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THE REACTION OF 2-DIMETHOXYMETHYL-3-METHOXYPROPIONITRILE WITH ACETAMIDINE. THE ISOLATION AND THE BEHAVIOR OF 2-METHYL-4-AMINO-5-DIMETHOXYMETHYL-5,6-DIHYDROPYRIMIDINE

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The reaction of 2-dimethoxymethyl-3-methoxypropionitrile (I) with acetamidine is very important for thiamine production, since it affords 2,7-dimethyl-5,6-dihydropyrimido(4,5-d)pyrimidine (Va), from which 2-methyl-4-amino-5-acetaminomethyl- (VIa) or 2-methyl-4-amino-5-aminomethylpyrimidine (VIIa) is obtainable (1). In previous papers (2, 3), we have proposed that the reaction should proceed via the pathway of I $\longrightarrow$ 2-dimethoxymethylacrylonitrile (II) $\longrightarrow$ 2-methyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (IIIa) $\longrightarrow$ Va, though IIIa could not be isolated. This paper reports the successful isolation of the key intermediate IIIa. A comparison of the behavior of IIIa with that of 2-phenyl-4-amino-5-dimethoxymethyl-5,6-dihydropyrimidine (IIIb) is also described.

A solution of I and acetamidine in methanol was stirred at 40°. After 4 hours, the solution was neutralized with methanolic hydrogen chloride. Ether was added to the solution and precipitates were removed by decantation. The removal of solvents gave syrupy crystals, which were washed with ether. The repeated recrystallization of the crystals from ether and methanol gave colorless plates.

Thus-obtained compound was converted into 2-methyl-4-amino-5-dimethoxymethylpyrimidine (X) (4) by treatment with p-quinone in benzene. Therefore, it was identified as the HCl salt of IIIa. The facts that the IR and the PMR spectra show the presence of an acetal and an amino group and the absence of a nitrile group and that the patterns of UV and PMR spectra are quite similar to those of 2-methyl-4-amino-5,6-dihydropyrimidine (XII) supported the structure. (XII was synthesized from the reaction of acrylonitrile with acetamidine (5). Its structure was confirmed by the conversion into XIII (see Chart 2).)

The reaction of IIIa with acetamidine or methyl acetimidate gave Va in a fairly good yield, and that with benzamidine gave 2-phenyl-4-amino-5-acetaminomethylpyrimidine (VIb). Further hydrolysis of VIb yielding

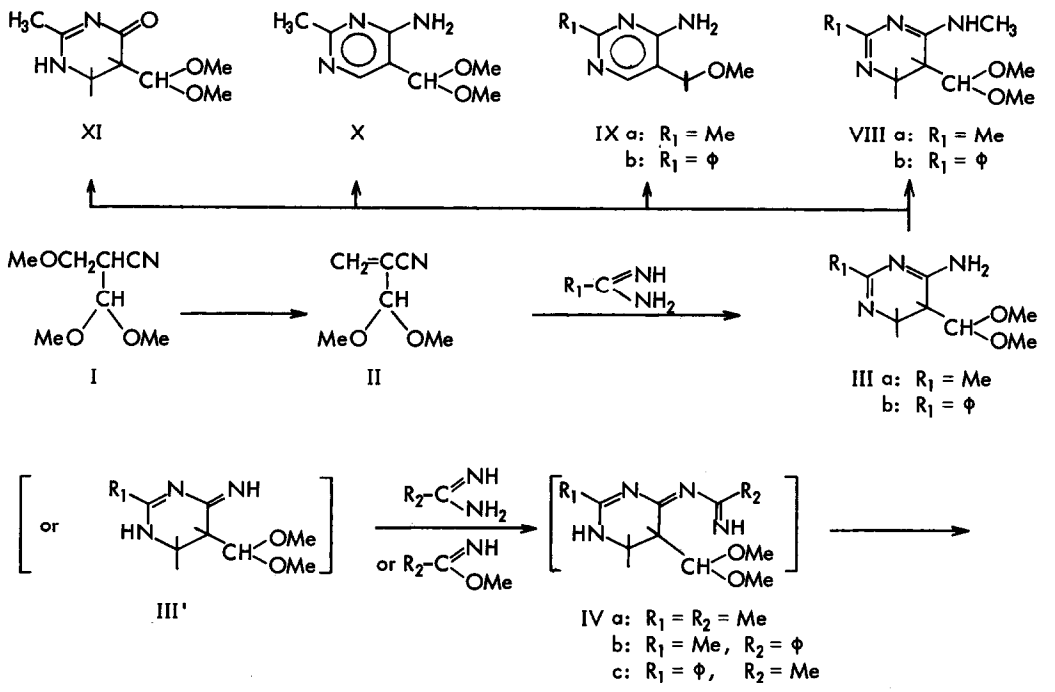

Chart 1

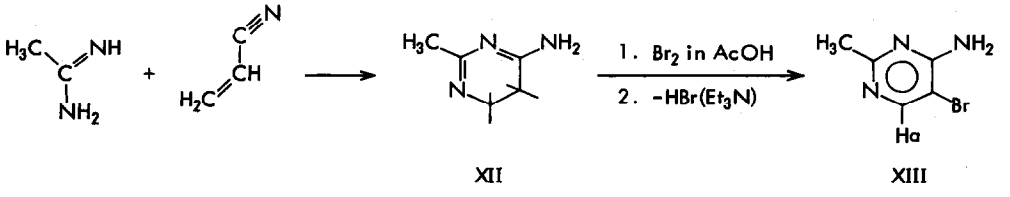

Chart 2

2-phenyl-4-amino-5-aminomethylpyrimidine (VIIb) (2) supported the structure of VIb and the formation of a pyrimidopyrimidine (Vb). A similar result was observed in the reaction of IIIb with acetamidine. The isolation of 2-methyl-4-amino-5-benzaminomethylpyrimidine (VIc) as a major product supported the exclusive formation of a pyrimidopyrimidine (Vc).

Several reactions of IIIa and IIIb were also carried out. When IIIa (or IIIb) was treated with methylamine in methanol, a transaminated compound (VIIIa) (or VIIIb) was obtained. Heating of IIIa (or IIIb) in methanol containing sodium methoxide gave a pyrimidine (IXa) (or IXb). On the other hand, treating of IIIa in methanol saturated with hydrogen chloride gave the HCl salt of a hydrolyzed product. Spectral data of this salt showed the presence of a carbonyl and an acetal group. Therefore, the structure of the salt was identified as the HCl salt of XI.

The data of new compounds are reported below (chemical shifts are expressed in τ-value). IIIa (HCl salt): mp 164° (dec.). IR $\overset{\text{Nujol}}{\underset{\text{cm}^{-1}}{}}$ 3340 (NH_2), 1686 (C=N). UV $\overset{\text{MeOH}}{\underset{\text{m}\mu}{}}$ 278 (ϵ 11.5 x 10^3), UV $\overset{\text{MeOH + NaOH}}{\underset{\text{m}\mu}{}}$ 260. PMR (DMSO-d_6) 7.87^s (5) (3H) (-$\overset{|}{\underset{|}{C}}$-$CH_3$), 6.72^s (3H), 6.68^s (3H) (OCH_3). VIb: mp 195-196.3°. PMR ($CDCl_3$) 7.98^s (3H) (N-Ac). VIc: mp 232-234°. PMR ($CDCl_3$) 7.53^s (3H) (C-CH_3). VIIIa: Syrup. (No satisfactory elemental analysis was obtained because of its instability, but the PMR spectra supported the structure.) PMR (CD_3OD) 6.92^s (3H) (N-CH_3). VIIIb: mp 102-104°. PMR ($CDCl_3$), 6.93^s (3H) (N-CH_3). XI (HCl salt): mp 197.5-199°. IR $\overset{\text{Nujol}}{\underset{\text{cm}^{-1}}{}}$ 1734 (C=O), 1668 (C=N). UV $\overset{\text{MeOH}}{\underset{\text{m}\mu}{}}$ 228 (ϵ 6.6 x 10^3). UV $\overset{\text{MeOH + NaOH}}{\underset{\text{m}\mu}{}}$ 210. PMR (DMSO-d_6) 7.67^s (6) (3H) (-$\overset{|}{\underset{|}{C}}$-$CH_3$), 6.65^s (6H) ($OCH_3$). XII: mp 188-192° (dec.). UV $\overset{95\%\ C_2H_5OH}{\underset{\text{m}\mu}{}}$ 264 (ϵ 9.6x10^3). UV $\overset{95\%\ C_2H_5OH + HCl}{\underset{\text{m}\mu}{}}$ 275. PMR (DMSO-d_6) 8.18^s (6), (3H) (C-CH_3). XIII: mp 138-140°. UV $\overset{95\%\ C_2H_5OH}{\underset{\text{m}\mu}{}}$ 237 (ϵ 1.06x10^4), 284 (ϵ 6.48x10^3). UV $\overset{95\%\ C_2H_5OH + HCl}{\underset{\text{m}\mu}{}}$ 249, 273. PMR (DMSO-d_6), 7.68^s (3H) (C-CH_3), 2.97 (2H) (NH_2), 1.90^s (1H) (Ha).

The above-described results unequivocally established the structure of key intermediate IIIa. The reaction of I with an amidine is tentatively proposed to proceed via the pathway of I $\longrightarrow$ II $\longrightarrow$ III (or III') $\longrightarrow$ IV $\longrightarrow$ V.

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