The Reaction Mechanism of 2-Dimethoxymethyl-3-methoxypropionitrile with Acetamidine. II.[1] A Novel Reaction Pathway[2]

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The reaction of 2-dimethoxymethyl-3-methoxypropionitrile (**1**) with acetamidine produces pyrimidopyrimidine (**8**) *via* the consecutive process of **1**→an intermediate→**8**. The intermediate was not isolated, but two structures have been proposed for it. We have now succeeded in the isolation of the intermediate and determined it to be 2-methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**4**). Several key intermediates were also successfully isolated. The novel reaction pathway for the title reaction was concluded to be as follows: the elimination of methanol from **1**, followed by the addition of acetamidine affords 3-acetamidinopropionitrile (**3**), the subsequent quick cyclization of which produces the intermediate, **4**; the further elimination of methanol from **4**, followed by a replacement reaction with acetamidine, gives an acetamidinomethylene compound (**6**), which is converted into the final product, **8**, *via* an intermediate (**7**). Some minor pathways will also be presented.

Although it has been known that enol ether and acetal derivatives of α-formylnitriles react with amidines to give the same final products,[3-5] Takamizawa and his co-workers have reported an unusual result on 2-formyl-3-alkoxypropionitriles.[6] When treated with acetamidine, 2-methoxymethylene-3-methoxypropionitrile (**12**) of an enol ether-type affords 2-methyl-4-amino-5-methoxymethylpyrimidine (**13**) of the usual type,[7] but 2-dimethoxymethyl-3-methoxypropionitrile (**1**) of an acetal type yields 2,7-dimethyl-5,6-dihydropyrimido-[4,5-*d*]pyrimidine (**8**) *via* an intermediate showing the absorption maximum at 262 mμ in methanol in the UV spectrum. An unusual product, **8**, is also obtained from 2-dimethoxymethylacrylonitrile (**2**); this reaction can be explained in terms of the fast conversion of **2** into **1** at the initial stage. As the hydrolyses of **8** give 2-methyl-4-amino-5-acetamidomethyl- (**9**) and 2-methyl-4-amino-5-aminomethylpyrimidine (**10**) quantitatively,[8] the reaction of **1** (or **2**) is very important for thiamine production. However, the reaction mechanism is not unequivocally established because of the unsuccessful isolation of the intermediate. For the structure of the intermediate, 2-acetamidinomethylene-3-methoxypropionitrile (**14**) has been proposed on the basis of a comparison with the reaction of 2-aminomethylene-3-alkoxypropionitrile with methyl acetimidate.[6] On the other hand, in view of the behavior of **1** under basic conditions we have proposed a revised structure, 2-methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (**4**), which would be formed *via* the pathway of **1**→**2**→2-dimethoxymethyl-3-acetamidinopropionitrile (**3**)→**4**.[1] The present investigation was carried out in order to establish the exclusive reaction pathway by isolating the intermediate.

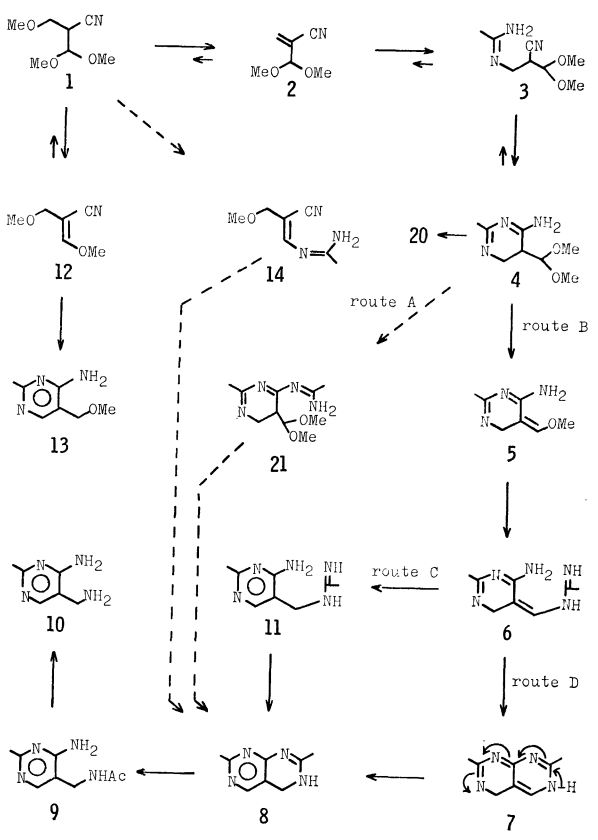


Chart 1

The reaction of **1** with acetamidine in methanol can be generalized into the equation of **1**→the intermediate →**8**.[6] Although the first step of this consecutive process proceeds even at room temperature to some extent, a reflux temperature and another one mole of acetamidine are required to conclude the second step. For the iso-

1) For part 1, see T. Nishino, M. Kiyokawa, Y. Miichi, and K. Tokuyama, This Bulletin, **45**, 1127 (1972). A part of this paper was reported in a preliminary form; T. Nishino, M. Kiyokawa, and K. Tokuyama, *Tetrahedron Lett.*, **1969**, 3553.

2) Pyrimidines, 10. For part 9, see F. Takami, S. Wakahara, and T. Maeda, *Chem. Lett.*, **1972**, 409.

3) D. J. Brown, "The Pyrimidines," Interscience, New York (1962), p. 59.

4) M. Hoffer, E. Gruberg, M. Mitrovic, and A. Brossi, *J. Med. Chem.*, **14**, 462 (1971).

5) R. M. Cresowell, J. W. Mentha, R. L. Seaman, and D. A. Yeowell, Abstracts of The Third International Congress of Heterocyclic Chemistry, Sendai, 1971, C-26-1.

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

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

8) A. Takamizawa, K. Ikawa, and M. Narisada, *Yakugaku Zasshi*, **78**, 637 (1958); A. Takamizawa, *ibid.*, **74**, 748 (1954).

9) Y. Okamoto, T. Tsuji, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo,) **17**, 2273 (1969).

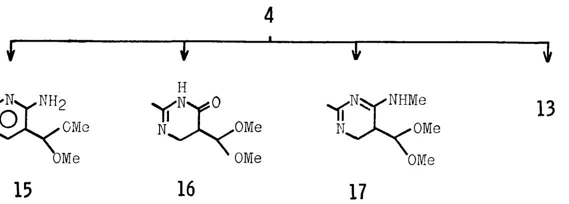
lation of the intermediate, the retardation of the rate of second step is naturally necessary, so it seemed to be desirable to use a relatively low reaction temperature and to deactivate the remaining acetamidine by neutralizing it when the formation of the intermediate to a considerable amount was observed.

The lack of success in the isolation of the intermediate has long been attributed to its instability. If the intermediate is **4**, it is conventionally isolated as a hydrochloride, since 4-amino-5,6-dihydropyrimidines are stable as hydrochlorides.[9] On the preparation of hydrochloride of **4**, however, the presence of moisture and an excess of hydrogen chloride should be avoided, because 4-amino- and 5-dimethoxymethyl (acetal) groups of **4** can easily be hydrolyzed under acidic conditions.[1]

When a solution of **1** and acetamidine in anhydrous methanol was kept at 55°C for 1 hr, the characteristic band due to the intermediate appeared strongly in the UV spectrum. To the solution, methanolic hydrogen chloride was added in amounts strictly equimolar with the acetamidine used, and then the solution was concentrated. The repeated recrystallization of the crystals which appeared gave a hydrochloride whose analytical data corresponded to those of the hydrochloride of **4**. The yield was about 44%. Its UV spectrum in methanol showed an absorption maximum at 278 mμ which was shifted to 262 mμ on neutralization. The reaction of the hydrochloride with acetamidine showed a consecutive increase in the absorbancy due to **8** at 305 mμ, and from the reaction mixture **8** was isolated. Therefore, the hydrochloride was identified as the hydrochloride of the intermediate.

The spectral data suggested that the intermediate was **4**. It showed a behavior similar to that of 2-methyl-4-amino-5,6-dihydropyrimidine (**18**)[1] in the UV spectrum, as has been described above, signals due to an acetal group (two singlets due to methyls at 3.32 δ and 3.37 δ and one doublet (J=7.5 Hz) due to the methine proton (H_Y) at 4.48 δ) in the NMR (DMSO-d_6), but no characteristic band due to a nitrile group in the IR. The signals of the remaining protons in the NMR also consisted of **4**. The H_6 signals constitute the AB portion (3.75 δ and 3.63 δ) of an ABXY system, whose X and Y portions are H_5 (3.10—3.40 δ) and H_Y respectively. The 2-methyl signal appears at 2.33 δ as a broad singlet due to homoallylic coupling with H_6.[1]

The treatment of the intermediate with p-quinone in benzene gave 2-methyl-4-amino-5-dimethoxymethylpyrimidine (**15**).[10] Therefore, the structure of the intermediate was established as **4**. Much as in the acid-catalyzed hydrolysis of **18** to 2-methyl-3H-4-oxo-5,6-dihydropyrimidine (**19**),[1] **4** was easily hydrolyzed to a 4-oxo-compound (**16**), whose structure was confirmed by the UV spectrum in methanol to show behavior similar to that of **19** and by the NMR spectrum to show a pattern quite similar to that of **4**. The reaction of **4** with methylamine gave a transaminated compound (**17**). The presence of an N-methyl signal[11] in the NMR supported this structure. Further, the treatment of **4** with sodium methoxide gave **13**. Therefore, the structure of the intermediate was unequivocally established as **4**.



15 16 17

Chart 2

The establishment of the structure of the intermediate clearly supported our idea that the first step in the reaction of **1** with acetamidine proceeds *via* the pathway of **1**→**2**→**3**→**4**.[1]

The treatment of **2** with acetamidine at 0°C in the absence of methanol, followed by neutralization with hydrogen chloride, gave another hydrochloride, whose elementary analytical data agreed with those of the hydrochloride of **4**. This hydrochloride showed the characteristic band due to a non-conjugate nitrile group in the IR spectrum and was quickly converted into **4** upon neutralization. Therefore, it was identified as the hydrochloride of **3**. The UV spectrum, showing an absorption maximum similar to that of acetamidine hydrochloride, and the NMR, showing the presence of an acetal group, a CH_2–C–H moiety, and a C-methyl group, also supported the structure. The fast reactions of **2**→**3** and **3**→**4** suggested that the step, **1**→**2**, was rate-determining in the first step. The fact that **2** was hardly detected in the tlc of the reaction of **1** with acetamidine also supported this idea.

The heating of **4** in the absence of acetamidine, followed by hydrolysis, gave **9** in a 25% yield. This means the existence of the reverse reaction of **4**, that is **4**→**3**→**2**+acetamidine, which reacted with **4**. Therefore, the first step, **1**→**4**, should be expressed as follows: **1**⇌**2**⇌**3**⇌**4**.

A minor product (**20**) was isolated from the above reaction. The analytical data and mass spectrum determined that it was a dimeric substance, $C_{14}H_{22}N_6O_2\cdot HCl$, which was thought to be formed from the dimerization of **4** by the elimination of two moles of methanol. The compound **20** was also detected in the reaction of **1** or **4** with acetamidine to a limited extent. Studies of the structure of **20** will be reported separately.

A small amount of **13** was newly obtained from the reaction of **1** with acetamidine. However, it was not isolated from the reaction of **4**. This fact suggested that **13** was formed *via* the pathway of **1**→**12**→**13**. Consequently, the existence of an equilibrium **1**⇌**12** under basic conditions due to the presence of an acetamidine base was confirmed.

On the basis of above facts, the reaction process of **1** with acetamidine should be **1**⇌**2**⇌**3**⇌**4**→**8**, in which

$$\begin{array}{ccccccc} \mathbf{1} & \rightleftharpoons & \mathbf{2} \rightleftharpoons \mathbf{3} & \rightleftharpoons & \mathbf{4} & \rightarrow & \mathbf{8} \\ \upharpoonleft\downharpoonright & & & & \downarrow & & \\ \mathbf{12}\rightarrow\mathbf{13} & & & & \mathbf{20} & & \end{array}$$

1→**2**→**3**→**4**→**8** is most important.

10) S. Mizukami and E. Hirai, *ibid.*, **14**, 1321 (1966).

11) R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York (1965), p. 16.

The second step, **4**→**8**, presented further interesting problems. For this step, two pathways route A (**4**→**21**→**8**) and route B (**4**→**5**→**6**→**8**), are possible (see Chart 1). If the reaction proceeds *via* route A, the reaction of **4** with methyl acetimidate can be expected to give **8** in a yield similar to that in the reaction with acetamidine.[8,12] However, the yield of **8** in the reaction with acetimidate was only 17%, which was similar to that from the reverse reaction of **4**. Further, the starting materials were recovered from the reaction of **18** or its phenyl analog **22**[13] with acetamidine. No transaminated compounds, such as **23** and **24**, were obtained from either reaction. Therefore, the possibility of the reaction pathway *via* route A was excluded.

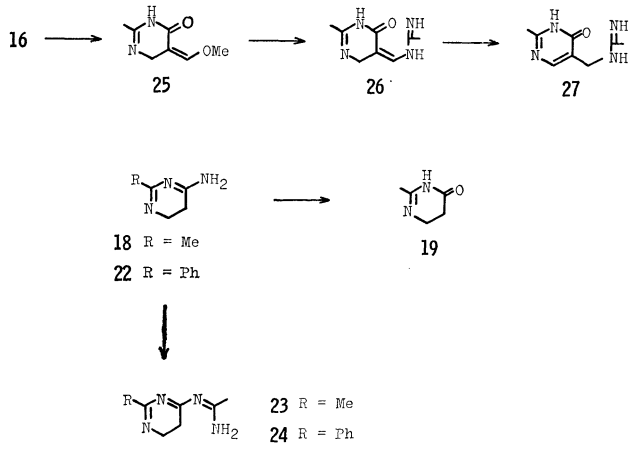


Chart 3

To examine the possibility of the pathway *via* route B, the reaction of a deaminated compound, **16**, was attempted. When treated with acetamidine in methanol at reflux temperature, **16** gave **27**, which was then purified as its dihydrochloride, $C_8H_{12}N_4O \cdot 2HCl$. The spectral data suggested that it was 2-methyl-3*H*-4-oxo-5-acetamidinomethylpyrimidine. The UV spectrum showed the characteristic band due to 2-methyl-4-hydroxypyrimidines in acidic or in alkaline media,[14,15] while the NMR spectrum showed signals due to methyl groups at C_2 position, and at the acetamidino moiety, the 5-methylene group and the pyrimidine-ring proton. It is quite natural to consider that the reaction of **16** proceeds *via* the pathway of **16**→**25**→**26**→**27**. Consequently, route B can be proposed as a reliable pathway. If this idea is probable, **16** and **4** can be said to react with acetamidine at comparable rates. By heating a mixture of one mole each of **4**, **16**, and acetamidine in methanol, **8** and **27** were formed in a 1 : 1 ratio, as expected. Therefore, the second step was confirmed to proceed *via* route B.

Two more pathways can be proposed for the final step of route B. One is route C (**6**→**11**→**8**), and the other is route D (**6**→**7**→**8**) (see Chart 1). For the determination of the predominant pathway, the reaction of **4** with propioamidine was carried out, in

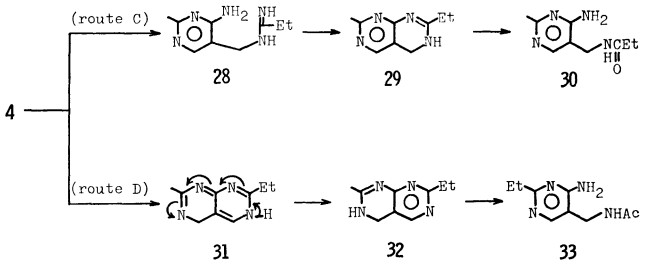


Chart 4

which the reaction product **29** should be formed when the reaction proceeds *via* route C, and **32**, when it proceeds *via* route D (see Chart 4). Both products, **29** and **32**, were easily identified by hydrolysis to 5-propioamidomethylpyrimidine (**30**) and 5-acetamidomethylpyrimidine (**33**) respectively. The heating of **4** and propioamidine in methanol, followed by hydrolysis, gave a mixture of the two pyrimidines in high yields. The major pyrimidine was isolated in a pure state. As the NMR spectrum showed a 3-proton singlet due to an acetyl methyl group, the major one was identified as **33**. The remaining signals also supported the structure; signals due to the ethyl group and singlets due to the methylene group and the pyrimidine-ring proton were observed. The attempt to isolate the minor pyrimidine was unsuccessful because of its low yield and because its solubilities are similar to those of **33**. However, it was identified as **30** by a comparison of the retention times in the gas chromatograms. The authentic sample of **30** was prepared by the propionylation of **10**. The relative ratio of **30** and **33** was about 8: 92, as determined by gas chromatography. This result clearly revealed that route D is predominant. The existence of a minor route, C, was also supported by the isolation of **11** from a reaction mixture of **1** and acetamidine, though its yield was very poor. Proof of the structure of **11** was provided by a comparison of the IR and mass spectra of an authentic sample, which was prepared by the reaction of **10**[7] with methyl acetimidate.

The presence of an acid, usually acetamidine hydrochloride, was desirable for the accelation of the second step **4**→**8**. This fact seemed to suggest that the elimination of methanol, **4**→**5**, was the rate-determining step. A detailed discussion on the reaction mechanism will be presented kinetically in a following paper.

In conclusion, the reaction of **1** with acetamidine has been established to proceed *via* the major pathway of **1**⇌**2**⇌**3**⇌**4**→**5**→**6**→**7**→**8**, along with the minor one of **6**→**11**→**8** and two side pathways of **1**→**12**→**13** and **4**→**20**.

Experimental

All the melting points were recorded on a Kofler block and have been uncorrected. The NMR spectra were taken with a Varian A-60-A spectrometer, using tetramethylsilane as the internal reference; the chemical shifts were expressed in δ unit (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, bs: broad singlet). The UV spectra were observed in methanol. The solvents used were removed under a reduced pressure. The percentages of methanolic sodium methoxide and hydrogen chloride are shown in w/w and the ratios of solvent systems used for the purification, in v/v.

12) T. Matsukawa, *Yakugaku Zasshi*, **62**, 417 (1942).
13) S. Pietra, *Boll. Sci. Fac. Chim. Ind. Bologna*, **11**, 78 (1953).
14) Ref. 3, p. 492.
15) A. Takamizawa, *Yakugaku Zasshi*, **74**, 756 (1954).

2-Methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (4). *(1) Isolation as Its Hydrochloride (4·HCl)*: 2-Dimethoxymethyl-3-methoxypropionitrile (**1**; 147 g) was added to an acetamidine solution, prepared from acetamidine hydrochloride (256 g) and 22% methanolic sodium methoxide (697 g), after which the solution was kept at 55°C. After 1 hr, 30% methanolic hydrogen chloride (220 g) was added to the solution below 10°C. After the concentration of the solution to 450 g, crystals appeared; they were collected by filtration. The repeated recrystallization of the crystals from methanol-ether (9: 1) gave cubics of **4·HCl** (89.7 g), mp 155—160°C (decomp.). UV: 278 (ε 11500); (+NaOH) 262 mμ (ε 7500). Found: C, 43.32; H, 7.45; N, 18.78%. Calcd for $C_8H_{15}N_3O_2 \cdot HCl$: C, 43.34; H, 7.28; N, 18.95%.

(2) Reaction with Acetamidine: *(i) Isolation of the Product*: To a solution of sodium (517 mg) in methanol (20 m*l*), we added hydrochlorides of acetamidine (2.125 g) and **4** (1.662 g). The solution was refluxed for 4 hr, filtered from precipitated sodium chloride, and then evaporated to dryness. A solution of the residue in water (5 m*l*) was heated on a boiling-water bath for 1 hr and then evaporated to dryness. The recrystallization of the residue from water gave 2-methyl-4-amino-5-acetamidomethylpyrimidine (**9**; 652 mg); mp 208—209°C.[6]

(ii) Effect of the Presence of Acetamidine Hydrochloride: (a) Hydrochlorides of acetamidine (283 mg) and **4** (321 mg) were added to 6 m*l* of methanolic sodium methoxide [a methanol solution (20 m*l*) containing sodium (431 mg)]. The solution was diluted to 20 m*l* with methanol and then refluxed for 1.5 hr. The yield of **8** was 35%, which was determined using the absorption maximum of **8** at 310 mμ in the UV spectrum. (b) Hydrochlorides of acetamidine (425 mg) and **4** (329 mg) were dissolved in 10 m*l* of methanolic sodium methoxide [a methanol solution (50 m*l*) containing sodium (517 mg)] and then diluted to 20 m*l* with methanol. The solution was refluxed for 1.5 hr, after which the yield of **8** was determined. The yield was 76%.

(3) Dehydrogenation with p-Quinone: The hydrochloride (**4·HCl**, 4.42 g) was neutralized with methanolic sodium methoxide, which had been prepared from sodium (460 mg) and methanol (10 m*l*). The methanol solution was shaken for a few minutes, and quickly filtered from the precipitated sodium chloride, and the methanol was removed. To a benzene solution (250 m*l*) of the residue, we then added *p*-quinone (2.5 g) dissolved in benzene (20 m*l*), after which the solution was refluxed for 3 hr. After cooling, the insoluble materials were eliminated by decantation. The benzene layer was washed with 1N sodium hydroxide (10 m*l*×2) and water (10 m*l*×1), and dried, and the solvent was removed. The subsequent recrystallization of the residue from benzene and *n*-hexane gave 2-methyl-4-amino-5-dimethoxymethylpyrimidine (**15**, 53 mg), mp 107—108°C.[10]

(4) Hydrolysis: 21% Methanolic hydrogen chloride (890 mg) was added to a solution of **4·HCl** (1.1 g) in methanol (20 m*l*) containing water (90 mg) at −30°C. The solution was kept at 0°C for 2 hr, and then the solvent was removed. The recrystallization of the residue gave the hydrochloride of 2-methyl-3*H*-4-oxo-5-dimethoxymethyl-5,6-dihydropyrimidine (**16**) as needles; mp 212—213°C (decomp.). The yield was 816 mg. UV: 228 (ε 6500); (+NaOH) 220 mμ. NMR (DMSO-d_6): 4.75 (d, 1H, C$\underline{H}$(OMe)$_2$, J=4 Hz), 3.37 (s, 6H, OMe), 3.1—3.4 (m, 1H, H_5), 3.6—3.8 (m, 2H, H_6), 2.23 (bs, 3H, –C(–)–Me). Found: C, 43.38; H, 6.34; N, 12.48%. Calcd for $C_8H_{14}N_2O_3 \cdot HCl$: C, 43.15; H, 6.74; N, 12.58%.

(5) Reaction with Methylamine: The hydrochloride of **4** (395 mg) was neutralized with methanolic sodium methoxide, which had been prepared from sodium (41 mg) and methanol (17 m*l*). To the solution we then added methylamine (4.6 g) in methanol (30 m*l*). The mixture was kept at room temperature for 2 days, neutralized with 1% methanolic hydrogen chloride (3.5 g), and filtered from the precipitates, and the solvent was removed. The residue was extracted with chloroform. The subsequent removal of the chloroform gave the syrup of 2-methyl-4-methylamino-5-dimethoxymethyl-5,6-dihydropyrimidine hydrochloride (**17·HCl**; 318 mg). No satisfactory elementary analysis was obtained for **17·HCl** because of its hydroscopicities, but the UV and NMR data supported the structure. UV: 280; (+NaOH) 260 mμ. NMR (methanol-d_4): 4.55 (d, 1H, –C$\underline{H}$(OMe)$_2$, J=7 Hz), 3.7—3.5 (m, 2H, H_6), 3.40 (s, 6H, OMe), 3.08 (s, 3H, N–Me), 2.25 (t, 3H, C–Me, J≒1 Hz).

(6) Treatment with Sodium Methoxide: The hydrochloride of **4** (1.88 g) was neutralzed with methanolic sodium methoxide, which had been prepared from sodium (1.67 g) and methanol (26 m*l*), and then the solution was refluxed. After 8 hr, the solution was neutralized with methanolic hydrogen chloride, filtered from precipitated sodium chloride, and evaporated to dryness. The residue was chromatographed on silica gel (Wakogel Q-23, 100—200 mesh, 40 g). Elution with acetone (100 m*l*) and, subsequently, with acetone-methanol (20: 1, 400 m*l*) gave 2-methyl-4-amino-5-methoxymethylpyrimidine (**13**, 913 mg), mp 118—120°C.[16]

(7) Reverse Reaction (The Formation of 8 and 20): A solution of **4·HCl** (590 mg) was added to a sodium methoxide solution, which had been prepared from sodium (46 mg) and methanol (6 m*l*), and then the mixture was warmed at 60°C for 7 hr. After cooling, the solution was filtered from precipitated sodium chloride and the solvent was removed. The yellow residue was chromatographed over alumina (Wako activated alumina, 300 mesh, 9.2 g). Elution with ethyl acetate-benzene-methanol (2: 1: 1) gave **8** (144 mg) as the first fraction (500 m*l*), a mixture of **8** and **20** (285 mg) as the second one (300 m*l*), and **8** (133 mg) as the third one (30 m*l*). The second crop was further chromatographed over the alumina (10 g). Elution with benzene-methanol (50: 1, 100 m*l*) gave **8** (54 mg), while subsequent elution with benzene-methanol (25: 1, 100 m*l*) gave **20** (153 mg). This **20** was purified by recrystallization from methanol and ethyl acetate. Mp 208—210°C (decomp.). MS 306 (M^+). Found: C, 49.04; H, 6.65; N, 24.36; Cl, 10.63%. Calcd for $C_{14}H_{22}N_6O_2 \cdot HCl$: C, 49.13; H, 6.78; N, 24.58; Cl, 10.37%.

(8) Reaction with Methyl Acetimidate: i) Hydrochlorides of methyl acetimidate (3.28 g) and **4** (2.217 g) were added to methanolic sodium methoxide, which had been prepared from sodium (690 mg) and methanol (20 g). After the removal of the precipitated sodium chloride by filtration, the total weight of the filtrate was made to 21 g by adding methanol, and then the solution was refluxed. The reaction mixture was quenched with acetic acid, and the yield of **8** was determined by gas chromatography (30% Apiezon grease L; column temperature, 236.5°C; flow rate, 90 m*l*/min; carrier gas, He; retention time of **8**, 2.2 min) as follows: 13.1% (after 0.5 hr), 13.1% (after 2 hr), and 13.1% (after 3 hr). ii) Hydrochlorides of methyl acetimidate (1.64 g) and **4** (1.11 g) were neutralized with a sodium methoxide solution, which had been prepared from sodium (450 mg) and methanol (15 m*l*). The mixture was worked up in a way similar to the above. The yield of **8** was 16.7% (after 1 hr) and 13.3% (after 2 hr).

(9) Reaction with Propioamidine: A solution of sodium methoxide in methanol, which had been prepared from

16) A. Takamizawa and R. Maeda, *ibid.*, **74**, 746 (1954).

sodium (138 mg) and methanol (6 ml), was added to a mixture of hydrochlorides of propioamidine (651 mg) and **4** (443 mg) and then quickly filtered from the precipitated sodium chloride. The filtrate was refluxed for 5 hr and then evaporated to dryness. To the residue we added water (8 ml), after which the aqueous solution was heated on a boiling-water bath for 1 hr. The removal of the water gave syrupy crystals (1.01 g) of a mixture of 2-methyl-4-amino-5-propioamidomethyl- (**30**) and 2-ethyl-4-amino-5-acetamidomethylpyrimidine (**33**). The relative ratio of **30** and **33** was 8: 92, which was determined by means of the peak height in the gas chromatogram (4% polyethyleneglycol 20M; column temperature, 240°C; flow rate, 100 ml/min; carrier gas, He; retention time, **30**: 13 min and **33**: 11 min). After a part of the syrupy crystals (120 mg) had been used for gas-chromatographic analysis, the crystals were collected by filtration. The subsequent recrystallization of the crystals from acetone gave leaflets of **33** (111 mg); mp 206.5—207.5°C. UV: 236 (ε 8900), 275 (ε 5400); (+HCl) 251 mμ. NMR (methanol-d_4): 7.93 (s, 1H, H_6), 4.28 (s, 2H, $-CH_2-$), 2.69 (q, 2H), 1.23 (t, 3H) (C_2H_5, J=7 Hz), 1.93 (s, 3H, CH_3CO). Found: C, 55.87; H, 7.07; N, 28.68%. Calcd for $C_9H_{14}N_4O$: C, 55.65; H, 7.27; N, 28.85%.

The mother liquors of the filtration of the syrupy crystals and the recrystallization of **33** were combined, and the combined solution was evaporated to dryness. The residue was chromatographed over the alumina (12 g). Elution with benzene-methanol (50: 3, 100 ml) gave **33** (180 mg), while further elution with the same solvent-system gave a syrup (170 mg) which contained **30** and/or **33** (46.5 mg), as determined by studying UV spectrum.

2-Methyl-4-amino-5-propionylamidomethylpyrimidine (30). Freshly-distilled propionyl chloride (750 mg) was added to a solution of 2-methyl-4-amino-5-aminomethylpyrimidine (**10**; 850 mg)[7] in pyridine under cooling, and the mixture was kept in a refrigerator overnight. The solvent was then removed. The residue was neutralized with N sodium hydroxide and then evaporated to dryness. The recrystallization of the residue from acetone gave needles of **30** (320 mg); mp 181°C. UV: 236 (ε 11400), 275 (ε 7100); (+HCl) 250 mμ. NMR (chloroform-d): 7.80 (s, 1H, H_6); 4.30 (s, 1H), 5.82 (s, 1H) ($-CH_2-$); 2.25 (q, 2H, J=7.3 Hz), 1.25 (t, 3H) (C_2H_5-). Found: C, 55.66; H, 7.29; N, 28.67%. Calcd for $C_9H_{14}N_4O$: C, 55.65; H, 7.25; N, 28.85%.

2-Dimethoxymethyl-3-acetamidinopropionitrile (3). *(1) Isolation*: Acetamidine hydrochloride (4.2 g) was added to a solution of sodium (0.95 g) in methanol (20 ml); the mixture was shaken and quickly filtered from the precipitated sodium chloride, and then the methanol was removed. Under stirring, 2-dimethoxymethylacrylonitrile (**2**; 3 g) was added drop by drop, to a solution of the residue in 1,2-dimethoxyethane (17 ml) at 0°C. After 3 hrs' stirring, the solution was kept in a refrigerator for 2 days and then neutralized with 30% methanolic hydrogen chloride (4.5 g). The crystals which appeared (5.4 g) were collected by filtration and recrystallized from ethanol. Cubics of the hydrochloride of **3** (2.97 g) were obtained; mp 144—146°C. UV: 206 mμ (ε 6170). IR_{KBr}: 2256 cm^{-1} (non-conjugate nitrile). NMR (methanol-d_4): 2.32 (s, 3H, C-CH_3), 3.8—3.14 (m, 3H, $CH_2-\underset{|}{C}H-\underset{|}{C}$), 4.70 [d, 1H, $C\underline{H}(OMe)_2$, J=5 Hz], 3.51 (s, 6H, $C(OMe)_2$]. Found: C, 43.16; H, 7.08; N, 19.00%. Calcd for $C_8H_{15}N_3O_2\cdot HCl$: C, 43.34; H, 7.28; N, 18.95%.

(2) Cyclization to 4: The hydrochloride of **3** (350 mg) was neutralized with methanolic sodium methoxide, prepared from sodium (46 mg) and methanol (5 g), and kept at room temperature for 2 hr. The solution was neutralized with 36% methanolic hydrogen chloride (300 mg) and filtered from the precipitated sodium chloride, and then the methanol was removed. The recrystallization of the residue (511 mg) from ether and methanol gave **4·HCl** (200 mg).

2-Methyl-4-amino-5-acetamidinomethylpyrimidine (11). *(1) Isolation*: Acetamidine hydrochloride (20 g) and **1** (26 g) were added to methanolic sodium methoxide, which had been prepared from sodium (3.68 g) and methanol (58 ml), and the mixture was stirred at 43°C for 3 hr. After cooling, 43% methanolic hydrogen chloride (9.2 g) was added to the solution. The yellow crystals which appeared were collected by filtration and washed with ethyl acetate (100 ml). The residue was dissolved with hot methanol, and the methanol solution was cooled to 0°C. The precipitates (the monohydrochloride of **11**) were collected by filtration and washed with a small portion of methanol. The yield was 134 mg; mp 246—250°C (decomp.). UV: 233 (ε 10900), 273 (ε 4930); (+HCl) 246 mμ. MS: 179 (M^+), 162 (M^+-NH_3), 122 ($M^+-NH-\overset{NH}{\overset{\|}{C}}-Me$). Found: C, 44.26; H, 6.68; N, 31.75%. Calcd for $C_8H_{13}N_5\cdot HCl$: C, 44.55; H, 6.54; N, 32.47%.

(2) Synthesis: A solution of 2-methyl-4-amino-5-aminomethylpyrimidine (**10**, 13.8 g)[7] in methanol (30 ml) was added, drop by drop and over a 20-min period, to a solution of methyl acetimidate hydrochloride (11 g) in methanol (5 ml) at 15°C. After stirring at 15°C for 1 hr, precipitates which appeared (the monohydrochloride of **11**) were collected by filtration and washed with a mixture of methanol (9 ml) and pyridine (5 ml). The yield was 870 mg; mp 246—250°C (decomp.).

Reaction of 2-Methyl-4-amino-5,6-dihydropyrimidine (18) with Acetamidine. (1) Acetamidine hydrochloride (473 mg) and **18** (556 mg)[1] were added to a solution of sodium methoxide, prepared from sodium (115 mg) and methanol (14 g), and then filtered from the precipitated sodium chloride. The solution was refluxed for 4 hr and then evaporated to dryness. The residue was extracted with acetonitrile (100 ml), and the acetonitrile was removed. The recrystallization of the residue from acetonitrile gave **18** (113 mg).

(2) A solution of acetamidine hydrochloride (945 g) and **18** (555 mg) in methanol (5 ml) was refluxed for 4 hr. The UV spectrum of the reaction mixture showed only the characteristic band due to the hydrochloride of **18**.

Reaction of 2-Phenyl-4-amino-5,6-dihydropyrimidine (22) with Acetamidine. A solution of acetamidine hydrochloride (510 mg) and **22** (467 mg)[13] in methanol (5 g) was refluxed for 5 hr. The UV spectrum of the reaction mixture showed only the characteristic band due to the hydrochloride of **22**.

Reaction of 2-Methyl-3H-4-oxo-5-dimethoxymethyl-5,6-dihydropyrimidine (16) with Acetamidine. Hydrochlorides of **16** (550 mg) and acetamidine (630 mg) were added to methanolic sodium methoxide, prepared from sodium (204 mg) and methanol (20 ml), and then filtered from the sodium chloride thus precipitated. The solution was refluxed for 2 hr and then evaporated to dryness. The recrystallization of the residue from ethanol gave needles of 2-methyl-4-hydroxy-5-acetamidinomethylpyrimidine (**27**; 250 mg), (mp 218—238°C (decomp.)), which was subsequently purified as its dihydrochloride (mp 197—202°C (decomp.)). UV: 207 (ε 9000), 220 (shoulder), 278 (ε 5540); (+HCl) 224, 262; (+NaOH) 232, 262 mμ. NMR (methanol-d_4): 8.13 (s, 1H, H_6), 4.39 (s, 2H, $-CH_2-$), 2.28 (s, 3H, >C-Me), 2.68 (s, 3H, 2-Me). Found: C, 38.01; H, 5.67; N, 22.26; Cl, 28.70%. Calcd for $C_8H_{12}N_4O\cdot 2HCl$: C, 37.95; H, 5.53; N, 22.13; Cl, 28.01%.

Reaction of 2-Methyl-4-amino-5-dimethoxymethyl- (4) and 2-Methyl-3H-4-oxo-5-dimethoxymethyl-5,6-dihydropyrimidine (16) with Acetamidine. Hydrochlorides of **4** (372 mg), **16**

(372 mg) and acetamidine were added to a solution of sodium methoxide, which had been prepared from sodium (157 mg) and methanol (10 m*l*) and the mixture was refluxed for 5 hr. After cooling, the solution was filtered from the precipitated sodium chloride and then evaporated to dryness. A mixture of **8** and **27** was obtained as a yellow powder (708 mg). The relative ratio of **8** and **27** was about 1: 1, as determined from the NMR spectrum of the mixture in methanol-d_4. Singlets due to the methylene group of **8** at 4.95 and to that of **27** at 4.18 δ were used for the determination.

*Isolation of 2-Methyl-4-amino-5-methoxymethylpyrimidine (**13**) from the Reaction of 2-Dimethoxymethyl-3-methoxypropionitrile (**1**) with Acetamidine.* To methanolic sodium methoxide, prepared from sodium (0.64 g) and methanol (7 m*l*), we added **1** (1.6 g). The solution was refluxed for 4 hr, filtered from the precipitated sodium chloride, and then evaporated to dryness. The aqueous solution (6 m*l*) of the residue was warmed at 100°C for 1 hr and then evaporated to dryness. 48% Sodium hydroxide (3 g) was added to the residue, and the crystals which appeared were collected by filtration and washed with water and then with ethyl acetate. The evaporation of the ethyl acetate gave syrupy crystals, from which **13** was isolated by preparative tlc (a silica gel plate, chloroform-ethyl acetate, 1: 1). The recrystallization of crude **13** from benzene gave a pure product 141 mg); mp 118—120°C.[16]

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