9-Hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and Its Derivatives (1)

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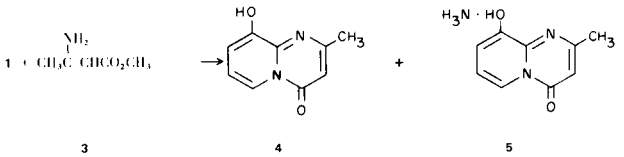
2-Amino-3-(*o*-bromobenzyloxy)pyridine (**1**) and ethyl acetoacetate gave 9-(*o*-bromobenzyloxy)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**) in 2% yield. When **1** and methyl β-aminocrotonate (**3**) were reacted, benzyl ether cleavage occurred and the products were 9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**4**) and its ammonium salt (**5**). These observations led to an alternative synthesis in which 2-amino-3-pyridinol (**6**) and either **3** or methyl acetoacetate, (**8**) in diethylbenzene at 185° gave **4** in 86 and 87% yields, respectively, and the anion of **4** and *o*-bromobenzyl bromide gave **2** in 61% yield. Even in diethylbenzene at 185°, **1** and **8** gave only trace amounts of **2**. Thus, *o*-bromobenzylation of the 3-hydroxyl group in **6** markedly decreased the reactivity of the amino group in **6** toward reactions with acetoacetic esters.

The reaction of 2-amino-3-picoline with ethyl acetoacetate has been reported to give 2,9-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, in very low yield (1). With this background, it was not unexpected to find that 2-amino-3-(*o*-bromobenzyloxy)pyridine (**1**) (3) and ethyl acetoacetate gave 9-(*o*-bromobenzyloxy)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**) in very low yield.

When large amounts of **2** were required for biological testing, an investigation was begun to develop a more practical synthesis of the compound.

Heating **1** and methyl β-aminocrotonate (**3**) first at 160-180° and then at 200-220° (4), resulted in the formation of a black fused mass that remained at the bottom of the reaction flask, and a small amount of yellow-colored sublimate that collected on the upper, cooler areas of the flask. The yellow-colored solid was shown to consist of a cyclohexane-soluble fraction that was identified as 9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**4**), m.p. 144-146°, and a cyclohexane-insoluble fraction that was shown to be the ammonium salt of **4**, namely **5**, m.p. 192-195°, with decomposition, to give **4**. Thus, cyclization had been accompanied by an unusual benzyl ether cleavage. It was apparent, furthermore, that the product **4** was a surprisingly strong acid that was capable of forming thermally stable salts with a weak base like ammonia, and,



as shall be shown below, with another weak base, 2-amino-3-pyridinol (**6**) (5). In addition, **4** and hydrogen bromide formed a stable *monohydrobromide* (**7**).

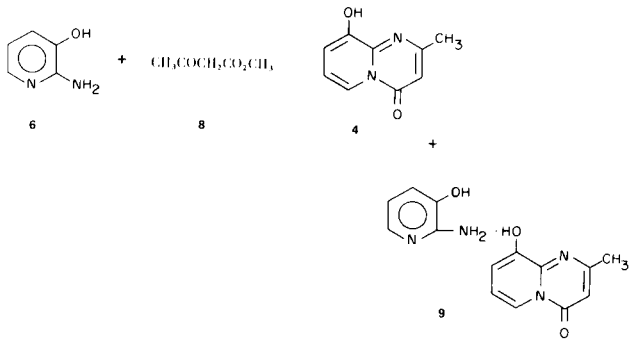
In view of the unexpected cleavage of the *o*-bromobenzyl group during the fusion reaction between **1** and **3**, there was good reason to study the reaction between **6** and **3**. When these reactants were fused at 125°, only **5** in essentially quantitative yield was obtained; however, when the temperature was raised from 125° to 175°, the mixture consisted of **4** and **5** in 23 and 74% yields, respectively.

In addition, it was observed that *in vacuo*, **5** slowly decomposed to give **4** at room temperature and the rate of decomposition was accelerated markedly at 56°. In actual practice, the decomposition of **5** was carried out in a large sublimation apparatus at 120°/1 mm, and this procedure gave **4** of high purity as the sublimate.

In the cyclization reactions discussed above, no third component solvent was used. From a practical point of view, a solvent reaction system was preferred. When **6** and **3** in approximately equimolar amounts in diethylbenzene solution were heated under reflux, the yield of **4** was 86%. Although not isolated, **5** probably was the intermediate since in a separate experiment, **5** in diethylbenzene, under reflux gave **4** in 87% yield. In contrast, **1** and **3** under the same conditions, gave **2** in only 2% yield.

The reaction of **6** and methyl acetoacetate (**8**) in

approximately equimolar amounts in diethylbenzene under reflux gave a mixture of **4** and **9**. This unexpected result had as its explanation the observation that as the solution



was being heated at an internal temperature of *ca.* 140°, a distillate consisting of acetone, methanol, and water was collected (6). Thus, a significant part of the **8** available was being decomposed during the reaction and this enabled **4** to form a salt with unreacted **6**. When an additional molar equivalent of **8** was added and the heating under reflux repeated, only **4** was obtained in 87% yield. Again, **4** and **9** were obtained when **6** and **8** in a molar ratio of 1:2 in diethylbenzene were heated at an internal temperature of 115° for one hour. Thus, even in the presence of an excess of **8**, **9** was present; this suggested that **9** was the intermediate in the formation of **4**, and it was the reaction rate of **9** with **8** that was accelerated by the elevation of the temperature to 185° and resulted in the isolation of **4** as the single product. Finally, **1** and **8** in a molar ratio of 1:2, under the optimal conditions described above for the preparation of **4**, gave only trace amounts of **2** and most of the **1** was recovered unchanged. Thus, alkylation of the 3-hydroxy group in **6** markedly reduced the reactivity of the 2-amino group; the major contribution toward this decreased reactivity was probably the steric effects of the *o*-bromobenzyl group.

It was of interest also that **6** and diketene in equivalent molar amounts in water at 20-35° gave both **4** and **9** in low yield (7).

Finally, with **4** readily available *via* the procedures described above, alkylation of its anion with *o*-bromobenzyl bromide in aqueous methanolic potassium hydroxide was found to be a practical procedure for large scale synthesis and gave **2** in 61% yield.

EXPERIMENTAL

The ir spectra were obtained on mineral oil mulls or in deuteriochloroform solutions, employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were obtained with a Varian A60, a Perkin-Elmer R12B, or a Varian Associates XL-100-15 spectrophotometer. The uv spectra were determined on a Cary 15 recording spectrophotometer. The authors are indebted to Mrs. B. Toeplitz, Dr. M. S. Puar, and Dr. J. Dunham of this Institute for these spectra. The microanalyses were carried out by Mr. Joseph Alicino and his associates of this Institute. The melting points were determined in capillary tubes in an electrically heated oil bath and are not corrected.

Reaction of 2-Amino-3-(*o*-bromobenzyloxy)pyridine (**1**) and Ethyl Acetoacetate. Preparation of 9-(*o*-Bromobenzyloxy)-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**2**).

A mixture of 2.79 g. (0.01 mole) of **1** and 13.0 g. (0.1 mole) of ethyl acetoacetate was heated by means of an oil bath so that the internal temperature was maintained at 100° for four hours. The mixture was concentrated to dryness *in vacuo* and the residue dissolved in 50 ml. of benzene was chromatographed on 25 g. of activated alumina (MCB, 200 mesh, chromatographic grade). Elution with benzene gave 0.80 g. of an oil that slowly solidified. This was extracted with two 55 ml. portions of pentane and the pentane insoluble material, 0.29 g., m.p. 138-140°, was recrystallized from 35 ml. of cyclohexane to give 0.075 g. (2% yield) of **2**, m.p. 142-143°; ν (deuteriochloroform): 1685 (s), 1640 (m), 1570 (w), 1540 (m), 1465 (s), 1425 (s) cm^{-1}; λ max (ethanol): 355, 340, 310, 300, 265, 258, mμ [ϵ (x 10^3) 11.70, 11.04, 7.94, 7.25, 10.07, 9.0]; pmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 5.40 (s, 2H, CH_2), 6.35 (s, 1H, *H* at position-3), 6.88-7.75 (m, 6*H*, all ar*H*, except 2*H* at positions-3 and -6), 8.63 (q, J = 4 Hz, 1H, *H* at position-6).

Anal. Calcd. for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; N, 8.12. Found: C, 55.93; H, 3.83; N, 8.00.

Reaction of **1** with Methyl β-Aminocrotonate (**3**). Preparation of 9-Hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**4**) and its Ammonium Salt (**5**).

A well-blended mixture of 9.1 g. (0.032 mole) of **1** and 4.2 g. (0.036 mole) of **3** was heated for 6 hours at 160-180° and for 1 hour at 200-220° (5). During this time, a black, fused mass remained on the bottom of the reaction flask, while a small amount of yellow-colored solid had sublimed onto the cooler walls of the flask. The yellow material was removed and dried on porous plate to give 0.50 g. of solid. The solid was extracted with 20 ml. of boiling cyclohexane and the boiling solution decanted from a yellow-colored insoluble material. The cyclohexane filtrate on cooling gave colorless crystals that were filtered and dried to give 0.10 g. of crude **4**, m.p. 140-142°. This was recrystallized again from 5 ml. of cyclohexane to give pure **4**, m.p. 144-146°; ir (mull) ν: 3340 (m), 3310 (m), 1690 (s), 1640 (s), 1580 (w), 1535 (s), 1470 (s), 1430 (s), 1390 (m) cm^{-1}; λ max (ethanol): 357, 342, 311, 300, 264, 258, 235 mμ [ϵ (x 10^3) 13.74, 11.54, 7.65, 6.78, 7.82, 7.08, 6.32]; pmr (deuteriochloroform) δ: 2.45 (s, 3H, CH_3), 6.35 (s, 1H, *H* at position-3), 6.88-7.32 (two overlapping q, 2H, 2*H* at positions-7 and -8), 7.50 [s, 1H, H of O*H* (equilibrates with deuterium oxide)], 8.54 (q, J = 3 Hz, 1*H* at position-6). In ethanol, **4** gave an intense blue color with aqueous ferric chloride.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.81. Found: C, 61.49; H, 4.74; N, 16.00.

The yellow-colored cyclohexane insoluble material (0.35 g.) was recrystallized from 35 ml. of methanol to give 0.25 g. of **5**, m.p. 192-195° dec., (sintered at 178°) (when allowed to solidify spontaneously, the m.p. sample remelted at 140-143°). An analytical sample of **5** was obtained by a second recrystallization from methanol; this material sintered at 180° and melted at 192-195° dec., (remelted at 141-143°); ir (mull) ν: 3300-2340

(s, broad), 1660 (s), 1640 (s), 1610 (m), 1550 (s), 1520 (s), 1480-1420 (s, broad) cm^{-1}; pmr (perdeuterioacetic acid) (insoluble in all other solvents) δ: 2.15 (s, 3H, CH_3), 5.98 (s, 1H, *H* at position-3), 6.82-7.25 (two overlapping q, 2*H* at positions-7 and -8), 8.12 (q, J = 2 Hz, 1H, *H* at position-6).

Anal. Calcd. for $C_9H_8N_2O_2 \cdot NH_3$: C, 55.95; H, 5.74; N, 21.75; N.E. ($HClO_4$), 97. Found: C, 56.10; H, 5.43; N, 21.80; N.E. ($HClO_4$), 101.

The black, fused reaction product (see above) was extracted with three 100 ml. portions of benzene and the benzene extracts were concentrated to dryness. The residue (8.5 g.) consisted of crystals distributed in a viscous resinous mass. Attempts at recrystallization failed to separate the crystalline material, hence, the mass was subjected to sublimation at 120° (1 mm); only the crystalline material sublimed to give 1.5 g. of **4**, m.p. 143-145°. Recrystallization from 40 ml. of cyclohexane gave 1.0 g. (18% yield) of **4**, m.p. and mixture m.p. with the sample of **4** described above, 144-146°; their ir spectra were identical in all respects.

When 1.0 g. (0.0057 mole) of **4** and 10 ml. of liquid ammonia were stirred for 0.5 hour, the ammonia then allowed to evaporate and the residue (1.0 g.), recrystallized from methanol; the yield of **5** was 0.80 g. (78%), sintered 180°, m.p. 192-195° dec., solidified and melted at 143-145°. The ir spectrum of this ammonium salt was identical in all respects with the ir spectrum of the **5** isolated from the sublimate described above.

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

To a solution of 2.5 g. (0.014 mole) of **4** in 25 ml. of glacial acetic acid, obtained by warming to 40°, was added 3.5 ml. of 30% hydrogen bromide in acetic acid and the mixture stirred for 0.5 hour at room temperature. The solid that separated was filtered, washed with anhydrous ether and air-dried to give 3.9 g. of **7**, m.p. 285-286° dec. Recrystallization from 65 ml. of 95% ethanol gave 3.8 g. (92% yield) of anhydrous **7**, m.p. 284-285° dec.; ir (mull) ν: 3115-2610 (s, broad), 1715 (s), 1635 (m), 1620 (m), 1590 (s), 1510 (s); pmr (deuterium oxide) δ: 2.58 (s, 3H, CH_3), 6.42 (s, 1H, *H* at position-3), 7.37-7.83 (two overlapping q, 2H, 2*H* at positions-7 and -8), 8.63 (q, J = 2 Hz, *H* at position-6). The anhydrous salt, when exposed to normal humidity, formed a stable monohydrate.

Anal. Calcd. for $C_9H_8N_2O_2 \cdot HBr$ (anhydrous): C, 42.02; H, 3.53; N, 10.90; Br, 31.08. Found: C, 41.71; H, 3.67; N, 10.75; Br, 31.43.

Anal. Calcd. for $C_9H_8N_2O_2 \cdot HBr \cdot H_2O$: C, 39.29; H, 3.99; N, 10.18; Br, 29.05. Found: C, 39.22; H, 3.87; N, 9.74; Br, 29.38.

Fusion Reaction Between **6** and **3** at 125° - Formation of **5**.

A well-blended mixture of 11.0 g. (0.1 mole) of **6** and 13.0 g. (0.113 mole) of **3** was heated for 4 hours by means of an oil bath maintained at 125°. Some of the **3** sublimed onto the cooler part of the flask during the heating. The solid product that remained at the bottom of the flask weighed 19.1 g. (theory, 19.3 g.), m.p. 185-190° dec. (sintered at 135°). This material was recrystallized from 1750 ml. of aqueous ammonia (490 ml. of 28% aqueous ammonia and 1260 ml. of water) by heating to 80°, filtering and allowing the **5** to crystallize spontaneously. The yellow-colored plates were filtered and dried to constant weight at room temperature *without vacuum* over drierite. The yield was 16.5 g. (90% yield), m.p. 193-195° (sintered at 178°). The ir spectrum of this material was identical in all respects with the two samples of **5** prepared above.

Anal. Calcd. for $C_9H_8N_2O_2 \cdot NH_3$: C, 55.95; H, 5.74; N, 21.75; N.E. ($HClO_4$), 97. Found: C, 55.76; H, 5.71; N, 21.93; N.E. ($HClO_4$), 98.

Fusion Reaction Between **6** and **3** - Formation of **4** and **5**.

A well-blended mixture of 110.0 g. (1.0 mole) of **6** and 130.0 g. (1.1 mole) of **3** was placed in a flask equipped with a paddle stirrer, still-head, condenser and receiver. The reaction flask was heated by means of an oil bath preheated to 125° and the temperature was then raised to 145° in 0.5 hour. At this time, with the internal temperature at 110°, a vigorous reaction occurred and 36 ml. of distillate was collected during a 10 minute period. During the next 3.5 hours, the oil bath temperature was raised to 175° the internal temperature remained at 110-115°, but only an additional 3 ml. of distillate was collected. The distillate weighed 31.0 g. (theory, of methanol, 32.0 g.). The cooled mass was extracted with four 500 ml. portions of boiling benzene and the combined benzene extracts were concentrated to 100 ml. and cooled to give 41.3 g. (23% yield) of **4**, m.p. 139-143°. The benzene-insoluble material **5**, 144.0 g. (74% yield) melted at 192-193° dec., and on cooling, solidified and remelted at 144-146°. A 1.0 g. sample recrystallized from 125 ml. of methanol gave 0.80 g. of **5**, m.p. 192-195° dec., solidified on cooling, and remelted at 143-145°; the ir spectrum of this sample of **5** was identical in all respects with the ir of **5** obtained in earlier experiments.

Crude **5**, (143.0 g.) was sublimed at 120-140° (oil bath temperature) and 1 mm to give 110.7 g. of **4**. The combined **4** (152.0 g.) was recrystallized from 1.5 l. of ethyl acetate to give 140.0 g. (80% yield) of **4**, m.p. and mixture m.p., 144-146°.

A stirred suspension of 10.0 g. (0.05 mole) of **5** in 1 l. of water (*p*H 8.3) was treated with powdered dry ice until the *p*H was 6.3. The solid was filtered and dried to give 5.0 g. (57% recovery of **4**, m.p. and mixture m.p., 144-146°.

Preparation of **4** by Reaction of **6** and **3** in Diethylbenzene.

A mixture of 55.0 g. (0.5 mole) of **6** and 65.0 g. (0.55 mole) of **3** in 100 ml. of diethylbenzene (8) was heated for 1 hour under reflux (185°) and filtered at the b.p. The filtrate was allowed to cool spontaneously to room temperature and the crystalline solid filtered, washed with hexane and dried to give 77.4 g. (87% yield) of **4**, m.p. 144-146°; a recrystallization from 1 l. of ethyl acetate did not change the m.p. and the recovery was 76.4 g. (86% yield).

Pyrolysis of **5** in Diethylbenzene.

A suspension of 10.0 g. (0.052 mole) of **5** and 100 ml. of diethylbenzene was stirred and heated for 1 hour at 185°. During this time, a solution formed and ammonia was evolved. The solid that crystallized from the cooled solution was filtered, washed with hexane, and dried to give 7.6 g. (84%) of **4**, m.p. 144-146°. Recrystallization from 90 ml. of ethyl acetate gave 6.7 g. of **4**, m.p. 144-146°.

Reaction of **6** and **8** (Molar Ratio 1:2) at 115° - Preparation of **4** and **9**.

A mixture of 33.0 g. (0.3 mole) of **6** and 69.6 g. (0.6 mole) of **8** in 300 ml. of diethylbenzene was stirred and heated for 1 hour so that the internal temperature was kept at 80°; a solution had not formed and a probe of the reaction mixture at that time revealed only unreacted **6**. The internal temperature was increased to 115° and maintained at 115° for one hour. The mixture was allowed to cool to 100° and filtered rapidly with suction since a significant amount of an unusual pale green-colored solid

had crystallized. The green solid was air-dried; it weighed 26.9 g., m.p. 161-163°. The filtrate was cooled to room temperature to give the characteristic orange-colored needles of **4**. These were filtered, washed with hexane, and air-dried to give 19.2 g. of **4**, m.p. 141-143°. Recrystallization of the 19.2 g. from 220 ml. of ethyl acetate gave 18.1 g. (34% yield) of **4**, m.p. and mixture m.p., 144-146°.

The pale green solid decomposed in part to a black tar during attempted recrystallizations from diethylbenzene, toluene or 2-propanol; from each of the three solvents, the recovery of pale green crystalline material was poor, but the m.p. was only slightly raised to 163.0-164.5°. Acetonitrile was found to be the solvent of choice; 26.0 g. was recrystallized from 515 ml. of acetonitrile to give 21.7 g. (25% yield) of **9** as green-colored needles, m.p. 164-166°; ir (mull) ν: 3350 (m), 3310 (m), 2840-2550 (s, broad), 1685-1620 (s, broad), 1575 (s), 1560 (m), 1480-1440 (s, broad) cm^{-1}; pmr (deuteriochloroform) δ: 2.45 (s, 3H, CH_3), 6.30-7.60 [m, 7H, 6ar H plus H of O*H* (equilibrates with deuterium oxide)], 7.6-9.6 [broad m (superimposed on this m is the q at 8.55, J = 3 Hz, of H at position-6), 2H, NH_2 (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_9H_8N_2O_2 \cdot C_5H_6N_2O$: C, 58.73; H, 4.93; N, 19.57; N.E. ($HClO_4$), 143. Found: C, 58.60; H, 4.95; N, 19.71; N.E. ($HClO_4$), 146.

A stirred suspension of 1.0 g. of finely ground **9**, 1.0 ml. of **8** and 10 ml. of diethylbenzene was immersed in a preheated oil bath at 155°. The internal temperature was maintained at 140° for 0.5 hour, then raised to reflux and kept at reflux for 0.5 hour. No tar formation was observed. The mixture was allowed to cool spontaneously to 20°. The orange-colored crystals that separated were filtered, washed with hexane, and air-dried to give 0.95 g. of **4**, m.p. 141-143°. Recrystallization from 10 ml. of ethyl acetate gave 0.72 g. of **4**, m.p. and mixture m.p., 144-146°.

Reaction of **6** with **8** (Molar Ratio 1:2) at 185° - Preparation of **4**.

A mixture of 11.0 g. (0.1 mole) of **6**, 23.6 g. (0.2 mole) of **8** and 100 ml. of diethylbenzene was heated under a Dean-Stark trap by means of an oil bath, preheated initially to 155°. The internal temperature rose slowly to 140° and remained constant for the next two hours. During this time, 9.5 ml. of distillate collected in the Dean Stark trap. In the following hour, the oil bath temperature was raised to 205°, while the internal temperature reached 185°, and these temperatures were maintained for 0.67 hour. An additional 2.5 ml. of distillate was collected. The hot solution was filtered and the filtrate was cooled. The crystalline solid filtered, triturated with 50 ml. of hexane, refiltered, and dried to give 15.4 g. (87% yield) of **4**, m.p. 144-146° alone or mixed with **4** prepared as described above.

The 12.0 ml. of distillate by vpc analysis contained 0.06 mole of acetone, 0.16 mole of methanol, and 0.04 mole of water.

Reaction of **6** and **8** (Molar Ratio 1:1) at 185° - Preparation of **4** and **9**.

A mixture of 11.0 g. (0.1 mole) of **6** and 11.6 g. (0.1 mole) of **8** in 100 ml. of diethylbenzene was immersed in a preheated oil bath at 150°. The oil bath temperature was raised to 160° in order to obtain an internal temperature at 140°. This temperature was maintained for 0.33 hour then increased until the diethylbenzene was under reflux, and the reflux continued for two hours. Ten ml. of the reaction mixture was removed, allowed to cool to 100°, and the green solid that separated was filtered rapidly with suction. The air-dried material weighed 0.78 g., m.p. 161-163°. Recrystallization from acetonitrile gave **9**, m.p. and mixture m.p. with **9** obtained above, 164-166°. The filtrate on cooling to 20° deposited brown crystals that were filtered, washed with 5 ml. of hexane, and air-dried to give 0.43 g. of **4**, m.p. 140-142°. Recrystallization from ethyl acetate gave **4**, m.p. and mixture m.p., 144-146°.

To the remaining diethylbenzene reaction mixture was added 11.6 g. of **8**, the mixture heated under reflux for 0.67 hour and filtered. The filtrate was cooled and the solid filtered to give 11.3 g. of **4**, m.p. 140.5-142.0°. Recrystallization gave **4**, m.p. and mixture m.p., 144-146°.

Reaction of **6** with Diketene - Preparation of **4** and **9**.

To 7.1 g. (0.064 mole) of **6** suspended in 65 ml. of distilled water at 24° (internal temperature) was added during 0.75 hour, 5.5 g. (0.065 mole) of freshly purified diketene (9). A solution formed 8 minutes after the addition started and the internal temperature had by then reached 31°. The maximum temperature (36°), was reached 22 minutes after the addition started. No separation of solid had occurred even though the mixture was kept at room temperature for 20 hours. The solution was concentrated below 40° *in vacuo* to give 12.0 g. of a sticky, pale green mass. After a considerable number of attempted recrystallizations that failed, the mass was dissolved in 50 ml. of 2-propanol and kept for two months at room temperature. During this time, crystalline material slowly separated. When this was filtered, it was found to be extremely hydroscopic; however, grinding to a fine powder under diisopropyl ether gave after filtration a non-hygroscopic green-colored powder that was air-dried to give 4.5 g. of solid, m.p. about 130-145°. The 4.5 g. of material and 46 ml. of diethylbenzene were heated to boiling, the solution decanted from a black tar and the solution allowed to cool spontaneously. The crystals that separated were filtered and air-dried to give 0.94 g. of green solid, m.p. 156-159°. Recrystallization from 20 ml. of acetonitrile gave 0.68 g. of **9**, m.p. and mixture m.p., 164-166°. The diethylbenzene filtrate was concentrated to dryness *in vacuo*; the residue (0.43 g.), m.p. 141-143° was recrystallized from 5 ml. of ethyl acetate to give 0.23 g. of **4**, m.p. and mixture m.p., 144-146°.

Reaction of **1** with **3** in Diethylbenzene - Preparation of **2**.

A mixture of 9.2 g. (0.035 mole) of **1**, 4.25 g. (0.037 mole) of **3** and 150 ml. of diethylbenzene was heated under reflux for 5 hours and then concentrated to dryness *in vacuo*. The viscous residue, 12.1 g., could not be induced to crystallize. It was dissolved in 150 ml. of benzene and chromatographed on 80 g. of alumina (MCB, 200 mesh, chromatographic grade) and eluted with benzene; a series of sixteen 50 ml. eluates were collected. The first five eluates gave low melting solids; the sixth eluate yielded 0.7 g. of solid, m.p. 88-135°; and, the following eleven eluates yielded non-crystalline oils. The 0.7 g. of solid from eluate 6 was extracted with 60 ml. of boiling pentane to leave as insoluble material, 0.4 g. of solid, m.p. 141-143°. Recrystallization from 40 ml. of cyclohexane gave 0.15 g. (2% yield) of **2**, m.p. and mixture m.p., 142-143°.

Reaction of **1** and **8** in Diethylbenzene - Preparation of **2**.

A mixture of 4.0 g. (0.015 mole) of **1** and 3.0 g. (0.03 mole) of **8** and 75 ml. of diethylbenzene was heated under reflux for 8 hours and then concentrated to dryness *in vacuo*. The residual oil (4.5 g.) would not crystallize; it was dissolved in 50 ml. of benzene and chromatographed on 50 g. of alumina (MCB, 200 mesh, chromatographic grade). The column was eluted with benzene; each eluate collected was 25 ml. The first two eluates yielded low melting solids, but the third eluate yielded 0.35 g. of solid, m.p. 90-100°; and, the following ten eluates yielded non-crystalline material. The 0.35 g. of solid from the third eluate was extracted

with 50 ml. of pentane to give 0.2 g. of solid, m.p. 90-125°. Recrystallization from cyclohexane gave 10 mg. of crude **2**, m.p. 135-139° and mixture m.p. with **2** was 141-143°; the ir spectrum of the crude **2** differed in only minor respects from pure **2**.

Reaction of **4** with *o*-Bromobenzyl Bromide - Preparation of **2**.

To 7.2 g. (0.11 mole) of 85% potassium hydroxide and 0.2 g. of potassium iodide in 100 ml. of water at 20° with stirring was added 17.6 g. (0.1 mole) of **4**. The deep-yellow colored, insoluble salt formed rapidly. To the suspension was added *dropwise* during 1 hour, a solution of 52.5 g. (0.11 mole) of *o*-bromobenzyl bromide in 150 ml. of methanol. The temperature rose spontaneously to 35°. The mixture was stirred subsequently for 18 hours at room temperature and then concentrated to remove methanol. The residual aqueous suspension formed a clear two-phase system when shaken with 500 ml. of chloroform. The water layer was separated, the chloroform solution extracted with two-100 ml. portions of 4% aqueous potassium hydroxide solution, then with water, dried and concentrated to dryness. The residue, 25.0 g., m.p. 141-143° was recrystallized from 100 ml. of toluene to give 21.0 g. (61% yield) of **2**, m.p. 142-143°, alone or mixed with the **2** obtained above. The ir spectra of the two samples were identical in all respects.

From the potassium hydroxide extracts, following adjustment of the *p*H to 5.2, unreacted **4** slowly separated. The solid was filtered and air-dried to give 1.8 g. (10% recovery) of **4**.

REFERENCES

(1) For the preceding paper on the pyrido[1,2-*a*]pyrimidin-4-ones, see H. L. Yale, B. Toeplitz, J. Z. Gougoutas, and M. Puar, *J. Heterocyclic Chem.*, 10, 123 (1973).

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

(4) These were the reaction conditions employed by H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951) in the preparation of 2-methylpyrido[1,2-*a*]pyrimidin-4-one from 2-aminopyridine and ethyl β-aminocrotonate.

(5) The reaction of 2-amino-3-pyridinol (**6**) with compounds containing activated methylene groups has been reported only by E. A. Ingalls and F. D. Popp [*J. Heterocylcic Chem.*, **4**, 523 (1967)] who stated in footnote (7), p. 526, of their paper that **6** and diethyl malonate gave a "compound that could not be adequately purifed". In a manuscript soon to be submitted for publication, we have found that **6** and ethyl ethoxymethylenemalonate react cleanly in diethylbenzene at 180° to give ethyl 9-hydroxypyrido[1,2-*a*]pyrimidin-4-one-3-carboxylate, m.p. 175-176°, in 93% yield.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.31; N, 11.96. Found: C, 56.68; H, 4.56; N, 12.10.

(6) The formation of acetone during the reaction of aniline with acetoacetic ester to give acetoacetanilide has been reported by F. Leuthardt and R. Brunner, *Helv. Chim. Acta*, **30**, 958 (1947).

(7) In our first paper in this series [*cf.* (1) above] we have discussed the reaction of diketene with 2-amino-3- and 2-amino-4-picoline in water, first reported by G. Stöckelmann, H. Specker, and W. Riepe, *Chem. Ber.*, **102**, 455 (1969).

(8) The diethylbenzene used was a commerical product obtained from the Sinclair-Koppers Co., Pittsburgh, Pa., 15214, and was used as received. The composition of this material is not indicated, but presumably consists mostly of the *para*-isomer.

(9) J. R. Johnson and V. J. Shriner, *J. Am. Chem. Soc.*, 75, 1350 (1953).