A Facile Preparation of 7-(Substituted amino)-6*H*-pyrrolo[3,4-*d*]-pyrimidine Derivatives[1)]

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Synopsis. 6-Phenyl-7-(substituted amino)-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **3** were obtained by the reaction of 5-formyl-1,3-dimethyl-6-[(substituted amino)-methyl]-2,4(1*H*,3*H*)-pyrimidinediones (**1**) with aniline (**2a**).

Recently, we reported a one-pot preparation of 6,7-dihydropyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives (**D**) from the reaction of 5-formyl-1,3,6-trimethyl-2,4(1*H*,3*H*)-pyrimidinedione (**A**) with primary amines.[2)] The cycloaddition reaction of 5,6-dihydro-5,6-bis(methylene)-2,4(1*H*,3*H*)-pyrimidinedione **B**, generated via 1,5-hydrogen shift of **A**, and aldimines from **A** and amines yielding 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **C** was the key step in this pyridopyrimidine synthesis.

In the continuation of the investigations on the preparation of fused pyrimidines, we wish to describe here a facile preparation of 7-(substituted amino)-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives from the reaction of 5-formyl-1,3-dimethyl-6-[(substituted amino)methyl]-2,4(1*H*,3*H*)-pyrimidinedione with primary amines.

Results and Discussion

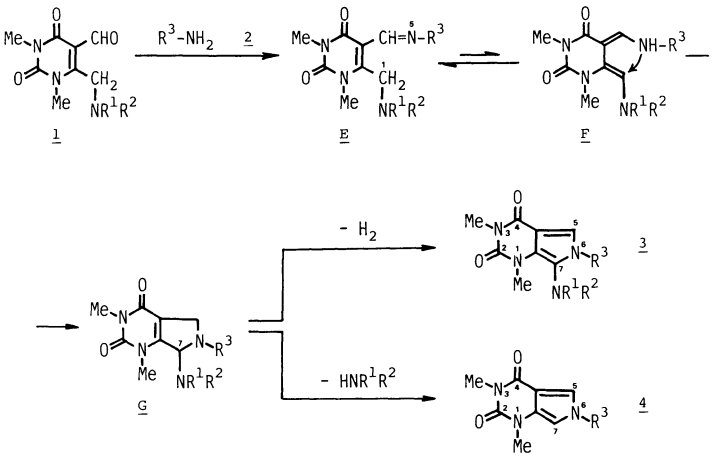
The reaction of 5-formyl-1,3-dimethyl-6-(morpholinomethyl)-2,4(1*H*,3*H*)-pyrimidinedione (**1a**) with aniline (**2a**) in benzene under reflux afforded 1,3-dimethyl-7-morpholino-6-phenyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3a**) in 59% yield. The reaction of other 5-formyl-6-[(substituted amino)methyl]-2,4(1*H*,3*H*)-pyrimidinediones (**1**) with aniline (**2a**) was also examined. The reaction patterns depended on the kind of the substituted amino groups; the reaction of 6-[(1-pyrrolidinyl)methyl]- (**1b**) afforded only **3b**, the same type product as **3a**, while the reaction of 6-[(diethylamino)methyl]- (**1c**) and 6-[(*N*-methylanilino)methyl]- (**1d**) afforded 1,3-dimethyl-6-phenyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4**)[3)] as a major product together with the corresponding 7-(substituted amino) derivatives **3c** and **3d**, respectively.

The structural elucidation of pyrrolopyrimidines **3** was accomplished on the basis of their spectral data comparing with those of **4**.

A pathway for these pyrrolopyrimidines **3** and **4** can be explained by the analogy to that for pyrido[3,4-*d*]pyrimidines **C** from **A** and primary amines. The 1,5-hydrogen shift of the aldimine **E** from **1** and aniline (**2a**) affords a 5-anilinomethylene-5,6-dihydro-6-[(substituted amino)methylene]-2,4(1*H*,3*H*)-pyrimidinedione intermediate (**F**). The 1,5-cyclization of **F** leads to a 6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**G**). The dehydrogenation of **G** gives the 7-(substituted amino) derivatives **3**, while the deamination of **G** gives pyrrolopyrimidine **4**.

The above pathway for the formation of **G** is related to that for 6-tosylamino-6*H*-pyrrolo[3,4-*d*]pyrimidine synthesis by the reaction of 1,2,3,4-tetrahydro-6-bromomethyl-1,3-dimethyl-2,4-dioxo-5-pyrimidinecarbaldehyde tosylhydrazone with triethylamine, in which the 1,5-cyclization of 1-azapentadienyl anion was proposed.[3)] The dehydrogenation of **G** leading to **3** is much of interest, because another process, the deamination leading to **4**, seems to be a favorable one. Although a plausible explanation for the results is not found yet, we suggest that the substituted amino group at the 7-position might stabilize the 6*H*-pyrrolo[3,4-*d*]pyrimidine system.

In order to survey the usefulness of this method, the



Scheme 1.

Table 1. Reaction of 5-Formyl-6-(substituted amino)methyl-2,4(1*H*,3*H*)-pyrimidinediones **1** with Primary Amines **2**[a]

3	R^1	R^2	R^3	Yield/%[b]	4 Yield/%[b]
3a	$-(CH_2)_2-O-(CH_2)_2-$		Ph	69	—
3b	$-(CH_2)_4-$		Ph	59	—
3c	Et	Et	Ph	33	53
3d	Me	Ph	Ph	23	59
3e	$-(CH_2)_2-O-(CH_2)_2-$		C_6H_4-OMe(*p*)	65	—
3f	$-(CH_2)_2-O-(CH_2)_2-$		C_6H_4-Me(*p*)	66	—
3g	$-(CH_2)_2-O-(CH_2)_2-$		C_6H_4-Br(*p*)	64	—
3h	$-(CH_2)_2-O-(CH_2)_2-$		C_6H_4-Cl(*p*)	65	—
3i	$-(CH_2)_2-O-(CH_2)_2-$		1-Naphthyl	50	—
3j	$-(CH_2)_2-O-(CH_2)_2-$		Benzyl	32	—

a) In dry benzene under reflux for 2 d. b) Based on isolated products.

reaction of **1a** with arylamines and benzylamine were examined. In these reaction the 7-(substituted amino)-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **3e—j** were obtained in good to fair yields. These results are summarized in Table 1.

Although much attention has been focused on the pharmacological potentialities of pyrrolo[3,4-*d*]pyrimidine derivatives, few reports on their preparation were found.[3-5] We believe that our method based on the 1,5-cyclization of 5-anilinomethylene-5,6-dihydro-6-[(substituted amino)methylene]-2,4(1*H*,3*H*)-pyrimidinediones serves as a new entry into 7-(substituted amino)-6*H*-pyrrolo[3,4-*d*]pyrimidines.

Experimental[6]

The new starting materials **1b** and **1c** were prepared from the reaction of 5-formyl-1,3-dimethyl-6-bromomethyl-2,4-(1*H*,3*H*)-pyrimidinedione and corresponding amines similarly to the reported method.[3]

5-Formyl-1,3-dimethyl-6-[(1-pyrrolidinyl)methyl]-2,4(1*H*,3*H*)-pyrimidinedione (1b): Mp 123—125 °C. Found: C, 57.42; H, 7.00; N, 16.43%. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.35; H, 6.82; N, 16.72%.

6-[(Diethylamino)methyl]-5-formyl-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione (1c): 73—74 °C. Found: C, 57.14; H, 7.83; N, 16.64%. Calcd for $C_{12}H_{19}N_3O_3$: C, 56.90; H, 7.56; N, 16.59%.

The Reaction of 1 with Aniline (2a). General Procedure: The solution of **1c** (1 mmol) and aniline (**2a**)(1 mmol) in dry benzene (5 mL) was heated under reflux for 2 d, and the solvent was evaporated to dryness. The residue was subjected to column chromatography on silica gel to afford 109 mg (33%) of **3c** as elution of benzene/chloroform (1/1) to chloroform and 154 mg (53%) of **4** as elution of chloroform/ethyl acetate (4/1), respectively.

1,3-Dimethyl-7-morpholino-6-phenyl-6*H*-pyrrolo[3,4-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (3a): Colorless prisms (benzene-ethanol); mp 218—219 °C; IR (KBr) cm^{-1}: 1690, 1640(CO); ^1H NMR ($CDCl_3$) δ=2.8—3.0, 3.4—3.7 (4H, each, 2m, $-CH_2-$), 3.40, 3.67 (3H, each, 2s, $-CH_3$), 7.19 (3H, s, 5-H), 7.3—7.6 (8H, total, m and s, phenyl and benzene); ^{13}C NMR ($CDCl_3$) δ=27.8, 31.5, 52.8, 67.0, 104.9 (4a-C), 118.2 (5-C), 120.8 (7a-C), 123.8 (7-C), 127.7, 128.3, 129.2 (benzene), 129.4, 139.3, 152.5 (2-C), 160.0 (4-C); MS *m/z*: 340 (M^+). Found: C, 66.79; H, 6.07; N, 14.81%. Calcd for $C_{18}H_{20}N_4O_3 \cdot 1/2C_6H_6$: C, 66.47; H, 6.12; N, 14.76%.

1,3-Dimethyl-6-phenyl-7-(1-pyrrolidinyl)-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (3b): Colorless plates (hexane-ethanol); mp 226—227 °C; IR (KBr) cm^{-1}: 1680, 1640 (CO); ^1H NMR ($CDCl_3$) δ=1.6—1.8, 2.9—3.1 (4H, each, 2 m, $-CH_2-$), 3.41, 3.56 (3H, each, 2s, $-CH_3$), 7.28 (1H, s, 5-H), 7.3—7.6 (5H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=26.1, 27.8, 30.3, 53.4, 104.9, (4a-C), 117.2 (5-C), 120.2 (7a-C), 121.9 (7-C), 126.3, 128.5, 129.2, 139.0, 152.6 (2-C), 160.2 (4-C); MS *m/z*: 324 (M^+). Found: C, 66.77; H, 6.20; N, 17.26%. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.22; N, 17.27%.

7-(Diethylamino)-1,3-dimethyl-6-phenyl-6*H*-pyrrolo[3,4-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (3c): Pale yellow prisms (hexane-ethanol); mp 164—166 °C; IR (KBr) cm^{-1}: 1690, 1650(CO); ^1H MNR ($CDCl_3$) δ=0.96 (6H, t, $-CH_3$, J=7 Hz), 2.88 (4H, q, $-CH_2-$, J=7 Hz), 3.45, 3.68 (3H, each, 2s, $-CH_3$), 7.29 (1H, s, 5-H), 7.3—7.6 (5H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=13.5, 27.8, 31.1, 48.8, 104.8 (4a-C), 118.0 (5-C), 121.2 (7a-C), 122.5 (7-C), 127.0, 128.9, 129.1, 139.8, 152.7 (2-C), 160.3 (4-C); MS *m/z*: 326 (M^+). Found: C, 66.40; H, 6.91; N, 17.34%. Calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16%.

1,3-Dimethyl-7-(*N*-methylanilino)-6-phenyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (3d): Colorless prisms (hexane-ethanol); mp 168—170 °C; IR (KBr) cm^{-1}: 1690, 1640 (CO); ^1H MNR ($CDCl_3$) δ=3.00, 3.28, 3.47 (3H, each, 3s, $-CH_3$), 6.6—7.5 (10H, m, phenyl), 7.54 (1H, s, 5-H); ^{13}C NMR ($CDCl_3$) δ=27.9, 30.2, 40.0, 105.5 (4a-C), 112.5 (5-C), 117.5 (7a-C), 122.2 (7-C), 118.0, 118.8, 125.2, 128.5, 129.4, 129.5, 137.8, 149.1, 152.3 (2-C), 159.9 (4-C); MS *m/z*: 360 (M^+). Found: C, 70.31; H, 5.61; N, 15.62%. Calcd for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55%.

6-(*p*-Methoxyphenyl)-1,3-dimethyl-7-morpholino-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (3e): Pale yellow prisms (hexane-ethanol); mp 192—194 °C; IR (KBr) cm^{-1}: 1690, 1650(CO); ^1H MNR ($CDCl_3$) δ=2.9—3.2, 3.5—3.8 (4H, each, 2m, $-CH_2-$), 3.50, 3.78, 3.99 (3H, each, 3s, $-CH_3$), 7.13 (1H, s, 5-H), 7.2—7.5 (4H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=27.8, 31.4, 52.8, 55.6, 67.0, 104.6 (4a-C), 114.3, 118.5 (5-C), 120.4 (7a-C), 124.0 (7-C), 128.8, 131.9, 152.5 (4-C), 160.0 (2-C), 160.2; MS *m/z*: 370 (M^+). Found: C, 61.62; H, 5.81; N, 15.00%. Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13%.

1,3-Dimethyl-7-morpholino-6-(*p*-tolyl)-6*H*-pyrrolo[3,4-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (3f): Colorless plates (hexane-ethanol); mp 218—219 °C; IR (KBr) cm^{-1}: 1690, 1650 (CO); ^1H NMR ($CDCl_3$) δ=2.48 (3H, s, $-CH_3$), 2.8—3.2, 3.4—3.7 (4H, each, 2m, $-CH_2-$), 3.44, 3.72 (3H, each, 2s, $-CH_3$), 7.20 (1H, s, 5-H), 7.2—7.4 (4H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=21.2, 27.8, 31.4, 52.8, 67.0, 104.7 (4a-C), 118.3 (5-C), 120.6 (7a-C), 123.8 (7-C), 127.4, 129.8, 136.8, 139.6, 152.5 (4-C), 160.0 (2-C); MS *m/z*: 354 (M^+). Found: C, 64.26; H, 6.30; N, 15.69%. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81%.

6-(*p*-Bromophenyl)-1,3-dimethyl-7-morpholino-6*H*-pyrrolo-[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (3g): Pale yellow

prisms (hexane–ethanol); mp 207—209 °C; IR (KBr) cm^{-1}: 1700, 1650 (CO); ^1H NMR ($CDCl_3$) δ=2.8—3.1, 3.4—3.7 (4H, each, 2m, $-CH_2-$), 3.39, 3.66 (3H, each, 2s, $-CH_2-$), 7.16 (1H, s, 5-H), 7.2—7.3, 7.6—7.7 (2H each, 2m, phenyl); ^{13}C NMR ($CDCl_3$) δ=27.9, 31.7, 52.9, 67.0, 105.3 (4a-C), 118.0 (5-C), 121.0 (7a-C), 123.4, 123.6 (7-C), 129.2, 132.5, 138.3, 152.4 (4-C), 159.8 (2-C); MS *m/z*: 420, 418 (M^+). Found: C, 51.64; H, 4.58; N, 13.16%. Calcd for $C_{18}H_{19}N_4O_3Br$: C, 51.56; H, 4.57; N, 13.36%.

6-(*p*-Chlorophenyl)-1,3-dimethyl-7-morpholino-6*H*-pyrrolo-[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (3h): Pale yellow prisms (hexane–ethanol); mp 206—208 °C; IR (KBr) cm^{-1}: 1700, 1650 (CO); ^1H NMR ($CDCl_3$) δ=2.8—3.2, 3.3—3.8 (4H, each, 2m, $-CH_2-$), 3.48, 3.75 (3H, each, 2s, $-CH_3$), 7.30 (1H, s, 5-H), 7.4—7.7, 7.4—7.7 (4H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=27.9, 31.7, 52.8, 67.0, 105.3 (4a-C), 118.1 (5-C), 121.0 (7a-C), 123.7 (7-C), 128.9, 129.5, 135.5, 137.8, 152.4 (2-C), 159.9 (4-C); MS *m/z*: 376, 374 (M^+). Found: C, 57.86; H, 5.13; N, 14.95%. Calcd for $C_{18}H_{19}N_4O_3Cl$: C, 57.68; H, 5.11; N, 14.95%.

1,3-Dimethyl-7-morpholino-6-(1-naphthyl)-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (3i): Pale yellow plates (ethanol); mp 231—232 °C; IR (KBr) cm^{-1}: 1690, 1660 (CO); ^1H NMR ($CDCl_3$) δ=2.9—3.1, 3.2—3.5 (4H, each, 2m, $-CH_2-$), 3.48, 3.74 (3H, each, 2s, $-CH_3$), 7.30 (1H, s, 5-H), 7.4—8.2 (7H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ=27.9, 31.5, 52.1, 53.0, 66.9, 67.0, 105.0 (4a-C), 119.3 (5-C), 120.4 (7a-C), 122.4, 124.9, 125.0 (7-C), 126.2, 127.1, 127.8, 128.3, 130.2, 131.5, 133.9, 135.8, 152.5 (2-C), 160.1 (4-C); MS *m/z*: 390 (M^+). Found: C, 67.63; H, 5.68; N, 14.34%. Calcd for $C_{22}H_{22}N_4O_3$: C, 67.67; H, 5.68; N, 14.35%.

6-Benzyl-1,3-dimethyl-7-morpholino-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (3j): Colorless plates (benzene–ethanol); mp 192—193 °C; IR (KBr) cm^{-1}: 1700, 1650 (CO); ^1H NMR ($CDCl_3$) δ=2.8—3.1, 3.5—3.8 (4H, each, 2m, $-CH_2-$), 3.37, 3.60 (3H, each, 2s, $-CH_3$), 5.17 (2H, s, $-CH_2-$), 7.18 (1H, s, 5-H), 7.2—7.5 (5H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=27.8, 32.3, 51.2, 52.5, 67.3, 104.2 (4a-C), 117.3 (5-C), 121.5 (7a-C), 121.9 (7-C), 126.3, 128.1, 129.0, 136.8, 152.4 (2-C), 160.0 (4-C); MS *m/z*: 354 (M^+). Found: C, 64.34; H, 6.30; N, 15.76%. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81%.

1,3-Dimethyl-6-phenyl-6*H*-pyrrolo[3,4-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (4): Colorless prisms (ethanol); mp 194—196 °C (lit,[3] 194—196 °C).

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6) The general experimental procedures were the same as in Part III.[2]