Department of Chemistry, State University of New York at Buffalo

The Synthesis and Some Reactions of 2-Methyl-4,5-pyrimidinedicarbonitrile (1)

Thomas J. Schwan and Howard Tieckelmann

Diethyl ethoxymethyleneoxalacetate and acetamidine gave 2-methyl-4,5-bis(carbethoxy)-pyrimidine. The ester was converted to 2-methyl-4,5-pyrimidinedicarbonitrile which gave 2-methyl-4-methoxy-5-pyrimidinecarbonitrile when treated with methanol at room temperature. Attempts to hydrogenate the dinitrile in the presence of nucleophiles led to displacement at C-4. Attempted hydrogenation of the dinitrile in dimethylformamide gave 2,2'-dimethyl-5,5'-dicyano-4,4'-bipyrimidine.

As part of a program in search of potential pyridoxine antagonists, it was of interest to synthesize 2-methyl-4,5-pyrimidinedicarbonitrile (I) as a possible intermediate to products with reduced functions in the 4- and 5-positions. However, the susceptibility of the 4-cyano group to substitution has prevented the direct conversion of I to reduced products in nucleophilic solvents even under mild conditions.

Diethyl ethoxymethyleneoxalacetate (2) and acetamidine were condensed to give 2-methyl-4,5-bis-(carbethoxy)pyrimidine (II). Attempts to effect the direct reduction of II to 2-methyl-4,5-bis(hydroxymethyl)pyrimidine proved fruitless. Attempted reduction with lithium aluminum hydride in ether at -70°, room temperature, or at reflux gave only intractable gums. The Boveault-Blanc method and treatment with an excess of sodium borohydride (3) were unsuccessful. Due to this difficulty, attention was turned to the dicarbonitrile I.

Treatment of the ester II with concentrated aqueous ammonia gave 2-methyl-4,5-pyrimidinedicarboxamide (III). Dehydration of III with phosphorus oxychloride employing a procedure which involved heating an aqueous solution of the product gave 2-methyl-4-hydroxy-5-pyrimidinecarbonitrile (IV). The dicarbonitrile I was prepared by the dehydration of the amide III using less vigorous conditions.

When I was allowed to react with methanol, 2-methyl-4-methoxy-5-pyrimidinecarbonitrile (V) was formed. The structure of V was confirmed by its conversion to 2-methyl-4-amino-5-pyrimidinecarbonitrile (VI) with aqueous ammonia. Yamanaka employed sodium alkoxide in refluxing alcohol in effecting a nitrile-alkoxide exchange in 2,6-dimethyl-4-pyrimidinecarbonitrile (4). Normal additions to this nitrile were observed in the absence of strong nucleophiles (5). In the present work, however, exchange with alcohols occurred at room temperature and in the absence of alkoxides. Such a facile transformation should not be altogether unexpected. The intermediate in this nucleophilic aromatic substitution would derive stabilization from the electron withdrawing 5-cyano group in addition to stabilization attributed to the annular nitrogens.

The enhanced susceptibility of the 4-cyano group to displacement also accounts for the formation of 2-methyl-4-hydroxy-5-pyrimidinecarbonitrile (IV) in the attempted preparation of the dicarbonitrile I. (Chart I.)

The conversion of the dicarbonitrile to 2-methyl-4,5-bis(aminomethyl)pyrimidine was then considered. Attempted hydrogenation of I in methanolic hydrogen chloride gave a cyanoester which was tentatively identified as 2-methyl-4-carbomethoxy-5-pyrimidinecarbonitrile (VII). While the nitrile absorption band at 4.5 μ was observed in the product, it has been shown that this band is not evident in 2-substituted-4-pyrimidinecarbonitriles (6), an observation which supports structure (VII). Presumably VII was formed by hydrolysis of the iminoester during isolation procedures.

Hydrogenation of the dicarbonitrile I using methanolic ammonia and Raney nickel catalysts gave only 2-methyl-4-hydroxy-5-aminomethylpyrimidine (VIII) isolated as a mixture of its mono- and dihydrochlorides. The structure of VIII was established by deamination to 2-methyl-4-hydroxy-5-hydroxymethylpyrimidine (IX). Apparently the 4-methoxypyrimidine formed by solvolysis subsequently was converted to the 4-pyrimidone during the work-up. Under the conditions used, hydrogenation at C-4 was not competitive with solvolysis at this position. In addition this solvolysis evidently preceded reduction of the 5-cyano group. If hydrogenation of the 5-cyano had occurred first it is unlikely that the 4-cyano group would have been sufficiently reactive to undergo solvolysis.

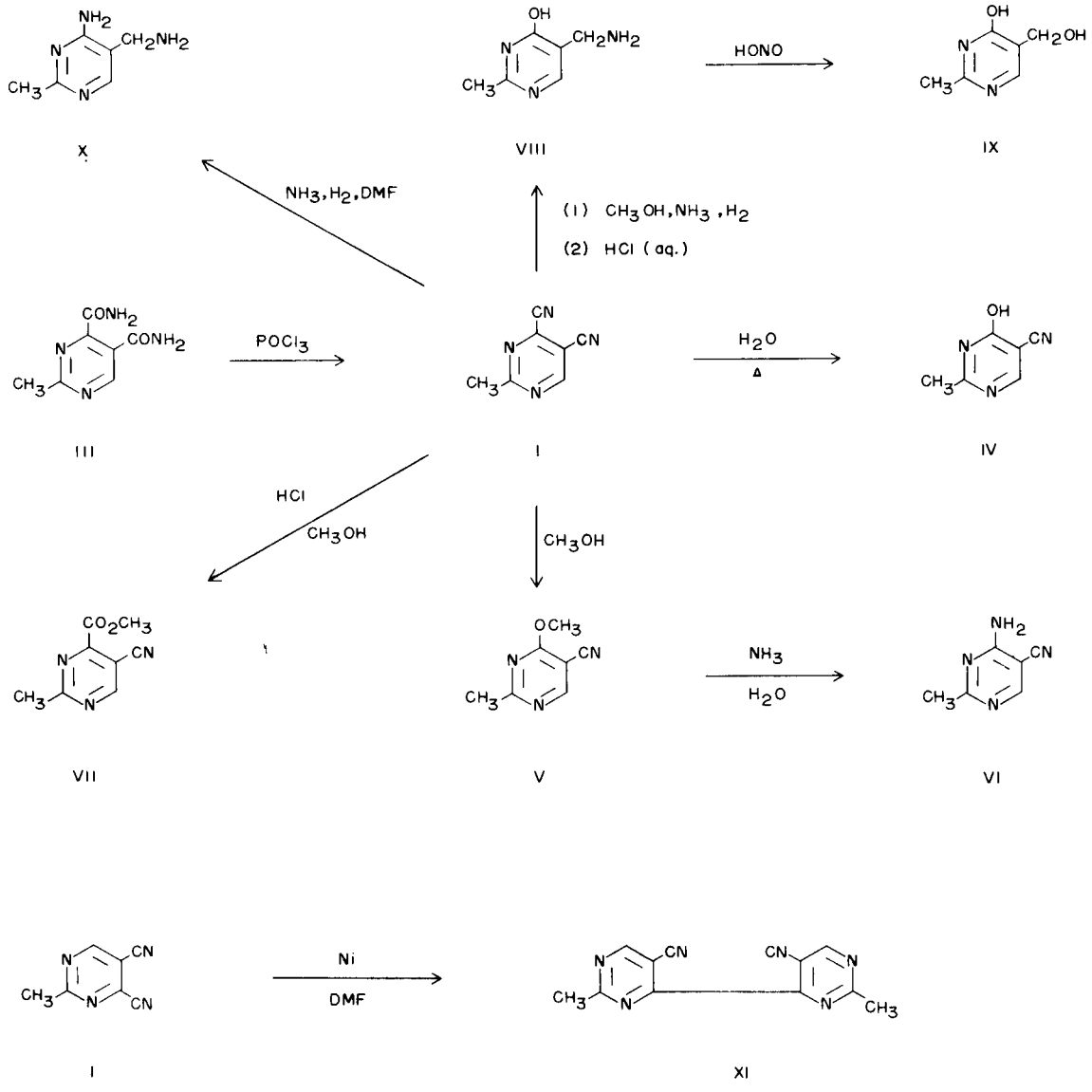
Because the solvolytic properties of methanol appeared to play an important role in these transformations, the dicarbonitrile was hydrogenated in

the presence of ammoniacal dimethylformamide using Raney nickel. The product, isolated as its dihydrochloride, was identified as 2-methyl-4-amino-5-aminomethylpyrimidine (X). The results of these hydrogenations are outlined in Chart I.

When the dicarbonitrile I was hydrogenated in dimethylformamide using Raney nickel in the absence of ammonia, 2,2'-dimethyl-5,5'-dicyano-4,4'-bipyrimidine (XI) was formed. The infrared spectrum of XI indicated the presence of a cyano group, while the nuclear magnetic resonance spectrum of the product was virtually identical to that of the starting nitrile I, exhibiting a methyl singlet at 6.95 τ and an aromatic singlet at 0.84 τ in a ratio of 3:1.

The formation of the bipyrimidine is at least superficially analogous to the well-documented Ullmann reaction, where biaryls are formed by the coupling of activated aryl halides in the presence of copper powder (7). In this way also, the dinitrile I may be functionally equivalent to an activated aryl halide.

CHART I



EXPERIMENTAL

Melting points were taken on a Mel-Temp apparatus. Microanalyses were performed by Alfred Bernhardt, Mülheim, Germany, and Drs. Weiler and Strauss, Oxford, England. Infrared spectra were obtained using a Beckman IR-5A spectrophotometer. Nuclear magnetic resonance spectra were obtained at 60 megacycles on a Varian Associates, Model A-60, spectrophotometer.

2-Methyl-4, 5-bis(carbethoxy)pyrimidine (II).

To a cooled solution of 0.36 g. atom of sodium in 300 ml. absolute ethanol was added 38.4 g. (0.40 mole) of acetamidine hydrochloride. Diethyl ethoxymethyleneoxalacetate (88.8 g., 0.36 mole) was added while the reaction mixture was cooled and stirred. Stirring was continued for 5 hours and the mixture was then filtered through a sintered glass funnel. The ethanolic filtrate was concentrated to dryness *in vacuo*, the residue taken up in one liter of water, and the aqueous suspension was extracted with five 200-ml. portions of chloroform. The chloroform extracts were combined, concentrated to dryness *in vacuo*, and the residue distilled under reduced pressure. The product distilled at 130-136° (0.4 mm.) and weighed 38.3 g. (45%). An analytical sample was collected at 118° (0.09 mm.). Significant infrared bands occurred at 5.8, 5.85 (C=O), and 6.4 μ (C=N).

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.54; H, 6.03; N, 11.67.

2-Methyl-4, 5-pyrimidinedicarboxamide (III).

A mixture of 18 g. (76 mmoles) of 2-methyl-4, 5-bis(carbethoxy)-pyrimidine (II) and 200 ml. concentrated aqueous ammonia was stirred at room temperature for 12 hours. At the end of this time the ester had completely dissolved. The mixture was cooled and the white solid which separated weighed 10.4 g. (76%) and melted at 226-229° (dec.). An analytical sample was obtained by recrystallization from 95% ethanol and then from water, m.p. 234-236° (dec.). Significant infrared bands occurred at 2.93, 3.02, 3.15 (N-H), 5.92, 6.02 (C=O), and 6.38 μ (C=N) in a Nujol mull.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.47; H, 4.51; N, 31.35.

2-Methyl-4, 5-pyrimidinedicarbonitrile (I).

A mixture of 18.8 g. (0.104 mole) of 2-methyl-4, 5-pyrimidinedicarboxamide (III), 100 ml. phosphorus oxychloride, and 250 ml. xylene was stirred and refluxed for 24 hours and after cooling, was poured slowly into 1 kg. ice water with vigorous stirring. The organic layer was separated and the brown aqueous layer was extracted with three 100-ml. portions of benzene. Upon concentration of the combined extracts solutions *in vacuo*, there remained 8.5 g. (57%) of the crude nitrile.

An analytical sample was prepared by extraction of the crude product with boiling ligroin (35-60°). Upon removal of the ligroin *in vacuo* there remained a solid residue which was vacuum sublimed at 40° (0.5 mm.), m.p. 36.0-38.5°. The infrared spectrum of a Nujol mull exhibited absorption at 4.45 (C≡N) and 6.38 μ C=N). The n.m.r. spectrum of a deuteriochloroform solution exhibited a methyl singlet at 7.03 τ and an aromatic singlet at 0.72 τ in an intensity ratio of 3:1.

Anal. Calcd. for $C_7H_4N_4$: C, 58.33; H, 2.80; N, 38.87. Found: C, 58.44; H, 2.69; N, 38.50.

2-Methyl-4-hydroxy-5-pyrimidinecarbonitrile (IV).

In a procedure similar to that reported for I, when the reaction mixture from 5.0 g. of the dicarboxamide III and 30 ml. phosphorus oxychloride in 200 ml. toluene was poured into 500 g. ice water, neutralized with dilute sodium hydroxide, concentrated to dryness and extracted with boiling ethyl acetate, there was isolated 1.4 g. (39%) of IV, m.p. 175-190°. The product was recrystallized from methanol, m.p. 227-230° (dec.); lit. (8) 233-235°. The infrared spectrum was identical to that of an authentic sample of IV prepared by the method of Todd and Bergel (8).

2-Methyl-4-methoxy-5-pyrimidinecarbonitrile (V).

A solution of 0.5 g. (3.4 mmoles) of 2-methyl-4, 5-pyrimidinedicarbonitrile (I) in 25 ml. methanol was refluxed for 24 hours. The methanol was removed *in vacuo* and the solidified residue was vacuum sublimed at 45° (0.1 mm.), m.p. 73-76°. Significant infrared bands occurred at 4.49 (C≡N) and 6.3 μ (C=N) in a Nujoll mull.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.36; H, 4.73; N, 28.18. Found: C, 56.65; H, 4.69; N, 28.20.

This transformation was also effected by stirring the carbonitrile I with methanol at room temperature for five days. At the termination of the reaction time there was sufficient starting material present to complicate purification of the methoxypyrimidine.

2-Methyl-4-amino-5-pyrimidinecarbonitrile (VI).

A solution of 0.2 g. of 2-methyl-4-methoxy-5-pyrimidinecarbonitrile (V) in 5 ml. methanol and 10 ml. concentrated aqueous ammonia was stirred at room temperature for 12 hours. The mixture was cooled for 3 hours and the solid which separated was recrystallized from 95% ethanol, m.p. 248.5-249.5°; lit. (9), 249°. The infrared spectrum was identical to that of an authentic sample of VI.

Hydrogenation of 2-Methyl-4,5-pyrimidinedicarbonitrile (I) using Methanolic Hydrogen Chloride. 2-Methyl-4-carbomethoxy-5-pyrimidinecarbonitrile (VII).

A mixture of 1.3 g. (9 mmoles) of the dicarbonitrile I, 1.0 g. 5% palladium on carbon, and 3 g. hydrogen chloride in 150 ml. methanol was hydrogenated at 50 p.s.i. for 2 hours. The suspension was filtered and the catalyst washed with 50 ml. of methanol. The filtrate and washings were combined and concentrated to dryness *in vacuo*. The residue was extracted with boiling ethyl acetate and upon removal of the solvent there remained 0.3 g. (20%) of the crude product.

An analytical sample was obtained by vacuum sublimation at 100° (0.05 mm.), m.p. 74-76°. Significant infrared bands occurred at 4.5 (C≡N), 5.8 (C=O, ester), and 6.4 μ (C=N) in a Nujol mull.

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.72. Found: C, 54.50; H, 4.19; N, 23.59.

Hydrogenation of 2-Methyl-4,5-pyrimidinedicarbonitrile (I) in Methanolic Ammonia. 2-Methyl-4-hydroxy-5-aminomethylpyrimidine (VIII).

A mixture of 1.5 g. (10 mmoles) of the dicarbonitrile I, 3 g. of W-4 (10) Raney nickel, and 8 g. ammonia in 200 ml. methanol was hydrogenated at 50 p.s.i. for 44 hours. The suspension was filtered and the catalyst was washed with two 100-ml. portions of boiling methanol. The filtrate and combined washings were concentrated to dryness *in vacuo* and the resulting residue was extracted with three 300-ml. portions of boiling carbon tetrachloride. Upon concentration of the combined extract solutions to dryness there was obtained 1.1 g. of the crude product which was dissolved in 100 ml. benzene. Dry hydrogen chloride was passed into the solution for 10 min. and the solid which separated was washed with 50 ml. cold benzene. Recrystallization from absolute ethanol gave an analytical sample, m.p. 234-237°; lit. (11), m.p. of dihydrochloride, 280°. Significant infrared bands occurred at 2.9 (N-H), 5.9 (C=O), and 6.4 μ (C=N) in a Nujol mull.

Anal. Calcd. for 2-methyl-4-hydroxy-5-aminomethylpyrimidine monohydrochloride, $C_6H_{10}ClN_3O$: C, 41.03; H, 5.74; N, 23.93; Cl, 20.18; dihydrochloride, $C_6H_{11}Cl_2N_3O$: C, 33.97; H, 5.23; N, 19.82; Cl, 33.43. Found: C, 34.58; H, 5.66; N, 20.81; Cl, 26.89.

Deamination: The crude product from the hydrogenation was dissolved in a solution of 50 ml. water and 2 ml. concentrated hydrochloric acid. A solution of 2.0 g. of sodium nitrite in 20 ml. water was added and the reaction mixture was stirred at 60° for 18 hours.

After neutralization with dilute sodium hydroxide the solution was continuously extracted with ethyl acetate for 24 hours to give 1.0 g. (78%) of crude 2-methyl-4-hydroxy-5-hydroxymethylpyrimidine (IX) after removal of the solvent. The purified product after recrystallization from ethyl acetate, melted at 208-212°; lit. (11), m.p. 215-216°. The infrared spectrum was identical to that of an authentic sample of IX which was prepared by the lithium aluminum hydride reduction of 2-methyl-4-hydroxy-5-carbethoxypyrimidine.

Hydrogenation of 2-Methyl-4, 5-pyrimidinedicarbonitrile (I) using Ammonia in Dimethylformamide. 2-Methyl-4-amino-5-aminomethylpyrimidine (X).

A mixture of 1.3 g. (9 mmoles) of the dicarbonitrile I, 3 g. W-4 (10) Raney nickel, and 3 g. ammonia in 100 ml. dimethylformamide was hydrogenated at 50 p.s.i. for 24 hours. The suspension was filtered and the catalyst washed with 100 ml. hot dimethylformamide. The filtrate and combined washings were concentrated to dryness and the residue was extracted with two 300-ml. portions of boiling heptane. After removal of the solvents from the extracts the residue was taken up in 50 ml. benzene. Dry hydrogen chloride was passed into the solution for 30 min. and the solid which separated was washed with benzene, dried, and vacuum sublimed at 230° (0.1 mm.). The product and an authentic sample of the dihydrochloride of 2-methyl-4-amino-5-aminomethylpyrimidine exhibited identical infrared spectra.

Hydrogenation of 2-Methyl-4,5-pyrimidinedicarbonitrile (I) in Dimethylformamide. 2,2'-Dimethyl-5,5'-dicyano-4,4'-bipyrimidine (XI).

A mixture of 1.2 g. (8.3 mmoles) of the dicarbonitrile I, 2 g. W-4 (10) Raney nickel, and 100 ml. dimethylformamide was hydrogenated at 54 p.s.i. for 20 hours. The catalyst was washed with 100 ml. hot dimethylformamide. Upon concentration of the combined filtrates and washings *in vacuo* the obtained residue was extracted with two 200-ml. portions of boiling benzene. Removal of the solvent gave the crude product which was recrystallized from heptane to give 0.5 g. (50%) of a white solid, m.p. 198-202°. An analytical sample was obtained by

vacuum sublimation at 180° (0.03 mm.), m.p. 202-204°. Significant infrared bands occurred at 4.46 (C≡N) and 6.39 μ (C=N) in a Nujol mull.

The n.m.r. spectrum of a deuteriochloroform solution of the product exhibited a methyl singlet at 6.95 τ and an aromatic singlet at 0.84 τ in a ratio of 3:1.

Anal. Calcd. for $C_{12}H_8N_6$: C, 61.01; H, 3.41; N, 35.58; mol. wt., 236. Found: C, 60.94; H, 3.89; N, 35.36; mol. wt., 247.

REFERENCES

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

(2) R. G. Jones, *J. Am. Chem. Soc.*, **73**, 3684 (1951).

(3) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).

(4) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **7**, 508 (1959); *Chem. Abstr.*, **54**, 18537 (1960).

(5) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **6**, 638 (1958); *Chem. Abstr.*, **54**, 14257 (1960).

(6) T. J. Schwan and H. Tieckelmann, *J. Heterocyclic Chem.*, **1**, 201 (1964); G. D. Daves, Jr., D. F. O'Brien, L. R. Lewis, and C. C. Cheng, *ibid.*, **1**, 130 (1964).

(7) P. E. Fanta, *Chem. Rev.*, **64**, 613 (1964).

(8) A. R. Todd and F. Bergel, *J. Chem. Soc.*, 364 (1937).

(9) R. Grewe, *Z. Physiol. Chem.*, **242**, 89 (1936).

(10) H. Adkins and A. A. Pavlic, *J. Am. Chem. Soc.*, **69**, 3039 (1947).

(11) A. R. Todd, F. Bergel, H. L. Fraenkel-Conrat and A. Jacob, *J. Chem. Soc.*, 1601 (1936).

Received February 8, 1965 Buffalo, New York 14214