Molecular and Crystal Structure of Eupolauramine, a Novel Type of Alkaloid from *Eupomatia laurina*

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Single-crystal *X*-ray structure analysis has shown the alkaloid eupolauramine, a constituent of the bark of *Eupomatia laurina* R. Br., is 6-methoxy-5-methyl-(4*H*)-1,5-diaza-acephenanthrylen-4-one. The ring system is novel. The previously reported spectroscopic and chemical properties of eupolauramine are satisfactorily explained in terms of the molecular structure.

Crystals are monoclinic, space group $P2_1$, a = 17.74(1), b = 9.22(1), c = 7.70(1) Å, β = 98.0(2)°, Z = 4. The structure was solved by direct (tangent refinement) procedures and refined by full-matrix least-squares methods to R 0.047 for 2 106 observed reflections. The two independent molecules in the asymmetric unit are enantiomorphic, but there are no significant differences between corresponding bond lengths and angles.

THE extraction of sixteen substances from the bark of *Eupomatia laurina* has been described elsewhere.[1,2] The plant is taxonomically anomalous.[1] Two types of natural products have been isolated from it: a new group of lignans called 'eupomatenoids' and five alkaloids.[1,2] Two of the alkaloids, liriodenine and norushinsonine, were previously known. A third alkaloid, eupolauridine, has recently been shown by synthesis to be 1,6-diazafluoranthene.[3] It was also established that the remaining alkaloids, eupolauramine and hydroxyeupolauramine, are not related to eupolauridine.[3] It was therefore of interest to determine the structure of eupolauramine, especially since the structure of eupolauridine had turned out to be quite novel. Only a small quantity of eupolauramine was available.

EXPERIMENTAL

Crystal Data.—$C_{16}H_{12}N_2O_2$, M = 264.1. Monoclinic, a = 17.74(1), b = 9.22(1), c = 7.70(1) Å, β = 98.0(2)°, U = 1 247 Å^3, D_m = 1.4 (by flotation), Z = 4, D_c = 1.40 g cm^{-3}, $F(000)$ = 552. Cu-K_α radiation, $\lambda(\text{Cu-}K_{\alpha 1})$ = 1.5405, $\lambda(\text{Cu-}K_\alpha)$ = 1.5443 Å; $\mu(\text{Cu-}K_\alpha)$ = 8.2 cm^{-1}. Systematic absences $0k0$ when $k = 2n + 1$, indicating space-group $P2_1$ (C_2^2, No. 4) or $P2_1/m$ (C_{2h}^2, No. 11).

Eupolauramine, isolated as described,[2] was obtained from ethanol as golden yellow prismatic crystals (m.p.

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[2] B. F. Bowden, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1972, **25**, 2659.

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189—190 °C). All crystal data were recorded on a computer-controlled Supper equi-inclination diffractometer.[4] Unit-cell dimensions were fitted to the θ values of a number of axial reflections measured with precision at high diffraction angles. Two crystals were used to record the intensity data for the layers $h0$—$8l$ and $hk0$—6, respectively. An ω-scan procedure was used as described in ref. 4. Data were corrected for Lorentz, polarisation and absorption effects, and were merged to a common scale.[5,6] Of 2 431 independent reflections recorded, 325 were considered unobserved, having $I < 3\sigma(I)$.

Structure Determination.—E-Values were calculated.* The usual statistical criteria were consistent with the noncentrosymmetric space group $P2_1$. The structure analysis was therefore carried out on the assumption that there were two molecules (40 non-hydrogen atoms) in the asymmetric unit. The phases of three reflections were assigned to define the origin, and a fourth to select the enantiomorph. A further two phases were calculated from the Σ_1 relationship.[7] In addition, the phase of 1,1,2 was initially assigned as $\pi/4$ and then allowed to vary. Tangent refinement procedures[8] then led to R_K 0.20 for reflections having $E > 1.5$. A Fourier synthesis using the phases at this stage revealed the locations of 36 atoms. Subsequent structure-factor calculations and electron-density maps enabled all 40 atoms to be found. When all atoms were treated as carbon, R was 0.25. Only data with $d \geqslant 1$ Å were used. Positional and isotropic thermal parameters were refined by the full-matrix least-squares method with unit weights, leading to a reduction of R to 0.104. The nitrogen and oxygen atoms were identified on the basis of their thermal parameters, and bond-lengths involving these atoms were consistent with the assignments. Nineteen of the 24 hydrogen atoms were unambiguously located in electron-density difference maps. In subsequent refinement cycles, they were placed in 24 calculated positions assuming C–H 0.95 Å.

The refinement was continued to convergence with anisotropic temperature factors for the non-hydrogen atoms. All the data were now included. The large number of parameters made it necessary to refine the two molecules in the asymmetric unit in alternate least-squares cycles. Scattering factors were taken from ref. 9 for the non-hydrogen atoms, and from ref. 10 for hydrogen. Variances σ^2 of the structure factors F_0 were assigned as follows.[11] If $F_o < B$, $\sigma^2 = AB/F_o$; if $B \leqslant F_o \leqslant C$, $\sigma^2 = A$; if $F > C$, $\sigma^2 = AF_o/C$. The values of A, B, and C were 2.8, 3, and 7, respectively. The values of $w\Delta^2$ (where $w = \sigma^{-2}$) averaged over ranges of F_o and $(\sin\theta)\lambda^{-1}$ were constant except for the values in the highest F_o range and the lowest $(\sin\theta)\lambda^{-1}$ range where the four most intense reflections appeared to be affected by extinction. At convergence, the residual R was 0.047, the weighted residual $R'\{= [\Sigma w\Delta^2/\Sigma wF_o^2]^{\frac{1}{2}}\}$ was 0.067, and the error-of-fit $\Sigma w\Delta^2/(m - n)$ was 1.5. A final difference-Fourier synthesis had no significant features.

Final atomic positional parameters are listed in Table 1.

TABLE 1

(*a*) Fractional positional co-ordinates ($\times 10^4$) for non-hydrogen atoms, with estimated standard deviations in parentheses

	x	y	z
Molecule (1)			
O(1)	2 086(2)	4 075	2 427(3)
O(2)	4 815(1)	5 965(4)	1 024(5)
N(1)	2 554(2)	9 679(4)	−24(4)
N(2)	3 623(2)	5 252(4)	1 547(4)
C(1)	3 269(3)	9 902(5)	−317(6)
C(2)	3 875(2)	8 921(5)	−65(6)
C(3)	3 716(2)	7 586(4)	564(5)
C(4)	2 973(2)	7 318(4)	873(4)
C(5)	2 405(2)	8 346(4)	584(5)
C(6)	1 657(2)	7 911(4)	998(5)
C(7)	1 046(2)	8 884(5)	863(5)
C(8)	354(2)	8 437(6)	1 273(6)
C(9)	256(2)	7 015(6)	1 832(6)
C(10)	850(2)	6 059(5)	1 980(5)
C(11)	1 575(2)	6 478(5)	1 574(4)
C(12)	2 204(2)	5 442(4)	1 795(4)
C(13)	2 895(2)	5 890(4)	1 457(4)
C(14)	4 142(2)	6 220(5)	1 036(5)
C(15)	3 822(3)	3 777(5)	2 084(6)
C(16)	1 758(3)	3 057(5)	1 143(6)
Molecule (2)			
O(1)	1 728(2)	4 808(3)	7 427(3)
O(2)	873(2)	10 250(4)	5 502(5)
N(1)	3 709(2)	8 816(4)	4 985(5)
N(2)	1 287(2)	7 914(4)	6 226(4)
C(1)	3 387(3)	10 114(6)	4 620(6)
C(2)	2 642(3)	10 488(5)	4 750(6)
C(3)	2 178(3)	9 439(5)	5 308(5)
C(4)	2 499(2)	8 099(4)	5 700(5)
C(5)	3 258(2)	7 789(5)	5 559(5)
C(6)	3 515(2)	6 352(5)	6 063(5)
C(7)	4 265(2)	5 892(5)	6 019(5)
C(8)	4 501(2)	5 434(6)	6 569(6)
C(9)	3 987(3)	3 578(6)	7 168(6)
C(10)	3 251(2)	3 988(5)	7 211(5)
C(11)	2 985(2)	5 375(4)	6 658(4)
C(12)	2 198(2)	5 781(5)	6 751(4)
C(13)	1 970(2)	7 128(4)	6 273(4)
C(14)	1 379(3)	9 321(5)	5 661(6)
C(15)	574(2)	7 353(7)	6 655(6)
C(16)	1 371(3)	3 753(6)	6 211(7)

(*b*) Calculated hydrogen atom positions ($\times 10^3$). All hydrogen atoms were assigned an isotropic thermal parameter of 5 Å^2

	Molecule (1)			Molecule (2)		
	x	y	z	x	y	z
H(1)	338	1 083	−75	369	1 083	424
H(2)	437	917	−32	245	1 148	445
H(7)	111	985	−49	460	651	562
H(8)	−6	910	118	502	424	654
H(9)	−22	671	211	416	259	757
H(10)	76	510	236	292	335	761
H(115)	435	362	202	64	705	784
H(215)	373	363	325	20	809	649
H(315)	352	312	133	42	655	592
H(116)	215	257	66	90	412	566
H(216)	146	237	168	169	356	535
H(316)	144	356	24	129	288	682

Observed and calculated structure factors and atomic thermal parameters are listed in Supplementary Publication No. SUP 21606 (17 pp., 1 microfiche).†

* The direct methods programs were the DP series of F. Ahmed, S. R. Hall, and C. P. Huber, National Research Council, Ottawa, Canada, 1969.

† See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue.

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RESULTS AND DISCUSSION

The molecular dimensions are listed in Table 2. There are no significant differences between the corresponding dimensions of the two molecules in the asymmetric unit. Figure 1 illustrates the structure of molecule (1) and gives the atom labels used in the structure analysis. It applies with only two reservations to molecule (2): (i) the vibrational ellipsoids in the two molecules are slightly different, and (ii) the two molecules are enantiomorphic.

TABLE 2

	Molecule (1)	Molecule (2)
(*a*) Interatomic distances (Å)		
O(1)–C(12)	1.377(4)	1.376(5)
O(1)–C(16)	1.427(5)	1.434(6)
O(2)–C(14)	1.218(4)	1.234(5)
N(1)–C(1)	1.335(5)	1.338(6)
N(1)–C(5)	1.354(5)	1.353(5)
N(2)–C(13)	1.412(4)	1.409(5)
N(2)–C(14)	1.379(5)	1.386(6)
N(2)–C(15)	1.450(6)	1.447(6)
C(1)–C(2)	1.397(7)	1.384(7)
C(2)–C(3)	1.367(6)	1.377(7)
C(3)–C(4)	1.393(5)	1.376(6)
C(3)–C(14)	1.488(6)	1.484(7)
C(4)–C(5)	1.378(5)	1.395(5)
C(4)–C(13)	1.405(5)	1.411(5)
C(5)–C(6)	1.463(5)	1.437(6)
C(6)–C(7)	1.400(5)	1.401(5)
C(6)–C(11)	1.407(6)	1.422(5)
C(7)–C(8)	1.372(6)	1.368(7)
C(8)–C(9)	1.397(7)	1.392(7)
C(9)–C(10)	1.365(7)	1.364(6)
C(10)–C(11)	1.419(5)	1.409(6)
C(11)–C(12)	1.461(5)	1.457(5)
C(12)–C(13)	1.352(5)	1.341(6)
(*b*) Interatomic angles (°)		
C(12)–O(1)–C(16)	115.1(3)	115.5(3)
C(1)–N(1)–C(5)	115.8(4)	116.2(4)
C(13)–N(2)–C(14)	111.1(3)	110.5(3)
C(13)–N(2)–C(15)	126.1(3)	126.0(4)
C(14)–N(2)–C(15)	122.8(3)	123.5(4)
N(1)–C(1)–C(2)	127.3(4)	126.2(4)
C(1)–C(2)–C(3)	116.1(3)	117.8(4)
C(2)–C(3)–C(4)	117.8(4)	116.8(4)
C(2)–C(3)–C(14)	136.5(3)	137.4(4)
C(4)–C(3)–C(14)	105.6(3)	105.8(4)
C(3)–C(4)–C(5)	122.6(4)	122.8(4)
C(3)–C(4)–C(13)	111.0(4)	111.4(4)
C(5)–C(4)–C(13)	126.4(4)	125.8(4)
C(4)–C(5)–N(1)	120.4(3)	120.2(4)
C(4)–C(5)–C(6)	116.2(3)	116.2(4)
N(1)–C(5)–C(6)	123.4(3)	123.7(4)
C(5)–C(6)–C(7)	121.7(4)	122.6(4)
C(5)–C(6)–C(11)	117.6(3)	118.1(3)
C(7)–C(6)–C(11)	120.8(3)	119.3(3)
C(6)–C(7)–C(8)	119.9(4)	121.3(4)
C(7)–C(8)–C(9)	120.4(4)	119.7(4)
C(8)–C(9)–C(10)	120.3(4)	120.4(4)
C(9)–C(10)–C(11)	121.1(4)	121.7(4)
C(6)–C(11)–C(10)	117.5(4)	117.6(3)
C(6)–C(11)–C(12)	122.7(4)	122.3(3)
C(10)–C(11)–C(12)	119.8(4)	120.1(4)
O(1)–C(12)–C(11)	119.2(3)	119.1(3)
O(1)–C(12)–C(13)	122.3(3)	122.2(3)
C(11)–C(12)–C(13)	118.4(3)	118.5(3)
N(2)–C(13)–C(4)	106.0(3)	105.8(3)
N(2)–C(13)–C(12)	135.3(3)	135.1(4)
C(4)–C(13)–C(12)	118.7(3)	119.1(3)
O(2)–C(14)–N(2)	124.9(4)	124.4(4)
O(2)–C(14)–C(3)	128.8(4)	129.2(5)
N(2)–C(14)–C(3)	106.3(3)	106.5(4)

TABLE 3

Least-squares planes through selected atomic groupings with deviations (Å), in square brackets, of relevant atoms. Equations are of the form $lX + mY + nZ + D = 0$ where l, m, and n are direction cosines of the plane normals relative to orthogonal axes, X, Y, and Z in Å. D is the distance from the origin of axes in Å. X is along the *a* axis, Y is in the *ab* plane, and Z along c^*. Equations and deviations for molecule (1) are listed above those for molecule (2)

	l	*m*	*n*	D
Plane (1): N(2), C(3), C(4), C(13), C(14)				
	−0.0961	−0.3136	−0.9447	3.235
	−0.1504	−0.2918	−0.9446	6.860
[N(2) 0.001, C(3) 0.008, C(4) −0.008, C(13) 0.004, C(14) −0.005, O(2) −0.038, C(15) 0.011]				
[N(2) 0.003, C(3) 0.001, C(4) 0, C(13) −0.002, C(14) −0.003, O(2) −0.005, C(15) 0.041]				
Plane (2): N(1), C(1)—(5)				
	−0.1078	−0.3288	−0.9382	3.403
	−0.1437	−0.2910	−0.9459	6.837
[N(1) −0.003, C(1) 0.0, C(2) 0.004, C(3) −0.004, C(4) 0.002, C(5) 0.002]				
[N(1) 0.007, C(1) −0.001, C(2) −0.004, C(3) −0.003, C(4) 0.003, C(5) −0.008]				
Plane (3): C(4)—(6), C(11)—(13)				
	−0.1080	−0.3049	−0.9463	3.238
	−0.1358	−0.3144	−0.9350	6.947
[C(4) −0.008, C(5) 0.017, C(6) −0.011, C(11) −0.002, C(12) 0.011, C(13) −0.006, O(1) −0.030, C(16) 1.230]				
[C(4) 0.004, C(5) 0.002, C(6) 0.003, C(11) 0.005, C(12) 0.002, C(13) 0.002, O(1) 0.077, C(16) 1.168]				
Plane (4): C(6)—(11)				
	−0.1414	−0.2858	−0.9478	3.211
	−0.1239	−0.3435	−0.9309	7.002
[C(6) 0.005, C(7) −0.003, C(8) −0.001, C(9) 0.002, C(10) 0, C(11) −0.004]				
[C(6) −0.007, C(7) 0.005, C(8) 0, C(9) −0.002, C(10) 0, C(11) 0.004]				
Plane (5): N(1), N(2), C(1)—(14)				
	−0.1197	−0.3128	−0.9423	3.352
	−0.1341	−0.3149	−0.9396	6.971
[N(1) 0.035, N(2) −0.024, C(1) 0.026, C(2) 0.002, C(3) −0.023, C(4) −0.006, C(5) 0.022, C(6) 0.014, C(7) −0.042, C(8) −0.055, C(9) −0.019, C(10) 0.026, C(11) 0.038, C(12) 0.047, C(13) 0.010, C(14) −0.053, O(1) 0.021, O(2) −0.114, C(15) −0.020, C(16) 1.290]				
[N(1) 0.029, N(2) −0.005, C(1) −0.015, C(2) −0.038, C(3) −0.015, C(4) 0.023, C(5) 0.031, C(6) 0.033, C(7) 0.019, C(8) −0.029, C(9) −0.050, C(10) −0.024, C(11) 0.024, C(12) 0.029, C(13) 0.027, C(14) −0.039, O(1) −0.051, O(2) −0.076, C(15) 0.026, C(16) 1.193]				

Angles (°) between planes

	(1)–(2)	(1)–(3)	(1)–(4)	(2)–(3)	(2)–(4)	(3)–(4)
Molecule (1)	1.2	0.9	3.1	1.4	3.2	2.2
Molecule (2)	0.4	1.6	3.4	1.5	3.3	1.9

The equations of planes fitted by least-squares to selected groups of atoms are shown in Table 3. The atoms in each of the four rings are coplanar [planes (1)—(4)]. The carbonyl oxygen O(2), methyl carbon C(15), and ether oxygen O(1) lie in the planes of the rings to which they are attached [planes (1) and (3)]. However, the normals to planes (1) and (2) make angles of *ca.* 3° with that to plane (4), so that the molecular ring system as a whole is not planar. If a plane is fitted to the entire molecule with the exception of the exocyclic atoms [plane (5)], some of the atomic positions deviate significantly and systematically from it. The deviations from planarity are in the same sense as, and slightly greater than, in phenanthrene.[12] The bending of phenanthrene has been ascribed to steric repulsion between the hydrogens bonded to the carbon atoms which correspond to C(7) and N(1) in the present structure. Since eupolauramine has no hydrogen on N(1), the bending of this molecule is presumably due to strains caused by the fusion of a five-membered with two six-membered rings. The same ring strains are probably also responsible for the significant distortions of the bond angles in the pyridine ring and in the central ring from their expected values of 120° (Table 2).

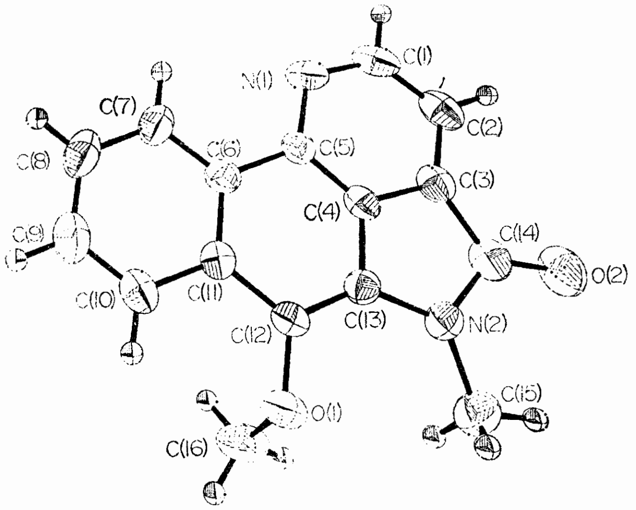

FIGURE 1 Molecular structure of eupolauramine [molecule (1)] showing vibrational ellipsoids (50% probability level)

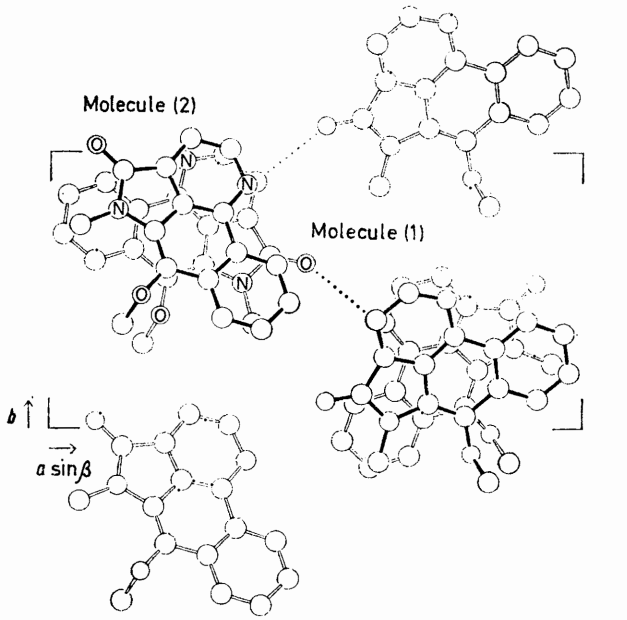

FIGURE 2 Projection of crystal structure. The z axis is perpendicular to the plane of the paper and points towards the observer

The packing of the molecules in the crystal is shown in Figure 2. The molecules are stacked in columns parallel to c. Molecules of the two crystallographically independent types, (1) and (2), alternate along each column. There are only two types of intermolecular contacts <3.30 Å: * O(2) $\cdots$ C(2^{I}) and C(2) $\cdots$ O(2^{II}) [all molecule (1)] 3.16 Å; O(1) (mol. 2) to C(16^{III}) (mol. 1) and C(16) (mol. 1) to O(1^{IV}) (mol. 2) 3.28 Å.

The first type of contact is between O(2) and C(2) atoms of equivalent molecules in columns related by the 2_1 axis. The second type is between the O(1) and C(16) atoms of the methoxy-groups of adjacent, non-equivalent molecules in the same column.

An interesting feature of the ring skeleton is the large range of carbon–carbon bond-lengths, especially in the central ring (Table 2). Bonds C(5)–C(6) and C(11)–C(12) have lengths close to the value (1.48 Å) expected for single C(sp^2)–C(sp^2) bonds,[13] while C(12)–C(13) is only slightly longer than a classical C(sp^2)=C(sp^2) double bond (1.33 Å).[13] The remaining three bond-lengths in the central ring correspond approximately to aromatic C–C bonds, as do those in the two terminal six-membered rings. The relationship between the various bond-lengths [including the two which involve N(1)] in eupolauramine is almost the same as in phenanthrene.[12]

Allowing for the fact that molecules (1) and (2) are mirror images of each other, the methoxy-groups have the same orientation with respect to the rest of the molecules. The dihedral angles about the C(12)–O(1) bond in C(11)–C(12)–O(1)–C(16) are equal (81.9, 82.3°). The carbon–oxygen distances exhibit a dependence on the state of hybridisation of the carbon atoms: by analogy with the lengths of C(sp^2)–C(sp^3) and C(sp^3)–C(sp^3) bonds,[13] C(12)–O(1) [1.377(4) Å] corresponds to C(sp^2)–O and O(1)–C(16) [1.427(5) Å] to O–C(sp^3).

The structure analysis confirms that eupolauramine (I) has a nucleus which is different from those of lioridenine (II), norushinsunine (III), and eupolauridine (IV). In the light of the structural results, the biogenesis of eupolauramine is obscure. The alkaloid may possibly originate from the co-occurring liriodenine (II).[14]

On the assumption that eupolauramine and eupolauridine (IV) were structurally related, Bowden *et al.*[3] suggested six possible structures for eupolauramine, but all were rejected for a variety of spectroscopic and chemical reasons. However, most of the structural features deduced from the spectroscopic measurements [3] are present in the molecule: a $C_{14}N_2$ skeleton with two methyl groups, a carbonyl group, two tertiary nitrogens, and an extended aromatic chromophore. The assignment of the ^{1}H n.m.r. doublets at δ 9.0 and 7.75 to two protons which are α and β, respectively, to a nitrogen

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* Superscripts refer to atoms with the following coordinates with respect to Table 1: I $1 - x, -\frac{1}{2} + y, -z$; II $1 - x, \frac{1}{2} + y, -z$; III $x, y, 1 + z$; IV $x, y, -1 + z$.

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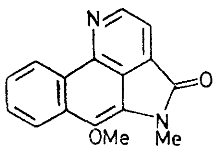
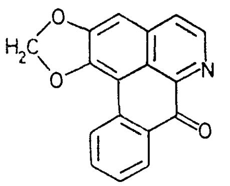
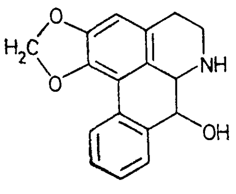


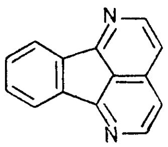
(I)



(II)



(III)



(IV)

atom is consistent with the structure. The remaining two one-proton doublets (δ 8.86 and 8.01) and the two-proton doublet (δ 7.62) are then correctly identified as originating from an AA′BB′ system forming part of an *o*-disubstituted benzene ring. However, the *o*-disubstitution is markedly less symmetrical than in eupolauridine, and the large de-shielding of the proton on C(7) is due to N(1) in the *peri*-position rather than to an ethereal or carbonyl oxygen atom.

Attempts to solve the eupolauramine structure extended over several years, and we thank Drs. J. Keith Fawcett, David A. Langs, and Ivan F. Taylor, jun., for their participation in this work.

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