

An Application of the Theory of Representations: The Structure of 2-Isopropoxy-5-isopropyl-3,7,8,10-tetramethyl-5,10-dihydrobenzo[g]pteridin-4(3H)-one

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Abstract

$C_{20}H_{28}N_4O_2$ is a by-product from the synthesis of 4a-isopropyl-3-methyl-4a,5-dihydrolumiflavin [Ghisla, Hartmann, Hemmerich & Müller (1973). *Justus Liebigs Ann. Chem.* pp. 589–597] and crystallizes in the triclinic system, space group $P\bar{1}$, with $a = 9.919$ (3), $b = 13.902$ (6), $c = 7.670$ (1) Å, $\alpha = 104.38$ (2), $\beta = 107.54$ (1), $\gamma = 87.41$ (1)°, $Z = 2$, $\mu = 0.65$ mm⁻¹. The structure was solved by direct methods, utilizing a strengthening formula for the triplet relationship in the *MULTAN* procedure. The structure was refined by full-matrix least-squares methods to an unweighted R of 0.064 for the 1532 observed reflexions.

Experimental

2898 reflexions up to $\theta = 60^\circ$ were collected on a Philips PW 1100 computer-controlled four-circle diffractometer (graphite-monochromatized Cu $K\alpha$ radiation, $\lambda = 1.5418$ Å) using the $\omega/2\theta$ scan mode (crystal size: 0.24 × 0.37 × 0.025 mm). Intensities were processed with a locally modified version of a program specifically written for the PW 1100 diffractometer by Hornstra & Stubbe (1972) to yield F_o and $\sigma(F_o)$. No absorption correction was applied. Space group $P\bar{1}$ was assumed on the basis of the statistical averages and the distribution of the normalized structure factors.

Structure solution and refinement

Normalization of E 's was carried out from a Debye curve (program *NORMAL*).

Initial phasing attempts using the 1976 version of *MULTAN* (Germain, Main & Woolfson, 1971) were unsuccessful. We then used the information contained in the second representation (Giacovazzo, 1977*b*) of the triplet invariants in order to obtain more reliable estimates of triplet cosines.

In this case $\varphi = \varphi_{h_1} + \varphi_{h_2} - \varphi_{h_1+h_2}$ is estimated *via* the special quintets $\psi = \varphi_{h_1} + \varphi_{h_2} - \varphi_{h_1+h_2} + \varphi_k - \varphi_k$, where \mathbf{k} is a free vector. Now φ depends on the following set of magnitudes.

$$\{B\}_2 = \{ |E_{h_1}|, |E_{h_2}|, |E_{h_1+h_2}|, |E_k|, |E_{h_1+k}|, |E_{h_2+k}|, |E_{h_1+k}|, |E_{h_2+k}| \}.$$

Following Giacovazzo (1976, 1977*a*), we have used the subset

$$\{ |E_{h_1}|, |E_{h_2}|, |E_{h_1+h_2}|, |E_k|, |E_{h_1+k}|, |E_{h_2+k}| \},$$

which gives the following sign probability:

$$P^+ \simeq 0.5 + 0.5 \tanh \left[C \left(1 + \frac{A}{1+B} \right) \right], \quad (1)$$

where P^+ is the probability that the sign of $E_{h_1}E_{h_2}E_{h_1+h_2}$ is positive, and

$$C = |E_{h_1}E_{h_2}E_{h_1+h_2}|/\sqrt{N},$$

$$A = (\sum \varepsilon_k \varepsilon_{h_1+k} \varepsilon_{h_2+k})/N,$$

$$B = \left[\varepsilon_{h_1} \varepsilon_{h_2} \varepsilon_{h_1+h_2} + \varepsilon_{h_1} \sum_k \varepsilon_k \varepsilon_{h_1+k} + \varepsilon_{h_2} \sum_k \varepsilon_k \varepsilon_{h_2+k} + \varepsilon_{h_1+h_2} \sum_k \varepsilon_k \varepsilon_{h_1+h_2+k} \right] / 2N,$$

$$\varepsilon_i = E_i^2 - 1.$$

In the calculations we used only \mathbf{k} vectors for which $2.0 \leq |E_{\mathbf{k}}| \leq 3.5$. Reflections with $|E_{\mathbf{k}}|$ larger than 3.5 were not used because of their 'non-statistical' character.

The *MULTAN* procedure estimates sign reliability according to

$$P^+ = 0.5 + 0.5 \tanh \frac{|E_{h_1} E_{h_2} E_{h_1+h_2}|}{\sqrt{N}}, \quad (1')$$

so the ratio $A/(1+B)$ in (1) allows an increase or decrease, according to its sign, of the argument of the hyperbolic tangent in (1'), strengthening the estimation of the triplet relation: Large positive values of A and small values of B will define strongly positive relations, while large negative values of A and small values of B will define strongly negative relations.

An *a posteriori* examination (after the crystal structure solution) of the triplet relations shows why the application of (1') was unsuccessful.

In each row of Table 1 is listed the number of triplet relations (n.r.) having the argument of the hyperbolic tangent greater than or equal to the corresponding value shown in the first column and the percentage (%) of correct relations.

As may be observed, these percentages, calculated by means of equation (1), are markedly better than those obtained by means of equation (1').

Furthermore, using equation (1) 964 triplets with 100% correct relations are available ($\tanh \arg \geq 3.40$), while only 391 triplets ($\tanh \arg \geq 2.80$) are obtained in the case of equation (1').

Table 1. Number of relations (n.r.) and percentage of correct relations of triplets for equations (1) and (1')

tanh arg	Equation (1)		Equation (1')	
	(n.r.)	(%)	(n.r.)	(%)
0.20	1716	97	1815	95
0.40	1716	97	1815	95
0.60	1716	97	1815	95
0.80	1716	97	1812	95
1.00	1715	97	1744	95
1.20	1709	97	1580	96
1.40	1692	97	1402	97
1.60	1651	97	1186	97
2.00	1539	97	823	99
2.40	1384	98	565	99
2.80	1222	99	391	100
3.20	1029	99	249	100
3.40	964	100	211	100
3.80	825	100	151	100
4.20	680	100	98	100
4.60	573	100	69	100
5.00	467	100	49	100
5.50	367	100	33	100
6.00	306	100	20	100
6.50	251	100	13	100
7.00	199	100	6	100
8.00	122	100	3	100
9.00	80	100	2	100

The Σ_2 relations, estimated according to (1), were introduced in a convergence procedure like that in *MULTAN*. The starting set (see Table 2) employing three origin-defining reflexions and five symbols yielded 32 possible solutions. With the conventional figures of merit, the correct solution was identified as having the third highest CFOM. The corresponding E map revealed 36 of the 52 non-hydrogen atoms correctly placed in the unit cell.

The remaining atoms were located in subsequent weighted Fourier syntheses.

The refinement of the structure was carried out by a local version of the full-matrix least-squares program *ORFLS* (Busing, Martin & Levy, 1962). Only the 1532 reflexions with $I > 3\sigma(I)$ were regarded as observed

Table 2. The starting set for phase determination

	hkl	E	Phase
Origin-fixing reflexions	2 8 5	2.53	360°
	5 8 1	2.41	360
	2 9 3	2.41	360
Other reflexions in the starting set	0 2 2	4.02	
	8 3 3	3.69	
	8 5 7	3.21	
	6 7 4	2.75	
	1 2 4	2.56	

Table 3. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters for the non-hydrogen atoms

	x	y	z	B_{eq} (\AA^2)
N(1)	12087 (4)	286 (2)	7631 (5)	2.8 (1)
C(2)	10846 (5)	578 (3)	7706 (6)	2.9 (1)
N(3)	9730 (4)	-45 (3)	7327 (5)	3.4 (1)
C(4)	9814 (5)	-1099 (3)	6848 (6)	2.9 (1)
C(4a)	11218 (4)	-1403 (3)	6879 (5)	2.7 (1)
N(5)	11464 (3)	-2448 (2)	6500 (5)	2.9 (1)
C(5a)	12606 (4)	-2684 (3)	5703 (5)	2.8 (1)
C(6)	12631 (5)	-3628 (3)	4526 (6)	3.2 (1)
C(7)	13760 (5)	-3912 (3)	3812 (6)	3.3 (1)
C(8)	14872 (5)	-3246 (3)	4241 (6)	3.3 (1)
C(9)	14817 (4)	-2282 (3)	5332 (6)	3.2 (1)
C(9a)	13680 (4)	-1998 (3)	6044 (5)	2.7 (1)
N(10)	13593 (3)	-1010 (2)	7113 (5)	2.9 (1)
C(10a)	12254 (4)	-721 (3)	7210 (5)	2.7 (1)
O(11)	10539 (3)	1535 (2)	8151 (4)	3.3 (1)
C(12)	8304 (4)	353 (3)	7445 (7)	4.7 (2)
O(13)	8771 (3)	-1623 (2)	6509 (4)	3.9 (1)
C(14)	13709 (6)	-4945 (3)	2544 (7)	5.0 (2)
C(15)	16132 (5)	-3506 (4)	3562 (8)	5.5 (2)
C(16)	14697 (4)	-279 (3)	7450 (6)	3.5 (1)
C(17)	11503 (5)	-2861 (3)	8132 (7)	4.1 (2)
C(18)	12878 (6)	-2697 (5)	9605 (8)	7.5 (3)
C(19)	10950 (9)	-3960 (4)	7420 (11)	10.5 (4)
C(20)	10910 (5)	3201 (3)	8178 (7)	4.2 (2)
C(21)	11657 (4)	2256 (3)	8476 (6)	3.3 (1)
C(22)	12675 (5)	2375 (3)	10431 (6)	4.8 (2)

E.s.d.'s are in parentheses. $B_{\text{eq}} = \frac{1}{3} \sum_i \sum_j \beta_{ij} \mathbf{a}_i \cdot \mathbf{a}_j$.

and were introduced in the refinement with unit weights. The starting *R* index was 0.15.

After three cycles of isotropic full-matrix least-squares refinement, the coordinates of the 28 H atoms

Table 4. Bond distances (Å) for non-hydrogen atoms

Standard deviations are in parentheses.

N(1)—C(2)	1.292 (5)	C(6)—C(7)	1.390 (6)
N(1)—C(10a)	1.370 (5)	C(7)—C(8)	1.379 (6)
C(2)—N(3)	1.352 (5)	C(7)—C(14)	1.515 (6)
C(2)—O(11)	1.334 (5)	C(8)—C(9)	1.401 (6)
N(3)—C(4)	1.425 (5)	C(8)—C(15)	1.490 (6)
N(3)—C(12)	1.515 (5)	C(9)—C(9a)	1.396 (6)
C(4)—C(4a)	1.432 (6)	C(9a)—N(10)	1.428 (5)
C(4)—O(13)	1.216 (5)	N(10)—C(10a)	1.389 (5)
C(4a)—N(5)	1.434 (5)	N(10)—C(16)	1.449 (5)
C(4a)—C(10a)	1.353 (4)	O(11)—C(21)	1.451 (5)
N(5)—C(5a)	1.431 (5)	C(17)—C(18)	1.469 (7)
N(5)—C(17)	1.491 (5)	C(17)—C(19)	1.555 (7)
C(5a)—C(6)	1.400 (6)	C(20)—C(21)	1.513 (6)
C(5a)—C(9a)	1.383 (5)	C(21)—C(22)	1.508 (6)

Table 5. Bond angles (°) for non-hydrogen atoms

Standard deviations are in parentheses.

C(2)—N(1)—C(10a)	116.1 (4)	C(8)—C(7)—C(14)	122.0 (4)
N(1)—C(2)—N(3)	123.9 (4)	C(7)—C(8)—C(9)	119.2 (4)
N(1)—C(2)—O(11)	122.8 (4)	C(7)—C(8)—C(15)	122.6 (4)
N(3)—C(2)—O(11)	113.3 (4)	C(9)—C(8)—C(15)	118.2 (4)
C(2)—N(3)—C(4)	123.2 (4)	C(8)—C(9)—C(9a)	121.0 (4)
C(2)—N(3)—C(12)	121.0 (4)	C(5a)—C(9a)—C(9)	119.5 (4)
C(4)—N(3)—C(12)	115.8 (4)	C(5a)—C(9a)—N(10)	119.0 (4)
N(3)—C(4)—C(4a)	111.7 (4)	C(9)—C(9a)—N(10)	121.5 (4)
N(3)—C(4)—O(13)	120.3 (4)	C(9a)—N(10)—C(10a)	115.9 (3)
C(4a)—C(4)—O(13)	127.9 (4)	C(9a)—N(10)—C(16)	119.5 (3)
C(4)—C(4a)—N(5)	117.5 (4)	C(10a)—N(10)—C(16)	120.9 (3)
C(4)—C(4a)—C(10a)	120.5 (4)	N(1)—C(10a)—C(4a)	124.3 (4)
N(5)—C(4a)—C(10a)	121.9 (4)	N(1)—C(10a)—N(10)	114.7 (4)
C(4a)—N(5)—C(5a)	111.5 (3)	C(4a)—C(10a)—N(10)	121.0 (4)
C(4a)—N(5)—C(17)	111.7 (3)	C(2)—O(11)—C(21)	116.8 (3)
C(5a)—N(5)—C(17)	117.0 (3)	N(5)—C(17)—C(18)	113.2 (4)
N(5)—C(5a)—C(6)	119.4 (4)	N(5)—C(17)—C(19)	110.0 (4)
N(5)—C(5a)—C(9a)	121.7 (4)	C(18)—C(17)—C(19)	114.4 (5)
C(6)—C(5a)—C(9a)	118.9 (4)	O(11)—C(21)—C(20)	105.2 (3)
C(5a)—C(6)—C(7)	121.4 (4)	O(11)—C(21)—C(22)	110.1 (3)
C(6)—C(7)—C(8)	119.6 (4)	C(20)—C(21)—C(22)	113.0 (4)
C(6)—C(7)—C(14)	118.3 (4)		

Table 6. Relevant torsion angles (°)

Standard deviations are in parentheses.

C(10a) N(1)—C(2)—N(3)	177.4 (5)	C(10a)—C(4a) N(5) C(17)	73.0 (4)	C(9a)—C(5a)—C(6)—C(7)	−175.2 (4)
C(2)—N(1) C(10a)—N(10)	0.9 (4)	C(4) C(4a) N(5) C(17)	105.3 (4)	N(5)—C(5a)—C(6)—C(7)	3.9 (3)
N(1) C(2) N(3)—C(4)	−178.4 (5)	C(4a) N(5) C(5a) C(9a)	153.5 (4)	C(14)—C(7)—C(8)—C(15)	177.3 (5)
N(1)—C(2)—O(11)—C(21)	−177.3 (4)	C(17) N(5) C(5a) C(9a)	76.1 (4)	C(8)—C(9)—C(9a)—N(10)	1.8 (3)
N(3)—C(2) O(11)—C(20)	30.9 (6)	C(4a) N(5) C(5a) C(6)	−27.3 (4)	C(16)—N(10)—C(9a)—C(9)	−179.2 (4)
C(12)—N(3) C(4)—C(4a)	3.4 (4)	C(17) N(5) C(5a) C(6)	103.1 (4)	C(5a)—C(9a)—N(10)—C(10a)	−159.9 (5)
C(12)—N(3) C(4)—O(13)	−177.9 (5)	C(5a) N(5) C(17) C(18)	−131.4 (4)	C(9)—C(9a)—N(10)—C(10a)	20.5 (3)
N(3)—C(4) C(4a)—C(10a)	175.8 (4)	C(5a) N(5) C(17) C(19)	99.2 (5)	C(5a)—C(9a)—N(10)—C(16)	−1.2 (4)
O(13)—C(4) C(4a)—N(5)	178.9 (5)	C(4a) N(5) C(17) C(18)	98.3 (4)	C(9a)—N(10)—C(10a)—C(4a)	158.9 (4)
O(13)—C(4) C(4a)—C(10a)	−2.7 (4)	C(4a) N(5) C(17) C(19)	−31.1 (5)	C(16)—N(10)—C(10a)—N(1)	179.7 (4)
C(4) C(4a)—C(10a)—N(10)	4.6 (4)	N(5) C(5a) C(9a) N(10)	175.6 (4)	C(16)—N(10)—C(10a)—C(4a)	−0.6 (4)
N(5) C(4a)—C(10a) N(10)	177.1 (5)	C(6) C(5a) C(9a) N(10)	5.2 (4)	C(9a)—N(10)—C(10a)—N(1)	−22.0 (3)
N(5) C(4a)—C(10a)—N(1)	1.9 (4)	N(5) C(5a) C(9a) C(9)	4.0 (3)	C(2)—O(11)—C(21)—C(20)	−21.8 (3)
C(10a) C(4a)—N(5) C(5a)	−153.9 (5)	C(6) C(5a) C(9a) C(9)	175.2 (5)	C(2)—O(11)—C(21)—C(22)	100.4 (4)
C(4) C(4a)—N(5)—C(5a)	27.7 (4)				

were determined on a difference Fourier map; they were inserted but not allowed to vary in the subsequent anisotropic refinement. The final unweighted *R* index was 0.064 for the observed reflexions.*

Scattering factors were those listed for neutral atoms in *International Tables for X-ray Crystallography* (1974).

Positional parameters and equivalent isotropic temperature factors for the non-hydrogen atoms are shown in Table 3. Bond lengths and angles and relevant torsion angles are listed in Tables 4–6.

Description of the structure

An *ORTEP* (Johnson, 1965) perspective view of the molecule is shown in Fig. 1. The 'butterfly-wing conformation' found is in accordance with the results of crystallographic analyses of other fully reduced 1,5-dihydroflavins, which were also examined with spectroscopic techniques (Hemmerich, Ghisla, Hartmann & Müller, 1971).

The dihedral angle between the two planes intersecting along the line N(5)—N(10) is 154.6°, somewhat larger than the values quoted so far for other bent 1,5-dihydro derivatives (Kierkegaard *et al.*, 1971). N(10) shows a significant deviation from the expected *sp*³ hybridization: bond angles and lengths (see Tables 4 and 5), in particular N(10)—C(10a), strongly suggest a partial delocalization of the N(10) lone pair in the π -electron system of the isoalloxazine ring. Moreover, the bond N(10)—C(16), 1.449 (5) Å, is considerably shorter than those usually found for the alkyl substituents on the flavin moiety, and shorter than the usual C—N single-bond length [1.479 (5) Å] (*International Tables for X-ray Crystallography*, 1962).

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35996 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

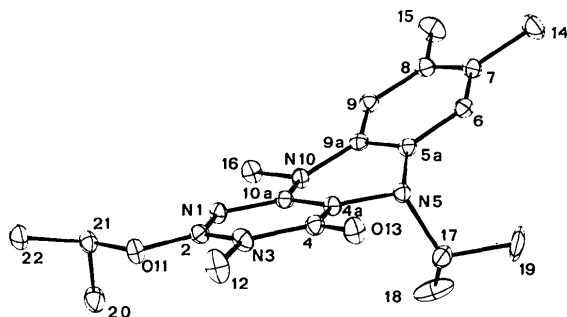


Fig. 1. ORTEP perspective view of the molecule, showing the crystallographic numbering scheme. Thermal ellipsoids are drawn at 20% probability.

Table 7. Least-squares planes and atom deviations (Å) from them

The equations of the planes are expressed in direct space as $ax + by + cz - d = 0$. The atoms listed are those included in the plane calculations.

Plane I: $a = 2.4761$, $b = -6.9207$, $c = 6.1774$, $d = 8.5018$

N(5)	0.047 (4)	C(7)	-0.32 (4)	C(9a)	0.002 (4)
C(5a)	0.000 (3)	C(8)	0.047 (4)	N(10)	-0.043 (3)
C(6)	-0.067 (4)	C(9)	0.041 (4)		

Plane II: $a = -0.4042$, $b = -3.0276$, $c = 7.398$, $d = 5.0537$

N(1)	0.016 (4)	C(4)	-0.052 (4)	N(10)	-0.035 (4)
C(2)	0.034 (4)	C(4a)	0.007 (4)	C(10a)	0.003 (4)
N(3)	-0.012 (4)	N(5)	0.033 (4)		

Interplanar angle: $25.4 (3)^\circ$.

It must be pointed out that the N(1)—C(2) double bond has not previously been found in either oxidized or reduced flavins, and is apparently related to the reaction which has occurred at the O(11) center. The reactivity of O(11) towards alkylation is known for reduced flavins in which N(3) and N(5) are protected (Hemmerich, 1976); the biological relevance of this particular reactivity is unexplored.

The mean value of the benzene-ring C—C bonds, 1.391 \AA , is in good agreement with the expected value of 1.394 \AA (Hemmerich, 1976). The agreement extends to the C(4a)—C(10a) bond length. No H atoms are available for ordinary hydrogen bonding; the molecular packing does not show significant intermolecular contacts.

Least-squares planes and atom deviations are in Table 7.

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