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THE REACTION OF 2-DIMETHOXYMETHYL-3-METHOXYPROPIONITRILE WITH ACETAMIDINE. THE ISOLATION OF UNUSUAL PRODUCTS (1)

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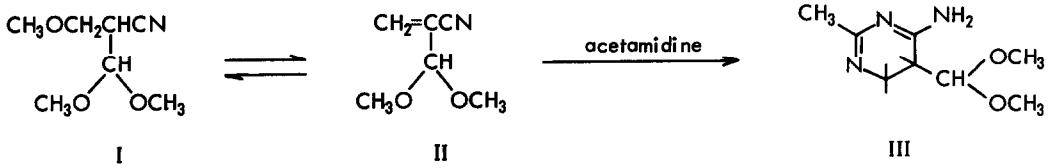
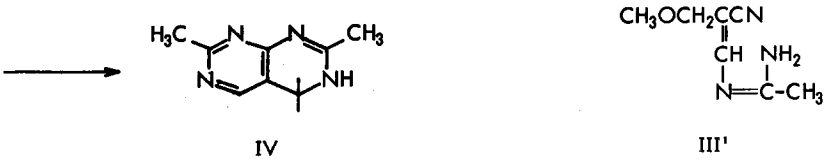
It was proposed in our preceding paper that 2-methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (III), instead of 2-amidinomethylene-3-methoxypropionitrile (III'), should be a key intermediate in the reaction of 2-dimethoxymethyl-3-methoxypropionitrile (I) with acetamidine and, consequently, this reaction proceeds via the pathway of I → 2-dimethoxymethylacrylonitrile (II) → III → 2,7-dimethyl-5,6-dihydropyrimido(4,5-d)pyrimidine (IV), which is an important product for thiamin synthesis (2, 3). In the course of studies of this reaction, we have newly isolated interesting products, 2-methyl-4-amino-5-(2'-cyano-2'-dimethoxymethyl-3'-methoxy)propylpyrimidine (V) and 2-methyl-6-dimethoxymethyl-6-methoxymethyl-7-amino-5,6-dihydropyrido(2,3-d)pyrimidine (VI). The formation of the both compounds also supported the presence and the structure of III.

Their structures were confirmed by the following sequence of reactions (see Chart 2). The combined data on the PMR, UV, and IR spectra showing the presence of an acetal, methoxyl and nitrile groups and of 4-aminopyrimidine moiety supported the structure of V. Heating of V in pyridine containing sodium hydroxide afforded VI, in which IR spectrum no band due to a nitrile group was observed. As the UV spectrum is quite similar to that of IV, the bicyclic structure of VI was established. The hydrolysis of VI with acetic acid gave VII. As the band due to a carbonyl group appeared in the IR spectrum, its structure was identified as 2-methyl-6-dimethoxymethyl-6-methoxymethyl-7-oxo-8H-5,6-dihydropyrido(2,3-d)pyrimidine. Further hydrolysis of VII with hydrochloric acid yielded 2-methyl-6-methoxymethyl-7-oxo-8H-5,6-dihydropyrido(2,3-d)pyrimidine (VIII), whose structure was confirmed by the spectral data showing one methoxyl group in the PMR spectrum and no band due to an acetal group in the IR spectrum.

To obtain further evidence, 2-methyl-6-carbethoxy-7-oxo-8H-5,6-dihydropyrido(2,3-d)pyrimidine (XI) was synthesized from 2-methyl-4-amino-5-formylpyrimidine (IX) (4) by the scheme outlined in Chart 3.

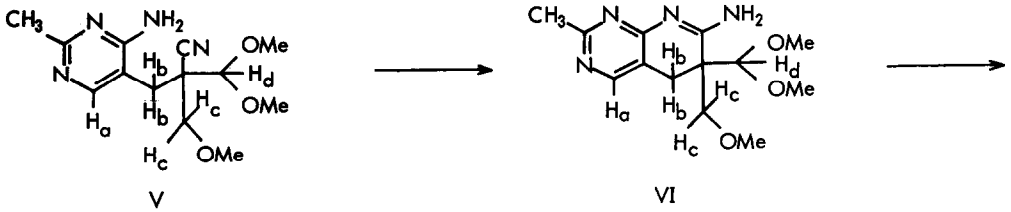


I II III

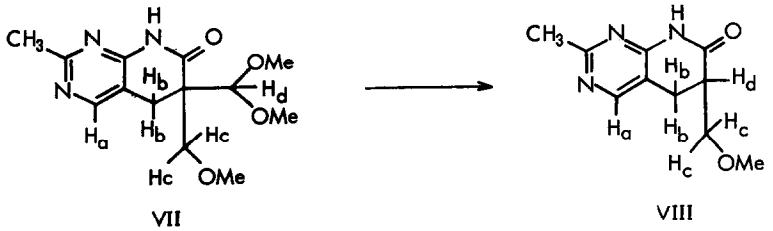


IV III'

Chart 1

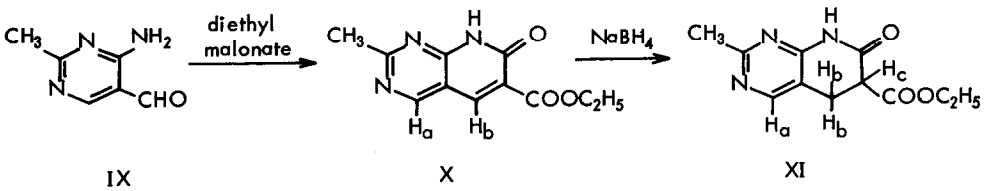


V VI



VII VIII

Chart 2



IX X XI

Chart 3

The pattern of the PMR spectrum and changes in the UV spectrum of XI were quite similar to those of VII and VIII. These facts supported the bicyclic structures of VII and VIII. Consequently, the structures of V and VI were confirmed.

The data on the above-described compounds are reported below (chemical shifts are expressed in τ-value) (5) V: m.p. 139-140°. IR $\overset{\text{Nujol}}{\underset{\text{cm}^{-1}}{}}$ 3380, 3190 (NH_2), 2240 (C≡N), 1660 (C=N), 1100, 1070 (acetal). UV $\overset{\text{EtOH}}{\underset{\text{mμ}}{}}$ 235 (ε 6900), 278 (ε 3400). UV $\overset{\text{EtOH + HCl}}{\underset{\text{mμ}}{}}$ 252. PMR $_{CDCl_3}$ 1.93^s (1H, Ha), 5.61^s (1H, Hd), 6.43^s (6H, $-C(OMe)_2$), 6.51^s (2H, Hb or Hc), 6.59^s (3H, $\perp OMe$), 7.15^m (2H, H_c or Hb), 7.53^s (3H, 2-Me). VI: m.p. 195-195.2°. IR $\overset{\text{Nujol}}{\underset{\text{cm}^{-1}}{}}$ 3400 (NH_2), 1100, 1090, 1070 (acetal, $\perp OMe$). UV $\overset{\text{EtOH}}{\underset{\text{mμ}}{}}$ 221 (ε 13200), 301 (ε 14100). UV $\overset{\text{EtOH + HCl}}{\underset{\text{mμ}}{}}$ 290, 307. PMR $_{C_5D_5N}$ 1.67^s (1H, Ha), 5.35^s (1H, Hd), 6.47^s (2H, Hb or Hc), 6.57^s (6H, $-C(OMe)_2$), 6.83^s (3H, $\perp OMe$), $7.0\text{-}7.1^m$ (2H, Hc or Hb), 7.28^s (3H, 2-Me). VII: m.p. 125-125.3°. IR $\overset{\text{Nujol}}{\underset{\text{cm}^{-1}}{}}$ 3200 (NH), 1700 (C=O), 1120, 1100, 1070 (acetal, $\perp OMe$). UV $\overset{\text{EtOH}}{\underset{\text{mμ}}{}}$ 242 (ε 5600), 275 (ε 10700). UV $\overset{\text{EtOH + HCl}}{\underset{\text{mμ}}{}}$ 280. UV $\overset{\text{EtOH + NaOH}}{\underset{\text{mμ}}{}}$ 280, 301. PMR $_{CDCl_3}$ 1.73^s (1H, Ha), 5.26^s (1H, Hd), 6.22-7.02 (4H, Hb and Hc), 6.47^s (6H, $-C(OMe)_2$), 6.73^s (3H, $\perp OMe$), 7.18^s (3H, 2-Me). VIII: m.p. 185-186°. IR $\overset{\text{Nujol}}{\underset{\text{cm}^{-1}}{}}$ 3400 (NH), 1710 (C=O), 1100 ($\perp OMe$). UV $\overset{\text{EtOH}}{\underset{\text{mμ}}{}}$ 240 (ε 8300), 272 (15500). UV $\overset{\text{EtOH + HCl}}{\underset{\text{mμ}}{}}$ 277. UV $\overset{\text{EtOH + NaOH}}{\underset{\text{mμ}}{}}$ 299. PMR $_{CDCl_3}$ 0.5 (1H, NH), 1.63^s (1H, Ha), 6.25^m (2H, Hb or Hc), 6.61^s (3H, OMe), 7.05^m (3H, Hd and Hc or Hb), 7.33^s (3H, 2-Me). X: m.p. 230-231.5°, IR $\overset{\text{Nujol}}{\underset{\text{cm}^{-1}}{}}$ 1680 (C=O). UV $\overset{\text{EtOH}}{\underset{\text{mμ}}{}}$ 265 (ε 3400), 274 (ε 3100), 324 (ε 9300). UV $\overset{\text{EtOH + HCl}}{\underset{\text{mμ}}{}}$ 265, 275, 320. UV $\overset{\text{EtOH + NaOH}}{\underset{\text{mμ}}{}}$ 256, 272, 353. PMR $_{CDCl_3}$ -0.5 (1H, NH), 1.03^s (1H, Hb), 1.53^s (1H, Ha), 5.59^q (2H, $OC\underline{H}_2CH_3$), 7.17^s (3H, 2-Me), 8.58^t (3H, $OCH_2C\underline{H}_3$). XI: m.p. 200-200.5°. IR $\overset{\text{Nujol}}{\underset{\text{cm}^{-1}}{}}$ 1730, 1700 (C=O). UV $\overset{\text{EtOH}}{\underset{\text{mμ}}{}}$ 240 (ε 8200), 271 (ε 14100). UV $\overset{\text{EtOH + HCl}}{\underset{\text{mμ}}{}}$ 277. UV $\overset{\text{EtOH + NaOH}}{\underset{\text{mμ}}{}}$ 298. PMR $_{CDCl_3}$ 0.7 (1H, NH), 1.63^s (1H, Ha), 5.78^q (2H, $OC\underline{H}_2CH_3$), 6.5^m (1H, Hc), 6.8^m (2H, Hb), 7.35^s (3H, 2-Me), 8.75^t (3H, $OCH_2C\underline{H}_3$).

It can be said that V might be formed by the reaction of III and I (or II), though the detailed mechanism of the reaction is not obvious. Therefore, the proposed structure of the key intermediate III in the reaction of I with acetamidine is more reliable as compared to the formerly proposed one III'.

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5. Satisfactory elemental analyses have been obtained for all new compounds.