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Reaction of Heterocyclic Amino Compound with Malonaldehyde Derivatives

Shinzo Tamura and Machiko Ono

School of Pharmaceutical Science, Toho University[1]

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Heterocyclic analogs of β-arylaminoacrolein were synthesized from corresponding heterocyclic amino compounds and malonaldehyde derivatives.

The difference between the reactions of malonaldehyde with 4-aminopyridine (V) and with other aromatic primary amines was discussed.

Keywords——β-(4-pyridylamino) acrolein; β-(2-pyridylamino) acrolein; β-(2-thiazolylamino) acrolein; 1-(4′-pyridylamino)-3-(4″-pyridylimino)-1-propene; pyrido-[1,2-*a*]pyrimidinium chloride; thiazolo[3,2-*a*]pyrimidinium chloride; malonaldehyde bis (diethyl acetal)

In the previous paper[2a] we have reported the synthesis of β-arylaminoacrolein derivatives (I) from β-ethoxyacrolein (II) and aromatic primary amines.

β-(3-Pyridylamino)acrolein (III) was obtained by the reaction of II and 3-aminopyridine, while β-(4-pyridylamino)acrolein (IV) could not be isolated from the reaction mixture of II and 4-aminopyridine (V). When V and malonaldehyde bis (diethyl acetal) (VI) reacted in aqueous ethanol in the presence of hydrochloric acid, hydrochloride of IV (VII) was precipitated from the reaction mixture as white needles. In the case of aromatic primary amines, malonaldehyde dianil hydrochlorides (X) are obtained under the same conditions.[3] The presence of enaminoaldehyde structure in IV is suggested by the nuclear magnetic resonance (NMR) spectrum of IV (Fig. 1a), but the alternative structure IX can not be rejected from the elemental analysis and NMR data (Chart 1). The reduction of IV by sodium borohydride gave 3-(4′-pyridylamino)propanol-1 (XI) which was identified with the authentic sample prepared from 4-bromopyridine and 3-aminopropanol-1. The structure is confirmed, therefore, as expressed by IV.

1-(4′-Pyridylamino)-3-(4″-pyridylimino)propene-1 (malonaldehyde dianil of V) (XII) was obtained as follows: When V and IV were mixed in acetic acid containing hydrogen chloride, hydrochloride of XII (XIII) was precipitated as yellow crystals from the solution. The salt (XIII) was also obtained under the same conditions from V and sodium salt of malonaldehyde.[4] Rapid treatment of XIII with cold aqueous sodium bicarbonate gave XII. The NMR spectrum of XII showed following signals: A doublet (2H, J=11 Hz) of 1- and 3-positions at δ 8.23 and a triplet (1H, J=11 Hz) of 2-position at δ 6.04 in dimethyl sulfoxide-d_6, and a doublet (2H, J=6 Hz) of 1- and 3-positions at δ 7.75 and a triplet (1H, J=6 Hz) of 2-position at δ 5.32 in deuterochloroform. These signals indicate that XII is in *s-trans* form (XII) in dimethyl sulfoxide-d_6 and in *s-cis* form (XIV) in deuterochloroform (Chart 1).[2b]

The ultraviolet absorption (UV) spectrum of IV in ethanol containing hydrogen chloride (5×10^{-5} mol) showed an absorption maximum at 325 nm (ε=40000) immediately after dissolution, and gradually changed so that extinction coefficient at 325 nm decreased while the optical densities in the region of 250—280 nm were increased (Fig. 2a). With the higher concentration of hydrogen chloride (5×10^{-2} mol) the above-mentioned change was nearly

1) Location: *2-2-1, Miyama, Funabashi, 274, Japan.*

2) *a*) S. Tamura and E. Yabe, *Chem. Pharm. Bull.* (Tokyo), **21**, 2105 (1973); *b*) In this reference the stereochemistry of the aminoacrolein system is discused.

3) C.F. Jelinek and R.F. Kleinschmidt, U.S. Patent 2549097 (1951) [*C.A.*, **45**, 8035 (1951)].

4) T.V. Protopopova and A.P. Skoldinov, *Zh. Obshch. Khim.*, **28**, 240 (1958) [*C.A.*, **52**, 12754 (1958)].

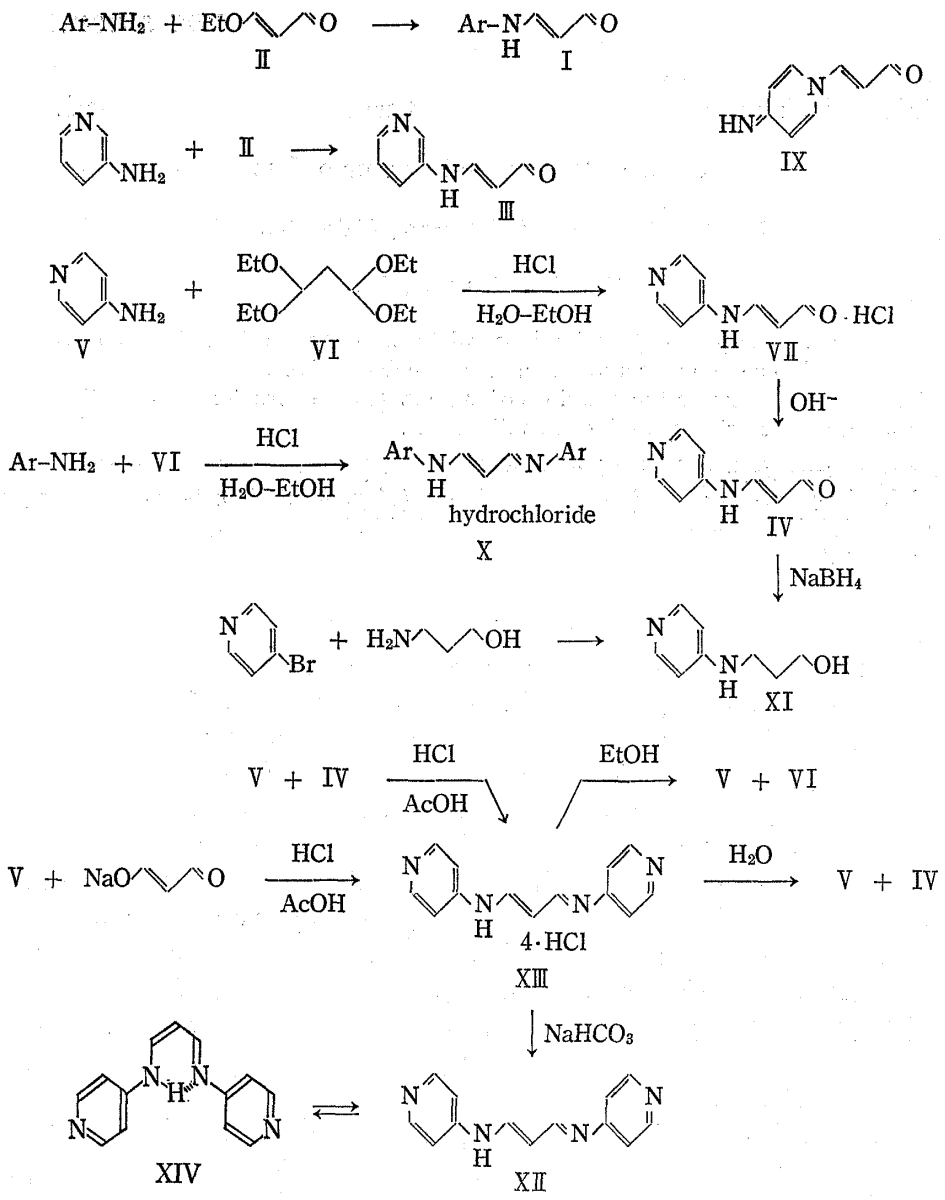


Chart 1

completed within 30 min after dissolution, and after 24 hr the absorption pattern in the region of 220—265 nm was changed as shown in Fig. 2b. This implies that IV is alcoholysed to give V and II, and afterward the latter reacts with ethanol to form VI in the acidic media. A similar change was observed in the NMR spectrum of VII in deuteromethanol (Fig. 1b, c). The spectrum which closely resembled that of IV in the same solvent changed gradually, and a day after, the signals of V and β-deuteromethoxyacrolein (XV) were observed (Fig. 1c). After 15 days, the signals of XV disappeared, and the signals of malonaldehyde-2-*d* bis (dideuteromethyl acetal) (XVI) and malonaldehyde-2-d_2 bis (dideuteromethyl acetal) (XVII) were detected at δ 4.43 (1- and 3-position) and at δ 1.84 (2-position). The same alcoholysis reaction was observed in UV spectrum of β-(*p*-toluidino)acrolein (XVIII) in ethanol containing hydrogen chloride. The pseudo first order rate constant of each reaction in ethanol containing hydrogen chloride (5×10^{-2} mol) at 25° were calculated from the change of optical densities at 324 (k_1, k_3, Chart 2) and 242 nm (k_2, Chart 2) and following values were obtained: $k_1=1.25\times10^{-3}$, $k_2=6.95\times10^{-5}$ and $k_3=5.93\times10^{-4}$ sec^{-1}.

The signals of NMR spectrum of VII in deuterium oxide were at a slightly lower magnetic field than those of IV and had spin–spin coupling pattern similar to that of IV in the same

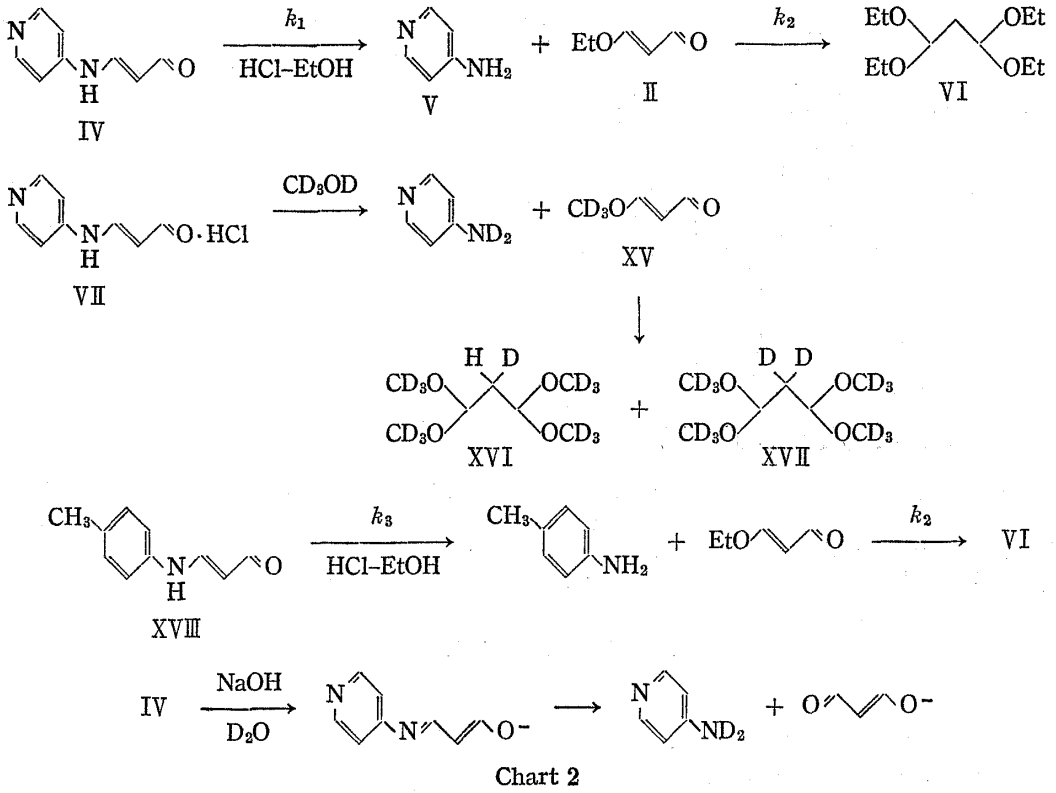


Chart 2

solvent, and showed no change for 24 hr (Fig. 1d). In the presence of excess deuterium chloride, however, the slow degradation of IV to V and exchange of hydrogen atom at the α-position with deuterium atom of IV were observed in its NMR spectrum. From the similarity of NMR spectra of IV and VII it was concluded that the protonation in conjugate acid of IV occurs at its ring nitrogen atom while XVIII is protonated at its oxygen atom[5] (Chart 3). In the NMR spectrum of XVIII in sulfuric acid the signal of aldehyde hydrogen atom shifted toward a higher magnetic field while the signal of the β-position slightly shifted toward a lower magnetic field as compared with those of XVIII in deuteromethanol. Each coupling constant to the α-position was nearly equal so that signal of the α-position was observed as a triplet.

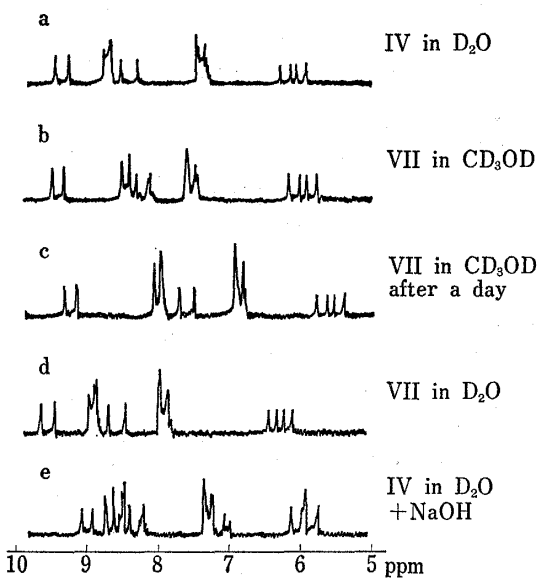
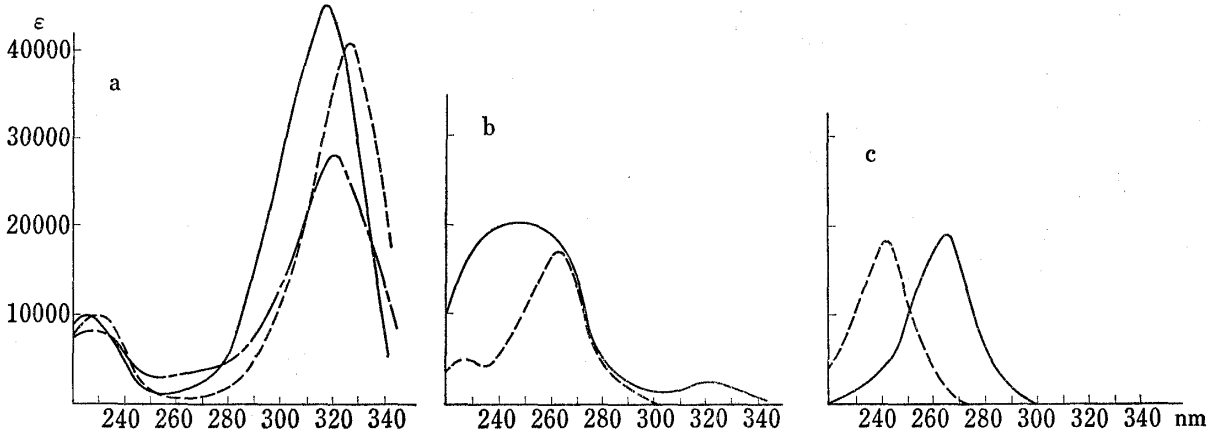


Fig. 1. NMR Spectra of IV and Its Salt

The dissociation constant of conjugate acid of IV was calculated from the measurement of pH of aqueous solution of VII, and a value of $pK_{BH^+}=5.50$ was obtained. Consequently, IV is much stronger base than XVIII whose pK_{BH^+} value is 0.96.[6] The pK_{BH^+} values of V[7]

5) S. Tamura, R. Imamura, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **26**, 930 (1978).
6) S. Tamura and K. Furuyama, The 97th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1977.
7) A. Fischer, W.J. Galloway, and J. Vaughan, *J. Chem. Soc.*, **1964**, 3591.



——: IV in EtOH
------: IV in 5×10^{-5} HCl–EtOH immediately after dissolution
—·—: IV in 5×10^{-5} HCl–EtOH after 2 days
——: IV in 5×10^{-2} HCl–EtOH 30 min after dissolution
------: IV in 5×10^{-2} HCl–EtOH after a day
——: V in 5×10^{-2} HCl–EtOH
------: II in 5×10^{-2} HCl–EtOH

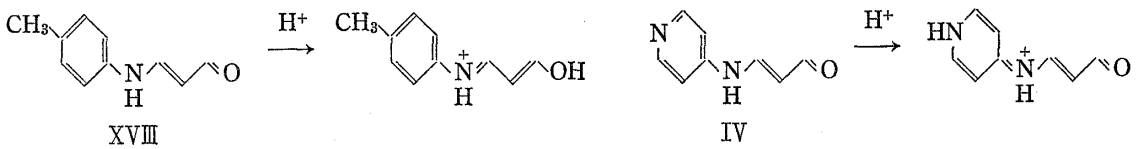
Fig. 2. UV Spectra of II, IV and V

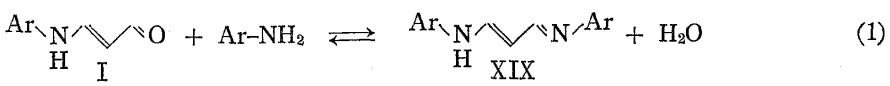
and *p*-toluidine[8] are 9.12 and 5.08, respectively. The monoanils of malonaldehyde (I) are therefore, much weaker bases than the corresponding arylamines.

The NMR spectrum of IV in deuterium oxide containing sodium hydroxide (Fig. 1e) indicates that IV is in a form of its conjugate base in the solvent, and is hydrolyzed to form V and malonaldehyde.

The compound XII is very unstable in the aqueous acidic media. When the aqueous solution of XIII was neutralized with sodium carbonate, IV was precipitated from the solution and NMR spectrum of the solution of XIII in dimethyl sulfoxide-d_6 showed only the signals of VII and hydrochloride of V. The salt (XIII) is almost insoluble in cold ethanol, and on the short warming a clear solution was obtained in which only V and VI were detected on its NMR spectrum.

Malonaldehyde dianil (XIX), a vinylog of amidine, is believed to be a stronger base as compared with the corresponding monoanil (I) and arylamine, while I, a vinylog of amide, is the weakest one as already described in the present paper.





(1)

Chart 3

In the reversible reaction (1) (Chart 3), the apparent equilibrium constant K' is markedly affected by the acidity of the medium. With the increased acidity, the equilibrium (1) shifts toward right in the range that the activity of lyonium ion is smaller than the dissociation constant of the conjugate acid of I, the weakest base. Otherwise the equilibrium (1)

8) A.I. Biggs and R.A. Robinson, *J. Chem. Soc.*, **1961**, 388.

shifts to the left with the increase of acidity.[9] The dissociation constant of the conjugate acid of IV is much smaller than the lyonium ion activity of the medium used for the preparation of VII. In the reaction of VI with V and with other aromatic primary amines, the relation between the equilibrium and the acidity of media, together with the solubility of each salt, led to the different products under the same conditions.

β-(2-Pyridylamino)acrolein (XX) could not be isolated from the reaction mixture of II and 2-aminopyridine (XXII). β-(2-Thiazolylamino)acrolein (XXI) could not be isolated from the reaction mixture of II and 2-aminothiazole (XXIII).

Sawyer *et al.*[10] reported the preparation of β-(2-pyridylamino) derivatives of α,β-unsaturated ketone by alkaline hydrolysis of pyrido[1,2-*a*]pyrimidinium salts obtained from XXII and β-diketones under acidic conditions. Shul'ga *et al.*[11] had obtained thiazolo[3,2-*a*]pyrimidinium perchlorate from VI and hydroperchlorate of XXIII. But their presumed structures were based merely on the analytical and spectral data.

We obtained pyrido[1,2-*a*]pyrimidinium chloride (XXIV) as hygroscopic crystals from the reaction mixture of XXII and VI in ethanol containing hydrogen chloride. Thiazolo-[3,2-*a*]pyrimidinium chloride (XXV) was obtained from XXIII and VI by the same method. The NMR spectra of XXIV and XXV in deuterium oxide were shown in Fig. 3a, b. These patterns are consistent with the structures of XXIV and XXV. Chemical evidence for each structure was obtained by permanganate oxidation of XXIV and XXV in diluted sulfuric acid to give known 4*H*-pyrido[1,2-*a*]pyrimidin-4-one[12] (XXVI) and 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one[13] (XXVII), respectively (Chart 4). In the NMR spectrum of XXIV in deuteromethanol, signals of 4*H*-4-deuteromethoxypyrido[1,2-*a*]pyrimidine deuterochloride (XXVIII) were observed at δ 5.53 (double doublet, J=4 and 8 Hz, 3-position), δ 6.66 (doublet, J=4 Hz, 4-position), δ 7.06 (doublet, J=8 Hz, 2-position), δ 7.49 (doublet, J=8 Hz, 6- and 7-position) and δ 8.40 (doublet, J=8 Hz, 5- and 8-position) besides the signals of XXIV at δ 8.16 (multiplet, 3- and 6-position), δ 8.66 (doublet, J=2 Hz, 8-position), δ 8.70 (double doublet, J=2 and 6 Hz, 7-position), δ 9.38 (double doublet, J=2 and 6 Hz, 2-position), δ 9.55 (double doublet, J=2 and 4 Hz, 5-position) and δ 9.71 (double doublet, J=2 and 6 Hz, 4-position). The relative integrated intensities of both signals indicate that the ratio of XXVIII and XXIV is 1: 1.4 in the solution. On the addition of triethylamine to the solution, only the signals of 4*H*-4-deuteromethoxypyrido[1,2-*a*]pyrimidine (XXIX) were observed at δ 5.14 (double doublet, J=4.5 and 7.5 Hz, 3-position), δ 6.38 (doublet, J=4.5 Hz, 4-position), δ 6.68 (triplet, J=8 Hz, 6-position), δ 6.88 (doublet, J=10 Hz, 8-position), δ 6.99 (doublet, J=7.5 Hz, 2-position), δ 7.45 (double doublet, J=8 and 10 Hz, 7-position) and δ 7.70 (doublet, J=8 Hz, 5-position).

Neutralization of the aqueous solution of XXIV with sodium bicarbonate gave XX. The pattern of the NMR spectrum of XX (Fig. 3c) is consistent with its structure. Another possible structure (XXX) (Chart 4) was ruled out by the reduction of XX with sodium borohydride to give known 3-(2'-pyridylamino)propanol-1[14] (XXXI).

9) The apparent equilibrium constant K' for the reversible reaction (1) in acidic media is represented approximately by the equation,

$$K' = K \times \frac{K_{AH^+} \times K_{MH^+}}{K_{DH^+}} \times \frac{K_{DH^+} + a_{H^+}}{(K_{AH^+} + a_{H^+})(K_{MH^+} + a_{H^+})}$$

where K is the true equilibrium constant for 1), a_{H^+} is the activity of lyonium ion and K_{AH^+}, K_{MH^+} and K_{DH^+} are the dissociation constants of conjugate acids of arylamine, I and XIX in the given medium, respectively.

10) J.R.H. Sawyer and D.G. Wibberley, *J. Chem. Soc. Perkin I*, **1973**, 1138.

11) S.I. Shul'ga and V.A. Chuiguk, *Ukr. Khim. Zh.*, **38**, 169 (1972).

12) R. Adams and I.J. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).

13) D.W. Dunwell and D. Evans, *J. Chem. Soc. (C)*, **1971**, 2094.

14) T. Yamazaki, M. Nagata, H. Araki, and F. Nohara, *Yakugaku Zasshi*, **88**, 212 (1968).

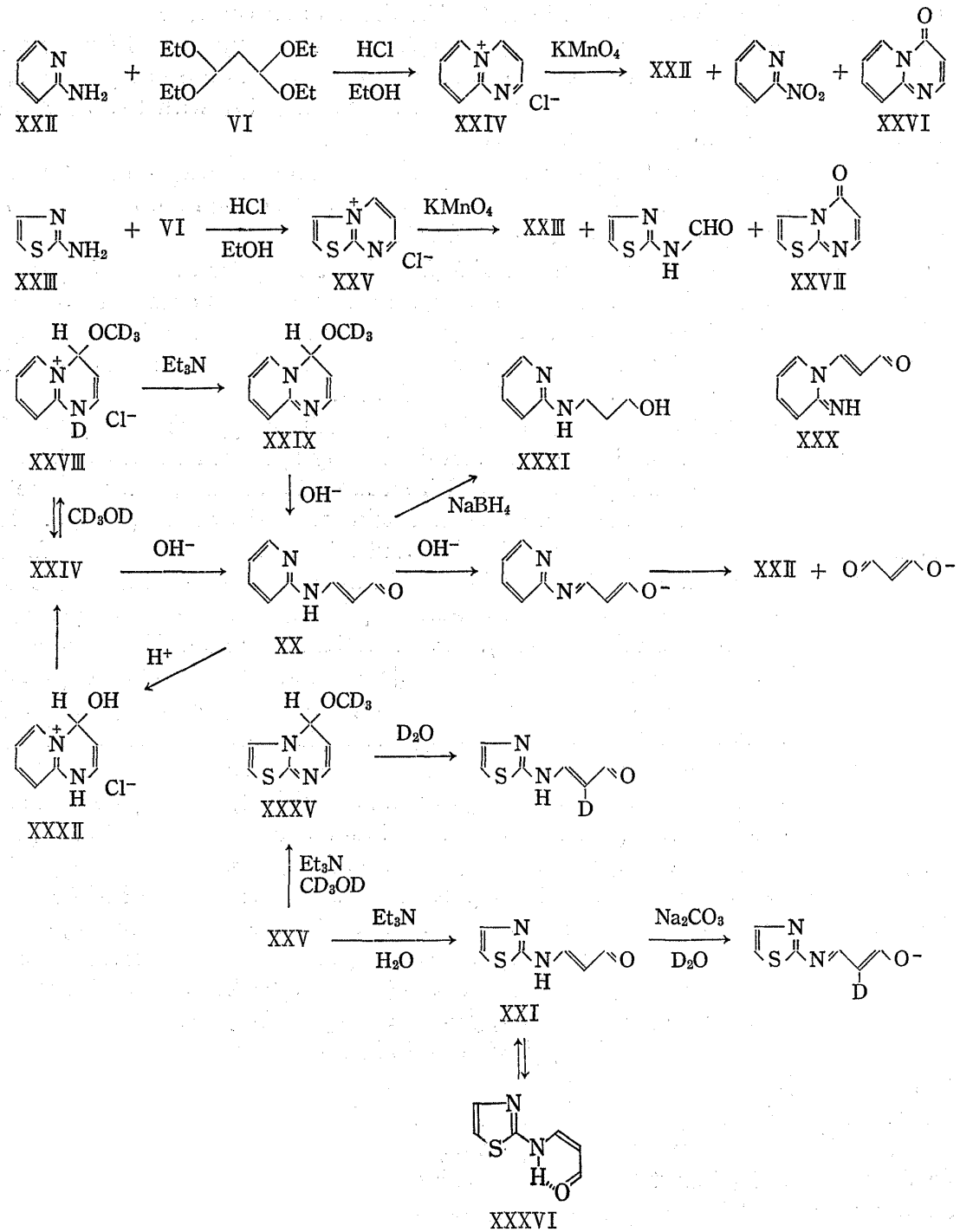


Chart 4

In the NMR spectrum of XX in 0.5 N hydrochloric acid, signals of 4*H*-4-hydroxypyrido-[1,2-*a*]pyrimidine hydrochloride (XXXII) were observed at δ 7.07 (doublet, J=4 Hz, 4-position) and δ 7.36 (doublet, J=8 Hz, 2-position) besides the signals of XXIV immediately after dissolution. The signals of XXXII disappeared after 90 min suggesting that cyclodehydration of XX to XXIV in aqueous acidic solution proceeds *via* XXXII.

UV spectra of XX and XXIV in ethanol under various conditions were shown in Fig. 4. The UV spectrum of XXIV in ethanol containing hydrogen chloride (5×10^{-5} mol) showed no change on standing, while that of XX in the same medium showed a medial pattern between those of XXIV and of XX in ethanol immediately after dissolution, and afterward

changed to show the identical pattern with that of XXIV in the same medium, suggesting that XX undergoes cyclodehydration to give XXIV in the acidic medium. In the presence of triethylamine (3×10^{-3} mol), the UV spectrum of XXIV had quite different pattern from those of XXIV in acidic media and of XX in ethanol. This fact, together with the fact observed in the NMR spectrum of XXIV in deuteromethanol containing triethylamine, implies that XXIV is changed to 4*H*-4-ethoxypyrido[1,2-*a*]pyrimidine in the medium. The UV spectrum of XXIV in ethanol showed a similar pattern to that of XXIV in the presence of excess hydrogen chloride immediately after dissolution, and gradually changed so that extinction coefficient at 225 nm was decreased while those at 280 and 325 nm were increased suggesting that XXIV was partially hydrolyzed to form XX in a weakly acidic medium. A similar hydrolysis reaction was observed in the UV spectrum of XXIV in water, while the NMR spectrum of XXIV in deuterium oxide showed no change on standing. The different result observed in the two spectra is attributable to the concentration at which the spectra were measured. Hydrolysis of XXIV increases the acidity of the solution, but this effect is negligible at the low concentration (at which UV spectrum of XXIV was measured). The UV spectrum of XXIV in diluted hydrochloric acid (5×10^{-2} mol) showed no change on standing.

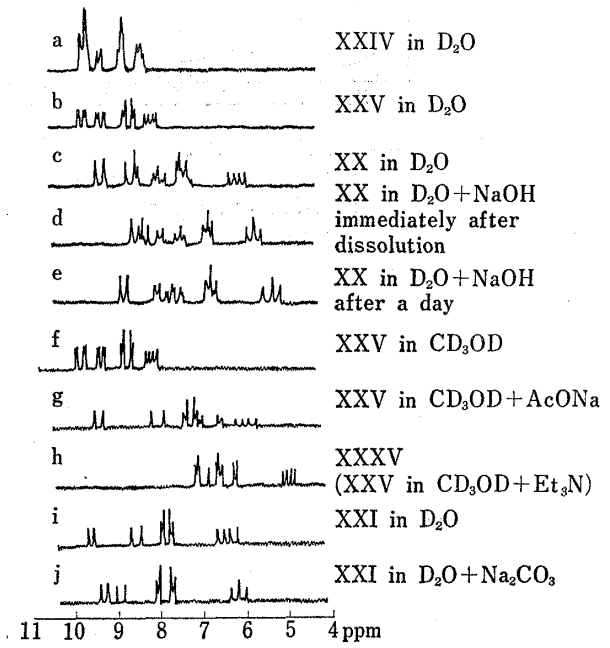


Fig. 3. NMR Spectra of XX, XXI, XXIV and XXV

The NMR spectrum of XX in deuterium oxide (Fig. 3c) changed on the addition of sodium hydroxide as shown in Fig. 3d suggesting that XX was converted to its conjugate base in the medium, and the conjugate base of XX was hydrolyzed to form XXII and the conjugate base of malonaldehyde after a day (Fig. 3e).

β-(4-Methyl-2-pyridylamino)acrolein (XXXIII) and β-(6-methyl-2-pyridylamino)acrolein (XXXIV) were obtained from each corresponding aminopicoline by the same method used for the preparation of XX.

Neutralization of the aqueous solution of XXV with sodium carbonate or sodium bicarbonate afforded a resinous product and XXI could not be isolated from the product. The NMR spectrum of XXV in deuteromethanol was shown in Fig. 3f. On the addition of sodium acetate trihydrate, signals of XXI were observed in the NMR spectrum of the solution (Fig. 3g), but after a day only the signals of XXIII were detected suggesting that XXI was hydrolyzed to form XXIII and malonaldehyde, and that the latter was polymerized. Evaporation of the methanolic solution of XXV containing sodium acetate trihydrate gave a resinous residue, from which XXI could not be isolated. On the addition of triethylamine to the deuteromethanolic solution of XXV, the NMR spectrum of the solution showed signals of 5*H*-5-deuteromethoxythiazolo[3,2-*a*]pyrimidine (XXXV) at δ 5.07 (double doublet, J=4 and 8 Hz, 6-position), δ 6.38 (doublet, J=4 Hz, 5-position), δ 6.68 (doublet, J=5 Hz, 2-position), δ 6.82 (doublet, J=8 Hz, 7-position) and δ 7.10 (doublet, J=5 Hz, 3-position) (Fig. 3h). On the addition of deuterium oxide to the above solution, formation of XXI were observed in its NMR spectrum which showed no change after a day except the exchange of hydrogen atom at α-position for deuterium atom.

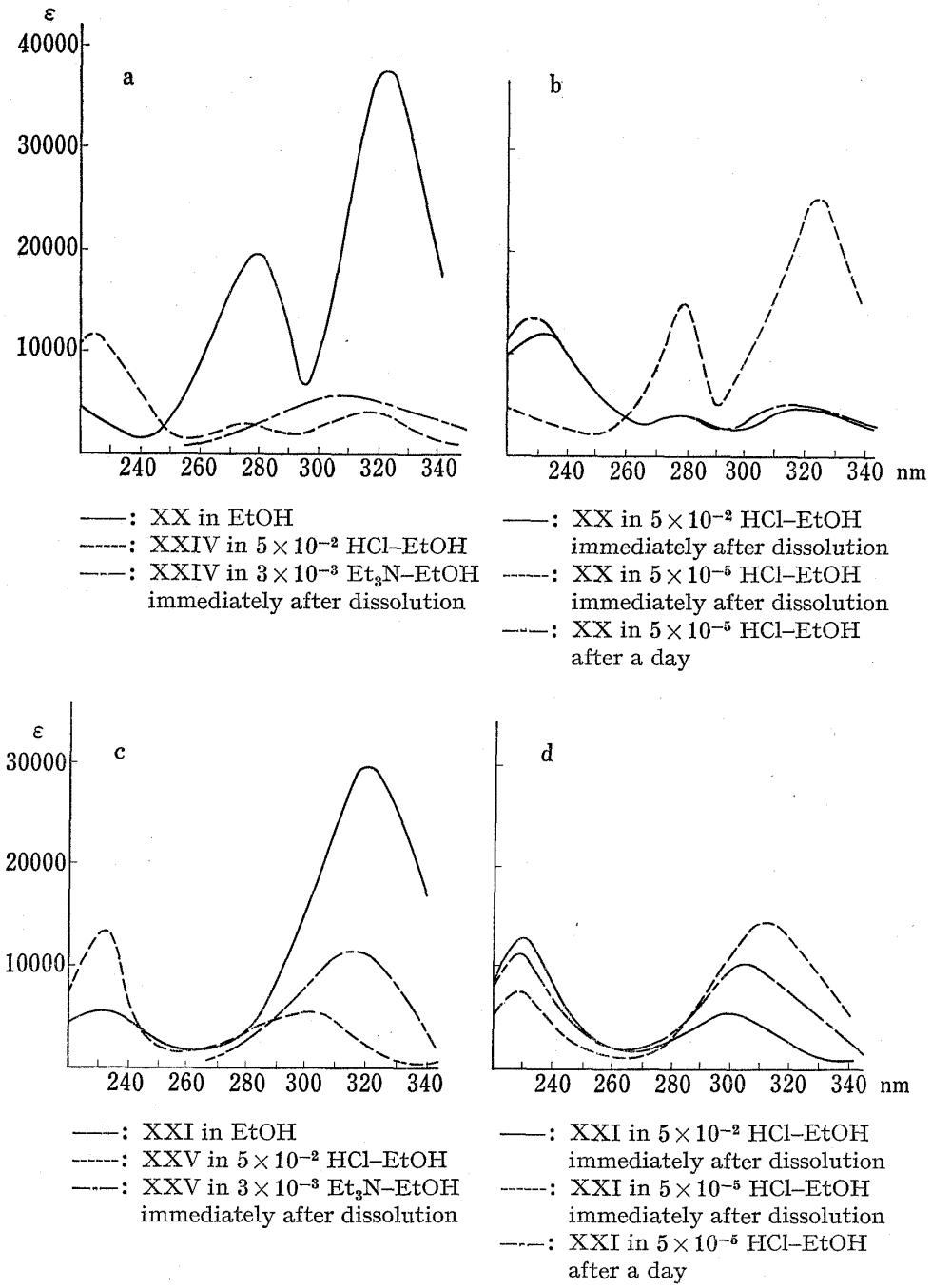


Fig. 4. UV Spectra of XX, XXI, XXIV and XXV

The addition of triethylamine to the aqueous solution of XXV gave XXI as orange crystals. The NMR spectrum of XXI in deuterochloroform indicates that XXI consists of both *s-trans* (XXI) and *s-cis* form (XXXVI) in the medium (Chart 4).[25b] The NMR spectrum of XXI in deuterium oxide containing sodium carbonate showed signals of the conjugate base of XXI (Fig. 3j) suggesting that XXI is a more acidic substance as compared with IV and XX, both of which showed no change in their NMR spectra in deuterium oxide on the addition of sodium carbonate. The NMR spectrum of XXI in deuterium oxide containing sodium carbonate showed no change after a day except the exchange of hydrogen atom at α-position for deuterium atom. Therefore XXI is in a form of its stable conjugate base in the alkaline solution contrary to the case of XXV which undergoes rapid polymerization under the same condition.

The UV spectra of XXI and XXV in ethanol under various conditions were shown in Fig. 4. The UV spectrum of XXV in ethanol containing hydrogen chloride (5×10^{-2} mol) showed no change on standing, and was identical with that of the solution of XXI in the same solvent. The UV spectrum of XXV in ethanol showed a similar change to that observed in the case of XXIV while that of XXV in water showed no change on standing contrary to the case of XXIV in the same medium.

Experimental

All melting points are uncorrected. The UV spectra were measured on Hitachi spectrophotometer model 139 and the NMR spectra were recorded on JNM-PMX 60 NMR spectrometer using tetramethylsilane as standard. Following abbreviations are used: singlet (s), doublet (d), double doublet (dd), triplet (t) and double triplet (dt).

β-(3-Pyridylamino)acrolein (III)——To a stirred solution of 0.94 g (0.01 mol) of 3-aminopyridine in 20 ml of MeOH was added 1.00 g (0.01 mol) of freshly distilled II in portions and allowed to stand for 2 days at room temperature. MeOH was evaporated *in vacuo* and to the residue was added 10 ml of benzene and resulting crystals were filtered with suction. The yield of crude product was 0.88 g (59.5%). The product was recrystallized from EtOH to yield III (0.27 g, 18.2%) as pale yellow crystals, mp 165° (dec.). NMR (CD_3SOCD_3, δ): 5.58 (1H, dd, J=9 and 13 Hz, α-position), 8.12 (1H, t, J=13 Hz, β-position), 9.33 (1H, d, J=9 Hz, aldehyde) and 10.17 (1H, d, J=13 Hz, NH). *Anal.* Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.89; H, 5.24; N, 18.88.

β-(4-Pyridylamino)acrolein (IV)——To a stirred solution of 1.88 g (0.02 mol) of V in 10 ml of EtOH were added 4 ml of conc. HCl and 4.40 g (0.02 mol) of VI under water cooling. The reaction mixture was allowed to stand overnight at room temperature. From the solution VII was precipitated as yellow needles. The precipitate was filtered with suction to yield 2.40 g (64.9%) of VII. The recrystallization from AcOH afforded pure VII as colorless needles, mp 214° (dec.). NMR (D_2O, δ): 6.39 (1H, dd, J=9 and 13 Hz, α-position), 7.93 (2H, d, J=8 Hz, 3- and 5-position), 8.60 (1H, d, J=13 Hz, β-position), 8.90 (2H, d, J=8 Hz, 2- and 6-position), and 9.76 (1H, d, J=9 Hz, aldehyde). *Anal.* Calcd. for $C_8H_9ClN_2O$: C, 52.04; H, 4.91; N, 15.17. Found: C, 51.94; H, 4.86; N, 15.12.

Neutralization of a solution of 2.40 g of VII in 10 ml of H_2O with calculated amount of $NaHCO_3$ gave 1.82 g of IV. The recrystallization from H_2O afforded pure IV as colorless crystals, mp 172°. NMR (D_2O, δ): 6.17 (1H, dd, J=9 and 13 Hz, α-position), 7.53 (2H, d, J=7 Hz, 3- and 5-position), 8.47 (1H, d, J=13 Hz, β-position), 8.78 (2H, d, J=7 Hz, 2- and 6-position) and 9.55 (1H, d, J=9 Hz, aldehyde). *Anal.* Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.40; H, 5.35; N, 18.50.

Reduction of IV with $NaBH_4$——To a stirred solution of 2.75 g (0.02 mol) of IV in 60 ml of MeOH was added 1.52 g (0.04 mol) of $NaBH_4$ in portions and allowed to stand overnight at room temperature. To the mixture was added 30 g of CH_3COCH_3 in order to decompose excess $NaBH_4$ and allowed to stand overnight and the solvent was removed *in vacuo* and to the residue was added aqueous $NaHCO_3$ and extracted with ether continuously for 2 days. The extract was dried over K_2CO_3 and evaporated *in vacuo*. The residue was recrystallized from $CHCl_3$ to yield 0.04 g of XI, mp 99°. NMR ($CDCl_3$, δ): 1.87 (2H, dt, J=6 and 12 Hz, 2-position), 2.98 (1H, s, OH), 3.30 (2H, dd, J=6 and 12 Hz, 3-position), 3.80 (2H, t, J=6 Hz, 1-position), 4.73 (1H, s, NH), 6.42 (2H, d, J=6 Hz, 3′- and 5′-position) and 8.12 (2H, d, J=6 Hz, 2′- and 6′-position). *Anal.* Calcd. for $C_8H_{12}N_2O$: C, 63.08; H, 7.94; N, 18.47. Found: C, 62.66; H, 7.94; N, 18.28. It was identified with the authentic sample prepared from 4-bromopyridine and 3-aminopropanol-1 (next section) by the comparison of their IR spectra and mixed melting point measurement.

3-(4′-Pyridylamino)propanol-1 (XI)——To a stirred solution of 0.80 g (0.02 mol) of NaOH in 50 ml of EtOH were added 3.88 g (0.02 mol) of 4-bromopyridine hydrochloride and 1.50 g (0.02 mol) of 3-aminopropanol-1. EtOH was removed *in vacuo*. The residue was heated at 170° for 5 hr. After cooling, the mixture was dissolved in 10 ml of H_2O and to the solution was added 25 ml of 7% $NaHCO_3$. The separated oil was extracted with ether continuously for 2 days. The extract was dried over K_2CO_3 and evaporated *in vacuo*. The residue was recrystallized from $CHCl_3$ to yield 0.19 g (6.3%) of XI as white needles, mp 99°.

1-(4′-Pyridylamino)-3-(4″-pyridylimino)-1-propene Hydrochloride (XIII)——(a) To 14 ml of AcOH containing HCl (5%) was added Na salt of malonaldehyde[4] and filtered. To a stirred solution of 1.88 g (0.02 mol) of V in 20 ml of AcOH were added the above filtrate and 24 ml of AcOH containing HCl (5%). The resulting precipitate of XIII was collected as yellow crystals, mp 166°. Yield 1.39 g (37.6%). *Anal.* Calcd. for $C_{13}H_{12}N_4\cdot4HCl$: C, 42.19; H, 4.36; N, 15.14. Found: C, 42.07; H, 4.90; N, 14.63.

(b) To a stirred solution of 0.74 g (0.005 mol) of IV in 6 ml of AcOH were added a solution of 0.47 g (0.005 mol) of V and 10 ml of AcOH containing HCl (5%). The resluting precipitate was collected. The yield of XIII was 1.25 g (67.6%).

1-(4′-Pyridylamino)-3-(4″-pyridylimino)-1-propene (XII)——To 14 ml of 7% aqueous $NaHCO_3$ was added 1.00 g of XIII in portions under ice cooling. The resulting precipitate was collected and quickly

dried on a clay plate, and recrystallized from benzene to yield 0.15 g (24.6%) of XII as yellow crystals, mp 156°. *Anal.* Calcd. for $C_{13}H_{12}N_4$: C, 69.00; H, 5.30; N, 24.90. Found: C, 69.09; H, 5.38; N, 24.79.

β-(2-Pyridylamino)acrolein (XX)——To a solution of 2.82 g (0.03 mol) of XXII in 10 ml of EtOH were added 50 ml of EtOH containing HCl (5.1%) and 6.60 g (0.03 mol) of VI. The solution was warmed at 80° in a water bath for 6 hr. EtOH was evaporated *in vacuo* and the residue (4.96 g) was recrystallized from EtOH–ether to yield pure XXIV, mp 233° (dec.). *Anal.* Calcd. for $C_8H_7ClN_2$: C, 57.67; H, 4.24; N, 16.81. Found: C, 57.67; H, 4.41; N, 16.16.

A solution of 2.00 g of XXIV in 10 ml of H_2O was neutralized with $NaHCO_3$ and the resulting precipitate was collected and recrystallized from H_2O to yield 1.13 g (63.5%) of XX, mp 138°. NMR (CD_3SOCD_3, δ): 5.68 (1H, dd, $J=8$ and 14 Hz, α-position), 8.38 (1H, t, $J=14$ Hz, β-position), 9.35 (1H, d, $J=8$ Hz, aldehyde) and 10.56 (1H, d, $J=14$ Hz, NH). *Anal.* Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.98; H. 5.43; N, 18.78.

Reduction of XX with $NaBH_4$——To a stirred solution of 3.30 g (0.02 mol) of XX in 60 ml of MeOH was added 1.52 g (0.04 mol) of $NaBH_4$ in portions and allowed to stand overnight at room temperature. To the mixture was added 30 g of CH_3COCH_3 in order to decompose excess $NaBH_4$ and allowed to stand overnight. The solvent was removed *in vacuo* and the residue was dissolved in H_2O and neutralized with 7% aqueous $NaHCO_3$ and extracted with ether. The extract was dried over K_2CO_3, and evaporated *in vacuo*. The residue was distilled under reduced pressure. To the distillate was added EtOH containing HCl and evaporated *in vacuo*. The residue was recrystallized from EtOH to yield 1.67 g (40.0%) of XXXI·HCl, mp 132°. It was identified with the authentic sample prepared in a route of Yamazaki *et al.*[14] by the comparison of their IR spectra and mixed melting point measurement.

Oxidation of XXIV with $KMnO_4$——To a stirred solution of 3.30 g (0.02 mol) of XXIV in 20 ml of 2 N H_2SO_4 was added 12 g of $KMnO_4$ in portions. The solution was extracted continuously with ether for 2 days. The ether was removed *in vacuo* and the residue was dissolved in benzene, and separated by column chromatography over Al_2O_3 using benzene as an eluant. The evaporation of the first fraction followed by recrystallization from petroleum benzine afforded a trace of 2-nitropyridine, mp 71°, which was identified with the authentic sample prepared in a route of Kirpal and Böhm[15] by the comparison of their IR spectra and mixed melting point measurement. The evaporation of the second fraction followed by recrystallization from petroleum benzine afforded 0.03 g of XXVI, mp 126°, which was identified with the authentic sample prepared in a route of Adams and Pachter[13] by the comparison of their IR spectra and mixed melting point measurement. From the third fraction was obtained 0.21 g of XXII.

β-(2-Thiazolylamino)acrolein (XXI)——To a solution of 3.00 g (0.03 mol) of XXIII in 10 ml of EtOH were added 50 ml of EtOH containing HCl (5.1%) and 6.60 g (0.03 mol) of VI. The solution was warmed at 80° in a water bath for 6 hr. EtOH was evaporated *in vacuo*. The residue was recrystallized from EtOH to yield 3.21 g (62.0%) of XXV as colorless hygroscopic needles, mp 197° (dec.). NMR (CD_3OD, δ): 8.12 (1H, dd, $J=5$ and 8 Hz, 6-position), 8.59 (1H, d, $J=5$ Hz, 2-position), 8.85 (1H, d, $J=5$ Hz, 3-position), 9.39 (1H, dd, $J=2$ and 5 Hz, 5-position) and 9.83 (1H, dd, $J=2$ and 8 Hz, 7-position). *Anal.* Calcd. for $C_6H_5ClN_2S$: C, 41.74; H, 2.92; N, 16.23. Found: C, 41.15; H, 3.28; N, 15.77.

A solution of 2.00 g of XXV in 10 ml of H_2O was neutralized with Et_3N and extracted with $CHCl_3$, and the extract was dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was washed with a small amount of ether and dissolved in CH_2Cl_2. To the solution was added petroleum ether to yield 0.12 g (6.7%) of XXI as orange crystals, mp 97°. NMR ($CDCl_3$, δ): 5.53 (dd, $J=2$ and 8 Hz, α-position of *s-cis* form), 5.86 (dd, $J=8$ and 13 Hz, α-position of *s-trans* form), 7.41 (d, $J=8$ Hz, β-position of *s-cis* form), 7.74 (d, $J=13$ Hz, β-position of *s-trans* form), 9.45 (d, $J=2$ Hz, aldehyde of *s-cis* form) and 9.45 (d, $J=8$ Hz, aldehyde of *s-trans* form). *Anal.* Calcd. for $C_6H_6N_2OS$: C, 46.78; H, 3.92; N, 18.17. Found: C, 46.39; H, 3.85; N, 17.93.

Oxidation of XXV with $KMnO_4$——To a stirred solution of 3.00 g (0.02 mol) of XXV in 42 ml of 2 N H_2SO_4 was added 88 ml of 5% aqueous $KMnO_4$ in portions and was neutralized with 40% aqueous NaOH. The solution was extracted continuously with ether for a day. The ether was removed *in vacuo*, and the residue was dissolved in benzene, and separated by column chromatography over Al_2O_3 using benzene–AcOEt (1 : 1) as an eluant. The evaporation of the first fraction followed by recrystallization from petroleum benzine afforded a trace of 2-thiazolylformamide, mp 157°, which was identified with the authentic sample prepared in a route of Huffman[16] by the comparison of their IR spectra and mixed melting point measurement. The evaporation of the second fraction followed by recrystallization from petroleum benzine afforded a small amount of XXVII, mp 116°, which was identified with the authentic sample prepared in a route of Dunwell and Evans[13] by the comparison of their IR spectra and mixed melting point measurement. From the third fraction was obtained 0.023 g of XXIII.

β-(4-Methyl-2-pyridylamino)acrolein (XXXIII)——To a solution of 3.24 g (0.03 mol) of 2-amino-4-methylpyridine in 10 ml of EtOH were added 50 ml of EtOH containing HCl (5.1%) and 6.60 g (0.03 mol)

15) A. Kirpal and W. Böhm, *Ber.*, **65**, 680 (1932).
16) C.W. Huffman, *J. Org. Chem.*, **23**, 727 (1958).

of VI. The solution was warmed at 80° in a water bath for 6 hr. EtOH was removed *in vacuo*. The residue crystallized immediately after evaporation of the solvent, but was too hygroscopic to purify by recrystallization. After drying in a desiccator, 2 g of the residue was dissolved 10 ml of H_2O. The solution was neutralized with $NaHCO_3$ and resulting precipitate was collected and recrystallized from benzene to yield 1.02 g (56.7%) of XXXIII, mp 144°. NMR (CD_3SOCD_3, δ): 5.67 (1H, dd, $J=9$ and 13 Hz, α-position), 8.40 (1H, t, $J=13$ Hz, β-position), 9.38 (1H, d, $J=9$ Hz, aldehyde) and 10.47 (1H, d, $J=13$ Hz, NH). *Anal.* Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.58; H, 6.22; N, 17.50.

β-(6-Methyl-2-pyridylamino)acrolein (XXXIV)——To a solution of 3.24 g (0.03 mol) of 2-amino-6-methylpyridine in 10 ml of EtOH were added 50 ml of EtOH containing HCl (5.1%) and 6.60 g (0.03 mol) of VI. The solution was warmed at 80° in a water bath for 6 hr. EtOH was removed *in vacuo*. The residue crystallized immediately after evaporation of the solvent, but was too hygroscopic to purify by recrystallization. After drying in a desiccator, 2 g of the residue was dissolved in 10 ml of H_2O. The solution was neutralized with $NaHCO_3$ and resulting precipitate was collected and recrystallized from benzene to yield 0.36 g (20.0%) of XXXIV, mp 148°. NMR (CD_3SOCD_3, δ): 5.66 (1H, dd, $J=9$ and 13 Hz, α-position), 8.43 (1H, t, $J=13$ Hz, β-position), 9.33 (1H, d, $J=9$ Hz, aldehyde) and 10.47 (1H, d, $J=13$ Hz, NH). *Anal.* Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.92; H, 6.29; N, 17.16.

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