The Synthesis and Structure of 5-Hydroxy-2-methyl-2-(2-pyridinyl)hexahydro-1,3-pyrimidine

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The synthesis and the x-ray structure of 5-hydroxy-2-methyl-(2-pyridinyl)hexahydro-1,3-pyrimidine are reported. The compound was prepared by reaction of 2-acetylpyridine and 1,3-diamino-2-hydroxypropane in a 2:1 molar ratio. The colourless crystals are monoclinic, space group $P2_1/c$ with cell parameters, a = 10.385(5), b = 11.171(5), c = 17.415(6)Å, β = 93.05(37)° for Z = 8. The asymmetric unit of the structure is composed of two independent molecules of the compound which are in the chair form and adopt the same conformation with equatorial -OH and $-CH_3$ groups and axial pyridine substituents. The packing of the molecule seems to be controlled by two independent hydrogen-bonding sequences.

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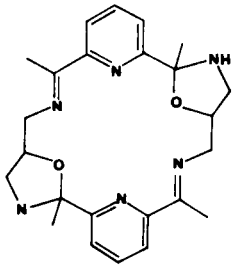
In the course of a recent study on the synthesis of '2+2' tetraimino-Schiff Base macrocycles from heterocyclic dialdehydes or diketones and α,ω-alkanediamines a metal ion controlled ring contraction to produce an oxazolidine-containing macrocycle was found [1]. The reaction of 2,6-diacetylpyridine with 1,3-diamino-2-propanol in methanol in the presence of lead(II) cations yielded the lead(II) complex of macrocycle **1**. In contrast use of the barium(II) cation as a templating device led to the formation of the barium complex of macrocycle **2**.



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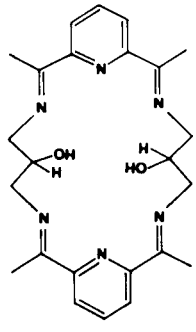

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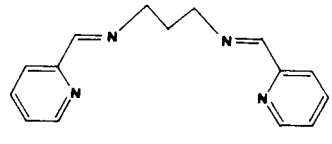
Although the tetradentate acyclic Schiff Bases **3** and **4a** have been reported for the reaction of 2-pyridinecarboxaldehyde with 1,3-diaminopropane and 1,3-diamino-2-propanol respectively [2], little attention has been paid to the corresponding reactions with 2-acetylpyridine. The reaction of 2-acetylpyridine with 1,3-diaminopropane gives on work up an oil the ir of which shows both ν C=O and ν C=N to be present and suggested a mixture of product including the starting materials [3].

The reaction of 2-acetylpyridine with 1,3-diamino-2-propanol however gave a white solid the analysis and ms (P^+ = 193) of which indicated that a 1 + 1 condensation reaction had occurred. The ir of this product showed no bands between 1600 and 1750 cm^{-1} suggesting that neither ketone nor imine bands were present, and gave a strong sharp signal at 3623 cm^{-1} with weaker bands at 3295, 3241 and 3136 cm^{-1}. This information hinted at ring closure and furthermore that of the possible closures available a 6-endo-trig closure had occurred to give a hexahydropyrimidine ring **5** [4] rather than a 5-endo-trig closure to give an oxazolidine ring **6**. Such a closure would be in accord with Baldwin's rules [5] for ring closure.



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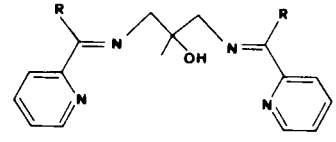
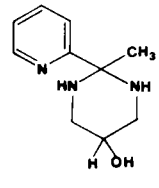


a: R = H
b: R = CH_3

4



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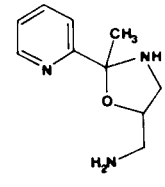

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Table 1

Atomic Coordinates

Atom	X	Y	Z
O(1)	0.2189(4)	0.5269(3)	0.3197(2)
O(2)	0.2721(4)	0.7211(3)	0.0307(2)
C(1)	0.2509(4)	0.9248(4)	0.2447(2)
C(2)	0.1609(5)	0.9385(4)	0.1849(3)
C(3)	0.2033(6)	0.9658(4)	0.1124(3)
C(4)	0.3349(6)	0.9777(4)	0.1040(3)
C(5)	0.4163(5)	0.9648(4)	0.1661(3)
C(6)	0.2120(4)	0.9004(4)	0.3272(2)
C(7)	0.0991(4)	0.7124(4)	0.3014(3)
C(8)	0.2034(4)	0.6450(4)	0.3474(2)
C(9)	0.3300(4)	0.7133(4)	0.3460(2)
C(10)	0.1929(6)	1.0228(4)	0.3647(3)
C(11)	0.2426(4)	0.3163(4)	0.0663(2)
C(12)	0.3338(4)	0.2682(4)	0.0186(2)
C(13)	0.2906(6)	0.1995(4)	−0.0430(3)
C(14)	0.1602(6)	0.1788(4)	−0.0559(3)
C(15)	0.0776(5)	0.2298(4)	−0.0063(3)
C(16)	0.2829(4)	0.3866(4)	0.1386(2)
C(17)	0.3957(4)	0.5478(4)	0.0744(2)
C(18)	0.2878(4)	0.6358(4)	0.0902(2)
C(19)	0.1633(4)	0.5675(4)	0.1010(2)
C(20)	0.3009(4)	0.2993(4)	0.2047(2)
N(1)	0.3785(3)	0.9393(3)	0.2369(2)
N(2)	0.0883(3)	0.8377(3)	0.3247(2)
N(3)	0.3108(3)	0.8354(3)	0.3738(2)
N(4)	0.1156(3)	0.2965(3)	0.0534(2)
N(5)	0.4060(3)	0.4467(3)	0.1275(2)
N(6)	0.1849(3)	0.4758(3)	0.1597(2)

Table 1 continued

Atom	X	Y	Z
H(1)	0.1660(44)	1.0126(42)	0.4159(28)
H(2)	0.2749(48)	1.0648(44)	0.3731(27)
H(3)	0.1224(44)	1.0659(41)	0.3322(25)
H(4)	0.0661	0.9284	0.1906
H(5)	0.1285	0.9697	0.0821
H(6)	0.3635	0.9923	0.0448
H(7)	0.5123	0.9750	0.1757
H(8)	0.3898	0.8735	0.3761
H(9)	0.4027	0.6769	0.3813
H(10)	0.3616	0.7054	0.2921
H(11)	0.1841	0.6295	0.4119
H(12)	0.2039	0.5235	0.2527
H(13)	0.1021	0.7083	0.2454
H(14)	0.0040	0.6720	0.3019
H(15)	0.0652(51)	0.8371(49)	0.3668(28)
H(16)	0.3456	0.3368	0.2530
H(17)	0.3677	0.2422	0.1950
H(18)	0.2179	0.2554	0.2106
H(19)	0.4283	0.2832	0.0360
H(20)	0.3570(42)	0.1623(40)	−0.0696(25)
H(21)	0.1166(41)	0.1332(39)	−0.1007(25)
H(22)	−0.0092(34)	0.2156(29)	−0.0131(18)
H(23)	0.4536	0.4681	0.1759
H(24)	0.4825	0.5903	0.0823
H(25)	0.3750	0.5192	0.0202
H(26)	0.3289	0.6741	0.1385
H(27)	0.2653(45)	0.6912(42)	−0.0135(25)
H(28)	0.1258	0.5332	0.0503
H(29)	0.0902	0.6263	0.1115
H(30)	0.1075	0.4384	0.1595

Table 1 continued

Anisotropic Temperature Factors in the Form $T = \exp[-2\pi^2(\Sigma_{ij} U_{ij} h_i h_j a_i^* a_j^*)]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	.0899(26)	.0322(17)	.0419(18)	−.0012(15)	.0097(17)	−.0027(18)
O(2)	.0959(28)	.0329(18)	.0369(17)	.0029(15)	.0159(19)	.0063(18)
C(1)	.0397(24)	.0252(20)	.0325(22)	.0006(18)	.0061(19)	−.0005(20)
C(2)	.0517(29)	.0399(26)	.0407(26)	.0005(22)	−.0010(22)	−.0018(24)
C(3)	.0879(43)	.0417(28)	.0382(27)	.0037(23)	−.0113(27)	−.0011(29)
C(4)	.0873(40)	.0342(26)	.0400(27)	.0058(22)	.0167(26)	−.0042(27)
C(5)	.0646(33)	.0418(27)	.0507(30)	.0090(24)	.0215(26)	−.0038(25)
C(6)	.0351(24)	.0341(23)	.0303(21)	−.0034(18)	.0071(18)	−.0001(19)
C(7)	.0395(25)	.0419(27)	.0480(26)	−.0034(23)	.0053(21)	−.0098(22)
C(8)	.0495(28)	.0312(23)	.0347(23)	−.0046(19)	.0102(20)	−.0024(21)
C(9)	.0417(25)	.0347(23)	.0324(22)	.0000(19)	.0075(19)	.0056(21)
C(10)	.0625(36)	.0363(27)	.0437(29)	−.0069(24)	.0110(26)	.0060(26)
C(11)	.0340(23)	.0318(23)	.0350(22)	.0030(19)	.0108(18)	.0037(19)
C(12)	.0477(27)	.0393(25)	.0387(25)	−.0001(21)	.0132(21)	.0089(22)
C(13)	.0748(39)	.0384(27)	.0394(26)	−.0030(22)	.0187(26)	.0186(27)
C(14)	.0765(38)	.0393(28)	.0378(26)	−.0067(22)	.0021(25)	.0045(27)
C(15)	.0446(28)	.0429(27)	.0483(28)	−.0034(23)	.0017(23)	−.0039(23)
C(16)	.0358(24)	.0355(23)	.0282(20)	.0008(19)	.0079(18)	.0021(19)
C(17)	.0370(26)	.0446(27)	.0426(25)	.0008(21)	.0115(20)	−.0079(21)
C(18)	.0513(29)	.0384(25)	.0321(22)	.0008(20)	.0074(20)	.0012(22)
C(19)	.0363(24)	.0384(24)	.0345(22)	−.0057(20)	.0052(19)	.0074(21)
C(20)	.0534(28)	.0461(28)	.0368(24)	.0062(22)	.0047(22)	.0053(24)
N(1)	.0448(23)	.0399(21)	.0411(21)	.0031(18)	.0130(17)	−.0016(19)
N(2)	.0327(20)	.0391(21)	.0426(22)	−.0012(19)	.0122(18)	.0009(16)
N(3)	.0352(21)	.0340(19)	.0329(18)	−.0021(16)	.0048(16)	−.0010(16)
N(4)	.0407(21)	.0380(21)	.0346(19)	−.0069(17)	.0052(16)	−.0011(18)
N(5)	.0304(19)	.0443(22)	.0365(20)	.0010(17)	.0049(15)	.0020(17)
N(6)	.0290(19)	.0349(19)	.0312(18)	−.0036(15)	.0117(14)	.0010(16)

In order to verify the nature of the product the X-ray crystal structure of the recrystallised sample was undertaken. A view of the structure with the numbering scheme is shown in Figure 1. The asymmetric unit of the structure

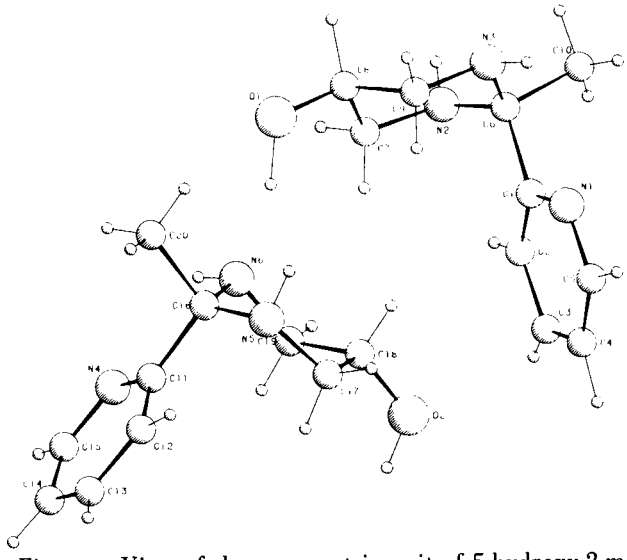


Figure. View of the asymmetric unit of 5-hydroxy-2-methyl-2-(2-pyridinyl)hexahydro-1,3-pyrimidine.

Table 2

Bond Distances (Å)

N(1)—C(1)	1.346(1)	N(4)—C(11)	1.341(5)
C(1)—C(2)	1.368(6)	C(11)—C(12)	1.398(5)
C(2)—C(3)	1.393(6)	C(12)—C(13)	1.374(6)
C(3)—C(4)	1.385(7)	C(13)—C(14)	1.377(7)
C(4)—C(5)	1.343(7)	C(14)—C(15)	1.372(6)
C(5)—N(1)	1.345(5)	C(15)—N(4)	1.323(5)
C(1)—C(6)	1.537(5)	C(11)—C(16)	1.524(5)
C(6)—C(10)	1.533(6)	C(16)—C(20)	1.512(6)
C(6)—N(2)	1.459(5)	C(16)—N(5)	1.463(5)
C(6)—N(3)	1.465(5)	C(16)—N(6)	1.493(5)
N(2)—C(7)	1.463(6)	N(5)—C(17)	1.460(5)
C(7)—C(8)	1.510(6)	C(17)—C(18)	1.525(6)
C(8)—C(9)	1.519(6)	C(18)—C(19)	1.518(6)
C(9)—N(3)	1.464(5)	C(19)—N(6)	1.456(5)
C(8)—O(1)	1.417(5)	C(18)—O(2)	1.411(5)

Contact distances (Å)

N(3)...O(2)	2.854(5)
N(6)...O(1)	2.848(5)

is composed of two independent molecules of the compound. Both molecules are in the chair form and adopt the same conformation having equatorial OH and CH_3 groups and axial pyridine substituents. The packing of the molecules apears to be controlled by two independent hydrogen-bonding sequences. The first sequence comprises a single hydrogen bond from the donor hydroxyl O(1) of one molecule to the acceptor nitrogen atom N(6) of the second molecule of the same asymmetric unit. The bond is moderately weak with an oxygen-nitrogen separation of 2.85 Å. The second sequence comprises donation from the hydroxyl oxygen O(2) to the nitrogen atom N(3) of the symmetry-

Table 2 continued

Bond Distances (Å) Involving Hydrogen Atoms. The Errors are ≤ 0.05 Å

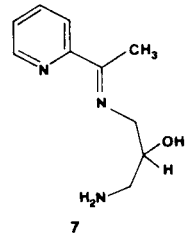
C(2)—H(4)	1.00	C(12)—H(19)	1.02
C(3)—H(5)	0.95	C(13)—H(20)	0.95
C(4)—H(6)	1.10	C(14)—H(21)	1.02
C(5)—H(7)	1.01	C(15)—H(22)	0.91
C(10)—H(1)	0.96	C(20)—H(16)	1.03
C(10)—H(2)	0.97	C(20)—H(17)	0.96
C(10)—H(3)	1.02	C(20)—H(18)	1.00
N(2)—H(15)	0.78	N(5)—H(23)	0.98
C(7)—H(13)	0.98	C(17)—H(24)	1.02
C(7)—H(14)	1.08	C(17)—H(25)	1.01
C(8)—H(11)	1.16	C(18)—H(26)	1.02
C(9)—H(9)	1.03	C(19)—H(28)	1.02
C(9)—H(10)	1.01	C(19)—H(29)	1.03
N(3)—H(8)	0.92	N(6)—H(30)	0.90
O(1)—H(12)	1.17	O(2)—H(27)	0.84

Probable hydrogen bonds

N(3)...H(27)	2.06
N(6)...H(12)	1.71

related molecule at x, 1.5-y, 0.5+z and donation from the hydroxyl oxygen O(2) of the molecule at x, 1.5-y, 0.5+z to the nitrogen atom N(3). These interactions, which are equivalent by symmetry, are of separation 2.85 Å. Bond details in the two independent units compare very favourably amongst themselves confirming the reliability of the results on the whole. In particular the C-N bond lengths in the different ring types are very close to the values expected for saturated and conjugated heterocycles [7] (mean lengths in **5** are 1.46 and 1.33 Å respectively).

The ^{1}H nmr of the crystalline sample shows that the hexahydropyrimidine form is maintained in solution. However the ^{1}H nmr of the bulk sample shows a second set of signals (in 28% abundance based on the CH_3 signal ratio) which is indicative of some Schiff Base presence. It is interesting to note that if the reaction to prepare **5** is carried out in the presence of lead(II) perchlorate as a likely template then the product is the complex (**4b**), lead(II) diperchlorate. The ir shows ν C=N at 1640 cm^{-1} and ν OH at 3550 cm^{-1} with no carbonyl or amine bands in evidence. If (**5**) is reacted with copper(II) dichloride monohydrate in ethanol then the complex **7**, copper(II) diperchlorate monohydrate is recovered, a ring opening to the 'half-unit' Schiff base having occurred. In this complex the ir



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has bands at 3300 and 3250 cm^{-1} (ν NH_2), 3420 cm^{-1} (ν OH) and 1625 cm^{-1} (ν C=N). Satisfactory analytical data were obtained for both complexes.

Table 3

Bond Angles (Deg)

N(1)—C(1)—C(2)	122.9(4)	N(4)—C(11)—C(12)	121.7(4)
C(1)—C(2)—C(3)	118.7(4)	C(11)—C(12)—C(13)	118.4(4)
C(2)—C(3)—C(4)	118.4(5)	C(12)—C(13)—C(14)	119.8(4)
C(3)—C(4)—C(5)	119.0(4)	C(13)—C(14)—C(15)	117.9(5)
C(4)—C(5)—N(1)	124.0(5)	C(14)—C(15)—N(4)	124.0(5)
C(5)—N(1)—C(1)	117.0(4)	C(15)—N(4)—C(11)	118.2(4)
N(1)—C(1)—C(6)	115.0(4)	N(4)—C(11)—C(16)	116.5(3)
C(2)—C(1)—C(6)	122.0(4)	C(12)—C(11)—C(16)	121.6(4)
C(1)—C(6)—C(10)	106.6(3)	C(11)—C(16)—C(20)	108.3(3)
C(1)—C(6)—N(2)	109.3(3)	C(11)—C(16)—N(5)	109.3(3)
C(1)—C(6)—N(3)	113.3(3)	C(11)—C(16)—N(6)	112.9(3)
C(10)—C(6)—N(2)	107.9(4)	C(20)—C(16)—N(5)	108.9(3)
C(10)—C(6)—N(3)	107.9(4)	C(20)—C(16)—N(6)	107.6(3)
N(2)—C(6)—N(3)	111.4(3)	N(5)—C(16)—N(6)	109.7(3)
C(6)—N(2)—C(7)	112.8(3)	C(16)—N(5)—C(17)	113.8(3)
N(2)—C(7)—C(8)	113.2(4)	N(5)—C(17)—C(18)	114.4(3)
C(7)—C(8)—C(9)	109.6(3)	C(17)—C(18)—C(19)	109.5(3)
C(8)—C(9)—N(3)	109.3(3)	C(18)—C(19)—N(6)	109.9(3)
C(9)—N(3)—C(6)	112.4(3)	C(19)—N(6)—C(16)	112.4(3)
C(7)—C(8)—O(1)	112.1(4)	C(17)—C(18)—O(2)	111.1(3)
C(9)—C(8)—O(1)	110.4(4)	C(19)—C(18)—O(2)	111.4(4)
C(8)—O(1)—H(12)	111.0(1)	C(18)—O(2)—H(27)	114.0(1)
O(1)—H(12)...N(6)	163.6(5)		
O(2)—H(27)...N(3)	156.7(5)		

EXPERIMENTAL

Microanalyses were carried out by the University of Sheffield microanalytical service. The ir spectra were recorded as potassium bromide discs using a Perkin-Elmer 297 spectrometer. The ms were recorded using a Kratos MS25 spectrometer and ^{1}H nmr were recorded using a Bruker 400 MHz spectrometer.

5-Hydroxy-2-methyl-2-(2-pyridinyl)hexahydropyrimidine.

A mixture of 2-acetylpyridine (16 mmoles, 1.92 g), 1,3-diamino-2-hydroxypropane (8 mmoles, 0.72 g) and triethylorthoformate (1 ml) was refluxed in absolute ethanol (125 ml) for six hours. The resulting pale yellow solution was concentrated to 10 ml using a rotary evaporator and diethyl ether (50 ml) was added. The solution was stored at $-18°$ for three days after which time the hexahydropyrimidine was isolated as colourless crystals, yield, 36% (based on the diamine), mp 98-100°; ms: (M^+) = 193; ^{1}H nmr (deuteriochloroform): 1.38 (3H, s, CH_3), 2.70 and 2.87 (2H, m, CH_2), 3.44 (1H, m, CH), 7.20 (1H, d, Hpy), 7.71 (1H, t, Hpy), 7.81 (1H, d, Hpy) and 8.60 (1H, d, Hpy) ppm.

Anal. Calcd. for $C_{10}H_{15}N_3O$: C, 62.1; H, 7.8; N, 21.7. Found: C, 61.6; H, 7.7; N, 22.0.

The Lead Complex.

2-Acetylpyridine (4 mmoles, 0.48 g) and 1,3-diamino-2-hydroxypropanol (2 mmoles, 0.18 g) were added to a solution of lead perchlorate (2 mmoles, 0.92 g) in absolute methanol (50 ml). The resulting white suspension was refluxed for two hours and then cooled to room temperature. The complex was isolated by filtration, yield, 86% (based on the diamine).

Anal. Calcd. for $C_{10}H_{15}N_3O{\cdot}PbCl_2O_8$: C, 29.1; H, 2.9; N, 8.0; Cl, 10.1. Found: C, 29.2; H, 3.2; N, 7.9; Cl, 11.2. [8].

The Copper Complex.

A solution of copper(II) chloride (1 mmole, 0.17 g) in ethanol (10 ml) was added dropwise with stirring to a solution of 5-hydroxy-2-methyl-2-(2-pyridinyl)hexahydropyrimidine (1 mmole, 0.19 g) in ethanol (10 ml). The resulting dark blue solution was heated for thirty minutes and on cooling to room temperature blue crystals of the copper(II) complex were isolated, yield , 45% (based on the pyrimidine).

Anal. Calcd. for $C_{10}H_{15}N_3O{\cdot}CuCl_2H_2O$: C, 34.7; H, 5.0; N, 12.2; Cl, 20.5 Found: C, 34.5; H, 5.0; N, 12.3; Cl, 18.8 [8].

X-Ray Data.

A crystal with maximum dimension 0.2 mm was used for the collection of X-Ray data on a Phillips 1100 Automatic Diffractometer using monochromated MoKα radiation. Accurate lattice parameters were obtained from the settings of 25 medium-angle reflections. Crystal data are: $C_{10}H_{15}N_3O$, F.W. = 193, monoclinic, space group $P2_1/c$ from systematic absences h01 for l odd, and 0k0 for k odd; general positions +(x, y, z; x, 1/5-y, 1/2+z); cell parameters, a = 10.385(5), b = 11.171(5), c = 17.415(6)Å, β = 93.05(3)°, V = 2012 Å^3; Dc = 1.28 gcm^{-3} for Z = 8, and (MoKα) = 1.01 cm^{-1}. Intensities up to ϑ = 25° were measured with a scan speed of 2 min^{-1} with $\vartheta/2\vartheta$ scan. Of the 3749 reflections measured, 2070 with I > 3(I) were considered observed and were used in subsequent calculations. Corrections were made for Lp and for absorptions [9]. The intensities of two standard reflections were monitored at intervals and showed that the crystal remained stable during irradiation. The structure was solved by means of direct methods. The computer program EES, included in the SHELX program package [10], yielded a sufficient number of phases to identify some of the 28 "heavy" atoms of the two independent molecules of the asymmetric unit. Subsequent Fourier alternated with cycles of least-squares refinement of the coordinates established the identity of the individual atoms and the conformation of the two molecules. The conventional residue R was at this stage 0.133 but was improved to 0.094 by inclusion of anisotropic thermal parameters in the refinement. The contribution from the hydrogen atoms was believed to be significant, once they were localised from difference Fourier maps we used a fixed isotropic thermal parameter (U_{iso} = 0.05 Å^2) for the hydrogen atoms and the refinement was terminated when the residuals had reached R = 0.055. There was no residual electron density above 0.25 eA^{-3}. The atomic form factors for C, N and O were provided internally by SHELX, those for H were from reference 11. Fractional atomic coordinates and their thermal parameters are given in Table 1, bond lengths and angles in Tables 2 and 3 respectively.

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REFERENCES AND NOTES

[1] N. A. Bailey, D. E. Fenton, I. T. Moody and C. O. Rodriguez de Barbarin, *J. Chem. Soc., Chem. Commun.*, 1463 (1983).

[2] T. G. Campbell and F. L. Urbach, *Inorg. Chem.*, **12**, 1837 (1973).

[3] D. E. Fenton and R. Moody, unpublished results.

[4] Although hexahydropyrimidines are mostly prepared from 1,3-diaminopropanes in the presence of an aldehyde or ketone to provide the C_2 we have found no example in the literature with a comparable substituent arrangement to that found in **5** [6].

[5] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).

[6] R. F. Evans, in "The Pyrimidines: Supplement 1", Chapter 12, D. J. Brown, ed, Wiley-Interscience, New York, 1970.

[7] L. E. Sutton, "Tables of Interatomic Distances and Configuration in Molecules and Ions", Special Publication No. 18, London, The Chemical Socity, 1965.

[8] The difference of calculated and found chlorine percentage is probably due to the presence of heavy metals.

[9] A. C. T. North, D. C. Phillips and F. S. Mathews, *Acta Crysta.*, **A24**, 351 (1968).

[10] G. M. Sheldrick, "SHELX", Program for crystal structure determination, University of Cambridge, England, 1975.

[11] R. F. Stewart, E. R. Davison and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).