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The Reaction Mechanism of 2-Dimethoxymethyl-3-methoxypropionitrile with Acetamidine. I. A Revised Structure of the Intermediate[1]

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The reaction of 2-dimethoxymethyl-3-methoxypropionitrile (**1**) with acetamidine yields 2,7-dimethyl-5,6-dihydropyrimido[4,5-*d*]pyrimidine (**6**) *via* an intermediate, λ_{max}^{MeOH} 262 mμ. This intermediate has been identified as 2-acetamidinomethylene-3-methoxypropionitrile (**5**) without being isolated. However, this assignment seems to be somewhat inconsistent with the stabilities of an acetal group in basic media and with the UV spectra of compounds with structures similar to **5**. The reaction of **1** with sodium methoxide gave a dimeric compound (**8**). This result suggests the formation of **2**-dimethoxymethylacrylonitrile (**2**) in the initial stage of the reaction of **1** with acetamidine. The reaction of acrylonitrlie with acetamidine yielded 2-methyl-4-amino-5,6-dihydropyrimidine (**23**), whose UV spectrum in methanol showed its absorption maximum at 270 mμ in neutral media and at 258 mμ in basic media. Therefore, the structure of the intermediate may be concluded to be 2-methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**27**) instead of **5**, and the reaction may be concluded to proceed *via* the pathway of **1**→**2**→**27**→**6**.

Interesting and rather complicated results have been reported by Takamizawa and his co-workers dealing with the syntheses of some pyrimidines from derivatives of 2-formyl-3-methoxypropionitrile with acetamidine.[2] Two types of pyrimidines are obtainable by the reactions: 2-methyl-4-amino-5-methoxymethylpyrimidine (**7**) can be obtained directly by the reaction of 2-methoxymethylene-3-methoxypropionitrile (**3**), while 2,7-dimethyl-5,6-dihydropyrimido[4,5-*d*]pyrimidine (**6**) can be obtained from 2-dimethoxymethyl-3-methoxypropionitrile(**1**) or 2-dimethoxymethylacrylonitrile (**2**) *via* a complex pathway, which is proposed to be as shown in Chart 1.[2] An intermediate can be detected spectrophotometrically, λ_{max}^{MeOH} 262 mμ or λ_{max}^{EtOH} 275 mμ, without being successfully isolated. When heated with another mole of acetamidine, this intermediate is converted into **6**. This intermediate has been identified as 2-acetamidinomethylene-3-methoxypropionitrile (**5**).

As acetamidine is a strong base (pK_a 12.4),[3] the reactions proceed under basic conditions. The reaction of **3**→**7** is quite natural, judging from the literatures.[4,5] On the other hand, the formation of **6** from **1** or **2** is very unusual and interesting. However, further investigation is thought to be required before we can reach any final conclusion on the reaction mechanism, since the step of **1**→**4**→**5** seems to be inconflict with the stabilities of an acetal group in basic media.[6]

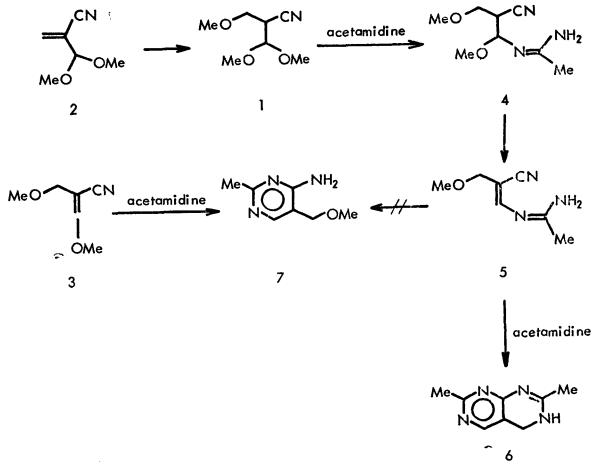

Chart 1

A further question has been raised on the basis of the comparison of the UV spectra of compounds with structures similar to **5**. The absorption maximum of ethyl acetamidinomethylenecyanoacetate[7] appears at 330 mμ in ethanol, and that of 2-aminomethylene-3-ethoxypropionitrile appears at 270 mμ in methanol.[2] From these data the absorption maximum of **5** is expected to appear at a wavelength longer than 270 mμ.

1) Pyrimidines, 8. For Part 7, see F. Takami, S. Wakahara, and T. Maeda, *Chem. Lett.*, **1972**, 159.

2) A. Takamizawa, K. Tokuyama, and K. Tori, This Bulletin, **32**, 188 (1959), and earlier papers in this series.

3) P. A. S. Smith, "The Chemistry of Open Chain Organic Nitrogen Compounds," Vol. 1, W. A. Benjamin, New York (1965), p. 178.

4) H. Andersag and K. Westphal, *Ber.*, **70**, 2035 (1937); R. Grewe, *Z. Phys. Chem.*, **242**, 89 (1936).

5) G. V. Chelinstev and Z. V. Benevalenskaya, *J. Gen. Chem.*, **14**, 1142 (1944); *Chem. Abstr.*, **40**, 4069 (1946).

6) E. Schmitz and E. Eichhorn, "The Chmistry of the Ether Linkage," Interscience, New York (1967), p. 329.

7) T. Matsukawa, *Yakugaku Zasshi*, **62**, 417 (1942),

Consequently, the establishment of unequivocal structure of the intermediate is desired. For this purpose, studies of the behavior of **1** toward bases were attempted.

The treatment of **1** with sodium methoxide at 40°C for 2 hr gave a viscous oil (**8**). The analytical data and the integration of the NMR spectrum showed it to be a dimeric substance, $C_{12}H_{18}N_2O_4$, which was thought to be obtained from the dimerization of **1** by the elimination of one mol of methanol. The UV spectrum in ethanol showed the absorption maximum at 232 mμ suggesting the presence of a partial structure of MeO–C=C–CN.[8] The IR spectrum showed characteristic absorption bands due to non-conjugate and conjugate nitriles, double bond, and acetal and methoxy groups. Therefore, **8** was determined to be 2-dimethoxymethyl-2-methoxymethyl-4-methoxymethyleneglutaronitrile and to be, as will be described below, a mixture of *trans* and *cis* isomers.[9]

Figure 1 shows the NMR spectrum of **8** in carbon tetrachloride. With the 4-methoxymethylene group, the signal due to the methine proton appeared as two singlets at 2.98 τ (⅔H, a) and 3.18 τ (⅓H, b), while the signal due to the methyl group also appeared as two singlets, at 6.10 τ (2H, a) and 6.08 τ (1H, b). The signal due to the methylene proton at the 3-position appeared as an AB-type quartet at 7.43 τ and 7.55 τ (J 14 Hz, ⅔H, a), and as a singlet at 7.57 τ (⅔H, b). These data clearly supported the idea that **8** was a mixture of two isomers whose ratio was about 2 : 1.

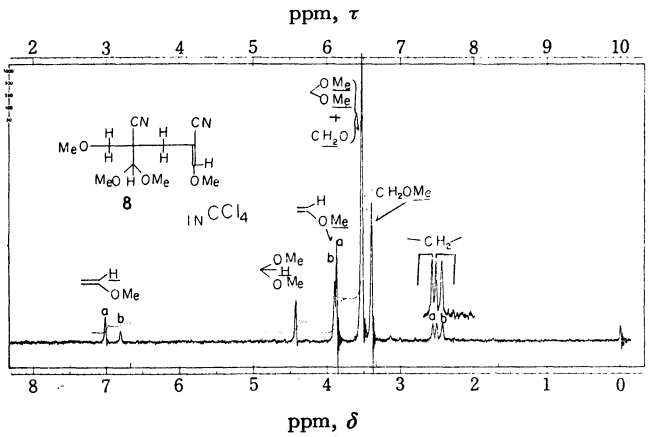

Fig. 1. NMR spectrum of **8** (a mixture of *cis* and *trans* isomers) in carbon tetrachloride at 60 MHz.

The assignment of the other signals was also consistent with the proposed structure. The methyl signal of the 2-methoxymethyl group was observed as a three-proton singlet at 6.60 τ and the two methyls of the acetal group, as a six-proton singlet at 6.45 τ, which overlapped with the two-proton singlet due to the methylene proton of the 2-methoxymethyl group. The methine proton of the acetal group was observed as an one-proton singlet at 5.60 τ.

8) A. Takamizawa, K. Hirai, and S. Sumimoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 238 (1966).

9) "*Cis*" means that the methoxy group of the 4-methoxymethylene moiety is located on the same side of the nitrile group, while "*trans*" means that it is found on the opposite side.

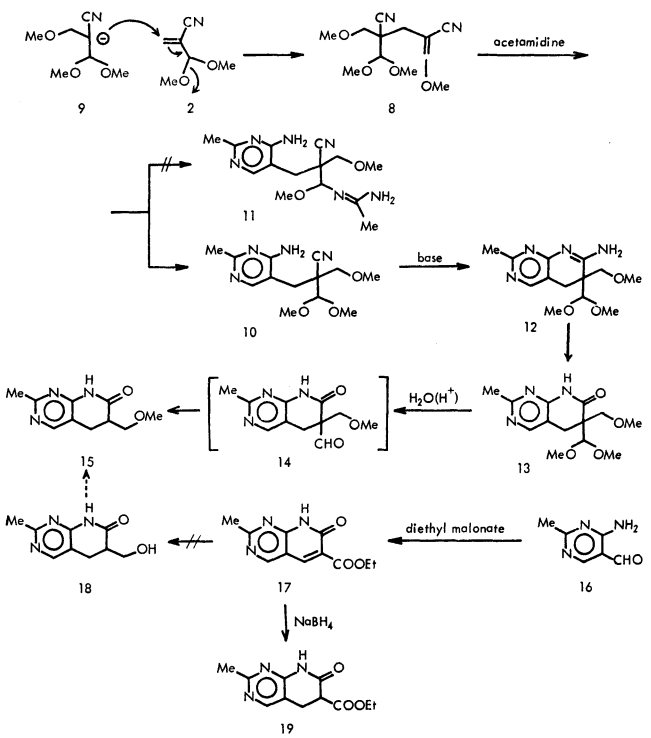

Chart 2

A reasonable pathway for the formation of **8** has been proposed; it is shown in Chart 2. Under basic conditions, an equilibrium of **1**⇌carbanion (**9**)⇌**2** can give **8**. Although the formation of **3** from **9** was also expected, the addition product of **9** to **3** was scarecely detected. Therefore, the initial step of the reaction of **1** under basic conditions must be the predominant formation of **2**. Consequently, in the reaction of **1** with acetamidine, the Michael-type addition of acetamidine to **2** initially formed may be expected as the second step. The disagreement for the initial step of the reaction of **1** with acetamidine between this conclusion (**1**→**2**→Michael-type addition compound→**6**) and the mechanism proposed by Takamizawa *et al.* (**2**→**1**→**5**→**6**)[2] has prompted us to study the reaction of **8** with acetamidine.

If the reaction of **1** with acetamidine proceeded only by the Michael-type addition of acetamidine to a double bond, **8** would be converted into a pyrimidine (**10**), in which the acetal group of **8** remained unchanged. On the other hand, if the reaction of **1** could proceed by the direct substitution of the acetal part, **8** could be converted into another pyrimidine (**11**), which has no acetal group. When **8** was treated with acetamidine in 1,2-dimethoxyethane (DME) at a reflux temperature, a compound, $C_{13}H_{20}N_4O_3$, was obtained which was proved to be 2-methyl-4-amino-5-(2′-cyano-2′-dimethoxymethyl-3′-methoxy)propylpyrimidine (**10**) by physical and chemical methods, as will be reported in detail below.

The UV spectrum showed the characteristic bands due to 4-aminopyrimidines[10,11] and the IR spectrum

10) A. Takamizawa, *Yakugaku Zasshi*, **74**, 748 (1954).

11) D. J. Brown, "The Pyrimidines," Interscience, New York (1962), p. 447.

showed the bands due to non-conjugate nitrile and acetal groups. The NMR spectrum also suggested the presence of pyrimidine ring and an acetal group. Therefore, the structure of **10** was established.

The structure of **10** was further confirmed by the following reactions. The heating of **10** in pyridine containing sodium hydroxide afforded **12**. The IR spectrum showed the absence of a nitrile group and the UV spectrum in ethanol showed the absorption maxima at 221 and 301 mμ, which were shifted to 281 and 322 mμ in acidic media. As these spectral data suggested the presence of a bicyclic structure, **12** was concluded to be 2-methyl-6-dimethoxymethyl-6-methoxymethyl-7-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine.

The hydrolysis of **12** with acetic acid gave **13**, $C_{13}H_{19}N_3O_4$, which was identified as 2-methyl-6-dimethoxymethyl-6-methoxymethyl-7-oxo-8*H*-5,6-dihydropyrido[2,3-*d*]pyrimidine (**13**) from its IR spectrum, which showed the bands due to amidocarbonyl, acetal, and methoxymethyl groups. The UV spectrum in ethanol showing absorption maxima at 242 and 275 mμ which were shifted to 280 mμ in acidic media and to 280 and 301 mμ in alkaline media, also supported the structure. Hydrolysis of **12** under strongly acidic conditions gave **15**, $C_{10}H_{13}N_3O_2$. The IR and NMR spectra showed the absence of an acetal group, and the behavior in the UV spectrum was quite similar to that of **13**. Therefore, the structure of **15** is probably 2-methyl-6-methoxymethyl-7-oxo-8*H*-5,6-dihydropyrido[2,3-*d*]pyrimidine, which can be derived *via* a formyl compound (**14**). To obtain further evidence for the above-described structures, the synthesis of **15** was attempted by means of the scheme outlined in Chart 2 (**16**→**17**→**18**→**15**). 2-Methyl-6-carbethoxy-7-oxo-8*H*-pyrido[2,3-*d*]pyrimidine (**17**) was prepared by the reaction of 2-methyl-4-amino-5-formylpyrimidine (**16**)[12] with diethyl malonate, using piperidine as the catalyst. The IR spectrum, which showed the characteristic band due to the amidocarbonyl group, and the NMR spectrum, which showed signals of the ethoxy group, the methyl group, the pyrimidine-ring proton, and the pyridone-ring proton, confirmed the structure. The behavior in the UV spectrum also supported the structure.

The reduction of **17** with lithium aluminum hydride to **18** was unsuccessful because of the formation of many unexpected products. However, another reduced product (**19**) was obtained by using sodium borohydride as a reducing reagent. The IR spectrum showed two carbonyl bands, and the NMR spectrum exhibited signals due to the ethyl group, the pyrimidine-ring proton, the methyl group on the pyrimidine-ring, and the $-CH_2-CH-$ moiety appearing as an ABX pattern.

These data suggested that **19** was 2-methyl-6-carbethoxy-7-oxo-8*H*-5,6-dihydropyrido[2,3-*d*]pyrimidine. Although the attempt to prepare the expected compound, **18**, for the synthesis of **15** through a different scheme was unsuccessful, the behavior of **19** in the UV spectrum was quite similar to that of **15**. Therefore, the structures of the **13** and **15** and, consequently, the structure of **10** were confirmed. The formation of **10** from only the reaction of **8** with acetamidine suggested that the acetal group of **1** was inert for the substitution with acetamidine under basic conditions and that the Michael-type addition of acetamidine to double bonds was preferable.

As has been described above, under basic conditions, **1** would be predominantly converted into **2** in the initial stage and the Michael-type addition of acetamidine to a double bond would more easily occur as compared with the case of the low reactivity of an acetal group. Therefore, the intermediate, detected spectrophotometrically, is derived from the reaction of **2** with acetamidine, not directly from the reaction of **1**.

Pietra has reported a reaction of acrylonitrile with benzamidine which yields 2-phenyl-4-amino-5,6-dihydropyrimidine (**21**).[13] As no detailed data were presented, however, we reinvestigated this reaction under milder conditions. In the initial stage of the reaction, a new compound (**20**) was isolated; it was then easily converted into **21** on heating. The compound **20** showed the ba nddue to a non-conjugate nitrile group in the IR spectrum and the signal due to an ethylene group appearing as an A_2B_2 pattern in the NMR spectrum (chloroform-*d*). Therefore, **20** was determined to be 3-benzamidinopropionitrile, and this reaction was concluded to proceed through the Michael-type addition of benzamidine to acrylonitrile, followed by cyclization. Consequently, the most likely structure of the intermediate, λ_{max}^{MeOH} 262 mμ, is 2-methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**27**), which is formed by the cyclization of 2-dimethoxymethyl-3-acetamidinopropionitrile (**26**), the addition product of acetamidine to **2**. To obtain further rational evidence of this idea, the synthesis of a model compound, 2-methyl-4-amino-5,6-dihydropyrimidine (**23**), was attempted. The treatment of acetamidine with acrylonitrile afforded a syrup, which was then converted into crystals at room temperature. The crystals, $C_5H_9N_3$, showed no band due to a nitrile group in the IR spectrum. Therefore, it was identified as 2-methyl-4-amino-5,6-dihydropyrimidine (**23**). The purification of the intermediate syrup was unsuccessful, but its IR spectrum, showing the band due to a non-conjugate nitrile group, suggested that it was 3-acetamidinopropionitrile (**22**).

The structure of **23** was also supported by the NMR spectrum in dimethyl sulfoxide-d_6 (Fig. 2), which showed a broad signal due to an amino group at 5.20 τ, a narrow triplet due to the methyl group at the 2-position at 8.18 τ, and signals due to H_5 (7.99 τ) and H_6 (6.78 τ) appearing as an A_2B_2 pattern. The triplet of the methyl group and the broad signal of H_6 must be caused by homoallyl coupling between them (J 1Hz). The value of the coupling constant was consistent with those of the coupling constants of **28** (J

12) S. Mizukami and E. Hirai, *Chem. Pharm. Bull.* (Tokyo), **14**, 1321 (1966).

13) S. Pietra, *Boll. Sci. Fac. Chem. Ind. Bologna*, **11**, 78 (1953).

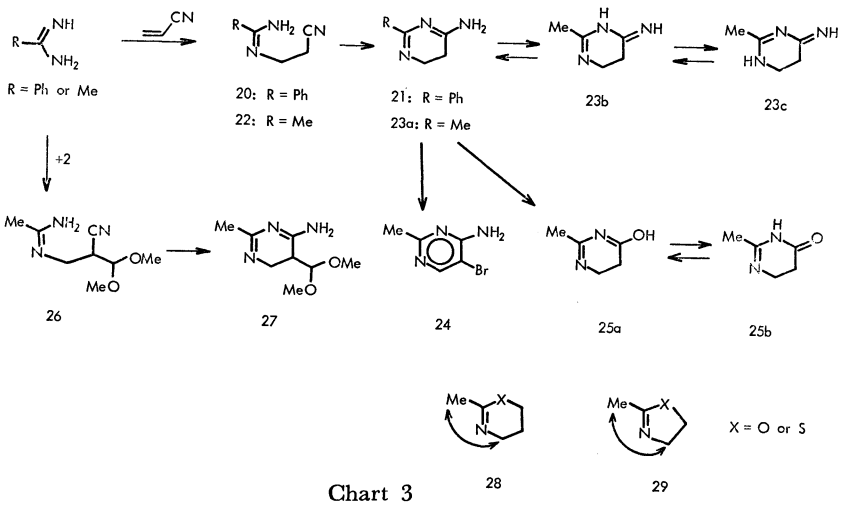

Chart 3

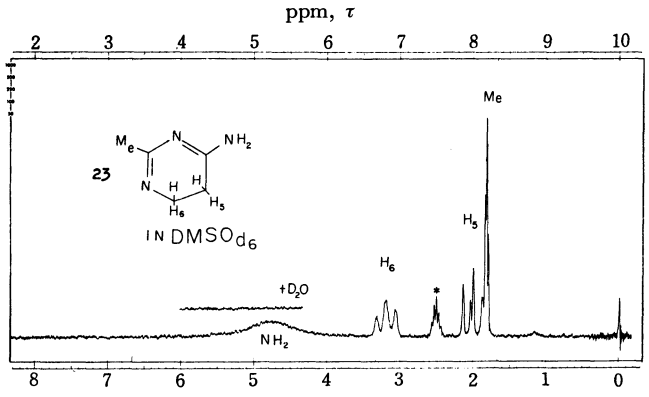

Fig. 2. NMR spectrum of **23** in DMSO-d_6 at 60 MHz (* DMSO-d_5).

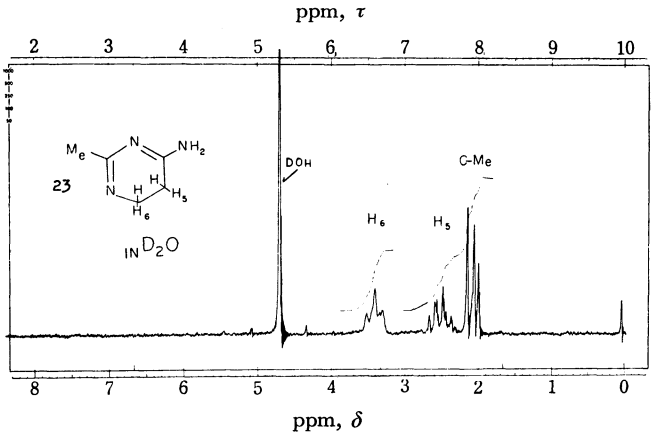

Fig. 3. NMR spectrum of **23** in deuterium oxide at 60 MHz.

1.5 Hz),[14] and **29** (J 1.38—1.65 Hz).[15] The methyl signal of **23** appeared as one triplet in dimethyl sulfoxide-d_6, but as three broad methyl singlets in deuterium oxide (Fig. 3). The spectrum seemed to suggest the existence of three kinds of tautomers, such as **23a**, **23b**, and **23c**.

The structure of **23** was unequivocally established by the following reactions. The bromination of **23** with bromine in acetic acid, followed by dehydrobromination with triethylamine, gave 2-methyl-4-amino-5-bromopyrimidine (**24**).[16] The addition of hydrochloric acid to a methanol solution of **23** immediately gave colorless crystals (**25**), whose molecular formula agreed with that of the hydrolized product of **23**. The NMR spectrum of **25** in methanol-d_4 showed a narrow triplet due to the methyl group, and signals due to H_5 and H_6 appeared as an A_2B_2 pattern. Therefore, **25** was determined to be 2-methyl-4-hydoxy-5,6-dihydropyrimidine (isolated as the HCl salt). As the IR spectrum of **25** showed the band due to an amidocarbonyl group, it seemed to have preferably the **25b** structure in a crystalline state rather than the **25a** structure. Easy hydrolysis of 4-amino group of **23** supported the presence of the partial structure of amidine, and the structure of **23**.[17]

The behavior of **23** in the UV spectrum was very important. The spectrum in methanol showed its absorption maximum at 270 mμ (ε 8,100); it was shifted to 275 mμ in acidic media and to 258 mμ in basic media. The values of the absorption maxima, 270 mμ and 258 mμ, were close to that of 262 mμ of the intermediate previously observed under basic conditions because of the presence of acetamidine. Therefore, the idea that **27** is the intermediate instead of **5** was supported.

In conclusion, for the reaction of **1** with acetamidine we would like to propose the following pathway **1**→**2**→**26**→**27** (the intermediate, λ_{max}^{MeOH} 262 mμ) → **6**, which accounts for the observed results. The mechanism of the step of **27**→**6** is also interesting; studies of it will be presented separately.

Experimental

All the melting points were recorded on a Kofler block and have not been corrected. The NMR spectra were taken with a Varian A-60-A spectrometer, using tetramethylsilane as the internal reference, and the chemical shifts were expressed in τ value (s: singlet, d; doublet, t: triplet, q:

14) E. Cherbuliez, *Helv. Chem. Acta*, **50**, 331 (1967).
15) M. A. Weinberger and R. Greenhalgh, *Can. J. Chem.*, **41**, 1038 (1963).
16) Z. Buděšisky, *Collect. Czech. Chem. Commun.*, **14**, 223 (1949).
17) L. Doub and U. Krolls, *J. Heterocycl. Chem.*, **7**, 527 (1970).

quartet, m: multiplet). The molecular weights were determined by means of a vapor-pressure osmometer in chloroform unless otherwise stated. The solvents used were removed under reduced pressure.

*Reaction of 2-Dimethoxymethyl-3-methoxypropionitrile (**1**) with Sodium Methoxide.* A mixture of sodium methoxide (2.5 g) and **1** (50 g) was stirred at 40°C, while the methanol produced during the reaction period was eliminated under reduced pressure. After 2 hr, the mixture was dissolved in benzene (600 ml); the benzene solution was washed with water, 1 N hydrochloric acid, saturated sodium bicarbonate, and water, dried, and then the solvent was removed. The distillation of the residue (40 g) gave 2-dimethoxymethyl-2-methoxymethyl-4-methoxymethyleneglutaronitrile (**8**) (22.3 g, bp 177—183°C/2 mmHg). $UV_{m\mu}^{EtOH}$ 232 (ε 11100) $IR_{cm^{-1}}^{film}$ 2250, 2240 (CN), 1640 (C=C), 1080, 1150 (C–O–C, acetal). Found: C, 56.74; H, 7.33; N, 10.98%; mol wt, 260 (benzene). Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.14; N, 11.02%; mol wt, 254.28.

*Reaction of 2-Dimethoxymethyl-2-methoxymethyl-4-methoxymethyleneglutaronitrile (**8**) with Acetamidine.* Acetamidine hydrochloride (2.6 g) was neutralized by methanolic sodium methoxide prepared from sodium (554 mg), and then the methanol was removed. To the residue, DME (100 ml) and **8** (2.2 g) were added, after which the mixture was refluxed for 2 hr. The solvent was evaporated to dryness and then extracted with ether (50 ml). From the ether layer, **8** (748 mg) was recovered. The recrystallization of the ether-insoluble residue from ethyl acetate gave 2-methyl-4-amino-5-(2′-cyano-2′-dimethoxymethyl-3′-methoxy)propylpyrimidine (**10**) (needles; 985 mg). Mp 139—140°C. $UV_{m\mu}^{MeOH}$ 235 (ε 6900), 278 (ε 3400); (+HCl) 252 $IR_{cm^{-1}}^{KBr}$ 2240 (CN), 1100, 1070 (acetal). NMR ($CDCl_3$) 1.93^s (1H, H_6), 5.63^s (1H, C<u>H</u>$(OMe)_2$), 7.53^s (3H, 2-Me), 6.43^s (6H, CH($O\underline{Me}$)$_2$), 6.59^s (3H, $CH_2O\underline{Me}$), 7.13^q (2H, $C\underline{H}_2OMe$). Found: C, 55.70; H, 7.10; N, 20.21%, mol wt, 279. Calcd for $C_{13}H_{20}N_4O_3$: C, 55.70; H, 7.19; N, 19.99%; mol wt, 280.32.

*2-Methyl-6-dimethoxymethyl-6-methoxymethyl-7-amino-5,6-dihydropyrido[2,3-*d*]pytimidine (**12**).* To a solution of 2-methyl-4-amino-5-(2′-cyano-2′-dimethoxymethyl-3′-methoxy)propylpyrimidine (**10**; 300 mg) in pyridine (1.5 g), a 48% sodium hydroxide solution (1 g) was added; the solution was then heated at 100°C for 20 min. After the removal of the pyridine, the residue was extracted with chloroform (200 ml), and then the chloroform was removed. The recrystallization of the residue from acetonitrile gave **12** (needles; 44 mg). Mp 195—196°C. $UV_{m\mu}^{EtOH}$ 221 (ε 13200), 301 (ε 14200); (+HCl) 281, 322. Found: C, 55.85; H, 7.18; N, 19.86%; mol wt, 285. Calcd for $C_{13}H_{20}N_4O_3$: C, 55.70; H, 7.19; N, 19.99%; mol wt, 280.32.

*2-Methyl-6-dimethoxymethyl-7-oxo-8H-5,6-dihydropyrido[2,3-*d*]pyrimidine (**13**).* A solution of 2-methyl-6-dimethoxymethyl-6-methoxymethyl-7-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine (**12**; 0.5 g) in 10% acetic acid (10 ml) was heated at 100°C for 0.5 hr. The solution was concentrated and neutralized with a saturated sodium carbonate solution, and then the solvent was evaporated to dryness. The residue was extracted with ethyl acetate. From the extract, crude crystals of **13** were obtained (400 mg; mp 118—120°C). Recrystallization from ether gave pure plates of **13** (mp 125–125.3°C). $UV_{m\mu}^{EtOH}$ 242 (ε 5600), 275 (ε 10700); (+HCl) 280; (+NaOH) 280,301. $IR_{cm^{-1}}^{KBr}$ 1700 (CONH), 1065, 1100, 1120 (C–O–C, acetal). NMR ($CDCl_3$) 1.73^s (1H, H_4), 5.25^s (1H, C<u>H</u>$(OMe)_2$), 6.48^s (6H, CH($O\underline{Me}$)$_2$), 6.28^d, 6.33^d (2H, $C\underline{H}_2OMe$, J 9 Hz), 6.73^s (3H, $CH_2O\underline{Me}$), 6.82^m, 7.03^m (2H, H_5), 7.35^s (3H, 2-Me). Found: C, 55.52; H, 6.77; N, 15.07%, mol wt, 285. Calcd for $C_{13}H_{19}N_3O_4$: C, 55.52; H, 6.76; N, 14.95%, mol wt, 281.31.

*2-Methyl-6-methoxymethyl-7-oxo-8H-5,6-dihydropyrido[2,3-*d*]pyrimidine (**15**).* A solution of 2-methyl-6-dimethoxymethyl-6-methoxymethyl-7-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine (**12**; 1 g) in 1 N hydrochloric acid (7 g) was heated at 100°C for 50 min. The solution was neutralized with a saturated sodium bicarbonate solution and then concentrated to 2 ml. After the extraction of this solution with chloroform (20 ml), the chloroform was evaporated to give a powder (723 mg). Recrystallization from methanol gave **15** (175 mg). Mp 185—186°C (columns). NMR ($CDCl_3$) 1.63^s (1H, H_4), 6.25^m (2H, $-CH_2O-$), 6.61^s (3H, OMe), 7.05^m (2H, H_5), 7.05^m (1H, H_6), 7.33^s (3H, 2-Me). Found: C, 58.11; H, 6.43; N, 20.37%. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28%.

*2-Methyl-6-carbethoxy-7-oxo-8H-pyrido[2,3-*d*]pyrimidine (**17**).* A mixture of 2-methyl-4-amino-5-formylpyrimidine[12] (**16**; 1.35 g), diethyl malonate (1.6 g), benzoic acid (45 mg), piperidine (100 mg) and benzene (18 ml) was refluxed for 2 hr, during which time the water produced was removed by azeotropic distillation with benzene. Then, more piperdine (110 mg) was added to the solution, and it was refluxed for an additional 4 hr. After cooling, the crystals which appeared were separated from the solution by filtration. The crystallization of the crystals from ethanol–methanol gave **17** (1.36 g). Mp 230—231.5°C (needles). $UV_{m\mu}^{EtOH}$ 265 (ε 3400), 274 (ε 3100), 324 (ε 9300), (+HCl) 265, 275, 320; (+NaOH) 256, 275, 353. $IR_{cm^{-1}}^{KBr}$ 1690 (CONH). NMR ($CDCl_3$) 5.29^q (2H), 8.58^t (3H)(OC_2H_5), 7.17^s (2-Me), 1.53^s (1H, H_4), 1.05^s (1H, H_5). Found: C, 56.39; H, 4.69; N, 17.79%; mol wt, 249. Calcd for $C_{11}H_{11}N_2O_3$: C, 56.65; H, 4.75; N, 18.02%; mol wt, 233.32.

*Reduction of 2-Methyl-6-carbethoxy-7-oxo-8H-pyrido[2,3-*d*]pyrimidine (**17**) with Sodium Borohydride.* To a solution of **17** (1.08 g) in ethanol (84 ml), sodium borohydride (470 mg) was added at 0°C. After the solution has been stirred for 1 hr at 0°C, the solution was adjusted to pH 4 with hydrochloric acid and then evaporated to dryness under reduced pressure. The residue was extracted with acetone (80 ml), and then the solvent was removed. The residue (powder 1.169 g) was purified by silica gel column chromatography [Wakogel Q-23 (30 g) was used]. The desired 2-methyl-6-carbethoxy-7-oxo-8*H*-5,6-dihydro[2,3-*d*]pyrimidine (**19**) was eluted with a mixture of chloroform and ethanol (8 : 1 v/v, 250 ml) after initial elution with chloroform (150 ml). The recrystallization of the eluted compound from ethanol gave **19** (333 mg). Mp 200—200.5°C. $UV_{m\mu}^{EtOH}$ 240 (ε 8200), 271 (ε 14100); (+HCl) 277; (+NaOH) 298. $IR_{cm^{-1}}^{KBr}$ 1740, 1690 (C=O). NMR ($CDCl_3$) 5.78^q (2H), 8.75^t (3H) (OC_2H_5), 1.63^s (1H, H_4), 7.35^s (3H, 2-Me), 6.78^m (2H, $-\underline{CH}_2-CH$), 6.32^m (1H, $-CH_2-C\underline{H}-$). Found: C, 56.21; H, 5.65; N, 17.71%; mol wt, 249. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.77; N, 17.86%, mol wt, 235.24.

Reaction of Acrylonitrile with Benzamidine. Benzamidine (4.5 g) was dissolved completely in acrylonitrile (2 g) at −30°C and then left at room temperature. After 1 hr, crystals of 3-benzamidinopropionitrile (**20**) appeared. $IR_{cm^{-1}}^{Film}$ 2280 (CN). NMR ($CDCl_3$) 6.48^m (2H, H_3), 7.27^m (2H, H_2). The crystals were heated for 20 min on a boiling water-bath and then recrystallized from chloroform-benzene. Colorless plates of 2-phenyl-4-amino-5,6-dihydropyrimidine (**21**) (mp 178—180°C)[13] were thus obtained (3.1 g).

Reaction of Acrylonitrile with Acetamidine. A solution of acetamidine hydrochloride (11.8 g) in methanol (30 ml) was neutralized with methanolic sodium methoxide pre-

pared from sodium (2.56 g) and methanol (50 ml). The solution was filtered, and then the filtrate was evaporated to dryness. To the residue, acrylonitrile (4 g) was added at 10—20°C, after which the solution was allowed to stand at room temperature for 1 day. The reaction mixture was then solidified. Recrystallization from ethanol–ether (3/8 v/v) gave crude crystals of 2-methyl-4-amino-5,6-dihydropyrimidine (**23**). The further recrystallization of **23** from ethanol gave a pure sample (cubics, 1.45 g). Mp 188—192°C. Found: C, 53.85; H, 8.39; N, 37.82%; mol wt, 125 (ethanol). Calcd for $C_5H_9N_3$: C, 54.03; H, 8.16; N, 37.81%; mol wt, 111.15.

*Dehydrogenation of 2-Methyl-4-amino-5,6-dihydropyrimidine (**23**).* Into a solution of **23** (222 mg) in acetic acid (6 ml) in portions was stirred below 15°C. After the solution had been stirred for 40 min, precipitates were collected by filtration and washed with ethanol. A mixture of precipitates, triethylamine (300 mg), and ethanol (3 g) was refluxed for 3 min, evaporated to dryness, and extracted with benzene, and the benzene was removed. The recrystallization of the residue from water gave 2-methyl-4-maino-5-bromopyrimidine (**24**) (80 mg), mp 138—140°C.[16]

*Hydrolysis of 2-Methyl-4-amino-5,6-dihydropyrimidine (**23**).* To a solution of **23** (111 mg) in methanol, 21% methanolic hydrochloric acid (w/w 0.4 g) was added. Crystals of hydrochloric acid salt of **23** thus appeared. Water (25 mg) was added to the solution, and the solution was stirred at room temperature. After 1 hr, the crystals dissappeared and columnar crystals were newly precipitated. Recrystallization of the columnar crystals from methanol gave 2-methyl-4-hydroxy-5,6-dihydropyrimidine hydrochloride (**25**) (40 mg). Mp>250°C. $UV_{m\mu}^{MeOH}$ 227 (ε 7,570); (+NaOH) 208. $IR_{cm^{-1}}^{KBr}$ 1740 (CONH). NMR (CD_3OD) 7.60^s (3H, 2-Me), 7.15^m (2H, H_5), 6.15^m (2H, H_6). Found: C, 40.41; H, 6.10; N, 18.86%. Calcd for $C_5H_9N_2OCl$: C, 40.36; H, 6.14; N, 19.06%.

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