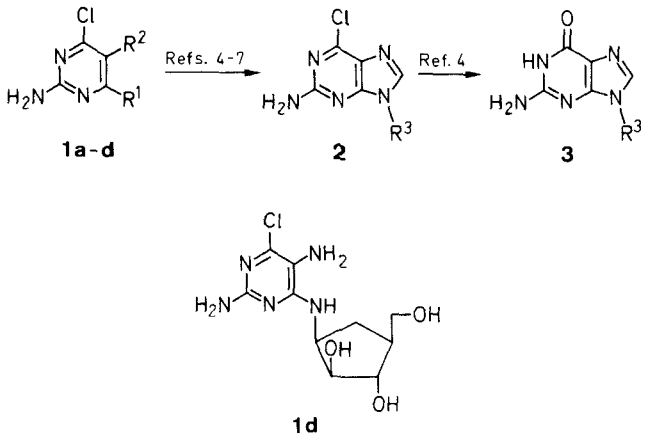
A New Route to 2,5-Diamino-4,6-dichloropyrimidine, A Key Precursor of 9-Substituted Guanines

Michel Legraverend,* Hassane Boumchita, Emile Bisagni
URA 1387 CNRS. Institut Curie, section de Biologie, Bât. 110–112, Centre Universitaire, F-91405 Orsay, France

An improved synthesis of 2,5-diamino-4,6-dihydroxypyrimidine (**7**) is reported. The direct chlorination of **7** provides the shortest (2 step) synthesis of 2,5-diamino-4,6-dichloropyrimidine (**5**) reported to date. The procedure described here affords an easy approach to **5**, a key intermediate to various 9-substituted guanines.

Among the different methods that can be envisaged toward the synthesis of 9-substituted guanines **3**,[1-5] the route outlined in Scheme **A**, which starts from the commercial precursor **1a**, via the diazo intermediate **1c** is one of the most widely used.[4-7] The intermediate **1d** is thus obtained in three steps in variable yields (20–60%).



1	R^1	R^2
a	Cl	H
b	NHR^3	H
c	NHR^3	$N{=}N{-}C_6H_4Cl$-4
d	NHR^3	NH_2

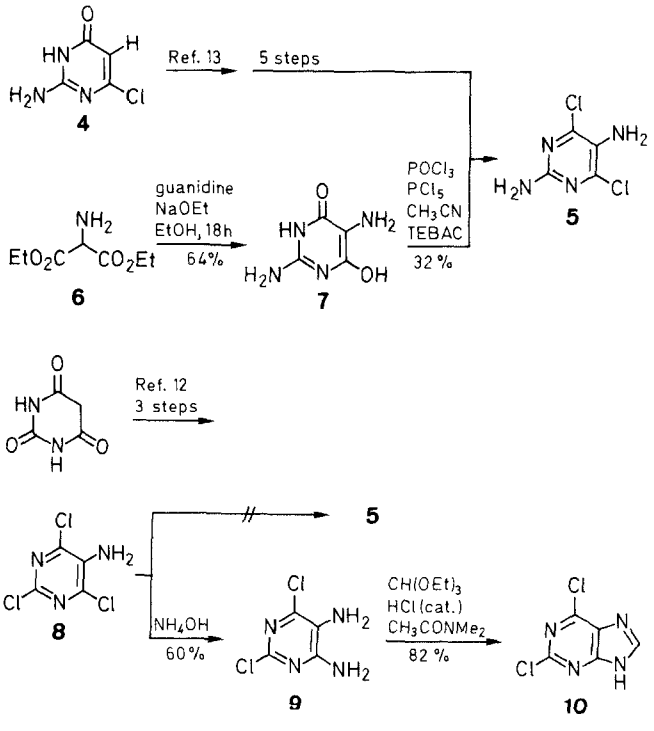
R^3 = mono or dihydroxycyclopentanemethanol

Scheme **A**

The same intermediate **1d** could also, *a priori*, be obtained in one step from 2,5-diamino-4,6-dichloropyrimidine (**5**) and therefore it is surprising to note that this route, with two recent exceptions, has not been widely used.[1,8] In view of the great interest of **5** as a key precursor to 9-substituted guanines **3** and also to pteridine derivatives such as folate analogs,[9-11] we have re-examined its synthesis and report here a new synthesis.

A four-step synthesis of **5** starting from barbituric acid was claimed in 1954[12] in 10% yield, but this putative intermediate **5**, was never used to synthesize guanines **3**. The direct amination of 5-amino-2,4,6-trichloropyrimidine (**8**) with ammonium hydroxide and water under reflux did not lead, in our hands, to **5** as shown by a different melting point (mp 260°C) and R_f value (R_f = 0.48), as compared with those of an authentic sample of **5** obtained according to the non-ambiguous method[13] [R_f = 0.59, TLC on silica gel, eluent: dichloromethane/ethanol (9:1), mp 188–191°C]. This discrepancy in melting points had already been noticed.[13] In addition UV spectrum (methanol) of the diaminodichloropyrimidine prepared as described[12] confirmed (with two absorptions, λ_{max} = 301 (ε = 8300), 262 (ε = 8000) that direct amination of 5-amino-2,4,6-trichloropyrimidine (**8**) does not give **5** but compound **9** (60%) having the same elemental analyses and molecular weight (mass spectrum). Definite proof was provided by a cyclisation experiment, in which this diaminodichloropyrimidine obtained from **8**[12] was treated with triethyl orthoformate and a catalytic amount of concentrated hydrochloric acid in *N,N*-dimethylacetamide. The new compound thus obtained (82%), which crystallized from water clearly corresponded to 2,6-dichloropurine (**10**), as shown by its melting point (188–190°C) (Lit.[14] mp = 188–190°C), ^{1}H-NMR spectrum in DMSO-d_6 [a sharp singlet at δ = 8.74 (H-8) and a broad singlet at δ = 13.81 (NH)], and mass spectrum by chemical ionization in NH_3 [m/z = 189 (100%), m/z = 191 (63%)].

However, the synthesis of **5** was performed in five steps and 15% overall yield from commercial 2-amino-6-chloropyrimidin-4-one (**4**)[13] (Scheme **B**). However, for unexplained reasons the chlorination of *N*-(6-chloro-5-



Scheme **B**

nitro-4-pyrimidinone-2-yl)acetamide with phosphoryl chloride failed to go to completion after 4 hours.[13] Unreacted pyrimidinone was present in significant amounts in every chlorination experiment, even with careful workup of the acidic reaction medium in ice, and lengthening the reaction time did not improve the yield. For these reasons, we turned to the synthesis as outlined in Scheme **B**.

The synthesis of 2,5-diamino-4,6-dihydroxypyrimidine (**7**) was reported previously[15] in 31% yield by condensation of diethyl hydroxyiminomalonate and guanidine followed by reduction with sodium dithionite. However, we found it advantageous to carry out the condensation of diethyl aminomalonate (**6**)[16] with guanidine. Under these conditions the yield of **7** was improved (65%), and it could be prepared on a large scale. Although direct chlorination of **7** was reported[13] to fail with phosphoryl chloride, some product **5** was actually detected by TLC after boiling the residue of evaporation of the reaction in water for a few minutes. The yield of this chlorination was improved by using a modification of the method[17] by boiling **7** for 4 hours in acetonitrile containing fifty equivalents of phosphoryl chloride, four equivalents of benzyltriethylammonium chloride and one equivalent of phosphorus pentachloride. The complex thus obtained was decomposed in boiling water after neutralisation with ammonium hydroxide yielding **5** in 32% yield after chromatography. UV spectra in methanol of 2,5-diamino-4,6-dichloropyrimidine (**5**) prepared as described in this paper and of an authentic sample[13] were identical.

The utility of the pyrimidine **5** as a key intermediate to 9-substituted guanines **3** was illustrated by the synthesis of the known precursor **1d**,[5] which was obtained here from **5** in one step and 72% yield (with R^3 being the carbocyclic analog of arabinofuranosyl residue).

Despite the modest yield of the chlorination step (32%) the route to **5** reported here (Scheme **B**) is much shorter than other preparations described to date[13] owing to the improved synthesis of the 2,5-diamino-4,6-dihydroxypyrimidine (**7**).

Furthermore, whereas the intermediate **1c** requires a reduction step, which in some cases may be incompatible with some functions present at R^1 (Scheme **A**), compound **5** allows the introduction at position 4 (R^1) of an amino group bearing other reducible functions such as an unsaturation. Thus, the procedures described here are suitable for the synthesis of various 9-substituted guanines **3**.

Melting points were taken on a Kofler apparatus and are not corrected. Elemental analyses were carried out by the "Service de Microanalyses", CNRS, ICSN, 91198 Gif sur Yvette. UV spectra were recorded on a Cary 118 spectrophotometer. IR spectra were recorded on a Nicolet MX-S FT Infrared spectrophotometer. ^{1}H-NMR spectra were recorded using a Varian XL 100 instrument. Mass spectra were obtained with a Ribermag spectrometer, ICMO, Université de Paris XI, 91405 Orsay.

Unless otherwise noted, all chemicals including diethyl aminomalonate are commercially available.

2,5-Diamino-4,6-dihydroxypyrimidine (7):
Powdered guanidine hydrochloride (28.21 g, 0.295 mol) is added to a solution of NaOEt (60.2 g, 0.885 mol) in EtOH (400 mL) and stirred for 30 min at r.t. A solution of diethyl aminomalonate[16] (**6**; 51.7 g, 0.295 mol) in EtOH (200 mL) is then added and stirring is continued for 18 h. The mixture is refluxed for 1 h and cooled. Approximately half of the EtOH is evaporated and the resulting solid is diluted with H_2O (100 mL). The title compound **7** is precipitated as its hydrochloride by adding an excess of conc HCl. The solid is filtered, washed with cold H_2O (30 mL), EtOH (100 mL) and recrystallized from a mixture of EtOH/2N HCl (1:1). It is then dried in an oven at 100–110 °C for 3 h to afford colorless needles; yield: 37 g (64%); mp > 260 °C.

$C_4H_6N_4O_2 \cdot HCl$	calc.	C 26.89	H 3.92	N 31.37	Cl 19.88
(178.5)	found	27.02	3.94	31.15	20.02

IR (KBr): ν = 3148–2963, 1697, 1657, 1448, 1398, 1192, 822, 746, 654, 548, 480 cm^{-1}.

2,5-Diamino-4,6-dichloropyridine (5):
A solution of **7** (3.56 g, 18.1 mmol), $POCl_3$ (84 mL), benzyltriethylammonium chloride (16.5 g, 72.4 mmol) and PCl_5 (3.77 g, 18.1 mmol) in CH_3CN (77 mL) is refluxed for 4 h with stirring. After evaporation to dryness, the resulting oily residue is poured into H_2O and ice (50 mL) and neutralized with conc NH_4OH. This aqueous solution is boiled for 2 min, cooled, saturated with NaCl and extracted with EtOAc. The organic phase is dried ($MgSO_4$), filtered, and evaporated to dryness. The solid thus obtained is purified by chromatography on silica gel eluting with CH_2Cl_2; yield: 1.14 g (32%); white needles (EtOH); mp 198 °C (Lit.[13] mp 188–191 °C).

UV (MeOH): λ_{max} = 247 (ε = 15000), 347 nm (ε = 5200).

MS (DEI): m/z = 179 (M^+, 100%), 181 ($M^+ + 2$, 64%).

(±)-(1*S*,2*S*,3*S*,5*S*)-3-[(2,5-Diamino-6-chloro-pyrimidin-4-yl)-amino]-5-(hydroxymethyl)cyclopentane-1,2-diol (1d):
A solution of **5** (287 mg, 1.6 mmol), (1*S*,2*S*,3*S*,5*S*)-3-amino-5-(hydroxymethyl)cyclopentane-1,2-diol[18] (352 mg, 2.4 mmol), and Et_3N (3 mL) in BuOH (25 mL) is refluxed under N_2 for 3 d. Evaporation to dryness gives a solid; yield: 334 mg (72%); mp 236–238 °C (H_2O/EtOH) (Lit.[5] mp 236–238 °C).

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.20–1.50 (m, 1H, H-4'), 1.65–1.90 (m, 1H, H-5'), 1.97–2.24 (m, 1H, H-4'), 3.31–3.74 (m, 4H, H-1',2' + C$\underline{H}_2$OH), 3.84 (s, 2H, NH_2), 4.39 (m, 1H, H-3'), 4.53 (t, 1H, $CH_2O\underline{H}$), 4.50 (d, 1H, OH, J = 5.1 Hz), 4.91 (d, 1H, OH, J = 4.5 Hz), 5.63 (s, 2H, NH_2), 6.10 (d, 1H, NH, J = 8.1 Hz).

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– Freeman, F.; Keindl, M.C.; Po, H.N.; Brinkman, E.; Masse, J.A. *Synthesis* **1989**, 714. On page 714 the data for compounds **2d** and **2e** in the Table should be corrected as follows:
2d:
^{1}H-NMR (500 MHz, DMSO-d_6): δ = 7.213 (H-5), 7.225 (H-6), 7.547 (H-4), 7.558 (H-7); $J_{4,7}$ = 5.94 Hz, $J_{5,6}$ = 6.03 Hz, $J_{4,7}$ = 166.61 Hz, $J_{4,5}$ = 166.70 Hz.
^{13}C-NMR (500 MHz, DMSO-d_6): δ = 119.0 (br, C-7), 119.1 (br, C-4), 126.60 (C-5, C-6), 143.27 (C-3a, C-7a), 151.21 (C-2).
2e: mp 190–191 °C.

$C_{16}H_{14}N_4S_2.1.5H_2O$ (353.5)	calc.	C54.37	H4.85	N15.85	S18.14
	found	54.71	4.63	15.66	17.94

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 2.39 (s, 3H, CH_3), 7.04 (d, 1H, J = 8.11 Hz, H-5), 7.34 (s, 1H, H-7), 7.43 (d, 1H, J = 8.11 Hz, H-4).
^{13}C-NMR (500 MHz, DMSO-d_6): δ = 25.24 (CH_3), 118.05 (v. br, C-4, C-7), 128.13 (C-5), 136.14 (C-6), 142.42 (v. br, C-3a, C-7a), 150.37 (br, C-2).
EIMS (70 eV): m/z = 326 (m^+, 9.8%), 164 (100%).
CIMS: m/z = 327 (MH^+, 7.9%), 165 (100%).

1990

– Lin, Z.-Y.; Shi, W.; Zhang, L. *Synthesis* **1990**, 235. On page 236 compound **4b** should be named 7-acetoxy-4,8-dioxo-5-oxatetracyclo[8.2.1.$0^{2,9}$.$0^{3,7}$]tridec-11-ene; and compound **5** should be named 4,8-dioxo-5-oxatetracyclo-[8.2.1.$0^{2,9}$.$0^{3,7}$]tridec-11-ene.

– Lee, C.; Field, L. *Synthesis* **1990**, 391. On page 392 column 2, line 19, the statement in parenthesis should read: (cf. **7**; see Scheme **B** for general equation). While Scheme **C** should be: R^1SO_2X + 4-MeC_6H_4SH (2 equiv) (conditions: 1. Et_3N (2 equiv)/CH_2CH_2, −76 °C; 2. conc HCl → R^1SO_2H
On page 393 in Scheme **D** the temperature of the reaction of **16** with **17** should be −76 °C.
On page 394–395 in Table 1, the yield of sulfinic acid **15g** should read: 80 $(-)^{21}$; the reference in footnote e should be Ref. 2 and not Ref. 22.
On page 396 in Table 2 for compound **10p** the molecular formula should be referenced to Ref. 10; the 1130 cm^{-1} absorption in its IR spectral data should be designated (s).
On page 397 the sentence should read: The structure of **21** (C, H anal ± 0.3%) is confirmed by heating ...

– Lajoie, G.; Crivici, A.; Adamson, J.G. *Synthesis* **1990**, 571. On page 572 in the Table, compounds **1** and **2** should be **3** and **4**, respectively.

– Legraverend, M.; Boumchita, H.; Bisagni, E. *Synthesis* **1990** 587.
On page 588, 2,5-diamino-4,6-dichloropyridine (**5**) should be replaced by 2,5-diamino-4,6-dichloropyrimidine (**5**).

– Tietze, L.F.; Wünsch, J.R. *Synthesis* **1990**, 985.
On page 989, in the general procedure of the photoklysis sodium hydrogen carbonate (1.1 mmol) should be used instead of sodium hydrogen sulfate.