Syntheses of Pyrimidine Derivatives. XVII. On the Reaction Mechanism of Some Pyrimidine Syntheses

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Some interesting reactions have been presented in the previous papers[1-4] dealing with the syntheses of pyrimidine derivatives from 3-alkoxypropionitriles and acetamidine. These reactions can be divided into two types according to their reaction behavior, which are represented by A and B. In the case of reaction A, 2-methyl-4-amino-5-ethoxymethylpyrimidine (II) can be obtained directly by the reaction of 2-methoxymethylene-3-ethoxypropionitrile (I) with acetamidine. On the other hand, in the case of the reaction of 2-methoxyethoxymethyl-3-ethoxypropionitrile (III) (derived from I) with acetamidine in alcohol, an intermediate IV′ can be detected spectrophotometrically in the reaction mixture (λ_{max}= 275 mμ), without being successfully isolated. Being heated with another one mole of acetamidine, the intermediate IV′ is converted into 2,7-dimethyl-5,6-dihydropyrimido(4,5-d) pyrimidine (V), hydrolysis of which produces 2-methyl-4-amino-5-acetaminomethylpyrimidine (VI), but treatment of IV′ with hydrogen chloride results in II (Reaction B). In view of these facts, the structure of IV′ has reasonably been supposed as 2-acetamidinomethylene-3-ethoxypropionitrile (IV). Besides the above-mentioned facts, it has been shown[5,6] that 2-methyl-4-hydroxy-5-ethoxymethylpyrimidine (VII) could be obtained by the reaction of ethyl 2-methoxymethylene-3-ethoxypropionate (VIII) or ethyl 2-methoxyethoxymethyl-3-ethoxypropionate (IX) with acetamidine in ethanol. One of the important purposes of the present investigations is to identify IV′ with IV, and to present the most reasonable mechanism of these reactions. Another purpose is to check and see if the mechanism of analogous reactions can be explained in a similar manner.

Identification of the Intermediate IV′.— In order to compare the structure of the intermediate IV′ with that of IV, the

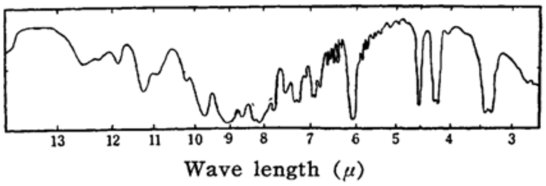

Fig. 1. Infrared absorption spectrum of 2-ethoxymethylene-3-ethoxypropionitrile (X) in nujol. 4.51 μ (conj. C≡N), 6.08 μ (—C=C—), 8.17 μ (=C—O—C). (Perkin-Elmer Model 12C IR spectrometer).

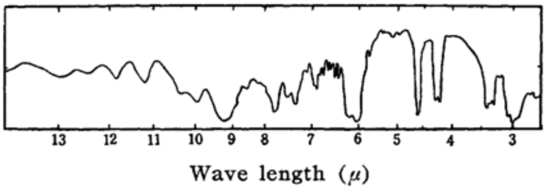

Fig. 2. Infrared absorption spectrum of 2-aminomethylene-3-ethoxypropionitrile (XI) in nujol. 2.85 μ, 2.95 μ (NH_2), 4.56 μ (conj. C≡N), 6.05 μ (—C=C—), 6.19 μ (δ NH_2). (Perkin-Elmer Model 12C IR spectrometer).

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1) M. Tomita, S. Uyeo, A. Takamizawa and R. Maeda, *J. Pharm. Soc. Japan*, (*Yakugaku Zasshi*), **74**, 742 (1954); A. Takamizawa and R. Maeda, ibid., **74**, 746 (1954); A. Takamizawa, ibid., 748, 759 (1954).

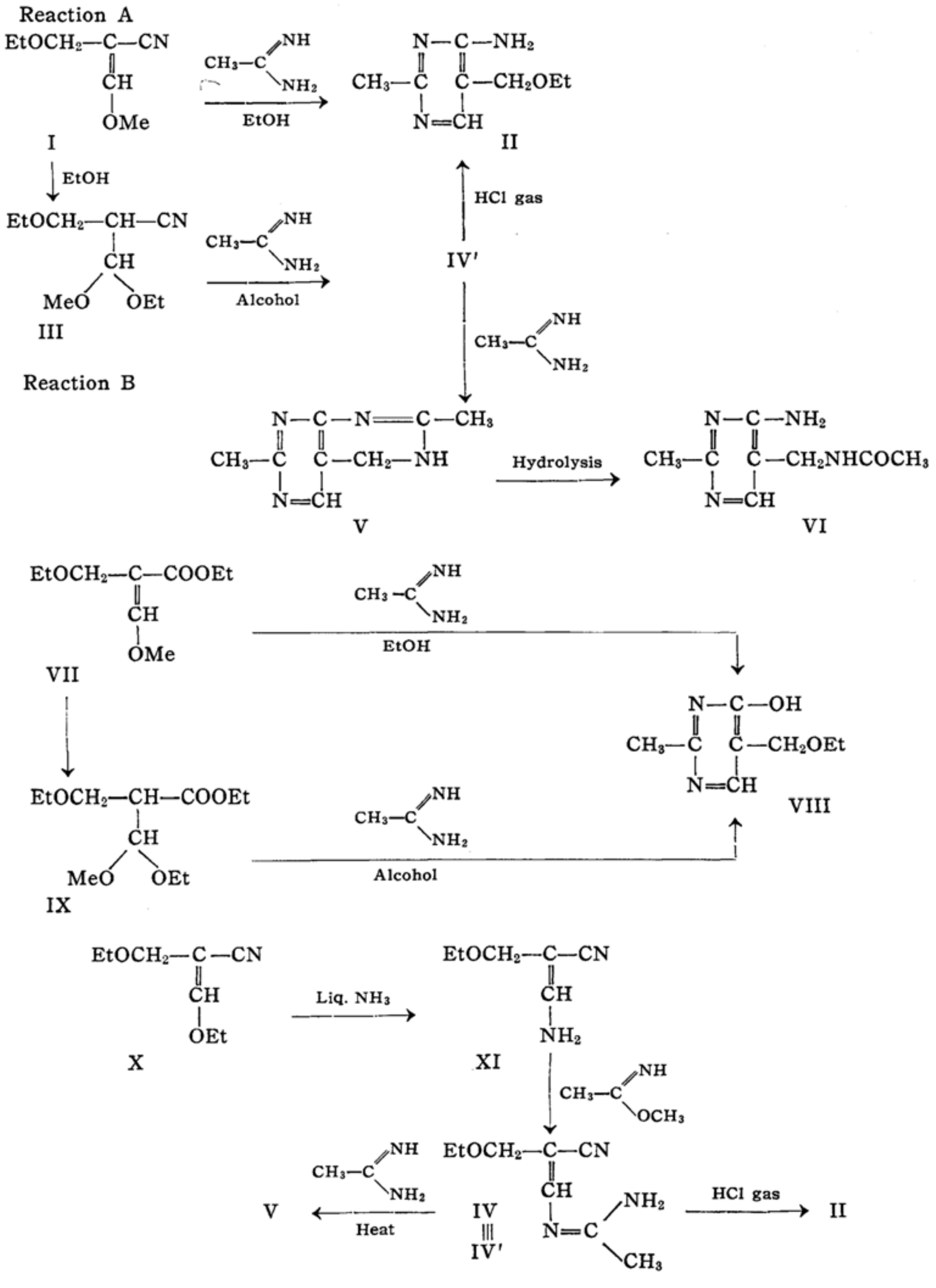
2) A. Takamizawa, K. Ikawa and M. Narisada, ibid., **78**, 832, 637, 643 (1958).

3) A. Takamizawa, K. Ikawa and K. Tori, ibid., **78**, 649 (1958).

4) A. Takamizawa, S. Hayashi and K. Tori, ibid., **78**, 1166 (1958).

5) A. Takamizawa, ibid., **74**, 752, 756 (1954).

6) A. Takamizawa, K. Tokuyama and H. Satoh, ibid., **79**, (1959), in press.



synthesis of the latter from 2-aminomethylene-3-ethoxypropionitrile (XI) and acetiminomethyl ester was undertaken. 2-Ethoxymethylene-3-ethoxypropionitrile (X) was dissolved in liquid ammonia, and after this solution was kept for a long time at room temperature, XI was obtained as a dark brown viscous liquid. The infrared spectra of this product and X were measured. From the results given in Figs. 1 and 2, it is clear that the absorption band due to —C=C—O— group of initial substance X disappears and that of an amino group newly appears. XI thus obtained being unstable, it easily liberated ammonia on heating. Furthermore, its picrate, hydrochloride, etc. could not be derived because of its weak basicity, and the expected derivatives could not be formed by the reactions of XI with acetic anhydride, methyl iodide and 2, 4-dinitrobromobenzene, but acetamide, ammonium iodide and 2, 4-dinitroaniline were obtained, respectively.

It is quite natural to expect that IV can be prepared by the reaction of XI with acetiminomethyl ester. The reaction process was traced spectrophotometrically. The result given in Fig. 3 shows that the product has an absorption band (λ_{max}= 275 mμ) identical with that of the intermediate IV′ in the reaction B. The reaction mixture was converted into II by adding hydrochloric acid under cooling and into V by treating with acetamidine under heating. From the above facts, it seems conclusive that the intermediate IV′ is identical with IV.

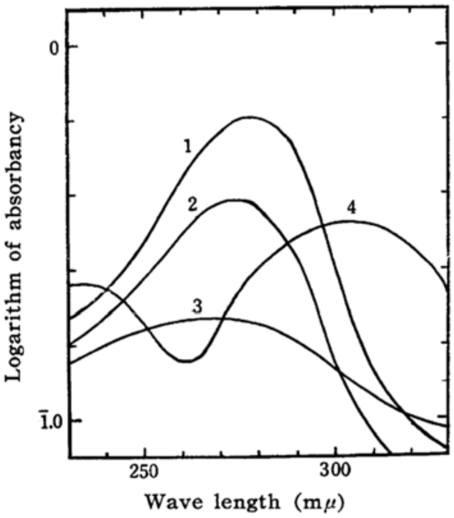
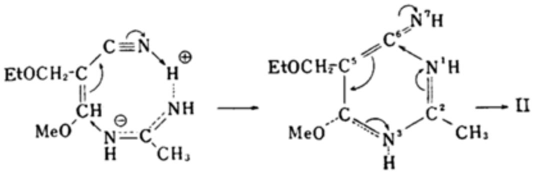


Fig. 3. Changes of ultraviolet absorption spectra of the reaction mixture, XI and acetiminomethyl ester. Curve (1), XI: (2), after 12 hr. at room temperature (IV was formed): (3) after treating IV (curve (2)) with hydrochloric acid gas: (4) after treating IV (curve (2)) with acetamidine. (Beckman DU spectrophotometer).

Reaction Mechanism of Pyrimidine Syntheses.—Thus it is easily inferred that there are two reaction processes for pyrimidine syntheses: namely, the first (reaction B) is the reaction of III with acetamidine whose characteristic is to produce the intermediate IV which is converted into V by heating with acetamidine, and the second (reaction A) is that of I with acetamidine in which II is formed directly without passing through any detectable intermediate.

On the basis of all the present data, the mechanisms of these two reactions may be surmised as below. In the first step of reaction A, the Michael type addition of acetamidine to I may conceivably occur. Then, the resulting intermediate XII may be immediately converted into II, since C^6 in $C^5=C^6=N^7H$ group in XII is positively charged to some extent owing to the polarity of C=N bond and N^1 in the acetamidino group has of course some amount of negative charge and therefore C^6 and N^1 can easily be bonded[7].



In the case of reaction B, however, the intermediate IV is derived from III by the replacement reaction. The N^1 atom in IV has probably a somewhat positive charge since the electron attracting effect of the $C^2=N^3$ bond and of the nitrile group is considerably large[8]. Moreover, the great dipole moment of $C^6\equiv N^7$ bond (3.5 D) suggests that the C^6 atom is charged positively to a large extent. Therefore, the bond formation between C^6 and N^1 may be very difficult. In addition to this, the intermediate IV can be stabilized by the resonance of the ordinary structure with polar structures where non-bonding electrons in the NH_2 group migrate to C=N and C≡N groups. These are the reasons why IV is fairly stable in the solution and can be detected spectrophotometrically. By heating the solution, the prototropy may occur continually to form the structure XIII, because of the strong electron attracting effect of the nitrile group. Then, another acetamidine molecule may be added to XIII, resulting in XIV which is finally converted into V eliminating an ammonia molecule[9].

However, by treating IV with a reagent such as hydrochloric acid, the nitrile group

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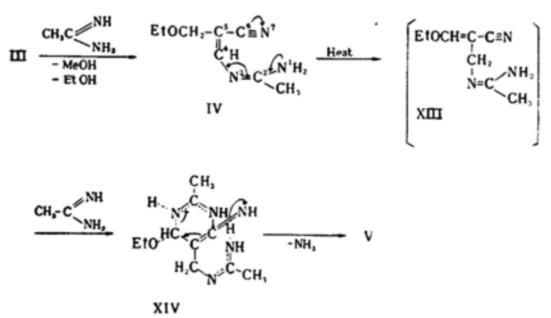
[7] In the structure XII, C^6 and N^7 have respectively about 16% positive and negative charges because of the difference in the electronegativity values between C^6 and N^7 of C=NH group. The above value can be evaluated by the aid of the bond moment of C=N. (0.9 D; C. P. Smyth, " Dielectric Behavior and Structure ", McGraw Hill, New York, (1955), p. 245).

[8] N^1 has a positive charge because of the strong electron attracting power of $C^2=N^3$ bond and of nitrile group affecting through the conjugated system of IV, although N^1 seems to charge negatively due to the difference of electronegativity between C^2 and N^1 of C^2-N^1H_2 group, the moment of which is only 0.22 D.

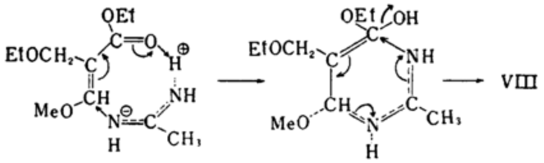
[9] Further investigation seems to be required for the final conclusion on these reaction mechanisms.



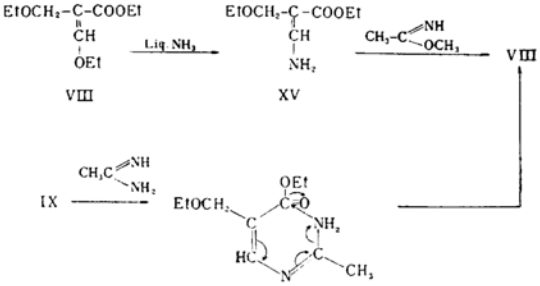
in it may be broken. Thereby the strong electron attracting effect of this group probably decreases and IV is conceivably converted into II[10] through a course similar to that of reaction A mentioned above.

In short, the important difference between these two reactions is that intermediate IV in reaction B has a nitrile group with strong electron attracting power and an amino group with electron donating property at both ends of its conjugated system and between these two groups resonance is possible, whereas the intermediate XII in the reaction A has no longer such a resonating system, since its nitrile group is converted into imino type.

It is quite natural from the above consideration that ethyl 2-methoxymethylene-3-ethoxypropionate (VII) gives 2-methyl-4-hydroxy-5-ethoxymethylpyrimidine (VIII) by the reaction with acetamidine[5,6] in the same manner as in the reaction A.



The situation is the same for the reaction of ethyl 2-aminomethylene-3-ethoxypropionate (XV) and acetiminomethyl ester. In this case, VIII was also obtained directly[11]. Now let us consider the reaction of ethyl 2-methoxyethoxymethyl-3-ethoxypropionate (IX) with acetamidine. In the course of this reaction, the intermediate like IV could not be observed spectrophotometrically but the reaction product VIII was obtained directly[5,6]. At the first glance, this fact looks strange because in the intermediate of this reaction, the stabilization due to resonance between the electron attracting (COOEt) and donating (NH_2) groups may be expected. However, this fact may probably be explained by taking account of the small electron attracting power of the carbethoxyl group compared with that of the nitrile group[12]. Further mention on this point will be made below.



According to these two reaction mechanisms for pyrimidine syntheses, it is possible to explain consistently some analogous reactions indicated in the literatures, which have been re-investigated in our laboratory.

The reactions of ethoxymethylenemalondinitrile (XVI) (reaction C) and ethyl ethoxymethylenecyanoacetate (XVII) (reaction D) with acetamidine give 2-methyl-4-amino-5-cyanopyrimidine (XVIII) (reaction C) and 2-methyl-4-hydroxy-5-cyanopyrimidine (XIX) with 2-methyl-4-amino-5-carbethoxypyrimidine (XX) (reaction D), respectively. On the other hand, aminomethylenemalondinitrile (XXI) (reaction E) and ethyl aminomethylenecyanoacetate (XXII) (reaction F) are converted by the reaction with acetiminomethyl ester into acetamidinomethylenemalondinitrile (XXIII) and ethyl acetamidinomethylenecyanoacetate (XXIV), respectively[13-15], yielding the corresponding pyrimidines only by treating with alkali. It is probably that in the cases of the reaction C and D, the intermediates, XXV and XXVI, are led to the corresponding pyrimidines directly in a way similar to that of reaction A, since their nitrile groups disappear, whereas in the cases of the reactions E and F the

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[10] 2-Methyl-5-carbethoxy-3,4-dihydropyrimidine is also obtained. In this case, it must be considered that the nitrile group is converted into an iminoester group.

[11] A. Takamizawa and K. Tokuyama, *J. Pharm. Soc. Japan*, (*Yakugaku Zasshi*), **79**, (1959), in pretss.

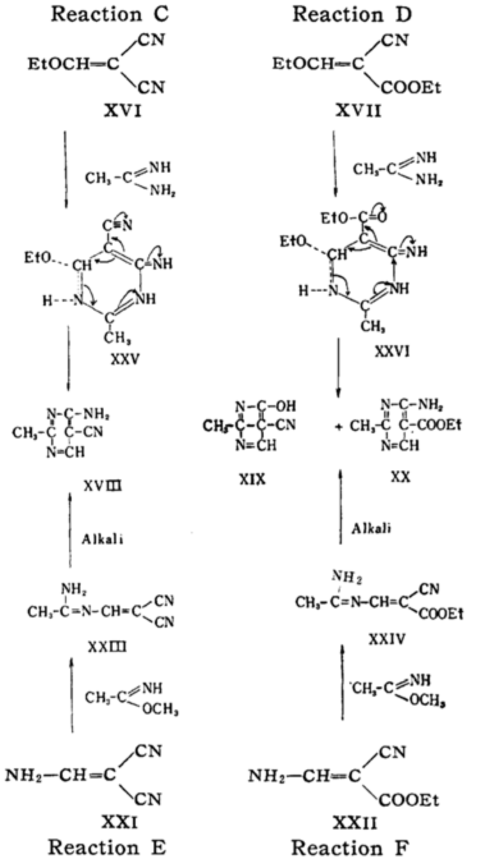
[12] This is inferred from the fact that the σ vlaue (Hammett's substituent constant) for the nitrile group is apparently larger than that for the carboxyl group.

[13] A. R. Todd and F. Bergel, *J. Chem. Soc.*, **1937**, 364.

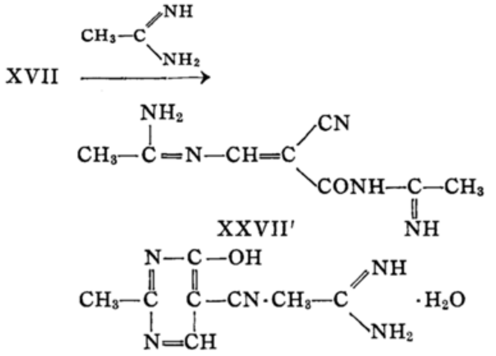
[14] T. Matsukawa, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **62**, 417 (1942).

[15] Y. Sawa and T. Tsuji, This work was read at the Kinki Congress of Pharmaceutical Society of Japan, Osaka, 1955.

intermediates, XXVII and XXVIII, have still their nitrile groups and therefore do not react further without treating with alkali. That is to say, this mechanism is similar to that of reaction B.

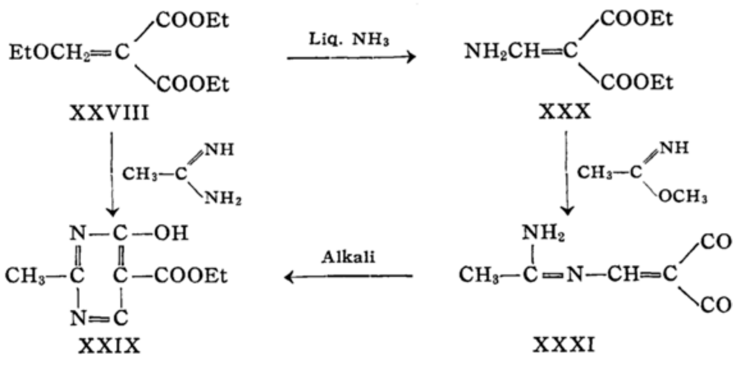


According to Todd[13], the intermediate XXVI was obtainable in the course of the reaction D, but this assertion has been refuted by Sawa and Tsuji[15], who reported that XXVI could not be obtained under the experimental conditions they employed. This result seems to be consistent with the above consideration that the intermediate like XXVI is too unstable to be detected. Moreover, Sykes et al.[16] have reported that XXVII′ was obtained by the reaction of XVII with two moles of acetamidine, but their result is not convincing. It contradicts the present authors' opinion. Inspecting more completely their data on the melting point and elemental analysis, we are led to the conclusion that the compound obtained by Sykes et al. is acetamidinate XXVII[15] of XIX.



XXVII

As mentioned above, the electron attracting effect of one carbethoxy group is weaker than that of a nitrile group, but the following fact indicates that two carbethoxy groups roughly correspond to one nitrile group in their electron attracting power. While 2-methyl-4-hydroxy-5-carbethoxypyrimidine (XXIX) was obtained at once by the reaction of diethyl ethoxymethylenemalonate (XXVIII) with acetamidine, diethyl aminomethylenemalonate (XXX) was converted with acetiminomethyl ester into diethyl acetamidinomethylenemalonate (XXXI), which gave XXIX on treatment with alkali.



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[16] P. Nesbitt and P. Sykes, *J. Chem. Soc.*, **1954**, 3057.

Experimental

2-Aminomethylene-3-ethoxypropionitrile (XI).—A solution of 2-ethoxymethylene-3-ethoxypropionitrile (X) (5.0 g.) dissolved completely in liquid ammonia (20 cc.) was left at room temperature for 45 days. After removal of the liquid ammonia and the alcohol produced under reduced pressure, a dark brown liquid (3.8 g.) was obtained. $n_D^{20.5}$, 1.4759.

Anal. Found: C, 56.62; H, 7.64; N, 22.21; $-OC_2H_5$, 34.66. Calcd. for $C_6H_{10}N_2O$: C, 57.11; H, 7.99; N, 22.21; $-OC_2H_5$, 35.71%.

Reaction of 2-aminomethylene-3-ethoxypropionitrile (XI) with acetiminomethyl ester.—To an ice-cold solution of sodium (0.3 g.) in absolute methanol (50 cc.), was added acetiminomethyl ester hydrochloride (1.5 g.); the mixture was shaken for few minutes and quickly filtered from precipitated sodium chloride. To the cooled filtrate was added 2-aminomethylene-3-ethoxypropionitrile (XI) (1.3 g.) in portions with shaking. After being allowed to stand overnight at room temperature, (i) dry hydrochloric acid was vigorously passed into the solution during three hours at 10~15°C, and the solution was again allowed to stand overnight. After removal of methanol in a vacuum, the residue was neutralized with sodium carbonate, washed with ethyl acetate, made strongly alkaline with sodium hydroxide and extracted with benzene. The benzene layer was dried over sodium sulfate and purified by passing through an alumina column. After evaporation of the solvent, 2-methyl-4-amino-5-ethoxymethylpyrimidine (II) was given; it was crystallized from ethanol in colorless rods, m. p. 89~90°C. Yield, 10 mg., (5.86%). Picrate, m. p. 189~190°C.

Anal. Found: C, 42.44; H, 4.18; N, 21.57. Calcd. for $C_{14}H_{16}N_6O_8$ (as picrate): C, 42.42; H, 4.44; N, 21.21%.

(ii) A mixture of absolute methanol (20 cc.), sodium (0.3 g.) and acetamidine hydrochloride (1.4 g.) was added. After being boiled for three hours, the precipitated sodium chloride was filtered off and the solvent was removed. To the residue was added 10% aqueous solution of sodium hydroxide; the mixture was heated on a water-bath for one hour. After cooling, colorless crystals separated on salting out with 50% aqueous solution of sodium hydroxide. Recrystallization from water gave 2-methyl-4-amino-5-acetaminomethylpyrimidine (VI) of colorless prisms (1.0 g.), m. p. 204~206°C. Picrate was yellow needles, m. p. 200°C.

Anal. Found: N, 23.98. Calcd. for $C_{14}H_{15}N_7O_8$ (as picrate): N, 23.96%.

Reaction of diethyl aminomethylenemalonate (XXX) with acetiminomethyl ester.—To an ice-cold solution of sodium (0.6 g.) in absolute ethanol (50 cc.), was added acetiminomethyl ester hydrochloride (3.2 g.); the mixture was shaken for a few minutes and quickly filtered from precipitated sodium chloride. To the cooled filtrate was added diethyl aminomethylenemalonate (XXX) (3.7 g.) in portions with shaking. After being allowed to stand overnight at room temperature, the solvent was removed in a vacuum. The residue, m. p. ca. 190°C, decomposed by recrystallization. This may be diethyl acetamidinomethylenemalonate (XXXI).

The above product was heated on a water-bath for 15 minutes with an ethanolic sodium ethoxide (0.2 g.; 50 cc.). The yellow solution was cooled, acidified with acetic acid, and concentrated in vacuo to about half the original volume. On standing, 2-methyl-4-hydroxy-5-carbethoxypyrimidine (XXIX) separated; it crystallized from acetone in colorless needles, m. p. 190°C. Yield, 0.1 g.

Anal. Found: N, 15.11. Calcd. for $C_8H_{10}N_3O$: N, 15.38%.

Summary

The mechanism of the reactions of 2-alkoxymethylene-3-alkoxypropionitrile and 2-dialkoxymethyl-3-alkoxypropionitrile with acetamidine was studied. The results show that these two nitriles react with acetamidine in completely different manners. In the case of the reaction of 2-alkoxymethylene-3-alkoxypropionitrile with acetamidine, the final product (2-methyl-4-amino-5-alkoxymethylpyrimidine) can be obtained directly, while in the case of the reaction of the other nitrile with acetamidine, the intermediate with the absorption maximum at 275 mμ can be detected spectrophotometrically. This intermediate could be identified with 2-acetamidinomethylene-3-alkoxypropionitrile. The difference in the mechanism between these two reactions might be explained by taking into consideration the fact that the intermediate in the latter case can be stabilized by the resonance among the usual structure and the polar structures in which non-bonding electrons on the nitrogen atom of the amino group migrate into C≡N or C=N group.

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