The Reactions of β-Amino α,β-Unsaturated Esters with Amines. II. Syntheses of Some New Derivatives of Quinazolines

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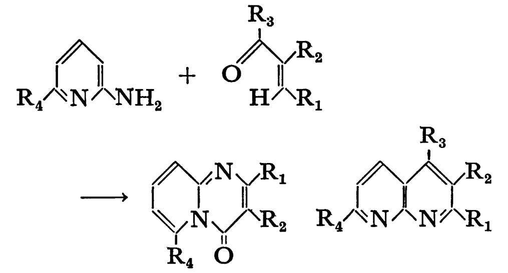
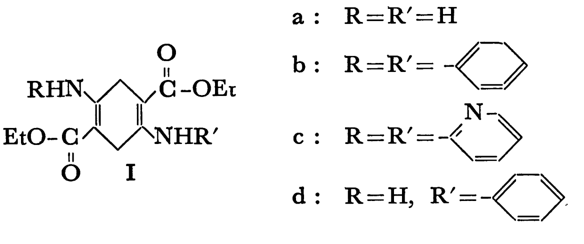
The reaction of 1,4-bis(ethoxycarbonyl)-2,5-diamino-1,4-cyclohexadiene(Ia) with aniline in aprotic solvents gave *N,N′*-diphenylurea, whereas in the presence of a proton acid this reaction gave an amine-exchanged product, 1,4-bis(ethoxycarbonyl)-2,5-dianilino-1,4-cyclohexadiene(Ib). However, when 2-aminopyridine was used in place of aniline for this reaction, 1,4-bis(ethoxycarbonyl)-2,5-bis(2-pyridylamino)-1,4-cyclohexadiene(Ic) was not isolated but its cyclyzed analogue, 6,7,14,15-tetrahydropyrido[2,1-*b*]pyrido[1′,2′ : 1,2]pyrimido[4,5-*g*]quinazoline-7,15-dione(IIa), was obtained. The reaction of 2-amino-6-methylpyridine with Ia also gave a quinazoline derivative without producing a 1,8-naphthyridine derivative. Since this reaction took place easily in a weak acid, AcOH, this cyclization could proceed by an intramolecular proton-transfer mechanism.

Aminopyridines have two basic nitrogen atoms in the molecule, and their reaction with β-keto esters or β-amino α,β-unsaturated esters is of interest. The condensation of 2-aminopyridine with β-keto ester followed by cyclization in Dowtherm A (a mixture of 23.5% by weight of biphenyl and 76.5% of diphenyl ether) affords the pyridopyrimidines.[1] When the 2-aminopyridine is substituted in the 6-position with an electron-releasing group, the naphthyridine is formed.[2]



Antaki and Petrow have studied the reaction of 2-aminopyridines with ethyl β-aminocrotonate, and obtained pyridopyrimidines and *N,N′*-bis(6-methyl-2-pyridyl)urea.[3] However, this reaction has not been further investigated.

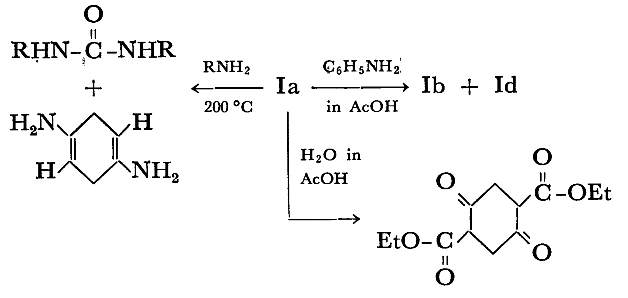
Therefore, in this work, 1,4-bis(ethoxycarbonyl)-2,5-diamino-1,4-cyclohexadiene(Ia) was used as a β-amino α,β-unsaturated ester, and its reaction with 2-aminopyridines was studied. Some new compounds were synthesized and possible reaction mechanisms were investigated by comparing the reactivity to Ia of 2-aminopyridine with that of aniline.



Results and Discussion

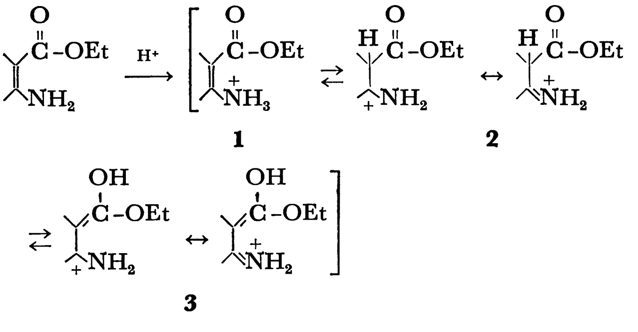
When a mixture of Ia and aniline was heated in *N*-methyl-2-pyrrolidone(NMP) or dimethyl sulfoxide (DMSO) under a nitrogen atmosphere at 200 °C for 2 hr, *N,N′*-diphenylurea was the main product.

However, when a proton acid was used as a catalyst, the amino groups of Ia were replaced by anilino groups, giving Ib and 1,4-bis(ethoxycarbonyl)-2-amino-5-anilino-1,4-cyclohexadiene(Id). When glacial acetic acid was used as the solvent, the yield of Ib was higher. On the other hand, when the reaction was carried out in aqueous acetic acid at elevated temperatures, the amino groups of Ia were replaced by hydroxyl groups, and 1,4-bis(ethoxycarbonyl)-2,5-cyclohexanedione(diethyl succinylsuccinate, DSS) was formed.



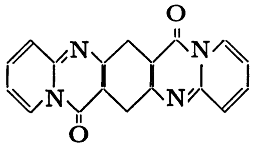
DSS

These results indicate that in the absence of a proton acid the nucleophilic attack of an amine takes place upon the carbonyl carbon atom, whereas in the presence of a proton acid this attack takes place upon the β-carbon atom. The former reaction-mechanism has been reported previously.[4] In the latter case, the protonation of β-amino α,β-unsaturated esters could take place on the nitrogen, α-carbon or carbonyl oxygen atom, giving **1**, **2**, or **3**, respectively. The iminium ions **2** and **3** are expected to react with nucleophiles easily.[5] Therefore, an amine-exchange or amine-hydrolysis reaction should proceed readily.

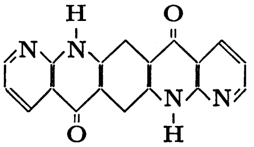


The product expected from the reaction between Ia and 2-aminopyridine in glacial acetic acid is Ic. However, its elemental analysis showed the empirical formula $C_9H_6N_2O$. Possible structures are 6,7,14,15-

tetrahydropyrido[2,1-*b*]pyrido[1′,2′ : 1,2]pyrimido[4,5-*g*]quinazoline-7,15-dione(IIa) and 5,6,7,12,13,14-hexahydropyrido[2′,3′ : 2,3]quino[6,7-*b*]-1,8-naphthyridine-7,14-dione (IIb).



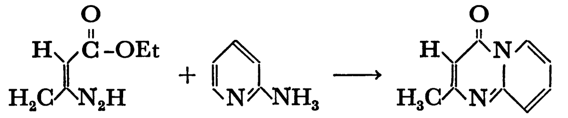
IIa



IIb

The same compound was also obtained when DSS was allowed to react with 2-aminopyridine in glacial acetic acid. This compound was determined to be IIa on the basis of its UV, IR, and NMR spectrum.

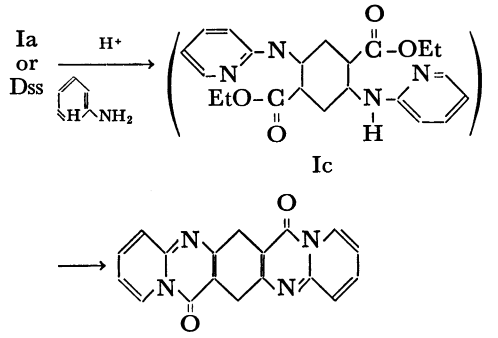
A similar reaction has been studied by Antaki and Petrow. That is, they have reported that 2-methylpyrido[1,2-*a*]pyrimidin-4-one(III) was obtained by heating ethyl β-aminocrotonate with 2-aminopyridine in the absence of a solvent at 160—180 °C for 6—8 hr, and then for a further hour at 200—220 °C.[3] Adams and Pachter confirmed the structure of III by studying its UV spectrum.[1b]



III

However, we easily obtained the same compound by heating ethyl acetoacetate and 2-aminopyridine in glacial acetic acid.

Therefore, it seems that intramolecular cyclization takes place directly in acetic acid, and the reaction between Ia and 2-aminopyridine is postulated to proceed as follows: the amino groups of Ia are replaced by the 2-pyridylamino groups and the Ic formed is converted to IIa by intramolecular cyclization.



IIa

Furthermore, 2-amino-3-,4-, and 5-methylpyridine also reacted with Ia or DSS in acetic acid to give 6,7,14,15-tetrahydrodimethylpyrido[2,1-*b*]pyrido[1′,2′ : 1,2]pyr-imido[4,5-*g*]quinazoline-7,15-diones(IIc–e).

On the other hand, Lappin has reported that the condensation of 2-amino-6-methylpyridine with ethyl ethoxymethylenemalonate followed by cyclization affords the 1,8-naphthyridine.[1a] Antaki and Petrow have described the reaction of ethyl β-aminocrotonate with 2-amino-6-methylpyridine and have obtained *N,N′*-bis(6-methyl-2-pyridyl)urea.[3] Therefore, 2-amino-6-methylpyridine was treated with Ia or DSS in acetic acid, and 6,7,14,15-tetrahydro-1,9-dimethylpyrido[2,1-*b*]pyrido[1′,2′ : 1,2]pyrimido[4,5-*g*]quinazoline-7,15-dione(IIf) was formed.

These compounds were identified on the basis of elemental analyses, IR, UV, and NMR spectra. Tables 1 and 2 show some pertinent data on II and III.

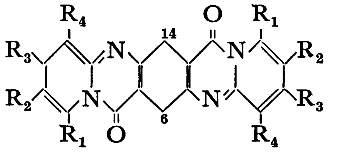
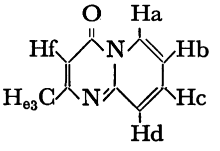
These results indicate that β-amino α,β-unsaturated esters react with 2-aminopyridine or its methyl-derivatives in acetic acid to give only pyridopyrimidines

Table 1. Physical properties of compounds II and III

Compound	Reaction[a)] Time (hr)	Reaction[a)] Yield (%)	Mp (°C)	Found (Calcd) % C	Found (Calcd) % H	Found (Calcd) % N	IR absorption maxima $\nu_{C=O}$	$\nu_{C=N}$	$\nu_{C=C}$	$\delta_{C=H}$ (cm^{-1})	UV absorption maxima[b)] nm (ε)
IIa	2	12	>300	68.11 (68.35)	3.80 (3.83)	17.59 (17.70)	1670	1630	1570 1530 1490	770	240(19,000) 322(21,000)
IIc	3.5	9.7	>300	69.04 (69.77)	4.51 (4.65)	16.28 (16.28)	1680	1635	1580 1547 1485	768	244(15,000) 324(25,000)
IId	11	6.8	>300	69.43 (69.77)	4.51 (4.65)	16.23 (16.28)	1672	1640	1570 1520 1485	777	237(27,000) 320(28,000)
IIe	13	26	>300	69.26 (69.77)	4.87 (4.65)	16.16 (16.28)	1675	1640	1569 1533 1482	781	245(12,000) 322(9,000)
IIf	15	14	>300	67.57 (69.77)	4.91 (4.65)	16.30 (16.28)	1670	1640	1590 1550 1483	805	245(33,000) 343(37,000)
III	2	70	121—122	67.53 (67.50)	4.97 (5.00)	17.45 (17.50)	1710	1635	1575 1540 1473	825	240(6,000) 249(6,200) 311(7,800)

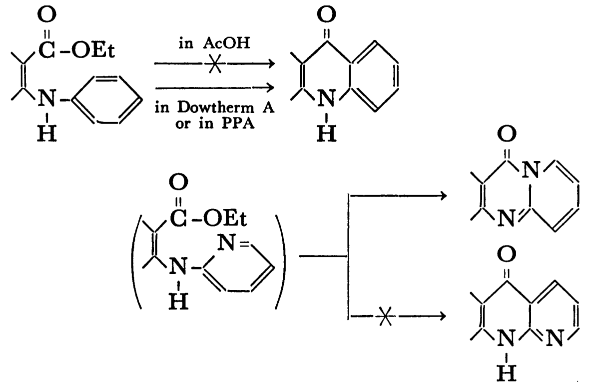
a) The reactions were carried out by refluxing in AcOH. b) In 0.5 M H_2SO_4.

Table 2. NMR spectral data of compounds II and III

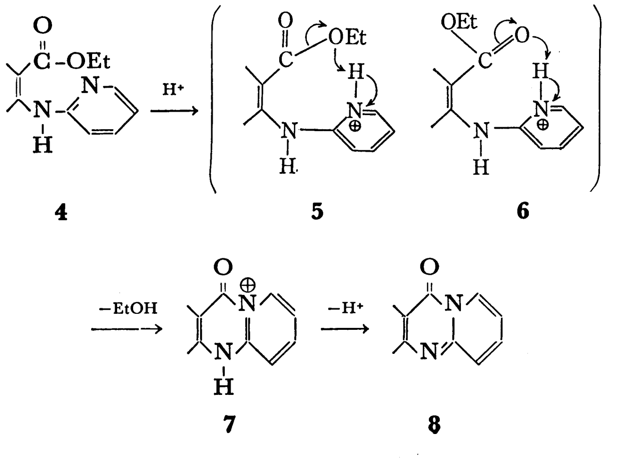
Compound		δR_1	δR_2	δR_3	δR_4	δ(6, 14) ppm
	IIa	d 2H 9.38	t 2H 7.84	t 2H 8.55	d 2H 8.08	s 4H 4.36
	IIc	d 2H 9.30	t 2H 7.76	d 2H 8.39	(CH_3) s 6H 2.80	s 4H 4.39
a : $R_1=R_2=R_3=R_4=H$	IId	d 2H 9.20	d 2H 7.64	(CH_3) s 6H 2.78	s 2H 7.82	s 4H 4.30
c : $R_1=R_2=R_3=H$, $R_4=CH_3$ d : $R_1=R_2=R_4=H$, $R_3=CH_3$	IIe	s 2H 9.18	(CH_3) s 6H 2.67	d 2H 8.41	d 2H 7.98	s 4H 4.32
e : $R_1=R_3=R_4=H$, $R_2=CH_3$ f : $R_2=R_3=R_4=H$, $R_1=CH_3$	IIf	(CH_3) s 6H 3.22	d 2H 7.43	t 2H 8.23	d 2H 7.76	s 4H 4.10
 III	a	d 1H 9.40				
	b	t 1H 7.84				
	c	t 1H 8.54				
	d	d 1H 8.10				
	e	s 3H 2.70				
	f	s 1H 6.63				

directly without producing a 1,8-naphthyridine derivative.

When Ia or DSS was allowed to react with aniline in glacial acetic acid, only Ib was formed and no further cyclization took place. The cyclization of Ib was achieved by heating in inert solvents at high temperature[6] or in polyphosphoric acid (PPA).[7]

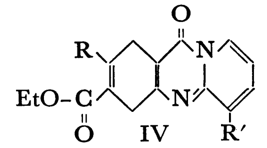


However, the cyclization of Ic occurs more easily than that of Ib in weak acid, acetic acid. This may be explained by assuming the following reaction mechanism. That is, the proton on the nitrogen atom of the pyridinium ion, **5** and **6**, transfers to the oxygen atom of the ethoxy or the carbonyl group. Then, the carbonium ion formed attacks the nitrogen atom of the pyridine nucleus.



4 **5** **6** **7** **8**

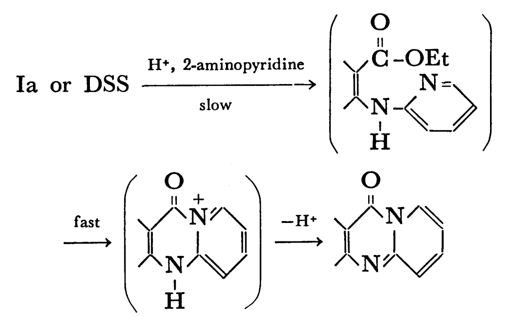
When the reaction of Ia or DSS with 2-aminopyridine in glacial acetic acid was carried out at lower temperatures, the products were 8-amino-7-ethoxycarbonyl-6,9-dihydro-10*H*-pyrido[2,1-*b*]quinazolin-10-one(IVa) or 7-ethoxycarbonyl-6,9-dihydro-8-hydroxy-10*H*-pyrido[2,1-*b*]quinazolin-10-one(IVb), respectively, but Ic was not isolated. The reaction of Ia with 2-aminopyridine in NMP in the presence of *p*-toluenesulfonic acid at 200 °C gave a mixture of IIa and IVa, and that with 2-amino-3-methylpyridine gave a mixture of IIc and 8-amino-7-ethoxycarbonyl-6,9-dihydro-4-methyl-10*H*-pyrido[2,1-*b*]quinazolin-10-one(IVc).



IV

a : $R=NH_2$, $R'=H$
b : $R=OH$, $R'=H$
c : $R=NH_2$, $R'=CH_3$

These observations suggest that the condensation between 2-aminopyridine and Ia or DSS is slow but that the intramolecular cyclization step is very fast.



Compounds II and III are basic compounds and are soluble in acidic solutions such as sulfuric acid or trifluoroacetic acid, and they are reprecipitated upon neutralization or dilution. The UV spectra of III are greatly affected by the change of pH of the solution, as shown in Fig. 1. The absorption of III at 338 nm

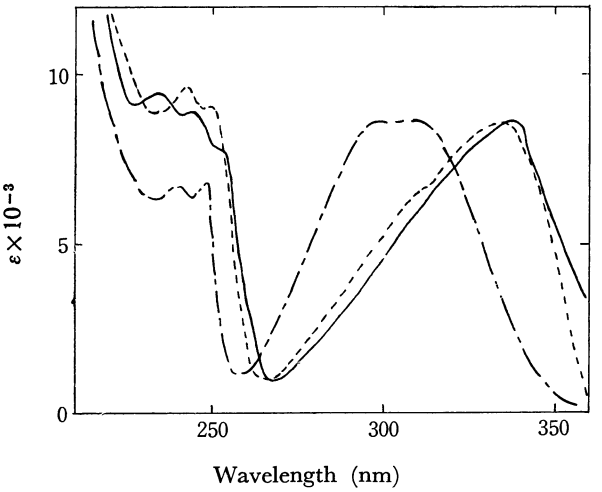
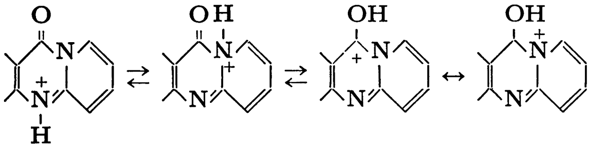


Fig. 1. Electronic absorption spectra of III.
——: in 95% ethanol; ----: in water; — — —: in 0.5 M H_2SO_4.

(attributed to the carbonyl group) showed a hypsochromic shift in 0.5 M sulfuric acid solution. The acidic solutions of II showed similar absorptions. These findings suggest that II and III exist in aqueous sulfuric acid solution as tautomers.



Experimental

The IR spectra were determined in KBr disks with a Hitachi EPI–G3 infrared spectrophotometer. The UV spectra were recorded with a Hitachi EPS–3T recording spectrophotometer. The NMR spectra were obtained with a Varian HA-100 high resolution NMR spectrometer, using TMS as an internal standard. For thin layer chromatography (tlc), a plate of Silica-gel HF (E. Merck) was used. Plates were developed with a mixture of benzene and tetrahydrofuran (1 : 1 v/v). Melting points were uncorrected.

Materials. All the reagents except those listed below were obtained from commercial sources and were used without further purification. DMSO and NMP were dried over aluminum oxide and distilled before use. Aniline and 2-amino-3-methylpyridine were dried over synthetic zeolite (Zeolum A–4, Tekkosha) and distilled before use. 2-Aminopyridine, 2-amino-4-, 5-, and 6-methylpyridine were purified by recrystallization. 1,4-Bis(ethoxycarbonyl)-2,5-di(amino- or anilino)-1,4-cyclohexadiene(Ia: mp 117—119 °C, Ib: mp 164—165 °C) were prepared according to the methods described in the literature.[8]

Reactions. *The Reaction of Ia with Aniline*: *a)* A mixture of Ia (9 g), aniline (8 g), and NMP (50 ml) was heated at 197—200 °C for 2 hr while being stirred under a nitrogen atmosphere. The red solution obtained was then cooled and added with stirring to ice-cold 1 M hydrochloric acid (500 ml). The product was extracted with three 200 ml portions of benzene. The combined benzene extracts were washed once with 1 M hydrochloric acid, twice with water, twice with 10% potassium carbonate, once with water, and were finally dried over anhydrous sodium sulfate. The benzene was removed by distillation at reduced pressure, and the residue was washed with methanol, and dried under vacuum. Yield 1.5 g, mp 122—123 °C, Found: C, 56.14; H, 6.13%. IR (cm^{-1}): 1672(C=O), 1640(C=C), 122 and 1070 (ester). The compound was identified as diethyl succinylsuccinate(DSS) by a comparison of its IR spectrum, mp, and tlc R_f value with those of an authentic sample.[9]

White precipitates were formed from the water layer, and were collected by filtration, washed with water, and dried at 60 °C; 2.5 g of white crystals were obtained. The product was determined to be *N*,*N*′-diphenylurea(DPU) on the basis of a mixed-melting-point determination and a comparison of its IR spectrum and tlc R_f value with those of an authentic sample: mp 242 °C, IR (cm^{-1}): 3325 and 3280(–NH–), 1652, 1557, and 1319 (amide), 755 and 695(phenyl).

b) A mixture of Ia (5 g), aniline (5 g), and DMSO (50 ml) was heated at 186—196 °C for 2 hr with stirring under a nitrogen atmosphere. By the procedure described in *a*), unreacted Ia was recovered from the benzene layer, and 0.3 g of DPU was isolated from the water layer. Both compounds were confirmed by a mixed-melting-point determination and a comparison of their IR spectra and tlc R_f value with those of authentic samples.

c) A mixture of Ia (5 g), aniline (5 g), and NMP (50 ml) was stirred at room temperature for 2 hr under a nitrogen atmosphere. The orange crystals which appeared were collected by filtration, washed with methanol, and dried in a vacuum to give Ib, which was confirmed by a comparison of its IR spectrum with that of an authentic sample.

d) To a mixture of Ia (5 g), aniline (5 g), and benzene (50 ml), glacial acetic acid (3 ml) was added. The solution was refluxed for 2 hr with stirring under a nitrogen atmosphere. After it was cooled, it was washed with water (120 ml) and concentrated by distillation at reduced pressure. The residue was washed with methanol yielding 2.0 g of Ib as pale orange crystals. The melting point was not depressed when mixed with an authentic sample. The methanol washings were concentrated to give 3.8 g of orange crystals, which were recrystallized from methanol-water: its structure was determined to be 1,4-bis(ethoxycarbonyl)-2-amino-5-anilino-1,4-cyclohexadiene by IR spectroscopy and elemental analysis. Found: C, 65.37; H, 6.61; N, 8.42%. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48%. IR (cm^{-1}): 3460 and 3330 (–NH–), 1650—1670, 1230, and 1100(ester), 750 and 690 (phenyl).

The Hydrolysis of I: A mixture of Ia (5 g), water (5 ml), and glacial acetic acid (50 ml) was refluxed for 2 hr while being stirred under a nitrogen atmosphere. After cooling the solution, pale yellow crystals separated out, yield 70%. This compound was determined to be DSS by a comparison of its IR spectrum, mp, and tlc R_f value.

In a similar manner, the hydrolysis of Ib gave DSS, yield 52%.

The Reaction of Ia or DSS with 2-Aminopyridines: *a)* A mixture of Ia (5.0 g), 2-aminopyridine (5.0 g), and glacial acetic acid (50 ml) was refluxed with stirring under a nitrogen atmosphere for 3 hr. White solids separated, and they were collected on a filter, washed with acetic acid and methanol, and dried at 60 °C. This compound was soluble in strong acid solutions, such as aqueous sulfuric acid or trifluoroacetic acid, and it was reprecipitated upon neutralization or dilution. The UV spectrum was measured in a 0.5 M aqueous sulfuric acid solution, and the NMR spectrum was recorded in trifluoro acetic acid. Its yield and analytical data are listed in Tables 1 and 2. These results proved that the compound was 6,7,14,15-tetrahydropyrido[2,1-*b*]pyrido[1′,2′ : 1,2] pyrimido[4,5-*g*]quinazoline-7,15-dione(IIa).

b) Diethyl succinylsuccinate (5.0 g) also reacted with 2-aminopyridine (5.0 g) under the same reaction conditions described above to give 1.5 g of IIa.

c) The reactions of Ia with 2-amino-3-, 4-, 5-, and 6-methylpyridine were carried out in a similar way to that described in *a*). The yields, products, and analytical data of each run are listed in Tables 1 and 2.

The Reaction of Ethyl Acetoacetate with 2-Aminopyridine: An equimolar admixture of ethyl acetoacetate (13.5 ml) and 2-aminopyridine (12 g) was refluxed in glacial acetic acid (50 ml) for 2 hr. After evaporation of the mixture to dryness under reduced pressure, the residue was recrystallized from petroleum benzine as white needles. It was dried at 60 °C, mp 121—122 °C. Its IR, NMR, and UV absorption, and analytical data are summarized in Tables 1 and 2. These results proved that this compound was 2-methylpyrido-[1,2-*a*]pyrimidin-4-one(III).

*8-Amino-7-ethoxycarbonyl-6,9-dihydro-10*H*-pyrido[2,1-*b*]quinazolin-10-one(IVa)*: *a)* A mixture of Ia (5.0 g) and 2-aminopyridine (11.0 g) was heated in glacial acetic acid (50 ml) at 100 °C for 30 min under a nitrogen atmosphere. After cooling, the precipitate was collected by filtration, washed with methanol, and dried under vacuum, yielding 5.0 g of white crystals. This compound was soluble in strong acid solutions from which it was reprecipitated on neutralization. The reprecipitated solid was used for analyses, and its structure was determined to be IVa on the basis of its IR spectrum and elemental analysis. Found: C, 63.07; H, 5.21; N, 14.72%. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.16; H, 5.26; N, 14.74%. IR (cm^{-1}): 3425 and 3325 (-NH_2), 1680, 1270, and 1060 (ester).

b) A mixture of Ia (5.0 g) and 2-aminopyridine (5.0 g) was refluxed in NMP (50 ml) in the presence of small amounts of *p*-toluenesulfonic acid for 3 hr under a nitrogen atmosphere. After the reaction mixture was cooled, the precipitate was collected by filtration, washed with methanol, and extracted with hot glacial acetic acid. The residue (2.0 g) was determined to be IIa on the basis of its IR spectrum. The extract was diluted with water and neutralized with aqueous ammonia. The white crystals obtained were identified as IVa on the basis of their IR spectra, and the yield was 1.6 g.

*7-Ethoxycarbonyl-6,9-dihydro-8-hydroxy-10*H*-pyrido[2,1-*b*]quinazolin-10-one(IVb)*: A mixture of DSS (15 g) and 2-aminopyridine (15 g) was refluxed in glacial acetic acid (100 ml) for an hour while being stirred under a nitrogen atmosphere. The resulting solid (4.5 g) was filtered out at 60 °C, and was determined to be IIa. After cooling the filtrate to room temperature, a white solid separated out. This precipitate was collected and recrystallized from ethanol, yielding 4.7 g of pale yellow crystals. The purified precipitate showed a single spot on tlc and was identified as IVb on the basis of the IR spectrum and elemental analysis. Mp 219—220 °C, IR (cm^{-1}): 1680 (C=O), 1640 (C=C), 1270 and 1060 (ester), Found: C, 62.72; H, 4.95; N, 9.76%. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.94; H, 4.90; N, 9.79%.

*8-Amino-7-ethoxycarbonyl-6,9-dihydro-4-methyl-10*H*-pyrido[2,1-*b*] quinazolin-10-one (IVc)*: The reaction of Ia (5.0 g) with 2-amino-3-methylpyridine (5.0 g) gave IIc (1.5 g) and IVc (1.4 g). The structure of IVc was confirmed on the basis of the IR spectrum and elemental analysis. IR (cm^{-1}): 3430 and 3325 (-NH_2), 1665—1680 (C=O), 1635 (C=C), 1250 and 1060 (ester), Found: C, 65.18; H, 5.97; N, 14.40%. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.21; H, 5.69; N, 14.47%.

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9) This compound was probably formed by the hydrolysis of Ia with moisture in the NMP or in the atmosphere. It is also possible that the oxygen atom of NMP attacked a β-carbon atom of Ia and the complex obtained was hydrolyzed during the subsequent treatment. No further treatment of the product was undertaken.