4-Methoxy-11-oxo-5-azabenzo[b]fluorene N-Oxide and its Free Base

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Abstract

The crystal structures of 4-methoxy-11-oxo-5-azabenzo-[b]fluorene N-oxide, $C_{17}H_{11}NO_3$, (1), and its free base, 4-methoxy-11-oxo-5-azabenzo[b]fluorene, $C_{17}H_{11}NO_2$, (2), have been determined. The 2-phenylquinoline skeleton in both compounds has been stiffened by linking the 3 and 6' positions with the rigid >C=O group. The presence of the N-oxide group in the 'bay region' of molecule (1) causes steric stress which is relieved by significant changes in the geometry of the molecule. Despite the planarity of the molecules, there is no other evidence for conjugation across the five-membered ring.

Comment

In the course of our studies on the mechanism of the surprisingly easy stepwise deoxygenation of orellanine (3,3',4,4'-tetrahydroxy-2,2'-bipyridine-1,1'-dioxide) (Antkowiak & Gessner, 1979), we have shown that 2-phenylpyridine derivatives could serve as model compounds for this reaction (Antkowiak & Gessner, 1984; Kubicki, Borowiak, Antkowiak & Antkowiak, 1990). Recently, we reported the crystal structures of some compounds in which the 2-phenylpyridine skeleton was bridged at the 3 and 6' positions (C4a and C5a in Figs. 1 and 2) by the —CH₂—CH₂— group in order to limit the conformational freedom around the central C11a—C11b bond (Kubicki, Borowiak, Chruścicki & Antkowiak, 1993; Kubicki, Borowiak, Antkowiak, Antkowiak & Chruścicki, 1994). We have also shown that the presence of an additional phenyl ring fused at the 5 and 6 positions (at C6a and C10a) has no significant effect on the 'bay region' (O1, C1, C11b, C11a and N11) (Kubicki, Borowiak & Antkowiak, 1995). We have also performed X-ray crystallographic studies of molecules with more restricted conformations, *i.e.* containing the rigid >C=O group instead of

the flexible ethylene bridge. In this paper, we present the results for two compounds: 4-methoxy-11-oxo-5-azabenzo[b]fluorene N-oxide, (1), and its free base, 4-methoxy-11-oxo-5-azabenzo[b]fluorene, (2). The presence of a 4-azafluorene skeleton, which occurs in ony-chine alkaloids from Brazilian and African *Annonaceae* species (Koyama, Okatani, Tagahara & Irie, 1989; Bou-Abdallah, Jossang, Tadic & Cave, 1989), makes the intramolecular interactions in these compounds of interest.

(1)   (2)
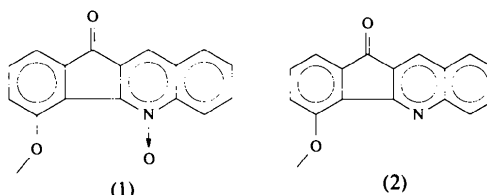
Introduction of the N-oxide function into the bay region induces significant steric stress. It is relieved mainly through a change of geometry at the bay region (*e.g.* an increase of all exocyclic bond angles within this region), but it also changes the overall shape of the molecule. While molecule (2) is almost perfectly planar, there is significant folding in molecule (1). For (2), all deviations from the least-squares plane through the 17 skeleton atoms are within 5σ, both O atoms are perfectly coplanar with this plane [with deviations of 0.025 (7) Å for O1 and 0.005 (7) Å for O5] and the dihedral angle between the terminal ring planes, B and C, is 1.3 (3)°. For (1), the folding is apparent in every parameter: the deviations from the plane are within 40σ, the O atoms lie significantly out of this plane [by 0.208 (3), −0.196 (3) and −0.177 (3) Å for O1, O5 and O11, respectively] and the dihedral angle between the ring planes B and C is 3.9 (1)°.

The changes in the geometry at the bay region of (1) result in a shorter non-bonding H2···C12 contact than in (2), while the O1···N11 distance is longer than in (2). This conformational change can be also seen by comparing the angles O1—C1—C2, O1—C1—C11b and C1—O1—C12 (Table 3). Whereas the main factor determining the geometry of the bay region in (2) is a weak H···H₃C repulsion, the O1···O11 interaction is crucial in (1). However, the O1···O11 distance of 2.626 (3) Å is still much shorter than the sum of the van der Waals radii (Bondi, 1964), and is also *ca* 0.1 Å shorter than the corresponding value in compounds with a flexible ethylene bridge. Despite the planarity of the five-membered ring, the bond lengths and angles indicate only slight, if any, conjugation across this ring. The weighted mean values of the C11a—C11b, C4a—C5 and C5—C5a bond lengths, 1.47 (2) Å for (1) and 1.477 (3) Å for (2), agree with the typical value of 1.478 Å for a non-conjugated C_{sp^2}—C_{sp^2} single bond (Allen, Kennard, Watson, Bramer, Orpen & Taylor, 1987). Such lack of conjugation has been observed for

other fluorene derivatives, but is in contrast to that found for the fluorenyl anion (Zerger, Rhine & Stucky, 1974) and 9-diazafluorenone (Tulip, Corfield & Ibers, 1987, and the discussion therein).

The fusion of the five-membered ring D causes a decrease in the angles adjacent to the points of fusion, in agreement with the findings of Allen (1981). The N—O bond length in (1), 1.284 (2) Å, is close to the value of 1.2806 (4) Å found for pyridine N-oxide (Sørensen, Mahler & Rastrup-Andersen, 1974) and is typical for an N—O bond uninvolved in hydrogen bonding.

The packing of both compounds are similar and involve centrosymmetric pairs of the molecules extending into columns along [001]. The distances between the planes of the molecules [about 4.1 Å for (1) and 3.7 Å for (2)] are too long to allow significant π-stacking interactions. Similar crystal packing has been observed in some other oxofluorene derivatives, e.g. in 9-oxofluorene-4-carboxylic acid (Kennard, Smith & Katekar, 1981, and references therein).

Experimental

The preparation of both compounds has been described elsewhere (Antkowiak, Antkowiak & Czerwiński, 1990). Crystals of (1) were obtained by slow evaporation of a CHCl₃–benzene mixture, while crystals of (2) were obtained (with difficulty) from toluene.
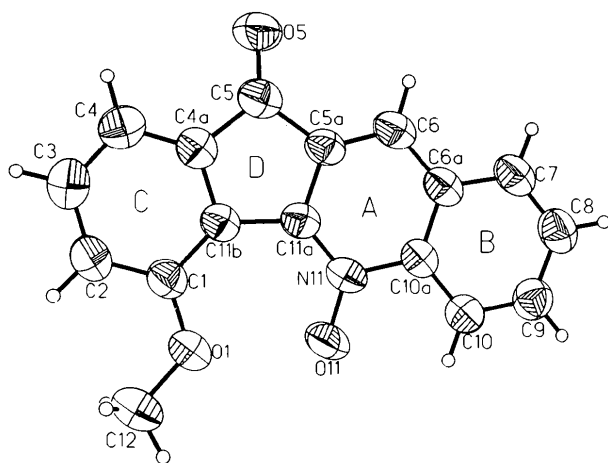

Fig. 1. Displacement ellipsoid representation of (1) with the labelling scheme. The ellipsoids are drawn at the 50% probability level for non-H atoms; H atoms are drawn as spheres with arbitrary radii.
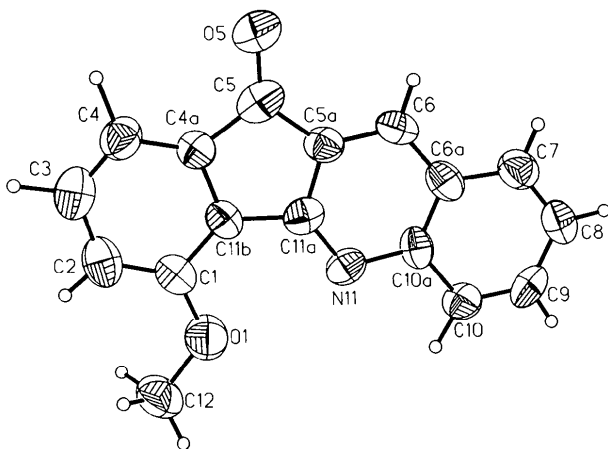

Fig. 2. Displacement ellipsoid representation of (2) with the labelling scheme. The ellipsoids are drawn at the 50% probability level for non-H atoms; H atoms are drawn as spheres with arbitrary radii.

Compound (1)

Crystal data

$C_{17}H_{11}NO_3$	Cu $K\alpha$ radiation
$M_r = 277.27$	$\lambda = 1.54178$ Å
Orthorhombic	Cell parameters from 15
$Pbca$	reflections
$a = 21.023 (1)$ Å	$\theta = 18.06–47.15°$
$b = 14.907 (1)$ Å	$\mu = 0.815$ mm^{-1}
$c = 8.2059 (7)$ Å	$T = 293 (2)$ K
$V = 2571.6 (3)$ Å^3	Prism
$Z = 8$	$0.35 \times 0.20 \times 0.18$ mm
$D_x = 1.432$ Mg m^{-3}	Red

Data collection

Syntex $P2_1$ diffractometer	$\theta_{max} = 57.28°$
$\omega/2\theta$ scans	$h = 0 \rightarrow 22$
Absorption correction:	$k = 0 \rightarrow 16$
none	$l = 0 \rightarrow 8$
1204 measured reflections	2 standard reflections
1204 independent reflections	monitored every 100
1199 observed reflections	reflections
$[I > 2\sigma(I)]$	intensity decay: 2.4%

Refinement

Refinement on F^2	$\Delta\rho_{max} = 0.153$ e Å^{-3}
$R[F^2 > 2\sigma(F^2)] = 0.0380$	$\Delta\rho_{min} = -0.109$ e Å^{-3}
$wR(F^2) = 0.0825$	Extinction correction:
$S = 1.087$	$F_c^* = kF_c[1 + (0.001$
1200 reflections	$\times F_c^2\lambda^3/\sin2\theta)]^{-1/4}$
191 parameters	Extinction coefficient:
H-atom parameters not	0.0022 (3)
refined	Atomic scattering factors
$w = 1/[\sigma^2(F_o^2) + (0.0276P)^2$	from *International Tables*
$+ 1.5593P]$	*for Crystallography* (1992,
where $P = (F_o^2 + 2F_c^2)/3$	Vol. C, Tables 4.2.6.8 and
	6.1.1.4)

Compound (2)

Crystal data

$C_{17}H_{11}NO_2$	Cu $K\alpha$ radiation
$M_r = 261.27$	$\lambda = 1.54178$ Å
Monoclinic	Cell parameters from 15
$P2_1/n$	reflections
$a = 7.470 (1)$ Å	$\theta = 13.31–25.73°$
$b = 20.033 (2)$ Å	$\mu = 0.744$ mm^{-1}
$c = 8.970 (2)$ Å	$T = 293 (2)$ K
$\beta = 111.91 (1)°$	Thin prism

$V = 1245.4$ (4) Å^3
$Z = 4$
$D_x = 1.393$ Mg m^{-3}

$0.20 \times 0.08 \times 0.05$ mm
Pale yellow

Data collection

Syntex $P2_1$ diffractometer
$\omega/2\theta$ scans
Absorption correction:
  refined from ΔF
  (*DIFABS*; Walker & Stuart, 1983)
1203 measured reflections
1203 independent reflections
743 observed reflections
  $[I > 2\sigma(I)]$

$\theta_{max} = 57.33°$
$h = 0 \rightarrow 8$
$k = 0 \rightarrow 21$
$l = -9 \rightarrow 8$
2 standard reflections monitored every 100 reflections
intensity decay: 3%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0771$
$wR(F^2) = 0.1561$
$S = 2.423$
1195 reflections
182 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.0300P)^2]$
  where $P = (F_o^2 + 2F_c^2)/3$

$\Delta\rho_{max} = 0.216$ e Å^{-3}
$\Delta\rho_{min} = -0.210$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for (1)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
C1	0.57903 (13)	0.6377 (2)	0.2845 (3)	0.0560 (7)
O1	0.61256 (10)	0.56501 (12)	0.2382 (3)	0.0880 (7)
C12	0.5903 (2)	0.4795 (2)	0.2729 (5)	0.117 (2)
C2	0.52269 (14)	0.6315 (2)	0.3742 (3)	0.0654 (8)
C3	0.49124 (14)	0.7066 (2)	0.4292 (4)	0.0684 (8)
C4	0.51424 (14)	0.7914 (2)	0.3971 (3)	0.0635 (8)
C4a	0.56918 (13)	0.7980 (2)	0.3056 (3)	0.0547 (7)
C5	0.60084 (13)	0.8816 (2)	0.2526 (4)	0.0595 (7)
O5	0.58187 (9)	0.95806 (12)	0.2721 (3)	0.0811 (7)
C5a	0.65757 (12)	0.8533 (2)	0.1595 (3)	0.0515 (7)
C6	0.70319 (13)	0.9033 (2)	0.0868 (3)	0.0594 (8)
C6a	0.75146 (14)	0.8585 (2)	−0.0008 (3)	0.0542 (7)
C7	0.80213 (14)	0.9031 (2)	−0.0782 (4)	0.0675 (8)
C8	0.84722 (14)	0.8565 (2)	−0.1630 (4)	0.0698 (8)
C9	0.84325 (13)	0.7635 (2)	−0.1757 (4)	0.0643 (8)
C10	0.79527 (13)	0.7174 (2)	−0.1017 (3)	0.0575 (7)
C10a	0.74956 (12)	0.7642 (2)	−0.0137 (3)	0.0505 (7)
N11	0.69994 (10)	0.71444 (12)	0.0630 (3)	0.0532 (6)
O11	0.69883 (10)	0.62939 (11)	0.0385 (3)	0.0850 (7)
C11a	0.65651 (11)	0.7581 (2)	0.1522 (3)	0.0478 (7)
C11b	0.60206 (11)	0.72315 (14)	0.2462 (3)	0.0490 (6)

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for (2)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
C1	0.9814 (9)	0.3958 (4)	0.2138 (8)	0.057 (2)
O1	1.0062 (7)	0.4402 (2)	0.3369 (6)	0.076 (2)
C12	1.1103 (10)	0.4170 (4)	0.5003 (8)	0.079 (2)
C2	1.0595 (10)	0.3318 (4)	0.2325 (9)	0.070 (2)
C3	1.0271 (10)	0.2911 (4)	0.0975 (10)	0.069 (2)
C4	0.9145 (10)	0.3122 (3)	−0.0512 (9)	0.066 (2)
C4a	0.8405 (9)	0.3759 (3)	−0.0743 (8)	0.049 (2)
C5	0.7155 (11)	0.4131 (4)	−0.2189 (9)	0.070 (2)
O5	0.6556 (8)	0.3896 (3)	−0.3592 (6)	0.093 (2)
C5a	0.6766 (10)	0.4769 (3)	−0.1690 (7)	0.051 (2)
C6	0.5691 (9)	0.5310 (3)	−0.2535 (8)	0.057 (2)
C6a	0.5550 (9)	0.5882 (3)	−0.1709 (8)	0.054 (2)
C7	0.4523 (9)	0.6466 (4)	−0.2457 (9)	0.065 (2)
C8	0.4469 (10)	0.7012 (4)	−0.1576 (9)	0.067 (2)
C9	0.5508 (9)	0.7004 (3)	0.0096 (9)	0.064 (2)
C10	0.6480 (10)	0.6463 (3)	0.0877 (8)	0.054 (2)
C10a	0.6593 (9)	0.5891 (3)	−0.0027 (8)	0.049 (2)
N11	0.7643 (8)	0.5348 (3)	0.0865 (6)	0.053 (2)
C11a	0.7694 (8)	0.4832 (3)	0.0004 (7)	0.049 (2)
C11b	0.8725 (9)	0.4194 (3)	0.0603 (8)	0.048 (2)

Table 3. *Selected geometric parameters (Å, °) for (1) and (2)*

	(1)	(2)
C1—O1	1.348 (3)	1.374 (8)
C1—C2	1.397 (4)	1.392 (9)
C1—C11b	1.398 (3)	1.394 (8)
O1—C12	1.387 (3)	1.456 (7)
C2—C3	1.377 (4)	1.404 (9)
C3—C4	1.378 (4)	1.353 (9)
C4—C4a	1.381 (4)	1.376 (8)
C4a—C11b	1.399 (3)	1.434 (8)
C4a—C5	1.479 (4)	1.484 (8)
C5—O5	1.218 (3)	1.260 (7)
C5—C5a	1.478 (4)	1.419 (9)
C5a—C6	1.354 (3)	1.393 (8)
C5a—C11a	1.421 (3)	1.421 (8)
C6—C6a	1.412 (4)	1.390 (8)
C6a—C7	1.407 (4)	1.423 (8)
C6a—C10a	1.409 (3)	1.416 (8)
C7—C8	1.366 (4)	1.360 (9)
C8—C9	1.394 (4)	1.408 (8)
C9—C10	1.364 (3)	1.347 (8)
C10—C10a	1.390 (3)	1.424 (8)
C10a—N11	1.427 (3)	1.404 (7)
N11—C11a	1.339 (3)	1.300 (7)
N11—O11	1.284 (2)	–
C11a—C11b	1.475 (3)	1.485 (8)
O1—C1—C2	122.6 (2)	125.0 (6)
O1—C1—C11b	119.2 (2)	115.4 (7)
C2—C1—C11b	118.2 (2)	119.6 (7)
C1—O1—C12	120.3 (2)	117.6 (6)
C1—C2—C3	121.7 (3)	120.1 (7)
C2—C3—C4	121.0 (3)	120.8 (7)
C3—C4—C4a	117.5 (3)	120.4 (7)
C4—C4a—C11b	123.1 (2)	120.3 (6)
C4—C4a—C5	126.6 (2)	133.1 (6)
C5—C4a—C11b	110.3 (2)	106.5 (6)
O5—C5—C5a	126.9 (3)	127.8 (7)
O5—C5—C4a	127.1 (3)	124.0 (7)
C4a—C5—C5a	105.9 (2)	108.2 (6)
C5—C5a—C6	129.9 (2)	132.3 (6)
C5—C5a—C11a	107.2 (2)	110.0 (6)
C6—C5a—C11a	122.9 (3)	117.7 (6)
C5a—C6—C6a	118.2 (2)	119.6 (6)
C7—C6a—C10a	117.3 (3)	118.5 (6)
C6—C6a—C7	123.3 (2)	124.2 (6)
C6—C6a—C10a	119.3 (2)	117.2 (6)
C6a—C7—C8	121.0 (3)	121.1 (7)
C7—C8—C9	120.2 (3)	119.1 (7)
C8—C9—C10	120.9 (3)	122.6 (7)
C9—C10—C10a	119.3 (2)	119.1 (6)
C10—C10a—C6a	121.4 (2)	119.4 (6)
C10—C10a—N11	118.2 (2)	116.0 (6)
C6a—C10a—N11	120.4 (2)	124.4 (6)
O11—N11—C11a	123.6 (2)	–
O11—N11—C10a	117.3 (2)	–
C10a—N11—C11a	119.1 (2)	114.3 (5)
C5a—C11a—N11	119.9 (2)	126.5 (6)
N11—C11a—C11b	130.0 (2)	126.6 (6)
C5a—C11a—C11b	110.0 (2)	106.9 (6)
C1—C11b—C4a	118.4 (2)	118.6 (6)
C1—C11b—C11a	135.1 (2)	132.9 (7)
C4a—C11b—C11a	106.5 (2)	108.4 (5)

The poor quality of the crystals of (2) and their weak diffraction power are probably responsible for the relatively high value for R. In this case, DIFABS (Walker & Stuart, 1983) was used for an absorption correction as the appropriate number of strong reflections with useful setting angles was not found.

For both compounds, data collection: P2₁ software; cell refinement: P2₁ software; data reduction: PRADIR (Jaskólski, 1990); program(s) used to solve structures: SHELXS86 (Sheldrick, 1990); program(s) used to refine structures: SHELXL93 (Sheldrick, 1993); molecular graphics: Stereochemical Workstation (Siemens, 1989); software used to prepare material for publication: SHELXL93.

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A Baccatin III Derivative

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Abstract

The title compound, 3,4,6,8,11-pentahydroxy-4-demethyl-1-triethylsiloxy-5,4-epoxymethanotaxen-12-one ($C_{26}H_{44}O_8Si$), has been prepared in the search for new semi-synthetic analogues of taxol. It has been obtained from 2-debenzoyl-4,10-bisdeacetyl-7-triethylsilyl-baccatin III when treated in an alkaline or acidic medium. The structure was established as part of a contribution to the knowledge of structure–activity relationships. An intramolecular hydrogen bond is established between the hydroxyl groups HO13 and HO4. In addition, a hydrogen-bond network engaging all the hydroxyl groups of the molecule links the different molecules in the crystal.

Comment

Taxol paclitaxel, a diterpene isolated in only low yield from the bark of several species of the Taxus genus (Wani, Taylor, Wall, Coggon & McPhail, 1971) and taxotere, a semi-synthetic analogue, are two of the most promising new drugs studied in the field of cancer chemotherapy (Guénard, Guéritte-Voegelein & Potier, 1993; Rose, 1992; Horwitz, 1992; Therre, 1993). They act by a unique mechanism: both promoting the assembly of tubulin into microtubules and stabilizing the microtubule assembly against depolymerization. The knowledge of the three-dimensional structure of either active or inactive compounds in this series is important in order to establish structure–activity relationships. The title compound, (1), has been obtained by rearrangement of 2-debenzoyl-4,10-bisdeacetyl-7-triethylsilyl-baccatin III (2) in an alkaline or acidic medium (Wahl, Guéritte-Voegelein, Guénard, Le Goff & Potier, 1992; Farina & Huang, 1992), 10-deacetyl-baccatin III being a natural precursor of taxol isolated from yew leaves (Chauvière, Guénard, Picot, Senilh & Potier, 1981). After introduction of the taxotere-O13-side-chain in compound (1), the product thus obtained shows no inhibition of the rate of diassembly ($IC_{50} = 0$) of tubulin.