

study was carried out in order to determine the hydrogen-bond scheme of the *trans* compound and the similarities between the conformations of both isomers.

The molecules are arranged in infinite strings along the *x* axis and are held together by intermolecular hydrogen bonds [2.643 (2) and 2.645 (2) Å] between molecules related by inversion centres at (0.0, 1.0, -0.5) and (0.5, 1.0, -0.5) respectively.

The bond lengths of the *trans* isomer are equal, within the limits of accuracy, to those of the *cis* isomer. The lengths C(1)–C(2) and C(1)–C(5) are rather large probably as a result of the steric interactions of the substituents at C(1), C(2) and C(5) (see Table 2). Bond angles are in Table 3.

The dihedral angles in the cyclopentene ring are 40, -30, 9, 16 and -35° for C(1)–C(2), C(2)–C(3) *etc.*, indicating that the ring is in a conformation between an envelope and a half-chair. Similar dihedral angles were found in the *cis* isomer (Kops & Schenk, 1974).

Table 2. Bond lengths (Å) with standard deviations

C(1)–C(2)	1.561 (4)	C(5)–H(6)	0.97 (2)
C(1)–C(5)	1.560 (2)	C(6)–O(1)	1.220 (2)
C(1)–C(6)	1.510 (3)	C(6)–O(2)	1.314 (4)
C(1)–C(7)	1.526 (2)	C(7)–O(3)	1.243 (2)
C(2)–C(3)	1.533 (3)	C(7)–O(4)	1.274 (2)
C(2)–C(8)	1.515 (3)	C(8)–H(7)	0.98 (4)
C(2)–H(1)	0.97 (3)	C(8)–H(8)	0.98 (2)
C(3)–C(4)	1.512 (4)	C(8)–H(9)	1.08 (2)
C(3)–H(2)	0.96 (3)	C(9)–H(10)	1.00 (3)
C(3)–H(3)	1.01 (3)	C(9)–H(11)	0.90 (2)
C(4)–C(5)	1.541 (4)	C(9)–H(12)	0.97 (3)
C(4)–H(4)	0.97 (3)	O(2)–H(13)	0.95 (3)
C(4)–H(5)	1.05 (3)	O(4)–H(14)	1.18 (5)
C(5)–C(9)	1.526 (3)		

Table 3. Bond angles (°) of the non-hydrogen atoms

C(2)–C(1)–C(5)	102.8 (2)	C(3)–C(4)–C(5)	107.3 (2)
C(2)–C(1)–C(6)	114.0 (1)	C(1)–C(5)–C(4)	104.1 (2)
C(2)–C(1)–C(7)	109.9 (2)	C(1)–C(5)–C(9)	112.2 (1)
C(5)–C(1)–C(6)	112.0 (2)	C(4)–C(5)–C(9)	111.8 (2)
C(5)–C(1)–C(7)	112.2 (1)	C(1)–C(6)–O(1)	123.9 (2)
C(6)–C(1)–C(7)	106.1 (1)	C(1)–C(6)–O(2)	112.7 (2)
C(1)–C(2)–C(3)	102.3 (2)	O(1)–C(6)–O(2)	123.4 (2)
C(1)–C(2)–C(8)	117.4 (2)	C(1)–C(7)–O(3)	120.9 (1)
C(3)–C(2)–C(8)	114.7 (2)	C(1)–C(7)–O(4)	115.6 (1)
C(2)–C(3)–C(4)	107.4 (2)	O(3)–C(7)–O(4)	123.5 (2)

The carboxylic group C(6)O(1)O(2) has the usual conformation, the C=O bond eclipsing a bond of the ring. For the other COOH group this conformation is sterically impossible and O(3) is rotated by 20° out of the eclipsed position. In the *cis* isomer this rotation is 30° indicating a somewhat larger steric hindrance.

The authors thank Professor F. Bickelhaupt and Dr P. A. Verbrugge for providing the crystals. Mr D. Heijndrijk carried out the X-ray measurements.

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Diaveridine: 2,4-Diamino-5-(3',4'-dimethoxybenzyl)pyrimidine*

BY THOMAS F. KOETZLE AND GRAHEME J. B. WILLIAMS†

Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973, USA

(Received 3 June 1977; accepted 1 September 1977)

Abstract. C₁₃H₁₆N₄O₂, *M_r* = 260.92, crystallizes from wet ethanol in the monoclinic space group *C2/c*, *a* = 18.140 (5), *b* = 12.796 (3), *c* = 12.332 (3) Å, β = 114.78 (1)°. *D_c* (for eight molecules in the cell of

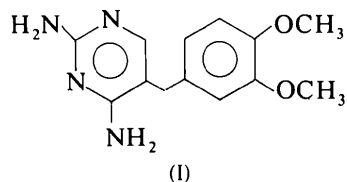
volume 2598.93 Å³) = 1.169 g cm⁻³. The structure was solved with *MULTAN* and refined by full-matrix least-squares techniques based upon 1838 unique *F_o*² terms to yield agreement factors *R* = 0.057 and *R_w* = 0.089. The pyrimidine bases are linked together in infinite ribbons by hydrogen bonds involving the amino groups and ring-nitrogen atoms. Both methyl C atoms are approximately coplanar with the phenyl ring. The ether O atom bound to C(3') is positioned 3.47 Å

* Research performed at Brookhaven National Laboratory under contract with the US Department of Energy and supported by its Division of Basic Energy Sciences.

† Author to whom correspondence should be addressed.

above the centroid of the phenyl ring from an adjacent molecule related to the first by a center of inversion.

Introduction. Diaveridine (I) is one of the 2,4-diaminopyrimidine class of dihydrofolate reductase inhibitors (for a review of such inhibitors, which are often referred to as antifolates, see Hitchings & Burchall, 1965). Diaveridine differs from the popular antibacterial inhibitor trimethoprim in that it is a 3,4-dimethoxybenzyl derivative rather than a 3,4,5-trimethoxybenzyl derivative of 2,4-diaminopyrimidine. The present study was undertaken in order to test further the ubiquity of the hydrogen-bonding scheme found in all other antifolate crystal structures (see, for example, Koetzle & Williams, 1976; Sternglanz & Bugg, 1973). A further point of interest is to examine whether the absence of one methoxy group would allow the existence of some additional self-associative modes which were not present in the trimethoprim structure (Koetzle & Williams, 1976).



Suitable crystals exhibiting $2/m$ diffraction symmetry and with systematic absences hkl , $h + k = 2n + 1$; $h0l$, $l = 2n + 1$; and $0k0$, $k = 2n + 1$ were obtained by cooling a solution in wet ethanol. The eightfold occupancy of the unit cell, the magnitude distribution of the normalized structure factors (Karle, Dragonette & Brenner, 1965) and the success of the structure analysis indicate that our choice of space group $C2/c$ over the equally permissible Cc is correct. The unit-cell dimensions given in the *Abstract* were obtained by a least-squares analysis of the diffractometer setting angles for 14 reflections with $79^\circ \leq 2\theta \leq 115^\circ$ [$\lambda(\text{Cu } K\alpha) = 1.5418 \text{ \AA}$]. An approximately equidimensional crystal with largest diameter 0.4 mm was chosen for data collection and intensities of 2997 reflections were measured with Ni-filtered Cu K radiation. These data were corrected for absorption by the method of Busing & Levy (1957) [$\mu(\text{Cu } K\alpha) = 6.367 \text{ cm}^{-1}$] and the usual Lorentz and polarization terms applied. After averaging symmetry-related observations, F_o^2 values were obtained for a total of 1838 unique and space-group-permissible reflections. Seventeen reflections were remeasured at a lower tube current in order to offset the effects of coincidence losses, but the two strongest of these, 002 and 040, could not be estimated reliably and eventually were given very small weights in the least-squares refinement.

Structure solution was achieved straightforwardly using the *MULTAN* system (Germain, Main & Woolfson, 1971) which unambiguously revealed the

complete nonhydrogen-atom skeleton. The tautomeric form of the 2,4-diaminopyrimidine was confirmed and locations of the methyl H atoms were obtained from difference electron density syntheses. All other H atoms were positioned according to known geometric constraints. Full-matrix least-squares refinement of this model employing anisotropic thermal-vibration terms for the nonhydrogen atoms and isotropic temperature factors for the H atoms together with a scale factor and a Zachariasen isotropic extinction parameter (Coppens & Hamilton, 1970) (237 parameters) was performed using the program *FLINUS* (for a description of the computer programs used in this study see Berman, Bernstein, Bernstein, Koetzle & Williams, 1976). Refinement was carried out minimizing $\Sigma w|F_o^2 - k^2 F_c^2|^2$, with scattering factors for the nonhydrogen atoms taken from Cromer & Mann (1968) and that for the H atoms from Stewart, Davidson & Simpson (1965). Weighting factors were derived for each reflection from $w^{-1} = \sigma_c^2 + (0.02F_o^2)^2 + [0.02(F_o^2 - AF_o^2)]^2$, where σ_c^2 is the variance from counting statistics and A is the correction term for absorption. Absorption

Table 1. *Final atomic coordinates* ($\times 10^5$, for H $\times 10^4$) for one molecule of diaveridine

	<i>x</i>	<i>y</i>	<i>z</i>
N(1)	63742 (8)	72737 (10)	-4283 (12)
C(2)	63584 (9)	82624 (12)	-811 (14)
N(3)	57004 (8)	88033 (10)	-1622 (12)
C(4)	49856 (9)	82945 (13)	-6218 (14)
C(5)	49327 (10)	72371 (13)	-9809 (14)
C(6)	56463 (10)	67944 (14)	-8628 (15)
N(2)	70821 (9)	87568 (13)	4431 (15)
N(4)	43232 (9)	88472 (13)	-7339 (16)
C(7)	41386 (11)	66490 (17)	-14857 (18)
C(1')	37527 (9)	64726 (12)	-6181 (14)
C(2')	29159 (10)	63208 (12)	-10670 (15)
C(3')	25406 (9)	61749 (11)	-3097 (15)
C(4')	30018 (10)	61911 (11)	9288 (15)
C(5')	38292 (11)	63187 (15)	13733 (17)
C(6')	42007 (11)	64604 (15)	5947 (16)
O(3')	17301 (7)	60243 (10)	-6566 (11)
C(8)	12397 (13)	58027 (23)	-18821 (20)
O(4')	25675 (7)	60648 (9)	16014 (10)
C(9)	29838 (15)	62609 (18)	28519 (18)
H(1N2)	7544 (12)	8462 (15)	434 (16)
H(2N2)	7086 (11)	9426 (16)	594 (16)
H(1N4)	4390 (12)	9553 (19)	-410 (18)
H(2N4)	3846 (13)	8535 (15)	-847 (17)
H(6)	5639 (10)	6065 (14)	-1126 (15)
H(71)	4246 (11)	5945 (16)	-1788 (17)
H(72)	3770 (13)	7017 (17)	-2163 (20)
H(2')	2597 (10)	6313 (12)	-1916 (17)
H(5')	4170 (12)	6316 (15)	2243 (18)
H(6')	4783 (12)	6572 (14)	904 (17)
H(81)	1200 (14)	6426 (19)	-2379 (22)
H(82)	1453 (15)	5167 (20)	-2138 (20)
H(83)	719 (16)	5606 (22)	-1879 (22)
H(91)	2589 (13)	6223 (15)	3192 (19)
H(92)	3434 (13)	5700 (18)	3273 (18)
H(93)	3233 (12)	6965 (17)	2985 (18)

and Lp corrections were applied to σ_c^2 . Final agreement indices over 1838 reflections are $R = \Sigma |F_o^2 - k^2 F_c^2| / \Sigma F_o^2 = 0.057$, $R_w = (\Sigma |F_o^2 - k^2 F_c^2|^2 / \Sigma w F_o^4)^{1/2} = 0.089$, and $S = [\Sigma w |F_o^2 - k^2 F_c^2|^2 / (N_o - N_v)]^{1/2} = 3.77$. The two reflections noted above (002 and 040) were severely downweighted in the final cycles of refinement, as was reflection $\bar{6}08$. This latter reflection inexplicably showed very poor agreement throughout the analysis. A difference electron density map calculated near the end of the refinement revealed deviations from zero of only $0.1 \text{ e } \text{Å}^{-3}$. The final value for the extinction parameter is $g = 1.2(2) \times 10^4$.*

Discussion. Atomic coordinates describing the final model are given in Table 1. Fig. 1 displays the bond distances and interbond angles for the nonhydrogen atoms as well as the atomic nomenclature. The 12 C—H bond distances all fall within the range $0.95(2)$ to $1.05(2) \text{ Å}$, without any corrections for thermal-vibration effects.

In each NH_2 group one H atom is involved in a hydrogen bond to a ring-nitrogen atom of a symmetry-related pyrimidine base but the other does not engage in any such interaction (refer to Fig. 2). The N—H distances in the two hydrogen-bonded bases are $0.92(2)$ and $0.97(2) \text{ Å}$ respectively, whereas the other two N—H bonds are $0.88(2)$ and $0.91(2) \text{ Å}$ respectively. This pattern of N—H bond distances has been observed previously in similar situations (Koetzle & Williams, 1976; Kvik, Thomas & Koetzle, 1976). The differences observed here are only of marginal statistical significance but their consistency with the results from neutron diffraction confirms that useful information regarding details of hydrogen bonding can be derived

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32986 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

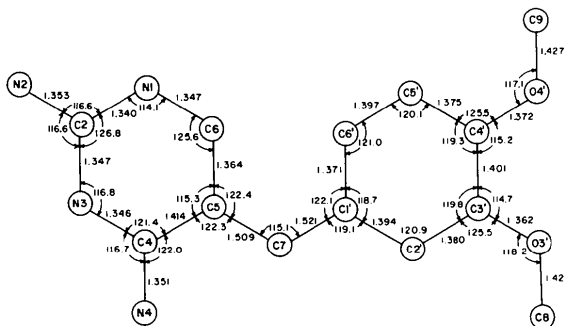


Fig. 1. Bond distances (Å), interbond angles ($^\circ$) and atomic nomenclature for diaveridine. Standard deviations for the bond distances range from 0.0019 to 0.0023 Å and those for the angles are between 0.14 and 0.16° . The standard deviations in these and other molecular parameters quoted in this paper were determined by the method of Busing, Martin & Levy (1964).

from X-ray studies. The disparity between the C(5)—C(4) and C(5)—C(6) distances has also been noted previously (Clews & Cochran, 1949; Koetzle & Williams, 1976).

Only very small deviations from planarity are observed for the atoms of the two aryl rings. For the pyrimidine ring the largest deviation is $0.019(1) \text{ Å}$, for C(2), and in the case of the phenyl ring the greatest displacement is $0.011(1) \text{ Å}$, for C(4'). The non-hydrogen substituents of these rings also lie quite close to their respective planes. In the case of the pyrimidine ring N(2) is displaced by $0.100(1) \text{ Å}$, while for the phenyl group C(7) deviates by $0.039(1) \text{ Å}$.

The diaveridine molecule has four degrees of conformational freedom. These are: (1) The two rotations about the C—C bonds linking the two rings. The torsion angles* C(4)—C(5)—C(7)—C(1') and C(2')—C(1')—C(7)—C(5) are -65.8 and 155.3° respectively, which may be compared with the values of -89.4 and 153.3° for the corresponding angles in trimethoprim. The angle between normals to the planes of the two rings is 75.8° in the present structure and 71.3° in trimethoprim. (2) The positioning of the methyl groups with respect to the plane of the phenyl ring. The torsion angles C(2')—C(3')—O(3')—C(8) and C(5')—C(4')—O(4')—C(9) are 12.5 and 11.5° respectively, indicating that the methyl C atoms are displaced by small amounts to opposite sides of the ring.

There are two important intermolecular interactions in the crystal structure. Fig. 2 illustrates the hydrogen bonding between the aryl bases. This scheme is identical to that found in trimethoprim (Koetzle & Williams, 1976), 2,4,7-triamino-6-chloroquinazoline

* Torsion angles are defined in accordance with the IUPAC—IUB Commission on Biochemical Nomenclature (1970) recommendation.

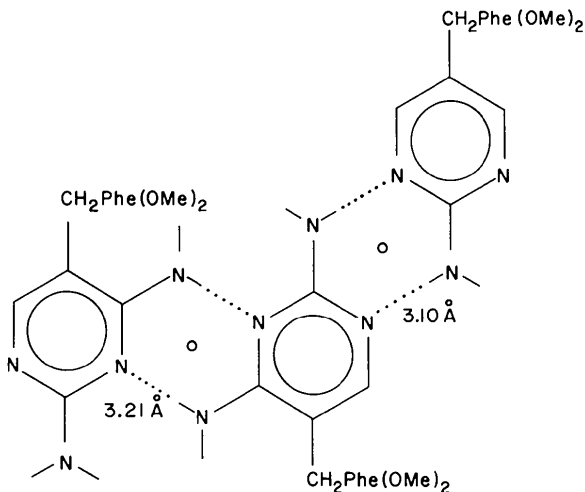


Fig. 2. A diagram showing the intermolecular hydrogen bonding. Two inversion centers are indicated.

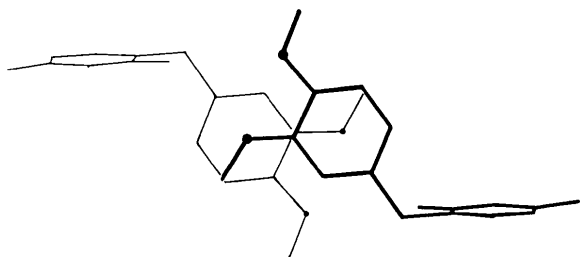


Fig. 3. A projection of two molecules linked by the dipole-induced dipole interactions viewed along the line from O(3') to the centroid of the inversion-related ring. Oxygen atoms are denoted by filled circles.

(Rogan & Williams, 1977) and all other known antifolate crystal structures. The second self-associative mode involves the exocyclic oxygen atom O(3'), which lies approximately over the centroid of the phenyl ring of an adjacent molecule and is of the dipole-induced dipole type documented by Bugg, Thomas, Sundaralingam & Rao (1971). This latter interaction is illustrated in Fig. 3. The distance of O(3') to the centroid of the adjacent ring is 3.47 Å and the angle between the line joining O(3') to the centroid and normal to the phenyl ring is 8.2°. Because the two molecules are related by an inversion center, the C—O dipoles are antiparallel.

Recently obtained results on the structure of a dihydrofolate reductase/methotrexate binary complex (Matthews *et al.*, 1977) suggest that some of the hydrogen-bonded interactions observed here do have their counterparts in the enzyme/inhibitor complex. However, Matthews *et al.* (1977) have indicated that N(1) is very probably protonated when a 2,4-diaminopyrimidine is bound to the enzyme. It may, therefore, donate a hydrogen bond to the enzyme rather than accept a bond as is observed in structures of the inhibitors themselves.

We thank Dr M. Poe of the Merck Institute for Therapeutic Research for the sample of diaveridine and

Drs D. Matthews and J. Kraut for supplying us with a copy of the dihydrofolate reductase paper prior to publication.

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