

9-Hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, 9-Hydroxy-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, 9-Methyl-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, Ethyl 9-Hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylate and Their Derivatives

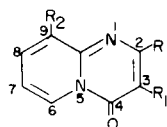
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Recent publications (1,2) from these Laboratories have described the synthesis of a number of derivatives of the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one heterocycle. Although interesting pharmacological activity was observed with several of these compounds, the most outstanding was **1**. In a program designed to prepare a series of related structures, a study was undertaken to develop a procedure for the alkylation and aralkylation of **2**, **3**, and **4**. While **2**, **3**, and **4** are readily soluble in many organic solvents, their 9-alkoxide derivatives are essentially insoluble, even in dimethylsulfoxide or *N,N*-dimethylformamide at reflux temperature. These salts reacted sluggishly or not at all with alkylating and aralkylating agents (3). Since no reaction occurred in the absence of an inorganic base or in the presence of an organic base, this investigation was concerned with determining whether an insoluble, weak inorganic base, which did not form salts with **2**, **3**, or **4**, would be useful in preparing the desired ethers. We are reporting that while the yields were variable, we were able to prepare a representative series of compounds, employing, under anhydrous conditions, ethyl methyl ketone as the solvent, and either potassium carbonate, potassium bicarbonate, or dipotassium hydrogen phosphate as the inorganic base. Typical procedures for these alkylations are included in the Experimental and all of the data are summarized in Tables I and II.

The interaction of 2-amino-3-pyridinol, **5**, and diethylmalonate was reported by Ingalls and Popp (4) to give a product that could not be purified. We are now reporting two procedures for the preparation of **4** *via* the reaction of **5** with ethyl ethoxymethylenemalonate. In addition, procedures are described for the preparation of **3** as well as of 9-methyl-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **6**.



1. R = CH₃, R₁ = H, R₂ = *o*-BrC₆H₄CH₂O
2. R = CH₃, R₁ = H, R₂ = HO
3. R = C₆H₅, R₁ = H, R₂ = HO
4. R = H, R₁ = CO₂C₂H₅, R₂ = HO
6. R = C₆H₅, R₁ = H, R₂ = CH₃

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 Perkin-Elmer R12B or a Varian Associates XL-100-15 spectrophotometer. The authors are indebted to Mrs. B. Toeplitz and Dr. M. S. Puar 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.

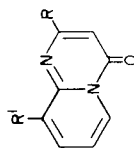
9-[(2,4-Dichlorobenzyl)oxy]-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **7**. Method A.

To 22 ml. of a solution prepared from 6.50 g. (0.1 mole) of 85% potassium hydroxide, 0.20 g. of potassium iodide, and 100 ml. of water, was added, with stirring, 3.52 g. (0.02 mole) of **2**. A solution existed momentarily and was then replaced by a precipitate of the deep yellow potassium salt. To this suspension was added 4.70 g. (0.024 mole) of 2,4-dichlorobenzyl chloride in 25 ml. of methanol. The mixture was stirred at room temperature for 18 hours, the solid isolated, and partitioned by vigorous agitation between 50 ml. each of chloroform and water. The chloroform layer was separated, the water layer was extracted with two 20 ml. portions of chloroform, the several chloroform solutions were combined, washed with 10 ml. of saturated aqueous sodium chloride solution, dried, and concentrated. The residue, 3.20 g. crystallized partially to an oily solid. Freed of oil, the solid melted at 162-166°. Recrystallization from 40 ml. of acetonitrile gave 0.46 g. of **7**, m.p. 180-182°; ir (deuteriochloroform): ν 1685 (s), 1590 (w), 1560 (w), 1540 (m), 1465 (s), 1425 (s) cm⁻¹; pmr (deuteriochloroform): δ 2.55 (s, 3H, CH₃), 5.42 (s, 2H, CH₂), 6.87-7.67 (m, 3H, 3-Py-H), 8.32-8.82 (m, 3H, 3 Ar-H).

Ethyl 4-Oxo-9-[(2-propynyl)oxy]-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate, **8**. Method B.

A mixture of 1.80 g. (0.006 mole) of **4**, 2.20 g. (0.018 mole) of propynyl bromide, 1.10 g. (0.008 mole) of anhydrous potassium carbonate, and 150 ml. of ethyl methyl ketone was heated and stirred, under reflux, for 60 hours. The insoluble material was removed by filtration and the filtrate was concentrated *in vacuo* to give 2.45 g. of solid, m.p. 143-145°. Recrystallization from toluene gave **8**, m.p. 146-148°; ir (deuteriochloroform): ν 3310 (m), 1740 (s), 1710 (s), 1630 (m), 1570 (w), 1525 (s), 1480 (s) cm⁻¹; pmr (deuteriochloroform): δ 1.72 [t (J = 7 Hz), 3H, OCH₂CH₃], 2.64 [t (J = 2 Hz), 1H, C≡CH], 4.45 [q (J = 7, 14 Hz), 2H, CH₂CH₃],

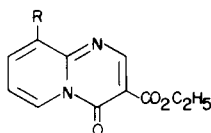
TABLE I
Alkylated Derivatives of 9-Hydroxypyrido[1,2-a]pyrimidin-4-one of the Structure



R	R ¹	Prepn. Method	M.P., °C	Recrystn. Solvent	Yield %	Mol. Formula	Calcd. C	Calcd. H	Calcd. N	Analyses C	Analyses H	Analyses N	Notes
Me	HC:CHCH ₂ O	B	197-198	2-PrOH	31	C ₁₂ H ₁₀ N ₂ O ₄	67.29	4.71	13.08	67.10	4.60	12.94	
Me	CH ₂ :CHCH ₂ O	B	112-115	C ₇ H ₁₆	17	C ₁₂ H ₁₂ N ₂ O ₂	66.65	5.59	12.96	66.66	5.46	12.88 (a)	
Me	n-BuO	D	93-94	C ₆ H ₁₂	11	C ₁₃ H ₁₆ N ₂ O ₂	67.22	6.94	12.05	67.19	7.09	12.01	
Me	C ₂ H ₅ OCCH ₂	B	149-151	C ₆ H ₁₂	40	C ₁₃ H ₁₄ N ₂ O ₄	59.52	5.39	10.68	59.67	5.59	10.75	
Me	C ₆ H ₅ CH ₂ O	D	110-112	C ₆ H ₁₂	72 (b)	C ₁₆ H ₁₄ N ₂ O ₂	72.16	4.93	10.51	72.26	5.23	10.76	
Me	o-ClC ₆ H ₄ CH ₂ O	B	166-168	C ₆ H ₁₂	75	C ₁₆ H ₁₃ ClN ₂ O ₂	63.91	4.36	9.31	63.80	4.32	9.23	
Me	o-F ₃ CC ₆ H ₄ CH ₂ O	B	130-132	C ₆ H ₁₂	39	C ₁₇ H ₁₃ F ₃ N ₂ O ₂	61.26	3.94	8.40	61.17	4.23	8.21	
Me	m-F ₃ CC ₆ H ₄ CH ₂ O	B	159-161	PhMe	76	C ₁₇ H ₁₃ F ₃ N ₂ O ₂	61.26	3.94	3.40	61.35	4.15	8.12	
Me	p-F ₃ CC ₆ H ₄ CH ₂ O	B	166-167	2-PrOH	81	C ₁₇ H ₁₃ F ₃ N ₂ O ₂	61.26	3.94	8.40	61.17	4.23	8.21	
Me	o-MeO ₂ CC ₆ H ₄ CH ₂ O	B	175-177	MeCN	15	C ₁₈ H ₁₆ N ₂ O ₄	66.67	4.98	8.64	66.73	5.18	8.92	
Me	2,4-Br(Cl) ₂ C ₆ H ₃ CH ₂ O	A	182-184	MeCN	31	C ₁₆ H ₁₂ BrClN ₂ O ₂	50.63	3.18	7.37 (c)	50.62	3.35	7.14	
Me	2,4-Cl ₂ C ₆ H ₃ CH ₂ O	A	180-182	MeCN	6	C ₁₆ H ₁₂ Cl ₂ N ₂ O ₂	57.30	3.61	8.36	57.29	3.68	8.31	
Me	PhCH ₂ CH ₂ O	C	191-193 (d)	2-PrOH	7	C ₁₇ H ₁₄ N ₂ O ₂ ·C ₂ H ₂ O ₄	61.61	4.90	7.57	61.39	4.97	7.55	
Me	PhCH:CHCH ₂ O	D	154-155	C ₆ H ₁₂	14	C ₁₈ H ₁₆ N ₂ O ₂	73.95	5.52	9.58	73.70	5.56	9.30	
Ph	PhCH ₂ O	D	177-179	PhMe	69	C ₂₁ H ₁₆ N ₂ O ₂	76.81	4.92	8.53	71.95	5.05	8.36	

(a) Calcd.: N.E. (perchloric acid), 216. Found: N.E. (perchloric acid), 217. (b) Method E gave a 38% yield; anhydrous sodium acetate in place of the potassium bicarbonate gave a 24% yield. (c) Calcd.: Br, 21.05; Cl, 9.34; N.E. (perchloric acid), 380. Found: Br, 21.39; Cl, 9.20; N.E. (perchloric acid), 381. (d) Salt with 1 mole oxalic acid.

TABLE II

Alkylated Derivatives of 9-Hydroxypyrido[1,2-*a*]pyrimidin-4-one-carboxylates of the Structure

R	Prepn. Method	M.P., °C	Recrystn. Solvent	Yield %	Mol. Formula	Analyses					
						Caled.		Found			
						C	H	N	C	H	N
CH ₂ :CHCH ₂ O	B	160-162	Pr ₂ O	31	C ₁₄ H ₁₄ N ₂ O ₄	61.30	5.51	10.21	61.43	5.20	10.46
HC:CCH ₂ O	B	146-148	PhMe	55	C ₁₄ H ₁₂ N ₂ O ₄	61.76	4.45	10.29	61.61	4.65	10.20
PhCH ₂ CH ₂ O	E	128-129	2-PrOH	8	C ₁₉ H ₁₈ N ₂ O ₄	67.44	5.37	8.28	67.18	5.53	8.11
<i>o</i> -BrC ₆ H ₄ CH ₂ O	B	164-166	2-PrOH	60	C ₁₈ H ₁₅ BrN ₂ O ₄	53.61	3.75	6.95	53.58	3.85	6.68
2,4-Cl(Br)C ₆ H ₃ O	B	167-169	2-PrOH	33	C ₁₈ H ₁₄ BrClN ₂ O ₄	49.41	3.22	6.41	49.31	3.16	6.24

5.06 [d (J = 2 Hz), 2H, OCH₂], 7.15-7.50 (m, 2H, H at positions-7 and -8), 8.84 [q (J = 2, 4 Hz), H at position-6], 9.01 (s, 1H, H at position-2).

2-Methyl-9-[(phenethyl)oxy]-4H-pyrido[1,2-*a*]pyrimidin-4-one, Oxalate Salt, **9**. Method C.

The reaction was carried out between 3.52 g. (0.02 mole) of **2**, 4.10 g. (0.022 mole) of phenethyl bromide, 3.30 g. (0.024 mole) of anhydrous potassium carbonate, and 200 ml. of ethyl methyl ketone. The mixture was stirred and heated under reflux for 96 hours. Workup as described for **6** gave the product as an oil that could not be induced to crystallize. To the oil, 3.50 g. in 5 ml. of acetonitrile was added a solution of 1.10 g. (0.01 mole) of oxalic acid monohydrate in 7 ml. of acetonitrile. The solid that crystallized was filtered and air-dried to give 1.35 g. of material, m.p. 183-185°. Recrystallization from 75 ml. of 2-propanol gave 0.54 g. of **9**, m.p. 191-193°, ir (mull): ν 3130-3030 (broad, w), 1720 (s), 1650 (m), 1630 (s), 1585 (s), 1510 (s), 1460 (m), 1450 (m) cm⁻¹; pmr (trifluoroacetic acid): δ 2.69 (s, 3H, CH₃), 3.30 [t (J = 7 Hz), 2H, PhCH₂], 4.76 [t (J = 7 Hz), 2H, PhCH₂CH₂], 6.68 (s, 1H, H at position-3), 6.85-7.10 [m, 2H, H at positions-7 and -8]-7.37 (s, 5H, 5-Ar-H), 7.78 [q (J = 4, 5 Hz), 1H, H at position-6], 7.86 (s, 2H, (CO₂H)₂).

9-[(Cinnamyl)oxy]-2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one, **10**. Method D.

A mixture of 2.10 g. (0.02 mole) of finely ground sodium bromide, 3.10 g. (0.02 mole) of cinnamyl chloride, and 200 ml. of ethyl methyl ketone was heated and stirred under reflux for two hours, cooled, and 3.52 g. (0.02 mole) of **2** and 6.60 g. (0.066 mole) of potassium bicarbonate added. The whole was stirred and heated under reflux for 21 hours. Workup as described for **8** gave 1.02 g. of crude **10**, m.p. 141-146°. Recrystallization from 770 ml. of cyclohexane gave 0.82 g. of **10**, m.p. 154-155°; ir (deuteriochloroform): ν 1680 (s), 1635 (m), 1656 (w), 1535 (m), 1465 (s), 1420 (s) cm⁻¹; pmr (deuteriochloroform): δ 2.50 (s, 3H, CH₃), 4.98 [d (J = 5 Hz), 2H, CH₂O], 6.20-7.37 (m, 5H, 3 Py-H plus 2-vinyl H), 8.66 [q (J = 3.5 Hz), 1H, H at position-6].

Ethyl 4-Oxo-9-[(phenethyl)oxy]-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate, **11**. Method E.

A suspension of 9.40 g. (0.042 mole) of **4**, 7.40 g. (0.084 mole) of phenethyl bromide, 7.00 g. (0.04 mole) of dipotassium hydrogen phosphate, and 350 ml. of ethyl methyl ketone was stirred and heated under reflux for a total of 120 hours. Additional 3.00 g.

quantities of phenethyl bromide were added after 24, 48, and 72 hours of this heating period. The cooled reaction mixture was filtered at room temperature and the filtrate concentrated to dryness *in vacuo* to give 19.7 g. of a dark oily solid. This was distributed between 100 ml. of chloroform and 60 ml. of 5% aqueous potassium hydroxide solution. The yellow potassium salt that separated was removed by filtration, the chloroform layer was separated in the filtrate, the water layer was extracted with two-25 ml. portions of chloroform, the chloroform solutions were combined, washed with saturated aqueous sodium chloride solution, dried, and concentrated to give 11.6 g. of a dark oil. Dilution with 25 ml. of ligroin gave 2.4 g. of a solid that was recrystallized once from 60 ml. of 2-propanol to give 1.2 g. of solid, m.p. 127-129° and that product recrystallized again from 40 ml. of 2-propanol to give 1.1 g. of **11**, m.p. 128-129°, ir (deuteriochloroform): ν 1745 (s), 1710 (s), 1630 (m), 1580 (w), 1530 (s), 1485 (s) cm⁻¹; pmr (deuteriochloroform): δ 1.41 [t (J = 4 Hz), 3H, CH₃], 3.30 [t (J = 4 Hz), 2H, PhCH₂], 4.30-4.56 (two overlapping triplets, 4H, PhCH₂CH₂ plus OCH₂CH₃), 7.14-7.26 (m, 2H, H at positions-7 and -9), 7.30 (s, 5H, 5-Ar-H), 8.84 [t (J = 2 Hz), 1H, H at position-6], 9.05 (s, 1H, H at position-2).

Diethyl [(3-Hydroxy-2-pyridyl)amino]methylene]malonate, **12**.

A mixture of 113.0 g. (1.0 mole) of **5** and 216.0 g. (1.0 mole) of diethyl ethoxymethylenemalonate (EMME) was heated and stirred in an oil bath maintained at 110°. During that heating period, the mixture effervesced, the **5** dissolved partially, but soon the entire mixture set to a solid mass. It weighed 281.0 g., m.p. 144-147°; it showed it to be a complex mixture, however, and much effort was required to evolve a procedure to isolate pure **10**. The solid was extracted with 4300 ml. of chloroform at room temperature, filtered, and the filtrate was concentrated to dryness to give 173.6 g. of solid, m.p. 152-160°. This material was recrystallized once from 4.0 liters of acetonitrile and the product isolated again recrystallized from 2.8 liters of acetonitrile to give 75.6 g. (27% yield) of **12**, m.p. 180-181°; ir (mull): ν 3040-3140 (broad s), 1680 (s), 1675 (s), 1660 (s), 1600 (m), 1565 (s), 1480 (s), 1465 (s) cm⁻¹; pmr (DMSO-d₆): δ 1.20-1.40 [m, 6H, (CH₂CH₃)₂], 4.05-4.40 [m, 4H, (CH₂CH₃)₂], 7.20 [q (J = 3.5 Hz), 1H, H at position-5 of Py], 7.26 [q (J = 1.5 Hz), 1H, H at position-4 of Py], 7.84 [q (J = 1.2 Hz), 1H, H at position-6 of Py], 9.04 [d (J = 7 Hz), 1H, CH coupled to NH(5)], 10.80 (broad s, 1H, OH), 11.12 [d (J = 7 Hz), 1H, NH].

Anal. Calcd. for C₁₃H₁₆N₂O₅: C, 55.70; H, 5.76; N, 10.00. Found: C, 55.88; N, 5.71; N, 10.11.

Ethyl 9-Hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate, **4**. Method F.

To 750 ml. of Dowtherm A, preheated to 220°, with stirring was added rapidly a total of 90.0 g. (0.32 mole) of **12**. Subsequently, the mixture was stirred and heated at 215° for 0.25 hour, cooled, and poured into 4.0 liters of petroleum ether, with stirring. The solid that separated was stirred with 250 ml. of fresh petroleum ether, and refiltered. The air-dried solid, 80.5 g., 800 ml. of 1% aqueous sodium hydroxide, 5.0 g. of Darco, and 2.5 g. of Hyflo were stirred for 0.25 hour at room temperature, filtered, and the filtrate adjusted to pH 5.5. The solid that separated was filtered, washed with water, and dried to give 56.4 g. of solid, m.p. 149-173°. Recrystallization from 1400 ml. of ethyl acetate gave 39.5 g. (52% yield) of **4**, m.p. 178-179°, ir (deuteriochloroform): ν 3490 (m), 1740 (s), 1710 (s), 1640 (m), 1580 (m), 1525 (s), 1485 (s), 1440 (s) cm^{-1} ; pmr (deuteriochloroform): δ 1.40 [t (J = 7 Hz), 3H, CH_2CH_3], 4.40 [q (J = 7, 14 Hz), 2H, CH_2CH_3], 6.50 [broad s, 1H, OH (exchanges with deuterium oxide)], 7.00-7.55 (m, 3H, H at positions-1, -7, and -8), 8.80 [q (J = 2.4 Hz), 1H, H at position-6], 8.97 (s, 1H, H at position-2).

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_4$: C, 56.41; H, 4.31; N, 11.96. Found: C, 56.43; H, 4.59; N, 12.10.

Method G.

A stirred suspension of 6.6 g. (0.06 mole) of **5**, 22.0 g. of (0.12 mole) of EMME, and 100 ml. of diethylbenzene was heated by means of an oil bath maintained at 140° for two hours and then at 180° for two hours. During this heating period, volatile products were collected in a Dean-Stark trap. The hot solution was filtered and the filtrate cooled; the crystalline product that separated was filtered and air-dried to give 13.0 g. of solid, m.p. 174-175°. Recrystallization from 600 ml. of ethyl acetate gave 10.9 g. (78% yield) of **4**, m.p. 178-179°, whose ir and pmr spectra were identical with those obtained with the product prepared as described by Method F.

9-Hydroxy-2-propyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **13**, and its Salt with *p*-Toluenesulfonic Acid, **14**.

A mixture of 31.5 g. (0.2 mole) of ethyl butyrylacetate, 11.0 g. (0.1 mole) of **5**, 125 ml. of ethyleneglycol monomethyl ether, and 1.0 g. of *p*-toluenesulfonic acid was stirred and heated under reflux for 21 hours and then cooled. The product crystallized spontaneously. It was filtered and air-dried to give 10.1 g. of solid, m.p. 92-94°. Recrystallization from 200 ml. of diisopropyl ether gave 8.4 g. of **13**, m.p. 95-96°. The ethyleneglycol monomethyl ether filtrate was concentrated to 0.5 volume and cooled to give 5.8 g. of additional solid, m.p. 92-94°, but containing a small amount of higher melting solid. The 5.8 g. of solid was extracted successively with two 50 ml. portions of diisopropyl ether, and filtered, in each instance from an insoluble solid (A); from these extracts was eventually isolated an additional 3.8 g. of **13**, m.p. 95-96°. The combined yield of **13** was 12.2 g. (60%). The following spectral properties were obtained with **11**; ir (deuteriochloroform): ν 3380 (m), 1680 (m), 1645 (s), 1575 (w), 1535 (s), 1460 (s) cm^{-1} ; pmr (deuteriochloroform): δ 1.0 [t (J = 6 Hz), 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$], 1.50-2.70 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.66 [t (J = 7 Hz), 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$], 6.32 (s, 1H, H at position-3), 6.80-7.25 (m, 2H, H at positions-7 and -8), 7.55 (s, 1H, OH), 8.55 [q (J = 4 Hz), 1H, H at position-6].

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$: C, 64.69; H, 5.92; N, 13.71. Found: C, 64.87; H, 5.93; N, 14.00.

Solid A, remaining after the successive extractions with diisopropyl ether, weighed 1.0 g. Recrystallization from 40 ml. of

acetonitrile gave 0.60 g. of the *p*-toluenesulfonic acid salt of **13**, **14**, m.p. 202-204°, ir (mull): ν 3250-2050 (s, broad), 1715 (s), 1640 (m), 1620 (m), 1590 (s), 1510 (s), 1450 (m), 1440 (m) cm^{-1} .

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2 \cdot \text{C}_7\text{H}_8\text{O}_3\text{S}$: C, 57.43; H, 5.36; N, 7.45; N.E. (sodium hydroxide), 188; N.E. (perchloric acid), 0.0. Found: C, 57.53; H, 5.52; N, 7.43; N.E. (sodium hydroxide), 182; N.E. (perchloric acid), 0.0.

The same salt was prepared by mixing rapidly a hot solution of 1.40 g. (0.0068 mole) of **13** in 15 ml. of acetonitrile and a hot solution of 1.30 g. (0.0068 mole) of *p*-toluenesulfonic acid monohydrate in 15 ml. of acetonitrile. A clear solution formed from which **14** separated on cooling. This was recovered and recrystallized from 130 ml. of acetonitrile to give 2.16 g. (84% yield) of pure **14**, m.p. 202-204°, whose ir and pmr spectra were identical with the same spectra obtained with the product isolated as described above.

9-Hydroxy-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **15**. Method H.

A mixture of 76.8 g. (0.4 mole) of ethyl benzoylacetate, 22.0 g. (0.2 mole) of **5**, and 250 ml. of diethylbenzene was heated by means of an oil bath as described in Method G. When the two-step heating period was completed, the mixture was cooled to give 41.7 g. of solid, m.p. 180-185°. This was recrystallized from 800 ml. ethyleneglycol monomethyl ether to give 22.9 g. (47% yield) of **15**, m.p. 234-235°; ir (mull): ν 3310 (s), 1660 (s), 1640 (s), 1570 (w), 1530 (m), 1500 (m), 1470 (s), 1430 (s), 1420 (s) cm^{-1} ; pmr (DMSO- d_6): δ 3.30-3.80 (broad s, 1H, OH), 7.03 (s, 1H, H at position-3), 7.14-7.76 (m, 5H, 5-Ar-H), 8.30-8.70 (m, 2H, H at positions-7 and -8).

Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$: C, 70.58; H, 4.24; N, 11.76. Found: C, 70.84; H, 4.37; N, 12.01.

Method I.

A solution of 11.0 g. of **5**, 38.4 g. of ethyl benzoylacetate, 250 ml. of ethyleneglycol monomethyl ether, and 0.5 g. of *p*-toluenesulfonic acid was stirred and heated under reflux for 20 hours. The solid that crystallized from the reaction mixture on cooling was filtered and air-dried to give 3.2 g. of material, m.p. 231-233°. Recrystallization from 64 ml. of ethyleneglycol monomethyl ether gave 2.6 g. (11% yield) of **15**, m.p. 234-235°; the ir and pmr spectra of this product were identical with those obtained with the product prepared by Method H.

9-Methyl-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **16**. Method J.

A solution of 9.6 g. (0.05 mole) of ethyl 3-aminocinnamate, 5.4 g. (0.05 mole) of 2-amino-3-methylpyridine, and 50 ml. of diethylbenzene was heated by means of an oil bath as described in Method G. The crude product, m.p. 154-167°, weighed 1.45 g. Recrystallization from 35 ml. of ethyl acetate gave 1.2 g. (10% yield) of **16**, m.p. 180-182°; ir (deuteriochloroform): ν 1670 (s), 1630 (s), 1560 (w), 1530 (m), 1490 (s), 1460 (s), 1440 (m), 1415 (s) cm^{-1} ; pmr (deuteriochloroform): δ 2.70 (s, 3H, CH_3), 6.85-8.40 (m, 8H, 3-Py-H plus 5-Ar-H), 9.00 [q (J = 1, 12 Hz), 1H, H at position-6].

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}$: C, 76.25; H, 5.12; N, 11.85. Found: C, 75.99; H, 5.38; N, 11.88.

Salts of **2** with Organic Acids.

In a typical preparation, 0.88 g. (0.005 mole) of **2** in 25 ml. of warm acetonitrile was treated with 0.67 g. (0.005 mole) of fumaric acid in 10 ml. of warm acetonitrile. A clear solution formed on mixing and the salt separated only on cooling. The crude salt, 0.85 g., m.p. 172-174°, was recrystallized from 14 ml. of 2-propanol to

give 0.67 g. (55% yield) of the fumaric acid salt (0.5:1) of **2**, m.p. unchanged at 172-174°.

Anal. Calcd. for $C_9H_8N_2O_2 \cdot 0.5 C_4H_4O_4 (C_{11}H_{10}N_2O_4)$: C, 56.41; H, 4.31; N, 11.96; N.E. (sodium hydroxide), 117; N.E. (perchloric acid), 234. Found: C, 56.38; H, 4.57; N, 11.96; N.E. (sodium hydroxide), 120; N.E. (perchloric acid), 240.

In similar fashion was prepared the malic acid salt (0.5:1) of **2**, m.p. 131-133°, after recrystallization from ethyl methyl ketone-hexane. The yield was 47%.

Anal. Calcd. for $C_9H_8N_2O_2 \cdot 0.5 C_4H_4O_5 (C_{11}H_{10}N_2O_{4.5})$: C, 54.55; H, 4.17; N, 11.57. Found: C, 54.41; H, 4.41; N, 11.58.

The maleic acid salt (1:1) of **2**, m.p. 154-156° dec. was obtained in 86% yield after recrystallization from acetonitrile.

Anal. Calcd. for $C_9H_8N_2O_2 \cdot C_4H_4O_4$: C, 53.43; H, 4.14; N, 9.58; N.E. (perchloric acid), 292. Found: C, 53.69; H, 4.41; N, 9.66; N.E. (perchloric acid), 300.

The tartaric acid salt (1:1) of **2**, m.p. 163-165° dec. was obtained in 75% yield, after recrystallization from acetonitrile.

Anal. Calcd. for $C_9H_8N_2O_2 \cdot C_4H_6O_4$: C, 47.85; H, 4.33; N,

8.58; N.E. (perchloric acid), 326. Found: C, 47.90; H, 4.49; N, 8.59; N.E. (perchloric acid), 330.

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(3) In contrast, while 8-hydroxyquinoline forms a deep-red, insoluble sodium alkoxide, at room temperature, it can literally be "titrated" with a variety of alkylating agents, *i.e.*, the deep-red solid and solution, in each instance, change to yellow when precisely one molar equivalent of the alkylating agent has been added (Unpublished studies by the author).

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