

# SYNTHESIS OF 4,4'-BIS-PYRIMIDINES AND SOME RELATED BIS-FUSED PYRIMIDINES

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## Abstract

2,2'-Disubstitutedamino-4-4'-bis-pyrimidines (3a-m) have been prepared by linking 2,4-dichloro-6-methyl-5-nitropyrimidine (1) with several diamines and subsequent reaction with suitable amines. Some of these compounds (3c and 3j) which were reduced catalitically, on treatment with nitrous acid, urea in pyridine, and boiling thionyl chloride gave the corresponding bis-triazolopyrimidin (6), bis-purines (7), and bis-isothiazolopyrimidines (8). Two bis-imidazo[1,2-a] pyrimidines (9 and 10) have also been prepared.

## Introduction

2,4-Dichloro-6-methyl-5-nitropyrimidine (1) has been used as a versatile starting material for preparation of several heterocyclic systems of pharmacological importance [1-2]. It is known that the 4-chlorine atom of the dichloro compound (1) is substantially more reactive than 2 towards nucleophilic displacement [3-4]. Therefore, it offers the possibility of linking two pyrimidine rings together by using a diamine as the substituent at position 4 and establishing a 4,4'-linkage between these two rings forming compounds of type (2a-c). A survey of the literature revealed no reports on the use of the dichloro compound (1) for the preparation of 4,4'-bis-pyrimidines. The only few references are those regarding the 4-aminolysis of other substituted pyrimidines [5-7].

The 4,4'-bis-pyrimidines and their amino analogues are suitable compounds for producing some new bis-fused pyrimidines of pharmacological interest such as bis-purines, bis imidazo[1,2-a] pyrimidines, bis-isothiazolopyrimidines and bis-triazolopyrimidines. Here we would like to report our investigation for the synthesis of 4-4'-bis-pyrimidines and some

related bis-fused pyrimidines.

## Results and Discussion

2,4-Dichloro-6-methyl-5-nitropyrimidine (1) was conveniently condensed with a number of diamines (e.g. piperazine, 1,2-diaminoethane, and hydrazine hydrate) in equimolar proportion to link two pyrimidine rings together for obtaining the corresponding 4,4'-bis-pyrimidines [(2a-c) (Table 1)]. At first it was expected that the condensation with diamines would be assisted by including a tertiary base. This technique has been used extensively when introducing substituted amino groups into dichloropyrimidines [8]. For example, treatment of a dichloro compound with one mole of ethylamine and one mole of triethylamine yields the ethylaminopyrimidine and triethylamine hydrochloride. This is an alternative to using two moles of the amine. However, attempts to condense two moles of the dichloro compound with one mole of a diamine in the presence of two moles of triethylamine always gave red solutions from which no recognisable product could be isolated. It appeared that some kind of charge transfer complexes were being formed. Eventually, it was found best to leave out the tertiary base altogether and simply add the

**Keywords:** Ultrasonic absorption; Amino acid absorption; Protein absorption; Amino acid mixture absorption

**Table 1.** Formation of 2,2'-dichloro-4,4'-bis-pyrimidines (2a-c)

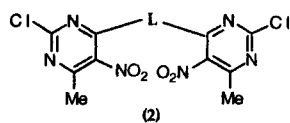
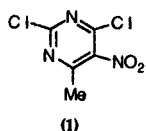
Compound	L	M.p. (°C)	Yield(%)	Recrystln. solvent	Reaction solvent	Formula	Found			Required		
							C	H	N	C	H	N
2a	-N N-	280(dec.)	26	toluene	chloroform	C <sub>14</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>8</sub> O <sub>4</sub>	39.3	3.4	26.3	39.2	3.3	26.1
2b	-(NHCH <sub>2</sub> ) <sub>2</sub>	240-42	32	toluene	chloroform	C <sub>12</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>8</sub> O <sub>4</sub>	35.6	3.2	28.1	35.8	3.0	27.8
2c	-(NH-) <sub>2</sub>	235(dec.)	27	toluene	ethanol	C <sub>10</sub> H <sub>8</sub> Cl <sub>2</sub> N <sub>8</sub> O <sub>4</sub>	32.4	2.2	30.3	32.0	2.1	29.9

**Table 2.** Formation of 2,2'-di-substitutedamino-4,4'-bis-pyrimidines (3a-m)

Compound	X	L	M.p. (°C)	Yield(%)	Recrystln solvent	Reaction solvent	Formula	Found			Required		
								C	H	N	C	H	N
3a	NHMe	-N N-	269-71	53	toluene	toluene	C <sub>16</sub> H <sub>22</sub> N <sub>10</sub> O <sub>4</sub>	46.0	5.1	32.0	45.9	5.3	32.3
3b	NHEt	-N N-	225-6	76	toluene	toluene	C <sub>18</sub> H <sub>26</sub> N <sub>10</sub> O <sub>4</sub>	48.5	5.8	31.2	48.4	5.8	31.4
3c	NMe <sub>2</sub>	-N N-	274-6(dec.)	87	toluene	toluene	C <sub>18</sub> H <sub>26</sub> N <sub>10</sub> O <sub>4</sub>	48.6	5.9	31.3	48.4	5.8	31.4
3d	NEt <sub>2</sub>	-N N-	232	76	toluene	toluene	C <sub>20</sub> H <sub>30</sub> N <sub>10</sub> O <sub>4</sub>	52.8	6.8	27.7	52.6	6.8	27.4
3e	Mor <sup>+</sup>	-N N-	270-1	60	toluene	toluene	C <sub>22</sub> H <sub>30</sub> N <sub>10</sub> O <sub>6</sub>	50.0	5.5	26.7	49.8	5.7	26.4
3f	Pip <sup>**</sup>	-N N-	246	62	toluene	toluene	C <sub>24</sub> H <sub>34</sub> N <sub>10</sub> O <sub>4</sub>	54.6	6.6	26.6	54.8	6.5	26.6
3g	NHCH <sub>2</sub> CH <sub>2</sub> OH	-N N-	212-14	63	n-butanol	THF	C <sub>18</sub> H <sub>26</sub> N <sub>10</sub> O <sub>6</sub>	45.1	5.6	29.4	45.2	5.4	29.3
3h	NHCH <sub>2</sub> CH <sub>2</sub> Cl	-N N-	195(dec.)	70	isopropanol	SOCl <sub>2</sub>	C <sub>18</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>10</sub> O <sub>4</sub>	42.1	5.1	26.8	42.0	4.7	27.2
3i	NHMe	-(NHCH <sub>2</sub> ) <sub>2</sub>	247	91	DMF	THF	C <sub>14</sub> H <sub>20</sub> N <sub>10</sub> O <sub>4</sub>	42.9	5.2	35.7	42.9	5.1	35.7
3j	Mor	-(NHCH <sub>2</sub> ) <sub>2</sub>	220	68	toluene	THF	C <sub>20</sub> H <sub>28</sub> N <sub>10</sub> O <sub>6</sub>	48.0	5.8	27.8	47.6	5.6	27.8
3k	Pip	-(NHCH <sub>2</sub> ) <sub>2</sub>	210	52	toluene	THF	C <sub>22</sub> H <sub>32</sub> N <sub>10</sub> O <sub>4</sub>	52.8	6.5	27.9	52.8	6.4	28.0
3l	Mor	-(NH-) <sub>2</sub>	305	95	toluene	THF	C <sub>18</sub> H <sub>24</sub> N <sub>10</sub> O <sub>6</sub>	45.6	4.8	29.2	45.4	5.1	29.4
3m	Pip	-(NH-) <sub>2</sub>	304	53	toluene	THF	C <sub>20</sub> H <sub>28</sub> N <sub>10</sub> O <sub>4</sub>	50.6	6.2	29.2	50.8	6.0	29.6

\* Morpholine; \*\* Piperidine

diamines slowly to two equivalents of the stirred dichloro compound. Treatment of the products (2a-c) with different amines, followed by refluxing, gave a series of substituted amino analogues [(3a-m) (Table 2)].

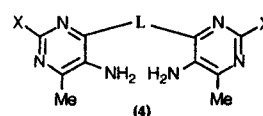
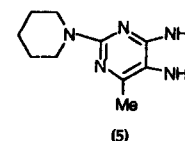


L = Linking diamine

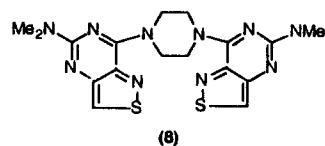
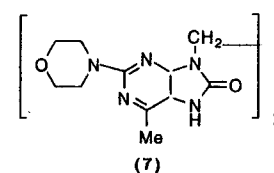
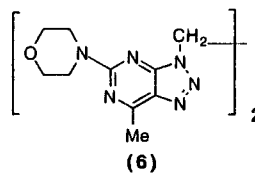


Catalytic hydrogenation of these derivatives [(3a-k) (Table 2)] using Raney nickel and hydrogen under 1 atmosphere pressure at room temperature was not effective, and in all cases starting material was recovered. However, reduction of the nitro group was achieved successfully with the compounds derived from ethylenediamine and piperazine (e.g. 3c and 3j) under 50 atmosphere pressure of hydrogen at 65°C and gave the corresponding amino derivatives (4a-b). However, catalytic hydrogenation of the hydrazine derivative [(3m) (Table 2)] under the same conditions led to the cleavage of the rather weak N-N-bond and a

diaminopyrimidine (5) was obtained.

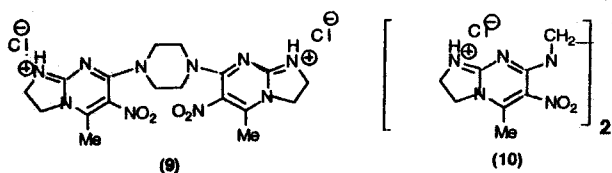
a: X = Me<sub>2</sub>N; L: B: X = Morpholino; L:  $-(NACH_2)_2$ 

The conversion of the bis-diamino compounds (3c and 3j) to their corresponding bis-fused derivatives was studied further. Treatment of compound (3j) with nitrous acid, afforded a bis-triazolopyrimidine (6) and on treatment with urea in boiling pyridine underwent condensation to give a bis-(8'-hydroxypurine) (7).



Compound (3c), with piperazine linkage, on treatment with thionyl chloride, gave the rather unexpected bis-isothiazolo pyrimidine (8). The  $^1\text{H}$  NMR spectrum of this product showed a singlet at  $\delta$  8.84 assignable to two aromatic protons. The structure was also supported by accurate mass measurements and analytical data.

Two bis-imidazo [1,2-a] pyrimidines (9) and (10) were prepared by first condensing the corresponding bis-chloro derivatives (2a and 2b) by either 2-chloroethylamine or ethanolamine and treating with thionyl chloride. The substituted derivatives were then cyclised in boiling 2-propanol as in normal imidazopyrimidine syntheses [1-2,4].



### Experimental Section

$^1\text{H}$  NMR spectra were recorded on a Perkin-Elmer R32 spectrometer at normal probe temperature, unless otherwise specified, using tetramethylsilane as internal standard. Mass spectra were recorded on an AEI MS 902S instrument using an ionising energy of 70 eV and introduction by direct insertion probe. Microanalysis was performed by Butterworth Laboratories, Ltd., Teddington, Middlesex, England.

#### 1,2-, and 1,4-Bis-(2,2'-dichloro-6,6'-dimethyl-5,5'-dinitropyrimidine-4,4'-diyl)diamine [(2a-c) (Table 1)]

A solution of the diamine (0.1 mole) in an appropriate solvent (30 ml) was added during 45 minutes to a stirred solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (0.1 mole) in the solvent (100 ml) at room temperature. After the addition was completed, the mixture was stirred for a further one hour. The product was filtered off, washed with water and recrystallised from a suitable solvent. Yields, melting points, reaction solvents, recrystallising solvents and microanalysis data are given in Table 1.

#### 1,2-, and 1,4-Bis-(2,2'-disubstituted-amino-6,6'-dimethyl-5,5'-dinitropyrimidine-4,4'-diyl)diamine [(3a-m) (Table 2)]

A solution of the appropriate amines (0.004 mole) in a suitable solvent (20 ml) was added to a stirred

solution of the foregoing chloro compound (2a-c) (0.001 mole) in the solvent (50 ml). The mixture was heated under reflux for two hours, then cooled to room temperature. The solid product was filtered off, washed with water and recrystallised from a suitable solvent. Yields, melting points, reaction solvents, recrystallising solvents and microanalysis data are given in Table 2.

#### 1,4-Bis-(5,5'-diamino-2,2'-bis-dimethyl amino-6,6'-dimethylpyrimidine-4,4'-diyl)piperazine (4a)

The piperazine derivative [(3c) (Table 2)] (2g) in toluene (250 ml) was shaken with Raney nickel (10 g) under 50 atmosphere pressure of hydrogen at 65°C overnight. The catalyst was filtered off, washed with toluene and the combined filtrate was evaporated to dryness under reduced pressure to give the title compound (1.5 g, 88.5%): m.p. 197-199°C (from ethanol);  $^1\text{H}$  NMR ( $\text{CF}_3\text{CO}_2\text{D}$ ) (4.6, s, 2H and 5.45, s, 2H, piperazine resonance), (3.43, s, 6H,  $\text{Me}_2\text{N}$ -), (2.7, s, 3H.). Anal. Calcd. for  $\text{C}_{18}\text{H}_{30}\text{N}_{10}$ : C, 56.0; H, 7.8; N, 36.3. Found: C, 56.1; H, 7.8; N, 35.9

#### 1,2-Bis-(5,5'-diamino-6,6'-dimethyl-2,2'-dimorpholinopyrimidine-4,4'-diylamino)ethane (4b)

The corresponding nitro derivative [(3c) (Table 2)] (4.5 g) was reduced according to the above procedure to give the title compound (2.5 g, 64%): m.p. 213-214°C (from toluene); which was purified as its formylamino derivative for microanalysis (see below).

#### 1,2-Bis-(5,5'-formamino-6,6'-dimethyl-2,2'-dimorpholinopyrimidine-4,4'-diylamino)ethane (4b)

The foregoing amino derivative (4b) (0.2 g) in formic acid (5 ml) was heated under reflux for 10 hours. The volatile material was evaporated in a water bath under reduced pressure. The residue was dissolved in water and made alkaline with 2N sodium hydroxide solution. The product was filtered off, washed with water and recrystallised from aqueous dimethyl sulfoxide to give the title compound (0.15 g, 68%): m.p. 285°C;  $^1\text{H}$  NMR ( $\text{CF}_3\text{CO}_2\text{D}$ ) (8.2, s, 1H; 7.9, s, 1H, -NHs), (4.57, m, 4H and 3.44, m, 4H, morpholine resonance), (2.7, 3H, -Me), (9.4, s, 1H, -CHO). Anal. Calcd. for  $\text{C}_{22}\text{H}_{32}\text{N}_{10}\text{O}_4$ : C, 52.8; H, 6.5; N, 28.0. Found: C, 52.7; H, 6.4; N, 27.9.

#### 4,5-Diamino-6-methyl-2-piperidinopyrimidine (5)

Catalytic hydrogenation of the hydrazine derivative [(3k) (Table 1)] (1.3 g) in toluene (250 ml) as in above procedure gave the title compound (0.9 g, 70%): m.p.

146°C (Lit. 146°C).

**1,2-Bis-[4,4'-dimethyl-6,6'-dimorpholinotriazolo(5,4-d)pyrimidine-1,1'-diyl]ethane (6)**

The amino derivative (3j) (0.2 g) was dissolved in 2N HCl (1 ml) and treated at 0°C with a solution of sodium nitrite (0.2 g) in water (4 ml). The solution was then warmed in a water bath for 5 minutes, then cooled in ice. The product was filtered off and recrystallised from tetrahydrofuran to give the title compound (0.15 g, 75%), m.p. 267°C (decomp.); <sup>1</sup>H NMR (d<sub>6</sub> DMSO) (4.98, s, 2H, -CH<sub>2</sub>-), (3.97, s, 8H, morpholin resonance), (2.7, s, 3H, -Me). Anal. Calcd. for C<sub>20</sub>H<sub>26</sub>N<sub>12</sub>O<sub>2</sub>: C, 51.5; H, 5.6; N, 36.0. Found: C, 51.5; H, 5.5; N, 36.3.

**1,2-Bis-[4,4'-dimethyl-6,6'-dimorpholinopurin-2,2'(3,3'-H)-dione-1,1'-diyl]ethane (7)**

The amino compound (3j) (0.2 g) was ground with urea (1.2 g) and then suspended in pyridine (6 ml). The suspension was heated under reflux for 6 hours; the precipitate was then filtered off and recrystallised from aqueous dimethyl sulfoxide to give the title compound (0.45 g, 34%) m.p. 300°C; <sup>1</sup>H NMR (d<sub>6</sub> DMSO) (8.2, s, 1H, -NH), (5.1, s, 2H, -CH<sub>2</sub>-), (3.8, s, 8H, morpholin resonance), (2.6, s, 3H, -Me). Anal. Calcd. for C<sub>22</sub>H<sub>28</sub>N<sub>10</sub>O<sub>4</sub>: C, 53.2; H, 5.7; N, 28.2. Found: C, 53.4; H, 5.7; N, 28.2.

**1,4-Bis-[5,5'-bis-dimethylaminoisothiazolo(4,3-d)pyrimidine-7,7'-diyl]piperazine dihydrochloride (8)**

The amino derivative (3c) (0.3 g) in thionyl chloride (15 ml) was heated under reflux in a water bath for 20 minutes. The product was separated and recrystallised from boiling water to give the title compound (0.2 g, 53%) m.p. 300°C; <sup>1</sup>H NMR (d<sub>6</sub> DMSO) (8.84, s, 1H, -CH-S-), (5.4, s, 4H and 4.55, s, 4H, piperazine resonance), (3.4, s, 3H, -Me). Anal. Calcd. for C<sub>18</sub>H<sub>22</sub>N<sub>10</sub>S<sub>2</sub>, 2HCl: C, 41.9; H, 4.7; N, 27.2. Found: C, 41.9; H, 4.6; N, 27.0.

**1,4-Bis-[2,2'-(2,2'-dichloroethylamino)-6,6'-dimethyl-5,5'-dinitropyrimidine-4,4'-diyl]piperazine (3h)**

The 2-hydroxyethylamino derivative (3g) (0.4 g) was added portionwise to thionyl chloride (25 ml) and the resulting solution was allowed to stand overnight. The excess of thionyl chloride was removed under reduced pressure with the minimum of heating and the oily residue dissolved in water. The solution was then made alkaline with dilute ammonia and the product was filtered off and washed with water to give the title

compound (data in Table 2).

**1,4-Bis-[2,2',3,3'-bis-dihydro-5,5'-dimethylimidazo(1,2-a)pyrimidine-7,7'-diyl]piperazine dihydrochloride (9)**

The foregoing 2-chloroethylamino compound (3h) (0.3 g) was suspended in isopropanol (80 ml) and the mixture was heated under reflux for 8 hours. The product was separated and washed with ether to give the title compound (0.28 g, 93%), m.p. 250°C (decomp.) (C<sub>18</sub>H<sub>22</sub>N<sub>10</sub>O<sub>4</sub>, 2HCl, (Required, C, 41.9; H, 4.7; N, 27.2; Found, C, 41.8; H, 4.8; N, 26.8). <sup>1</sup>H NMR (4.62, m, 2H, and 4.17, m, 2H, imidazo resonance), (3.95, s, 8H, piperazine resonance), (3.6, s, 3H, -Me). Anal. Calcd. for C<sub>18</sub>H<sub>22</sub>N<sub>10</sub>O<sub>4</sub>, 2HCl: C, 41.9; H, 4.7; N, 27.2. Found: C, 41.8; H, 4.8; N, 26.8.

**1,2-Bis-[2,2'-3,3'-bis-dihydro-5,5'-dimethyl-6,6'-dinitroimidazo(1,2-a)pyrimidine-7,7'-diylamine]ethane dihydrochloride (10)**

a) A mixture of the chloro derivative (3c) (0.005 mole), 2-chloroethylamine (0.01 mole) and anhydrous sodium acetate (0.02 mole) in ethanol (50 ml) was heated under reflux for 4 hours. The sodium chloride was filtered off and most of the ethanol was evaporated; ether was then added to the point of precipitation and the mixture cooled. The title compound (1.5 g, 68%) was separated and purified as its picrate as follows: It was dissolved in water (20 ml) and treated with a saturated solution of picric acid in water. The precipitate was filtered off and recrystallised from dimethyl sulfoxide-water (1:1), m.p. 285°C (decomp.); Anal. Calcd. for C<sub>28</sub>H<sub>26</sub>N<sub>16</sub>O<sub>16</sub>: C, 38.4; H, 3.0; N, 25.6. Found: C, 38.2; H, 3.2; N, 25.4.

b) The free base was obtained by dissolving the dihydrochloride (0.2 g) in water (3 ml) and adding dilute sodium hydroxide until alkaline. The product was separated, washed with water and recrystallised from methanol, m.p. 210-212°C; <sup>1</sup>H NMR (4.62, m, 2H, and 4.17, m, 2H, imidazo resonance), (3.6, s, 3H, -Me). Anal. Calcd. for C<sub>16</sub>H<sub>20</sub>N<sub>10</sub>O<sub>4</sub>: C, 46.1; H, 4.8; N, 33.6. Found: C, 46.4; H, 4.6; N, 33.7.

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