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The Reaction of Methyl 2-Dimethoxymethyl-3-methoxypropionate with Amidines[1,2]

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The reaction of methyl 2-dialkoxymethyl-3-methoxypropionate with acetamidine has been reported to afford 2-methyl-4-hydroxy-5-methoxymethylpyrimidine (**13a**) by a different mode than the reaction of 2-dimethoxymethyl-3-methoxypropionitrile (**1**), which affords dihydropyrimidopyrimidine (**4**). As the presence of this difference seemed to be somewhat curious from the viewpoint of the reaction mechanism, the reaction of methyl 2-dimethoxymethyl-3-methoxypropionate (**7**) with acetamidine was reinvestigated. The reaction products were **13a** and acetamidinomethylpyrimidine (**17a**). Similar results were obtained by the reaction of **7** with benzamidine. As the compound **17** corresponds to **4**, the reaction of **7** was concluded to proceed in a manner similar to that of **1**; that is, no essential difference exists between the reactions of **1** and **7** with amidines.

In previous papers,[2-5] we have presented the pathway of the reaction of 2-dimethoxymethyl-3-methoxypropionitrile (**1**) with amidines. The reaction proceeds mainly *via* the pathway of **1** → 2-dimethoxymethylacrylonitrile (**2**) → dihydropyrimidines (**3**) → dihydropyrimidopyrimidines (**4**). The existence of the minor pathway of **1** → 2-methoxymethylene-3-methoxy-

1) Pyrimidines, 12, for Part 11, see Ref. 2. A part of this paper was reported in a preliminary form: T. Nishino, Y. Miichi, and K. Tokuyama, *Tetrahedron Lett.*, **1970**, 4335.

2) T. Nishino, M. Kiyokawa, Y. Miichi, and K. Tokuyama, This Bulletin, **46**, 253 (1973).

3) T. Nishino, M. Kiyokawa, Y. Miichi, and K. Tokuyama, *ibid.*, **45**, 1127 (1972).

4) T. Nishino, M. Kiyokawa, Y. Miichi, and K. Tokuyama, *ibid.*, **45**, 2010 (1972).

5) M. Tanaka and K. Tokuyama, paper read at the 92nd annual meeting of The Pharmaceutical Society of Japan, Kinki University, Higashiosaka, Osaka, April, 1972, Abstract 6M4-3.

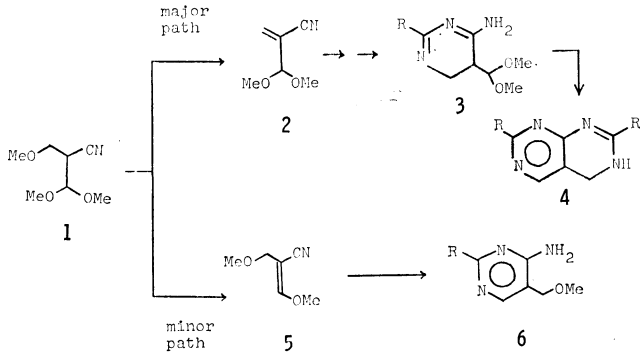

Chart 1.

propionitrile (**5**) → 5-methoxymethylpyrimidines (**6**) was also established.

Similar results can naturally be expected in the reaction of the ester analog of **1**. However, the reaction of the ester analog with acetamidine did not yield products corresponding to **3** and **4**, but only the product corresponding to **6**.[6] Although an explanation of this remarkable difference between the two reactions had been proposed, it seems to be somewhat in conflict with the revised mechanism of the reaction of **1** with acetamidine. Therefore, we attempted to reinvestigate the reaction of the ester analog.

Methyl 2-dimethoxymethyl-3-methoxypropionate (**7**), 2-dimethoxymethylacrylate (**9**), and 2-methoxymethylene-3-methoxypropionate (**10**) were prepared by the usual methods[6] and were used as the starting materials. Their structures were identified by a comparison of their spectra with the spectra of the corresponding propionitriles.[6-8]

At the outset, the possibility of the conversion of **7** into **9** was examined. When a mixture of **7** and sodium methoxide was left at room temperature overnight, the spot of **7** disappeared in the tlc. Without purification, the product was treated with acetamidine to give a pyrimidine (**12**), $C_{14}H_{22}N_2O_6$, which showed the bands due to ester and acetal groups in the IR spectrum and a behavior similar to that of 2-methyl-4-hydroxy-5-methoxymethylpyrimidine (**13a**)[9] in the UV. Therefore, its structure was identified as 2-methyl-4-hydroxy-5-(2′-carbomethoxy-2′-dimethoxymethyl-3′-methoxy)-propylpyrimidine. The NMR spectrum also supported this structure.

By analogy with the base-catalyzed reaction of **1**,[3] a dimeric substance of **7** (**11**) should exist in the product. The possible intermediate, **11**, suggested the presence of the equilibrium, **7** ⇌ the anion of **7** (**8**) ⇌ **9** under basic conditions, since **11** would be formed by the reaction of **8** with **9**, as shown in Chart 2. Consequently, the formation of the reaction products with **9**, corresponding to the product from the major pathway

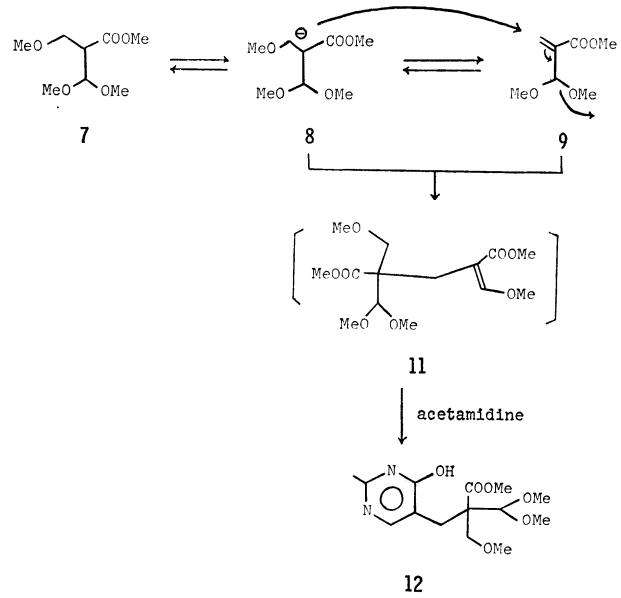

Chart 2.

of the reaction of **1**, was anticipated in the reaction of **7** with acetamidine.

When a mixture of **7** and acetamidine was refluxed in methanol, **13a** and another product (**17a**) were obtained as expected. The structure of **17a** was identified as 2-methyl-4-hydroxy-5-acetamidinomethylpyrimidine by a comparison of the spectral data with those of an authentic sample.[4] The relative ratio of the yields of **13a** and **17a** was about 3: 2, as determined by NMR spectroscopy.

It is quite natural to consider that **17a** was formed *via* a pathway corresponding to that of the reaction of **1**. Chart 3 shows a possible pathway *via* **9** and a dihydropyrimidine (**14**) as key intermediates.

The step **14**→**17a** was proved in a previous paper.[4] The treatment of **9** with acetamidine in 1,2-dimethoxy-

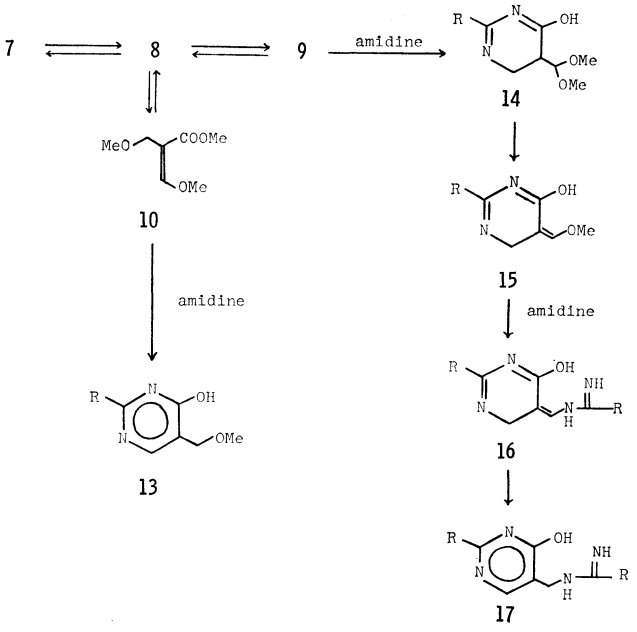

Chart 3.

6) A. Takamizawa, K. Tokuyama, and H. Satoh, *Yakugaku Zasshi*, **79**, 664 (1959).
7) A. Takamizawa, K. Ikawa, and M. Narisada, *ibid.*, **78**, 632, 637 (1958).
8) A. Takamizawa, K. Hirai, and S. Sumimoto, *Chem. Pharm. Bull.* (Tokyo), **14**, 238 (1966).
9) A. Takamizawa, *Yakugaku Zasshi*, **74**, 756 (1954).

ethane at a low temperature did not afford **13a**, but **14a** as the major product, along with a limited amount of **17a**. On the other hand, that of **10** in 1,2-dimethoxyethane instantly yielded only **13a** in a high yield. These results support the above pathway.

Similar results were obtained in the reaction of **7** with benzamidine. When a mixture of **7** and benzamidine was refluxed in methanol for a long time, crystals appeared which had a correct analysis for $C_{18}H_{16}N_4O$. Therefore, the structure of the crystals was identified as that of the phenyl analog of **17a** (**17b**). The structure was also confirmed by the spectral data. From the mother liquor, the phenyl analog of **13a** (**13b**) was isolated, its structure was confirmed from the combined data of elemental and spectral analyses.

The above results support the idea that the reaction with benzamidine proceeded in a manner similar to that with acetamidine. The relative ratio of the yields of **13b** and **17b** was about 2: 1.

As has been described above, the pathway of the reaction of **1** with amidines can be applied to the reaction of **7**. It can be concluded that there is no essential difference between the two reactions.

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 δ values (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, bs: broad singlet). The UV spectra were observed in methanol and are reported in nm. The molecular weights were determined by means of a vapor-pressure osmometer in benzene. The solvents used were removed under reduced pressure.

Methyl 2-Dimethoxymethyl-3-methoxypropionate (7) was prepared by the usual method.[6] Bp 62°C/2 mmHg. $N_D^{26.2}$ 1.4211. IR_{film} 1744 cm^{-1} (ester), 1100, 1070 (acetal). NMR (CCl_4) 3.42—3.58 (m, 2H, H_3, AB part), 2.86 (m, 1H, H_2, M part; J_{AM} 4.5 Hz, $J_{BM}=J_{MX}$ 8 Hz), 4.43 (d, 1H, C<u>H</u>$(OMe)_2$, X part), 3.65 (s, 3H, COOMe), 3.23 (s, 3H), 3.25 (s, 3H, CH$(O\underline{Me})_2$), 3.28 (s, 3H, 3-MeO). Found: C, 50.06; H, 8.42%; mol wt, 200. Calcd for $C_8H_{16}O_5$: C, 49.99; H,8.39%; mol wt, 192.

Methyl 2-Dimethoxymethylacrylate (9) and Methyl 2-Methoxymethylene-3-methoxypropionate (10) were prepared by the usual methods.[6] **9**: Bp 42—44°C/3.5 mmHg. $N_D^{26.2}$ 1.4295. IR_{film} 1730 cm^{-1} (ester), 1630 (C=C), 1100, 1075, 1055 (acetal, C–O–C). NMR (CCl_4) 6.23 (d, 1H, H_3, $J_{3,3'}$ 2 Hz), 5.90 (q, 1H, H_3', $J_{3,A}$ 1 Hz), 5.10 (d, 1H, H_A, C<u>H</u>$(OMe)_2$), 3.27 (s, 6H, CH$(O\underline{Me})_2$), 3.72 (s, 3H, COOMe). Found: C, 52.49; H, 7.70%; mol wt, 191. Calcd for $C_7H_{12}O_4$: C, 52.94; H, 7.55%; mol wt, 160. **10**: purified by gas chromatography (Column, PEG 20 M 20%, 176±2°; flow rate, helium 25.0 ml/min). $N_D^{26.5}$ 1.4644. IR_{film} 1712 (ester), 1642 cm^{-1} (C=C). UV 237 (ε 15200). NMR (CCl_4), 3.98 (s, 2H, H_3), 7.33 (s, 1H, =C<u>H</u>OMe), 3.18 (s, 3H, 3-MeO), 3.85 (s, 3H, =CHO<u>Me</u>), 3.65 (s, 3H, COOMe). Found: C, 52.69; H, 7.73%, mol wt, 162. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55%; mol wt 160.

Reaction of Methyl 2-Dimethoxymethyl-3-methoxypropionate (7) with Sodium Methoxide. A mixture of **7** (2 g) and sodium methoxide (265 mg) was left at room temperature overnight. The spot due to **7** disappeared in the tlc. A solution of acetamidine, which has been prepared from acetamidine hydrochloride (1.32 g), sodium (200 mg), and methanol (13 ml), was then added to the mixture. The solution was refluxed for 5 hr, and then the solvent was removed. The residue was extracted with ether. The ether-extracted syrup was fractionated by column chromatography (alumina, 40 g,; benzene 7: methanol 1: ethyl acetate 2, v/v). From the initial fractions, crystals were obtained. The recrystallization of the crystals from ethyl acetate gave acetamide. From the mother liquor, needles of **12** were obtained; this substance was then recrystalized from ether. The yield was 30 mg. Mp 132.4—133°C. IR_{KBr} 1740 cm^{-1} (ester), 1650 (C=N), 1100 (C–O–C). UV 278 (ε 6000), +HCl 265. +NaOH 276. MS 314 (M^+). NMR (CD_3OD) 7.73 (s, 1H, H_6), 4.58 (s, 1H, C<u>H</u>$(OMe)_2$), 3.58 (s, 2H, –C<u>H</u>$_2$–OMe), 3.65 (s, 3H, COOMe), 3.47 (s, 6H, CH$(O\underline{Me})_2$), 3.20 (s, 3H, $CH_2O\underline{Me}$), 2.88 (s, 2H, C_5-CH_2), 2.33 (s, 3H, C_2-Me). Found: C, 53.69; H, 7.15; N, 9.07%. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91%.

Reaction of Methyl 2-Dimethoxymethyl-3-methoxypropionate (7) with Amidines. (1) Reaction with Acetamidine: (i) Acetamidine hydrochloride (2.25 g) was dissolved in a solution of sodium (0.505 g) in methanol (15 ml) and then the sodium chloride thus precipitated was filtered out. To the filtrate, **7** (2 g) was added, after which the solution (18.65 g) was refluxed for 6 hr. One gram of the solution was used for the determination of the relative ratio of **13a** and **17a** by NMR spectroscopy, using methanol-d_4 as the solvent. Singlets due to the methylene group of **13a** at 4.30 δ and that of **17a** at 4.20 δ were integrated. The ratio (**13a** : **17a**) was 3: 2. The remainder of the solution was evaporated to dryness, and the residue was fractionated by column chromatography [silica gel (40 g), ethanol]. From the initial fractions, **13a** (720 mg, 45%) was obtained.[9] (ii) Five grams of **7** were treated in methanol (20 ml) with acetamidine hydrochloride (5.4 g), and sodium (1.2 g). The solvent was then removed, and the residue was washed with dioxane (100 ml) and subsequently recrystallized from ethanol. Plates of **17a** (132 mg) were obtained; they were purified as the dihydrochlorides [mp 237—240°C (dec)].[4]

(2) Reaction with Benzamidine: A solution of **7** (1.5 g) and benzamidine (2.1 g) in methanol (10 ml) was refluxed for 15 hr. After cooling, there appeared crystals (**17b**, 345 mg) which were collected by filtration. The filtrate was evaporated to dryness and then washed with petroleum ether. The petroleum ether contained **7**. The residue was chromatographed over silica gel (30 g). The first fraction, eluted with ether (150 ml) afforded a mixture of **13b** and **17b** (37 mg). The second fraction, eluted with a mixture (150 ml) of ether (10 parts) and ethanol (1 parts) and the third one, eluted with a mixture (120 ml) of ether (1 part) and ethanol (1 part) gave needles of **13b** (565 mg). **13b**: mp 188.5—191.2°C (dec), (recryst. from ethanol). UV 242 (ε 15200), 296 (ε 1100), +HCl 242, 281, +NaOH 237, 282, 295. IR_{KBr} 1663 cm^{-1} (C=C, C=N). NMR ($CDCl_3$) 8.18 (bs, 1H, H_6), 4.44 (d, 2H, –CH_2–, J=1 Hz), 3.32 (s, 3H, MeO–). Found: C, 66.62; H, 5.48; N, 12.88%. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96%. **17b**: leaflets, mp 255.5—257°C (dec) (recryst. from methanol). UV 235 (ε 28300), 295 (ε 10000), +HCl 235, 285, +NaOH 234, 285, 294. IR_{KBr} 1695, 1625 cm^{-1} (C=C, C=N). MS 304 (M^+), 287 (M^+–NH_3), 200 (M^+–$\overset{NH}{\overset{\|}{C}}$–Ph), 185 ($M^+$–HN–$\overset{NH}{\overset{\|}{C}}$–Ph). Found: C, 71.27; H, 5.28; N, 18.59%. Calcd for $C_{18}H_{16}N_4O$: C, 71.03; H, 5.30; N, 18.41%.

Reaction of Methyl 2-Dimethoxymethylacrylate (9) with Aceta-

midine. Acetamidine hydrochloride (5.3 g) was added to a methanolic sodium methoxide, prepared from methanol (20 ml) and sodium (1.2 g), after which the solution was filtered to remove precipitates. The filtrate was evaporated to dryness, and to the residue 1,2-dimethoxyethane (7 ml) was added. Under stirring, a solution of **9** (3 g) in 1,2-dimethoxyethane (7 ml) was added to the solution in portions at below 5°C. The solution was left in a refrigerator for 2 days and then neutralized with methanolic hydrogen chloride. The crystals of the dihydrochloride of **17a** (2.3 g)[4] were collected by filtration.

*Reaction of Methyl 2-Methoxymethylene-3-methoxypropionate (**10**) with Acetamidine.* Acetamidine hydrochloride (1.2 g) was added to methanolic sodium methoxide, which had been prepared from methanol (6 ml) and sodium (302 mg). The solution was filtered from precipitated sodium chloride and then evaporated to dryness. A solution of **10** (700 mg) in 1,2-dimethoxyethane (2 ml) was added to a mixture of the residue and 1,2-dimethoxyethane (3 ml). Crystals appeared instantly; they were collected by filtration and then extracted with chloroform. The evaporation of the chloroform gave **13a** (635 mg).[9]

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