS$: C, 49.54; H, 2.78; N, 25.69; S, 14.69. Found: C, 49.52; H, 2.88; N, 25.85; S, 14.65.

2,4-Dihydroxy-6-cyano-7-methylthiopyrido[2,3-*d*]pyrimidine (22).—A solution of 9.6 g. of sodium metal in 50 ml. of absolute ethanol was treated with 1.0 g. (18 mmoles) of **17**[7] and 10 ml. of diethyl carbonate. After refluxing for 45 min. and cooling, 50 ml. of water was added which dissolved most of the solid. The solution was filtered and treated with acetic acid. After cooling overnight in a refrigerator, the precipitate was collected and washed with water to give 0.9 g. (79%) of a white powder. The analytical sample was recrystallized from dimethylformamide to give colorless flakes which began to decompose at 232°. Pertinent infrared bands were at 3.15, 4.43, 5.88, and 5.97 μ.

Anal. Calcd. for $C_9H_6N_4O_2S$: C, 46.16; H, 2.57; N, 23.93; S, 13.89. Found: C, 46.32; H, 2.36; N, 23.57; S, 13.59.

2,4-Dihydroxy-6-cyano-7-methylsulfonylpyrido[2,3-*d*]pyrimidine (23).—A stirred suspension of 3.0 g. (12.8 mmoles) of **22** in 100 ml. of 3% hydrochloric acid was treated with chlorine gas for 15 min. at 0–5°. The initial suspension became thick as the reaction proceeded. The crude solid was collected while cold and washed with ice–water, acetone, and ether, and dried overnight under vacuum to give 3.2 g. of **23** (94%). The analytical sample was obtained by recrystallization from 95% ethanol and melted at 290–293° dec. Pertinent infrared bands were at 4.47, 5.80, 5.92, 7.67, and 8.71 μ.

Anal. Calcd. for $C_9H_6N_4O_4S$: C, 40.60; H, 2.27; N, 21.04. Found: C, 40.79; H, 2.52; N, 20.96.

2,4-Dihydroxy-6-cyano-7-aminopyrido[2,3-*d*]pyrimidine (24).—A solution of 3.0 g. (11.2 mmoles) of **23** in 150 ml. of concentrated ammonium hydroxide was shaken for 1 hr. at room temperature. A white solid formed which was collected and washed well with water and acetone; crude yield, 1.80 g. (78%). The analytical sample was obtained by recrystallization from dimethylformamide–water and decomposed above 295.5°. Pertinent infrared bands were at 2.93, 3.13, 4.48, 5.83, and 5.90 μ.

Anal. Calcd. for $C_8H_5N_5O_2$: C, 47.29; H, 2.48; N, 34.48. Found: C, 47.29; H, 2.61; N, 33.88.

2,4-Dihydroxy-6-(N-carbethoxy)carboxamidopyrido[2,3-*d*]-pyrimidine (25).—Five grams (27.8 mmoles) of **6** in a solution of 5.0 g. of sodium in 200 ml. of alcohol was heated to reflux. Diethyl carbonate (35 ml.) was added dropwise with stirring to the refluxing solution. After the addition was comp ete, the mixture was refluxed with stirring for an additional 2 hr. and then cooled to room temperature. The reaction mixture was poured into 600 ml. of cold water, and almost all solids dissolved. The solution was filtered, acidified with dilute hydrochloric acid, and cooled overnight. This gave 4.2 g. of a pale yellow amorphous solid. Concentration of the filtrate gave an additional 1.25 g. (5.45 g., 70.7%). The analytical sample which decomposed above 275° was obtained by recrystallization from dimethylformamide–water. Pertinent infrared bands were at 5.70, 5.75, 5.79, 6.00, and 8.40 μ.

Anal. Calcd. for $C_{11}H_{10}N_4O_5$: C, 47.47; H, 3.63; N, 20.14. Found: C, 47.44; H, 3.99; N, 20.15.

2,4-Dihydroxy-6-carbethoxypyrido[2,3-*d*]pyrimidine (26).—A mixture of 4.5 g. (11.6 mmoles) of **25** in 100 ml. of absolute ethyl alcohol and 15 ml. of concentrated sulfuric acid was heated at reflux for 5 hr. The solid which formed on cooling was collected and washed with water, acetone, and ether (3.7 g.). The analytical sample was obtained by recrystallization from water, m.p. 278.5–280.5°. Pertinent infrared bands were at 5.83, 5.87, 5.94, and 8.16 μ.

Anal. Calcd. for $C_{10}H_9N_3O_4$: C, 51.07; H, 3.86; N, 17.86. Found: C, 51.26; H, 3.97; N, 17.47.

2,4-Dihydroxy-6-pyrido[2,3-*d*]pyrimidinecarboxamide (27).—A mixture of 5.25 g. (18.8 mmoles) of **25** and 250 ml. of glacial acetic acid was refluxed with stirring for 4 hr. After cooling, the white solid was collected and washed with water, acetone, and ether (3.8 g., 94%). The analytical sample was obtained by recrystallization from dimethylformamide–water; decomposition occurred at greater than 354°. Pertinent infrared bands were at 2.96, 5.80, 5.94, and 5.99 μ.

Anal. Calcd. for $C_8H_6N_4O_3$: C, 46.61; H, 2.93. Found: C, 46.53; H, 3.10.

2,4-Dihydroxy-6-cyanopyrido[2,3-*d*]pyrimidine (9). Method A.—Four grams (19.4 mmoles) of **27** in 200 ml. of phosphorus oxychloride was refluxed for 8 hr. After cooling to 0° a tan solid separated which was collected and washed with acetone and ether, 2.75 g. (75%). The analytical sample was recrystallized from water, m.p. 353–355° dec. Pertinent infrared bands were at 4.51, 5.85, and 5.97 μ.

Anal. Calcd. for $C_8H_4N_4O_2$: C, 51.07; H, 2.14; N, 29.78. Found: C, 50.81; H, 2.16; N, 29.42.

Method B.—2-Amino-5-cyano-3-pyridinecarboxamide (**8**, 0.75 g., 4.6 mmoles) was added to a solution of 0.75 g. of sodium in 60 ml. of absolute ethanol and heated to reflux. Diethyl carbonate (6 ml.) was added slowly with occasional agitation. The reaction mixture was refluxed for 1 hr. and then poured into 400 ml. of water and filtered. Upon acidification with dilute acetic acid and concentration to a volume of 100 ml., 0.6 g. of a yellow solid precipitated which decomposed above 350°. The infrared spectra of samples from methods A and B were identical and a mixture melting point showed no depression.

4-Amino-6-cyanopyrido[2,3-*d*]pyrimidine (28).—One gram (7 mmoles) of **1** in 45 ml. of formamide was heated at 100 ± 5° for 30 min. under nitrogen. As the reaction proceeded, the solution became quite dark. The solution was decolorized, heated briefly to boiling, and filtered. Upon cooling to 20° a yellow-tan solid separated which was collected and washed with water, acetone, and ether (crude yield, 1.5 g., 97%). The crude solid was recrystallized several times from water to yield colorless flakes which decomposed above 335°. Pertinent infrared bands were at 3.00 and 4.47 μ.

Anal. Calcd. for $C_8H_5N_5$: C, 56.13; H, 2.94; N, 40.92. Found: C, 55.88; H, 3.20; N, 40.72.

Reduction of 2-Amino-3,5-dicarbethoxypyridine (10) with Lithium Borohydride in Diglyme.[13]—Three grams (12.3 mmoles) of **10** was added to a stirred solution of 2.1 g. of anhydrous lithium bromide and 0.92 g. of sodium borohydride in 100 ml. of anhydrous diglyme. The mixture was stirred 3 hr. at room temperature under nitrogen. The reaction mixture was then poured into a mixture of ice and 20 ml. of concentrated hydrochloric acid. The clear aqueous solution was adjusted to pH 6 with sodium bicarbonate and was extracted several times with chloroform. The chloroform was extracted once with aqueous bicarbonate. Evaporation of the dried chloroform gave a yellow oil, which upon treatment with 25 ml. of benzene gave 0.91 g. (30%) of a yellow solid. Recrystallization from toluene gave an analytical sample that melted at 145–147°: λ_{max}^{EtOH} for **29**, 251.5 mμ, and for **10**, 273.5 mμ; infrared data (Nujol mull) for carbonyl **10**, 5.83 and 5.88 μ, and carbonyl **29**, 5.94 and 5.99 μ. The analysis corresponded to a dihydro-2-amino-3,5-dicarbethoxypyridine (**29**).

Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.98; H, 6.71; N, 11.66. Found: C, 54.97; H, 6.89; H, 11.82.

2-Amino-5-aminomethyl-3-pyridinecarboxamide (30).—To a mixture of 150 ml. of dimethylformamide, 40 ml. of concentrated ammonium hydroxide, and 10 ml. of water was added 7.0 g. (43 mmoles) of **8**. Approximately 25 g. of W-4 Raney nickel was added and the mixture was shaken with hydrogen at 60 p.s.i. for 25 hr. After separation of the catalyst, the filtrate was evaporated to dryness under reduced pressure giving 3.25 g. of a gummy solid. Extraction of the catalyst with boiling water gave, after evaporation, an additional 0.70 g. of solid. Recrystallization of the crude product from 2-propanol gave a colorless solid, m.p. 208–215°; total yield was 3.95 g. (55%). An analytical sample was obtained by recrystallization from ethanol–toluene and had m.p. 214–216°, λ_{max}^{water} 251 and 321.5 mμ, λ_{min}^{water} 273 mμ.

Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.60; H, 6.06; N, 33.71. Found: C, 50.58; H, 6.39; N, 33.13.

The Base-Catalyzed Autoxidation of Hydrocarbons in Diphenyl Sulfoxide[1]

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The use of diphenyl sulfoxide (DPSO) as a solvent for the base-catalyzed autoxidation of weak hydrocarbon acids has been investigated. Stability studies indicate that DPSO is much more stable than DMSO in the presence of potassium *t*-butoxide and molecular oxygen. This is attributed to the different types of carbon–hydrogen bonds in the two sulfoxides. It was possible to autoxidize diphenylmethane, toluene, and *o*-xylene in potassium *t*-butoxide–DPSO at 100° at reasonable rates. The rates of oxygen consumption were dependent on the base/hydrocarbon ratio, type of base employed (KO-*t*-Bu *vs.* KOH), and the acidity of the hydrocarbons. The results are consistent with a carbanion-radical autoxidation process.

In the past few years, solvent effects in the base-catalyzed oxidation of acidic hydrocarbons,[2,3] the isomeric picolines,[4] and sulfur compounds[5–7] have been reported. These studies have been carried out in solvents such as dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), pyridine, and ethers which are all capable of accelerating base-catalyzed reactions.[8,9] Despite these findings, a suitable solvent medium for carrying out the low-temperature anionic oxidation of inert hydrocarbons such as toluene has not been uncovered. This is due to one of two factors: (a) inability of existing solvents to effectively ionize carbon–hydrogen bonds with pK_a values of 50–60, and (b) preferential oxidation of the solvent instead of the hydrocarbon. The present paper summarizes our studies on this problem using molten diphenyl sulfoxide (DPSO) as the solvent.

Results

In order to determine the suitability of DPSO as a solvent for the anionic oxidation of weak hydrocarbon acids, the stability of the solvent to heat, weak bases, and oxygen was determined. DPSO was heated at 80–140° for periods of 2–3 days. Temperature-programmed gas chromatographic analyses on a 2-ft. silicone rubber column indicated that diphenyl sulfide and diphenyl sulfone were not present, thus eliminating the possibility of a disproportionation reaction (eq. 1).

$$2R_2SO \longrightarrow R_2S + R_2SO_2 \qquad (1)$$

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