# New Syntheses of Pyrido[3,2-*d*]pyrimidines (1)



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New synthetic routes to pyrido[3,2-*d*]pyrimidines starting with 5-amino-1,3,6-trimethyluracil (I) or 1,3,6-trimethyl-5-nitrouracil (X) are described. Thus, condensation of I with arylaldehydes gave 5-arylideneamino-1,3,6-trimethyluracils (IIa-h), which upon heating with dimethylformamide dimethylacetal afforded 6-aryl-1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (Va-h) *via* 5-arylideneamino-1,3-dimethyl-6-(2-dimethylaminovinyl)uracils (IIIa-h). On the other hand, reaction of X with phenylacetaldehyde in the presence of base yielded Va and its 5-oxide (XI).

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The pyrido[3,2-*d*]pyrimidine system should be of biological interest, since it can be regarded not only as 8-deazapteridine but also as 5-deazaquinoline (2). We now report two new synthetic routes to this heterocycle (3) starting with 5-amino-1,3,6-trimethyluracil (I) (4) and 1,3,6-trimethyl-5-nitrouracil (X) (4).

Refluxing of the uracil I with the appropriate arylaldehydes in ethanol for 3 hours gave the 5-arylideneaminouracils (IIa-h) in high yields (83-97%) (Table I).

Heating of the appropriate uracils IIa-h with excess dimethylformamide dimethylacetal (DMFDMA) at 130° for 7-20 hours afforded the corresponding pyridopyrimidines (Va-h) as major products and the dimethylaminovinyluracils (IIIa-h) as minor products in 48-93 and 2-35% yields, respectively. In general, the pyridopyrimidines V were readily precipitated out from the reaction mixture, while the dimethylaminovinyluracils III were isolated by concentration of the filtrate (Table 2).

The structures of IIIa-h and Va-h were supported by the satisfactory elemental analyses and spectral data. In particular, the structure of Va was unequivocally established by the alternate synthesis (*vide infra*). The optimal temperature for the formation of III and subsequent conversion into V seems to exist at around 130°. Attempted reaction at the higher temperature (170°) caused the recovery of the starting material II.

It is interesting to note that the careful examination on the reaction of IIa with DMFDMA resulted in the isolation of the pyrrolopyrimidine (VII) albeit in low yield (3%) along with IIIa and Va. The structure of VII was confirmed by the alternative synthesis. Thus, treatment of the known pyrrolopyrimidine (VIII) (5) with Vilsmeier reagent (dimethylformamide-phosphorus oxychloride) gave VII in high yield (88%).

The reaction of II with DMFDMA leading to the pyridopyrimidine V can be best explained by assuming the in-

Scheme I

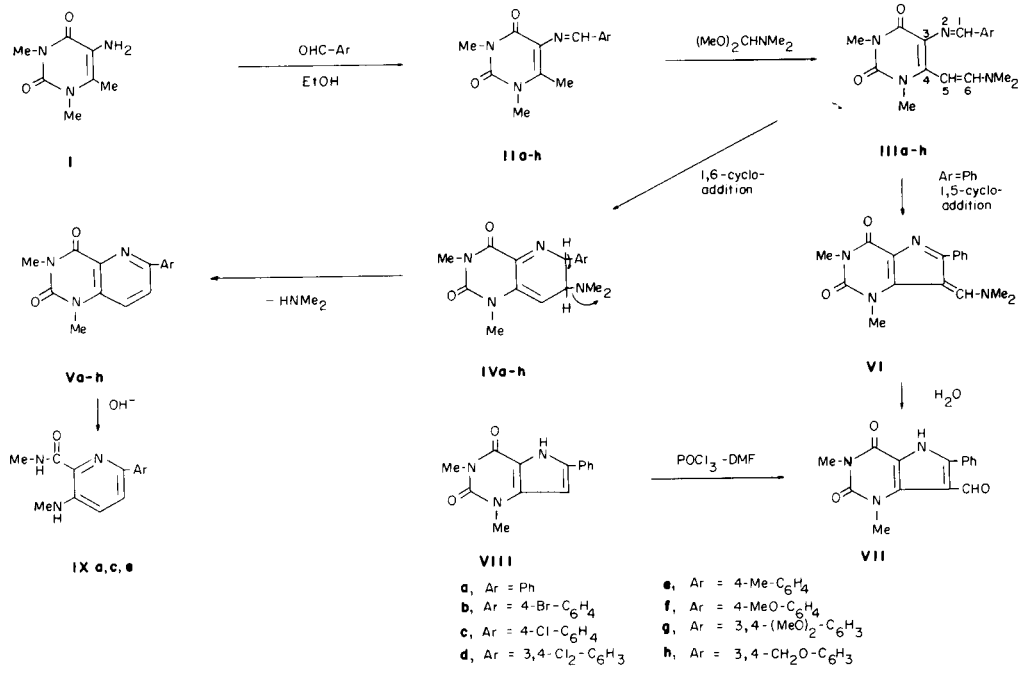


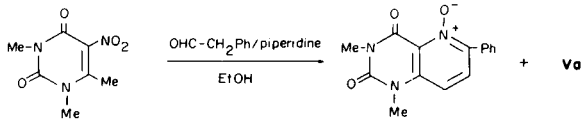
Table I

5-Arylideneamino-1,3,6-trimethyluracils (IIa-h)

| Compound Number | Mp (°C) (a) (Recrystn. solvent) | Yield (%) | Calcd. (%) C | H | N | Formula | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| IIa | 155.6 (EtOH) | 90 | 65.35 | 5.88 | 16.33 | $C_{14}H_{15}N_3O_2$ | 65.13 | 5.67 | 16.38 |
| IIb | 174.9 (EtOH-DMF) | 95 | 50.00 | 4.21 | 12.50 | $C_{14}H_{14}BrN_3O_2$ | 50.07 | 4.08 | 12.39 |
| IIc | 167.3 (EtOH-DMF) | 95 | 57.63 | 4.85 | 14.41 | $C_{14}H_{14}ClN_3O_2$ | 57.53 | 4.71 | 14.30 |
| IId | 201.7 (EtOH-DMF) | 94 | 51.54 | 4.02 | 12.88 | $C_{14}H_{13}Cl_2N_3O_2$ | 51.46 | 3.95 | 12.83 |
| IIe | 162.4 (EtOH) | 90 | 66.40 | 6.32 | 15.49 | $C_{15}H_{17}N_3O_2$ | 66.36 | 6.14 | 15.36 |
| IIf | 151.8 (EtOH) | 83 | 62.70 | 5.96 | 14.63 | $C_{15}H_{17}N_3O_3$ | 62.68 | 5.87 | 14.44 |
| IIg | 204.6 (EtOH-DMF) | 97 | 60.55 | 6.04 | 13.24 | $C_{16}H_{19}N_3O_4$ | 60.41 | 6.02 | 13.20 |
| IIh | 215.9 (DMF) | 90 | 59.79 | 5.02 | 13.95 | $C_{15}H_{15}N_3O_4$ | 59.54 | 4.89 | 14.01 |

(a) Melting points were taken on a Mettler FP-61 melting point apparatus.

Scheme II




X XI

itial formation of III, which possesses an azahexatriene-type structure. This could undergo intramolecular 1,6-cycloaddition to the dihydropyridopyrimidine (IV) and subsequent aromatization accompanied by elimination of dimethylamine. On the other hand, the formation of the pyrrolopyrimidine VII presumably involves the intramolecular 1,5-cycloaddition of the azahexatriene III by the action of enamine to the intermediate (VI), followed by hydrolysis during the work-up. This type of cyclization of azahexatrienes has been demonstrated in the synthesis of various fused pyrimidines; purines (6-7), pyrazolo[3,4-*d*]-pyrimidines (6,8), pteridines (7,9), pyrimido[4,5-*b*]quinolines (10), pyrimido[4,5-*c*]pyridazines (11), and pyrimido-[5,4-*e*]-*as*-triazines (12) (Scheme I).

In addition to the two-step synthesis of pyridopyrimidines described above, we next investigated the direct route to this heterocyclic system starting with the readily accessible uracil X. Thus, heating of X in ethanol with phenylacetaldehyde in the presence of excess piperidine at 70° for 10 hours afforded the pyridopyrimidine 5-oxide (XI) and Va in 16 and 3% yield, respectively. The oxide XI was readily precipitated out from the reaction mixture, while the Va was isolated by the column chromatography of the filtrate. The structure of XI was supported by the presence of its parent ion and the strong M-16 ion in the mass spectrum (Scheme II).

The pyridopyrimidines V prepared served as useful starting materials for the synthesis of pyridine derivatives. Namely, refluxing of the appropriate pyridopyrimidines (Va, Vc, Ve) in ethanolic potassium hydroxide for 1 hour gave the corresponding pyridines (IXa, IXc, IXe) in 40-57% yields.

## EXPERIMENTAL

Melting points were taken on a YANACO micro-hot-stage melting point apparatus or a Mettler FP-61 melting point apparatus and are uncorrected. Nmr spectra were determined at 100 MHz with a JEOL JNM-PS-100 spectrometer using tetramethylsilane as internal standard, and the ir spectra were determined in Nujol on a JASCO A-100 spectrophotometer. The uv spectra were performed on a Hitachi 124 spectrophotometer and the molecular weight for all compounds were correctly analyzed by mass spectroscopy with a JEOL D-300 spectrometer by a direct-inlet system at 70 eV.

5-Arylideneamino-1,3,6-trimethyluracils (IIa-h); General Procedure (Table I).

A mixture of 5-amino-1,3,6-trimethyluracil (I) (4) (0.85 g, 0.005 mole) and the appropriate arylaldehyde (0.006 mole) in ethanol (20 ml) was refluxed for 3 hours. After the reaction mixture was cooled to ambient temperature, the precipitates were filtered, washed with ethanol, and recrystallized to give the corresponding 5-arylideneamino-1,3,6-trimethyluracils (IIa-h).

5-Arylideneamino-1,3-dimethyl-6-(2-dimethylaminovinyl)uracils (IIIa-h) and 6-Aryl-1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (Va-h). General Procedure (Table II).

A suspension of the appropriate uracils (IIa-h) (0.002 mole) in dimethylformamide dimethylacetal (DMFDMA) (3 ml) was heated at 130° for 7-20 hours. After the reaction mixture was cooled to ambient tem-

Table II

6-Arylideneamino-1,3-dimethyl-6-(2-dimethylaminovinyl)uracils (IIIa-h)

| Starting Material | Reaction Time (hr) | Product | Mp (°C) (a) (Recrystn. solvent) | Yield (%) | Calcd. (%) C | H | N | Formula | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IIa | 7 | IIIa | 160-163 (MeOH) | 7 | 65.36 | 6.45 | 17.94 | $C_{17}H_{20}N_4O_2$ | 65.20 | 6.35 | 17.69 |
| IIb | 10 | IIIb | 175-177 (EtOH) | 6 | 52.18 | 4.90 | 14.32 | $C_{17}H_{19}BrN_4O_2$ | 52.03 | 4.75 | 14.13 |
| IIc | 10 | IIIc | 171-173 (EtOH) | 8 | 58.86 | 5.53 | 16.16 | $C_{17}H_{19}ClN_4O_2$ | 58.87 | 5.36 | 16.08 |
| IId | 10 | IIId | 174-175 (MeOH) | 7 | 53.55 | 4.77 | 14.70 | $C_{17}H_{18}Cl_2N_4O_2$ | 53.51 | 4.68 | 14.63 |
| IIe | 10 | IIIe | 154-158 (MeOH) | 2 | 66.23 | 6.79 | 17.17 | $C_{18}H_{22}N_4O_2$ | 66.34 | 6.81 | 17.15 |
| IIf | 10 | IIIf | 180-181 (MeOH) | 5 | 63.14 | 6.48 | 16.36 | $C_{18}H_{22}N_4O_3$ | 62.82 | 6.41 | 16.70 |
| IIg | 15 | IIIg | 179-182 (MeOH) | 2 | 61.27 | 6.48 | 15.05 | $C_{19}H_{24}N_4O_4$ | 61.45 | 6.55 | 15.10 |
| IIh | 20 | IIIh | 198-201 (EtOH-DMF) | 35 | 60.66 | 5.66 | 15.72 | $C_{18}H_{20}N_4O_4$ | 60.59 | 5.50 | 15.64 |

6-Aryl-1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (Va-h)

| Starting Material | Reaction Time (hr) | Product | Mp (°C) (b) (Recrystn. solvent) | Yield (%) | Calcd. (%) C | H | N | Formula | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IIa | 7 | Va | 247.4 (DMF-EtOH) | 74 | 67.40 | 4.90 | 15.72 | $C_{15}H_{13}N_3O_2$ | 67.33 | 4.76 | 15.73 |
| IIb | 10 | Vb | 215.6 (DMF) | 67 | 52.03 | 3.50 | 12.14 | $C_{15}H_{12}BrN_3O_2$ | 51.74 | 3.44 | 12.17 |
| IIc | 10 | Vc | 198.3 (DMF-EtOH) | 49 | 59.70 | 4.02 | 13.93 | $C_{15}H_{12}ClN_3O_2$ | 59.43 | 3.98 | 13.81 |
| IId | 10 | Vd | 239.9 (DMF) | 85 | 53.58 | 3.30 | 12.50 | $C_{15}H_{11}Cl_2N_3O_2$ | 53.39 | 3.18 | 12.53 |
| IIe | 10 | Ve | 210.3 (DMF) | 92 | 68.31 | 5.38 | 14.94 | $C_{16}H_{15}N_3O_2$ | 68.13 | 5.34 | 15.00 |
| IIf | 10 | Vf | 182.2 (DMF-EtOH) | 87 | 64.63 | 5.09 | 14.14 | $C_{16}H_{15}N_3O_3$ | 64.37 | 5.05 | 14.02 |
| IIg | 15 | Vg | 220.3 (DMF) | 93 | 62.37 | 5.24 | 12.84 | $C_{17}H_{17}N_3O_4$ | 61.98 | 5.11 | 12.77 |
| IIh | 20 | Vh | 285.0 (DMF) | 48 | 61.73 | 4.21 | 13.50 | $C_{16}H_{13}N_3O_4$ | 61.58 | 4.15 | 13.54 |

(a) Due to the thermal instability of IIIa-h, their melting points were taken on a YANACO micro-hot stage melting point apparatus. (b) Melting points were taken on a Mettler FP-61 melting point apparatus.

perature, the precipitates were filtered, washed with ethanol and recrystallized to give the corresponding 6-aryl-1,3-dimethylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (Va-h).

The filtrate, from which product Va-h has been removed, was concentrated *in vacuo* and the residue was triturated with chilled methanol. The separated precipitates were filtered and recrystallized to give the corresponding 5-arylideneamino-1,3-dimethyl-6-(2-dimethylaminovinyl)uracils (IIIa-h).

In the cases of IIIb and IIIc, the crude products were subjected to column chromatography through activated alumina with ethyl acetate-chloroform (50:50) prior to recrystallization.

As typical examples, the spectral data of IIIa and Va are shown below.

Compound IIIa.

This compound had ms: m/e 312 ($M^+$); ir: 1665 $cm^{-1}$ (CO); nmr (DMSO-$d_6$); δ 2.97 (s, 6H, $NMe_2$), 3.24 (s, 3H, NMe), 3.48 (s, 3H, NMe), 4.90 (d, 1H, J = 12 Hz, -C*H*=CH-N=), 7.24-7.84 (m, -CH=C*H*-N= and 5H arom), 9.48 (s, 1H, -C*H*-N=). On proton spin decoupling, the vinyl proton signal is δ 7.48 (d, 1H, J = 12 Hz); uv (ethanol): λ max (log ε) 279 (4.40), 350 (4.14), 395 nm (4.14).

Compound Va.

This compound had ms: m/e 267 ($M^+$); ir: 1702, 1650 $cm^{-1}$ (CO); nmr (deuteriotrifluoroacetic acid): $\delta$ 3.59 (s, 3H, NMe), 3.90 (s, 3H, NMe), 7.68-8.16 (m, 5H arom), 8.71 (d, 1H arom, J = 9 Hz), 8.87 (d, 1H arom, J = 9 Hz); uv (ethanol): $\lambda$ max (log $\epsilon$) 277 (4.33), 335 nm (3.66).

7-Formyl-1,3-dimethyl-6-phenylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (VII). Method A.

A suspension of IIa (0.002 mole) in DMFDMA (3 ml) was heated at 130° for 7 hours. After removal of the products IIIa and Va as described above, the filtrate was again concentrated *in vacuo* and the residue was triturated with chilled methanol. The separated precipitates were filtered and recrystallized from dimethylformamide to give 7-formyl-1,3-dimethyl-6-phenylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (VII) (0.017 g, 3%), mp >300°.

*Anal.* Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.52; H, 4.53; N, 14.95.

Method B.

A mixture of 1,3-dimethyl-6-phenylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (VIII) (5) (0.255 g, 0.001 mole) and phosphorus oxychloride (0.31 g, 0.002 mole) in dimethylformamide (3 ml) was heated at 95° for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was triturated with water. The precipitates were filtered and recrystallized from dimethylformamide to give VII (0.25 g, 88%), mp >300°, which was identical with the compound obtained by the Method A.

1,3-Dimethyl-6-phenylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione 5-Oxide (XI) and Va.

A suspension of 1,3,6-trimethyl-5-nitrouracil (X) (4) (1.0 g, 0.005 mole) and phenylacetaldehyde (0.9 g, 0.0075 mole) in ethanol (30 ml) containing piperidine (2.55 g, 0.03 mole) was heated at 70° for 10 hours. After the reaction mixture was cooled to ambient temperature, the precipitates were filtered, washed with ethanol and recrystallized from ethanol to give 1,3-dimethyl-6-phenylpyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione 5-oxide (0.226 g, 16%), mp 256-258°.

*Anal.* Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.30; H, 4.59; N, 14.65.

The filtrate, from which product XI has been removed, was concentrated *in vacuo* and the residue was subjected to column chromatography through activated alumina with benzene. The eluent was concentrated *in vacuo* and the residue was triturated with ethanol. The insoluble material was filtered and recrystallized from ethanol-dimethylformamide to give Va (0.04 g, 3%), mp 247.4°, which is identical with the product obtained by the reaction of IIa with DMFDMA.

2-Aryl-5-methylamino-*N*-methylpyridine-6-carboxamide (IXa, IXc, IXe).

A suspension of the appropriate pyridopyrimidine (Va, Vc, Ve) (0.0005 mole) in a mixture of ethanol (45 ml) and water (5 ml) containing potassium hydroxide (5 g) was refluxed for 1 hour. The resulting solution was evaporated *in vacuo* and the residue was triturated with water. The precipitates were filtered, washed well with water and recrystallized from ethanol to give the corresponding 2-aryl-5-methylamino-*N*-methylpyridine-6-carboxamides (IXa, IXc, IXe).

Compound IXa.

This compound had mp 107-108° (0.048 g, 40%).

*Anal.* Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 70.05; H, 6.31; N, 17.48.

Compound IXc.

This compound had mp 168-169° (0.066 g, 48%).

*Anal.* Calcd. for $C_{14}H_{14}ClN_3O$: C, 60.98; H, 5.12; N, 15.24. Found: C, 60.85; H, 5.06; N, 15.39.

Compound IXe.

This compound had mp 159-161° (0.073 g, 57%).

*Anal.* Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.53; H, 6.70; N, 16.55.

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