Tetrahydro- and Octahydropyrido[1,2-*a*]pyrimidin-4-ones

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The catalytic hydrogenation of 2-methyl-, **1** 2,8-dimethyl-, **2**, 2,9-dimethyl-, **3**, 9-methyl-2-propyl-, **4**, 2,3,9-trimethyl-, **5**, 9-methyl-2-phenyl-, **6**, 9-hydroxy-2-methyl-, **7**, 9-acetoxy-2-methyl, **8**, 9-carboxy-2-methyl-, **16**, 9-carboethoxy-2-methyl-, **17**, 9-carbomethoxy-2-methyl-, **18**, and several 9-carboxamido-2-methyl-, **19**, **20**, and **21**, derivatives of the pyrido[1,2-*a*]pyrimidin-4-one heterocycle has led to a series of novel 6,7,8,9-tetrahydro- and fully saturated, octahydro analogs. In deuteriochloroform or DMSO-d_6 solution, the pmr spectra of the tetrahydro derivatives derived from **1-7** revealed only the 6,7,8,9-tetrahydro structures. In the pmr spectra of **16-21**, there was evidence of a facile 1,3-prototropic shift of the proton from position-9 to position-1, resulting in equilibria between tautomeric species, *i.e.*, >CH-C=N- ⇌ >C=C-NH-. The ratio of tautomers present at equilibrium, with the esters, favored the enamine conformation, whereas, with both the carboxylic acid and the amides, the imine structure predominated. Supportive evidence for the enamine structure with the esters was derived also from the ir spectra. Alkylation of the anion derived from the tetrahydro 9-carbomethoxy derivative with sodium hydride led exclusively to derivatives of 6,7,8,9-tetrahydro system.

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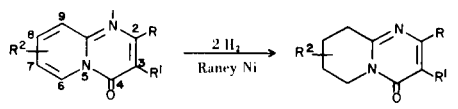
In earlier papers (2a-d), we have reported the synthesis of a variety of substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. In this paper we are describing the catalytic hydrogenation of several of those compounds as well as a number of hitherto unreported derivatives; these hydrogenations led to novel 6,7,8,9-tetrahydro and fully-saturated, octahydro derivatives (3).

I. Structure, Pmr, and Ir Spectra.

Employing Raney nickel as catalyst, in absolute methanol or ethanol, at ambient temperature, 2-methyl-, **1**, 2,8-dimethyl-, **2**, 2,9-dimethyl-, **3**, 9-methyl-2-propyl-, **4**, 2,3,9-trimethyl-, **5**, 9-methyl-2-phenyl-, **6**, and 9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **7** (4), gave the corresponding 6,7,8,9-tetrahydro derivatives, **9-15**, respectively. The pmr spectra of compounds **1-4**, **6**, **7**, in deuteriochloroform showed a one-proton, sharp singlet at *ca.* δ 6.35, that was absent in **5**, and that resonance, therefore, was assigned to the proton at position-3. The pmr spectra of the tetrahydro compounds derived from **1-3**, **5-7**, in deuteriochloroform or in DMSO-d_6 revealed the same one-proton, sharp singlet at *ca.* δ 6.35; hence, this signal indicated that those compounds, both in the crystalline state and in solution, possessed the 6,7,8,9-tetrahydro structure.



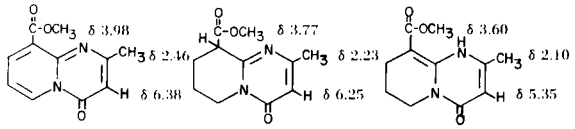
1-8; 16-21 → **9-15; 22-27**

1, **9**, R = Me, R^1, R^2 = H	**16**, **22**, R = Me, R^1 = H, R^2 = CO_2H
2, **10**, R = Me, R^1 = H, R^2 = 8-Me	**17**, **24**, R = Me, R^1 = H, R^2 = CO_2Et
3, **11**, R = Me, R^1 = H, R^2 = 9-Me	**18**, **23**, R = Me, R^1 = H, R^2 = CO_2Me
4, **12**, R = Pr, R^1 = H, R^2 = 9-Me	**19**, **25**, R = Me, R^1 = H, R^2 = $CONH_2$
5, **13**, R, R^1 = Me, R^2 = 9-Me	**20**, **26**, R = Me, R^1 = H, R^2 = CONHMe
6, **14**, R = Ph, R^1 = H, R^2 = 9-Me	**21**, **27**, R = Me, R^1 = H, R^2 = $CONH(CH_2)_3NMe_2$
7, **15**, R = Me, R^1 = H, R^2 = 9-HO	
8, R = Me, R^1 = H, R^2 = AcO_2	

In contrast, the pmr spectra of the tetrahydro ester derivatives, **23** and **24**, derived from **18** and **17**, respectively, showed the presence of tautomers. For example, with **23**, in DMSO-d_6 solution, the spectrum revealed two signals, which together integrated for three protons, associated with the methyl group at position-2: a major singlet at δ 2.10 and a minor one at δ 2.23. Again, the resonance of the protons in the -OCH_3 of the ester group was associated with a major singlet at δ 3.60 and a minor singlet at δ 2.77. Significantly, the proton at position-3 was now represented by a *minor singlet at δ 6.35 and a major, truncated singlet at δ 5.35*, and, finally, an NH proton, readily exchangeable with deuterium oxide, was seen as a broad singlet at δ 12.14. A second consequence of the deuterium oxide exchange was the sharpening of

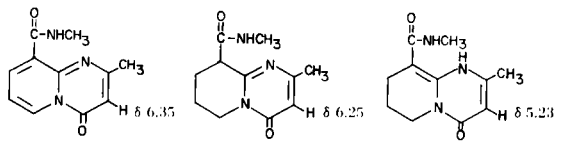
the singlet at δ 5.35, an observation that confirmed the anticipated small spin-spin coupling constant between the protons at positions-1 and -3 in the original spectrum. Identical observations were made in the pmr spectrum of the deuteriochloroform solution, with the single difference being that there was present lesser amounts of the minor tautomer, *i.e.*, *ca.* 5% in deuteriochloroform *vs.* the *ca.* 15% seen in DMSO-d_6.

These data can be used to support a concept that the proton at position-9 in **23a** can readily undergo a 1,3-prototropic shift to give the enamine, **23b**, so that at equilibrium, *i.e.*, the integration on a spectrum obtained from a solution kept 5 days at ambient temperature was unchanged from the original spectrum, the latter tautomer was favored. Dilution studies in both the ir and pmr served to give evidence of strong hydrogen bonding in solutions of the esters, **23** and **24** (5).



18 23a 23b

The pmr spectra of the tetrahydro amides, **25-27**, obtained from **19-21**, also showed the presence of tautomers, but the ratios were reversed, in that the equilibrium favored the imine structure. For example, in deuteriochloroform solution, the pmr spectrum of **20** revealed the resonance of the proton at position-3 at δ 6.35 while with **26**, that group was represented by a major, sharp singlet at δ 6.25 and a minor, somewhat broadened singlet at δ 5.23; integration of the two resonances indicated that the ratio of tautomers was *ca.* 72:18. The NH at position-1 was represented by a broad, deuterium oxide exchangeable, multiplet at δ 3.05-3.55, and, again, the secondary effect of the deuterium oxide exchange was to convert the minor signal at δ 5.23 to a sharp singlet at δ 5.20. Evidence from their ir spectra supported the concept that strong intermolecular hydrogen bonding was present in solutions of **25-27**.

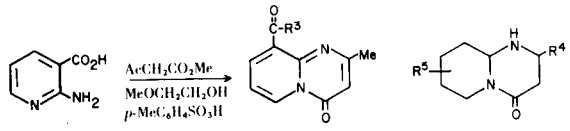


20 26a 26b

Finally, the anion derived from **23** by means of sodium hydride in *N,N*-dimethylformamide, was treated with methyl iodide and with α-bromotoluene to give, in each instance, only the 9-methyl-, **28**, and the 9-benzyl-, **29**, derivatives, respectively (6). In **28** and **29**, the methyl protons of each ester group was found to resonate as a single, one-proton singlet at δ 3.70 while the proton at position-3 in each compound, was seen as a single, one-proton singlet at δ 6.22; these signals established the compounds as 6,7,8,9-tetrahydro derivatives.

Chemistry.

The preparation of **1-7** involved a procedure previously described, employing ethylene glycol monomethyl ether, **30**, as the solvent (2d). Since 2-aminonicotinic acid, **31**, is a remarkably insoluble compound, its annulation with methyl acetoacetate, although carried out in that solvent under reflux for 96 hours, gave **16** in only 16% yield; the insoluble material after 96 hours of heating was the remaining unreacted **31**. When the more soluble methyl 2-aminonicotinate replaced **31**, unidentified tarry substances were formed and the single product that could be isolated, and then only in low yield, was the 2-methoxyethyl ester, **32**, of **16**. Authentic **32** was prepared from **16**, **30**, and dry hydrogen chloride; **17** and **18** were prepared by the esterification of **16** with the appropriate alcohol in the presence of sulfuric acid. The hydrogenation of **16** in methanol, in methanolic sodium methoxide, or aqueous sodium hydroxide, employing Raney nickel as catalyst at ambient temperature, gave largely the tetrahydro decarboxylated product, **9**; authentic **9** was prepared by the hydrogenation of **1**. The saponification of **23** in aqueous ethanolic sodium hydroxide at ambient temperature gave the sodium salt of the tetrahydro-9-carboxylic acid, **22** but attempts to isolate the 9-carboxylic acid resulted in spontaneous decarboxylation and the formation of **9**. Although **23** did not react with either ammonia or primary amines, **18** reacted readily with those reagents to give **19-21**; paradoxically, neither **18** nor **23** reacted with secondary amines. The octahydro derivatives, **33-36** were prepared *via* the platinum catalyzed hydrogenation of either **3** or **11**, **14**, **7**, or **8**, respectively.



31

16, R^3 = HO
17, R^3 = EtO
18, R^3 = MeO
32, R^3 = $MeOCH_2CH_2O$

33, R^4 = Me, R^5 = 9-Me
34, R^4 = Ph, R^5 = 9-Me
35, R^4 = Me, R^5 = 9-HO
36, R^4 = Me, R^5 = AcO_2

EXPERIMENTAL

The ir spectra were obtained on mineral oil mulls or on deuteriochloroform solutions, employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were obtained on deuteriochloroform, deuteriodimethyl sulfoxide or trifluoroacetic acid solutions with a Perkin Elmer R12B spectrophotometer. These spectra, as well as the microanalyses, were obtained by the staff of the Analytical Department of this Institute. The meltings

points were determined in capillary tubes in an electrically heated oil bath and are uncorrected.

9-Methyl-2-propyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**4**).

A solution of 31.60 g. (0.20 mole) of ethyl butyrylacetate, 11.00 g. (0.10 mole) of 2-amino-3-methylpyridine, and 2.00 g. of *p*-toluenesulfonic acid monohydrate in 125 ml. of ethylene glycol monomethyl ether was heated under reflux for 50 hours, and then concentrated *in vacuo* to dryness. The residual liquid was extracted with 250 ml. of boiling pentane; the insoluble solid, 1.20 g., was shown to be the *salt*, $C_6H_8N_2 \cdot C_7H_7SO_3H$, m.p. 145-147°, by comparison with an authentic sample of the salt, employing ir spectra and mixture m.p. comparisons. The pentane solution was cooled to -20° to give 12.50 g. of solid, m.p. 45-55°; a second recrystallization of this solid from 200 ml. of pentane gave 8.00 g. (40% yield) of **4**, m.p. 57-59°; ir (mull): ν 1695 (s), 1660 (m), 1620 (s), 1570 (w), 1540 (m), 1455 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.00 [t (J = 6 Hz), 3H, CH_2CH_3], 1.45-2.15 (m, 2H, CH_2CH_3), 2.60 (s, 3H, CH_3 at position-9), 2.65 [t (J = 6 Hz), 2H, $CH_2CH_2CH_3$], 6.35 (s, 1H, *H* at position-3), 7.00 [t (J = 6 Hz), 8.95 [q (J = 2, 6 Hz), 1H, *H* at position-6].

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.24; H, 6.98; N, 13.85; N.E., 202. Found: C, 71.45; H, 7.06; N, 14.14; N.E. ($HClO_4$), 207.

2,3,9-Trimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**5**), and its *p*-Toluenesulfonic Acid Salt (1:1) (**5a**).

A solution of 11.00 g. (0.10 mole) of 2-amino-3-methylpyridine, 28.80 g. (0.20 mole) of ethyl 2-methylacetoacetate, and 125 ml. of ethylene glycol monomethyl ether was stirred and heated under reflux for 116 hours, and then cooled to ambient temperature. The solid that crystallized was filtered and dried to give 6.60 g. of solid, m.p. 105-107°. The filtrate, concentrated to one-half volume, gave an additional 8.00 g. of dried solid, m.p. 102-104°. The 14.40 g. were recrystallized from 280 ml. of diisopropyl ether to give 11.13 g. (59% yield) of **5**, m.p. 105-107°; ir (deuteriochloroform): ν 1650 (s), 1635 (s), 1575 (w), 1540 (m), 1470 (s), 1430 (m) cm^{-1}; pmr (deuteriochloroform): δ 2.26 (s, 3H, CH_3 at position-3), 2.53 (s, 3H, CH_3 at position-2), 2.60 (s, 3H, CH_3 at position-9) (no signal between δ 2.60-6.80), 6.91 [t (J = 6 Hz), 1H, *H* at position-8], 7.25-7.60 (m, 2H, *H* at positions-7 and -8).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.31; H, 6.73; N, 14.71.

Further concentration of the filtrate from the 8.00 g. of crude **5** to one-quarter the original volume gave 5.50 g. of solid, m.p. 116-174°. This was extracted with 160 ml. of boiling diisopropyl ether, and filtered hot. From the filtrate was recovered 2.20 g. of additional **5**. The solid insoluble in the diisopropyl ether, 1.45 g., m.p. 190-193°, was recrystallized from 25 ml. of acetonitrile to give **5a**, m.p. 203-205°.

Anal. Calcd. for $C_{11}H_{12}N_2O \cdot C_7H_8O_3S$: C, 59.98; H, 5.60; N, 7.78; N.E., 360. Found: C, 59.79; H, 5.53; N, 7.78; N.E. ($HClO_4$), 0.0; N.E. (NaOH), 353.

9-Acetoxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**8**).

To 3.50 g. (0.020 mole) of **7**, 4.00 g. (0.050 mole) of anhydrous pyridine, and 100 ml. of anhydrous benzene, at ambient temperature, was added 3.40 g. (0.040 mole) of acetyl chloride in 20 ml. of anhydrous benzene, dropwise and with stirring. Subsequently, the mixture was stirred for an additional 0.5 hours, heated for 2 hours at 60°, cooled, filtered from pyridine hydrochloride and the filtrate concentrated to dryness *in vacuo*. The residual solid, 4.50 g., was recrystallized from 700 ml. of hexane to give 2.80 g. of **8**, m.p. 97-99°; ir (deuteriochloroform): ν 1770 (s), 1685 (s), 1635 (s), 1570 (w), 1490 (m), 1465 (s), 1420 (s), 1410 (s) cm^{-1}; uv λ (ethanol, 1%): 249, 256, 318 (sh), 338 mμ (ϵ, 9,100, 9,000, 8,200, 9,100); pmr (deuteriochloroform): δ 2.45 (m, 6H, CH_3CO plus CH_3 at position-2), 6.36 (s, 1H, *H* at position-3), 7.06 [t (J = 6 Hz), 1H, *H* at position-7], 7.47 [q (J = 2,6 Hz), 1H, *H* at position-8], 8.97 [q (J = 2,6 Hz), 1H, *H* at position-6].

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84; N.E., 218. Found: C, 60.42; H, 4.49; N, 13.03; N.E. ($HClO_4$), 221.

6,7,8,9-Tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**9**).

a) *via* Concomitant Decarboxylation.

A suspension of 2.80 g. (0.014 mole) of **16**, 3.0 g. of Raney nickel, and 200 ml. of absolute ethanol was shaken at ambient temperature and under 50 psi of hydrogen. Hydrogen absorption ceased after 5 hours with a pressure drop equivalent to 0.021 moles of hydrogen. Workup gave 2.40 g. of solids; recrystallization from 200 ml. of pentane gave 1.70 g. (77% yield) of **9**, m.p. 77-79°; (deuteriochloroform): ν 1665 (s), 1590 (m), 1520 (s), 1470 (s), 1460 (s), 1450 (m), 1410 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.70-2.18 (m, 4H, CH_2 at positions-7 and -8), 2.22 (s, 3H, CH_3 at position-2), 2.70-3.05 (perturbed t, 2H, CH_2 at position-9), 3.70-4.05 (perturbed t, 2H, CH_2 at position-6), 6.15 (s, 1H, *H* at position-3).

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.79; H, 7.37; N, 17.04; N.E., 164. Found: C, 65.57; H, 7.27; N, 16.90; N.E. ($HClO_4$), 167.

b) *via* Reduction of 2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**1**).

A solution of 1.60 g. (0.010 mole) of **1** in 200 ml. of absolute methanol and 2.0 g. of Raney nickel were hydrogenated at 50 psi; reduction was complete in 0.75 hour. Workup as in *a* gave 1.60 g. (quantitative yield) of **9**, m.p. 77-79°. The products from (a) and (b) had identical R_f values, 0.38, on silica gel plates (acetone:benzene, 1:1), and identical ir and pmr spectra.

Anal. Found: C, 65.96; H, 7.44; N, 17.08; N.E. ($HClO_4$), 167.

6,7,8,9-Tetrahydro-2,8-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**10**).

To a solution of 3.40 g. (0.020 mole) of **2** in 200 ml. of absolute methanol was added 2.0 g. of Raney nickel catalyst and the suspension hydrogenated at ambient temperature and 50 psi. After 2 hours, the pressure drop indicated the absorption of 0.02 mole of hydrogen. The mixture was filtered and the filtrate concentrated to dryness *in vacuo*. The residual solid, 3.30 g., was recrystallized from 200 ml. of pentane to give 2.90 g. (88% yield) of **10**, m.p. 64-66°; ir (mull): ν 1650 (s), 1580 (m), 1520 (s), 1475 (w), 1450 (w), 1425 cm^{-1}; pmr (deuteriochloroform): δ 1.10 [d (J = 4 Hz), 3H, CH_3 at position-8], 1.25-2.20 (m, 3H, CH_2 at position-7 plus *H* at position-8), 2.20 (s, 3H, CH_3 at position-2), 2.45-3.25 (m, 2H, CH_2 at position-9), 3.30-4.50 (m, CH_2, 2H at position-6), 6.30 (s, 1H, H at position-3).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72; N.E., 178. Found: C, 67.26; H, 7.69; N, 15.58; N.E. ($HClO_4$), 179.

6,7,8,9-Tetrahydro-2,9-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**11**) and its Maleate Salt (**11a**).

The procedure employed to prepare **10**, gave with **3**, **11** in 74% yield, m.p. 76-78°, after recrystallization from pentane; ir (mull): ν 1635 (s), 1590 (m), 1540 (s), 1530 (s), 1500 (w), 1470 (w), 1460 (w), 1435 cm^{-1}; pmr (deuteriochloroform): δ 1.40 [d

(J = 4 Hz), 3H, CH_3, at position-9], 1.60-2.50 (m, 3H, *H* at position-7 plus CH_2 at position-8), 2.24 (s, 3H, CH_3 at position-2), 2.80-3.20 (m, 1H, *H* at position-9), 3.80-4.40 (2H, CH_2 at position-6), 6.20 (s, 1H, *H* at position-3).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72; N.E., 178. Found: C, 67.27; H, 7.99; N, 15.95; N.E. ($HClO_4$), 182.

A warm solution of 0.21 g. (0.0018 mole) of maleic acid in 2.0 ml. of 2-butanone was added to a solution of 0.260 g. (0.0015 mole) of pure **11** in 2.0 ml. of 2-butanone. The mixture was heated to reflux, allowed to cool, diluted with 10 ml. of anhydrous ether, the solid filtered, and dried to give 0.40 g. (90% yield) of the maleic acid salt, m.p. 95-97°.

Anal. Calcd. for $C_{10}H_{14}N_2O \cdot C_4H_4O_4$: C, 57.31; H, 6.17; N, 9.52; N.E., 147, 294. Found: C, 57.26; H, 6.40; N, 9.53; N.E. (NaOH), 149, ($HClO_4$), 300.

6,7,8,9-Tetrahydro-9-methyl-2-propyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**12**).

The procedure described for **10** gave with 2.00 g. (0.010 mole) of **4**, 2.00 g. of **12** as an oil, b.p. 128° (0.2 mm), n_D^{24} 1.5300; ir (neat): ν 3500 (w), 1670 (s), 1590 (m), 1530 (s), 1480 (m), 1470 (m), 1410 (m), 1414 (m) cm^{-1}; pmr (deuteriochloroform): δ 0.95 [t (J = 6 Hz), 3H, $(CH_2)_2CH_3$], 1.30 [d (J = 6 Hz), 3H, CH_3 at position-9], 1.45-2.25 (m, 6H, $CH_2CH_2CH_3$ plus CH_2 at positions-7 and -8), 2.65-3.20 (m, 1H, *H* at position-9), 3.50-4.15 (m, 1H, *H* at position-6), 6.10 (s, 1H, *H* at position-3).

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.82; H, 8.80; N, 13.57; N.E., 206. Found: C, 69.67; H, 9.10; N, 13.52; N.E. ($HClO_4$), 206.

6,7,8,9-Tetrahydro-2,3,9-trimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**13**).

To a solution of 5.60 g. (0.03 mole) of **5** in 200 ml. of absolute ethanol was added 6.0 g. of Raney nickel; reduction under 50 psi of hydrogen was incomplete at ambient temperature after 4 hours. A second addition of 5.0 g. of Raney nickel and 20 hours of shaking at 50 psi was required to complete the reduction. The yield of crude product was 5.70 g., recrystallization from pentane gave 3.20 g. (55% yield) of **13**, m.p. 73-75°; ir (deuteriochloroform): ν 1650 (s), 1635 (s), 1580 (m), 1540 (s), 1470 (m), 1450 (w), 1415 (w) cm^{-1}; pmr (deuteriochloroform): δ 2.25 (s, 3H, CH_3 at position-3), 2.53 [d (J = 4 Hz), 3H, CH_3 at position-2), 6.91 [t (J = 6 Hz), 1H, *H* at position-7], 7.40 [t (J = 6 Hz), 1H, *H* at position-8], 8.88 [q (J = 2, 6 Hz), 1H, *H* at position-6].

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.70; H, 8.39; N, 14.57; N.E., 192. Found: C, 69.04; H, 8.44; N, 14.87; N.E. ($HClO_4$), 196.

6,7,8,9-Tetrahydro-9-methyl-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**14**) and its *p*-Toluenesulfonate Salt (**14a**).

The procedure employed to prepare **10**, with **6**, gave **14** in 71% yield, m.p. 78-80°, after recrystallization from pentane; ir (mull): ν 1655 (s), 1600 (m), 1590 (m), 1565 (s), 1530 (s), 1490 (m), 1450 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.52 [d (J = 5 Hz), 3H, CH_3 at position-9], 1.55-2.40 (m, 4H, CH_2 at positions-7 and -8), 3.00 [t (J = 6 Hz), *H* at position-9], 3.80-4.20 (m, 1H, *H* at position-6), 6.75 (s, 1H, *H* at position-3), 7.26-8.20 (5H, 5 Ar-*H*).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.65; N.E., 240. Found: C, 75.01; H, 6.64; N, 11.79; N.E. ($HClO_4$), 244.

Solutions of 1.90 g. (0.01 mole) of *p*-toluenesulfonic acid monohydrate in 20 ml. of water and 1.80 g. (0.005 mole) of **14** in 56 ml. of 50% aqueous 2-propanol were mixed thoroughly and concentrated *in vacuo* to remove 2-propanol. The aqueous solution was lyophilized to give 2.70 g. of a gum which solidified when triturated with 100 ml. of anhydrous ether. The solid was filtered and dried to give 2.20 g. of **14a**, m.p. 130-133°.

Anal. Calcd. for $C_{15}H_{16}N_2O \cdot 2C_7H_8O_3S$: C, 59.57; H, 5.51; N, 4.79; S, 10.96. Found: C, 59.85; H, 5.74; N, 4.96; S, 10.74.

6,7,8,9-Tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**15** and its Hydrochloride (**15a**).

(a) A solution of 3.50 g. (0.020 mole) of **7** in 250 ml. of absolute ethanol and 3.0 g. of Raney nickel was hydrogenated at 50 psi at ambient temperature. Absorption was slow and 22 hours were required for the uptake of 0.04 mole of hydrogen. That a complex mixture of products had formed was shown by tlc. The brown, semi-solid residue, 3.5 g., in 30 ml. of chloroform was chromatographed on a column of 145 g. of silica gel (Grade 239, Davison, No. 923-0808, 100-200 mesh). Elution by acetone:chloroform (1:4) (5-100 ml. portions) gave 0.60 g. of solid, m.p. 115-120°. Continued elution with acetone:chloroform (3:7) gave 0.30 g. of solid, m.p. 115-120°. The combined solids, 0.90 g., showed a single spot on tlc [silica gel plates, acetone:chloroform (1:1)]. Recrystallization of the combined solids from 125 ml. of diisopropyl ether gave 0.55 g. (15% yield) of **15**, m.p. 98-100°; ir (mull): ν 3220 (broad s), 1660 (s), 1595 (w), 1520 (m), 1470 (m), 1460 (m), 1415 (m), 1400 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.50-2.36 (m, 4H, CH_2 at position-7 plus CH_2 at position-8), 2.24 (s, 3H, CH_3 at position-2), 3.70-4.00 (m, 2H, CH_2 at position-6), 4.15-4.65 [m, 2H, O*H* (exchanges with deuterium oxide) plus *H* at position-9], 6.20 (s, 1H, *H* at position-3).

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.54; N.E., 180. Found: C, 59.85; H, 6.52; N, 15.24; N.E. ($HClO_4$), 185.

(b) A solution of 5.20 g. (0.03 mole) of **15** in 200 ml. of absolute ethanol and 6 ml. of concentrated (37%) aqueous hydrochloric acid and 1.0 g. of 5% palladium-carbon was hydrogenated at 50 psi and 60°. Hydrogenation was complete in 6 hours. Concentration of the filtered solution gave 6.10 g. of solid, m.p. 260-263° dec. Recrystallization from 100 ml. of 1-butanol gave 4.20 g. (64% yield) of **15a**, m.p. 274-276°.

Anal. Calcd. for $C_9H_{12}N_2O_2 \cdot HCl$: C, 49.90; H, 6.04; N, 12.93; Cl, 16.36. Found: C, 49.74; H, 5.79; N, 13.15; Cl, 16.27.

2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-carboxylic Acid (**16**).

A mixture of 13.80 g. (0.10 mole) of 2-aminonicotinic acid, **31**, 23.20 g. (0.20 mole) of methyl acetoacetate, 0.50 g. of *p*-toluenesulfonic acid, and 100 ml. of ethylene glycol monomethyl ether was stirred and heated under reflux for 72 hours and filtered hot. The insoluble material was unchanged **31**. The filtrate when cooled gave 3.30 g. of solid, m.p. 220-221° dec. The unreacted **31**, the filtrate from the 3.30 g. of solid, and an additional 0.50 g. of *p*-toluenesulfonic acid were stirred and heated under reflux for an additional 24 hours, and, as above, gave 2.10 g. of additional solid, m.p. 220-221° dec. The combined solids, 5.40 g., were heated under reflux with 450 ml. of toluene and filtered hot to remove 1.10 g. of **31**; on cooling, the filtrate gave 3.30 g. (16% yield) of **16**, m.p. 233-235° dec.; ir (deuteriochloroform): ν 3110 (w), 2600 (broad w), 1690 (s), 1625 (m), 1590 (s), 1540 (s), 1470 (s), 1415 (s) cm^{-1}; pmr (deuteriochloroform): δ 2.54 (s, 3H, CH_3), 6.36 (s, 1H, *H* at position-3), 7.36 [t (J = 6 Hz), 1H, *H* at position-7], 8.90 [q (J = 2, 6 Hz), 1H, *H*-at position-8], 9.20 [q (J = 2, 6 Hz), 1H, *H*-at position-6], the CO_2H was not seen, due, presumably, to that proton being bound *via* intramolecular salt

formation.

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.83; H, 3.95; N, 13.72; N.E., 204. Found: C, 58.62; H, 4.24; N, 13.73; N.E. (NaOH), 206.

Ethyl 2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylate (**17**).

A suspension of 10.00 g. (0.050 mole) of **16** in 1 liter of absolute ethanol containing 5.0 g. of concentrated sulfuric acid was stirred and heated under reflux. A solution formed in 10 minutes and the solution was heated under reflux for 60 hours, when tlc [silica gel plates, 1:1, benzene:acetone; **16** had an Rf of *ca.* 0.55; **17** had an Rf of *ca.* 0.80] indicated the absence of **16**. The cooled mixture was treated with 9.0 g. of powdered sodium bicarbonate (*p*H 6.5), filtered, and the filtrate concentrated to dryness, *in vacuo*. The residual solid, 10.0 g., was recrystallized from 600 ml. of petroleum ether to give 6.10 (53% yield) of **17**, m.p. 73-75°; ir (deuteriochloroform): ν 3120 (w), 2990 (w), 1725 (s), 1680 (s), 1620 (s), 1570 (m), 1535 (s), 1460 (s) cm^{-1}; pmr (deuteriochloroform): 1.40 [t (J = 6 Hz), 3H, CH_2CH_3], 2.45 (s, 3H, CH_3 at position-2), 4.50 [q (J = 12, 6 Hz), 2H, CH_2CH_3], 6.35 (s, 1H, *H* at position-3), 7.05 [t (J = 6 Hz), 1H, *H* at position-7], 7.90 [q (J = 6, 2 Hz), 1H, *H* at position-8], 9.10 [q (J = 6, 2 Hz), 1H, *H* at position-6], uv λ (methanol, 1%): 236, 254, 335 nm (ϵ, 8,840, 9,930, 9,770).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.21; N, 12.07; N.E., 232. Found: C, 62.03; H, 5.00; N, 11.92; N.E. ($HClO_4$), 232.

Methyl 2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylate (**18**).

The procedure employed for **17**, but with the substitution of absolute methanol, gave a 60% yield of **18**, m.p. 75-77°, after recrystallization from diisopropyl ether (21 ml./g.); ir (deuteriochloroform): ν 3120 (w), 2960 (m), 1735 (s), 1740 (broad s), 1630 (s), 1575 (s), 1540 (s), 1460 (s), 1425 (s) cm^{-1}; pmr (deuteriochloroform): δ 2.46 (s, 3H, CH_3 at position-2), 3.98 (s, 3H, OCH_3), 6.35 (s, 1H, *H* at position-3), 7.10 [t (J = 6 Hz), 1H, *H* at position-7], 8.04 [q (J = 6, 2 Hz), 1H, *H* at position-8], 9.14 [q (J = 6, 2 Hz), 1H, *H* at position-6]; uv λ (methanol, 1%): 237, 254, 335 nm (ϵ, 8,790, 9,930, 9,810).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.85; N.E., 218. Found: C, 60.77; H, 4.87; N, 13.02; N.E. ($HClO_4$), 219.

2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxamide (**19**).

A suspension of 1.50 g. (0.007 mole) of **18** in 80 ml. of 3.6 *N* ethanolic ammonia was stirred in a pressure bottle at ambient temperature; within 5 minutes, a solution had formed, but shortly thereafter, a solid began to separate. The stirring was continued for 24 hours, the solid was filtered, and dried to give 1.30 g. of material, m.p. 243-245°. Recrystallization from 180 ml. of acetonitrile gave 0.95 g. (68% yield) of **19**, m.p. 247-249°; ir (mull): ν 3280 (s), 1720 (s), 1685 (s), 1620 (m), 1570 (m), 1540 (s), 1480 (s), 1450 (m) cm^{-1}; pmr (deuteriochloroform): δ 2.48 (s, 3H, CH_3 at position-2), 5.70-7.00 [broad s, 2H, NH_2 (equilibrates with deuterium oxide, slowly)], 6.35 (s, 1H, *H* at position-3), 7.20 [t (J = 6 Hz), 1H, *H* at position-7], 8.92 [q (J = 6, 2 Hz), 1H, *H* at position-6], 9.20 [q (J = 6, 2 Hz), 1H, *H* at position-8].

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.47; N, 20.68. Found: C, 59.07; H, 4.25; N, 20.94.

N,2-Dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxamide (**20**).

A suspension of 2.00 g. (0.01 mole) of **18** in 40 ml. of 5.2 *N* ethanolic methylamine was stirred in a sealed pressure flask at ambient temperature. Reaction was rapid with solution occurring within five minutes, followed quickly by the separation of a crystalline product. The yield of crude **20** was 2.10 g., m.p. 163-165°. Recrystallization from 10 ml. of acetonitrile gave 1.10 g. of **20**, m.p. 166-168°; ir (deuteriochloroform): ν 3210 (m, broad), 3120 (m), 1690 (s), 1660 (s), 1610 (m), 1595 (m), 1560 (s), 1485 (s), 1460 (s), 1415 (s) cm^{-1}; pmr (deuteriochloroform): δ 2.46 (s, 3H, CH_3 at position-2), 3.10 [d (J = 4 Hz), 3H, $NHCH_3$), 6.35 (s, 1H, H at position-3), 7.24 [t (J = 6 Hz), 1H, *H* at position-7), 8.96 [q (J = 6, 2 Hz), 1H, H at position-6), 9.15 [q (J = 6, 2 Hz), 1H, *H* at position-8).

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.11; N, 19.35. Found: C, 60.71; H, 5.07; N, 19.25.

N-[3-(Dimethylamino)propyl]-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidine-9-carboxamide (**21**).

A solution of 10.00 g. (0.1 mole) of 3-dimethylaminopropylamine and 2.00 g. (0.009 mole) of **18** in 50 ml. of absolute methanol was kept at ambient temperature for 48 hours, and then concentrated to dryness *in vacuo*. The residue, 3.30 g., was triturated with 50 ml. of cold diisopropyl ether to give 1.90 g. of solid, m.p. 75-78°. Recrystallization from 50 ml. of diisopropyl ether gave 1.60 g. (61% yield) of **21**, m.p. 76-78°; ir (deuteriochloroform): ν 3220 (w), 169 (s), 1650 (s), 1550 (m), 1535 (m), 1460 (s), 1420 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.65-2.20 (m, 2H, CH_2CH_3), 2.25 [s (6H, $N(CH_3)_2$], 2.30-2.40 (m, 2H, $CH_2N(CH_3)_2$], 2.50 (s, 3H, CH_3 at position-2), 3.35-3.75 [m, 2H, $CH_2CH_2CH_2N(CH_3)_2$], 6.35 (1H, *H* at position-3), 7.25 [t (J = 6 Hz), 1H, *H* at position-7), 8.95 [q (J = 6, 2 Hz), 1H, *H* at position-8], 9.20 [q (J = 6, 2 Hz), 1H, *H* at position-6], 10.30-11.20 [broad s, 1H, N*H* (equilibrates with deuterium oxide)].

Anal. Calcd. for $C_{15}H_{20}N_4O_2$: C, 62.47; H, 6.99; N, 19.43; N.E., 144. Found: C, 62.49; H, 6.82; N, 19.64; N.E. ($HClO_4$), 147.

Sodium 4,6,7,8-Tetrahydro-2-methyl-4-oxo-1*H*-pyrido[1,2-*a*]-pyrimidine-9-carboxylate (**22a**) and Sodium 6,7,8,9-Tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylate (**22b**).

To a solution of 0.33 g. (0.0015 mole) of **23** in 50 ml. of 50% aqueous ethanol was added 1.70 ml. of *N* aqueous sodium hydroxide and the solution kept at ambient temperature for 2 hours. The solution was concentrated to dryness *in vacuo* at ambient temperature and the solid residue triturated with 2-25 ml. portions of dichloromethane. The solid was dried at 56°/1-2 mm to give 0.31 g. (90% yield) of the hygroscopic salt, **22**, m.p. 210-220° dec.; ir (potassium bromide): 3440 (broad m), 2960 (m), 1670 (broad s), 1610 (broad s), 1530 (s), 1480 (m), 1455 (m) cm^{-1}; pmr (perdeuteriomethanol): δ 1.80-2.70 (m, *ca.* 6H, CH_3 at position-2, *H* at position-9, CH_2 at position-8), 3.70-4.20 (m, 2H, CH_2 at position-7), 4.80 (s, 2H, CH_2 at position-6), 5.10 (sharp s, *ca.* 0.2 H, *H* at position-3), 6.25 (sharp s, 0.8 H, *H* at position-3).

Anal. Calcd. for $C_{10}H_{11}N_2O_3Na$: C, 52.20; H, 4.82; N, 12.17; Na, 10.44. Found: C, 52.20; H, 4.85; N, 12.22; Na, 10.59.

A 2% solution of **22** in water had a *p*H of 9.5. When the cooled solution was treated dropwise, while agitated, with 20% acetic acid, carbon dioxide evolution commenced at *p*H *ca.* 7.5 and the rate increased as the *p*H was adjusted to 5.5. When the evolution of gas ceased, the solution was concentrated *in vacuo*. The residual solid was found to be **9**, by m.p. and ir spectral comparison.

Methyl 4,6,7,8-Tetrahydro-2-methyl-4-oxo-1*H*-pyrido[1,2-*a*]-pyrimidine-9-carboxylate (**23a**) and Methyl 6,7,8,9-Tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylate (**23b**).

A solution of 2.20 g. (0.01 mole) of **18** in 200 ml. of absolute methanol and 3.0 g. of Raney nickel was hydrogenated as in **10**; 0.02 mole of hydrogen was absorbed in 0.25 hour and no further uptake was observed during an additional 0.25 hour. Workup gave 2.00 g. of solid, m.p. 120-122°, and from this, by recrystallization from 140 ml. of diisopropyl ether was recovered 1.55 g. (70% yield) of **23**, m.p. 126-128°; ir (deuteriochloroform): 3280 (w), 3220 (w), 3160 (w), 1685 (w), 1670 (s), 1640 (s), 1590 (s), 1480 (m), 1430 (s) cm^{-1}; pmr (DMSO-d_6): δ 1.48-2.00 (m, 2H), 2.10 plus 2.23 (s, 3H), 2.30-2.60 (m, 2H), 3.25-3.50 (m, 2H), 3.60 plus 3.77 (s, 3H), 5.33 [truncated s (see below)], 6.16 [truncated s (see below)], 12.14 (broad s, 1H; N*H*). *NOTE:* the integration of the signals in these spectra did not change during five days at ambient temperatures; pmr (deuteriochloroform): δ 1.62-2.05 (m, 2H, 2*H* at position-7), 2.12 (s, 3H, CH_3 at position-2), 2.20-2.60 (m, 2H, CH_2 at position-8), 3.70 (s, 3H, OCH_3), 3.30-3.96 (m, CH_2 at position-6), 5.32 [truncated s, *ca.* 0.95 H, *H* at position-3 (see below)], 6.26 [s, *ca.* 0.05 H, *H* at position-3 (see below)] [the integrations of the signals at δ 5.32 and 6.26 were not altered when the solutions were kept at 25° for 3 days and the spectrum rerun], 12.30 [broad s, 1H, N*H* (exchanges with deuterium oxide]. Thus, at 25°, equilibrium in deuteriochloroform was represented by a ratio of **23a**:**23b** of *ca.* 5:95 while in DMSO-d_6, the ratio was *ca.* 15:85.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.43; H, 6.35; N, 12.60; N.E., 222; m/e 236. Found: C, 59.48; H, 6.36; N, 12.65; N.E. ($HClO_4$), 227; m/e, 226.

Ethyl 4,6,7,8-Tetrahydro-2-methyl-4-oxo-1*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylate (**24a**) and Ethyl 6,7,8,9-Tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylate (**24b**).

A solution of 3.50 g. (0.015 mole) of **17** in 200 ml. of absolute ethanol and 3.0 g. of Raney nickel was hydrogenated as described for **10**; reduction was complete in 70 minutes, and 0.03 moles of hydrogen were absorbed. Workup gave 3.30 g. of solid, m.p. 115-117°. Recrystallization from 110 ml. of diisopropyl ether yielded 2.60 g. (74%) of **24**, m.p. 120-121°; ir (deuteriochloroform): ν 3080 (w), 2990 (w), 2960 (w), 1725 (w), 1665 (s), 1635 (m), 1585 (s), 1520 (w), 1480 (w), 1460 (w) cm^{-1}; pmr (deuteriochloroform): δ 1.28 [t (J = 6 Hz), 3H, CH_3CH_2], 1.60-2.00 (m, 2H, CH_2 at position-7), 2.10 (s, 3H, CH_3 at position-2), 2.20-2.60 (m, 2H, CH_2 at position-8), 3.65-4.05 (m, 2H, CH_2 at position-6), 4.20 [q (J = 12, 6 Hz), 2H, CH_2CH_3], 5.35 [truncated s, *ca.* 0.80 H, *H* at position-3 (see below)], 6.25 [s, 0.20 H, *H* at position-3 (see below)], 12.35 [broad s, *ca.* 0.7 *H*, N*H* (exchanges with deuterium oxide); pmr (DMSO-d_6): δ 1.18 [t (J = 6 Hz), 3H, CH_3CH_2], 1.55-2.00 (m, 2H, 2*H* at position-7), 2.05 (s, 3H, CH_3 at position-2), 2.25-2.60 (m, 2H, CH_2 at position-8), 3.24-4.35 (m, 4H, CH_2 at position-6 plus CH_2CH_3), 5.30 [truncated s, *ca.* 0.80 H, *H* at position-3 (see below)], 6.13 [s, 0.20 H, *H* at position-3 (see below)], 12.25 [broad s, *ca.* 0.9 H, N*H* (exchanges with deuterium oxide)]; (trifluoroacetic acid): δ 1.45 [t (J = 6 Hz), 3H, CH_2CH_3], 2.50-2.55 (m, 4H, CH_2 at positions-6 and -7), 2.62 (s, 3H, CH_3 at position-2), 4.00-4.73 (m, 5H, *H* at position-9, CH_2 at position-8, and OCH_2CH_3), (no signal at *ca.* δ 5.35), 6.78 (s, 1H, *H* at position-3) (no other downfield signal). Thus, the percentages of **24a** and **24b** in equilibrium at 25° in deuteriochloroform and DMSO-d_6 are the same, *ca.* 80:20 while in trifluoroacetic acid, only **24a** is present.

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 62.07; H, 5.21; N, 12.07; N.E., 232. Found: C, 62.03; H, 5.00; N, 11.92; N.E. ($HClO_4$), 235.

4,6,7,8-Tetrahydro-2-methyl-4-oxo-1*H*-pyrido[1,2-*a*]pyrimidine-9-carboxamide (**25a**) and 6,7,8,9-Tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxamide (**25b**).

The hydrogenation of a suspension of 2.20 g. (0.011 mole) of **19** and 3.0 g. of Raney nickel in 200 ml. of absolute methanol was complete in 1 hour as described for **10**. Workup gave 2.30 g. of solid, m.p. 213-216° dec.; this was recrystallized from 100 ml. of 2-propanol to give 1.70 g. (73% yield) of **25**, m.p. 214-216° dec.; ir (mull): ν 3380 (s), 3200 (m), 1670 (s), 1660 (s), 1650 (s), 1585 (w), 1520 (s), 1470 (w), 1455 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.50-2.15 (m, 4H, CH_2 at positions-7 and -8), 2.25 (s, 3H, CH_3 at position-2), 3.60-4.00 (m, 2H, CH_2 at position-6), 4.20-5.82 [m, *ca.* 2.5 H, *ca.* 0.5 H of **25a** plus NH_2; exchange with deuterium oxide results in the sharp demarcation of the two signals at δ 5.27 and 6.22], 6.22 (s, *ca.* 0.5 H, *H* in position-3 of **25b**, 12.50-13.80 (m, *ca.* 0.4H, N*H* at position-1).

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28; N.E., 207. Found: C, 57.78; H, 6.52; N, 20.14; N.E. ($HClO_4$), 210.

6,7,8,9-Tetrahydro-*N*,2-dimethyl-4-oxo-1*H*-pyrido[1,2-*a*]pyrimidine-9-carboxamide (**26a**) and 1,6,7,8-Tetrahydro-*N*,2-dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxamide (**26b**).

In a hydrogenation carried out as in **10**, 2.20 g. (0.010 mole) of **20** gave 2.00 g. of solid, m.p. 151-153°; recrystallization from 50 ml. of toluene gave 1.56 g. (71% yield) of **26**, m.p. 158-160°; ir (deuteriochloroform): ν 3480 [sharp w, intramolecularly unbonded NH at position-1)], 3360 [broad, m, 1665 (s), 1590 (s), 1505 (s), 1465 (s), 1410 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.40-2.15 (m, 4H, 4*H* at positions-7 and -8), 2.25 (s, 3H, CH_3 at position-2), 2.85 [d (J = 4 Hz), 3H, $NHCH_3$], 3.50-4.25 [m, 3H, 2*H* at position-6 plus N*H* at position-1 (equilibrates with deuterium oxide)], 5.23 [truncated s, (see below)], 6.22 [s (see below)], 7.10-7.55 [m, 1H, $NHCH_3$ (equilibrates slowly with deuterium oxide)]. Integration of the two signals at δ 5.23 and 6.22 indicates that at equilibrium, in deuteriochloroform at *ca.* 25°, the ratio of **26a** to **26b** is 81:19.

Anal. Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.70; H, 6.84; N, 18.99; N.E., 221. Found: C, 59.54; H, 6.72; N, 18.99; N.E. ($HClO_4$), 224.

N-[3-(Dimethylamino)propyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxamide (**27a**) and *N*-[3-(Dimethylamino)propyl]-1,6,7,8-tetrahydro-2-methyl-4-oxo-1*H*-pyrido[1,2-*a*]pyrimidine-9-carboxamide (**27b**).

A suspension of 2.90 g. (0.010 mole) of **21**, 2.0 g. of Raney nickel, and 200 ml. of absolute methanol was hydrogenated as described for **10**. Recrystallization of the crude solid, 3.0 g., from 100 ml. of diisopropyl ether gave 1.80 g. (61% yield) of **27**, m.p. 89-91°; ir (deuteriochloroform): ν 1665 (s), 1625 (w), 1590 (m), 1510 (s), 1465 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.50-2.50 (m, 8H, CH_2 at positions-7 and -8, plus $CONHCH_2CH_2CH_2$), 2.15 [s, 6H, $N(CH_3)_2$], 2.25 (s, 3H, CH_3 at position-2), 3.20-3.75 [m, 3H, H at position-9 plus $CONHCH_2$ (see below)], 3.75-4.10 (m, 2H, CH_2 at position-6), 5.25 (s, *ca.* 0.17 H, *H* at position-3 in **27b**), 6.26 (s, *ca.* 0.83 H, *H* at position-3 in **27a**), 7.55-8.00 (m, *ca.* 1.2 H, CON*H* plus N*H* at position-1). The behavior of the 3.20-3.75 multiplet following equilibration with deuterium oxide was noteworthy; after 5 days, the multiplet had collapsed to a well-defined 2-proton triplet attributable to the $CONHCH_2$ portion of the molecule.

Anal. Calcd. for $C_{15}H_{24}N_4O_2$: C, 61.61; H, 8.27; N, 19.18; N.E., 146. Found: C, 61.41; H, 8.55; N, 18.99; N.E. ($HClO_4$), 147.

Methyl 6,7,8,9-Tetrahydro-2,9-dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidine-9-carboxylate (**28**).

A solution of 2.20 g. (0.010 mole) of **18** in 20 ml. of anhydrous *N,N*-dimethylformamide was added dropwise, under nitrogen to a suspension of 0.50 g. (0.01 mole) of 50% sodium hydride-mineral oil dispersion in 20 ml. of the same solvent. The mixture was stirred at room temperature for 3 hours, treated dropwise with a solution of 1.70 g. (0.010 mole) of iodomethane in 10 ml. of the same solvent, and the stirring continued at room temperature for 18 hours. The mixture was concentrated to dryness *in vacuo*, and the residue extracted with 100 ml. of dichloromethane and filtered. The filtrate showed a single spot, R_f 0.6 (silica gel plates, benzene: acetone, 1:1). The dichloromethane solution was concentrated to dryness, the residue, 3.20 g., was triturated with 25 ml. of pentane to remove mineral oil, and the solid remaining, 2.30 g., was recrystallized from petroleum ether to give 1.20 g. (52% yield) of **28**, m.p. 74-76°; ir (mull): ν 1730 (s), 1720 (s), 1660 (s), 1580 (m), 1525 (s), 1510 (s), 1500 (s), 1455 (s), 1445 (s) cm^{-1}; uv λ max (ethanol): 229 nm (ϵ, 10,000); pmr (deuteriochloroform): δ 1.68 (s, 3H, CH_3 at position-9), 1.70-2.20 (m, 4H, 4*H* at positions-7 and -8), 2.25 (s, 3H, CH_3 at position-2), 3.70 (s, 3H, OCH_3), 3.70-4.15 (m, 2H, 2*H* at position-6), (no resonances between δ 4.15 and 6.20), 6.22 (s, 1H, *H* at position-3).

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 60.99; H, 6.81; N, 11.85; OCH_3, 13.10; N.E., 236. Found: C, 61.29; H, 7.01; N, 11.95; OCH_3, 12.74; N.E. ($HClO_4$), 235.

Methyl 9-Benzyl-6,7,8,9-Tetrahydro-2-methyl-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidine-9-carboxylate (**29**).

The procedure was that described for **28**, with the modification that 1.75 g. (0.010 mole) of α-bromotoluene replaced the iodomethane. The product, **29**, was obtained in 14% yield, m.p. 72-74° after recrystallization from ligroin, ir (deuteriochloroform): ν 1730 (s), 1660 (s), 1585 (w), 1510 (s), 1490 (m), 1470 (m), 1445 (m), 1430 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.50-2.15 (m, 4H, 4*H* at positions-7 and -8), 2.32 (s, 3H, CH_3 at position-2), 3.50 [q (J = 24, 12 Hz), 2H, $PhCH_2$), 3.70 (s, 3H, OCH_3), 3.84-3.98 (m, 2H, 2*H* at position-6), (no resonances between δ 4.00 and 6.20), 6.22 (s, 1H, *H* at position-3), 6.80-7.30 (m, 5H, 5 Ar-*H*).

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.20; H, 6.45; N, 8.97; N.E., 312. Found: C, 69.08; H, 6.39; N, 8.97; N.E., 319.

2-Methoxyethyl 2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-9-carboxylate (**32**).

a. By Transesterification.

A solution of 5.00 g. (0.0330 mole) of methyl 2-aminonicotinate, 7.00 g. (0.066 mole) of methyl acetoacetate, 0.50 g. of *p*-toluenesulfonic acid monohydrate, and 40 ml. of ethylene glycol monomethyl ether was heated under reflux with stirring for 66 hours. The dark brown solution was concentrated *in vacuo* to give an oil. The oil was extracted with 300 ml. of boiling ether, the hot extract separated, and concentrated to give 1.05 g. of solid, m.p. 132-140°. Recrystallization from 375 ml. of diisopropyl ether gave 0.70 g. (8% yield) of **32**, m.p. 140-142°; ir (mull): ν 1730 (s), 1700 (s), 1680 (m), 1625 (m), 1570 (w), 1480 (m), 1470 (s), 1450 (s), 1405 (m) cm^{-1}; pmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3 at position-2), 3.40 (s, 3H, CH_2OCH_3), 3.76 [q (J = 3, 6 Hz), 2H, CH_2OCH_3], 4.59 [q (J = 6 Hz), 1H, *H* at position-7), 8.04 [q (J = 2, 6 Hz), 1H, *H* at position-6), 9.12 [q (J = 2, 6 Hz), 1H, *H* at position-8).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68; N.E., 262. Found: C, 59.73; H, 5.34; N, 10.61; N.E. ($HClO_4$), 270.

b. By Direct Esterification.

Dry hydrogen chloride was introduced continuously for 4 hours into a solution of 1.00 g. (0.005 mole) of **16** in 50 ml. of ethylene glycol monomethyl ether, at an internal temperature of 90-95°. The solution was kept at ambient temperature for 18 hours, concentrated to dryness *in vacuo*, the residue, 3.00 g., dissolved in 40 ml. of water, and the solution adjusted to *p*H 8, with cooling. The solid that separated was filtered and dried to give 0.6 g. of crude **32**, m.p. 138-142°. Recrystallization for 150 ml. of diisopropyl ether gave 0.48 g. (37% yield) of pure **32**, m.p. 140-142°. This product was identical with that obtained as described in a) by comparison of their ir and pmr spectra; both products had R_f *ca.* 0.7 by tlc [silica gel plate, benzene-acetone (1:1)].

Anal. Found: C, 59.61; H, 5.48; N, 10.64; N.E. ($HClO_4$), 268.

Octahydro-2,9-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**33**) and its Maleate Salt (1:1), (**33a**).

Procedure A.

To a solution of 3.60 g. (0.02 mole) of **11** in 200 ml. of absolute ethanol was added 0.30 g. of platinum oxide and the mixture hydrogenated as with **10** to give 3.50 g. of crude product. Recrystallization of 0.30 g. of this material from 10 ml. of pentane gave 0.20 g. (66% yield) of **33**, m.p. 51-57°; ir (mull): 3300 (s), 3280 (s), 1620 (s), 1500 (m), 1460 (s), 1440 (s), 1430 (s), 1410 (m) cm^{-1}; the pmr spectrum was very complex; 18 protons were counted in a series of overlapping signals in the region δ 0.85-5.00. There were no downfield signals.

Anal. Calcd. for $C_{10}H_{18}N_2O$: C, 65.88; H, 9.95; N, 15.37 N.E., 182. Found: C, 65.80; H, 9.94; N, 15.13; N.E. ($HClO_4$), 185.

To 3.00 g. (*ca.* 0.017 mole) of crude **33** in 15 ml. of 2-butanone at the b.p. was added a hot solution of 2.40 g. (0.02 mole) of maleic acid in 15 ml. of 2-butanone. After thorough mixing, the solution was allowed to cool and was then refrigerated. The crystalline product was filtered and dried to give 4.90 g. of solid, m.p. 147-150°. Recrystallization from 125 ml. of acetonitrile gave 3.30 g. (66% yield) of **33a**, m.p. 154-156°.

Anal. Calcd. for $C_{10}H_{18}N_2O \cdot C_4H_4O_4$: C, 56.36; H, 7.43; N, 9.39; N.E., 298. Found: C, 56.26; H, 7.46; N, 9.17; N.E. ($HClO_4$), 298.

Procedure B.

A suspension of 10.00 g. (0.058 mole) of **3**, 3.0 g. of 5% palladium-carbon catalyst, and 200 ml. of absolute ethanol was reduced at *ca.* 50° under 50 psi of hydrogen. Reduction was complete in 7 hours and gave 10.00 g. of crude **33b**; 0.60 g. recrystallized from 20 ml. of pentane gave 0.40 g. (67% yield) of **33b**, m.p. 51-61° whose ir and pmr spectra were identical with the corresponding spectra obtained with **33**.

Anal. Found: C, 65.60; H, 9.90; N, 15.12; N.E. ($HClO_4$), 185.

From 9.00 g. (*ca.* 0.05 mole) of crude **33b** in 45 ml. of 2-butanone and 7.20 g. (0.062 mole) of maleic acid, reacted as above, was obtained 13.50 g. of crude maleate, m.p. 151-153°. Recrystallization from 325 ml. of acetonitrile gave 9.90 g. of **33c**, m.p. 153-155°, whose ir and pmr spectra were identical with the corresponding spectra obtained with **33a**.

Anal. Found: C, 56.06; H, 7.27; N, 9.20; N.E. ($HClO_4$), 304.

Octahydro-9-methyl-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**34**).

A solution of 2.40 g. (0.01 mole) of **14**, 0.30 g. of platinum oxide, and 200 ml. of absolute methanol were shaken under 50 psi of hydrogen at ambient temperature; absorption of 0.02 mole of hydrogen was complete in 2 hours. Workup gave 1.90 g. of solid, m.p. 96-104°; recrystallization from 100 ml. of diisopropyl ether gave 1.20 g. (50% yield) of **34**, m.p. 96-104°; ir (mull): ν 3300 (s), 3260 (s), 1620 (s), 1500 (m), 1490 (s), 1460 (s), 1450 (s), 1440 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.10 [d (J = 5 Hz), 3H, C*H*$_3$ at position-9] 0.80-5.00 [complex m, 13H, C*H*$_2$ at positions-3, -4, -6, -7, -8, plus *H* at positions-1, -2, -9, plus NH (equilibrates with deuterium oxide)], 6.80-7.65 (m, 5H, 5 Ar-*H*).

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.71; H, 8.25; N, 11.46; N.E., 244. Found: C, 73.76; H, 8.05; N, 11.39; N.E. ($HClO_4$), 248.

Octahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**35**).

Isomers A (Base).

Hydrogenation of a mixture of 5.30 g. (0.03 mole) of **7**, 0.50 g. of platinum oxide, and 175 ml. of absolute ethanol at *ca.* 50° under 50 psi pressure was complete in 4 hours; tlc of the filtrate [silica gel plates, chloroform-ethanol (95:5)] showed the presence of two spots, R_f *ca.* 0.55 and 0.60. Workup gave 5.50 g. of crude residue which was recrystallized from 700 ml. of diisopropyl ether to give 3.30 g. (60% yield) of crystalline **35**, m.p. 108-111°, R_f (as above) *ca.* 0.60; ir (deuteriochloroform): ν 3460 (s), 3220 (s), 2620 (s), 2540 (s), 2480 (s), 2350 (m), 2260 (w), 2130 (w), 1650 (s), 1590 (m), 1580 (s), 1455 (s) cm^{-1}; the pmr spectrum consisted of a series of overlapping signals in the region δ 1.00-5.00; there were no downfield resonances.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.68; H, 8.76; N, 15.20; N.E., 184. Found: C, 58.51; H, 9.05; N, 15.51; N.E. ($HClO_4$), 186.

Isomers A (Hydrochloride).

To a solution of 2.20 g. (0.012 mole) of the crystalline **35** in 40 ml. of acetonitrile was added rapidly at ambient temperature 4.0 ml. of 4.8 *N* (0.02 mole) of 2-propanolic hydrogen chloride. Following the addition, within a few minutes, a microcrystalline product began to separate from the initially clear solution. The mixture was diluted with 40 ml. of anhydrous ether and filtered to give 2.50 g. of solid, m.p. 210-212° dec. The solid was dissolved in 275 ml. of boiling 2-propanol, filtered, and the filtrate was diluted to incipient cloudiness with anhydrous ether to give 2.10 g. (80% yield) of the *hydrochloride*, m.p. 216-218° dec.; ir (mull): ν 3460 (s), 3220 (s), 2620 (s), 2540 (s), 2480 (s), 1650 (s), 1590 (m), 1580 (m), 1460 (s), 1140 (m) cm^{-1}; the pmr spectrum in DMSO-d_6 was a complex of overlapping signals from δ 1.30-5.05, with no other downfield resonances.

Anal. Calcd. for $C_9H_{16}N_2O_2 \cdot HCl$: C, 48.99; H, 7.76; N, 12.69; N.E., 221. Found: C, 48.80; H, 8.06; N, 12.51; N.E. ($HClO_4$), 225.

Isomers B (Hydrochloride).

Concentration, *in vacuo* at 50°, of the diisopropyl ether filtrate from the above described crystalline solid to dryness gave a residual oil which could not be induced to crystallize. It was dissolved in 50 ml. of acetonitrile and the solution treated rapidly at ambient temperature with 4.0 ml. of 4.8 *N* (0.019 mole) of 2-propanolic hydrogen chloride. A crystalline product separated, and, after cooling the mixture, the solid was collected and dried; it weighed 1.70 g., m.p. 223-228° dec. Recrystallization from 45 ml. of methanol plus anhydrous ether added to the point of turbidity, gave 1.30 g. (50% yield) of the *hydrochloride*, m.p. 234-236° dec.; ir (mull): ν 3270 (s), 2540 (s), 2480 (s), 1665 (s), 1635 (s), 1610 (w), 1585 (m), 1460 (s) cm^{-1}; the pmr spectrum in DMSO-d_6 consisted of a complex of overlapping signals in the region δ 1.10-5.00; no other downfield resonances were seen.

Anal. Found: C, 49.29; H, 8.03; N, 12.96; N.E. ($HClO_4$), 222.

Octahydro-9-acetoxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**36**).

A suspension of 4.20 g. (0.020 mole) of **8**, 0.40 g. of platinum oxide, and 200 ml. of ethyl acetate was hydrogenated as with **10**. Reduction was complete in 7.5 hours. Workup gave 4.20 g. of a semi-solid residue, and this, triturated with 25 ml. of anhydrous ether gave 0.5 g. of a white solid, m.p. 138-141°. Recrystallization from 125 ml. of diisopropyl ether gave 0.3 g. (6% yield) of **36**, m.p. 156-158°, R_f *ca.* 0.5 [silica gel plates (acetone)]; ir (mull): ν 3275 (m), 1730 (s), 1630 (s), 1590 (w), 1480 (s), 1460 (s), 1440 (s) cm^{-1}; the pmr spectrum was a complex of overlapping signals in the region of δ 1.10-5.20. There were no downfield resonances.

Anal. Calcd. for $C_{11}H_{18}N_2O_3$: C, 58.23; H, 7.90; N, 12.20; N.E., 226, m/e, 226. Found: C, 58.48; H, 8.16; N, 12.38; N.E. ($HClO_4$), 232, m/e, 226.

The crystalline material was shown by the glc which preceded the introduction into the mass spectrometer to be a single component. The non-crystalline by-products soluble in anhydrous ether were shown by tlc to consist of about 6 components and these were not further investigated.

REFERENCES AND NOTES

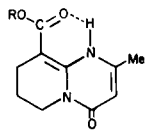
(1) To whom all correspondence should be addressed.

(2a) 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).

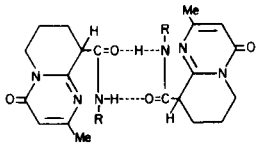
(3) Catalytic hydrogenation over Raney nickel of a "dimethylpyrido[1,2-*a*]pyrimidinone" has been reported by G. Stockelmann, H. Specker, and W. Riepe, *Chem. Ber.*, **102**, 455 (1969) but its structure is unknown because of the uncertainty as to the structure of his starting material; *cf.*, (2a) for a discussion of this problem. G. Naray-Szabo, I. Hermecz, and Z. Meszaros, *J. Chem. Soc., Perkin Trans. I*, 1753 (1974) have reported hydrogenations in 10% aqueous hydrochloric acid over 10% palladium/carbon of ethyl 4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylate as well as other 3,6-disubstituted derivatives. They obtained both tetrahydro and hexahydro derivatives.

(4) In general, absolute methanol or ethanol were the best solvents for these compounds, and were employed in all hydrogenations but one; with **8**, ethyl acetate was a more suitable solvent.

(5) It is recognized that NH enamines are uncommon and the few that have been prepared are reported to be somewhat unstable. The apparent stability of **23b** and **24b** in solution may be associated with the strong intramolecular hydrogen bonding, as shown below, that was demonstrated by carrying out dilutions studies on their deuteriochloroform solutions; no shift in the NH signal was observed in their ir and pmr spectra. The observation that with **25-27**, in contrast, the favored conformations in solution, were the imine structures, was best rationalized by the concept, as shown above, that the latter existed as intermolecular hydrogen bonded

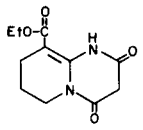


23b, 24b



25-27

species (*cf.*, L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen & Co., Ltd., London, 1968, pp. 283-287). Relevant to this discussion is the recent Communication by H. Wamhoff and L. Lichtenthaler [*Synthesis*, 426 (1975)] in which was reported the synthesis of the 2,4-dione, *A*. While there is good agreement



A

in the pmr assignments for *A* made by Dr. Wamhoff and those made by us on **25**, he has been unable to find any evidence of intramolecular hydrogen bonding in his compound. He has not carried out any alkylation experiments (Private communication). See, also, L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Edition, 1969, Pergamon Press, N.Y., N.Y., pp. 55-60, 298-300, 380-384.

(6) The mechanism by which these alkylations occurred has not been established. It is well-known that the alkylation of enamines leads only to carbon substitution in the final product, although *N*-alkylation followed by rearrangement to the carbon-alkylated derivative has to be considered as a possible mechanism; *c.f.*, J. Szmuszkovicz, in "Enamines," "Advances in Organic Chemistry," **4**, 1 (1963).