The Reaction of Aromatic Aldehydes with Methyl-substituted 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones

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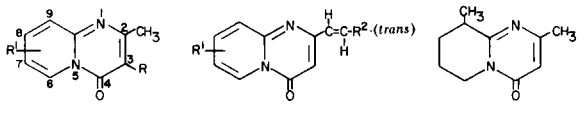
Sodium methoxide in methanol was the single effective reagent for the reactions between 2,8-dimethyl-, **3**, 2,9-dimethyl-, **1**, and 2,3,9-trimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **2**, and either benzaldehyde or 3,4,5-trimethoxybenzaldehyde. The phenylethenyl derivatives that were formed had the *trans*-configuration. Although an excess of aldehyde and sodium methoxide as well as long heating periods were employed, with **1** and **2** reaction occurred only at the 2-methyl substituent; with **3**, however, a trace amount of the 2,8-*bis*-(phenylethenyl) derivative was also isolated.

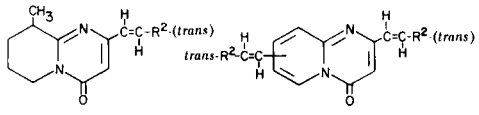
J. Heterocyclic Chem., 13, 869 (1976).

The availability of a diverse group of methylated 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**2a-e**) prompted us to investigate their behavior toward aromatic aldehydes. Reactions of this type have not previously been reported with derivatives of this heterocyclic system.

No reaction occurred when the 2,9-dimethyl compound, **1**, and benzaldehyde were heated, under reflux, in acetic anhydride alone or with the addition of fused sodium acetate. Although reaction did occur with all of the methylated derivatives in sodium methoxide-methanol, the rate of product formation was exceedingly slow; the use of potassium *t*-butoxide-*t*-butyl alcohol as a substitute, led to the formation of dark, unidentified resinous products. The heterocycle must be visualized as a cyclic amide that is susceptible to base-catalyzed cleavage at the bridgehead nitrogen atom (3).



1-3 4, 6-8, 12, 14 11



9, 10 13, 15

1, R = H, R^1 = 9-CH_3
2, R = CH_3, R^1 = 9-CH_3
3, R = H, R^1 = 8-CH_3
4, R, R^1 = H, R^2 = 3,4,5-$(CH_3O)_3C_6H_2$
5, R, R^1 = H
6, R = H, R^1 = CH_3, R^2 = Ph
7, R = H, R^1 = CH_3, R^2 = 3,4,5-$(CH_3O)_3C_6H_2$
8, R = CH_3, R^1 = 9-CH_3, R^2 = 3,4,5-$(CH_3O)_3C_6H_2$
9, R^2 = Ph
10, R^2 = 3,4,5-$(CH_3O)_3C_6H_2$
12, R^1 = 8-CH_3, R^2 = Ph
13, R^2 = Ph
14, R^1 = 8-CH_3, R^2 = 3,4,5-$(CH_3O)_3C_6H_2$
15, R^2 = 3,4,5-$(CH_3O)_3C_6H_2$

With **1** and the 2,3,9-trimethyl derivative, **2**, only the methyl group in the 2-position reacted, despite the prolonged heating under reflux; the 2,8-dimethyl compound, **3**, gave the 2-styryl derivative as the major product, along with trace amounts of the 2,8-*bis*-styryl compound.

In all instances, the pmr spectra of the styryl derivatives revealed that the vinylic protons were in the *trans*-configuration (4).

EXPERIMENTAL

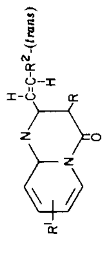
The ir and pmr spectra were obtained as described in our earlier papers (2a-e). These spectra, as well as the microanalyses, were obtained by the staff of the Analytical Department of this Institute. The melting points were determined in capillary tubes in an electrically heated oil bath and are uncorrected.

2-[*trans*-2-(3,4,5-Trimethoxyphenyl)ethenyl]-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**4**).

To a solution of 1.30 g. (0.02 mole) of sodium methoxide in 75 ml. of absolute methanol was added 3.20 g. (0.02 mole) of 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **5**, followed by 4.00 g. (0.02 mole) of 3,4,5-trimethoxybenzaldehyde. The mixture was stirred and heated, under nitrogen, for 24 hours, cooled, the yellow solid filtered, washed with water, and dried to give 1.30 g. of

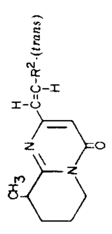
Table I

Derivatives of



6-8

and



9, 10

Compound No.	R	R^1	R^2	Reflux Time Hours	M.p. °C	Yield %	Recrystallization Solvent	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
6	H	9-CH_3	Ph	15	150-152	25	C_6H_{12}	77.84	5.39	10.68	77.95	5.20	10.95
7	H	9-CH_3	3,4,5-$(CH_3O)_3C_6H_2$	28	212-214	15	$CH_3O(CH_2)_2OH$	68.36	5.74	7.95	68.38	5.83	7.87
8	CH_3	9-CH_3	3,4,5-$(CH_3O)_3C_6H_2$	15	218-220	15	CH_3CN	68.83	6.05	7.64	68.84	6.15	7.73
9(a)	H	9-CH_3	Ph	52	108-110	6	2-PrOH	76.64	6.81	10.52	76.41	6.88	10.42
10(a)	H	9-CH_3	3,4,5-$(CH_3O)_3C_6H_2$	52	165-167	9	2-PrOH	67.58	6.81	7.88	67.27	7.04	7.64

(a) The preparation of 2,9-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, **11**, the intermediate employed in these reactions, is described in *J. Heterocyclic Chem.*, submitted for publication).

solid, m.p. 212-214° dec. Recrystallization from 60 ml. of acetonitrile gave 1.20 g. (17% yield) of **4**, m.p., unchanged, at 212-214°; tlc [silica gel plate, benzene:acetone (1:1)], R_f *ca.* 0.7; ir (deuteriochloroform): ν 1680(s), 1630(s), 1580(s), 1550(w), 1525(s), 1500(s), 1470(m), 1460(m), 1440(s), 1420(s) cm^{-1}; pmr (deuteriochloroform): δ 3.80[s, 9H, $(CH_3O)_3$], 6.45 (s, 1H, *H* at position-6), 6.89, 7.79 [ABXq (J = 16 Hz), 2H, *trans*-*CH*=*CH*], 6.70-8.00 (m, 3H, *H* at position-7, -8, and -9), 9.03 [d (J = 8 Hz), 1H, *H* at position-6).

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.48; H, 5.52; N, 8.30.

The above procedure was employed to prepare Compounds **6** to **10** in Table I.

8-Methyl-2-(2-phenylethenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**12**) and 2,8-bis(2-Phenylethenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**13**).

A solution of 1.20 g. (0.02 mole) of sodium methoxide in 100 ml. of absolute methanol, 1.70 g. (0.02 mole) of **3**, and 2.10 g. (0.02 mole) of benzaldehyde was heated under reflux, in a nitrogen atmosphere, for 48 hours, cooled, the solid filtered, washed with water, and dried. The crude product, 2.20 g., m.p. 253-256°, with sintering at 210°, was shown by tlc (as in **4**) to consist of a major spot at R_f *ca.* 0.7 and a minor spot at R_f *ca.* 0.9. Consecutive recrystallizations from 300 and 260 ml. of toluene gave 1.40 g. of **12**, m.p. 271-273°; R_f *ca.* 0.7; ir (mull): ν 1680(s), 1630(s), 1565(m), 1510(m), 1495(m), 1450(s), 1405(s) cm^{-1}; pmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3 at position-8), 6.33 (s, 1H, *H* at position-3), 7.15-7.80 (m, 9H, *H* at postions-7 and -9, *CH*=*CH*, 5 Ar-*H*), 9.02 [d (J = 8 Hz), 1H, *H* at position-6].

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.39; N, 10.68; m/e, 262. Found: C, 78.00; H, 5.39; N, 10.59; m/e, 262.

The toluene filtrates from the above recrystallizations were concentrated to dryness and the residual solid, 0.50 g., m.p. 189-270°, was recrystallized consecutively from 100 and 50 ml. each of methanol to give 0.050 g. of **13**, m.p. 196-198°; R_f *ca.* 0.9; ir (mull): ν 1680(s), 1630(s), 1590(m), 1570(m), 1525(w), 1510 (m), 1490(m), 1460(s) cm^{-1}; pmr (deuteriochloroform): δ (no signal, δ 0.0-6.40), 6.40 (s, 1H, *H* at position-3), 6.80-8.15 (m, 16H, *H* at positions-7 and -9, *CH*=*CH*, 10 Ar-*H*), 8.98 [d (J = 8 Hz), *H* at position-6].

Anal. Calcd. for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99; m/e, 350. Found: C, 81.84; H, 5.20; N, 7.90; m/e, 350.

8-Methyl-2-[2-(3,4,5-(trimethoxyphenyl)ethenyl]-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**14**), its Maleic Acid Salt (**14a**) and 2,8-bis[2-(3,4,5-(Trimethoxyphenyl)ethenyl]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**15**).

A solution of 1.70 g. (0.01 mole) of **3**, 4.00 g. (0.02 mole) of 3,4,5-trimethoxybenzaldehyde, and 1.20 g. (0.02 mole) of sodium methoxide in 100 ml. of absolute methanol was reacted as with **12**. The crude solid, 2.70 g., m.p. 190-200°, with sintering at 180°, was shown by tlc (as in **4**) to have a major spot at R_f *ca.* 0.6 and a minor spot at R_f *ca.* 0.8. Recrystallization of the crude product from several solvents failed to give material with satisfactory analyses. As a consequence, 1.70 g. of the solid in 125 ml. of hot 2-butanone was mixed with a hot solution of 1.20 g. (0.01 mole) of maleic acid. The solid that separated on cooling was filtered and dried to give 1.90 g. of material, m.p. 180-183°; recrystallization from 150 ml. of acetonitrile gave 1.40 g. (47% yield) of **14a**, m.p. 187-189°.

Anal. Calcd. for $C_{20}H_{20}N_2O_4 \cdot C_4H_4O_4$: C, 61.52; H, 5.10; N, 5.98. Found: C, 61.67; H, 5.00; N, 5.91.

To a solution of 0.25 g. of recrystallized **14a** in 25 ml. of water was added 5.0 ml. of 5% aqueous sodium bicarbonate. The solid that separated was filtered, washed with water, and dried *in vacuo*, at 78°, to give 0.14 g. of **14**, m.p. 218-220° dec.; tlc (as in **4**), one spot, R_f *ca.* 0.6; ir (deuteriochloroform): ν 1730(w), 1675(s), 1630(s), 1615(m), 1580(s), 1500(s), 1450(m), 1410(s) cm^{-1}; pmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3 at position-8), 3.90 [s, 9H, $(CH_3O)_3$], 6.23 (s, 1H, *H* at position-3), 6.80 (s, 2H, 2*H* at positions-3, and -6 of the phenyl group), 7.12-7.42 [ABXq (J = 16 Hz), 2H, *trans*-C*H*=C*H*], 7.20 (s, 1H, *H* at position-7), 7.25-7.40 (m, 1H, *H* at position-9), 8.97 [d (J = 8 Hz), 1H, *H* at position-6).

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.36; H, 5.74; N, 5.98; m/e, 352. Found: C, 68.19; H, 5.69; N, 7.95; m/e, 352.

When the filtrate from the above 2.70 g. of crude **14** was heated under reflux for an additional 96 hours, and cooled, workup, as above, gave 0.30 g. of solid, m.p. 219-221°. Although its m.p. was almost identical with that of **14**, tlc (as in **4**) showed one spot R_f *ca.* 0.8. Recrystallization from acetonitrile gave 0.17 g. of **15**, m.p. 222-223°; ir (deuteriochloroform): ν 1670(s), 1630 (s), 1570(w), 1550(m), 1510(s), 1490(m), 1470(s), 1440(s), 1410 (s) cm^{-1}; pmr (deuteriochloroform): δ (no signal from δ 0.0-3.90), 3.90 [s, 18 H, $(CH_3O)_6$], 6.40 (s, 1H, *H* at position-3), 6.83 [d (J = 3 Hz), 4H, 4*H* in 2,2′,6,6′-positions of two phenyl rings), 7.18, 7.80 [ABXq (J = 15 Hz), 4H, $(CH{=}CH)_2$], 8.93 [d, (J = 8 Hz), 1H, *H* at position-6].

Anal. Calcd. for $C_{30}H_{30}N_2O_7$: C, 67.90; H, 5.70; N, 5.29; m/e, 530. Found: C, 67.68; H, 5.51; N, 5.21; m/e, 530.

REFERENCES AND NOTES

(1) To whom all inquiries should be referred.

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(3) P. G. Gassman, P. K. G. Hodgson, and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1275 (1976), have shown that potassium *t*-butoxide is a remarkably effective base for the hydrolysis of amides even at ambient temperatures.

(4) Vicinal interproton coupling across a carbon-carbon double bond has been discussed by L. M. Jackman and S. Sternell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd Edition, 1969, Pergamon Press, New York, N. Y., pp. 301-302.