

жную сторону вращения. Конформации молекулы тетраметилдиамидохлорфосфита в точках оврагов представлены в Таблице 1.

Все три оврага шли различными путями и в каждом овраге найдены области с низкими значениями  $R$ . В то же время, если обратиться к данным Таблицы 1, становится очевидным, что каждый овраг прошел через несколько локальных минимумов, которым соответствуют одинаковые конформации молекулы. Значения минимизируемой функции и существенных переменных в этих локальных минимумах практически совпадают (например, точки\* 3<sub>1</sub>, 12<sub>2</sub> и 8<sub>3</sub>). Следовательно, в этой задаче можно было ограничиться расчетом лишь одной последовательности точек с низкими значениями  $R$ . Действительно, уже в первом овраге были найдены конформации со всевозможной ориентацией диметиламинных групп.

Как отмечалось выше, овраги прошли через несколько областей с низкими значениями  $R$ . Из них три области (с точками 3<sub>1</sub>, 1<sub>2</sub>, 12<sub>2</sub>, 3<sub>3</sub>, 8<sub>3</sub> и 15<sub>3</sub>; 7<sub>1</sub>, 8<sub>1</sub>, 9<sub>1</sub> и 20<sub>1</sub>, и 7<sub>2</sub>, 24<sub>2</sub> и некоторые другие) следует исключить из рассмотрения по той причине, что одно из межъядерных расстояний C...C в этих конформациях недопустимо мало  $\sim 2,19-2,55$  Å. Остальные точки с наименьшими значениями  $R$  (16<sub>1</sub>, 24<sub>1</sub>, 25<sub>1</sub> и 21<sub>2</sub>, и 12<sub>1</sub>, 19<sub>3</sub> и некоторые другие) принадлежат двум искомым локальным минимумам, которым отвечают две конформации молекулы. Таким образом, предварительными моделями молекулы тетраметилдиамидохлорфосфита являются две модели: 1)  $\varphi_1$  принимает значения в окрестности  $-60^\circ$ ,

\* Нижний индекс означает номер оврага.

а  $\varphi_2$  – в окрестности  $0^\circ$  и 2)  $\varphi_1$  принимает значения в окрестности  $0^\circ$ , а  $\varphi_2$  в окрестности  $-40^\circ$ .

Вместе с тем имеется несколько точек с относительно высокими значениями  $R$ , существенные переменные которых также находятся в этой области углов вращения. Однако эти точки являются не удовлетворительными, поскольку им соответствуют конформации с нереальными величинами валентных углов. Например, точке 11<sub>3</sub> соответствует конформация с углом N–P–N =  $86,5^\circ$ . Что же касается остальных рабочих параметров, то их величины в точках оврагов изменялись в следующих пределах: C1–P–N ( $97,0-102,6^\circ$ ), N–P–N ( $86,5-101,8^\circ$ ), C–N–C ( $116,0-124,5^\circ$ ) и P–N–C ( $117,7-122,0^\circ$ ). В точках, принадлежащих искомым локальным минимумам, валентные углы составляют C1–P–N ( $98,4-99,5^\circ$ ), N–P–N ( $94,8-99,1^\circ$ ), C–N–C ( $120,8-122,5^\circ$ ) и P–N–C ( $118,7-119,4^\circ$ ).

В заключение заметим, что успешное применение метода оврагов в задачах газовой электрографии в значительной степени зависит от правильного выбора независимых переменных, определяющих геометрию молекулы.

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## Crystal Structure and Chemical Configuration of 2,4-Diamino-5-methyl-6-benzylpyrido[2,3-*d*]pyrimidine Hydrobromide

HELENE STERNGLANZ AND CHARLES E. BUGG

*Institute of Dental Research and Laboratory of Molecular Biology, University of Alabama in Birmingham, University Station, Birmingham, Alabama 35294, U.S.A.*

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C<sub>15</sub>H<sub>16</sub>N<sup>+</sup>Br<sup>-</sup> is an inhibitor of bacterial dihydrofolate reductases. Crystals of this compound, grown by evaporating an aqueous solution at 6°C, are monoclinic, space group  $P2_1/c$ , with  $a = 23.780$  (3),  $b = 5.063$  (1),  $c = 14.447$  (4) Å,  $\beta = 120.66$  (2)°,  $Z = 4$ ,  $D_{\text{calc}} = 1.536$ , and  $D_{\text{obs}} = 1.5$  g cm<sup>-3</sup>. The structure was solved by use of X-ray diffraction data that were collected from an extremely small crystal with an automated diffractometer. This structural analysis establishes the chemical configuration of this compound.

### Introduction

A methylated derivative of 2,4-diamino-6-benzylpyrido[2,3-*d*]pyrimidine, with potent antibacterial activity

(Hurlbert, Ferone, Herrmann, Hitchings, Barnett & Bushby, 1968) was synthesized as one of a series of inhibitors of bacterial dihydrofolate reductases (Hurlbert, Ledig, Stenbuck, Valenti & Hitchings, 1968;

Hurlbert & Valenti, 1968). The synthesis of this compound was accomplished in several steps starting with the condensation of 2,4,6-triaminopyrimidine and ethyl  $\alpha$ -benzylacetoacetate. It seemed probable that the condensation occurred in such a way that the methyl group would be at the 5-position of the pyridopyrimidine, but the assignment of structure could not be regarded as unequivocal. We undertook the structural analysis to establish the chemical configuration of the compound.

### Experimental

We were unable to obtain large crystals of the compound, despite attempts with many solvent systems and various crystallization techniques. The crystals grew as small needles bound to clumps of amorphous material. Since density measurements had to be made of crystals contaminated with amorphous material, only an approximate estimate of the density was possible. All X-ray diffraction data were collected from an extremely small crystal with dimensions of 0.2, 0.04, and 0.01 mm. The space group  $P2_1/c$  was indicated by the systematic absence of reflections  $h0l$  with  $l$  odd and  $0k0$  with  $k$  odd. Three-dimensional X-ray intensity data were obtained with a Picker FACS-1 diffractometer (nickel-filtered copper radiation, a scintillation counter, and a  $\theta-2\theta$  scanning technique). Cell parameters were determined by a least-squares refinement of  $2\theta$  values for 12 low-angle reflections ( $Cu K\beta$ ,  $\lambda = 1.3922 \text{ \AA}$ ;  $23 \pm 2^\circ C$ ) that were measured with the diffractometer. Most high-angle reflections were too weak to observe; consequently, intensity measurements were made only for the 1536 unique reflections with  $2\theta \leq 100^\circ$ . The scanning speed was  $1^\circ/\text{min}$  and a 20 sec background measurement was performed at each ter-

minus of the scans. Three strong reflections (400, 202, and 020), which were monitored periodically, exhibited no significant variation of intensity during data collection. Those reflections with scan counts below background level (*i.e.* net negative intensities) were assigned intensities of 0.0. All intensities were assigned variances,  $\sigma^2(I)$ , according to the statistics of the scan and background counts plus a correctional term  $(0.03S)^2$ ,  $S$  being the scan counts. A large percentage of the reflections measured had extremely weak intensities; for example, 39% had  $I < \sigma(I)$  and 55% had  $I < 2\sigma(I)$ . The intensities and their variances were corrected for Lorentz and polarization factors. Absorption corrections were applied by use of the computer program *ORABS* (Wehe, Busing & Levy, 1962); the transmission factors ranged from 0.79 to 0.92. The data were then scaled by means of a Wilson (1942) plot.

We arrived at a suitable trial structure by the heavy-atom method: the coordinates of the bromide ion were found from a sharpened three-dimensional Patterson map, and the other non-hydrogen atoms were located in a Fourier map that was calculated by using phase angles derived from the bromide ion. Coordinates and anisotropic thermal parameters for the non-hydrogen atoms were refined by a modified version of the full-matrix least-squares program *ORFLS* (Busing, Martin & Levy, 1962). The quantity minimized was  $\sum w(F_o^2 - F_c^2/k^2)^2$ , where  $k$  is a scale factor and the weight  $w$  is equal to  $1/\sigma^2(F_o^2)$ . All 1536 reflections were included in the refinement. Scattering factors for the non-hydrogen atoms were from *International Tables for X-ray Crystallography* (1962), and anomalous dispersion correction factors for these atoms were from Cromer & Liberman (1970). Scattering factors for the hydrogen atoms were from Stewart, Davidson & Simp-

Table 1. *Final non-hydrogen-atom parameters and their estimated standard deviations*

All values for the bromide ion have been multiplied by  $10^4$ . For the other atoms, the  $x$ ,  $\beta_{11}$ , and  $\beta_{13}$  parameters have been multiplied by  $10^4$ , and the  $y$ ,  $z$ ,  $\beta_{22}$ ,  $\beta_{33}$ ,  $\beta_{12}$ , and  $\beta_{23}$  parameters have been multiplied by  $10^3$ . Temperature factors are in the form  $T = \exp(-\beta_{11}h^2 - \beta_{22}k^2 - \beta_{33}l^2 - 2\beta_{12}hk - 2\beta_{13}hl - 2\beta_{23}kl)$ .

	$x$	$y$	$z$	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
N(1)	8613 (7)	541 (3)	508 (1)	26 (4)	28 (8)	9 (1)	0 (2)	33 (6)	-4 (3)
C(2)	9234 (8)	467 (4)	547 (1)	39 (7)	41 (11)	7 (1)	3 (3)	41 (9)	-6 (4)
N(2)	9704 (5)	604 (3)	629 (1)	25 (4)	72 (10)	8 (1)	1 (2)	24 (5)	-4 (3)
N(3)	9397 (5)	277 (2)	503 (1)	23 (4)	27 (7)	2 (1)	-2 (2)	6 (5)	2 (2)
C(4)	8931 (8)	140 (3)	417 (1)	32 (6)	29 (9)	7 (2)	3 (2)	38 (8)	3 (3)
N(4)	9123 (5)	-44 (3)	381 (1)	19 (4)	36 (8)	6 (1)	1 (2)	17 (5)	-3 (3)
C(5)	7677 (9)	110 (3)	274 (1)	41 (6)	26 (9)	6 (2)	-4 (2)	44 (9)	-5 (3)
C(6)	7067 (9)	211 (4)	250 (1)	33 (7)	60 (12)	7 (2)	-2 (3)	31 (9)	5 (4)
C(7)	7028 (8)	405 (4)	311 (2)	29 (6)	55 (13)	8 (2)	3 (2)	28 (8)	2 (3)
N(8)	7524 (7)	514 (3)	400 (1)	28 (4)	54 (8)	8 (1)	1 (2)	33 (6)	-4 (3)
C(9)	8103 (9)	421 (3)	421 (1)	34 (7)	39 (12)	8 (2)	-5 (2)	42 (9)	-3 (3)
C(10)	8233 (8)	220 (4)	370 (1)	31 (6)	56 (11)	5 (1)	0 (2)	31 (9)	-2 (3)
C(11)	7760 (6)	-78 (3)	207 (1)	22 (5)	29 (10)	9 (1)	1 (2)	17 (7)	-4 (3)
C(12)	6438 (8)	118 (3)	150 (2)	28 (6)	61 (13)	12 (2)	-3 (2)	32 (9)	-5 (4)
C(13)	6254 (8)	275 (4)	51 (1)	17 (5)	83 (13)	9 (2)	-6 (3)	26 (10)	-7 (4)
C(14)	5597 (9)	318 (4)	-22 (2)	25 (7)	129 (17)	9 (2)	-3 (3)	14 (9)	-3 (4)
C(15)	5400 (9)	472 (6)	-113 (2)	40 (8)	138 (20)	10 (2)	1 (4)	7 (10)	8 (6)
C(16)	5850 (14)	589 (5)	-133 (2)	77 (12)	100 (19)	6 (2)	8 (4)	29 (12)	14 (4)
C(17)	6490 (9)	538 (5)	-61 (2)	43 (7)	82 (15)	10 (2)	-4 (3)	26 (10)	9 (6)
C(18)	6680 (7)	390 (3)	27 (1)	23 (5)	62 (12)	8 (2)	0 (2)	10 (8)	2 (3)
Br <sup>-</sup>	8753 (1)	4759 (3)	1753 (1)	31 (0)	389 (7)	70 (1)	-3 (3)	26 (1)	-4 (4)

son (1965). Coordinates for all hydrogen atoms except those of the methyl group were calculated toward the end of the refinement. A difference Fourier map computed at this stage showed regions of electron density ranging from 0.6 to 1.2 eÅ<sup>-3</sup> at all of the calculated hydrogen positions and revealed tentative coordinates for the hydrogen atoms of the methyl group. Hydrogen atoms were assigned the approximate isotropic temperature factors of the heavy atoms to which they are bonded, and were included in structure-factor calculations but not in the least-squares refinement. Because of the limited core-storage capacity of the computer it was impracticable to refine all parameters simultaneously; consequently, parameters for the atoms of the pyridopyrimidine were blocked together, parameters of the bromide ion were blocked together, and the separate blocks were refined in alternate cycles. During the last cycle of refinement, no parameter shifted more than one-tenth of its estimated standard deviation.

When all reflections are considered, the final  $R_1$  index [ $\sum||F_o| - |F_c|| / \sum|F_o|$ ] is 0.21, the  $R_2$  index [ $\sum|F_o^2 - F_c^2| / \sum F_o^2$ ] is 0.14, and the goodness-of-fit  $\{[\sum w(F_o^2 - F_c^2)^2 / (m - s)]^{1/2}\}$  is 0.95. If only the 698 reflections with  $I > 2\sigma(I)$  are considered,  $R_1 = 0.077$ ,  $R_2 = 0.092$ , and the goodness-of-fit = 1.28. A difference Fourier map calculated by using all reflections showed several troughs and peaks ranging from -1.5 to 1.3 eÅ<sup>-3</sup>; a difference Fourier map, calculated with only those reflections for which  $I > 2\sigma(I)$ , showed troughs and peaks ranging from -0.6 to 0.9 eÅ<sup>-3</sup>.

## Results

Table 1 lists the heavy-atom parameters and Table 2 gives the hydrogen-atom parameters. The standard deviations of the positional coordinates of the carbon and nitrogen atoms are large (0.02–0.03 Å) as would be expected considering the large number of weak reflections from the small crystal that was used for intensity measurements.\*

Fig. 1 shows the molecular conformation, thermal ellipsoids, and bond lengths between heavy atoms. Bond angles that involve non-hydrogen atoms are listed in Table 3. As suggested by chemical data, the methyl group is at the 5-position of the pyridopyrimidine ring. Atom N(1) is protonated. The 10 atoms of the pyridopyrimidine ring deviate from a least-squares plane through the ring by amounts ranging up to 0.06 Å; the two amino groups are 0.11 Å out of the plane, and atoms C(11) and C(12) deviate by 0.19 and 0.07 Å, respectively. The 6-membered phenyl ring is nearly

Table 2. *Hydrogen-atom parameters*

Values of the coordinates have been multiplied by 10<sup>3</sup>. All positional coordinates (except those of the methyl-hydrogen atoms) were calculated by assuming trigonal bonding to the heavy atoms and heavy atom-hydrogen atom distances of 0.95 Å. Coordinates for the methyl-hydrogen atoms were obtained from a difference Fourier map. The isotropic temperature factors are those of the heavy atom to which the hydrogen is bonded.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (Å <sup>2</sup> )
H(N1)	843	681	546	3.7
H(N2)	961	754	661	4.4
H(N2')	1017	567	662	4.4
H(N4)	959	-88	413	3.2
H(N4')	883	-154	320	3.2
H(C7)	658	476	284	4.6
H(C11)	818	-98	199	4.2
H(C11')	735	-54	131	4.2
H(C11'')	775	-257	224	4.2
H(C12)	608	107	164	4.7
H(C12')	650	-72	133	4.7
H(C14)	524	251	-11	7.0
H(C15)	494	485	-169	8.4
H(C16)	572	716	-196	8.5
H(C17)	684	627	-73	7.2
H(C18)	716	352	76	5.4

planar, with no deviations in excess of 0.01 Å. The phenyl ring is nearly perpendicular to the pyridopyrimidine ring (97°). The crystal packing and the hydrogen-bonding scheme are depicted in Fig. 2. All hydrogen atoms bonded to nitrogen atoms appear to participate in hydrogen bonding; however, two of the donor-acceptor contacts [N(4)–N(3) and N(4)–Br] are unusually long.

Table 3. *Bond angles involving only non-hydrogen atoms*

The estimated standard deviations are about 2°.

C(2)–N(1)–C(9)	122°	N(8)–C(9)–C(10)	129°
N(3)–C(2)–N(2)	119	N(1)–C(9)–C(10)	119
N(3)–C(2)–N(1)	123	C(9)–C(10)–C(5)	117
N(2)–C(2)–N(1)	118	C(9)–C(10)–C(4)	117
C(2)–N(3)–C(4)	121	C(5)–C(10)–C(4)	127
N(4)–C(4)–N(3)	117	C(13)–C(2)–C(6)	114
N(4)–C(4)–C(10)	124	C(18)–C(13)–C(14)	116
N(3)–C(4)–C(10)	119	C(18)–C(13)–C(12)	125
C(6)–C(5)–C(11)	123	C(14)–C(13)–C(12)	119
C(6)–C(5)–C(10)	115	C(13)–C(14)–C(15)	121
C(11)–C(5)–C(10)	121	C(16)–C(15)–C(14)	121
C(7)–C(6)–C(5)	120	C(17)–C(16)–C(15)	117
C(7)–C(6)–C(12)	119	C(18)–C(17)–C(16)	122
C(5)–C(6)–C(12)	121	C(17)–C(18)–C(13)	123
N(8)–C(7)–C(6)	127		
C(9)–N(8)–C(7)	112		
N(8)–C(9)–N(1)	112		

\* A table of observed and calculated structure factors has been deposited with the National Lending Library, England, as Supplementary Publication No. SUP 30146 (9pp). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

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