6- And 7-Substituted 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones. Synthesis *via* the Acid-catalyzed Isomerization of 2-(Acetoacetamido)pyridines (1).

Harry L. Yale (2) and E. R. Spitzmiller

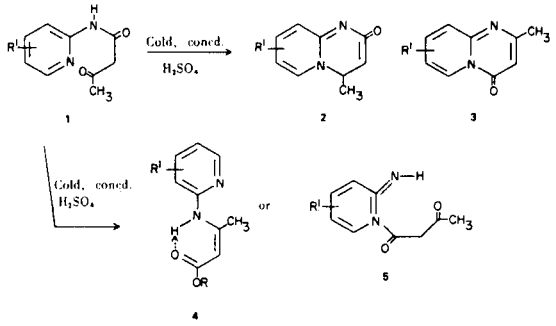
The Squibb Institute for Medical Research, Princeton, NJ 08540

Received March 25, 1977

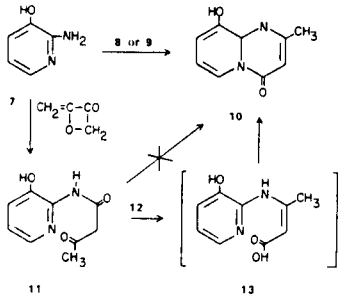
A novel procedure has been developed for converting a variety of substituted 2-(acetoacetamido)pyridines into substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. The reaction involves an acid-catalyzed isomerization of the 2-(acetoacetamido)pyridine derivatives into the corresponding *enamines*, under conditions that permit the latter to undergo cyclization to the 4-one, *in situ*. The method has been employed to prepare a number of hitherto unknown 2,6- and 2,7-di- and 2,7,9-trisubstituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

J. Heterocyclic Chem., 14, 637 (1977).

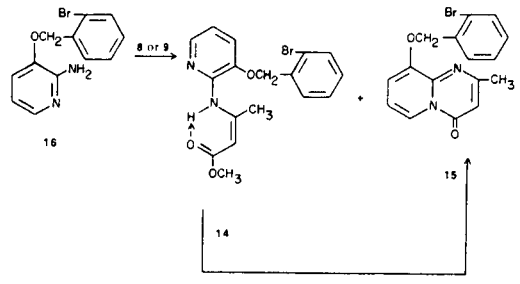
In 1939, Khitrik (3) reported that 2-(acetoacetamido)-pyridine, **1** (R^1 = H) dissolved in cold, concentrated sulfuric acid, gave 2*H*-4-methylpyrido[1,2-*a*]pyrimidin-2-one, **2** (R^1 = H), in low yield; no other product was identified. That his structure assignment was incorrect and that the product was the isomeric 4*H*-2-methylpyrido-[1,2-*a*]pyrimidin-4-one, **3**, was established by Antaki and Petrow (4), who, in addition to reproducing Khitrik's synthesis, reported that except for that procedure, all other attempts to convert **1** to **2** or **3** were unsuccessful. In order that the 4-one, **3**, be formed, the role of the sulfuric acid appears to be that of inducing a rearrangement of **1** to the enamine **4** (R^1 = H), or possibly, even the 1-acylated 2-pyridinimine, **5**, since either of those species could then undergo cyclodehydration to **3**. Enigmatically, even though it was reported that 2-aminopyridine and ethyl acetoacetate, **6**, at 100° for 4 hours gave good yields of **1**, and no **2** or **3**, the same reactants at 160° for 4 hours gave poor yields of **3**, and no **1** or **2**, along with large amounts of unidentified tars.



From our review of the literature and our investigations in this area of heterocyclic chemistry, we are led to the conclusion that from a 2-aminopyridine and an ester of acetoacetic acid or 3-aminocrotonic acid, the formation of **3**, under thermal, *non-catalytic conditions*, must be presumed to occur *via* **4** (R = H or C_2H_5, R^1 = H) or **5**, both being formed *ab initio*, but, not by rearrangement of **1**. One example to support this concept was found in the reaction between 2-amino-3-pyridinol, **7**, and methyl acetoacetate, **8**, or methyl 3-aminocrotonate, **9**: thermally, these reactions gave the bicycle, **10**, in essentially quantitative yield (1b). In contrast, the 2-(acetoacetamido) derivative, **11**, under those conditions, did not undergo any change. Yet, when a catalytic amount of *p*-toluenesulfonic acid, **12**, was added to the **11**, the formation of water was prompt, and the conversion to **10** was 82%. Although we have been unable to isolate the enamine, **13**, we are of the conviction that **13** was the intermediate formed by acid-catalyzed rearrangement.

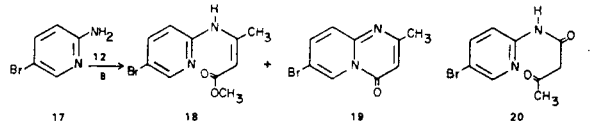


Another example supporting this concept can be found, again, in our own work (2c), where, for the first time, we isolated the enamine, **14**, along with the cyclized *4-one*, **15**, from the reaction of **16** with either **8** or **9**. Subsequently, we demonstrated that **14** could be cyclized *thermally*, in the absence of a catalyst, to **15**. Additional examples can be found again, in our more recent investigations. Thus, the reaction of 2-amino-5-bromopyridine,



17, with **8**, the latter serving both as reactant and solvent, in the presence of a catalytic amount of **12**, gave, after a

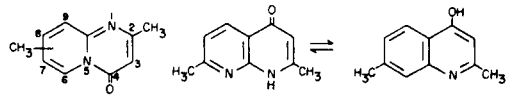
short reaction time, the enamine, **18**, and the cyclized product, **19**, in 21 and 25% yields, respectively. In the absence of the catalyst, **12**, under the same conditions,



the only product of the reaction of **17** and **8** was the 2-(acetoacetamido) derivative, **20**. In addition, we were able to demonstrate, again for the first time, that passage of a solution of **18**, through a silica gel column, converted that compound to **19**, quantitatively, but the same procedure had no effect on **20**.

The major purpose of this paper is, then, to describe a novel "isomerization-cyclization" procedure for the preparation of 4*H*-2-methylpyrido[1,2-*a*]pyrimidin-4-ones from the corresponding 2-acetacetamido derivatives, and, to show that *p*-toluenesulfonic acid, **12**, in catalytic amounts, in toluene, under reflux, can effect this synthesis *via* that rearrangement.

We were led to this new preparative route as a consequence of our desire to prepare the hitherto unreported 4*H*-2,6-dimethyl-, **21**, and 4*H*-2,7-dimethylpyrido[1,2-*a*]pyrimidin-4-one, **22**, for evaluation in our Central Nervous System (CNS) pharmacological screens. We had previously found a striking structure-activity relationship in the only two known isomers of **21** and **22**: the 2,8-dimethyl derivative, **23**, was devoid of all CNS activity in animal models designed to uncover that type of response, while the 2,9-dimethyl compound, **24**, showed a broad spectrum of activity in the same test procedures. Thus, with the synthesis of **21** and **22** there existed the possibility of uncovering even more interesting CNS pharmacodynamic activities.



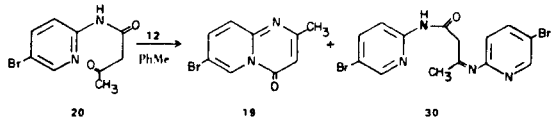
21, CH_3 in position 6
22, CH_3 in position 7
23, CH_3 in position 8
24, CH_3 in position 9

25a,b

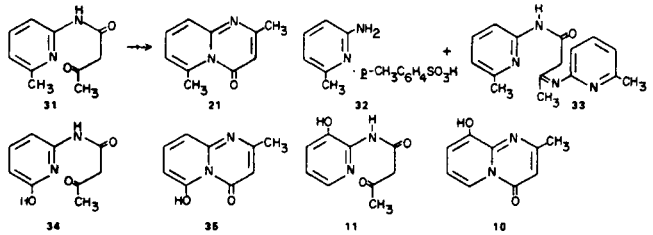
Our initial efforts were directed toward the synthesis of **22**, since there was good reason to suspect that attempts to prepare **21** would lead only to the 1,8-naphthyridin-4-one, **25a,b** (5). Employing procedures previously described (1a-1f), a trace amount of **22** was isolated in one instance, only, when 2-amino-5-methylpyridine, **26**, and **8** or **9** were reacted; no cyclization occurred even when the reactants were heated in diethylbenzene at 180°. When, however, 2-(acetoacetamido)-5-methylpyridine, **27**, prepared from **26** and either **8** or diketene, **28**, was reacted in a toluene solution containing a catalytic amount of **12**, so that the distilling vapors were dried by means of a calcium hydride trap before returning to the reaction flask (6), **22** was obtained in 85% yield. That procedure could also be abbreviated in the following manner: when the reaction mixture obtained by heating **26** and **28** in toluene, under reflux, and previously shown to have given **27** in 71% yield, was cooled, treated with a catalytic amount of **12**, and the heating continued in the same flask, but now under the calcium hydride drying trap, the overall yield of **22** from **26** was 70%.

Although the conversion of **27** to **22** could be followed by tlc, that technique afforded no information as to the presence in the reaction mixture of either an enamine or the isomeric 1-acylated pyridine, and neither of those intermediates was isolated during the workup. In the experiments involving **27**, only recrystallized compound was used, *i.e.*, material free of any **26**; it was significant, therefore, that in this instance, the only other product of this "isomerization-cyclization" reaction was the salt, **29**, of **26** and **12**, obtained in 3% yield.

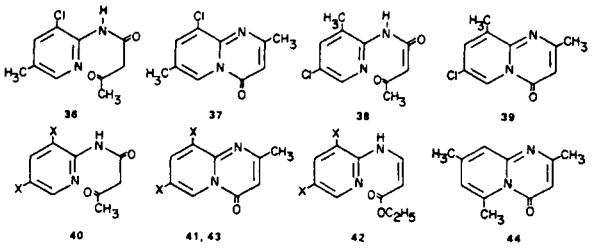
The successful application of the "isomerization-cyclization" procedure in the above instance served as a rational basis for an investigation into the general applicability of this synthetic method. It was next tried with 2-(acetoacetamido)-5-bromopyridine, **20**, and gave the cyclized compound, **19**, in 66% yield; the by-product, in this instance was **30** in 5% yield (7,8).



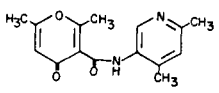
When the above procedure was employed to prepare **21** from **31**, tlc monitoring of the progress of the reaction indicated that a complex mixture of products was being formed; workup led to the isolation of **21** (9) in 1% yield, along with the by-products, **32** and **33**; it was of significance that no naphthyridine derivative could be detected. When the same procedure was tried with **34**, a complex mixture of products was formed; and workup resulted only in the recovery of small amounts of unchanged **34**. However, subjecting **11** to the procedure gave **10** in 84% yield. In addition, the procedure has been



applied to the synthesis of **37** from **36**, **39** from **38**, **41** and **43** from the corresponding **40**; these compounds, to our knowledge, are the first examples of 4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones carrying two substituents in the pyrido ring. For example, all of our attempts to prepare **44** have been unsuccessful; instead **45** was the only product identified in the reaction mixture (10).

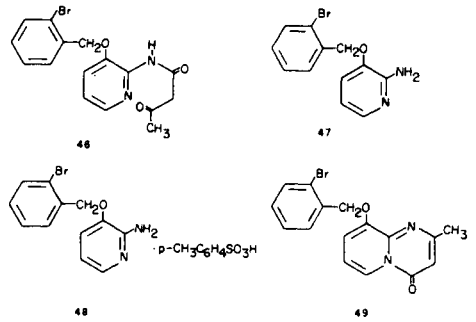


[Note: in 40, 41, and 43, both X are either Cl or Br; in 42, both X are Br]



45

In the final study involving the isomerization-cyclization procedure, we prepared **46** and subjected it to that procedure. The reaction, as anticipated, was the most sluggish encountered during the entire investigation. A complex mixture of products was formed, and of these, **47**, **48**, and **49** were identified.



In several of the syntheses reported in this paper, when difficulties were encountered in separating complex mixtures, it was found that the acid salts of the several components of the mixture were readily separable. We have, in addition, prepared a number of salts of a variety of 2-aminopyridines during these investigations, and these are described in the Experimental.

EXPERIMENTAL

The melting points were determined in an electrically heated oil bath and are uncorrected. The spectra and microanalyses were obtained from the Analytical Department of This Institute as described in our earlier papers (2a-2f).

2,7-Dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**22**). Preparation from 2-(Acetoacetamido)-5-methylpyridine (**27**).

2-(Acetoacetamido)-5-methylpyridine (**27**).

(a) To a stirred solution of 55.0 g. (0.5 mole) of **26** in 500 ml. of reagent grade toluene was added, dropwise, 46.0 g. (0.55 mole) of diketene during 35 minutes. Subsequently, the mixture was heated under reflux for 1.5 hours, cooled, and the solid filtered and dried *in vacuo* to give 68.6 g. (71% yield) of **27** m.p. 139-141°; this material was analytically pure, and had the following spectral characteristics: ir (potassium bromide): ν 3240(s), 1725(s), 1690(s), 1665(s), 1600(s), 1480(s) cm^{-1}; pmr (deuteriochloroform): 2.35 (d (J = 2 Hz), 6H, 2(CH_3)], 3.62 (s, 2H, CH_2), 7.30-8.30 (m, 3H, 3 Py-*H*), 9.50-10.00 [broad s, 1H, N*H* (equilibrates with deuteriumoxide)].

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.59. Found: C, 62.46; H, 6.16; N, 14.77.

When the filtrate from the above product was concentrated *in vacuo* to a volume of 100 ml., refrigerated, and the precipitated solid filtered, and dried, there was obtained 14.6 g. of solid, m.p. 125-140°. A tlc of this material showed two spots, R_f *ca.* 0.73 and *ca.* 0.50 (benzene:acetone 1:1), and was, therefore, a mixture of **27** and **22** (see below). When a solution of 12.2 g. of this solid, 0.80 g. of **12**, and 375 ml. of reagent grade toluene was heated under a calcium hydride drying still head as described below the recovery of pure **22** was 9.2 g. (84% yield).

(b) A mixture of 21.6 g. (0.2 mole) of **26**, 46.4 g. (0.4 mole) of methyl acetoacetate, and 200 ml. of diethylbenzene was heated for 5 hours at 180°; during that heating period, a distillate, 13.0 ml., was collected. It consisted of 20% acetone, 79% methanol, and 0.3% each of water and diethylbenzene. The mixture was concentrated to one-half volume *in vacuo*, filtered, and the filtrate cooled. The crystalline product that separated was filtered and dried at 78° *in vacuo* to give 27.0 g. of analytically pure **27**, m.p. 139-141°, whose ir and pmr spectra were identical with those obtained on the above sample.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.58. Found: C, 62.83; H, 6.30; N, 14.65.

2,7-Dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**22**).

(a) A suspension of 12.0 g. (0.06 mole) of **27**, 1.0 g. (0.065 mole) of *p*-toluenesulfonic acid·H_2O, **12**, and 450 ml. of reagent grade toluene was heated by means of an oil bath at 135-145° so that the distilling vapors were condensed and percolated downward through a bed of calcium hydride before returning to the reaction flask (6). The reaction was monitored by tlc [silica gel plates, acetone:benzone (1:1), R_f of **27**, *ca.* 0.73]. After heating for 72 hours, tlc showed only one spot, R_f *ca.* 0.50. The cooled solution was filtered to remove 0.5 g. of solid, m.p. 155-157°. Recrystallization from acetonitrile gave the salt, **26**, **12**·**29**, m.p. unchanged at 155-157°.

Anal. Calcd. for $C_6H_8N_2 \cdot C_7H_8O_3S$: C, 55.68; H, 5,75; N, 9,98; S, 11.44. Found: C, 55.93; H, 5.48; N, 9.97; S, 11.26.

The filtrate was concentreated to dryness *in vacuo* to give 12.0 g. of solid, and this was recrystallized from 1100 ml. of heptane to give 8.5 g. (85% yield) of **22**, m.p. 147-149°; uv λ max (methanol): 248, 255, 338 mμ [ϵ, (x10^3) 10.75, 10.70, 9.45]; ir (mull): ν 1695(s), 1680(s), 1570(w), 1530(s), 1480(s), 1450(s), 1410(s) cm^{-1}; pmr (deuteriochloroform): δ 2.45 [s, 6H, 2(CH_3) at positions -2 and -7], 6.35 (s, 1H, *H* at position-3), 7.75 (s, 2H, 2*H* at positions -8 and -9); 8.85 [d (J = 2 Hz), 1H, *H* at position -6].

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.78; N, 16.08; N.E., 174. Found: C, 69.10; H, 5.97; N, 16.16; N.E. ($HClO_4$), 175.

(b) "One-pot Synthesis of **22** from **26**.

To a solution of 22.0 g. (0.20 mole) of **26**, in 1500 ml. of reagent grade toluene, at 95° internal temperature, was added dropwise and with stirring, 21.0 g. (0.22 mole) of diketene in 0.25 hour, and subsequently heated under reflux for 2 hours. The mixture was cooled, 1.0 g. of **12** was added, the reaction flask was fitted with the calcium hydride trap, and the heating as described in (a) was continued for 72 hours when tlc showed a single spot, R_f *ca.* 0.62. The cooled mixture was filtered and

the filtrate concentrated to dryness *in vacuo* to give 28.7 g. of crude **22**, m.p. 142-144°. Recrystallization from 2 l. of cyclohexane gave 24.4 g. (70% yield) of pure **22**, m.p. 147-149°. A mixture m.p. with the product from (a) was 147-149° and their ir and pmr spectra were superimposable.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.78; N, 16.08; N.E., 174. Found: C, 68.68; H, 5,64; N, 15.96; N.E. ($HClO_4$), 176.

(c) Reaction of **26** and **8** in Trichlorobenzene. Formation of **22**.

A solution of 21.6 g. (0.2 mole) of **26**, 46.4 g. (0.4 mole) of methyl acetoacetate, and 100 ml. of trichlorobenzene was heated by means of an oil bath maintained at 210-215° for 4.5 hours; during that period, 11.5 ml. of distillate were obtained. The solution was clarified by filtration, and the filtrate concentrated to dryness *in vacuo* to give 21.8 g. of a mixture of crystals and black tar; this was dissolved in 100 ml. of benzene and the solution poured on a column of 100 g. of activated alumina (M, C, B, Chromatographic Grade, 200 mesh). The dark benzene solution which passed through the column, and the first 100 ml. elution of benzene-hexane (1:1) were combined and concentrated to dryness. The residue was extracted with ten 10 ml. portions of anhydrous diethyl ether at room temperature; the first three extracts were discarded, the last seven were combined, concentrated to dryness, and the yellow solid, 0.175 g. was recrystallized from 12 ml. of cyclohexane to give 0.080 g. of **22**, m.p. 147-149°, identical in all respects by mixture m.p., ir, and pmr spectra with the **22** prepared above.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.78; N, 16.08. Found: C, 68.69; H, 5.96; N, 15.80.

(d) 2,7-Dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, Maleate Salt (1:1).

To 1.70 g. (0.01 mole) of **22** in 20 ml. of reagent grade 2-butanone at the b.p. was added a boiling solution of 2.40 g. (0.02 mole) of maleic acid in 20 ml. of the same solvent. The salt separated promptly even from the hot solution; the cooled mixture was filtered to give 2.90 g. of solid, m.p. 193-195° dec. Recrystallization from 130 ml. of acetonitrile gave 2.40 g. (82% yield) of product, m.p. unchanged at 193-195° dec.; ir (potassium bromide): 2700-2200(broad w), 1710(s), 1685(s), 1660(s), 1640(s), 1620(s), 1470(s), 1400(s) cm^{-1}; pmr (DMSO-d_6): 2.40 (s, 6H, 2(CH_3) at positions -2 and -7), 6.28 (s, 3H, 2 vinylic *H* plus *H* at position -3), 7.50-8.00 (m, 2H, 2*H* at positions -8 and -9), 8.70-8.90 (m, 1H, *H* at position -6), 11.50-12.20 [m, 2H, 2(CO_2H)].

Anal. Calcd. for $C_{10}H_{10}N_2O \cdot C_4H_4O_4$: C, 57.92; H, 4.86; N, 9.65; N.E., 290. Found: C, 57.97; H, 4.66; N, 9,90; N.E. ($HClO_4$), 291.

(e) 2,7-Dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, Fumarate Salt (1:1).

To a solution of 0.85 g. (0.005 mole) of **22** in 10 ml. of boiling absolute ethanol was added a similar solution of 1.20 g. (0.01 mole) of fumaric acid in 10 ml. of 95% ethanol. The crude salt, 1.10 g., m.p. 209-210° dec. was recrystallized from 55 ml. of reagent grade acetonitrile to give 0.70 g. (48% yield) of the salt, m.p. unchanged at 208-210° dec.; ir (potassium bromide) 2700-2300(broad m), 1725(s), 1670(s), 1640(s), 1575(m), 1540(s), 1490(m), 1465(s), 1450(s), 1425(s) cm^{-1}; pmr (DMSO-d_6): 2.40 [s, 6H, 2(CH_3) at positions -2 and -7], 6.27 (s, 1H, *H* at position -3), 6.65 (s, 2H, 2 vinylic-*H*), 7.40-8.00 (m, 2H, 2*H* at positions -8 and -9), 8.75 [s, 1H, *H* at position -6), 12.55-13.60 (m, 2H, 2(CO_2H)].

Anal. Calcd. for $C_{10}H_{10}N_2O \cdot C_4H_4O_4$: C, 57.92; H, 4.86; N, 9.65; N.E., 290. Found: C, 58.20; H, 4.71; N, 9.67; N.E. ($HClO_4$), 287.

(f) 2,7-Dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, *p*-Toluenesulfonic Acid Salt.

To a boiling solution of 0.85 g. (0.005 mol) of **22** in 10 ml. of reagent grade acetonitrile was added a solution of 1.90 g. (0.01 mole) of **12**·H_2O in 10 ml. of the same solvent, at the b.p. The cooled solution was diluted with 20 ml. of anhydrous diethyl ether, and the solid filtered to give 1.30 g. of salt, m.p. 193-195° dec. Recrystallization from 50 ml. of 2-propanol gave 1.20 g. (66% yield) of product, with m.p. unchanged at 193-195° dec.

Anal. Calcd. for $C_{10}H_{10}N_2O \cdot C_7H_8O_3S$: C, 58.94; H, 5.23; N, 8.09; S, 9.26. Found: C, 58.79; H, 5.12; N, 7.93; S, 9.36.

7-Bromo-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**19**). Preparation by the Isomerization-Cyclization of **18**.

A solution of 15.6 g. (0.06 mole) of **18**, 0.2 g. of **12**, and 900 ml. of reagent grade toluene was heated under a calcium hydride drying still head for 20 hours. At that time, tlc [acetone:benzene (1:1), R_f of **18**, *ca.* 0.80] showed a major spot at R_f *ca.* 0.68 and a minor spot moving with the solvent front. The mixture was cooled to ambient temperature and the precipitated solid filtered to give 1.1 g. of crude **30**, m.p. 233-240°. Recrystallization from 58 ml. of toluene gave 0.41 g. (2% yield) of pure **30**, m.p. 244-246°; ir (mull): ν 3260(m), 3220(m), 1635(s), 1580(m), 1560(s), 1525(m), 1495(m), 1470(s), 1450(m), 1425(w) cm^{-1}; pmr (DMSO-d_6): δ 2.42 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 6.90-8.45 (m, 6 Py-*H*), 10.15-10.45 [m, 1H, (N*H*) (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{14}H_{12}Br_2N_4O$: C, 40.93; H, 2.94; Br, 38.89; N, 13.60; M^+, 410. Found: C, 40.80; H, 2.87; Br, 39.00; N, 13.61; M^+, 410.

The toluene filtrate from the **30** was concentrated *in vacuo*, and the residue, 13.0 g., m.p. 140-150°, was recrystallized from 200 ml. of reagent grade acetonitrile to give 9.5 g. (66% yield) of **19**, m.p. 165-167° (8) uv λ max (methanol): 214, 219(sh), 256, 418 mμ [ϵ (x10^3), 27.6, 25.0, 10.4, 6.3]; ir (mull): ν 1610(s), 1665(w), 1620(m), 1570(m), 1525(m), 1470(s), 1455(s), 1440(s), 1430(s) cm^{-1}; pmr (deuteriochloroform): δ 2.40 (s, 3H, CH_3 at position -2), 6.30 (s, 1H, *H* at position -3), 7.40 [d (J = 6 Hz), *H* at position -9]; 7.73 [q (J = 3,6 Hz), 1H, *H* at position -8), 9.10 [d (J = 3 Hz), 1H, *H* at position -6].

Anal. Calcd. for $C_9H_7BrN_2O$: C, 45.21; H, 2.95; N, 11.72; Br, 33.41; N.E. 239. Found: C, 45.30; H, 2.91; N, 11.79, Br, 33.20, N.E. ($HClO_4$) 238.

2-Acetoacetamido-5-bromopyridine (**20**).

(a) To a solution of 17.4 g. (0.1 mole) of 2-amino-5-bromopyridine in 250 ml. of reagent grade toluene at 100° was added, dropwise and with stirring, 10.0 g. (0.11 mole) of diketene in 0.25 hours. Subsequently, the mixture was stirred and heated under reflux for 1 hour, cooled, and the solid filtered to give 15.9 g. of solid, m.p. 145-162° dec.; tlc [acetone:benzene (1:1)] revealed three spots: R_f *ca.* 1.0, R_f *ca.* 0.80, and R_f *ca.* 0.70. The solid was extracted with 200 ml. of boiling acetonitrile, filtered hot, and the filtrate cooled to give 9.3 g. (34% yield) of **20**, m.p. 159-161°; ir (mull): ν 3240(m), 1710(s), 1680(s), 1660(s), 1585(m), 1560(s), 1530(s), 1450(s), 1405(m) cm^{-1}; pmr (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 8.05 [d (J = 1.5 Hz), 2H, 2*H* at positions -3 and -4], 8.45 [t (J = 1.5 Hz), 1H, H at position -6], 10.65-10.90 [m, 1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_9H_9BrN_2O_2$: C, 41.89; H, 3.52; N, 10.85; Br, 38.82. Found: C, 42.06; H, 3.62; N, 11.00; Br, 38.87.

The material insoluble in the boiling acetonitrile extraction weighed 1.90 g., recrystallization from 100 ml. of toluene gave 0.80 g. (2% yield) of **30**, m.p. 244-246°, whose ir and pmr spectra were identical in all respects with those of the **30** obtained in the previous experiment.

Anal. Calcd. for $C_{14}H_{12}Br_2N_4O$: C, 40.93; H, 2.94; Br, 38.89; N, 13.60. Found: C, 40.80; H, 2.87; Br, 39.00; N, 13.61.

Reaction of 2-Amino-5-bromopyridine, with **8** in the presence of **12**. Formation of **18** and **19**.

A suspension of 34.6 g. (0.20 mole) of 2-amino-5-bromopyridine and 300 ml. of **8** was stirred and heated under a Dean-Stark trap so that the internal temperature rose to 140° in 0.5 hour. A distillate began to collect in the trap. During the 2 hours total heating period at 140-150° internal temperature, 32 ml. of distillate was collected. The reaction mixture was concentrated *in vacuo* to a volume of 75 ml. and cooled to 0°. The solid separating at that time was filtered and dried; it weighted 30.6 g., m.p. 70-150°, and tlc showed two major spots along with several minor tailing spots. The solid was extracted with three separate 100 ml. portions of diisopropyl ether under reflux, decanting the boiling extract each time. The insoluble material after the three extractions was dried and weighed 12.2 g. (25% yield) of **19**, m.p. 163-166°. An analytical sample of **19**, from acetonitrile, melted at 165-167°; its ir and pmr spectra were superimposable on the same spectra obtained with **19** prepared above.

Anal. Calcd. for $C_9H_7BrN_2O$: C, 45.21; H, 2.95; N, 11.72; Br, 33.41; N.E. 239; Found: C, 45,48; H, 3.22; N, 11.73; Br, 33.62; N.E. ($HClO_4$), 243.

The diisopropyl ether extracts from above, *ca.* 300 ml., was concentrated to a volume of 50 ml., cooled, and the solid filtered and dried to give 11.1 g. (21% yield) of crude **18**, m.p. 80-86°. When 10.6 g. of this solid in 100 ml. of benzene was chromatographed on 250 g. of activated alumina (Chromatographic Grade, MCB #9296, 80-200 mesh) and eluted with 600 ml. of benzene, there was recovered 9.4 g. of pure **18**, m.p. 90-92°; ir (deuteriochloroform): ν 3400(s), 3280(s), 1710(s), 1680(s), 1640(w), 1620(w), 1500(s) cm^{-1}; pmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3, CH_3C), 3.65 (s, 3H, CH_3O), 4.70 (s, 1H, C=C*H*), 6.70 [d (J = 6 Hz), *H* at position -3], 7.65 [q (J = 2,6 Hz), 1H, *H* at position -4], 8.28 [d (J = 2 Hz), 1H, *H* at position -6], 11.05 [s,1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{10}H_{11}BrN_2O_2$: C, 44.30; H, 4.09; N, 10.34; Br, 29.49; M^+, 271. Found: C, 44.48; H, 4.10; N, 10.46; Br, 29.26; M^+, 271.

An additional 200 ml. of benzene eluates of the column after removal of the **18** yielded, on concentration, no solid; however, with 200 ml. of acetone there was obtained 0.90 g. of **19**, m.p. 165-167°, with ir and pmr spectra identical with those obtained from the **19** prepared above.

Cyclization of **18** to **19** by silica gel.

When 1.0 g. of **18** in 25 ml. of benzene was poured on a dry filled column of 30 g. of silica gel (Chromatographic Grade, Davison Chemical, Grade 923, 100-200 mesh; dried, before use, at 100°) and the elution carried out initially with nine-50 ml. portions of benzene, these eluates yielded no residue on concentration. Elution with five-25 ml. portions of acetone-benzene (1:4) gave the product, **19**, m.p. 165-167°, 0.85 g. (96% yield). The product was further identified by its ir and pmr spectra which were identical with those obtained from **19** above.

Anal. Calcd. for $C_{10}H_{11}BrN_2O_2$: C, 44.30; H, 4.09; N, 10.34; Br, 29.49. Found: C, 44.27; H, 4.03; N, 10.40; Br, 29.76.

2,6-Dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**21**).

(a) 2-(Acetoacetamido)-6-methylpyridine (**31**).

The preparation of **31** was mentioned in a paper by Seidel, *et al.*, (11), but no experimental details or physical properties were mentioned. Dr. Seidel was kind enough to furnish us with the experimental details and that procedure is used throughout this paper. To a solution of 22.0 g. (0.2 mole) of 2-amino-6-methylpyridine in 250 ml. of reagent grade toluene at 95° was added, in 0.5 hours, 18.5 g. (0.22 mole) of diketene. Workup as described gave 31.0 g. (80% yield) of **31**, m.p. 92-94°; ir (mull): ν 3240(m), 3200(m), 1715(s), 1670(s), 1660(s), 1595(m), 1570(s), 1540(s), 1450(s) cm^{-1}; pmr (deuteriochloroform): δ 2.32 and 2.45 [2s, 6H, 2(CH_3)], 3.60 (s, 2H, CH_2), 6.80-8.10 (m, 3H, 3 Py-*H*), 8.50-9.60 [m, 1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.58. Found: C, 62.22; H, 6.15; N, 14.51.

(b) 2,6-Dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**21**).

A solution of 13.4 g. (0.07 mole) of **31**, 1.5 g. of **12** and 450 ml. of reagent grade toluene was heated as above under a calcium hydride trap for 96 hours. At that time, tlc (acetone:benzene-1:1) showed the presence of four spots. The hot solution was clarified by filtration and the filtrate cooled. The precipitated solid was filtered and dried to give 1.90 g. (18% yield) of crude **32**, m.p. 133-135°; recrystallization from 35 ml. of acetonitrile gave 1.20 g. of pure **32**, m.p. unchanged at 133-135°. The m.p. and spectra were identical with those of an authentic sample of **32** (see below).

Anal. Calcd. for $C_6H_8N_2 \cdot C_7H_8O_3S$: C, 55.68; H, 5.75; N, 9.98; S, 11.44. Found: C, 55.92; H, 5.57; N, 10.04; S, 11.38.

The filtrate from the crude **32** was concentrated *in vacuo* to a volume of 50 ml., refrigerated, and the solid that separated was filtered to give 4.5 g. of a waxy semi-solid. A tlc of this material revealed it to be a mixture of several components. It was dissolved in 100 ml. of heptane and the solution allowed to cool to 20°. The solution was decanted from an oil that had separated, and the solution was then refrigerated to give 1.6 g. of solid, m.p. 82-87°; tlc showed the solid to be a mixture of 3 components. The solid, 1.5 g., was dissolved in 10 ml. of acetonitrile at the b.p. and the solution was treated with a solution of 0.5 g. of fumaric acid in 5 ml. of boiling 95% ethanol. A crystalline solid separated promptly. The mixture was stirred and heated under reflux for 2 hours and the hot solution filtered from the insoluble solid. That solid was dried and weighed 0.8 g., m.p. 142-168°. Recrystallization from 80 ml. of acetonitrile (see below, for filtrate) gave 0.55 g. of the fumaric acid salt of **33**, m.p. 178-180°.

Anal. Calcd. for $C_{16}H_{18}N_4O \cdot 0.5C_4H_4O_4$: C, 63.44; H, 5.92; N, 16.46. Found: C, 63.10; H, 5.70; N, 16.49.

The salt, 0.2 g. was distributed between 5 ml. of dichloromethane and 5 ml. aqueous sodium bicarbonate solution. The dichloromethane solution was separated, washed with water, dried, and concentrated to give a residual solid; that solid was recrystallized from pentane to give 0.10 g. of **33**, m.p. 113-116°. R_f [acetone:benzene (1:1)] (one spot] *ca.* 0.9; ir (deuteriochloroform): ν 3420(w), 1630(m), 1565(s), 1515(s), 1490(m), 1440(s) cm^{-1}; pmr (deuteriochloroform): δ 2.45 [s, 9H, 3(CH_3)], 4.70 (s, 2H, CH_2), 6.50-8.20 (m, 6H, 6 Py-*H*), 11.60-11.85 [m, 1H, NH (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.42; N, 19.89; M^+, 282. Found: C, 67.78; H, 6.53; N, 19.55; M^+, 282.

The acetonitrile filtrate from the fumaric acid salt of **33** was concentrated to a volume of 40 ml. and refrigerated. The solid that separated was filtered and dried to give 0.40 g. of material,

m.p. 138-146°. Recrystallization from 10 ml. of acetonitrile gave 0.18 g. (1% yield) of the fumaric acid salt of **21**, m.p. 149-151°; R_f [acetone:benzene (1:1)] of the base, **21**, obtained by treatment of the salt with aqueous sodium bicarbonate, showed one spot, *ca.* 0.60; ir (mull): ν 1715(m), 1690(s), 1630(m), 1585(w), 1550(w), 1450(s) cm^{-1}; pmr (DMSO-d_6): δ 2.25 (s, 3H, CH_3 at position -2), 2.90 (s, 3H, CH_3 at position -6), 6.10 (s, 1H, *H* at position -3), 6.17 (s, 1H, 1 vinylic *H*), 6.65-7.80 (m, 3H, 3 Ph-*H*), (no downfield signal in δ 8.0-10.0), 10.15-11.50 (m, 1H, CO_2H).

Anal. Calcd. for $(C_{10}H_{10}N_2O)_2 \cdot C_4H_4O_4$: C, 62.06; H, 5.20; N, 12.06. Found: C, 61.56; H, 5.55; N, 12.39.

The salt, 0.12 g., was suspended in 5 ml. of water, the solution saturated with solid sodium bicarbonate, and the solution extracted with two 10 ml. portions of methylene chloride. The solid recovered from the combined dried methylene chloride extracts was concentrated to give 0.05 g. of **21**, m.p. 99-101°, R_f [acetone:benzene (1:1)], one spot, *ca.* 0.50; ir (potassium bromide): ν 1700(s), 1630(s), 1580(w), 1550(m), 1480(s), 1470(s), 1450(s), 1420(m) cm^{-1}; pmr (deuteriochloroform): δ (s, 3H, CH_3 at position -2), 3.05 (s, 3H, CH_3 at position -6), 6.15 (s, 1H, *H* at position -3), 6.45-7.65 (m, 3H, 3 Py-*H*) (no other downfield signals).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 68.94; H, 5.78; N, 16.08. Found: C, 68.55; H, 5.51; N, 15.79.

(c) Preparation of Authentic **32**

To a solution of 1.0 g. (0.01 mole) of 2-amino-6-methylpyridine in 10 ml. of boiling acetonitrile was added a boiling solution of 1.90 g. (0.01 mole) of **12**·H_2O in 10 ml. of acetonitrile, in one portion. The product separated from the cooled solution and was filtered to give 2.30 g. of crude **32**, m.p. 133-135°. Recrystallization from 50 ml. of acetonitrile gave 1.50 g. (53%) of pure **32**, m.p. unchanged at 135-137°.

Anal. Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.68; H, 5.75; N, 9.98; S, 11.44; Found: C, 55.70; H, 5.66; N, 10.15; S, 11.29.

7-Chloro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**50**).

(a) 2-(Acetoacetamido)-5-chloropyridine (**51**) and *N*-[(5-Chloro-2-pyridinyl)]-3-[(5-chloro-2-pyridinyl)imino]butaneamide (**52**).

To a solution of 12.5 g. (0.1 mole) of 2-amino-5-chloropyridine in 600 ml. of anhydrous toluene at 100° was added, in 10 minutes, 10.0 g. (0.12 mole) of diketene; subsequently, the mixture was stirred and heated under reflux for 1.5 hours, filtered, and the filtrate cooled to give 9.6 g. of solid A, m.p. 115-120° but not clear to 230°. The filtrate was concentrated, *in vacuo* to a volume of 50 ml., cooled, and filtered to give 4.9 g. of solid B, m.p. 110-140°. Solids A and B were shown by tlc to contain the same three components, hence were combined and extracted with 1400 ml. of boiling diisopropyl ether (see below) and filtered from 1.20 g. of crude **52**, m.p. 205-210°. Recrystallization from 150 ml. of toluene gave 0.80 g. (5% yield) of **52**, m.p. 241-243° dec.; ir (potassium bromide): ν 3260(m), 1655(s), 1640(s), 1590(s), 1530(s), 1490(s), 1475(s), 1460(s), 1430(m) cm^{-1}; a pmr spectrum with good resolution could not be obtained, since **52** was essentially insoluble in all solvents, including DMSO.

Anal. Calcd. for $C_{14}H_{12}Cl_2N_4O$: C, 52.03; H, 3.74; N, 17.34; Cl, 21.94. Found: C, 52.04; H, 3.70; N, 17.49; Cl, 22.12.

Refrigeration of the above diisopropyl ether extracts gave 6.1 g. of solid C, m.p. 155-160° (turbid); concentration of the filtrate from the 6.1 g. to a volume of 225 ml. and refrigeration gave 3.5 g. of solid D, m.p. 110-112°. Recrystallization of solid D from 325 ml. of diisopropyl ether gave 0.6 g. of solid E, m.p. 158-161°. Solids C and E were combined and recrystallized from 670 ml. of diisopropyl ether (see below) to give 5.8 g. of solid, m.p. 158-161° (turbid); a second recrystallization from 100 ml. of ethyl acetate gave 5.3 g. (25% yield) of **51**, m.p. 158-160°; ir (potassium bromide): ν 3215(s), 1715(s), 1685(s), 1660(s), 1590(s), 1570(s), 1535(s), 1455(s), 1410(s) cm^{-1}; pmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3CO), 3.60 (s, 2H, CH_2CO), 7.65 [q (J = 9,3 Hz), 1H, *H* at position -4], 8.00-8.75 (m, 2H, 2 Py-*H* at positions -3 and -6), 9.25-9.70 [m, 1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_9H_9ClN_2O_2$: C, 50.85; H, 4.27; N, 13.18; Cl, 16.68. Found: C, 50.82; H, 4.13; N, 13.32; Cl, 16.91.

(b) 7-Chloro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**50**).

A solution of 4.2 g. (0.02 mole) of **51**, 0.3 g. of **12**, and 300 ml. of anhydrous toluene was heated under reflux under a calcium hydride trap for 18 hours and then refrigerated. The crystals that separated were filtered to give 1.70 g. of solid, m.p. 165-167°. The filtrate was concentrated to dryness, the residual solid, 2.1 g. after trituration with 25 ml. of diisopropyl ether, was combined with the 1.70 g., and the combined solids recrystallized from 350 ml. of diisopropyl ether to give 2.5 g. (64% yield) of **50**, m.p. 165-167°; ir (potassium bromide): ν 1700(s), 1670(s), 1560(s), 1525(s), 1470(s), 1440(s), 1420(s) cm^{-1}; pmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3 at position -2), 6.35 (s, 1H, *H* at position -3), 7.20-7.85 (m, 2H, 2*H* at positions -8 and -9), 9.05 (s, 1H, *H* at position -6).

Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.52; H, 3.63; N, 14.39; Cl, 18.21; Found: C, 55.35; H, 3.51; N, 14.26; Cl, 17.96.

2-(Acetoacetamido)-6-pyridinol (**34**).

To a suspension of 5.5 g. (0.05 mole) of 2-amino-6-pyridinol in 700 ml. of reagent grade toluene, under reflux, was added, in 0.75 hour, 5.5 g. (0.055 mole) of diketene in 40 ml. of toluene. Heating under reflux was continued for 0.5 hour when a clear solution was formed, followed almost immediately by the separation of a brown tar. At this point, the hot solution was filtered and the filtrate cooled to give 6.4 g. of crude **34**, m.p. 165-168° dec. Recrystallization from 320 ml. of acetonitrile gave 5.3 g. (54%) yield of pure **34**, m.p. 166-168° dec.; ir (potassium bromide): ν 3420(w), 1720(s), 1675(m), 1650(s), 1575(s), 1550(s), 1530(s), 1520(s), 1460(s) cm^{-1}; pmr (DMSO-d_6): δ 2.15 (s, 3H, CH_3 at position -2), 3.58 (s, 2H, CH_2), 6.30-7.75 (m, 3H, 3 Py-*H*), 10.30 (s, 1H, *HO*), 10.62 (s, 1H, N*H*).

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.20; N, 14.43; N.E., 194. Found: C, 55.49; H, 5.33; N, 14.30; N.E. (NaOH), 203.

Attempted Cyclization of **34** to **32**

A suspension of 1.30 g. (0.007 mole) of **34**, 0.09 g. of **12**, and 800 ml. of reagent grade toluene were heated under a calcium hydride trap as described above. After 1.5 hours of heating, no more water was evolved. Workup gave a non-crystalline gum that consisted of at least six components; 0.24 g. of **34** was recovered.

9-Hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**10**).

(a) 2-(Acetoacetamido)-3-pyridinol (**11**) and its Maleic Acid Salt.

To a suspension of 5.50 g. (0.05 mole) of **7** in 700 ml. of reagent grade toluene, under reflux, was added 5.0 g. (0.055 mole) of diketene in 25 ml. of toluene, in 0.25 hour. The mixture was stirred and heated, subsequently, under reflux, filtered, and the filtrate concentrated to dryness to give 10.2 g. of a residual oil that crystallized on keeping. A portion of the crude solid, m.p. 100-105°, 3.6 g., was recrystallized from 50 ml. of toluene to give 1.5 g. (41% yield) of **11**, m.p. 105-107°; ir (potassium bromide): ν 3460-3360 (broad w), 1710(w), 1640(s), 1620(s), 1560(s), 1500(s), 1450(s), 1430(s), 1415(s) cm^{-1}; pmr (DMSO-d_6): δ 2.30 (s, 3H, CH_3 at position -2), 3.82 (s, 3H, CH_3), 7.00-8.15 (m, 3H, 3 Py-*H*), 9.75-10.90 (m, 2H, N*H* + O*H*).

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.20; N, 14.43; N.E., 194. Found: C, 55.65; H, 5.20; N, 14.43; N.E. ($HClO_4$), 205.

To a solution of 2.00 g. (0.01 mole) of **11** in 20 ml. of boiling acetonitrile was added, in one portion, a boiling solution of 2.20 g. (0.02 mole) of maleic acid in 20 ml. of acetonitrile. The salt separated from the cooled reaction mixture; it was filtered to give 2.20 g. of solid, m.p. 128-129° dec. Recrystallization from 50 ml. of acetonitrile gave 1.90 g. of the maleic acid salt of **11**, m.p. 135-136° dec.

Anal. Calcd. for $C_9H_{10}N_2O_3 \cdot C_4H_4O_4$: C, 50.30; H, 4.55; N, 9.03; N.E., 310. Found: C, 50.33; H, 4.50; N, 9.30; N.E. 313.

(b) 9-Hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**10**).

A solution of 5.0 g. (0.025 mole) of **11**, in 150 ml. of reagent grade toluene was heated under a calcium hydride trap for 24 hours; continuous tlc monitoring of the reaction mixture showed no change [acetone:benzene-1:1, R_f of **11** was *ca.* 0.53]. Following the addition of 0.30 g. of **12**, and continuing the heating, formation of water was seen promptly, and after 30 hours, tlc showed only one spot, R_f *ca.* 0.24. Workup of the reaction mixture gave 3.80 g. (84% yield) of **10**, m.p. 138-140°, identical in all respects with an authentic sample (2b).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.81. Found: C, 61.19; H, 4.48; N, 16.01.

9-Chloro-2,7-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**37**).

(a) 2-(Acetoacetamido)-3-chloro-5-methylpyridine (**36**).

To a solution of 28.5 g. (0.2 mole) of 2-amino-3-chloro-5-methylpyridine (**12**) in 250 ml. of reagent grade toluene at 90° was added 19.0 g. (0.022 mole) of diketene in 0.33 hour. Reaction under reflux was complete in 1 hour. The mixture was concentrated to dryness *in vacuo* and the residual oil, 47.0 g., was triturated with 500 ml. of pentane to give 40.5 g. of **36**, m.p. 77-79°. An analytical sample, recrystallized from diisopropyl ether had a m.p. 81-83°; ir (potassium bromide): ν 3330(w), 3240(w), 3220(m), 3130(w), 3040(w), 2980(w), 2850(w), 1720(s), 1660(s), 1590(w), 1560(m), 1480(s) cm^{-1}; pmr (deuteriochloroform): δ 2.27 [s, 6H, 2(CH_3)], 3.80 (s, 2H, CH_2), 7.52 [d (J = 3 Hz), 1H, *H* at position -4], 8.07 [d (J = 3 Hz), 1H, *H* at position -6], 8.70-9.15 [m, 1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{10}H_{11}ClN_2O_2$: C, 52.98; H, 4.89; N, 12.36; Cl, 15.64. Found: C, 53.00; H, 4.93; N, 12.30; Cl, 15.52.

(b) 9-Chloro-2,7-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**37**).

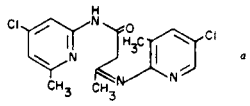
A solution of 9.0 g. (0.04 mole) of **36**, 0.2 g. of **12**, and 400 ml. of reagent grade toluene was heated under the calcium hydride trap for 24 hours; tlc indicated the formation of a complex mixture of products. The reaction mixture was concentrated to dryness *in vacuo* to give 7.2 g. of a dark semi-solid residue. During the concentration, a white crystalline compound sublimed and this was shown to be 2-amino-3-chloro-5-methylpyridine, a degradation product. The residue was dissolved in 10 ml. of acetonitrile and refrigerated to give 1.8 g. of solid, m.p. 122-155° dec. This solid was dissolved in 50 ml. of boiling acetonitrile and cooled. The solid that crystallized, 0.35 g., was a mixture of products. The acetonitrile filtrate was concentrated to 5 ml. and cooled to give 0.90 g. of solid, m.p. 141-147°. Recrystallization from 100 ml. of diisopropyl ether gave 0.70 g. (9% yield) of **37**, m.p. 158-160°; ir (deuteriochloroform): ν 1680(s), 1640(s), 1600(w), 1560(m), 1530(s), 1460(s), 1430(s) cm^{-1}; pmr (deuteriochloroform): δ 2.35 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 6.40 (s, 1H, *H* at position -3), 7.75 [d (J = 2 Hz), 1H, *H* at position -8], 8.80 [d (J = 2 Hz), 1H, *H* at position -6].

Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.55; H, 4.35; N, 13.43; Cl, 17.00. Found: C, 57.52; H, 4.48; N, 13.25; Cl, 16.94.

7-Chloro-2,9-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**39**).

(a) 2-(Acetoacetamido)-5-chloro-3-methylpyridine (**38**).

To a solution of 28.5 g. (0.2 mole) of 2-amino-5-chloro-3-methylpyridine (**12**) in 250 ml. of reagent grade toluene, at 90°, was added 19.0 g. (0.22 mole) of diketene in 0.33 hour. Subsequently, the mixture was heated under reflux for 0.5 hour and concentrated to dryness *in vacuo*. The viscous residue, 55.0 g., was extracted with two 200 ml. portions of boiling pentane and then gave 37.0 g. of solid, m.p. 62-112°. This was dissolved in 300 ml. of boiling acetonitrile and the solution cooled to give 2.6 g. (8% yield) of the by-product, *a*, m.p. 180-181° dec.; ir (potassium bromide): ν 3250(m), 3160(w), 3080(w), 2980(w),



a

2930(w), 1650(s), 1590(m), 1580(m), 1570(m), 1530(m), 1480(s), 1460(s), 1420(s) cm^{-1}; pmr (deuteriochloroform): δ 2.30 [2s, 6H, 2(Py-CH_3)], 2.50 (s, 3H, CH_3), 5.27 (s, 2H, CH_2), 7.35, 7.52 (2d (J = 3 Hz), 2H, 2 Py-*H* at 2 positions -4], 8.05, 8.27 [2d (J = 3 Hz), 2H, 2 Py-*H* at 2 positions -6], 11.70-11.90 [broad s, 1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{16}H_{16}Cl_2N_4O$: C, 54.70; H, 4.59; N, 15.95; Cl, 20.16; Found: C, 54.99; H, 4.24; N, 15.84; Cl, 20.46.

The acetonitrile filtrate from (a) was concentrated to dryness *in vacuo* to give 38.0 g. of an oily solid, m.p. 70-80°. This was extracted with 200 ml. of boiling pentane to give 32.0 g. of solid, m.p. 77-82°. Recrystallization from 1500 ml. of diisopropyl ether gave 23.6 g. (52% yield) of **38**, m.p. 81-83°, ir (potassium bromide): ν 3260(s), 3080(w), 3040(w), 3000(w), 2960(w), 2920(w), 1730(s), 1670(s), 1600(m), 1580(m), 1530(s), 1470(m), 1430(m), 1420(m) cm^{-1}; pmr (deuteriochloroform): δ 2.20 (s, 3H, CH_3 at position -3), 2.25 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 7.50 [d (J = 3 Hz), 1H, *H* at position -4], 8.15 [d (J = 3 Hz), 1H, *H* at position -6], 9.05-9.50 [broad s, 1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{10}H_{11}ClN_2O$: C, 52.98; H, 4.89; N, 12.06; Cl, 15.64. Found: C, 53.16; H, 4.85; N, 12.28; Cl, 15.54.

7-Chloro-2,9-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**39**).

A solution of 4.50 g. (0.02 mole) of **38**, 0.1 g. of **12**, and 300 ml. of reagent grade toluene was heated under a calcium hydride trap for 24 hours and then concentrated to dryness *in vacuo*. The residue was triturated with 20 ml. of acetonitrile to give 1.90 g. of solid, m.p. 172-174° dec., and this solid was recrystallized from 35 ml. of acetonitrile to give 1.30 g. (31% yield) of **39**, m.p. unchanged at 172-174° dec.; ir (potassium bromide): 3110(m), 3040(m), 2980(w), 2960(w), 2220(w), 1700(s), 1630(s), 1580(m), 1540(s) cm^{-1}; pmr (deuteriochloroform): δ 2.45 [2s, 6H, 2(CH_3) at positions -2 and -9], 6.35 (s, 1H, *H* at position -3), 7.50 [d (J = 2 Hz), 1H, *H* at position -8], 8.95 [d (J = 2 Hz), 1H, *H* at position -6].

Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.55; H, 4.35; N, 13.43; Cl, 17.00. Found: C, 57.78; H, 4.36; N, 13.68; Cl, 17.14.

7,9-Dichloro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (**41**).

The intermediate 2-acetoacetamido derivative, **40**, was formed from 7.5 g. (0.046 mole) of diketene in 200 ml. of anhydrous toluene by the procedure described above, but was not isolated.

Subsequently, 0.3 g. of **12** was added and the mixture stirred and heated under reflux under a calcium hydride still head for 56 hours. The hot solution was clarified by filtration and the filtrate concentrated to dryness *in vacuo*. The residue, 9.0 g., was recrystallized from 500 ml. of diisopropyl ether to give 4.2 g. (41% yield) of **41**, m.p. 152-154°; ir (potassium bromide): ν 1690(s), 1675(s), 1645(w), 1610(s), 1560(s), 1520(s), 1460(s) cm^{-1}; pmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3 at position -2), 6.42 (s, 1H, *H* at position -3), 7.87 [d (J = 3 Hz), 1H, *H* at position -8], 9.00 [d (J = 3 Hz), 1H, *H* at position -6].

Anal. Calcd. for $C_9H_6Cl_2N_2O$: C, 47.16; H, 2.64; N, 12.22; Cl, 30.94. Found: C, 47.01; H, 2.48; N, 12.43; Cl, 30.92.

7,9-Dibromo-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**43**).

(a) Ethyl 3-[(3,5-dibromo-2-pyridinyl)amino]-2-butenoate (**42**).

This intermediate was prepared by the procedure of Adams and Pachter (5). The yield was 51%, m.p. 106-108°. The identity of this product as an enamine has now been confirmed by spectral means; ir (potassium bromide): ν 3430(m), 1660(s), 1625(s), 1600(m), 1560(s), 1540(m), 1490(s), 1470(w), 1430(s) cm^{-1}; pmr (deuteriochloroform): δ 1.30 [t (J = 6 Hz), 3H, CH_3CH_2], 2.48 (s, 3H, CH_3C=CH), 4.20 [q (J = 12.7 Hz), 2H, CH_3CH_2], 4.95 (s, 1H, CH_3C=C*H*), 7.93 [d (J = 3 Hz), 1H, *H* at position -4], 8.22 [d (J = 3 Hz), 1H, *H* at position -6].

Anal. Calcd. for $C_{11}H_{12}Br_2N_2O_2$: C, 36.29; H, 3.32; N, 7.70; Br, 43.90. Found: C, 36.25; H, 3.10; N, 7.94; Br, 44.19.

Passage of **42** through a column of activated silica gel as described for **18** resulted only in the isolation of 2-amino-3,5-dibromopyridine.

(b) 7,9-Dibromo-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**43**) and *N*-(3,5-Dibromo-2-pyridinyl)-3-[(3,5-dibromo-2-pyridinyl)-imino]butanamide (**53**).

The procedure described for the corresponding dichloro derivative, **41**, was employed with 12.6 g. (0.05 mole) of 2-amino-3,5-dibromopyridine, 4.6 g. (0.055 mole) of diketene, and 600 ml. of anhydrous toluene. Following the usual reflux period, 0.5 g. of **12** was added and heating under a calcium hydride still head, under reflux, continued for 36 hours. Concentration, *in vacuo*, to dryness gave 14.5 g. of oily residue. This was extracted with 100 ml. of dichloromethane and filtered from 0.1 g. of solid, m.p. 195-197° dec. The dichloromethane solution was concentrated *in vacuo* to give 12.7 g. of a waxy solid; trituration with 25 ml. of cold acetonitrile gave 4.3 g. of material, m.p. 143-147°. The latter was extracted with 200 ml. of boiling acetonitrile; 0.5 g., m.p. 192-200° dec. was insoluble and 0.3 g., m.p. 205-206°, crystallized in the filtrate (see below). The combined three solids, 0.9 g., were recrystallized form 50 ml. of toluene to give 0.6 g. of **53**, m.p. 209-211° dec.; ir (potassium bromide): ν 3370(m), 1620(s), 1564(s), 1540(m), 1480(s), 1465(s), 1445(s) cm^{-1}; pmr (DMSO-d_6): δ 2.42 (s, 3H, CH_3C=N), 3.25 (s, 2H, CH_2), 5.20 (s, 1H, =CH), 8.30 (s, 2H, 2-Py-*H* at positions -4 and 4'), 8.50 [q (J = 6,6 Hz), 2H, 2-Py-H at positions -6 and 6'), 13.2 [s, 1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{14}H_{10}Br_4N_4O$: C, 29.51; H, 1.77; N, 9.83; Br, 56.09. Found: C, 29.62; H, 1.87; N, 9.89; Br, 56.50.

The above acetonitrile filtrate was concentrated *in vacuo* to give 3.0 g. of solid, m.p. 152-157°. Recrystallization from 125 ml. of diisopropyl ether gave 2.2 g. (14% yield) of **43**, m.p. 163-165°; ir (mull): 1700(s), 1660(m), 1600(m), 1560(w), 1520(m), 1450(s) cm^{-1}; pmr (deuterium oxide): δ 2.50 (s, 3H, CH_3 at position -2), 6.43 (s, 1H, *H* at position -3), 8.12 [d (J = 1.5 Hz), 1H, *H* at position -8), 9.12 [3 (J = 1.5 Hz), 1H, *H* at position -6].

Anal. Calcd. for $C_9H_6Br_2N_2O$: C, 33.99; H, 1.91; N, 8.81; Br, 50.26; N.E., 318. Found: C, 33.86; H, 1.76; N, 8.88; Br; 50.46; N.E. ($HClO_4$), 323.

Attempted Isomerization of 2-Acetoacetamido-4,6-dimethylpyridine (**54**) with **12**; Isolation of *N*-4,6-Dimethyl-2-pyridinyl)-2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxamide (**45**).

(a) 2-Acetoacetamido-4,6-dimethylpyridine (**54**) and its Maleate Salt (1:1).

This product has been described as an oil; while the elemental analyses were given, no physical properties were reported (11).

The reaction was carried out as described above between 31.0 g. (0.25 mole) of 2-amino-4,6-dimethylpyridine, **55**, 23.0 g. (0.27 mole) of diketene, in 250 ml. of reagent grade toluene. A portion of the crude residue, 47.0 g., was distilled *in vacuo* to give, first, trace amounts of unreacted **55** followed by **54**, b.p. 173-175° (0.3 mm); ir (deuteriochloroform): ν 3400(m), 3300(w), 3020(m), 2960(w), 2920(w), 1715(s), 1680(s), 1650(m), 1620(s), 1570(s), 1530(s), 1430(s) cm^{-1}; pmr (deuteriochloroform): δ 2.35 [s 6H, 2(CH_3) at positions -4 and -6], 2.45 (s, 3H, CH_3CO), 3.50 (s, 2H, CH_2), 7.25 (s, 1H, *H* at position -5), 7.80 (s, 1H, *H* at position -3), 8.75 [m, 1H, NH (exchanges with deuterium oxide)], R_f *ca.* 0.70 [acetone:benzene (1:1)].

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.07; H, 6.84; N, 13.56. Found: C, 64.24; H, 6.87; N, 13.36.

To a hot solution of 2.0 g. (0.01 mole) of crude **54** in 20 ml. of 2-butanone was added, in one portion 2.2 g. (0.02 mole) of maleic acid in 20 ml. of hot 2-butanone. The solid that separated on cooling was filtered to give 3.0 g. of the crude salt; recrystallization from 25 ml. of acetonitrile gave 2.60 g. (80% yield) of the maleate salt of **54**, m.p. 140-142° dec.

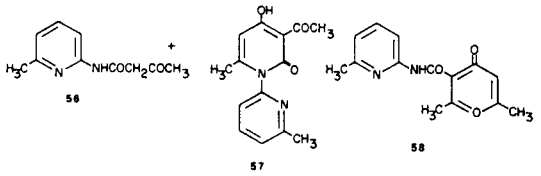
Anal. Calcd. for $C_{11}H_{14}N_2O_2 \cdot C_4H_4O_4$: C, 55.90; H, 5.56; N, 8.72; N.E., 161, 322. Found: C, 56.15; H, 5.51; N, 8.66; N.E. (NaOH), 154; N.E. ($HClO_4$), 318.

(b) Attempted Isomerization of **54**. Formation of **45**.

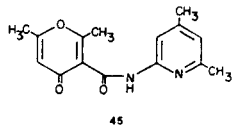
A solution of 41.0 g. (0.2 mole) of crude **54**, 1.0 g. of **12**, and 400 ml. of reagent grade toluene was heated under a calcium hydride trap for 24 hours; at that time, tlc [same system as in (a)] showed a major spot at R_f *ca.* 0.70 and a minor spot at R_f *ca.* 0.80. An additional 1.0 g. of **12** was added and the heating continued for an additional 64 hours, when tlc showed the presence of 6 components. The solution was refrigerated and the crystals that separated were filtered to give 6.0 g. of solid, m.p. 168-190°. Successive recrystallizations from 100 ml. and 60 ml. of acetonitrile gave 2.60 g. of solid, m.p. 197-199° dec., that was contaminated with a trace of a sulfur containing impurity. The 2.60 g. were dissolved in 100 ml. of dichloromethane and the solution washed with 5% aqueous sodium carbonate solution, then water, the organic phase dried and concentrated to give 2.2 g. of solid, m.p. 196-198° dec. Recrystallization of that material from 30 ml. of acetonitrile gave 1.5 g. (3% yield) of **45**, m.p. 198-200° dec., tlc single spot, R_f *ca.* 0.75 [same system as in (a)]; ir (potassium bromide): ν 3580-3350(broad m), 1680(s), 1660(m), 1615(m), 1600(m), 1570(m), 1535(s), 1430(s) cm^{-1}; pmr (deuteriochloroform): δ [s, 6H, 2(CH_3)$_2$ at 4,6-positions in Py], 2.42, 2.80 [2s, 6H, 2(CH_3) in positions -6 and -2, respectively, in pyran], 6.27 (s, 1H, Py-*H* at position -5), 6.72 (s, 1H, Py-*H* at position -3), 7.87 (s, 1H, *H* at position -5 in pyran), 12.05 [broad s, 1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; N.E., 272; M^+, 272. Found: C, 65.91; H, 5.79; N, 10.27; N.E. ($HClO_4$), 266; M^+, 272.

The assignment of structure to **45** is based on the work of Kato, and his co-workers (10), who reported that the reactions of ketene with monomethylated 2-aminopyridines gave three products,



i.e., **56**, **57**, and **58** were obtained with 2-amino-6-methylpyridine. Compounds **57** and **58** are isomers; their pmr spectra could be used to differentiate their structures. Thus, Kato assigned the singlet at *ca.* δ 12.0 to the NH proton of **58** and the singlet at *ca.* δ 15.8 to the enolate proton in **57**. The pmr spectrum of **45** showed a singlet at δ 12.05, and must, therefore, have the structure shown below. The mechanism for the formation of **45** is not known.



3-[(*o*-Bromobenzyl)oxy]-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**15**).

(a) 2-(Acetoacetamido)-3-[(*o*-bromobenzyl)oxy]pyridine (**59**).

To a solution of 16.5 g. (0.065 mole) of 2-amino-3-[(*o*-bromobenzyl)oxy]pyridine (**13**) in 600 ml. of toluene, at 100-105°, was added 6.0 g. (0.071 mole) of diketene during 0.25 hours, and, subsequently, the mixture was stirred and heated under reflux for 1 hour. The reaction mixture was concentrated *in vacuo* to a volume of 200 ml. and refrigerated. The solid that separated was filtered and dried to give 18.8 g. of crude **59**, m.p. 136-138°. It was recrystallized from 190 ml. of acetonitrile to give 16.4 g. (70% yield) of **59**, m.p. 138-140°. ir (potassium bromide): ν 3250(m), 1720(s), 1660(s), 1590(m), 1575(m), 1520(s), 1470(m), 1450(s) cm^{-1}; pmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3CO), 3.95 (s, 2H, CH_2CO), 5.18 (s, 2H, CH_2Ph), 6.25-8.20 (m, 7H, 4 Ar-*H* plus 3 Py-*H*), 8.60-8.85 [m, 1H, NH (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{16}H_{15}BrN_2O_3$: C, 52.91; H, 4.17; N, 7.72; Br, 22.01. Found: C, 52.78; H, 3.88; N, 7.75; Br, 22.23.

(b) 3-[(*o*-Bromobenzyl)oxy]-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**15**).

A solution of 7.2 g. (0.02 mole) of **59**, 0.20 g. of **12**, and 350 ml. of anhydrous toluene was heated under a calcium hydride still head for 18 hours; tlc monitoring showed that the major component was the unchanged **59**. The mixture was refrigerated. The solid that separated was filtered to give 0.50 g. of solid, m.p. 185-190°. Recrystallization from 30 ml. of acetonitrile gave the *p*-toluenesulfonic acid salt of 2-amino-3-[(*o*-bromobenzyl)oxy]-pyridine, m.p. 191-192°.

Anal. Calcd. for $C_{19}H_{19}BrN_2O_4S$: C, 50.55; H, 4.23; N, 6.21; Br, 17.66; S, 7.10. Found: C, 50.56; H, 4.07; N, 6.48; Br, 17.79; S, 7.36.

The filtrate from the above solid was concentrated *in vacuo* to give 7.0 g. of an oil that could not be induced to crystallize. It was dissolved in 100 ml. of benzene and chromatographed on 210 g. of activated alumina (MCB, 200 mesh, Chromatographic Grade). Elution with ethyl acetate gave 2.4 g. of a solid, m.p. 85-105° that resisted further purification. A sample in tetrahydrofuran when subjected to glc analysis showed the presence of **15** and 2-amino-[3-(*o*-bromobenzyl)oxy]pyridine in a ratio of 1:3; however, since **59** was not detectable in this glc system employed, the yield of **15** cannot be estimated.

2-Aminopyridine, Fumaric Acid Salt (1:1) (**60**).

Boiling solutions of 0.90 g. (0.01 mole) of 2-aminopyridine in 10 ml. of absolute ethanol and 2.30 g. (0.02 mole) of fumaric acid in 20 ml. of 95% ethanol were mixed, the solution allowed to cool, and the solid that separated was filtered to give 1.80 g. of material, m.p. 188-189° dec. Recrystallization from 100 ml. of 2-propanol gave 1.50 g. (75% yield) of **60**, m.p. unchanged at 188-189°; ir (potassium bromide): ν 3315(s), 3080(s), 1670(s), 1630(s), 1575(s), 1545(s), 1490(s), 1430(m) cm^{-1}.

Anal. Calcd. for $C_5H_4N_2 \cdot C_4H_4O_4$: C, 51.42; H, 4.80; N, 13.33; N.E., 210. Found: C, 51.44; H, 4.73; N, 13.33; N.E. ($HClO_4$), 210.

2-Aminopyridine, Maleic Acid Salt (2:3) (**61**).

The reaction was carried out between hot solutions of 1.88 g. (0.02 mole) of 2-aminopyridine in 18 ml. of reagent grade 2-butanone and 4.24 g. (0.04 mole) of maleic acid in 46 ml. of 2-butanone. The crude product, 5.3 g., m.p. 112-115° was recrystallized form 100 ml. of acetonitrile to give 4.40 g. (83% yield) of **61**, m.p. 114-116° dec.; ir (potassium bromide): ν 3320(m), 3140(s), 1720(s), 1700(s), 1670(s), 1640(s), 1620(s), 1500(s), 1380(s) cm^{-1}.

Anal. Calcd. for $C_5H_6N_2 \cdot 1.5C_4H_4O_4$: C, 49.25; H, 4.54; N, 10.54; N.E., 268. Found: C, 49.17; H, 4.34; N, 10.67; N.E. ($HClO_4$), 262.

2-Aminopyridine, Oxalic Acid Salt (1:1) (**62**).

To 1.10 g. (0.011 mole) of 2-aminopyridine in 10 ml. of reagent grade acetonitrile, at the b.p. was added a hot solution of 2.20 g. (0.24 mole) of oxalic acid in 35 ml. of acetonitrile. The salt separated promptly from the hot solution. Following refrigeration, the solid was filtered to give 2.50 g. of material m.p. 123-125°; recrystallization from 450 ml. of acetonitrile gave 1.60 g. (88% yield) of **62**, m.p. 154-155°; ν (potassium bromide): 3425(w), 3100-2780(multiplet of m signals), 1700(s), 1650(s), 1640(s), 1630(s), 1615(s), 1570(s), 1500(s) cm^{-1}.

Anal. Calcd. for $C_5H_6N_2 \cdot C_2H_2O_4$: C, 45.65; H, 4.38; N, 15.21; N.E., 184. Found: C, 45.88; H, 4.29; N, 15.21; N.E. ($HClO_4$), 184.

2-Amino-3-methylpyridine, Maleic Acid Salt (1:1.5) (**63**).

To 1.10 g. (0.01 mole) of 2-amino-3-methylpyridine in 10 ml. of reagent grade 2-butanone, at the b.p., was added, in one portion, a hot solution of 2.30 g. (0.02 mole) of maleic acid in 20 ml. of 2-butanone. The solution was refrigerated and the solid that separated was filtered and dried *in vacuo* to give 2.20 g. (78% yield) of **63**, m.p. 145-146° dec.; ir (potassium bromide): ν 3330(m), 3150(m), 1710(s), 1665(s), 1645(s), 1620(s), 1570(m), 1495(s), 1470(s) cm^{-1}.

Anal. Calcd. for $C_6H_8N_2 \cdot 1.5C_4H_4O_4$: C, 51.06; H, 5.00; N, 9.91; N.E., 282. Found: C, 51.14; H, 4.99; N, 10.18; N.E. ($HClO_4$), 278.

2-(Formamido)-3-methylpyridine, Maleic Acid Salt (1:2) (**64**).

(a) 2-(Formamido)-3-methylpyridine (**65**).

To 40.0 g. of crude phenyl formate (**14**) shown by glc to contain 24.5 g. (0.2 mole) of phenyl formate, at 5°, was added with stirring, in portions, a total of 16.0 g. (0.15 mole) of 2-amino-3-methylpyridine during 0.5 hour. The solution that formed was stirred at ambient temperature for 16 hours, 200 ml. of diisopropyl ether was added, and the solid filtered and dried to give 14.5 g. of solid, m.p. 128-130°. Recrystallization from 200 ml. of 2-propanol gave 11.5 g. of **65**, m.p. 132-134° (15); ir (potassium bromide): ν 3240(s), 1700(s), 1595(s), 1490(s), 1465(s), 1410(s)

cm^{-1}; pmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3), 6.80-8.25 (m, 3H, 3 Py-*H*), 8.25-9.05 [m, 1H, N*H* (equilibrates with deuterium oxide)], 9.50 [d (J = 10 Hz), 1H, C*H*O].

Anal. Calcd. for $C_7H_8N_2O$: C, 61.77; H, 5.92; N, 20.57, N.E., 136. Found: C, 61.46; H, 6.03; N, 20.29; N.E., ($HClO_4$), 137.

(b) 2-(Formamido)-3-methylpyridine, Maleic Acid Salt (1:2) (**64**).

Boiling solutions of 2.30 g. (0.02 mole) of maleic acid in 20 ml. of 2-butanone and 1.30 g. (0.01 mole) of the product from (a) in 10 ml. of 2-butanone were mixed rapidly, the whole allowed to cool, refrigerated, and the solid filtered to give 2.40 g. of solid, m.p. 78-80°. Recrystallization from 40 ml. of 2-butanone gave 1.60 g. (43% yield) of **64**, m.p. 81-83°.

Anal. Calcd. for $C_7H_8N_2O \cdot 2C_4H_4O_4$: C, 48.92; H, 4.38; N, 7.60; N.E., 92 and 368. Found: C, 49.13; H, 4.34; N, 7.86; N.E. (NaOH), 93; N.E. ($HClO_4$), 366.

2-(Acetamido)pyridine, Maleic Acid Salt (1:1) (**66**).

Prepared as above from 1.40 g. (0.01 mole) of 2-(acetamido)-pyridine in 14 ml. of 2-butanone and 2.30 g. (0.02 mole) of maleic acid in 25 ml. of 2-butanone; the yield of **66**, m.p. 112-114° dec., was 1.70 g. (68% yield); ir (potassium bromide): ν 3450-3280(broad m), 3150(s), 1725(m), 1710(m), 1670(s), 1625(s), 1550(m), 1480(m), 1410(s) cm^{-1}.

Anal. Calcd. for $C_7H_8N_2O \cdot C_4H_4O_4$: C, 52.39; H, 4.80; N, 11.11; N.E., 252. Found: C, 52.29; H, 4.76; N, 11.22; N.E. ($HClO_4$), 248.

2-Formamido-3-pyridinol, Maleic Acid Salt (1:1) (**67**).

Prepared as above, in 72% yield, **67** had a m.p. of 138-139°; ir (potassium bromide): ν 3350(m), 3100(s), 2880(s), 1685(s), 1645(s), 1615(s), 1570(s), 1505(s), 1480(s), 1450(s), 1415(s) cm^{-1}.

Anal. Calcd. for $C_6H_6N_2O_2 \cdot C_4H_4O_4$: C, 47.24; H, 3.94; N, 11.02; N.E., 254. Found: C, 47.51; H, 3.90; N, 11.28; N.E. ($HClO_4$), 258.

2-(acetoacetamido)pyridine, Maleic Acid Salt (1:1) (**68**).

Prepared as above in 69% yield, **68** had a m.p. 85-87°; ir (potassium bromide): ν 3420(m), 3170(m), 1730(s), 1635(s), 1615(s), 1580(s), 1525(s), 1440(s) cm^{-1}.

Anal. Calcd. for $C_9H_{10}N_2O_2 \cdot C_4H_4O_4$: C, 53.06; H, 4.80; N, 9.52; N.E., 294. Found: C, 53.18; H, 4.88; N, 9.68; N.E. ($HClO_4$), 292.

2-Acetoacetamido-3-pyridinol, Maleic Acid Salt (1:1) (**69**).

To a solution of 2.00 g. (0.01 mole) of **11** in 15 ml. of acetonitrile, at the b.p., was added a hot solution of 2.20 g. (0.02 mole) of maleic acid in 20 ml. of acetonitrile. The clear solution that formed was refrigerated to give 2.20 g. of solid, m.p. 128-129° dec. Recrystallization from 50 ml. of acetonitrile gave 1.90 g. (61% yield) of **69**, m.p. 135-136°; the ir spectrum in potassium bromide pellet showed poor resolution.

Anal. Calcd. for $C_9H_{10}N_2O_3 \cdot C_4H_4O_4$: C, 50.30; H, 4.55; N, 9.03; N.E., 310. Found: C, 50.33; H, 4.50; N, 9.30; N.E. ($HClO_4$), 313.

REFERENCES AND NOTES

(1) For earlier papers in this series, see (a) H. L. Yale, B. Toeplitz, J. Z. Gougoutas, and M. Puar, *J. Heterocyclic Chem.*, **10**, 123 (1973); (b) H. L. Yale and J. T. Sheehan, *ibid.*, **10**, 143 (1973); (c) H. L. Yale, *ibid.*, **11**, 739 (1974); (d) H. L. Yale, *ibid.*, **12**, 427 (1975); (e) H. L. Yale and E. R. Spitzmiller, *ibid.*, **13**, 797 (1976); (f) *idem.*, *ibid.*, **13**, 869 (1976).

(2) To whom inquiries should be addressed.

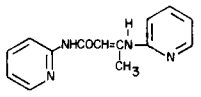
(3) S. N. Khitrick, *J. Gen. Chem. USSR*, **9**, 1109 (1939). The synthesis of these bicycles has been reviewed by W. L. Mosby in "Heterocyclic Systems with Bridgehead Nitrogen Atoms", Part 2, Interscience Publishers, Inc., New York, N.Y., 1961, pp. 1141-1153. The confusion in the earlier literature as to whether the annulation of a 2-aminopyridine by means of a 1,3-functionalized adduct led to the pyrimidin-2-one or -4-one, or , indeed, to the 1,8-naphthyridin-4-one continues even in contemporary literature; *cf.* K. Bowden and T. H. Brown, *J. Chem. Soc., C*, 2163 (1971).

(4) H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951). From our own observations, all attempts to cyclize 2-(acetoacetamido)pyridines thermally, lead frequently to the formation of dark colored, resinous materials and no identifiable products.

(5) The literature on the 1,8-naphthyridin-4-ones is quite extensive; *cf.*, R. Adams and I. J. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).

(6) H. L. Yale and M. Kalkstein, *J. Med. Chem.*, **10**, 334 (1967).

(7) References (3) and (4) have described the formation of *a* as a by-product of the reaction of 2-aminopyridine and ethyl acetacetate or 2-(acetoacetamido)pyridine and 2-aminopyridine. We have examined the pmr and mass spectra of **30** and the related derivative, **33**, and conclude that these criteria clearly establish that these compounds have the structures shown and not that suggested by *a*.



a

(8) V. F. Kucherov, *J. Gen. Chem.*, **20**, 1890 (1950), prepared **19** from 2-amino-5-bromopyridine and ethyl acetoacetate and reported a m.p. of 164-165°.

(9) We have shown (2e) that the diagnostic signal for the pyrido[1,2-*a*]pyrimidin-4-one heterocycle is the presence in the pmr spectrum of the singlet at *ca.* δ 6.25, the resonance of the proton at positions -3. In **21**, this signal was seen at δ 6.15. In addition, the second characteristic signal, that of a singlet at *ca.* δ 9.00 due to the proton at position -6, was absent in the spectrum of **21**.

(10) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.*, **20**, 133 (1972).

(11) M. C. Seidel, G. C. Van Tuyle, and W. D. Weir, *J. Org. Chem.*, **35**, 1476 (1970).

(12) T. J. Kress, L. L. Moore, and S. M. Costantino, *ibid.*, **41**, 93 (1976).

(13) H. L. Yale and J. Pluscec, *J. Org. Chem.*, **35**, 4254 (1970).

(14) H. L. Yale, *ibid.*, **36**, 328 (1971).

(15) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 603 (1945), prepared this compound by a different method and reported a m.p. of 138-139°.