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Geometry of the Unperturbed Flavin Nucleus. The Crystal Structure of 10-Methylisoalloxazine

By Mei Wang and Charles J. Fritchie Jr.

Richardson Chemical Laboratories, Tulane University, New Orleans, Louisiana 70118, *U.S.A.*

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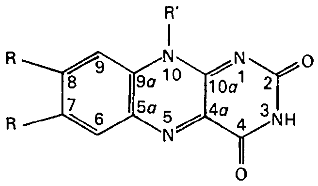
The structure of a simple analogue of quinoid flavin, 10-methylisoalloxazine, which is unperturbed by charge-transfer complexing or protonation, has been determined by X-ray crystallographic methods. The crystals have triclinic symmetry $P\bar{1}$, with a lattice having constants $a=7{\cdot}179$ (3), $b=6{\cdot}725$ (4), $c=10{\cdot}857$ (3) Å, $\alpha=103{\cdot}10$ (1)°, $\beta=75{\cdot}08$ (2)°, $\gamma=109{\cdot}07$ (2)°, $Z=2$, $\varrho_{\text{obs}}=1{\cdot}61$ g cm^{-3}, and $\varrho_{\text{calc}}=1{\cdot}60$ g cm^{-3}. The final residual, R, based on 947 counter-measured reflections is 6·0%. Heavy atoms were given ellipsoidal thermal parameters and hydrogen atoms given fixed isotropic thermal parameters. Comparison with N(1)-protonated flavins shows that protonation leads to extensive bond-length changes in the pyrimidinoid ring and in the bond N(10)–C(10*a*). In contrast, the bonds in the yellow molecular complex lumiflavin bis(naphthalene-2,3-diol) agree well with those in this structure except for a possible general contraction in the regions of C(4*a*) and C(9*a*) and in the bond C(4)–C(4*a*) in the complex.

Introduction

Isoalloxazine, (I) (shown in oxidized or quinoid form)) is the aromatic moiety of riboflavin, the cofactor of flavoenzymes.



(I)

These redox enzymes occur widely in biological systems, most importantly in the electron transport chain which links foodstuff oxidation with production of adenosine triphosphate, ATP (Ehrenberg & Hemmerich, 1968; Wainio, 1970). The extensive flavin structural studies so far published deal with either N(1)-protonated forms (Tanaka, Ashida, Sasada & Kakudo, 1969; Fritchie & Trus, 1968; Trus & Fritchie, 1969; Bear, Waters & Waters, 1970; Tillberg & Norrestam, 1972; Karlsson, 1972), metal complexes (Fritchie, 1972*a*, *b*; Wade & Fritchie, 1973), molecular complexes (Langhoff & Fritchie, 1970; Bear, Waters & Waters, 1970; Trus, Wells, Johnston, Fritchie & Marsh, 1971; Voet & Rich, 1971; Kuo, Dunn & Fritchie, 1972; Tillberg & Norrestam, 1972; Karlsson, 1972), or compounds highly modified by chemical substitution (von Glehn, Kierkegaard & Norrestam, 1970; Kierkegaard 1971; von Glehn & Norrestam, 1972; Norrestam, 1972). Because the rationale of many of the above investigations is determining the effect on the isoalloxazine moiety of the particular perturbation, it is highly desirable, even essential, to study an unperturbed model compound. Since isoalloxazine itself (I, with R′ = R=H) tautomerizes immediately to alloxazine by a 10 → 1 proton shift and the latter compound has quite different electronic properties, the 10-methyl derivative is one of the simplest derivatives suitable for flavin model studies, and we report here its crystal structure. Another essentially unperturbed isoalloxazine, 3-methyl-lumiflavin, has also recently been studied (Norrestam & Stensland, 1972).

Experimental

Yellow crystals of 10-methylisoalloxazine were grown by very slow (6 months) evaporation of concentrated solutions of the flavin in dimethyl sulfoxide. Most were twinned, but one untwinned blade-shaped crystal was mounted on the blade axis (b) and used for all further

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* Author to whom correspondence should be addressed.

measurements. Weissenberg and precession photographs, prepared with Cu $K\alpha$ and Mo $K\alpha$ radiation respectively, indicated triclinic symmetry. In the absence of contradictory evidence, the space group was assumed to be $P\bar{1}$. Crystallographic data are listed in Table 1. The unit-cell parameters were determined by a least-squares fit of 28 $\sin^2\theta$ values measured on a Picker four-circle diffractometer with Mo $K\alpha$ radiation ($\lambda = 0{\cdot}7107$ Å).

Table 1. *Physical data of* 10-*methylisoalloxazine*

Molecular formula	$C_{11}H_8N_4O_2$
Molecular weight	228
Crystal size	0·22 × 0·28 × 0·12 mm
Density	1·60 g cm^{-3} (calc) 1·61 g cm^{-3} (observed by flotation in a mixture of CCl_4 and $BrCH_2CH_2Br$)
Space group	$P\bar{1}$
Lattice constants	
a	7·179 (3) Å
b	6·725 (4)
c	10·857 (3)
α	103·10 (1)°
β	75·08 (2)
γ	109·07 (2)
Volume	472·8 Å^3
Z	2
μ	9·83 cm^{-1}

All independent reflections to a limit of 120° were measured by a card-controlled diffractometer in 2θ scan mode using Ni-filtered Cu $K\alpha$ radiation. The radiation detector was a scintillation counter with a pulse-height discriminator set to receive about 90% of the $K\alpha$ pulse distribution. The scan rate in 2θ was 1° min^{-1}, and the range approximately 2°. Two standard reflections were measured approximately every two hours to detect misorientation or decomposition of the crystal or any trouble with the diffractometer. Less than 1% change was detected.

A total of 947 reflections were measured, with two classed as unobserved and 945 observed according to the criterion $I_{\text{obs}} \geq 2\sigma_I$, where σ_I is estimated by $\sigma_I^2 = [C + (t_C/2t_B)^2(B_1 + B_2) + p^2I^2]$. In this equation, C is the integrated scan count, t_C the time of scan, t_B the time of each background, B_1 and B_2 are the background counts, p is 0·02, and I is the net intensity after subtraction of the background. Lorentz and polarization factors were used to derive values of $|F_o|$, and the standard deviation, σ_F, in each structure factor was found by the relation $\sigma_F = \sigma_I/(2|F_o|\text{Lp})$, where L and p are the Lorentz and polarization factors. No absorption corrections were applied because of the small crystal size and small value of μ (9·83 cm^{-1}).

Structure solution and refinement

The structure was solved by use of the Patterson function, taking advantage of the heavy intra- and intermolecular vectors produced by multiple overlap in this roughly centrosymmetrical molecule (Patterson, 1939). The first Fourier map, phased by the 14 atoms in the fused-ring system, showed the two oxygen appendages and a second map revealed the methyl group. Refinement of an isotropic model using $1/\sigma_F^2$ as the weight of each reflection, converged at $R = 29\%$, from an initial R of 35%. Study showed that the weights were all dominated by the p^2I^2 term and that the very weak reflections were given inordinately high weights. Change to unit weights resulted in smooth, rapid refinement to $R = 14{\cdot}7\%$. An ellipsoidal model was introduced and converged at 9·0%. Difference maps revealed all hydrogen atoms, including three fairly localized methyl hydrogen atoms. The model containing 17 anisotropic heavy atoms and eight isotropic hydrogen atoms essentially converged at $R = 6{\cdot}03\%$. Because of high standard deviations, the thermal parameters for the hydrogen atoms were reset approximately to average values for the heavier atoms to which they are attached, and not refined further. A few additional cycles resulted in convergence at $R = 5{\cdot}97\%$.

Table 2. *Atomic parameters*

Temperature factors are of the form $\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)]$.
Parameters are multiplied by 10^3 for hydrogen atoms and 10^4 for other atoms. The B value is 4·5 for H(1) to H(9) and 6·0 for H(11*a*) to H(11*c*).

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N(1)	1354 (5)	−1434 (5)	−4612 (3)	168 (8)	129 (8)	32 (3)	48 (13)	38 (8)	−9 (8)
C(2)	2804 (6)	−128 (6)	−5387 (4)	126 (6)	132 (10)	53 (4)	3 (15)	6 (10)	48 (10)
N(3)	3476 (5)	2068 (5)	−4936 (3)	155 (8)	122 (8)	38 (3)	10 (13)	27 (8)	28 (8)
C(4)	2785 (6)	3083 (6)	−3764 (4)	159 (10)	155 (10)	37 (4)	29 (16)	16 (10)	28 (10)
C(4*a*)	1176 (6)	1694 (6)	−2909 (4)	141 (9)	152 (10)	51 (4)	61 (15)	−9 (10)	60 (10)
N(5)	405 (5)	2526 (5)	−1774 (3)	151 (7)	93 (7)	41 (3)	48 (12)	−8 (8)	2 (8)
C(5*a*)	−1020 (6)	1180 (6)	−1003 (4)	105 (9)	124 (10)	43 (4)	−2 (15)	21 (9)	54 (10)
C(6)	−1820 (6)	2060 (6)	261 (4)	148 (9)	182 (11)	52 (4)	115 (16)	22 (10)	4 (11)
C(7)	−3185 (6)	782 (7)	1099 (4)	146 (10)	190 (11)	64 (4)	39 (17)	28 (11)	81 (11)
C(8)	−3778 (6)	−1408 (7)	676 (4)	120 (10)	235 (11)	63 (4)	12 (17)	36 (10)	136 (11)
C(9)	−3058 (6)	−2354 (6)	−553(4)	158 (10)	151 (10)	53 (4)	38 (16)	18 (11)	45 (11)
C(9*a*)	−1655 (6)	−1053 (6)	−1400 (4)	126 (8)	117 (9)	45 (4)	93 (14)	−2 (9)	−7 (10)
N(10)	−819 (5)	−1863 (5)	−2640 (3)	138 (7)	93 (7)	49 (3)	19 (12)	−3 (8)	36 (8)
C(10*a*)	617 (6)	−576 (6)	−3446 (4)	104 (8)	138 (10)	46 (4)	30 (14)	3 (9)	46 (10)
C(11)	−1434 (7)	−4197 (6)	−3103 (4)	212 (11)	101 (10)	60 (4)	−22 (18)	5 (12)	9 (11)
O(12)	3563 (5)	−775 (5)	−6478 (3)	256 (8)	178 (8)	48 (3)	28 (14)	77 (8)	−13 (8)
O(13)	3440 (5)	4991 (4)	−3435 (3)	219 (8)	111 (7)	66 (3)	−32 (12)	65 (8)	21 (8)

Table 2 (*cont.*)

	x	*y*	*z*
H(1)	444 (7)	295 (8)	−550 (5)
H(6)	−147 (6)	353 (6)	51 (4)
H(7)	−382 (7)	126 (8)	192 (5)
H(8)	−475 (5)	−228 (5)	127 (3)
H(9)	−334 (7)	−395 (7)	−80 (5)
H(11*a*)	−85 (8)	−445 (8)	−404 (5)
H(11*b*)	−289 (6)	−466 (7)	−300 (4)
H(11*c*)	−121 (7)	−487 (7)	−252 (4)

The final atomic parameters are given in Table 2 and the calculated and experimental values of the structure factors are given in Table 3. Scattering factors were taken from *International Tables for X-ray Crystallography* (1962), including anomalous scattering terms where applicable, except that the scattering factor for hydrogen was that given by Stewart, Davidson & Simpson (1965). All calculations were performed on the Tulane Computer Laboratory IBM 7044 computer, using primarily the X-ray program system *LOKI*. This is a single program written under the Fortran chain option which contains a highly modified version of *UCLALS*1 by Gantzel, Sparks & Trueblood for block-diagonal least-squares refinement, and *FOURIE* and *GENFOR* by Fritchie, for normal and general plane Fourier summation. *ORABS* by Busing, *ORTEP* by Johnson, and *GSET*4 by Prewitt were also used.

Discussion

The isoalloxazine molecule is approximately but not strictly planar as seen in Table 4. Planes I and II reveal that the major distortion is a slight folding approximately along the N(5)–N(10) axis. The angle between the two halves, that is planes III and V, is 2·9°. In contrast with some other isoalloxazine structures, the carbonyl oxygen atoms are essentially in the pyrimidinoid plane.

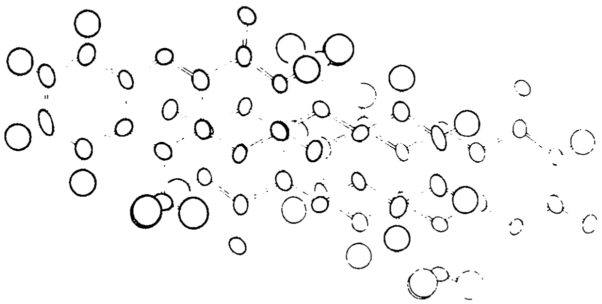

Fig. 1. Molecular overlap.

Table 3. *Observed and calculated structure factors*

Each group of three columns contains *l*, $10|F_o|$ and $10F_c$, and is headed by the values of *h* and *k* common to the group.

L	FO	FC
	0	0
1	135	-132
2	97	102
3	197	183
4	132	-137
5	318	-296
6	174	175
7	124	-126
8	21	19
9	18	-9
10	67	-74
	0	1
9	43	-43
8	19	14
7	46	-46
6	46	47
5	338	-321
4	89	-87
3	199	-200
2	173	163
1	102	99
0	508	561
-1	34	36
-2	277	282
-3	217	-221
-4	35	37
-5	65	63
-6	102	-104
-7	22	23
-8	97	90
-9	128	120
-10	41	41
	0	2
-10	33	-34
-9	313	326
-8	39	34
-7	57	-54
-6	37	40
-5	74	-73
-4	495	-477
-3	201	193
-2	86	-81
-1	235	-229
0	96	-94
1	198	-199
2	184	-170
3	156	153
4	47	-45
5	91	-89
6	72	73
7	22	-8
8	33	-35
9	55	56
	0	3
8	17	-17
7	48	-51
6	87	85
5	242	240
4	17	19
3	18	4
2	14	-19
1	168	-153
0	374	-351
-1	84	78
-2	41	48
-3	87	-87
-4	279	-265
-5	16	16
-6	117	-112
-7	31	31
-8	21	13
-9	26	22
	0	4
-9	81	-85
-8	42	-41
-7	66	-67
-6	39	45
-5	52	50
-4	45	43
-3	32	32
-2	123	119
-1	145	-141
0	16	19
1	18	20
2	105	-103
3	21	20
4	64	55
5	119	118
6	128	124
	0	5
4	58	67
3	54	-50
2	32	24
1	36	-36
0	26	-26
-1	21	-9
-2	58	59
-3	23	13
-4	409	418
-5	34	-27
-6	20	12
-7	26	23
	0	6
-4	160	153
-3	51	49
-2	43	41
-1	39	-44
0	17	-13
1	111	-125
	1	5
-6	23	-20
-5	46	-46
-4	57	54
-3	147	150
-2	257	-264
-1	38	31
0	62	61
1	71	-70
2	42	40
3	130	136
4	69	-97
	1	4
6	17	7
5	91	-79
4	37	35
3	36	-34
2	45	-48
1	77	76
0	65	68
-1	37	-41
-2	124	121
-3	62	62
-4	15	1
-5	23	17
-6	34	31
-7	17	6
-8	55	-67
	1	3
-9	36	41
-8	60	-54
-7	36	40
-6	52	63
-5	41	-37
-4	124	-121
-3	71	71
-2	40	-45
-1	63	85
0	103	104
1	223	-222
2	256	238
3	49	-48
4	93	-47
5	19	21
6	50	64
7	374	-381
8	59	60
	1	2
9	28	-29
8	36	31
7	172	-170
6	17	11
5	75	-78
4	25	26
3	11	9
2	326	313
1	239	-239
0	38	36
-1	35	-38
-2	47	39
-3	168	160
-4	275	-258
-5	33	33
-6	15	10
-7	25	24
-8	23	18
-9	225	226
	1	1
-9	343	346
-8	56	-55
-7	52	49
-6	73	75
-5	23	-14
-4	27	-26
-3	136	131
-2	287	-293
-1	132	130
0	113	-122
1	113	-101
2	345	344
3	64	-64
4	87	-87
5	95	93
6	15	-12
7	57	58
8	84	89
9	17	-10
10	32	-35
	1	0
10	15	-11
9	14	9
8	59	-55
7	203	198
6	83	75
5	34	-14
4	103	96
3	48	47
2	381	-387
1	93	84
0	273	282
-1	47	50
-2	193	-194
-3	147	-146
-4	89	90
-5	12	9
-6	75	-76
-7	133	131
-8	17	-15
-9	18	-14
	1	-1
-9	102	-119
-8	20	4
-7	20	-8
-6	77	72
-5	297	-283
-4	94	-91
-3	51	51
-2	106	-102
-1	53	-62
0	378	393
1	130	-131
2	223	-222
3	14	-11
4	142	141
5	101	102
6	58	-63
7	17	-15
8	42	43
9	103	-99
10	15	4
	1	-2
10	22	18
9	39	-33
8	42	-42
7	14	-2
6	28	22
5	94	-89
4	211	215
3	111	-110
2	111	114
1	106	94
0	339	-344
-1	63	54
-2	91	91
-3	117	-115
-4	46	49
-5	61	-57
-6	107	-113
-7	26	17
-8	47	52
	1	-3
-8	81	-80
-7	37	40
-6	23	-12
-5	203	203
-4	16	-14
-3	85	87
-2	24	-30
-1	21	-21
0	300	-289
1	230	228
2	29	-19
3	19	21
4	51	-47
5	118	-108
6	208	198
7	25	-26
8	19	-14
9	23	-16
10	20	-16
	1	-4
9	32	-29
8	31	-34
7	20	9
6	84	81
5	43	-35
4	36	33
3	67	-68
2	92	-89
1	197	192
0	233	-219
-1	55	55
-2	92	86
-3	27	-31
-4	72	-75
-5	418	421
-6	60	-72
	1	-5
-5	68	59
-4	21	-14
-3	84	82
-2	40	-36
-1	31	28
0	37	37
1	66	-67
2	51	-54
3	38	42
4	113	107
5	63	-59
6	21	-14
7	19	-6
8	27	-22
	1	-6
6	47	-46
5	120	-122
4	212	210
3	29	-23
2	49	-45
1	63	60
0	34	-38
-1	126	-131
-2	80	85
	2	-6
-2	45	-53
-1	45	39
0	23	-15
1	44	42
2	19	13
3	20	9
4	41	-40
5	43	-41
6	289	-295
	2	-5
8	27	-28
7	41	-37
6	55	-52
5	34	-34
4	91	-82
3	82	84
2	17	-16
1	17	-9
0	76	73
-1	19	-15
-2	45	-47
-3	104	-104
-4	127	-127
	2	-4
-6	18	13
-5	47	46
-4	104	-104
-3	235	-236
-2	14	-14
-1	19	8
0	17	22
1	138	128
2	234	226
3	54	-54
4	17	-21
5	43	46
6	171	165
7	15	-10
8	58	54
9	27	-14
	2	-3
10	25	-21
9	27	25
8	32	-31
7	55	50
6	299	290
5	91	-91
4	45	36
3	128	123
2	97	89
1	182	184
0	126	123
-1	123	-129
-2	34	38
-3	72	70
-4	87	-89
-5	25	25
-6	33	36
-7	69	-67
	2	-2
-8	131	149
-7	42	44
-6	21	-22
-5	49	49
-4	36	-35
-3	330	314
-2	59	58
-1	157	162
0	124	-124
1	48	-48
2	361	-351
3	49	43
4	135	-128
5	125	128
6	18	-21
7	20	-15
8	57	58
9	26	-21
10	68	-65
	2	-1
10	19	-14
9	65	69
8	112	-112
7	185	173
6	71	71
5	93	-87
4	53	-59
3	119	122
2	1529	-1555
1	69	73
0	114	-114
-1	170	-161
-2	145	148
-3	333	317
-4	173	-177
-5	147	148
-7	20	11
-8	93	108
	2	0
-9	60	-55
-8	51	-50
-7	125	-122
-6	94	-91
-5	19	-20
-4	127	127
-3	77	-73
-2	51	-54
-1	184	189
0	248	-254
1	82	-88
2	485	-487
3	83	-81
4	88	-85
5	118	123
6	65	62
7	226	217
8	37	-34
9	32	28
10	17	-5
	2	1
8	36	-33
7	65	61
6	48	46
5	80	-89
4	96	95
3	117	120
2	91	89
1	182	185
0	63	63
-1	209	-206
-2	495	493
-3	74	70
-4	38	-42
-5	76	72
-6	43	-41
-7	369	-383
-8	33	30
-9	32	-33
	2	2
-8	31	-29
-7	28	-26
-6	27	-25
-5	38	-38
-4	143	147
-3	19	6
-2	293	288
-1	84	91
0	32	-35
1	53	-53
2	325	310
3	138	123
4	15	13
5	14	-16
6	19	-17
7	186	-190
8	54	-50
9	43	46
	2	3
7	114	-113
6	58	-61
5	21	-17
4	79	79
3	15	-8
2	16	-1
1	141	141
0	120	-122
-1	17	-10
-2	26	-30
-3	47	-47
-4	44	-54
-5	72	77
-6	38	36
-7	98	107
-8	19	12
	2	4
-6	33	40
-5	36	-35
-4	19	-17
-3	29	20
-2	443	-458
-1	18	13
0	56	-55
1	18	12
2	26	23
3	33	34
4	29	-24
5	69	44
	2	5
3	110	121
2	18	16
1	39	44
0	42	-41
-1	58	-50
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-3	21	-11
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	3	4
4	34	-34
3	56	58
2	63	-59
1	37	-32
0	250	253
-1	133	-134
-2	59	-56
-3	45	43
-4	20	13
	3	3
-6	58	62
-5	16	-8
-4	36	-33
-3	25	-20
-2	15	9
-1	43	-47
0	102	101
1	25	25
2	56	-51
3	62	-62
4	28	31
5	39	35
6	28	-25
	3	2
8	36	-38
7	20	-1
6	62	56
5	25	24
4	168	-164
3	165	164
2	83	-77
1	64	-68
0	30	34
-1	71	-71
-2	118	112
-3	52	47
-4	61	-62
-5	44	-45
-6	58	50
-7	48	-51
	3	1
-8	33	31
-7	256	-258
-6	24	-18
-5	22	-22
-4	15	-12
-3	30	-31
-2	248	235
-1	158	-155
0	44	-36
1	48	50
2	14	-10
3	132	133
4	219	-211
5	16	2
6	18	-13
7	45	45
8	18	-10
9	118	116
	3	0
10	48	-51
9	43	-46
8	26	-15
7	40	-39
6	44	45
5	28	25
4	178	-179
3	83	81
2	49	45
1	104	-103
0	230	230
-1	99	-96
-2	22	17
-3	14	7
-5	51	-49
-6	72	73
-7	367	-364
-8	48	47
	3	-1
-8	26	-23
-7	24	22
-6	25	24
-5	126	-123
-4	70	73
-3	15	11
-2	43	-42
-1	99	96
0	112	117
1	27	-29
2	184	-178
3	-12	-45
4	226	217
5	-9	-16
7	24	19
8	62	-61
9	97	-93
10	36	32
	3	-2
10	24	-19
9	19	13
8	22	20
7	41	-39
6	66	-70
5	23	-21
4	114	109
3	114	118
2	224	-221
1	16	13
0	72	68
-1	41	-31
-2	70	66
-3	249	242
-4	54	-50
-5	17	11
-7	102	115
	3	-3
-6	58	-51
-5	14	-15
-4	85	89
-3	48	45
-2	44	-45
-1	58	57
0	54	-56
1	14	-7
2	184	185
3	65	-63
4	58	-60
5	57	56
6	89	-94
7	45	44
8	34	-28
9	20	15
10	23	18
	3	-4
9	23	19
8	120	-121
7	64	57
6	36	35
5	15	-6
4	14	-2
3	130	-132
2	160	170
1	20	16
0	22	24
-1	55	-54
-2	15	12
-3	190	-190
-4	17	-11
-5	33	-38
	3	-5
-4	45	45
-3	342	-347
-2	67	65
-1	16	17
0	61	-53
1	15	-36
2	135	133
3	114	-114
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5	36	36
6	21	-10
8	46	-45
	3	-6
6	65	-79
5	29	-30
4	30	30
3	41	39
2	26	-14
1	25	-19
0	35	29
-1	62	-61
	4	-6
0	26	23
1	17	5
2	41	-34
3	17	-5
5	36	-37
6	52	45
	4	-5
8	88	-88
7	21	-22
6	10	5
5	34	30
4	106	-110
3	94	-93
2	17	-10
1	16	-9
0	19	4
-1	176	182
-2	93	94
-3	39	-35
	4	-4
-4	29	-27
-3	20	-20
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-1	31	-25
0	20	-24
1	45	52
2	48	-51
3	112	-118
4	66	-62
5	49	-46
6	26	-17
7	30	27
8	141	-143
9	43	-37
	4	-3
10	25	-22
8	18	2
7	59	-61
6	53	49
5	45	-42
4	169	161
3	16	12
2	56	56
1	71	-76
0	27	-20
-1	214	-207
-2	21	9
-3	26	-30
-4	24	22
-5	35	-41
	4	-2
-6	135	-108
-5	22	-14
-4	16	15
-3	108	-111
-2	104	110
-1	211	-204
0	86	-92
1	70	67
2	78	75
3	13	-8
4	644	668
5	63	-64
6	23	20
7	31	28
8	30	-27
9	92	-90
10	55	54
	4	-1
10	30	22
9	119	-118
8	45	-43
7	55	-58
6	35	34
5	45	44
4	284	273
3	63	68
2	127	123
1	83	-83
0	43	47
-1	28	24
-2	93	-98
-3	20	21
-4	63	59
-5	97	98
-6	51	51
	4	0
-7	34	37
-6	18	-10
-5	348	353
-4	33	30
-3	69	-65
-2	31	29
-1	52	-45
0	302	-298
1	119	116
2	24	-21
3	68	-74
4	62	-58
5	48	-50
6	31	-28
7	21	23
8	34	-30
9	39	-30
	4	1
8	18	6
7	17	16
6	17	4
5	92	-84
4	188	-180
3	16	12
2	12	3
1	41	-49
0	217	-203
-1	47	-43
-2	120	-114
-3	34	33
-4	26	22
-5	38	37
-6	44	46
	4	2
-5	96	-100
-4	32	-26
-3	66	-67
-2	34	42
-1	32	28
0	24	21
1	25	-18
2	82	83
3	87	-90
4	28	-15
5	22	-9
6	40	-36
7	20	10
	4	3
5	37	-34
4	20	-10
3	18	-16
2	35	31
1	22	-15
0	373	381
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-2	28	29
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-4	37	-41
	5	2
5	35	33
4	27	28
3	19	-5
2	71	-69
1	28	24
0	19	-6
-1	20	13
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-3	18	13
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1	46	44
2	17	-7
3	33	34
4	38	34
5	81	-86
6	84	92
7	19	-12
	5	0
8	17	4
7	16	2
6	117	115
5	63	-61
4	17	-2
3	37	-34
2	27	22
1	106	104
0	158	-153
-1	23	21
-2	21	15
-3	19	11
-4	22	14
-5	229	228
	5	-1
-5	281	287
-4	56	-57
-3	39	34
-2	37	36
-1	19	7
0	29	-20
1	50	49
2	111	-112
3	45	46
4	15	-9
5	34	-30
6	68	67
7	22	-17
8	18	-12
9	20	12
	5	-2
9	24	-17
8	28	25
7	27	18
6	111	-116
5	17	4
4	103	102
3	20	14
2	51	-52
1	42	-37
0	16	-5
-1	23	-19
-2	44	-47
-3	87	81
-4	28	-25
-5	21	-17
	5	-3
-3	20	-14
-2	26	16
-1	138	-140
0	49	-46
1	33	24
2	33	-29
3	17	-9
4	111	107
5	57	-62
6	64	-61
7	26	18
8	38	35
9	20	10
	5	-4
8	29	29
7	21	-15
6	32	32
5	24	20
4	75	-72
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1	20	-13
0	28	24
-1	31	-26
-2	47	-44
-3	17	7
	5	-5
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1	31	25
2	19	-12
3	25	-19
4	88	-84
5	72	74
6	17	4
7	18	-4
	5	-6
4	66	-65
3	23	20
	6	-5
5	64	71
4	23	20
3	18	-10
2	17	8
	6	-4
-1	24	15
1	111	112
2	21	12
3	35	34
4	30	-25
5	18	-4
6	74	-74
7	30	28
	6	-3
7	34	29
6	274	-296
5	22	-19
4	41	-39
3	29	-25
2	37	39
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-1	53	56
-2	18	-8
	6	-2
-3	68	-68
-2	26	-24
-1	20	-14
0	53	53
1	20	8
2	22	-23
3	33	30
4	63	-61
5	47	-49
6	144	-148
7	26	-21
	6	-1
7	24	18
6	32	27
5	23	20
4	20	6
3	58	-53
2	134	135
1	44	41
0	20	-14
-1	40	38
-2	19	-13
-3	255	-253
	6	0
-2	21	-12
-1	21	-16
0	63	59
1	51	53
2	124	118
3	21	21
4	20	9
5	17	5
6	96	93
	6	1
4	44	-40
3	31	25
2	25	-18
1	17	-4
0	24	-25
-1	44	41
	7	-1
2	95	83
3	62	-62
	7	-2
4	43	43
3	28	-27
2	31	25
1	21	-10
	7	-3
2	23	18
4	27	25

Table 4. *Least-squares planes*

The planes are expressed as $Am+Bn+Cp=D$, where m, n and p are dimensions in Å relative to unit orthogonal axes $m\|\mathbf{b}\times\mathbf{c}^*$, $n\|\mathbf{b}$ and $p\|\mathbf{c}^*$. All atoms were given equal weight except that for distances in parentheses, the corresponding atom had zero weight.

Coefficients

Plane	*A*	*B*	*C*	*D*
I	−0·80381	0·47680	−0·35574	1·649
II	−0·80705	0·47075	−0·35646	1·653
III	−0·79229	0·48945	−0·36431	1·707
IV	−0·82819	0·45058	−0·33328	1·672
V	−0·82190	0·45629	−0·34100	1·661

Distances from each plane (Å)

	I	II	II	IV	V
N(1)	0·023	0·024	0·004	(−0·102)	
C(2)	−0·003	−0·009	0·003		
N(3)	−0·036	−0·052	−0·012	(−0·253)	(−0·184)
C(4)	−0·025	−0·044	−0·007	(−0·223)	(−0·162)
C(4*a*)	0·027	0·015	0·017	(−0·109)	(−0·066)
N(5)	0·057	0·042	0·040	(−0·058)	−0·022
C(5*a*)	0·057	0·049	(0·014)	−0·001	0·020
C(6)	0·036	0·025	(−0·015)	0·003	0·014
C(7)	−0·025	−0·030	(−0·102)	−0·001	−0·006
C(8)	−0·061	−0·056	(−0·155)	−0·003	−0·014
C(9)	−0·033	−0·025	(−0·120)	0·005	0·002
C(9*a*)	0·018	0·019	(−0·044)	−0·003	0·010
N(10)	0·021	0·025	−0·031	(−0·025)	−0·002
C(10*a*)	0·018	0·016	−0·008	(−0·085)	(−0·047)
C(11)	−0·020				
O(12)	0·005		0·020		
O(13)	−0·059		−0·024		

There is considerable overlap of centrosymmetrically related pyrimidinoid rings with an interplanar spacing of 3·23 Å, and of similarly related benzenoid rings with a spacing of 3·34 Å. Fig. 1 illustrates these interactions as viewed along the normal to the average molecular plane. The former very small spacing is probably the result of local dipole–dipole interactions in the highly polar pyrimidinedione rings; the latter spacing is small, but nearly normal for aromatic hydrocarbon rings. The combination of small interplanar spacing and nearly exact overlap of several atom pairs results in some of the shortest C· · ·C and C· · ·N contacts yet observed. Thus, the N(5)· · ·C(8) contact illustrated in Fig. 1 is 3·307 (7), C(6)· · ·C(9*a*) is 3·359 (7), and C(2)· · ·C(10*a*) is 3·239 (7) Å.

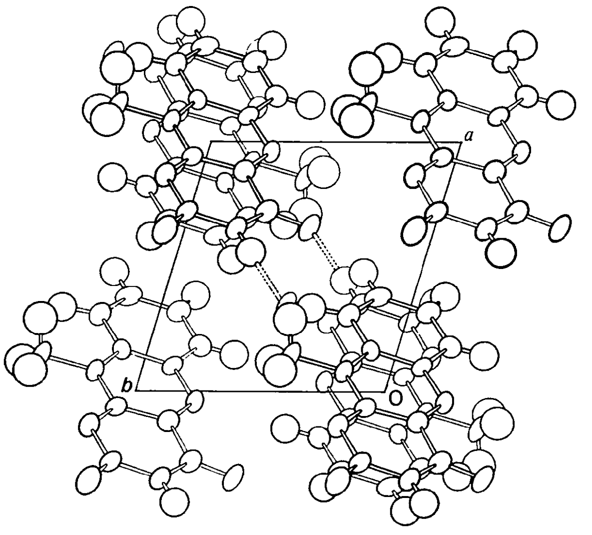

Fig. 2. [001] projection.

These short distances are not entirely without precedent, however. Bugg, Thomas, Sundaralingam & Rao (1971) draw attention to the rather small interplanar spacings of 3·3 to 3·35 Å in many pyramidine derivatives, with individual atomic separations as short as those reported here. Some of the shortest considered in relation to van der Waals radii are C· · ·C = 3·20 Å in calcium thymidine 5′-phosphate (Kim & Rich, 1968), 3·25 (1) Å in isocytosine (Sharma & McConnell, 1965), 3·285 (5) Å in 1-methylthymine: 9-methyladenine (Hoogsteen, 1963), and 3·30 (1) Å in 9-methylguanine: 1-methylcytosine (O'Brien, 1967).

These short van der Waals contacts generate a column of molecules running parallel to [001]. As Fig. 2 illustrates, molecules in a given stack are hydrogen bonded alternately to others in stacks related by $\pm(a+b)$ lattice translations. The result is a sheet-like structure with sheets parallel to $(1\bar{1}0)$.

Because 10-methylisoalloxazine contains a single possible hydrogen-bond donor, centrosymmetric base pairs involving N(3)–H(3) and either O(12) or O(13) are likely. The latter is found, with an N· · ·O distance of 2·941 (4) Å, an H· · ·O distance of 2·01 (5) Å, and an N–H· · ·O angle of 175 (4)°. Base pairing using N(3)–H(3) and O(13) is also found in the 10-propylisoalloxazine bis(naphthalene-2,3-diol) molecular complex (Kuo, Dunn & Fritchie, 1972) and in riboflavin dihydrobromide hydroquinone (Bear, Waters & Waters, 1970). N(3)–H(3)· · ·O(12) base pairing has not been observed although N(1)–H(1)· · ·O(12) pairing occurs in N(1)-protonated flavins (Langhoff & Fritchie, 1970; Bear, Waters & Waters, 1970).

The intramolecular bond distances and bond angles obtained in the present structure, given in Fig. 3, are compared with those obtained by Trus & Fritchie (1969) for 10-methylisoalloxazine hydrobromide dihydrate, by von Glehn, Kierkegaard & Norrestam (1970) for 9-bromo-3-methyl-lumiflavin hydrate, and by Norrestam & Stensland (1972) for 3-methyl-lumiflavin in Tables 5 and 6. Only the latter two structures are directly comparable with this one. No differences between corresponding bonds in this structure and in the brominated compound exceed three standard deviations. Four such statistically significant differences, in C(4*a*)–C(10*a*), C(7)–C(8), C(10*a*)–N(1), and N(10)–C(11), exist in comparison with 3-methyl-lumiflavin. There are unlikely to be genuine and probably reflect slightly underestimated standard deviations. In no case do bonds observed in this structure deviate by more than 3σ from corresponding ones in the 'ideal' flavin structure described in Table 5. Further comparison of 9-bromo-3-methyl-lumiflavin hydrate, 3-methyl-lumiflavin, and the present structure reveals that the 3-

methyl substitution does not significantly affect the geometry of the flavin nucleus. As Norrestam & Stensland suggest, bromination in the 9 position appears to increase nearby bond lengths slightly, and there might be a slight movement of O(13) away from the N(3) methyl group in this compound.

The protonated derivatives, 10-methylalloxazine hydrobromide dihydrate (Trus & Fritchie, 1969) and lumiflavinium bromide–sesqui(naphthalene-2,7-diol) (Langhoff & Fritchie, 1970), show that protonation of N(1) results in extensive bond-length changes through most of the pyrimidinoid ring and in the bond N(10)–C(10*a*). The bond C(4*a*)–N(5) seems unaffected.

Formation of the yellow π complex, lumiflavin bis-(naphthalene-2,3-diol) (Trus, Wells, Johnston, Marsh & Fritchie, 1971), seems to produce no significant changes in bond length, other than a possible shortening of C(4)–C(4*a*) from the 'ideal' value of 1·484 (3) Å to 1·447 (8) Å, and a possible slight general contraction in the regions around C(5*a*) and C(9*a*). None of the latter changes individually is significant.

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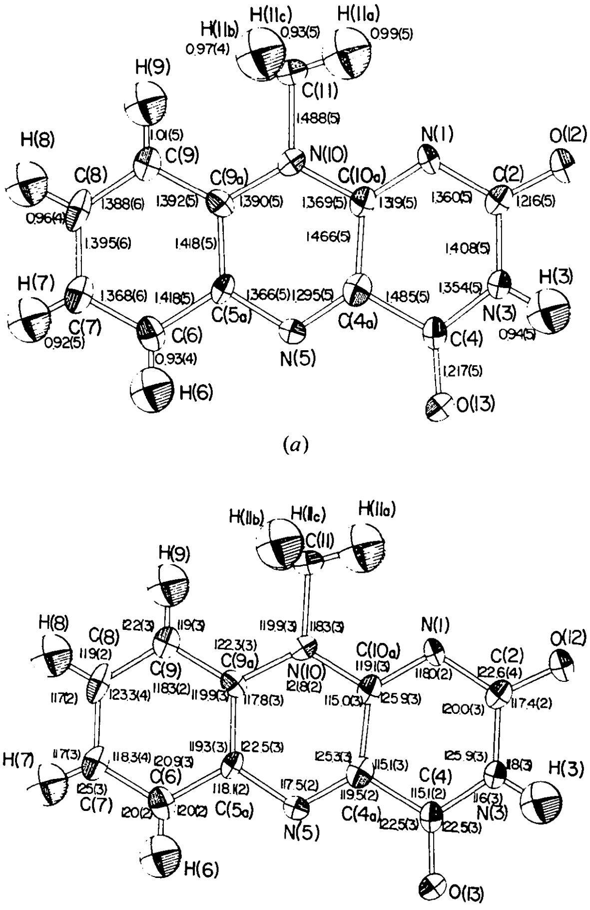

Fig. 3. (*a*) Bond distances. (*b*) Bond angles. Angles involving the C(11) hydrogen atoms are: N(10)–C(11)–H(11*a*) 108 (3), N(10)–C(11)–H(11*b*) 108 (3), N(10)–C(11)–H(11*c*) 108(3); H(11*a*)–C(11)–H(11*b*) 108 (4), H(11*a*)–C(11)–H(11*c*) 122 (4); H(11*b*)–C(11)–H(11*c*) 103 (4)°.

Table 5. *Comparison of bond distances*

	10-Methylisoalloxazine hydrobromide dihydrate*	9-Bromo-3-methyl lumiflavin hydrate†	3-Methyl lumiflavin‡	10-Methyl-isoalloxazine	'Ideal' lumiflavin§
N(1)—C(2)	1·408 (7) Å	1·387 (12) Å	1·368 (3) Å	1·360 (5) Å	1·368 (3) Å
C(2)—N(3)	1·379 (7)	1·389 (12)	1·410 (3)	1·408 (5)	1·407 (3)
N(3)—C(4)	1·388 (7)	1·375 (12)	1·362 (3)	1·354 (5)	1·361 (3)
C(4)—C(4*a*)	1·489 (7)	1·485 (12)	1·483 (3)	1·485 (5)	1·484 (3)
C(4*a*)—C(10*a*)	1·422 (7)	1·445 (12)	1·446 (3)	1·466 (5)	1·452 (3)
C(4*a*)—N(5)	1·299 (7)	1·297 (12)	1·300 (3)	1·295 (5)	1·298 (3)
N(5)—C(5*a*)	1·376 (7)	1·378 (12)	1·372 (3)	1·366 (5)	1·371 (3)
C(5*a*)—C(9*a*)	1·407 (7)	1·420 (12)	1·405 (3)	1·418 (5)	1·411 (3)
C(5*a*)—C(6)	1·411 (7)	1·398 (12)	1·406 (3)	1·418 (5)	1·409 (3)
C(6)—C(7)	1·348 (7)	1·372 (12)	1·371 (4)	1·368 (6)	1·370 (4)
C(7)—C(8)	1·415 (7)	1·416 (12)	1·421 (3)	1·395 (6)	1·413 (3)
C(8)—C(9)	1·362 (7)	1·414 (12)	1·376 (3)	1·388 (6)	1·380 (3)
C(9)—C(9*a*)	1·419 (7)	1·422 (12)	1·397 (3)	1·392 (5)	1·395 (3)
C(9*a*)—N(10)	1·386 (7)	1·418 (12)	1·380 (3)	1·390 (5)	1·388 (3)
N(10)—C(10*a*)	1·338 (7)	1·356 (12)	1·360 (3)	1·369 (5)	1·362 (3)
C(10*a*)-N(1)	1·364 (7)	1·324 (12)	1·303 (3)	1·319 (5)	1·311 (3)
C(2)—O(12)	1·209 (7)	1·221 (12)	1·207 (3)	1·216 (5)	1·212 (3)
C(4)—O(13)	1·211 (7)	1·212 (12)	1·219 (3)	1·217 (5)	1·216 (3)
N(10)—C(11)		1·489 (12)	1·466 (3)	1·488 (5)	1·476 (3)
C(7)—C(7*m*)†		1·508 (12)	1·499 (4)		1·501 (4)
C(8)—C(8*m*)†		1·509 (12)	1·502 (4)		1·504 (4)

* Trus & Fritchie (1969).

† von Glehn, Kierkegaard & Norrestam (1970).

‡ Norrestam & Stensland (1972).

§ The 'ideal' lumiflavin values are weighted averages ($w=1/\sigma^2$) of the three non-protonated structures, except for C(8)–C(9) and C(9)–C(9*a*), where the brominated compound is omitted, C(7*m*) and C(8*m*) are the methyl carbon atoms attached to C(7) and C(8) respectively. In lumiflavin the 'ideal' values for these bonds are the weighted averages of the two experimental values listed. The standard deviation, $\sigma_{\rm avg}$, in each ideal value is calculated from individual standard deviations, σ_i, by the equation $\sigma_{\rm avg}=1/[\sum_i 1/\sigma_i^2]^{1/2}$.

Table 6. *Comparison of bond angles*

	10-Methylisoalloxazine hydrobromide dihydrate	9-Bromo-3-methyl lumiflavin hydrate	3-Methyl lumiflavin	10-Methyl-isoalloxazine
N(1)—C(2)—N(3)	116·3 (4)°	121·7 (3)°	120·5 (2)°	120·0 (3)°
N(1)—C(2)—O(12)	120·4 (4)	119·1 (3)	121·0 (2)	122·6 (4)
O(12)—C(2)—N(3)	123·3 (4)	119·1 (3)	118·4 (2)	117·4 (2)
C(2)—N(3)—C(4)	126·1 (4)	124·2 (3)	124·1 (2)	125·9 (3)
N(3)—C(4)—C(4*a*)	115·0 (4)	114·2 (3)	114·8 (2)	115·1 (2)
N(3)—C(4)—O(13)	122·0 (4)	124·4 (3)	122·2 (2)	122·5 (3)
O(13)—C(4)—C(4*a*)	122·9 (4)	121·4 (3)	123·0 (2)	122·5 (3)
C(4)—C(4*a*)—C(10*a*)	119·4 (4)	118·3 (3)	117·1 (2)	115·1 (3)
C(10*a*)-C(4*a*)—N(5)	123·6 (4)	123·9 (3)	124·3 (2)	125·3 (3)
C(4*a*)—N(5)—C(5*a*)	117·7 (4)	118·1 (3)	117·2 (2)	117·5 (2)
N(5)—C(5*a*)—C(9*a*)	121·0 (4)	121·6 (3)	122·8 (2)	122·5 (3)
C(9*a*)—C(5*a*)—C(6)	120·0 (4)	121·0 (3)	118·6 (2)	119·3 (3)
N(5)—C(5*a*)—C(6)	119·0 (4)	117·2 (3)	118·7 (2)	118·1 (2)
C(5*a*)—C(6)—C(7)	119·8 (4)	121·3 (3)	121·9 (2)	120·9 (3)
C(6)—C(7)—C(8)	120·4 (4)	119·0 (3)	118·8 (2)	118·3 (4)
C(7)—C(8)—C(9)	121·4 (4)	120·5 (3)	120·1 (2)	123·3 (4)
C(8)—C(9)—C(9*a*)	119·0 (4)	120·0 (3)	120·8 (2)	118·3 (2)
C(9)—C(9*a*)—C(5*a*)	119·3 (4)	117·5 (3)	119·8 (2)	119·9 (3)
C(9)—C(9*a*)—N(10)	121·4 (4)	124·5 (3)	122·3 (2)	122·3 (3)
N(10)—C(9*a*)—C(5*a*)	119·4 (4)	117·9 (3)	117·9 (2)	117·8 (3)
C(9*a*)—N(10)—C(11)	119·9 (4)	122·5 (3)	119·5 (2)	119·9 (3)
C(11)—N(10)—C(10*a*)	121·0 (4)	117·8 (3)	119·4 (2)	118·3 (3)
C(9*a*)—N(10)—C(10*a*)	119·0 (4)	118·9 (3)	121·1 (2)	121·8 (2)
N(10)—C(10*a*)-N(1)	121·3 (4)	117·8 (3)	118·7 (2)	119·1 (3)
N(10)—C(10*a*)-C(4*a*)	119·2 (4)	118·3 (3)	116·8 (2)	115·0 (3)
N(1)—C(10*a*)-C(4*a*)	119·4 (4)	123·8 (3)	124·5 (2)	125·9 (3)
C(10*a*)-N(1)—C(2)	123·5 (4)	117·2 (3)	118·8 (2)	118·0 (2)

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