The Molecular and Crystal Structures of 9-Methyl- and 1,3,8,9-Tetramethylalloxazines

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The structures of 9-methylalloxazine (**1**) and 1,3,8,9-tetramethylalloxazine (**2**) have been determined by direct methods from three-dimensional diffractometer data. The monohydrate of **1** shows monoclinic symmetry ($P2_1/a$) with $Z = 4$ and $D_x = 1.492$ g cm^{-3}. The unit cell dimensions are $a = 12.954(1)$, $b = 12.536(1)$, $c = 6.799(1)$ Å and $\beta = 96.92(9)°$. The crystals of **2** are also monoclinic; space group $P2_1/n$, $a = 7.6915(5)$, $b = 16.0437(9)$, $c = 10.3800(6)$ Å, $\beta = 101.37(5)°$, $Z = 4$ ($Z = 4$) and $D_x = 1.430$ g cm^{-3}. The final R values are 0.051 for **1** and 0.073 for **2**, calculated using 1840 and 1280 reflections, respectively. Both molecules are planar. The results are briefly compared with available results of X-ray studies on the related isoalloxazine molecules.

Isoalloxazines (flavins) play an important role as redox cofactors in many biological reactions. The three-dimensional structure[1] and the physical and chemical properties[2] of flavin have been studied in great detail. Alloxazines are structurally very closely related to isoalloxazines (Fig. 1), but the two classes of compounds are not tautomers as suggested by their trivial names. However, alloxazines are products of photolysis of flavin[2] and therefore can be associated with flavin in biological materials. A possible biological role of alloxazines has not yet been demonstrated, except

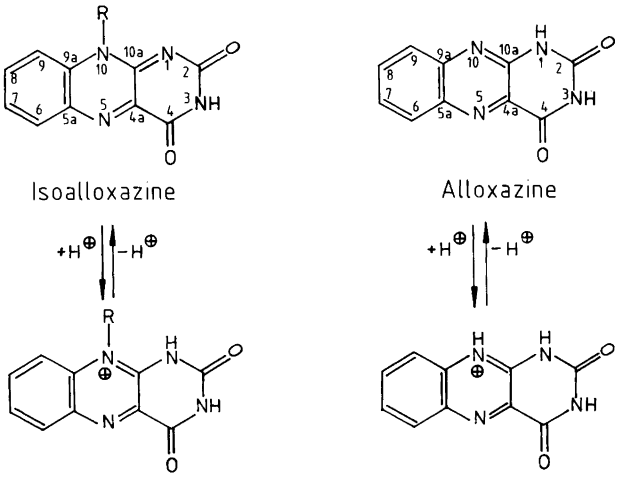

Fig. 1. The chemical structure of isoalloxazine and alloxazine.

Table 1. Crystal data for 9-methyllaloxazine monohydrate and 1,3,8,9-tetramethylalloxazine with some details of the intensity data collection.

Compound	9-Methylalloxazine (**1**)	1,3,8,9-tetramethylalloxazine (**2**)
Stoichiometry	$C_{11}H_8O_2N_4 \cdot H_2O$	$C_{14}H_{14}O_2N_4$
Formula weight	246.23	270.29
Z	4	4
F(000)	512	568
Space group	$P2_1/a$	$P2_1/n$
Unit cell: *a*/Å	12.954(1)	7.6915(5)
b/Å	12.536(1)	16.0437(9)
c/Å	6.799(1)	10.3800(6)
β/°	96.92(9)	101.37(5)
Cell volume/Å^3	1096.0(3)	1255.8(3)
D_{calc}/g cm^{-3}	1.492	1.430
Diffractometer	Philips PW 1100	Siemens/STOE AED 2
Radiation	Mo *K*α (λ = 0.7107 Å)	Cu *K*α (λ = 1.5418 Å)
θ range/°	2–32	1–67.5
Crystal size/mm	0.62×0.58×0.32	0.38×0.05×0.30
$\mu_{X\text{-ray, calc.}}$/cm^{-1}	1.053	7.765
No. of refl. measured	4122	3916
No. of unique non-zero refl.	3274	2060

for the fact that it can replace flavin in the bacterial bioluminescence reaction.[3]

The chemical properties of the two classes of compounds differ greatly in the oxidized state. The chemistry of alloxazines is much less well understood than that of flavins. This can, in part, be ascribed to the fact that theoretical calculations on alloxazines had to be based on the available three-dimensional data on flavins,[1] yielding often unsatisfactory results. Therefore, the crystalline structure of two alloxazines was elucidated in the hope of contributing to a better understanding of the physical and chemical properties of the molecule.[4] The results also provide a basis for a more in-depth comparison of the properties of the two classes of compounds.

Experimental

9-Methyl (**1**) and 1,3,8,9-tetramethyl (**2**) derivatives of alloxazine were synthesized as reported elsewhere[5]. Compound **1** was recrystallized from methanol solution with a layer of diisopropyl ether on top.

Details of the intensity data collections are summarized in Table 1. The unit cell parameters were refined against accurately measured angular settings of 38 and 30 strong, well-centered reflections for compounds **1** and **2**, respectively. All measurements were carried out at room temperature. The net intensities were corrected for Lorentz and polarization effects, but the rather small absorption effects were neglected.

Initial structural models were derived by direct methods, using the program systems SHELX[6] for **1** and MITHRIL[7] for **2**. These models were completed and refined with the SHELX program system. The oxygen atom of the water molecule in **1** and all the hydrogen atoms in both structures were located from difference electron density calculations.

In the final refinements, all non-hydrogen atoms were assumed to vibrate anisotropically, while the hydrogens were assigned isotropic temperature factors. At this stage it was noticed that some strong low-θ reflections had F_{obs} systematically lower than F_{calc}, suggesting extinction. These reflections (four for **1** and five for **2**) were excluded from last refinements, whereupon final linear *R* values of 0.051 [1840 reflections with $F/\sigma(F) > 6$] and 0.073 [1280 reflections with $F/\sigma(F) > 4$] were obtained for structures **1** and **2**, respectively. The weighted residual indexes, $R_w = \Sigma\sqrt{w} \cdot |\Delta F|/\Sigma\sqrt{w} \cdot |F_0|$ and $R_G = [\Sigma w \cdot |\Delta F|^2/\Sigma w \cdot |F_0|^2]^{1/2}$ became 0.052 and 0.060 for structure **1** and 0.074 and 0.083 for structure **2**. The weights

Table 2. Fractional atomic coordinates and equivalent isotropic/isotropic temperature factors with e.s.d.'s in parentheses.

Atom	*x/a*	*y/b*	*z/c*	U^a_{eq}/U(Å^2)
9-Methylalloxazine monohydrate				
N(1)	−0.0773(1)	0.2491(1)	0.2714(3)	0.0347(6)
C(2)	−0.0050(2)	0.1701(2)	0.3139(3)	0.0366(7)
O(2)	−0.0278(1)	0.0774(1)	0.3304(3)	0.0568(7)
N(3)	0.0983(1)	0.2029(1)	0.3353(3)	0.0360(6)
C(4)	0.1342(1)	0.3047(2)	0.3257(3)	0.0312(6)
O(4)	0.2268(1)	0.3262(1)	0.3508(3)	0.0428(5)
C(4a)	0.0523(1)	0.3867(2)	0.2840(3)	0.0275(6)
N(5)	0.0804(1)	0.4872(1)	0.2774(2)	0.0312(5)
C05a)	0.0028(2)	0.5604(2)	0.2395(3)	0.0321(6)
C(6)	0.0299(2)	0.6698(2)	0.2335(4)	0.0425(8)
C(7)	−0.0478(2)	0.7433(2)	0.1946(4)	0.0495(9)
C(8)	−0.1524(2)	0.7113(2)	0.1604(4)	0.0473(9)
C(9)	−0.1829(2)	0.6071(2)	0.1660(3)	0.0389(7)
C(91)	−0.2946(2)	0.5731(3)	0.1313(5)	0.0540(10)
C(9a)	−0.1032(2)	0.5282(2)	0.2082(3)	0.0316(6)
N(10)	−0.1308(1)	0.4238(1)	0.2182(2)	0.0321(6)
C(10a)	−0.0537(1)	0.3557(2)	0.2569(3)	0.0273(6)
O(W)	0.3008(2)	0.5604(1)	0.3937(3)	0.0499(6)
H(1)	−0.144(2)	0.233(2)	0.278(4)	0.052(7)
H(3)	0.143(2)	0.150(2)	0.384(4)	0.073(9)
H(6)	0.100(2)	0.687(2)	0.252(4)	0.050(7)
H(7)	−0.029(2)	0.816(2)	0.120(4)	0.059(8)
H(8)	−0.206(2)	0.765(2)	0.138(4)	0.055(7)
H(91A)	−0.335(3)	0.633(3)	0.088(5)	0.107(12)
H(91B)	−0.306(3)	0.519(3)	0.028(5)	0.092(12)
H(91C)	−0.319(3)	0.545(3)	0.251(5)	0.095(12)
H(W1)	0.246(3)	0.531(3)	0.367(6)	0.096(13)
H(W2)	0.349(3)	0.514(3)	0.380(5)	0.097(13)
1,3,8,9-Tetramethylalloxazine				
N(1)	0.9442(5)	0.0165(3)	1.2135(3)	0.048(1)
C(11)	0.9647(10)	0.1023(4)	1.2560(6)	0.061(2)
C(2)	1.0284(6)	−0.0442(3)	1.2968(4)	0.048(2)
O(2)	1.1236(5)	−0.0253(3)	1.4011(3)	0.071(2)
N(3)	1.0031(5)	−0.1269(3)	1.2602(3)	0.049(2)
C(31)	1.0912(10)	−0.1890(5)	1.3556(7)	0.071(3)
C(4)	0.8986(6)	−0.1543(3)	1.1424(4)	0.047(2)
O(4)	0.8828(6)	−0.2281(2)	1.1184(3)	0.073(2)
C(4a)	0.8130(6)	−0.0883(3)	1.0548(4)	0.044(2)
N(5)	0.7128(5)	−0.1099(2)	0.9418(3)	0.045(1)
C(5a)	0.6328(6)	−0.0468(3)	0.8637(4)	0.042(2)
C(6)	0.5224(7)	−0.0676(3)	0.7416(4)	0.052(2)
C(7)	0.4450(7)	−0.0046(4)	0.6642(5)	0.054(2)
C(8)	0.4662(6)	0.0797(3)	0.6993(4)	0.050(2)
C(81)	0.3761(9)	0.1456(5)	0.6034(6)	0.065(2)
C(9)	0.5711(6)	0.1026(3)	0.8200(4)	0.046(2)
C(91)	0.5955(11)	0.1903(4)	0.8664(7)	0.063(2)
C(9a)	0.6546(6)	0.0368(3)	0.9030(4)	0.040(2)
N(10)	0.7617(5)	0.0581(2)	1.0203(3)	0.043(1)
C(10a)	0.8345(6)	−0.0036(3)	1.0940(4)	0.040(2)
H(6)	0.494(6)	−0.126(3)	0.714(4)	0.05(1) contd

Table 2. (contd)

H(7)	0.379(7)	−0.012(3)	0.588(5)	0.05(2)
H(11A)	0.862(13)	0.133(6)	1.253(8)	0.16(4)
H(11B)	1.024(12)	0.103(5)	1.348(9)	0.14(3)
H(11C)	1.002(11)	0.135(5)	1.192(8)	0.11(3)
H(31A)	1.020(10)	−0.243(5)	1.359(7)	0.13(3)
H(31B)	1.098(12)	−0.160(6)	1.440(9)	0.14(4)
H(31C)	1.156(12)	−0.228(7)	1.319(9)	0.17(4)
H(81A)	0.477(9)	0.175(5)	0.552(6)	0.11(2)
H(81B)	0.328(8)	0.194(4)	0.659(6)	0.09(2)
H(81C)	0.289(15)	0.112(8)	0.557(11)	0.23(5)
H(91A)	0.650(11)	0.192(5)	0.954(8)	0.12(3)
H(91B)	0.487(15)	0.213(7)	0.870(9)	0.18(5)
H(91C)	0.607(13)	0.229(7)	0.808(9)	0.17(4)

[a] $U_{eq} = \frac{1}{3}\sum_i\sum_j a_i^* \cdot a_j^* \cdot U_{ij} \cdot \mathbf{a}_i \cdot \mathbf{a}_j$

were calculated as $w = 1/[\sigma^2(F_0) + g \cdot F_0^2]$, where $\sigma^2(F_0)$ is derived from counting statistics and where g was estimated as 0.00067 and 0.00052 for **1** and **2**, respectively.

The refinement of the structural model of 1,3,8,9-tetramethylalloxazine ended with rather high final R values, possibly deriving from the relatively poor quality of the intensity data. This in turn is a consequence of the poor scattering ability of the crystal of **2**. When it was later found that recrystallization of 9-methylalloxazine resulted in nice crystals, we therefore undertook the study of this compound also.

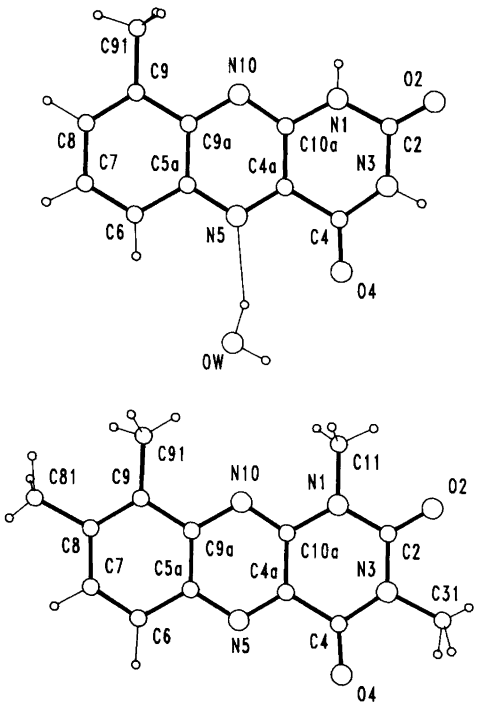

Fig. 2. Molecular structures of (a) 9-methylalloxazine monohydrate and (b) 1,3,8,9-tetramethylalloxazine, with atoms numbered as in the text.

Lists of structure factors, anisotropic thermal parameters for the non-hydrogen atoms, bond distances and angles, including the hydrogen atoms and intermolecular distances shorter than 3.5 Å (excluding the possible hydrogen bonds), have been deposited with the British Library Lending Divison. Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England, and also from the authors.

Crystallographic description of the structures

Crystal data for **1** and **2** are given in Table 1. The final atomic coordinates are given in Table 2. The atomic labelling used is shown in Fig. 2. The intramolecular bond lengths and angles, uncorrected for thermal motion, are listed in Tables 3 and 4. The bond distances and angles generally conform to expected values. The largest differences between corresponding values in the present two structures are observed around atoms N(1), N(3) and C(8), possibly due to the methyl substitution at these positions in compound **2**. All other values are in agreement within the experimental errors. Both molecules are flat; the fourteen ring atoms of the tricyclic alloxazine moieties are co-planar to within 0.068 and 0.026 Å in

Table 3. Intramolecular bond distances (Å) between the non-hydrogen atoms, with e.s.d.'s in parentheses. Comparison of the results of the present two studies of alloxazines with those of two isoalloxazines.

Distance	9-Methyl-alloxazine (**1**)	1,3,8,9-Tetramethyl-alloxazine (**2**)	10-Methyliso-alloxazine[a]	10-Methyliso-alloxazine hydrobromide dihydrate[b]
N(1)–C(2)	1.370(3)	1.376(6)	1.360(5)	1.408(7)
N(1)–C(10a)	1.377(3)	1.394(5)	1.319(5)	1.364(7)
N(1)–C(11)		1.446(8)		
C(2)–O(2)	1.207(3)	1.220(5)	1.216(5)	1.209(7)
C(2)–N(3)	1.391(3)	1.384(7)	1.408(5)	1.379(7)
N(3)–C(4)	1.363(3)	1.395(6)	1.354(5)	1.388(7)
N(3)–C(31)		1.473(8)		
C(4)–O(4)	1.221(2)	1.211(6)	1.217(5)	1.211(7)
C(4)–C(4a)	1.480(3)	1.465(6)	1.498(5)	1.489(7)
C(4a)–N(5)	1.314(3)	1.316(5)	1.295(5)	1.299(7)
C(4a)–C(10a)	1.417(3)	1.420(7)	1.466(5)	1.422(7)
N(5)–C(5a)	1.363(3)	1.365(6)	1.366(5)	1.376(7)
C(5a)–C(6)	1.416(3)	1.418(6)	1.418(5)	1.411(7)
C(5a)–C(9a)	1.422(3)	1.404(7)	1.418(5)	1.407(7)
C(6)–C(7)	1.367(4)	1.354(7)	1.368(6)	1.348(7)
C(7)–C(8)	1.410(4)	1.401(8)	1.395(6)	1.415(7)
C(8)–C(81)		1.523(8)		
C(8)–C(9)	1.367(4)	1.399(6)	1.388(6)	1.362(7)
C(9)–C(9a)	1.434(3)	1.432(6)	1.392(5)	1.419(7)
C(9)–C(91)	1.500(4)	1.486(8)		
C(9a)–N(10)	1.360(3)	1.372(5)	1.390(5)	1.386(7)
N(10)–C(10a)	1.317(3)	1.307(6)	1.369(5)	1.338(7)

[a]From Ref. 10. [b]From Ref. 11.

structures **1** and **2**, respectively. The molecular packings are, however, different.

The crystal structure of 9-methylalloxazine monohydrate is shown in Fig. 3. The planes of the alloxazine molecules are roughly perpendicular to the short *c* axis. Those molecules which are related by the symmetry operation $-x$, $-y$ $(+1)$, $-z$ $(+1)$ are stacked with an interplanar spacing of about 3.4 Å and give rise to several short (>3.5 Å) intermolecular contacts. The crystal structure is held together by hydrate-assisted, closed loops of hydrogen bonds. Every alloxazine molecule takes part in at least five hydrogen bonds. The water oxygen accepts a proton from N(3) and has short distances to three different possible acceptors: O(2), N(5) and O(4). Examination of the H···acceptor distances in these contacts (see Table 5) shows, however, that according to the proposed geometrical criterion for hydrogen bonding,[9] only the O(W)H···O(2) and O(W)H···N(5) contacts are hydrogen bonds. It seems probable that this arrangement, in which H(W1) is situated near to two potential acceptor atoms, is a packing effect. The hydrogen bond framework leads to a very short contact of 3.03 Å between two O(2) atoms and a few other distances of 3.3–3.4 Å between the water oxygen and the alloxazine molecule.

Fig. 4 shows the crystal structure of 1,3,8,9-tetramethylalloxazine. Examination of the intermolecular contact distances shows that most of the shorter approaches occur between a carbon atom in one molecule and an oxygen or nitrogen atom in another. This probably means that the crystal structure is stabilized by an electrostatistically favourable molecular packing in addition to the Van der Waals' interactions.

Table 4. Intramolecular bond angles (°) involving the non-hydrogen atoms, with e.s.d.'s in parentheses. Comparison of the results of the present two studies of alloxazines with those of two isoalloxazines.

Angle	9-Methyl-alloxazine (**1**)	1,3,8,9-Tetramethyl-alloxazine (**2**)	10-Methyliso-alloxazine[a]	10-Methyliso-alloxazine hydrobromide dihydrate[b]
C(2)–N(1)–C(10a)	124.3(2)	121.6(4)	118.0(2)	123.5(4)
C(2)–N(1)–C(11)		118.2(4)		
C(10a)–N(1)–C(11)		120.1(4)		
N(1)–C(2)–N(3)	115.7(2)	118.8(2)	120.0(3)	116.3(4)
N(1)–C(2)–O(2)	123.1(2)	120.5(5)	122.6(4)	120.4(4)
N(3)–C(2)–O(2)	121.1(2)	120.6(4)	117.4(2)	123.3(4)
C(2)–N(3)–C(4)	126.9(2)	124.7(4)	125.9(3)	126.1(4)
C(2)–N(3)–C(31)		116.3(4)		
C(4)–N(3)–C(31)		119.0(5)		
N(3)–C(4)–C(4a)	114.8(2)	115.3(4)	115.1(2)	115.0(4)
N(3)–C(4)–O(4)	122.3(2)	120.4(4)	122.5(3)	122.0(4)
C(4a)–C(4)–O(4)	122.9(2)	124.3(4)	122.5(3)	122.9(4)
C(4)–C(4a)–C(10a)	119.7(2)	120.1(4)	115.1(3)	119.4(4)
C(4)–C(4a)–N(5)	118.5(2)	118.4(4)		
N(5)–C(4a)–C(10a)	121.8(2)	121.4(4)	125.3(3)	123.6(4)
C(4a)–N(5)–C(5a)	116.8(2)	116.8(4)	117.5(2)	117.7(4)
N(5)–C(5a)–C(9a)	120.9(2)	121.4(4)	122.5(3)	121.0(4)
N(5)–C(5a)–C(6)	118.5(2)	118.5(4)	118.1(2)	119.0(4)
C(6)–C(5a)–C(9a)	120.6(2)	120.0(4)	119.3(3)	120.0(4)
C(5a)–C(6)–C(7)	118.6(2)	118.1(5)	120.9(3)	119.8(4)
C(6)–C(7)–C(8)	120.8(2)	123.4(5)	118.3(4)	120.4(4)
C(7)–C(8)–C(9)	123.0(3)	120.2(5)	123.3(4)	121.4(4)
C(7)–C(8)–C(81)		119.1(5)		
C(9)–C(8)–C(81)		120.7(5)		
C(8)–C(9)–C(9a)	117.5(2)	117.1(4)	118.3(2)	119.0(4)
C(8)–C(9)–C(91)	122.9(2)	123.5(5)		
C(9a)–C(9)–C(91)	119.6(2)	119.3(4)		
C(5a)–C(9a)–C(9)	119.5(2)	121.1(4)	119.9(3)	119.3(4)
C(9)–C(9a)–N(10)	119.1(2)	118.0(5)	122.3(3)	121.4(4)
C(5a)–C(9a)–N(10)	121.4(2)	120.8(4)	117.8(3)	119.4(4)
C(9a)–N(10)–C(10a)	115.9(2)	116.4(4)	121.8(2)	119.0(4)
C(4a)–C(10a)–N(10)	123.2(2)	123.0(4)	115.0(3)	119.2(4)
N(1)–C(10a)–N(10)	118.3(2)	117.4(4)	119.1(3)	121.3(4)
N(1)–C(10a)–C(4a)	118.5(2)	119.5(4)	125.9(3)	119.4(4)

[a]From Ref. 10. [b]From Ref. 11.

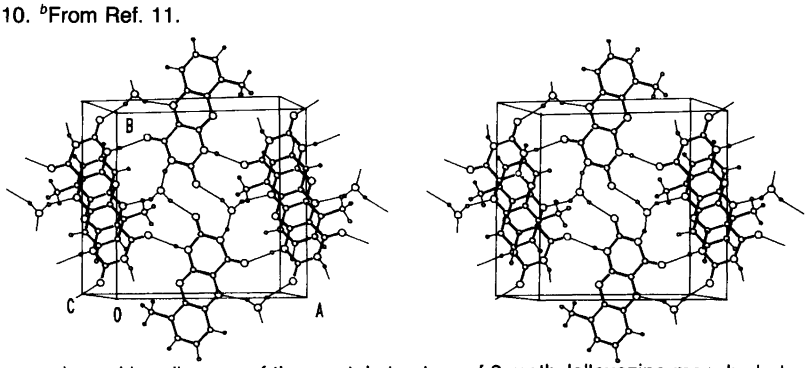

Fig. 3. Stereoscopic packing diagram of the crystal structure of 9-methylalloxazine monohydrate.

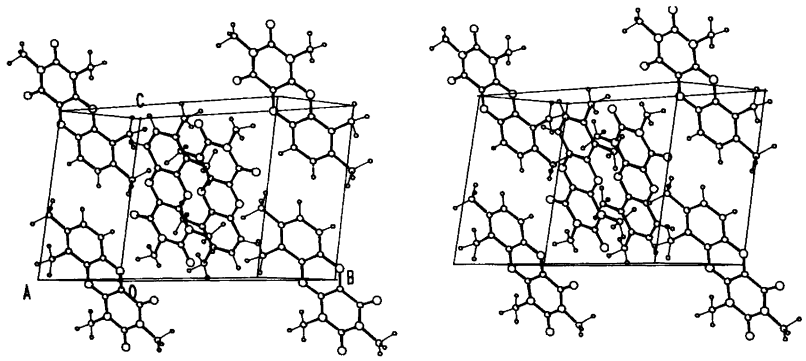

Fig. 4. Stereoscopic drawing of the crystal structure of 1,3,8,9-tetramethylalloxazine.

Comparison of the structures of alloxazine and isoalloxazine

Comparing the bond distances in alloxazine and isoalloxazine[10] (cf. Fig. 1), as calculated from crystallographic data, it is seen that the C(4a)−C(10a) and N(10)−C(10) bonds in 9-methylalloxazine (**1**) are much shorter than the corresponding bonds in 10-methylisoalloxazine.[10] On the other hand the C(10a)−N(1) and C(9)−C(9a) bond lengths in **1** are greater than those in isoalloxazine. While the increase of the latter bond reflects the methyl subtitution at C(9) in **1**, the other differences are in accord with the structural difference between the two compounds. A similar trend is observed for the bond angles involving the same atoms.

Protonation of alloxazine and isoalloxazine (cf. Fig. 1) increases the structural differences between the two classes of compounds.[12] It is interesting to note that the structure of the neutral alloxazine molecule **1** exhibits some similarities to that of the cationic isoalloxazine.[11] In fact, the similarities between these two compounds are greater than the similarities between the corresponding neutral molecules (Tables 3 and 4). This observation suggests that the chemical properties of alloxazine should resemble more those of catonic isoalloxazines than those of neutral alloxazines. Since no comparative experimental data are available, a test of the validity of this suggestion has to await future data.

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Table 5. Bond distances (Å) and angles (°) of possible hydrogen bonds in the crystal structure of 9-methylalloxazine. The e.s.d.'s are given in parentheses.

Atoms involved	Donor···Acceptor	Donor−H	H···Acceptor	Donor−H···Acceptor
N(3)−H(3)···O(W)[a]	2.777(3)	0.93(3)	1.94(3)	149(3)
N(1)−H(1)···O(4)[b]	2.820(3)	0.89(3)	1.95(3)	165(3)
O(W)−H(W2)···O(2)[c]	2.887(3)	0.87(4)	2.02(4)	172(4)
O(W)−H(W1)···N(5)[d]	3.013(3)	0.81(4)	2.22(4)	167(4)
O(W)−H(W1)···O(4)[d]	3.092(2)	0.81(4)	2.58(4)[e]	122(3)

Symmetry operations: [a] $-x+\frac{1}{2}, y-\frac{1}{2}, -z+1$; [b] $x-\frac{1}{2}, -y+\frac{1}{2}, z$; [c] $x+\frac{1}{2}, -y+\frac{1}{2}, z$; [d] x,y,z.
[e] See the text for explanation.

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