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THE REACTION OF 2-DIMETHOXYMETHYL-3-METHOXYPROPIONITRILE WITH BENZAMIDINE (1)

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The interesting and rather complicated behavior of 2-dimethoxymethyl-3-methoxypropionitrile (I) or 2-dimethoxymethylacrylonitrile (II) with acetamidine has been investigated by Takamizawa and his colleagues (2). This reaction affords 2,7-dimethyl-5,6-dihydropyrimido(4,5-d)pyrimidine (III), the intermediate for thiamine, and its mechanism has been proposed as shown in Chart 1. However, the structure of a key intermediate (IV) could not unequivocally be established, since its isolation was difficult (2). The authors have studied this reaction using benzamidine instead of acetamidine and successfully isolated an intermediate suggesting a novel mechanism for the above reaction.

The reaction of I with benzamidine was carried out in methanol or dimethoxyethane. When the reaction was interrupted at the initial stages, 2-phenyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (VI) and 2,7-diphenyl-5,6-dihydropyrimido(4,5-d)pyrimidine (XII) were obtained (3). Their structures were confirmed by the following series of reactions. The dehydrogenation of VI with chloranil yielded a pyrimidine (VII), which was hydrolyzed to an aldehyde (VIII). The reduction of this aldehyde VIII with $NaBH_4$-MeOH gave 2-phenyl-4-amino-5-hydroxymethylpyrimidine (IX). The chlorination of IX with phosphorus oxychloride, followed by methanolysis gave 2-phenyl-4-amino-5-methoxymethylpyrimidine (XI), which was obtainable from the reaction of 2-methoxymethylene-3-methoxypropionitrile (XV) with benzamidine in ethanol. On the other hand, XII was hydrolyzed to XIV via XIII. The compound XIV was easily converted into IX by the use of sodium nitrite.

The data of the above-described compounds are reported below (chemical shifts are expressed in τ value) (4). VI: m.p. 142° (dec.). IR $\overset{\text{Nujol}}{\underset{\text{cm}^{-1}}{}}$ 3200 (NH_2), 1020, 970 (acetal). UV $\overset{CH_3CN}{\underset{\text{m}\mu}{}}$ 243 (ε 15100), 279 (ε 4300). NMR$_{C_5D_5N}$ 5.13^{d} (-C$\underline{H}<^{O}_{O}$), 6.19^{s} (6H, $-OCH_3$), 5.87^{m}, 6.20^{m} (H_b, $H_{b'}$),

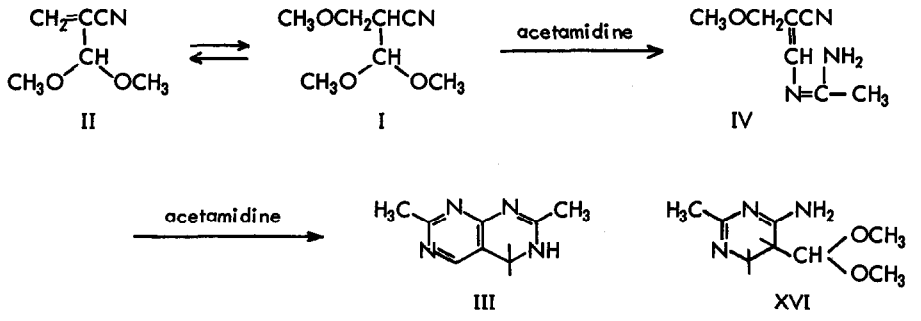

Chart 1

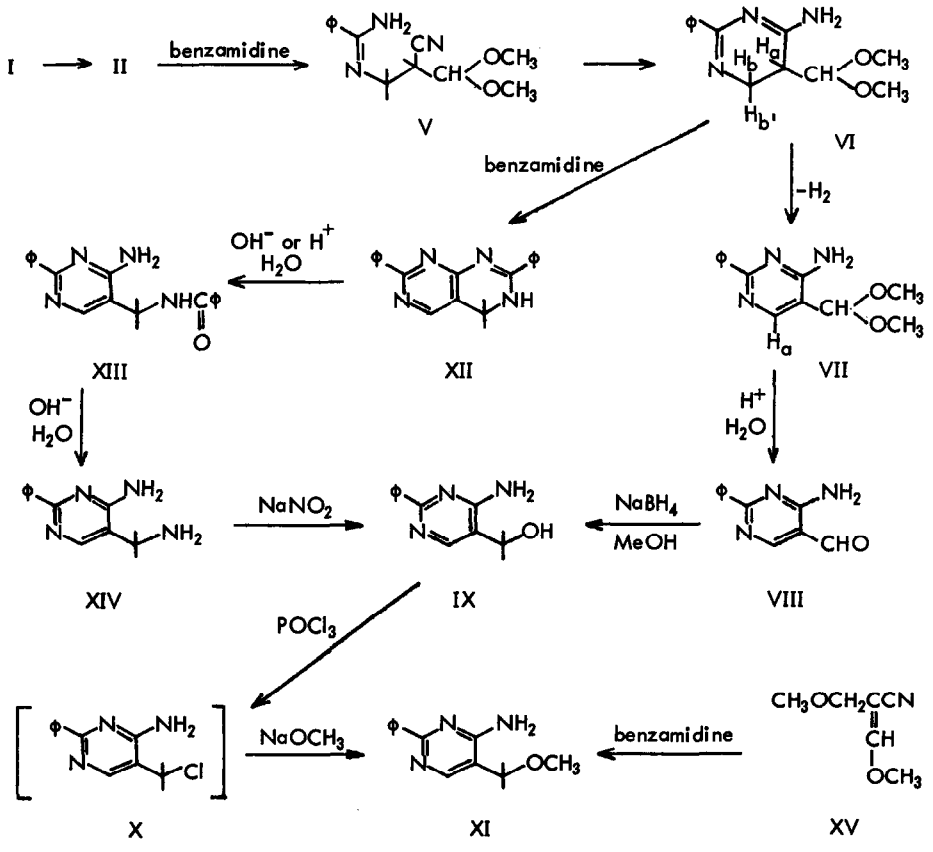

Chart 2

7.18^{m} (H_a). VII: m.p. 117-118°. IR $\overset{Nujol}{cm^{-1}}$ 3460, 3240 (NH_2), ~1630 (C=C, C=N), 1095, 1050 (acetal). UV $\overset{CH_3CN}{m\mu}$ 240 (ε 29400), 260 (sh., ε 20000), 282 (ε 12000), 296 (ε 1160). UV $\overset{CH_3CN+HCl}{m\mu}$ 252. NMR $_{CDCl_3}$ 1.46-1.73^{m} (3H, phenyl protons (ortho) + H_a), 2.34-2.69^{m} (3H, phenyl protons (meta, para)), 4.53^{s} (-C<u>H</u>$\langle$O O$\rangle$), 6.53^{s} (6H, OC<u>H</u>$_3$). VIII: m.p. 180-180.5°. IR $\overset{Nujol}{cm^{-1}}$ 1670, 2750 (CHO), 1625 (C=N). IX: m.p. 134-135.5°. IR $\overset{Nujol}{cm^{-1}}$ 3440, 3300, 3200 (NH_2, OH), 1627 (C=N). XI: m.p. 125-127°. IR $\overset{Nujol}{cm^{-1}}$ 3480, 3300 (NH_2), 1635 (C=N), 1085 (OCH_3). UV $\overset{CH_3CN}{m\mu}$ 238 (ε 21600), 258 (sh., ε 14700), 281 (ε 8800), 286 (sh., ε 8600), 297 (ε 8300). XII: m.p. 210.5-211.5°. IR $\overset{Nujol}{cm^{-1}}$ 3200 (NH), ~1580 (C=N, phenyl). UV $\overset{CH_3CN}{m\mu}$ 254 (ε 72800), 312 (ε 13800), 350 (ε 9700). XIII: m.p. 228-229.5°. IR $\overset{Nujol}{cm^{-1}}$ 3200 (NH_2), 1613 (C=O). UV $\overset{CH_3CN}{m\mu}$ 210 (ε 32500), 237 (ε 36200), 252 (sh., ε 19100), 284 (ε 11700), 298 (ε 12000). UV $\overset{CH_3CN+HCl}{m\mu}$ 254. XIV: isolated as HJ salt, m.p. 268-272° (dec.).

When the reaction was allowed to continue for longer periods of time, the amount of XII increased at the expense of VI. Therefore, the reaction process should be via the pathway I → II → V → VI → XII. The easy formation of VI from the reaction of II with benzamidine under milder conditions supported the pathway. This reaction also suggested the presence of an intermediate V. Although it could not be isolated in a pure state, its structure was proposed from the infrared spectrum showing characteristic bands due to acetal (1120, 1075 cm^{-1}), NH_2 (3450, 3250 cm^{-1}) and CN (non-conj. 2280 cm^{-1}).

As the reaction of I with acetamidine should proceed by a pathway similar to that with benzamidine, the correct structure of the intermediate IV, UV $\overset{MeOH}{max}$ 270 mμ, is suggested to be 2-methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (XVI). Therefore, the reaction of I with acetamidine is considered to proceed via a pathway of I → II → XVI → III.

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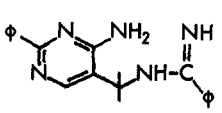
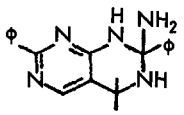
REFERENCES

1. Pyrimidines Part 1.
2. A. Takamizawa, K. Tokuyama and K. Tori, Bull Chem. Soc. Japan 32, 188 (1959); and earlier papers in this series.
3. Another product was isolated. Its structure was tentatively proposed to be XVII or XVIII, since it was easily converted into XII on heating and shows no signals due to C<u>H</u>$_3$O group in the NMR.



XVII



XVIII

4. Satsifactory elemental analytical data have been obtained for all new compounds.