Published in final edited form as:
J Chem Crystallogr. 2011 November ; 41(11): 1712–1716. doi:10.1007/s10870-011-0162-z.

Synthesis and Crystal Structure of the Azoxydichinyl Helicene, Pyrido[3,2-*f*]quinolino[6,5-*c*]cinnoline 5-Oxide Monohydrate

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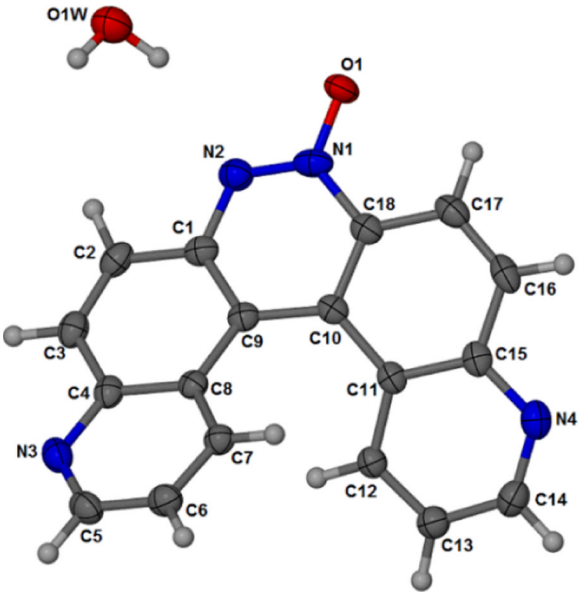
Abstract

The helicene, pyrido[3,2-*f*]quinolino[6,5-*c*]cinnoline 5-oxide, was prepared by treatment of 6-hydroxylaminoquinoline with xanthine oxidase or treatment of 6-nitroquinoline with glucose in 30% NaOH and the product characterized using NMR, high resolution mass spectrometry, and X-ray crystallography. The hydrogens on carbons 7 and 12 of the terminal aromatic rings are separated by 2.495 Å creating an angle of 25.0° between the planes of the two quinoline ring systems. In the crystal, water molecules serve to link the helicenes into a one dimensional chain structure forming a hydrogen bonded bridge between N2 of one molecule and N4 of another. The molecule ($C_{18}H_{10}N_4O•H_2O$) crystallized in the monoclinic $P2_1/n$ space group. Unit cell parameters for pyrido[3,2-*f*]quinolino[6,5-*c*]cinnoline 5-oxide monohydrate: a = 7.0829(12), b = 18.559(3), c = 11.0985(19) Å, β = 107.736(2)°, and Z = 4.



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Supplementary material X-ray crystallographic data reported in this paper is deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 819338. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK.

Keywords

Crystal structure; helicene; azoxy; pyrido[3,2-*f*]quinolino[6,5-*c*]cinnoline 5-oxide

Introduction

We have a longstanding interest in the enzymatic bioactivation of nitrogen-containing aromatic molecules.[1–4] During the course of recent studies on the enzymatic metabolism of 6-nit roquinoline, we observed formation of an unexpected product when 6-hydroxylaminoquinoline (**1**, Scheme 1) was treated with xanthine oxidase or when 6-nitroquinoline (**2**) was treated with NADPH:cytochrome P450 reductase and NADPH under anaerobic conditions. Characterization of the molecule by NMR, high resolution mass spectrometry, and X-ray crystallography revealed this product to be the helicene, pyrido[3,2-*f*]quinolino[6,5-*c*]cinnoline 5-oxide (**3**). This structure was first proposed in 1948 for the so-called azoxydichinyl product arising from the reaction of 6-nitroquinoline with sodium methoxide,[5,6] but subsequent studies provided evidence that the product of this reaction was actually **4**.[7,8] However, as part of his work, Farrar revised an original structure assignment by Galbraith et al.,[9] suggesting that **3** was produced in good yield by a different reaction involving reduction of 6-nitroquinoline in a solution of alkaline glucose, [7] but the structure of the product generated in this reaction has not been characterized by modern spectroscopic or crystallographic methods. We carried out the alkaline glucose reduction of 6-nitroquinoline by the method of Galbraith[9] and Farrar[7] and showed that the product of this reaction is, in fact, compound **3**, identical to the material obtained from our enzymatic reactions. To the best of our knowledge, the work described here provides the first modern characterization of the azoxydichinyl helicene (**3**). Our work further shows that the 1951 method of Galbraith,[9] as suggested by Farrar,[7] represents a remarkably simple synthesis of a structurally interesting helicene in one step from commercially available starting materials.

Experimental

The compound, 6-hydroxylaminoquinoline (100 mg, 0.625 mmol), was dissolved in DMF (1 mL) and sprayed into warm water (300 mL) while stirring vigorously. To this solution, warm sodium phosphate buffer (100 mL of pH 7.4, 500 mM) was added with stirring. To this mixture, an aliquot of xanthine oxidase (100 μL of 0.005 U/mL) was added every 12 h over the course of 3 d. The mixture was then extracted with ethyl acetate (3 × 100 mL), the organic extracts combined and extracted with brine (15 mL) and the organic layer then dried over magnesium sulfate. The ethyl acetate was removed by rotary evaporation and the products isolated by flash column chromatography on silica gel eluted with ethyl acetate and methanol. Compound **3** was obtained as a yellow powder (2 mg, R_f = 0.1; 4% MeOH:EtOAc) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (d, J = 4.5 Hz 1H), 9.05 (m, 2H), 8.87 (d, J = 9.0 Hz, 1H), 8.67 (d, J = 9.0 Hz, 1H), 8.43 (dd, J = 9.0 Hz & J = 9.0 Hz, 2H), 8.23 (d, J = 9.0 Hz, 1H), 7.46 (dd, J = 9.0 Hz, J = 4.5 Hz, 1H), 7.41 (dd, J = 9.0 Hz, J = 4.5 Hz, 1H). ^{13}C-NMR (500 MHz, $CDCl_3$) δ 153.34, 151.47, 149.70, 148.53, 144.07, 137.08, 136.01, 134.79, 134.27, 133.40, 128.00, 127.44, 123.52, 123.34, 121.74, 120.56, 120.46, 114.21; HRMS (ESI, $M+H^+$) *m*/*z* calcd for $C_{18}H_{10}N_4O$ 299.0933, found 299.0934. Material prepared by the method of Galbraith et al.[9] and isolated by column chromatography as described above was identical in all regards to the material **3** produced in our enzymatic reaction described above.

Crystallography

Crystals of the monohydrate **3a** were obtained by dissolving **3** in a minimum amount of warm methanol, followed by slow evaporation over 3 d in a 2 mL glass vial. Data was collected on a Bruker APEX II system at 173 K. The methanol used in crystallization was not dried. Presumably adventitious water present in the methanol crystallized with compound **3** to yield the monohydrate **3a** in the crystals. Crystal structures were solved and refined using the SHELX programs[10] with the aid of X-Seed.[11] Conditions for crystal structure data collection and structure refinement are given in Table 1. Hydrogen atoms on the water were located in a difference map and included in the model but not refined. All other hydrogen atoms were placed at calculated positions and included using a riding model. A residual electron density peak of 1.05 e remains 1.1 Å from N2, but not in a reasonable position for a hydrogen atom. It may represent some minor whole body disorder. It persisted through two additional data sets collected with different crystals.

Results and discussion

The monohydrate form of the helicene **3a** was crystallized in the monoclinic space group $P2_1/n$ and the crystallographic data are given in Table 1. The crystal structure of **3a** is shown in Figure 1. Atomic coordinates and equivalent isotopic displacement parameters for non hydrogen atoms of compound **3a** is given in Table 2. Bond distances, bond angles, and hydrogen bond lengths are given in Tables 3, 4, and 5 respectively. The terminal aromatic rings in the wings of **3a** are offset in a manner typical of helicenes.[12,13] The hydrogens on carbons 7 and 12 of the terminal aromatic rings are separated by 2.495 Å creating an angle of 25.0° between the least squares planes of the two quinoline ring systems (Figs. 2 and 3). Compound **3a** displays a pattern of alternating short and long carbon-carbon bonds analogous to 4,11-diazo[5]helicene (**5**),[12] perhaps induced by the strain inherent in the helical molecular geometry.[12] Thermal parameters are consistent with the assigned locations of the quinoline nitrogens. The asymmetric crystal structure of **3a** possesses a pseudo two-fold axis that bisects the azoxy bond between N_1 and N_2. Molecules of **3a** pack as anti-parallel pairs driven by stacking between the external aromatic rings to yield racemic columns (Fig. 2 and 3). The arrangement is analogous to the crystal structure solved previously for **5**.[12] In the crystal, water molecules serve to link the glide-related molecules through N2 and N4i giving one-dimensional chains which extend along the c axis, forming a hydrogen bonded bridge between N2 of one molecule and N4 of another.

Acknowledgments

We thank National Institutes of Health (CA 100757) for partial support of this work.

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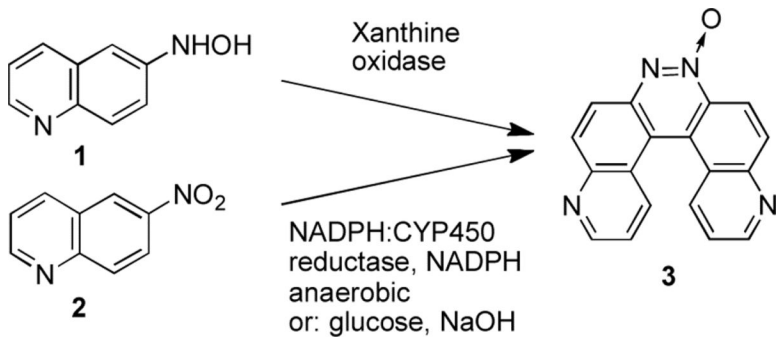

Scheme 1.
Synthesis of compounds **3**.

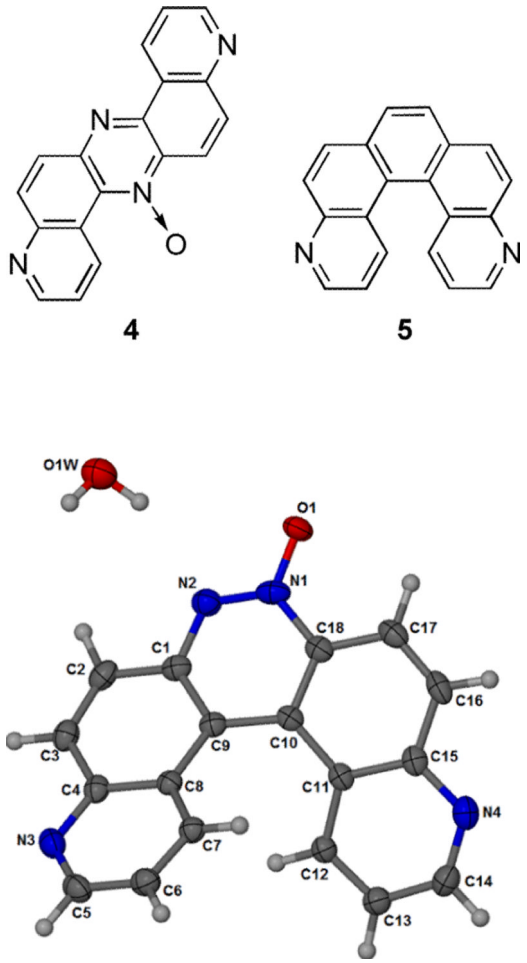

Figure 1.
Atom numbering scheme and thermal ellipsoid for **3a** drawn at the 50% probability level.

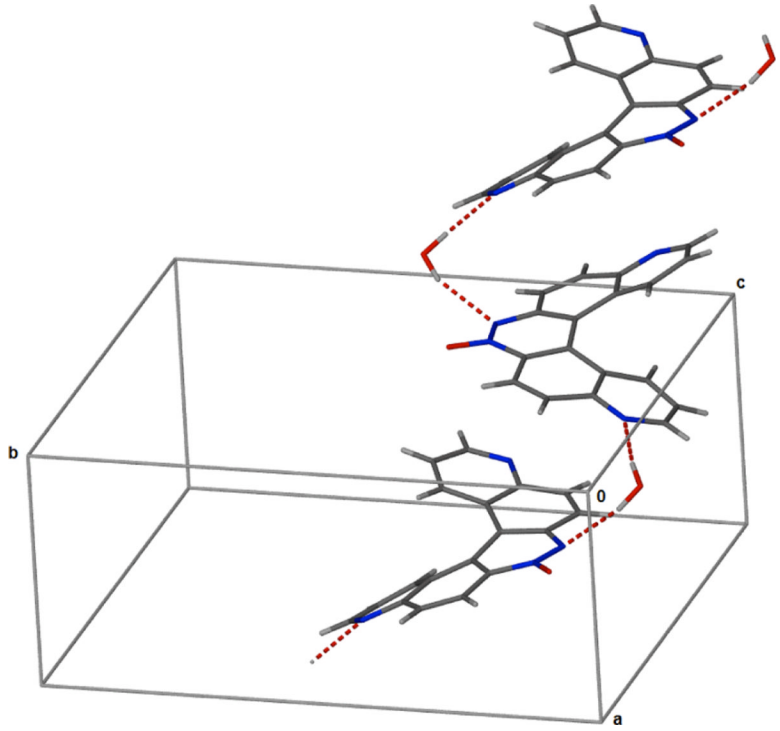

Figure 2.
View along the **a** axis showing antiparallel stacking of **3a**

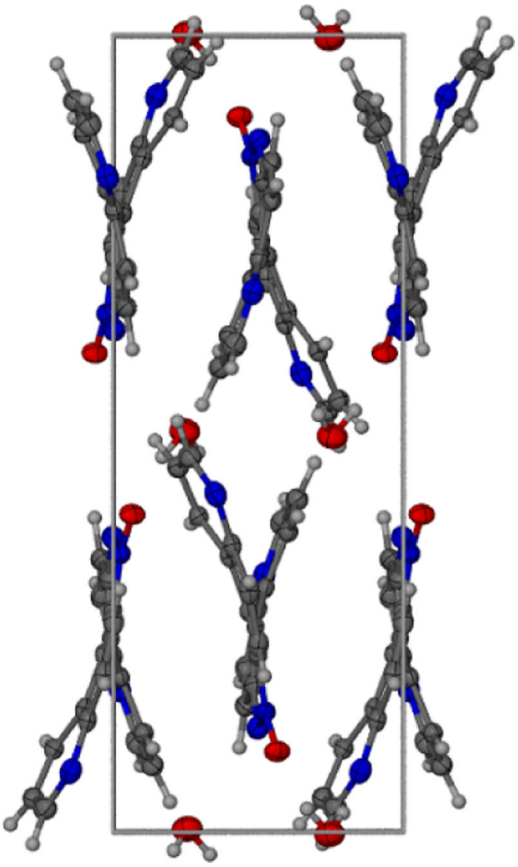

Figure 3.
Packing view of **3a** along the **c** axis

Table 1

Crystallographic data for **3a**.

Empirical formula	**$C1_8$ H_{10} N_4 O•H_2O**
Formula weight	316.32
Crystal system	Monoclinic
Space group	$P2_1/n$
Temperature	173(2) K
Unit cell dimensions	a = 7.0829(12) (Å)
	b = 18.559(3) (Å)
	c = 11.0985(19)(Å)
	$\beta = 107.736(2)^0$
Volume($Å^3$)	1389.6 (4)
Z	4
$Density_{calc}$(Mg/m^3)	1.512
Absorption coefficient	0.103 mm^{-1}
Total data	15979
Unique data collected	3339
Observed data	2700
Internal agreement of data(Rint)	0.029
Number of parameters refined	217
Goodness of fit(S)	1.032
R_1	0.0592
wR_2	0.1653

$$R_1 = \sum ||F_0| - |F_c|| / \sum |F_0|$$

$$wR_2 = \left\{ \sum \left[w\left(F_o^2 - F_c^2\right)^2 \right] / \sum \left[w\left(F_o^2\right)^2 \right] \right\}^{1/2}$$

Table 2

Atomic coordinates and equivalent isotopic displacement parameters of the non-hydrogen atoms for compound **3a**.

Atom	X	y	z	U(eq) (Å)
O1	4352(3)	1012(1)	847(2)	40(1)
N1	4756(2)	1505(1)	1690(2)	30(1)
C1	5185(3)	1834(1)	3727(2)	27(1)
N2	5023(3)	1304(1)	2850(2)	31(1)
C2	5453(3)	1581(1)	4987(2)	30(1)
N3	4805(3)	3220(1)	6573(2)	31(1)
C3	5450(3)	2053(1)	5905(2)	30(1)
N4	6475(3)	4241(1)	278(2)	31(1)
C4	5022(3)	2797(1)	5621(2)	26(1)
C5	4176(3)	3885(1)	6283(2)	33(1)
C6	3671(3)	4172(1)	5057(2)	31(1)
C7	3981(3)	3766(1)	4106(2)	25(1)
C8	4760(3)	3061(1)	4379(2)	23(1)
C9	5102(3)	2576(1)	3450(2)	24(1)
C10	5341(3)	2768(1)	2253(2)	23(1)
C11	6022(3)	3458(1)	1933(2)	23(1)
C12	7059(3)	3966(1)	2846(2)	24(1)
C13	7774(3)	4584(1)	2462(2)	29(1)
C14	7358(3)	4711(1)	1165(2)	32(1)
C15	5900(3)	3601(1)	655(2)	26(1)
C16	5319(3)	3039(1)	−267(2)	30(1)
C17	4994(3)	2362(1)	80(2)	30(1)
O(1W)	2543(3)	−32(1)	3254(2)	44(1)
C18	5027(3)	2224(1)	1336(2)	26(1)

Table 3

Bond distances (Å) for compound **3a**.

	3a
O1-N1	1.277(2)
N1-N2	1.298(3)
N1-C18	1.420(3)
C1-N2	1.363(3)
C1-C9	1.408(3)
C1-C2	1.432(3)
C2-C3	1.344(3)
C2-H2	0.9500
N3-C5	1.319(3)
N3-C4	1.362(3)
C3-C4	1.427(3)
C3-H3	0.9500
N4-C14	1.321(3)
N4-C15	1.363(3)
C4-C8	1.422(3)
C5-C6	1.402(3)
C5-H5	0.9500
C6-C7	1.368(3)
C6-H6	0.9500
C7-C8	1.416(3)
C7-H7	0.9500
C8-C9	1.444(3)
C9-C10	1.434(3)
C10-C18	1.402(3)
C10-C11	1.451(3)
C11-C12	1.415(3)
C11-C15	1.419(3)
C12-C13	1.373(3)
C12-H12	0.9500
C13-C14	1.398(3)
C13-H13	0.9500
C14-H14	0.9500
C15-C16	1.431(3)
C16-C17	1.354(3)
C16-H16	0.9500
C17-C18	1.410(3)
C17-H17	0.9500
O1W-H2W	0.8952
O1W-H1W	0.9406

Table 4

Bond Angles (°) for compound **3a**.

	3a
O1-N1-N2	116.94(19)
O1-N1-C18	119.28(19)
N2-N1-C18	123.62(18)
N2-C1-C9	124.0(2)
N2-C1-C2	114.7(2)
C9-C1-C2	121.2(2)
N1-N2-C1	117.12(19)
C3-C2-C1	119.8(2)
C3-C2-H2	120.1
C1-C2-H2	120.1
C5-N3-C4	117.41(19)
C2-C3-C4	120.8(2)
C2-C3-H3	119.6
C4-C3-H3	119.6
C14-N4-C15	117.75(19)
N3-C4-C8	122.8(2)
N3-C4-C3	116.94(19)
C8-C4-C3	120.2(2)
N3-C5-C6	124.0(2)
N3-C5-H5	118.0
C6-C5-H5	118.0
C7-C6-C5	119.1(2)
C7-C6-H6	120.4
C5-C6-H6	120.4
C6-C7-C8	119.2(2)
C6-C7-H7	120.4
C8-C7-H7	120.4
C7-C8-C4	116.92(19)
C7-C8-C9	124.27(19)
C4-C8-C9	118.48(19)
C1-C9-C10	115.93(17)
C1-C9-C8	117.29(18)
C10-C9-C8	126.77(19)
C18-C10-C9	117.12(19)
C18-C10-C11	116.66(18)
C9-C10-C11	126.04(18)
C12-C11-C15	116.87(19)
C12-C11-C10	123.49(18)
C15-C11-C10	119.06(19)

	3a
C13-C12-C11	119.63(19)
C13-C12-H12	120.2
C11-C12-H12	120.2
C12-C13-C14	118.6(2)
C12-C13-H13	120.7
C14-C13-H13	120.7
N4-C14-C13	124.0(2)
N4-C14-H14	118.0
C13-C14-H14	118.0
N4-C15-C11	122.4(2)
N4-C15-C16	117.68(19)
C11-C15-C16	119.7(2)
C17-C16-C15	120.6(2)
C17-C16-H16	119.7
C15-C16-H16	119.7
C16-C17-C18	119.8(2)
C16-C17-H17	120.1
C18-C17-H17	120.1
H2W-O1W-H1W	104.2
C10-C18-C17	122.6(2)
C10-C18-N1	118.69(19)
C17-C18-N1	118.74(19)

Table 5

Hydrogen bonds for **3a**.

D-H-A	d(D-H) (Å)	d(H…A) (Å)	d(D…A) (Å)	DHA (deg)	symm
O1W-H1W…N2	0.94	2.26	3.149(3)	158.1	
O1W-H2W…N4	0.90	2.09	2.967(2)	168.0	$x-1/2,-y+1/2,z+1/2$.