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REACTION OF METHYL 2-DIMETHOXYMETHYL-3-METHOXYPROPIONATE WITH ACETAMIDINE

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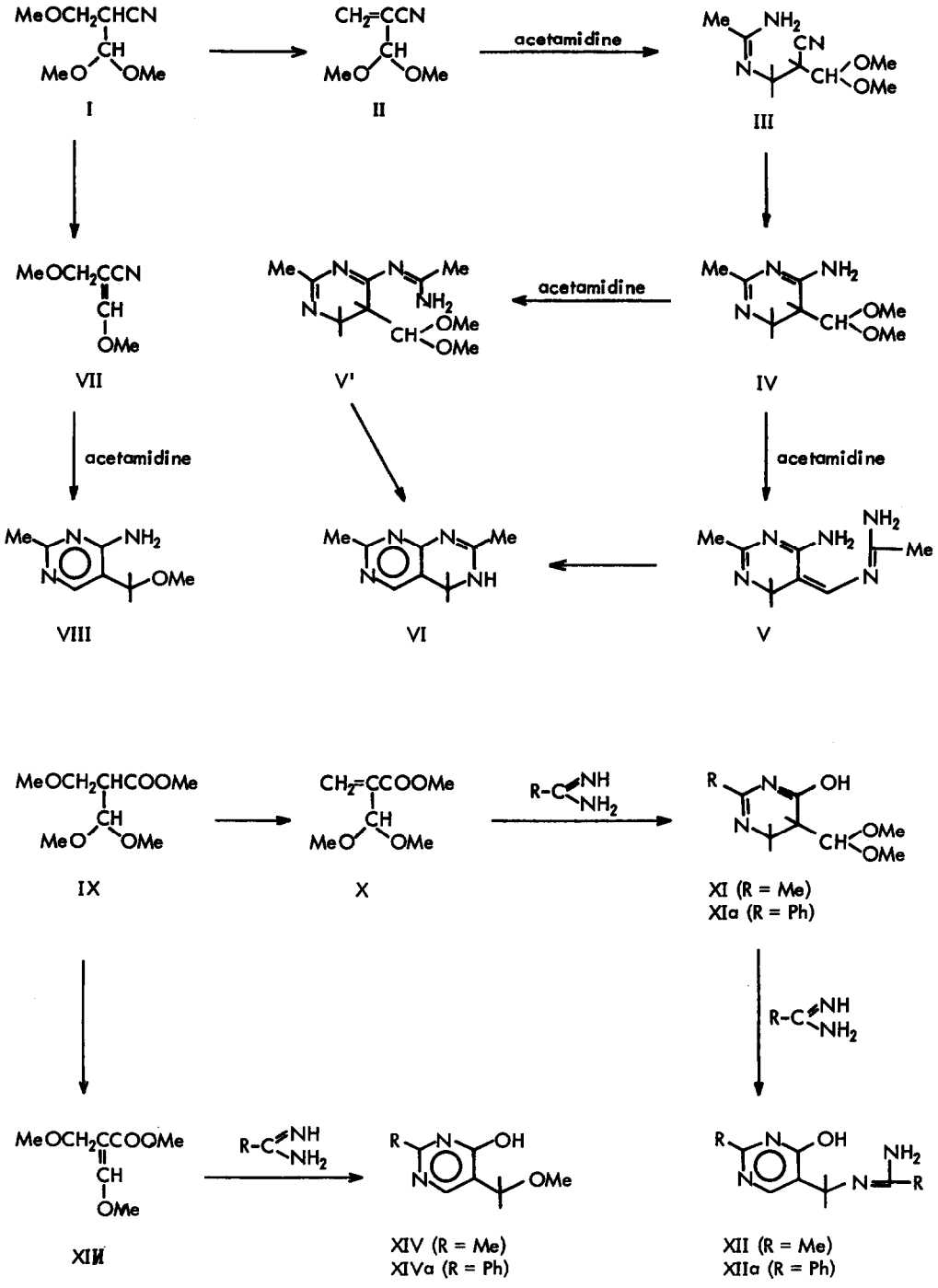
The reactions of 2-formyl-3-alkoxypropionitriles with acetamidine are rather complicated, though they are very important reactions for thiamine production (1). Especially, it is of interest that the compound I of an acetal type affords a pyrimidopyrimidine VI (2, 3, 4) by a different mode than the compound VII of an enol ether type which affords an expected pyrimidine VIII (5). For the former reaction, our preceding paper has proposed a novel pathway of I → II → III → IV → V' → VI (2). On the other hand, the formation of a usual pyrimidine XIV only was observed from the reactions of 2-formyl-3-alkoxypropioesters (6, 7). No reliable explanation was proposed on this remarkable difference in behavior between two acetals, I and IX. This communication refers to the studies on the reaction mechanism of propioesters.

Starting materials, IX, X and XIII were synthesized by usual methods (7). When IX was treated with acetamidine in methanol a smooth reaction proceeded at reflux temperature and from the products two major products were isolated, one of which was identified as XIV (5). The combined data of elemental analysis, the mass, uv, ir, and pmr spectra established that another one was XII. The yields of XII and XIV were 35% and 45% respectively. The formation of XII suggested that IX also reacted with acetamidine in a manner similar to I, that is, the reaction proceeds via two pathways, IX → X → XI → XII and IX → XIII → XIV.

The presence of the pathways was confirmed by the following facts. A spot corresponding to XI (2) was detected in the thin-layer chromatograms, though its isolation was unsuccessful. In dimethoxyethane, X reacted with acetamidine to form XI, but XIII to form XIV exclusively. On heating of XI with acetamidine in methanol, XII was isolated in a fairly good yield, but XIV was hardly detected. The presence of the pathway of XIV → XII was experimentally excluded. Similar results were also obtained


MeOCH2CHCN
CH
MeO OMe
I
CH2=CCN
CH
MeO OMe
II
acetamidine
Me NH2
CN
N
CH OMe
OMe
III
MeOCH2CCN
CH
OMe
VII
Me N N Me
NH2
N
CH OMe
OMe
V'
acetamidine
Me N NH2
N
CH OMe
OMe
IV
acetamidine
acetamidine
Me N NH2
N
OMe
VIII
Me N N Me
NH
VI
NH2
Me N NH2
Me
N N
V
MeOCH2CHCOOMe
CH
MeO OMe
IX
CH2=CCOOMe
CH
MeO OMe
X
R-C NH
NH2
R N OH
N
CH OMe
OMe
XI (R = Me)
XIa (R = Ph)
R-C NH
NH2
MeOCH2CCOOMe
CH
OMe
XIII
R-C NH
NH2
R N OH
N
OMe
XIV (R = Me)
XIVa (R = Ph)
R N OH
N
NH2
N R
XII (R = Me)
XIIa (R = Ph)

from the reactions of propioesters with benzamidine. Therefore, the presence of the two pathways was established. The relatively higher yield of XIV as compared to that of VIII must be caused by the difference of populations of XIII and VII in reaction media.

In conclusion, the reaction of IX proceeds in a manner similar to that of I (2); no difference exists in the pathways of both reactions. Furthermore, the formation of XII suggested that the reaction of IV→VI would proceed via another intermediate V. On this idea, investigation is now in progress.

The data of the above-described compounds are reported below (chemical shifts are expressed in τ value and uv spectra were measured in methanol).

IX: bp 62°C (2 mmHg), $n_D^{26.2°C}$ 1.4211. Ir (film) cm^{-1}: 1740 (COOMe), 1100, 1070 ($<^{OMe}_{OMe}$, CH_2OMe). Pmr (CCl_4): 5.58^d (1H, J = 8 Hz, $\underline{CH}<^{OMe}_{OMe}$), 6.35^s (3H, COO$\underline{Me}$), 6.42-6.58^m (2H, $-CH_2-$), 6.72^s, 6.75^s (9H, $<^{OMe}_{\underline{OMe}}$, $CH_2O\underline{Me}$), 6.97-7.32^m (1H, $-\underline{C}H-$).

X: bp 42-44°C (3.5 mmHg). $n_D^{26.2°C}$ 1.4295. Ir (film) cm^{-1}: 1730 (COOMe), 1630 (C=C), 1100, 1075, 1055 ($<^{OMe}_{OMe}$, CH_2OMe). Uv $_{nm}$: 220 (ε 2600). Pmr (CCl_4): 3.77^d (1H, J = 2 Hz, $\frac{H}{H}>C=C$), 4.10^q (1H, J = 2 Hz, J = 1Hz, $\frac{H}{\underline{H}}>C=C$), 4.90^d (1H, J = 1 Hz, $\underline{CH}<^{OMe}_{OMe}$), 6.28^s (3H, COO$\underline{Me}$), 6.73^s (6H, $<^{OMe}_{\underline{OMe}}$).

XII: mp 237-240°C (dec.). Ir (Nujol) cm^{-1}: 3480, 3280 (NH), 2700 (OH). Uv $_{nm}$: 207 (ε 7000), 227 (ε 5300), 275 (ε 4600). λ_{nm}^{+HCl} 210, 223, 261, λ_{nm}^{+NaOH} 208, 225 (sh), 271. Pmr (CD_3OD): 2.13^s (1H, pyrimidine ring proton), 5.80^s (2H, CH_2), 7.68^s (3H, CH_3-pyrimidine), 7.80^s (3H, $\underline{CH_3}-\overset{NH}{\overset{\|}{C}}-NH$), MS: 180 ($M^+$), 163 ($M^+-NH_3$), 138 ($M^+-\overset{NH}{\overset{\|}{C}}-CH_3$), 123 ($M^+-\underset{H}{N}-\overset{NH}{\overset{\|}{C}}-CH_3$).

XIII: $n_D^{26.5°C}$ 1.4644. Ir (film) cm^{-1}: 1712 (C=O), 1642 (C=C). Uv$_{nm}$: 237 (ε 15200). Pmr (CCl_4): 2.67^s (1H, $=C<^{\underline{H}}_{OMe}$), 6.02^s (2H, CH_2), 6.15^s (3H, $=C<^{H}_{\underline{OMe}}$), 6.35^s (3H, COO$\underline{Me}$), 6.82^s (3H, $CH_2O\underline{Me}$).

XIIa: mp 255.5-256.9°C (dec.). Ir (KBr) cm^{-1}: 3240, 3050 (NH, OH), 1630, 1620, 1590 (C=C, C=N, Ph). Uv $_{nm}$: 235 (ε 10000), 290.

XIVa: mp 188.5-191.2°C. Ir ($CHCl_3$) cm^{-1}: 1660, 1610, 1600 (C=C, C=N, Ph), 1109 (OMe). Uv $_{nm}$: 242 (ε 11000), 297. Pmr ($CDCl_3$) cm^{-1}: 6.68^s (O$\underline{Me}$), 5.58^q (CH_2), 1.82^s (pyrimidine ring proton), 1.5-1.19^m, 2.3-2.6^m (Ph).

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REFERENCES

1. A. Takamizawa, K. Tokuyama and K. Tori, Bull. Chem. Soc. Japan 32, 188 (1959); and references cited therein.
2. T. Nishino, M. Kiyokawa and K. Tokuyama, Tetrahedron Letters 1969, 3553.
3. T. Nishino, M. Kiyokawa and K. Tokuyama, ibid. 1968, 4321.
4. Recently, III was successfully isolated as its HCl salt by the present authors.
5. A. Takamizawa, K. Ikawa and K. Tori, Yakugaku Zasshi (J. Pharm. Soc. Japan) 78, 647 (1958).
6. A. Takamizawa, ibid. 74, 756 (1954).
7. A. Takamizawa, K. Tokuyama and H. Satoh, ibid., 79, 664 (1959).