The Reaction Mechanism of 2-Dimethoxymethyl-3-methoxypropiononitrile with Acetamidine. III.[1] The Reaction with Benzamidine[2]

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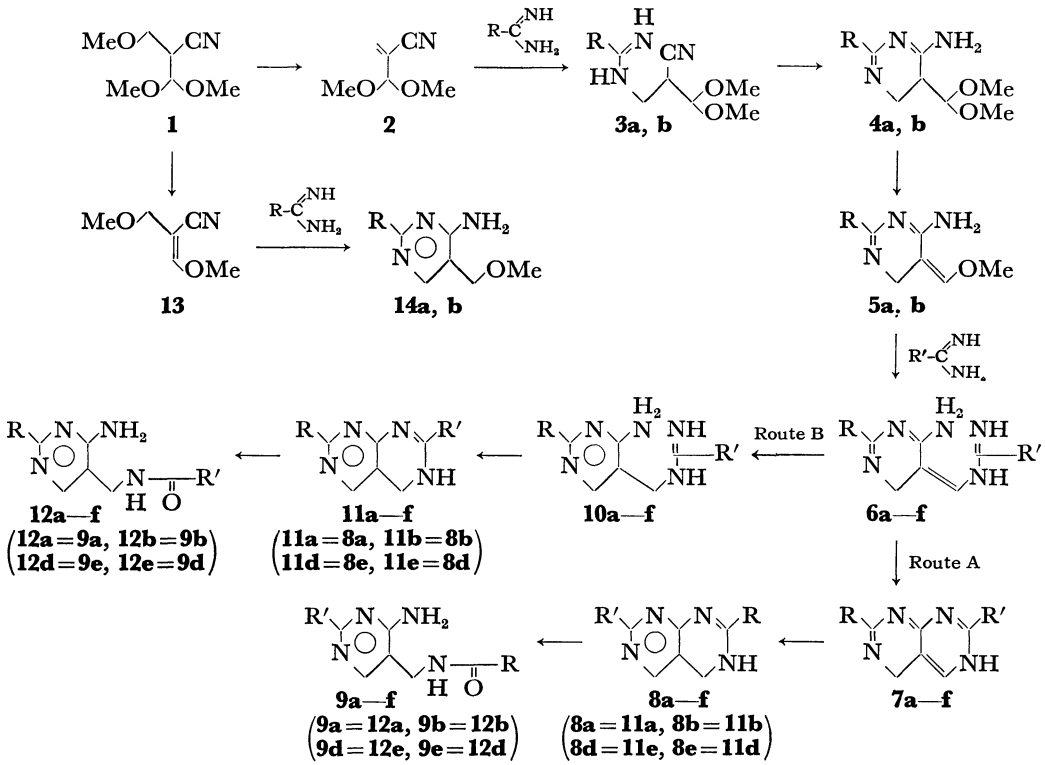
In order to elucidate the effect of basicities of amidines on their reactions with 2-dimethoxymethyl-3-methoxypropiononitrile (**1**), the reaction of **1** with benzamidine was studied. Products are similar to those from the reaction of **1** with acetamidine. The minor pathway in the reaction with acetamidine (Route B in Chart 1) was the major one in the reaction with benzamidine. This remarkable difference could be explained in terms of the electronic effect of 2-substituents of the intermediates (**4a** and **4b**) in both reactions and of basicities of acetamidine and benzamidine.

α-Formylpropiononitrile derivatives,[3] *e.g.*, 2-dimethoxymethyl-3-methoxypropiononitrile (**1**) and 2-dimethoxymethylacrylonitrile (**2**), are important building blocks for heterocyclic compounds.[4,5] When treated with acetamidine, **1** and **2** afford 2,7-dimethyl-5,6-dihydropyrimido[4,5-*d*]pyrimidine (**8a**), which is an important intermediate for thiamine since it is easily hydrolyzed to 2-methyl-4-amino-5-acetamidomethylpyrimidine (**9a**).[4] In previous papers we proposed a detailed pathway for the reactions as shown in Chart 1.[1,6] The pathway involves the major process **1**→**2**→**3a**→**4a**→**5a**→**6a**→**7a**→**8a** and minor ones **1**→**13**→**14a** and **6a**→**10a**→**11a** (=**8a**). Among the proposed intermediates, the key intermediate **4a** was successfully isolated in a fairly good yield but the others were not under usual reaction conditions.[1] To extend the scope of these reactions, the reaction of **1** with benzamidine was attempted. Since the basicities of reaction media were thought to play an important role for some steps of the reaction,[1] studies with less basic benzamidine[7] seemed necessary.

The reaction of **1** with benzamidine is expected to



a: R=R′=Me b: R=R′=Ph c: R=Ph, R′=*p*-tolyl
d: R=Me, R′=Ph e: R=Ph, R′=Me f: R=Me, R′=Et

Chart 1.

1) For part 2, see T. Nishino, M. Kiyokawa, Y. Miichi, and K. Tokuyama, This Bulletin, **45**, 2010 (1972). A part of this paper was reported in a preliminary form; T. Nishino, M. Kiyokawa, and K. Tokuyama, *Tetrahedron Lett.*, **1968**, 4321.

2) Pyrimidines Part 11. For part 10, see Ref. 1.

3) G. A. Chelinstev, *Chem. Abstr.*, **40**, 4069 (1946).

4) A. Takamizawa, K. Tokuyama, and K. Tori, This Bulletin, **32**, 188 (1959), and references cited therein.

5) A. Takamizawa, K. Hirai, Y. Sato, and K. Tori, *J. Org. Chem.*, **29**, 1740 (1964).

6) T. Nishino, M. Kiyokawa, Y. Miichi, and K. Tokuyama This Bulletin, **45**, 1127 (1972).

7) P. A. S. Smith, "The Chemistry of Open-chain Organic Nitrogen Compounds," Vol. 1, Bengamin, New York (1965), p. 178.

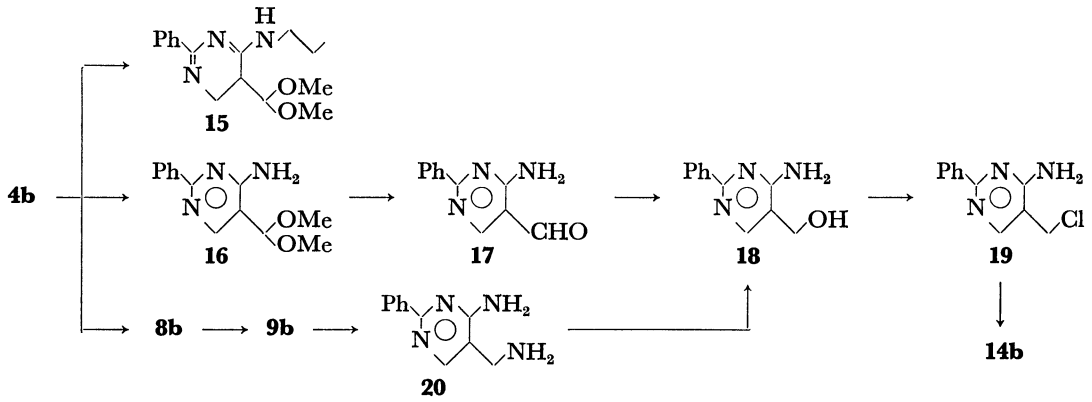


Chart 2.

proceed *via* the same pathway as that with acetamidine. When **1** with benzamidine was heated in methanol at 40°C for 6 hr, three products, **4b** (11%), **8b** (2.5%), and **10b** (6.8%), were obtained along with the recovery of 68% of **1**.

Compound **4b** showed an absorption band similar to that of 2-phenyl-4-amino-5,6-dihydropyrimidine in the UV spectrum.[6,8] **4b** was therefore tentatively characterized as 2-phenyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine, which corresponds to **4a**. The NMR spectrum supported the structure; *viz.*, it showed the signals of an ABXY system, in which H_6 and $H_{6'}$ constitute an AB part, H_5 an X part, and the methine proton of the acetal group a Y part, and of a 6-proton singlet due to two methoxy groups. When treated with *n*-propylamine, **4b** was easily converted into 4-*n*-propylamino analog of **4b** (**15**). This facile transamination suggested the existence of 4-aminodihydropyrimidine moiety.[1]

Unequivocal proof of the structure of **4b** was provided by its conversion into 2-phenyl-4-amino-5-methoxymethylpyrimidine (**14b**), an authentic sample of which was obtained from **13** and benzamidine in a way similar to the preparation of **14a** from **13** and acetamidine.[9] Treatment of **4b** with chloranil gave a pyrimidine (**16**), which was readily hydrolyzed to 5-formylpyrimidine (**17**). Reduction of **17** with sodium borohydride yielded 5-hydroxymethylpyrimidine(**18**), which was converted into **14b** *via* a 5-chloromethyl compound (**19**). The spectral and elementary analytical data supported the presence of the above intermediates **16**, **17**, and **18**.

The pathway **1**→**2**→**3b**→**4b**[1,6] was supported by the isolation of **4b**. When **2** was treated with benzamidine in 1,2-dimethoxyethane, the formation of **3b** was confirmed at the initial stages of the reaction. Although **3b** could not be isolated in a pure state because of its rapid cyclization to **4b**, its structure was supported by the IR and UV spectra which showed the presence of non-conjugate nitrile[1,6] and benzamidino groups.

Compound **8b**, $C_{18}H_{14}N_4$, showed the absorption maximum at 350 nm in the UV spectrum. It was also obtained by the further reaction of **4b** with benzamidine. Thus, **8b** should be the final product corresponding to **8a**. Hydrolysis of **8b** gave **9b**, which was further hydrolyzed to 2-phenyl-4-amino-5-aminomethylpyrimidine (**20**). Treatment of **20** with sodium nitrite gave the above-described 5-hydroxymethylpyrimidine **18**. These series of reactions and the NMR spectrum supported the structure of **8b**.

Compound **10b**, which gave a correct analysis for **8b** plus one mole of ammonia, was easily converted into **11b** (=**8b**) on heating and showed an absorption band similar to that of **9b** in the UV spectrum. Thus, **10b** was confirmed to be 2-phenyl-4-amino-5-benzamidinomethylpyrimidine corresponding to the intermediate of the minor pathway (Route B in Chart 1) in the reaction of **1** with acetamidine.

Formation of **8b** suggests that the second step of the reaction **4b**→**8b** also proceeded *via* the same pathway as that of the reaction with acetamidine **4a**→**8a**. However, it was somewhat surprising that the yield of **10b**, *viz.*, the contribution of Route B (see Chart 1), was much higher than in the case of the reaction of **1** with acetamidine.

To obtain the contribution ratio of Routes A (**6**→**7**→**8**) to B (**6**→**10**→**11**), the reaction of **4b** and *p*-toluamidine was examined. Treatment of **4b** with *p*-toluamidine in methanol followed by hydrolysis afforded a mixture of 2-phenyl-5-*p*-toluamidomethyl- (**12c**) and 2-*p*-tolyl-5-benzamidomethyl-4-aminopyrimidine (**9c**). The former pyrimidine **12c** was the product *via* Route B and the latter **9c** *via* Route A. Their structures were identified by comparison with those of authentic samples. The authentic **12c** was prepared by the reaction of **20** with *p*-toluchloride and **9c** by the reaction of **1** with *p*-toluamidine as outlined in Chart 3.

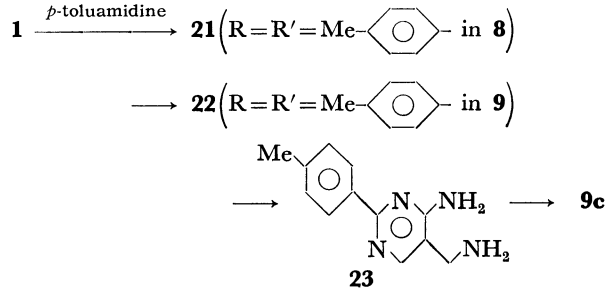


Chart 3.

8) S. Pietra, *Boll. Sci. Fac. Chim. Ind. Bologna*, **11**, 78 (1953).
9) A. Takamizawa and R. Maeda, *Yakugaku Zasshi*, **74**, 746 (1954).

Table 1. Yield of pyrimidines in the reactions of **4** and amidines

Starting material		Reaction time		Yield of pyrimidines (%) Molar ratio of amidine and amidine hydrochloride			
4	Amidine	hr		3:0[a)]	2:1	1:2	0:3
4b	*p*-Toluamidine	14	**9c**	(A) 30	75	67	48
			12c	(B) 46	12	6	trace
			9c+12c	70	87	73	48
4b	Acetamidine	5	**9e**	(A) 37	70	52	37.5
			12e	(B) 4	3	3	trace
			9e+12e	41	73	55	37.5
4a	Propioamidine	5	**9f**	(A) 44	87	—	28
			12f	(B) 6	8	—	6
			9f+12f	50	95	—	34
4a	Benzamidine	5.5	**9d**	(A) 22	65	36	trace
			12d	(B) 2	trace	trace	trace
			9d+12d	24	65	36	trace

A: Product *via* Route A. B: Product *via* Route B.

a) Containing a samll amount of sodium methoxide, since exact neutralization of the hydrochlorides of **4** and amidine was difficult.

The B/A ratio in the reaction of **4b** with *p*-toluamidine was determined by the integration of the respective singlets due to the methyl groups of *p*-tolyl moieties of **12c** and **9c** in the NMR spectrum of the product. The results are summarized in Table 1. The maximum yield of total pyrimidines was observed in the presence of some amount of benzamidine hydrochloride. On the other hand, the contribution of Route B increased with the decrease of the amidine hydrochloride; Route B became a major pathway in the absence of the hydrochloride. These interesting results prompted us to reinvestigate the reaction of **4a** with propioamidine under similar conditions. The ratio of two products, **12f** *via* Route B and **9f** *via* Route A, was determined by means of gas chromatography. The results are shown in Table 1. The maximum yield of total pyrimidines **12f** and **9f** was similarly observed in the presence of a similar amount of amidine hydrochloride, and the relative ratio of Route B increased with the decrease of the amidine hydrochloride. However, the contribution of Route B, *i.e.* the yield of **12f**, was always very low.

The remarkable contribution of Route B in the reaction of **4b** with benzamidines as compared with the reaction of **4a** with acetamidines can be explained in terms of the electronic effect of 2-substituents of possible intermediates **6a** and **6b**, and of the basicities of amidines.

The reactions of **4a** with benzamidine and of **4b** with acetamidine were carried out. Hydrolyzed products from the former reaction were **12d** (=**9e**) *via* Route B and **9d** (=**12e**) *via* Route A, and from the latter **12e** (=**9d**) *via* Route B and **9e** (=**12d**) *via* Route A. The structure of **9d** (=**12e**) was identified by its conversion into **9b** and that of **9e** (=**12d**) by comparison with an authentic sample prepared by the benzoylation of 2-methyl-4-amino-5-aminomethylpyrimidine (**24**).[10] The results were similar to those of the reaction of **4a** with propioamidine as shown in Table 1; Route B was always a minor pathway and the maximum yields of total pyrimidines were observed in the presence of suitable amounts of amidine hydrochlorides.

Table 1 shows that the relative ratio of Route B increases with the decrease of amidine hydrochloride. Route B proceeds by the abstraction of C_6 proton (H_6) of a possible intermediate **6** by an amidine base. Thus, it is reasonable that more basic conditions such as the absence of amidine hydrochlorides favors Route B.

For the abstraction of H_6 of **6**, the existence of an electron-attracting group such as the 2-phenyl group is more desirable. This is supported by the fact that the heating of a mixture of one mole each of **4a** and **4b** with sodium methoxide gave **14a** and **14b** in 1:10 ratio. The electronic effect can explain the fact that Route B was always minor in the reaction of **4a**. However, the yield of **12e** in the reaction of **4b** with acetamidine being lower than that of **12c** in the reaction of **4b** with *p*-toluamidine cannot be explained. Thus, Route B was expected to be favored in the former reaction since acetamidine is a stronger base than benzamidine.[7]

We considered the difference between the two reactions of **4b** to be caused by the faster cyclization of **6e**→**7e** than of **6c**→**7c**, and examined model reactions **10a**→**11a** (=**8a**) and **10b**→**11b** (=**8b**) for confirmation. Kinetic measurement for the reactions was carried out by following the increases of respective products. They showed first-order kinetics, the rate of **10a**→**11b** being higher than that of **10b**→**11b** at reflux temperature. By analogy, the cyclization of **6e**→**7e** would proceed faster than that of **6c**→**7c**. Therefore, two factors in **6c**, its slow cyclization to **7c** and the higher acidity of its C_6 position, favor Route B in the reaction of **4b** and *p*-toluamidine.

The appearance of maximum in the yields of total pyrimidines in the reaction of **4** and amidines (Table 1) may be accounted for as follows. As amidine hydrochloride catalyzes the elimination of methanol at the step **4**→**5**,[1] a higher concentration of amidine hydrochloride is desirable (see Chart 4). On th other

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

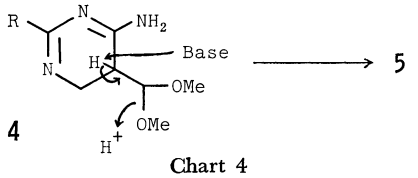


Chart 4

hand, a higher concentration of amidine is required for the step **5**→**6**. When the total amount of amidine and amidine hydrochloride is constant, both requirements can not be satisfied at the same time. Therefore, the maximum in yield appears at an appropriate ratio of amidine and amidine hydrochloride.

In conclusion, the reaction of **1** with benzamidine proceeds *via* the same pathway as that with acetamidine. The yields of the products depend on the amount of amidine hydrochlorides for both reactions. However, Route B, the minor pathway in the reaction with acetamidine, was observed as a major one in the reaction with benzamidine under the reaction conditions. The remarkable difference was essentially caused by the difference in electronic effect between phenyl and methyl groups.

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 an internal reference. The chemical shifts were expressed in terms of δ values (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). The molecular weights were determined by means of a vapor-pressure osmometer in acetone. The UV and IR spectra are shown in nm and cm^{-1}, respectively. The solvents used were removed under reduced pressure. The percentages of solutions of base and acid are given in w/w.

Reaction of 2-Dimethoxymethyl-3-methoxypropiononitrile (1) with Benzamidine. A solution of **1** (4.77 g) and benzamidine (3.87 g) in methanol (13 ml) was stirred at 40°C for 6 hr, and then evaporated to dryness. The residue was separated by alumina chromatography (Wakogel; 50 g). After removal of fraction 1 eluted with benzene (50 ml), fraction 2 was eluted with a mixture of benzene (25 ml) and ether (25 ml), and then the solvents were removed. A mixture of crystals, 2,7-diphenyl-5,6-dihydropyrimido[4,5-*d*]pyrimidine (**8b**), and an oil, **1**, was obtained. The crystals (199 mg; 2.5%) were collected by filtration, and **1** (3.8 g; 68%) was recovered from the filtrate. Recrystallization from acetonitrile gave columns of **8b** (35 mg). Fractions 3, eluted with ether (50 ml) and 4, eluted with a mixture of ether (96 ml) and ethanol (4 ml), gave 2-phenyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**4b**) (818 mg, 11%), which was purified by recrystallization from acetonitrile. The yield of pure **4b** was 198 mg (cubics). Fraction 5, further eluted with the above mixture (100 ml), gave 2-phenyl-4-amino-5-benzamidinomethylpyrimidine (**10b**) (570 mg, 6.8%), which was purified by recrystallization from acetonitrile. The yield of pure **10b** was 37 mg (cubics). **8b**: Mp 210.5—211.5°C. UV (CH_3CN) 254 (ε 72800), 312 (ε 13800), 350 (ε 9700). NMR (DMSO-d_6) 8.5—7.4 (m, 10H, phenyl), 8.35 (s 1H, H_4), 4.82 (s 2H, H_5). MS (*m/e*) 286 (M^+). Found: C, 75.50; H, 4.84; N, 19.35%. Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57%. **4b**: Mp 142°C (decomp.). UV (EtOH) 243 (ε 12900), 269 (ε 7000); (+HCl) 265, 286 (shoulder). IR(KBr) 1125, 1069 (acetal). NMR (pyridine-d_5) 7.3—7.5 (m 5H, phenyl), 4.13 (q, 1H, H_6, $J_{6,6'}$ 17.5 Hz, $J_{5,6}$ 6 Hz), 3.70 (q, 1H, $H_{6'}$, $J_{5,6'}$ 6 Hz), 2.80 (pair of triplet, 1H, H_5, J 8 Hz), 4.63 (d, 1H, C<u>H</u>$(OMe)_2$), 3.31 (s, 6H, CH$(O\underline{Me})_2$). MS (*m/e*) 247 (M^+), 215 (M^+-CH_3OH). Found: C, 63.27; H, 6.94; N, 16.78%. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99%. **10b**: Mp 156—158°C. UV (CH_3CN) 237 (ε 23000), 260 (shoulder), 284 (ε 8100), 297 (ε 7600); (+HCl) 254. NMR (DMSO-d_6) 7.3—8.0 (m, 10H, phenyl), 8.30 (s, 1H, H_6), 4.30 (s, 2H, $-CH_2-$). Found: C, 71.61; H, 5.51; N, 22.99%; mol wt, 293. Calcd for $C_{18}H_{17}N_5$: C, 71.26; H, 5.65; N, 23.09%; mol wt, 303.

Reaction of 2-Phenyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (4b). (1) Reaction with n-*Propylamine*: A mixture of **4b** (0.7 g) and *n*-propylamine (7 g) in a sealed tube was heated at 100°C for 2 hr. After evaporation of *n*-propylamine, the residue was recrystallized from benzene. Columns of 2-phenyl-4-*n*-propylamino-5-dimethoxymethyl-5,6-dihydropyrimidine (**15**) were obtained (430 mg). Mp 116—117°C. UV (EtOH) 248 (ε 10800), 281 (ε 7100); (+HCl) 258. 290, 305 (shoulder). IR(KBr) 1110, 1065 (acetal). NMR ($CDCl_3$) 8.2—7.2 (m, 5H, phenyl), 3.43—3.77 (m, 3H, H_5, H_6), 4.35 (d, 1H, J 8 Hz, C<u>H</u>$(OMe)_2$), 3.37 (s, 3H) 3.38 (s, 3H) (CH$(O\underline{Me})_2$), 2.37 (q, 2H, $-HN-C\underline{H}_2-CH_2-$), 1.58 (m, 2H, $-CH_2-C\underline{H}_2-CH_3$), 1.00 (t, 3H, $-CH_2-C\underline{H}_3$), 5.9 (m, 1H, NH). Found: C, 66.53; H, 7.79; N, 14.43%; mol wt, 279.8. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52%; mol wt, 289.4.

(2) Reaction with Benzamidine: (a) A solution of **4b** (1.3 g) and benzamidine (0.7 g) in 1,2-dimethoxyethane (20 ml) was refluxed for 18 hr. The solvent was evaporated to dryness. The residue was recrystallized from methanol to give **8b** (1.14 g, 80%). (b) A solution of **4b** (2.47 g) and benzamidine (1.2 g) in methanol (7 ml) was heated at 50°C for 5 hr. The solution was evaporated to dryness and the residue was recrystallized from benzene to give crude **8b** (600 mg). The mother liquor was evaporated to dryness and the residue was separated by alumina chromatography (Wakogel; 50 g). Fractions 1, eluted with benzene (100 ml), and 2, eluted with a mixture of benzene (45 ml) and ether (5 ml), afforded a mixture of **8b** and **10b** (876 mg). Recrystallization of the mixture from acetonitrile gave **8b** (403 mg). The mother liquor was evaporated to dryness. Recrystallization of the residue gave **10b** (166 mg).

(3) Dehydrogenation: A mixture of **4b** (269 mg) and chloranil (270 mg) in benzene (40 ml) was refluxed for 3 hr and then separated by decantation from the precipitates. The benzene solution was washed with 4% sodium hydroxide solution (20 ml), dried over magnesium sulfate and evaporated to dryness. Recrystallization of the residue from benzene gave 2-phenyl-4-amino-5-dimethoxymethylpyrimidine (**16**) (needles; 35 mg). Mp 117—118°C. UV (CH_3CN) 240 (ε 29400), 260 (shoulder), 282 (ε 12000), 296 (ε 11000); (+HCl) 252. IR (Nujol) 3400, 3240 (NH_2), 1095, 1050 (acetal). NMR ($CDCl_3$) 8.54—7.31 (m, 5H, phenyl), 8.42 (s, 1H, H_6), 6.47 (s, 1H, C<u>H</u>$(OMe)_2$), 3.47 (s, 6H, CH$(O\underline{Me})_2$). Found: C, 63.43; H, 6.30; N, 17.02%; mol wt, 246. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; N, 6.16; H, 17.13%; mol wt, 245.27.

2-Phenyl-4-amino-5-formylpyrimidine (17). A mixture of 2-phenyl-4-amino-5-dimethoxymethylpyrimidine (**16**; 485 mg), acetic acid (1.7 g), and water (2.7 ml) was heated at 100°C for 5 min. After cooling, crystals (342 mg) obtained were collected by filtration. Recrystallization of the crystals from methanol gave **17** (needles; 146 mg). Mp 180—180.5 °C. IR (Nujol) 2750, 1670 (CHO). NMR (DMSO-d_6) 7.4—8.5 (m, 5H, phenyl), 8.88 (s, 1H, H_6), 9.94 (s, 1H, CHO). Found: C, 66.20; H, 4.66; N, 20.88%. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.52; N, 21.10%.

2-Phenyl-4-amino-5-hydroxymethylpyrimidine (18). (i) Sodium borohydride (35 mg) was added to a methanol solution (10 ml) of **17** (200 mg), and the solution was stirred at room temperature for 30 min. After subsequent heating at 40—50°C for 30 min, the solvents was removed and the residue was extracted with acetone. The acetone extract was recrystallized from a mixture of acetone and benzene. Plates of **18** (107 mg) were obtained. Mp 134—135.5°C. IR (Nujol) 3440, 3300, 3200 (NH_2, OH). NMR ($CDCl_3$) 8.47—7.33 (m, 5H, phenyl), 8.07 (s, 1H, H_6), 4.60 (s, 2H, $-CH_2-$), 6.47 (2H, NH_2). Found: C, 65.65; H, 5.48; N, 20.71%. Calcd for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88%.

(ii) A mixture of crude **20** (1.88 g), concd. hydrochloric acid (980 mg), and water (25 ml) was heated on a boiling-water bath, and sodium nitrite (650 mg) was added to the mixture. After heating for 2.5 hr, an additional amount of sodium nitrite (0.63 g) was added, and the solution was further heated for 2 hr on a boiling-water bath. Resinous substances which appeared were eliminated by decantation, the solution was neutralized with sodium carbonate, extracted with chloroform (150 ml), and then the chloroform was removed. Recrystallization of the residue from a mixture of benzene and acetone afforded **18** (456 mg).

2-Phenyl-4-amino-5-methoxymethylpyrimidine (14b). (i) Under cooling, **18** (402 mg) was added to phosphorous oxychloride (1.224 g) and the solution was heated at 85°C for 3 hr. After cooling, methanol (1 ml) was added to the solution which was left at room temperature overnight. Crystals (**19**) obtained were collected by filtration, and washed with methanol and then with benzene (1 ml). They were dissolved in methanol (3 ml) containing sodium methoxide, which had been prepared from sodium (150 mg) and methanol (5 ml). After being left standing at room temperature overnight, the solution was filtered from precipitated sodium chloride and then evaporated to dryness. Recrystallization of the residue from benzene gave **14b** (leaflets; 63 mg). Mp 130°C. UV (CH_3CN) 238 (ε 21600), 258 (shoulder, ε 14700), 281 (ε 8800), 286 (shoulder, ε 8600), 297 (ε 8300). IR (Nujol) 3480, 3300 (NH_2), 1085 (OMe). NMR ($CDCl_3$) 8.5—7.4 (m, 5H, phenyl), 8.23 (s, 1H, H_6), 4.43 (s, 2H, $-CH_2-$), 3.33 (s, 3H, OMe). Found: C, 66.95; H, 6.05; N, 19.38%; mol wt, 218. Calcd for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52%; mol wt, 215.25.

(ii) To a solution of benzamidine (1.5 g) in 1,2-dimethoxyethane (50 ml), **13** (1.5 g)[11] was added in portions. After the solution was refluxed for 4.5 hr, the solvent was removed. Recrystallization of the residue from benzene gave **14b** (1.53g).

Reaction of 2-Dimethoxymethylacrylonitrile (2) with Benzamidine. To a stirred solution of benzamidine (18 g) in 1,2-dimethoxyethane (15 ml), **2** (22.7 g) was added at such a rate, as to keep the reaction temperature below 23°C within about 30 min. The solution was kept at room temperature. After 10 min a spot due to **3b** appeared in the tlc (a silica-gel plate; acetone, R_f 0.9—0.5). Isolation of **3b** in a pure state was unsuccessful. [**3b**: IR (Film) 2280 (non-conjugate CN). UV (CH_3CN) 225 (benzamidine moiety)]. After 1 day, crystals of 2-phenyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**4b**) appeared, which were collected by filtration. Recrystallization from acetonitrile yielded pure **4b** (15.4 g).

2-Phenyl-4-amino-5-benzamidomethylpyrimidine (9b). A mixture of 2,7-diphenyl-5,6-dihydropyrimido[4,5-*d*]pyrimidine (**8b**; 100 mg), potassium hydroxide (180 mg), ethanol (5 ml), and water (0.2 ml) was refluxed for 3 hr, and the solution was evaporated to dryness. The residue was recrystallized from a mixture of water and ethanol to give **9b** (leaflets; 64 mg). Mp 228—229.5°C. UV (CH_3CN) 210 (ε 11700), 298 (ε 12000); (+HCl) 254. IR (Nujol) 1613 (CONH). NMR (DMSO-d_6) 8.42—7.30 (m, 10H, phenyl), 8.17 (s, 1H,H_6), 4.35[s] (2H, $-CH_2-$). Found: C, 69.06; H, 5.21; N, 17.81%. Calcd for $C_{18}H_{16}N_4O \cdot \frac{1}{2}H_2O$: C, 68.93; H, 5.10; N, 17.87%.

2-Phenyl-4-amino-5-aminomethylpyrimidine (20). A mixture of **9b** (5.9 g), ethanol (35 ml), potassium hydroxide (12 g), ethanol (35 ml) and water (20 g) was refluxed for 30 hr and the solution was evaporated to dryness. Water (25 ml) was added to the residue. A brown oil appeared, which was extracted with chloroform (100 ml). The chloroform solution was dried over magnesium sulfate and then the solvent was removed. A brown oil (crude **20**; 4.03 g) was obtained. Concentrated hydroiodic acid was added to a part of the brown oil (187 mg), and crystals (**20**, hydroiodide) appeared. They were collected by filtration, washed with ethanol and recrystallized from methanol. The yield was 107 mg. Mp 268—272°C (decomp.). Found: C, 29.25; H, 3.14; N, 12.24%. Calcd for $C_{11}H_{12}N_4 \cdot 2HI$: C, 28.96; H, 3.09; N, 12.28%.

Cyclization of 2-Phenyl-4-amino-5-benzamidinomethylpyrimidine (10b). A solution of **10b** (40 mg) in methanol (4 ml) was refluxed for 6 hr and then evaporated to dryness. Recrystallization of the residue from acetonitrile gave 2,7-diphenyl-5,6-dihydropyrimido[4,5-*d*]pyrimidine (**8b**; 20 mg).

Reaction of 2-Phenyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (4b) with p-*Toluamidine. General Procedure*: A mixture of **4b** (3 g), *p*-toluamidine and its hydrochloride in methanol (20 g) was refluxed for 14 hr. 48% Sodium hydroxide solution (10 g) and water (10 ml) were added to the solution and then refluxed for 3 hr. After cooling, the solution was diluted with water (50 ml). A powder appeared was collected by filtration. The filtrate was evaporated to dryness and water (60 ml) was added to the residue. An insoluble powder was collected by filtration. The two powders were combined (**9c**+**12c**). The relative ratio was determined by means of NMR spectroscopy using the integration of methyl singlets of **9c** (2.26 δ) and **12c** (2.18 δ) in pyridine-d_5. The data are shown in Table 1. (i) When the molar ratio of **4b**, *p*-toluamidine and *p*-toluamidine hydrochloride was 1:1:1, the combined powder was recrystallized from methanol. 2-Phenyl-4-amino-5-toluamidomethylpyrimidine (**12c**; 600 mg) was obtained as leaflets. The mother liquor was evaporated to dryness. Recrystallization of the residue from methanol gave 2-*p*-tolyl-4-amino-5-benzamidomethylpyrimidine (**9c**), but its purification was unsuccessful because a small amount of contaminated **12c** could not be eliminated. (ii) When the molar ratio of **4b** and *p*-toluamidine was 1:3, the combined powder was worked up in a procedure similar to that for (i). Pure **9c** was obtained (289 mg).

*2-*p*-Tolyl-4-amino-5-benzamidomethylpyrimidine (9c).* A mixture of 2-*p*-tolyl-4-amino-5-*p*-toluamidomethylpyrimidine (**22**; 120 mg), potassium hydroxide (12 g), ethanol (7 ml) and water (20 g) was refluxed for 34 hr. The solution was concentrated to 25 g and then water (50 ml) was added. By extraction with chloroform (50 ml), a syrup was obtained (crude **23**). Benzoyl chloride (100 mg) was added to a solution of the syrup (57 mg) in pyridine (700 mg) and left at room temperature. After 1 day, a mixture of water (10 ml), a 48% sodium hydroxide solution (500 mg) and methanol (5 ml) was added to the solution. The solution was heated at 100°C for 10 min, concentrated and poured into water (50 ml). Crystals obtained were collected by filtration and then recrystallized from methanol. Twenty miligrams of

11) Contained about 15% of **1** (determined by means of gas chromatography).

9c were obtained. Mp 236—237°C. UV (EtOH) 208 (ε 15300), 250 (ε 12500), 263 (shoulder), 282 (ε 6400), 297 (shoulder); (+HCl) 205, 258, 278 (shoulder). IR (KBr) 1613 (CONH). NMR (pyridine-d_5) 8.27 (s, 1H, H_6), 4.80, 4.67 (s, 1H+s, 1H, $-CH_2-$), 2.26 (s, 3H, Me). Found: C, 71.66; H, 5.45; N, 17.75%. Calcd for $C_{19}H_{18}N_4O$: C, 71.67; H, 5.70; N, 17.60%.

*2-Phenyl-4-amino-5-*p*-toluamidomethylpyrimidine (**12c**).* To a solution of 2-phenyl-4-amino-5-aminomethylpyrimidine (**20**; 400 mg) in pyridine (2 ml), *p*-toluchloride (400 mg) was added at 0°C and the solution was left at room temperature for 1 day. To the solution, a mixture of water (20 ml), 48% sodium hydroxide solution (1 g) and methanol (5 ml) was added. The solution was left at room temperature for 1 hr and then evaporated to dryness. Water (30 ml) was added to the residue. Crystals obtained were collected by filtration. Recrystallization from methanol gave **12c** (270 mg). Mp 235—236.5°C. UV (MeOH) 206 (ε 15600), 240 (ε 16400), 257 (shoulder), 281 (ε 5000), 295 (shoulder); (+HCl) 205, 252. NMR (pyridine-d_5) 8.27 (s, 1H, H_6), 4.77, 4.65 (s, 1H, s, 1H, $-CH_2$), 2.18 (s, 3H, CH_3-). Found: C, 71.91; H, 5.87; N, 17.86%. Calcd for $C_{19}H_{18}N_4O$: C, 71.67; H, 5.70; N, 17.60%.

*2-*p*-Tolyl-4-amino-5-*p*-toluamidomethylpyrimidine (**22**).* A solution of 2-dimethoxymethyl-3-methoxypropiononitrile (**1**; 500 mg), *p*-toluamidine (700 mg) in methanol (3 ml) was refluxed for 8 hr (formation of **21**), and 15% sodium hydroxide solution (2 g) was added. The solution was refluxed for 1 hr, poured into water (50 ml), and the precipitates (574 mg) were collected by filtration. Recrystallization of precipitates gave **22** (needles; 91 mg). Mp 235—239°C. UV (MeOH) 205 (ε 16600), 242 (ε 14700), 260 (shoulder), 282 (ε 6400), 296 (shoulder); (+HCl) 204, 256, 286 (shoulder). IR (KBr), 1614 (CONH). NMR (pyridine-d_5) 8.28 (s, 1H, H_6), 4.80, 4.67 (s, 1H + s, 1H, $-CH_2-$), 2.27 (s, 3H, Me), 2.20 (s, 3H, Me). Found: C, 72.45; H, 5.89; N, 17.50%. Calcd for $C_{20}H_{20}N_4O$: C, 72.27; H, 6.07; N, 16.86%.

*Reaction of 2-Methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**4a**) with Propioamidine. General Procedure:*[1] Hydrochlorides of propioamidine (651 mg) and **4a** (443 mg) was added to methanolic sodium methoxide which had been prepared from an appropriate amount of sodium and methanol (6 ml). The solution was refluxed for 5 hr, filtered from precipitated sodium chloride and then evaporated to dryness. To the residue was added water (8 ml) and the aqueous solution was heated on a boiling-water bath for 1 hr. Removal of the water gave syrupy crystals. The total yield and relative ratio of **9f**[1] and **12f**[1] in the syrupy crystals were determined by means of UV spectroscopy and gas chromatography,[1] respectively. The data are shown in Table 1.

*Reaction of 2-Methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**4a**) with Benzamidine. General Procedure:* Hydrochlorides of **4a** (443 mg) and benzamidine were added to methanolic sodium methoxide which had been prepared from an appropriate amount of sodium and methanol (6 ml). The solution was refluxed for 5.5 hr and then evaporated to dryness. The residue was dissolved in 40% acetic acid solution (5 ml) and then heated on a boiling-water bath for 7 hr. The solution was concentrated and the residue was neutralized with a saturated bicarbonate solution and then diluted with water (20 ml). Crystals of a mixture of **9d** and **12d** were collected by filtration. The relative ratio of **9d** and **12d** in the crystals was determined by means of NMR spectroscopy using the integration of the methyl singlets of **9d** (1.98 δ) and **12d** (2,40 δ) in methanol-d_4. Recrystallization of the above crystals from acetonitrile gave **9d** in a pure state. When molar ratio of **4a**, benzamidine and benzamidine hydrochloride was 1: 2: 1, the yield of isolated **9d** was 212 mg. Mp 199—200°C (leaflets). UV (MeOH) 242 (ε 21000), 290 (ε 7500); (+HCl) 255. IR (Nujol) 1655 (CONH). NMR (CD_3OD) 1.98 (s, 3H, MeCONH), 8.01 (s, 1H, H_6), 4.40 (s, 2H, $-CH_2-$), 7.3—8.3 (m, 5H, phenyl). Found: C, 64.19; H, 5.93; N, 22.36%. Calcd for $C_{13}H_{14}N_4O$: C, 64.44; H, 5.82; N, 23.13%.

*The Conversion of **9d** into **9b**.* A mixture of 2-phenyl-4-amino-5-amidomethylpyrimidine (**9d**, 430 mg), 48% sodium hydroxide (25 g) solution, and ethylene glycol (20 ml) was refluxed for 5 hr, and then evaporated to dryness. A yellow syrup (**20**) was obtained by extraction with chloroform (50ml). The syrup was dissolved in pyridine (4 ml) and then benzoyl chloride (320 mg) was added to the solution at 0°C. The solution was left in a refrigerator for 4 hr and then poured onto ice-water. Crystals obtained were collected by filtration and recrystallized from acetonitrile. The yield was 210 mg.

*2-Methyl-4-amino-5-benzamidomethylpyrimidine (**9e**=**12d**).* To a mixture of 2-methyl-4-amino-5-aminomethylpyrimidine (500 mg) and pyridine (4 g) was added benzoyl chloride (2 g) at 0°C. The solution was kept at room temperature overnight, and then evaporated to dryness. 10% Sodium hydroxide solution (50 ml) was added to the residue. The solution was evaporated to dryness and washed with cold water (10 ml). Recrystallization of the residue from methanol gave **9e** (225 mg). Mp 232—234°C (columns). UV (EtOH) 231 (ε 21700), 275 (ε 6700); (+HCl) 237. IR (KBr) 1675 (CONH). NMR (CD_3OD) 2.40[s] (3H, 2-Me), 7.98 (s, 1H, H_6), 4.42 (s, 2H, $-CH_2-$), 7.93—7.40[m] (5H, phenyl). Found: C, 64.35; H, 5.97; N, 23.30%. Calcd for $C_{13}H_{14}N_4O$: C, 64.44; H, 5.82; N, 23.13%.

*Reaction of 2-Phenyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**4b**) with Acetamidine. General procedure:* Hydrochlorides of **4b** (741 mg) and acetamidine (850 mg) were added to methanolic sodium methoxide which had been prepared from appropriate amounts of sodium and methanol (10 ml), and the solution was refluxed for 5 hr. 80% Acetic acid (5 ml) was added to the solution which was refluxed for 1.5 hr and then extracted with chloroform (100 ml). The chloroform layer was washed with a saturated sodium bicarbonate solution (10 ml) and then water (10 ml) and dried, and the chloroform was removed. Crystals of a mixture of **9e** and **12e** were obtained. The relative ratio of **9e** and **12e** in the crystals was determined by means of NMR spectroscopy using the integration of methyl singlets of **9e** (2.40 δ) and **12e** (1.98 δ) in methanol-d_4. The data are shown in Table 1. Recrystallization of the above crystals from methanol gave **9e**. When the molar ratio of **4b**, acetamidine, and acetamidine hydrochloride was 1: 2: 1, the yield of **9e** was 358 mg.

*Reaction of 2-Phenyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**4a**) with Sodium Methoxide.* To a mixture of **4a** hydrochloride (443 mg) and **4b** (493 mg) was added a sodium methoxide solution which had been prepared from sodium (138 mg) and methanol (15 ml). The solution was refluxed for 4 hr, filtered from precipitated sodium chloride and then evaporated to dryness. Extraction of the residue with chloroform gave a syrup (458 mg), which was a mixture of 2-phenyl-4-amino-5-methoxymethylpyrimidine (**14b**) and 2-methyl-4-amino-5-methoxymethylpyrimidine (**14a**). The ratio of **14b** and **14a** was determined to be 91.4: 8.6 by means of gas chromatography (Apiezon grease L 30%, 1 m; column temperature, 234.5°C; carrier gas, He, flow rate, 90 ml/min; retention time, **14a**: 2.2 min, **14b**: 36.9 min). The syrup was chromatographed over alumina (Wakogel 10 g) with benzene (40 ml) and, subsequently, with a mixture of benzene

(30 ml) and ethyl acetate (30 ml). One hundred and sixty-three milligrams of **14b** was obtained.

*Cyclization Rates of 2-Methyl-4-amino-5-acetamidinomethylpyrimidine (**10a**) and 2-Phenyl-4-amino-5-benzamidinomethylpyrimidine (**10b**).* The rate constants for the two reactions were determined spectrophotometrically with a Perkin Elmer 139 spectrophotometer by following the increase of the absorbance at 310 nm due to **8a** in the reaction of **10a**, and that at 350 nm due to **8b** in the reaction of **10b** at reflux temperature (64.5°C).

*(1) The Decrease of **10a** (k_a)*: The hydrochloride of **10a** (6 mg) was dissolved in methanol in a 200 ml volumetric flask. The methanol solution was exactly neutralized with a dilute solution of potassium hydroxide in methanol and then the flask was filled to the mark with methanol at 26°C. $k_a = 7.3 \times 10^{-2} \mathrm{min}^{-1}$.

*(2) The Decrease of **10b** (k_b)*: Fourteen milligrams of **10b** was dissolved in methanol and then messed up to 200 ml at 26°C. $k_b = 4 \times 10^{-3} \mathrm{min}^{-1}$.

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