SYNTHESIS AND NOVEL CRYSTAL STRUCTURE OF (*E*,*Z*) 3-AMINOMETHYLENE-1-ETHYL-INDOL-2-ONE

Gang Chen,[1,*] Bin Liu,[2] Ying Tang,[1] Qiang Deng,[1] and Xiao-jiang Hao[3]

[1] *College of Chemistry and Chemical Engineering, Xi'an Shiyou University, Xi'an, 710065, China*
[2] *College of Environment and Chemical Engineering, Xi'an Polytechnic University, Xi'an, 710048, China*
[3] *State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, 650204, China*

ABSTRACT:

The title compounds, (*E*,*Z*)3-aminomethylene-1-ethyl-indol-2-one, were synthesized firstly by the reduction of 3-nitromethylene-1-ethyl-indol-2-one. The crystal structure was determined from single-crystal X-ray diffraction data. It crystallizes in the monoclinic space group, $P2_1/c$, with unit cell dimensions a = 8.7193 (5) Å, b =9.2507 (5) Å, and c = 23.6462 (15) Å. It was found that the novel crystal was consisted with centrosymmetric tetramer units, and the tetramer units were built up by the molecules linking as **ABAB** in a cycle, governed by intermolecular hydrogen bonds.

Key Words: (*E*,*Z*)3-aminomethylene-1-ethyl-indol-2-one, isatin, single crystal, tetramer.

INTRODUCTION

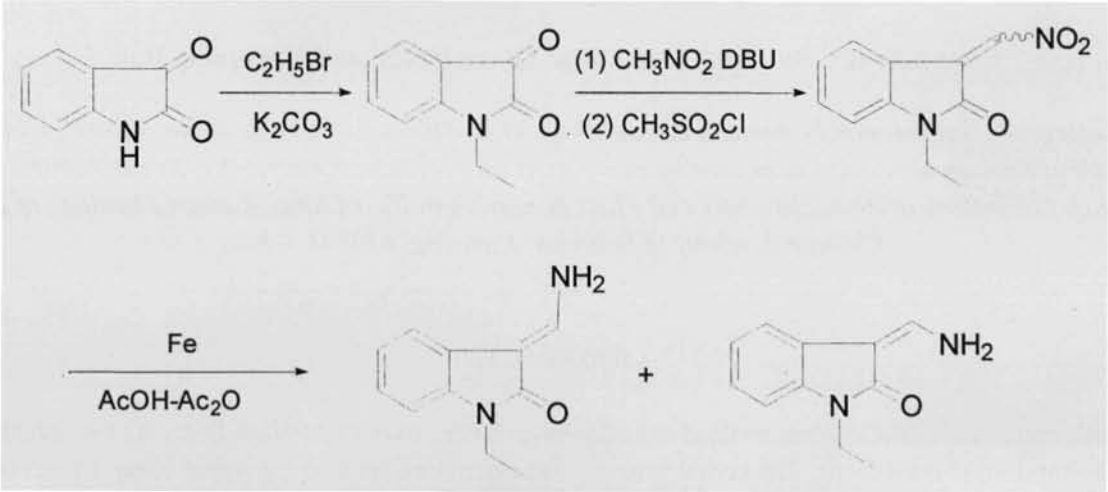
Isatin, as an important nature product with a diversity of effects, is found in many propagations and human body.[1] A variety of biological activities, such as anti-bacteria, anti-virus, anti-tumor and neuroprotection, make it catch great attention of many researchers as a versatile lead molecule for designing of potential drugs.[2-4]

Structure simplification of natural product has provided an efficient way to find new and less toxic lead compounds with certain bioactivity.[5] Compared with the structure of hamigeroxalamic acid,[6] ziziphines N and Q,[7] *N*-acetyl-β-aryl-1,2-didehydroethylamines can be viewed as a simplified baryl-1,2-didehydroethylamine alkaloid, which were synthesized by direct reduction-acetylation of β-aryl-nitroolefins and were found to be HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs).[8] With these findings, some oxindole-1,2-didehydroethylamine derivated from isatin were synthesized for the further research. In order to provide the structural information of these compounds, we studied the crystal structures of (*E*,*Z*) 3-aminomethylene-1-ethyl-indol-2- one (compound **A** and **B**) firstly.

RESULTS AND DISCUSSION

The title compounds were synthesized in a four-step reaction as shown in **Scheme 1**. 1-ethyl isatin was firstly synthesized by a substitution reaction of isatin with bromo ethane with a high yield of 98%. Then 1-ethyl isatin was treated with nitromethane catalized by DBU, followed by sulfurous oxychloride,[9] which gave 1-ethyl-3-nitromethylene-indol-2-one in the yield of 53%. At last the product was reducted by Fe-AcOH-Ac_2O to afford the title compounds in 21% yield.[8] The two compounds were gotten together for the similar structure and polar. Yellow crystals of the title compounds were obtained in ethanol by recrystallization suitable for X-ray analysis. The values of the geometric parameters of are within normal ranges and experimental errors.

Scheme 1



The molecular structure of compound **A** and **B** is illustrated in **Figure 1**. The structure analysis shows that, in the crystal, the asymmetric unit contains two independent molecules **A** and **B**. In each molecule, there are two coplanar cycles, and the amine is conjugated with the oxindole part through a C=C bound with the configuration of *E* or *Z*, in which the angle of C2–C11–N2 is 110.659(180)° (*Z*), while in the other molecule the angle of C2′–C11′–N2′ is 126.079(1190)° (*E*).

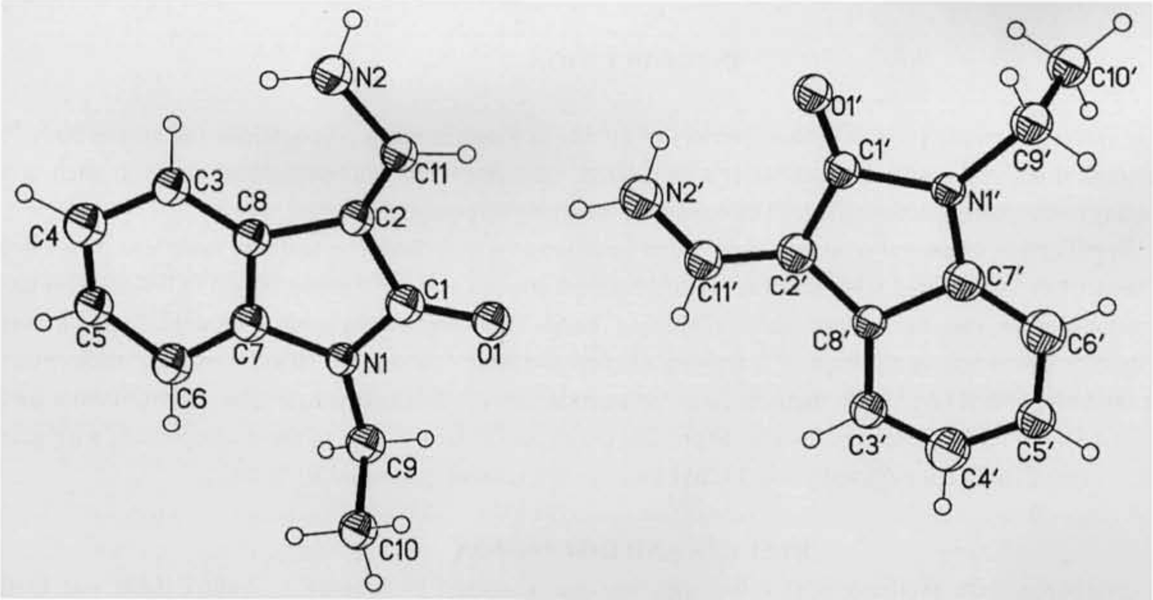


Figure 1 An ORTEP-3 drawing of compound **A** and **B**, with the atom-numbering scheme and 30% probability displacement ellipsoids.

In the crystal, there are centrosymmetric tetramer units consisted with two molecules of **A** and two molecules of **B** (shown as **Figure 2**). The molecules link as **ABAB** in a cycle, governed by intermolecular hydrogen bonds (**Table 1**). Each molecule is fixed by two hydrogen bonds of two other molecules. The $-NH_2$ act as a hydrogen bond donor and the oxygen atom of carbonyl group as a hydrogen bond accepter. But the two amine groups of compound **A** and **B** are different: the amine group of compound **B** devotes two N–H bonds for the hydrogen bonds, while in the other molecule, there is only one N–H is involved in the hydrogen bond. The details of the N1–H1A···O1′ bond are *d*(N1–H1A) = 0.86, *d*(H1A···O1′) = 1.80, *d*(N1···O1′) = 2.652(2), □N1–H1A···O1′ = 171.097(127)°. The details of the N1′–H1A′···O1′ bond are *d*(N1′–H1A′) = 0.86, *d*(H1A′···O1′) = 2.25, *d*(N1′···O1′) = 2.858(2), □N1′–H1A′···O1′ = 128.191(128)°. The details of the N1′–H1B′···O2 bond are *d*(N1′–H1B′) = 0.86, *d*(H1B′···O2) = 2.20, *d*(N1′···O2) = 2.893(2), □N1′–H1A′···O1′ = 138.083(130)°. The torsion angle of C_7–N_1–C_9–C_{10} is 86.296(275)°, while the torsion angle of C7′–N1′–C9′–C10′ is 83.444(239)°. The bound lengths of C11–N2(1.3678(28)Å) and C11′–N2′(1.3112(298)Å) involving in hydrogen bounds are shorter than the non-involving hydrogen C–N bounds.

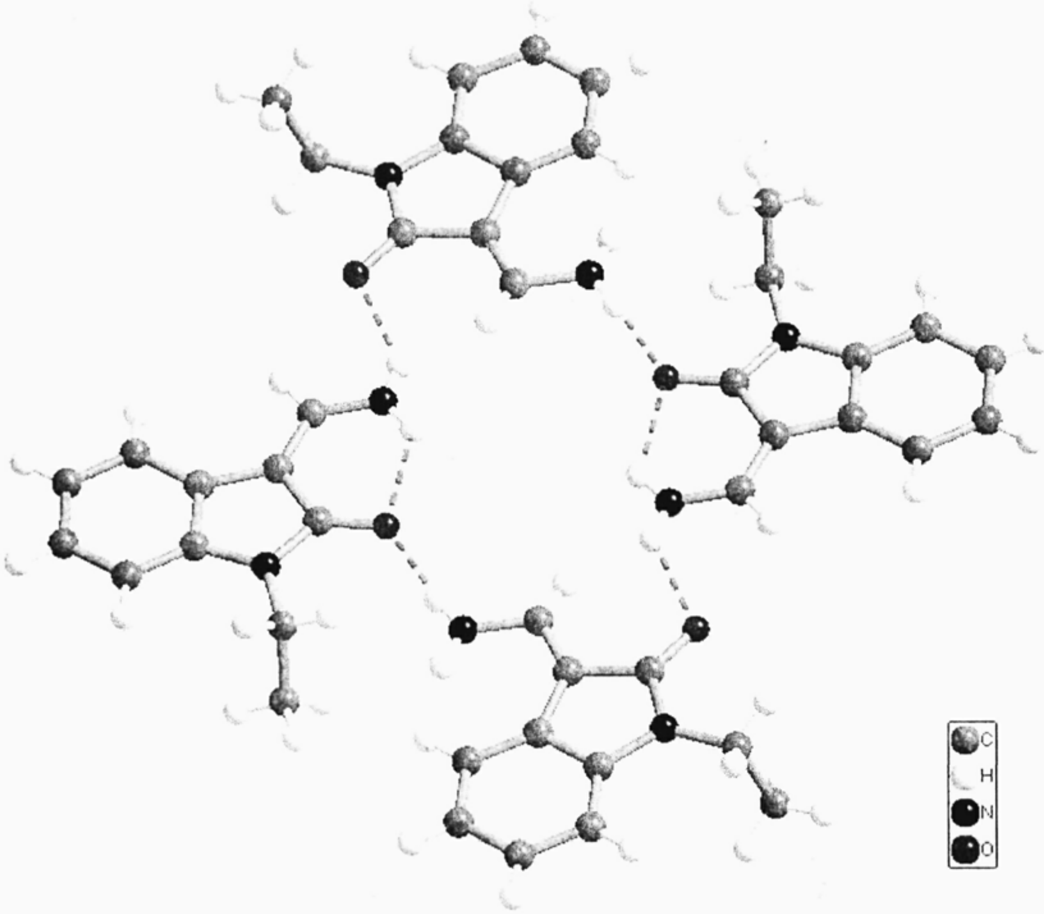


Figure 2 The four-molecule unit. (Hydrogen bonds are shown as dashed lines.)

Table 1 Hydrogen-bond geometry (Å, °)

D–H···A	D–H	H···A	D···A	D–H···A
N1–H1A···O1′	0.86	1.80	2.652(2)	171
N1′–H1A′···O1′	0.86	2.25	2.858(2)	128
N1′–H1B′···O2	0.86	2.20	2.893(2)	138

Symmetry code: (i) -x, y+1/2, -z+1/2; (ii)-x, -y, -z
(iii) x, -y-1/2, z-1/2

The discrete tetramers link together into an infinite 1D chain by face to face π-π stacking interactions between the oxindole moieties as shown in **Figure 3**.

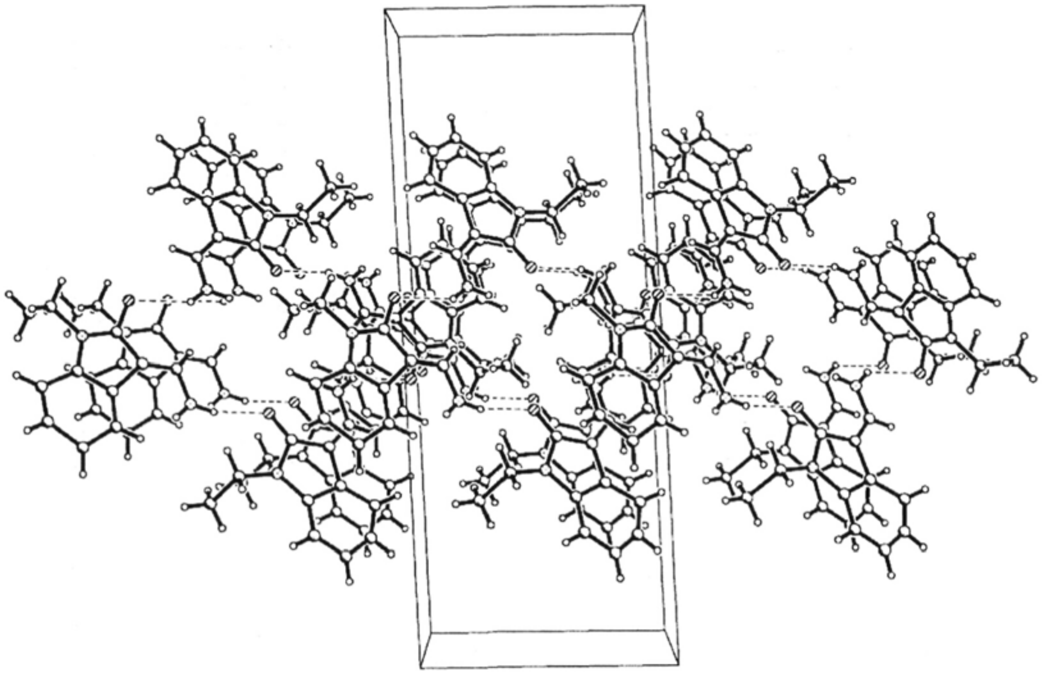


Figure 3 The crystal structure of compound **A** and **B**. (Hydrogen bonds are shown as dashed lines.)

EXPERMENTAL

All starting materials and solvents (A.R. grade) were commercially available and were used without further purification. NMR spectrum was recorded in the stated solutions, on a Bruker Drx-400 spectrometer, operating at 400 MHz for ^{1}H; δ values are reported in ppm and *J* values in hertz. Mass spectrum were recorded on a Micromass Platform[illegible] spectrometer using the direct-inlet system operating in the electron impact (EI) mode at 75 eV. Elemental analyses were performed by Atlantic Microlab, Norcross, GA, USA.

Preparation of compound A and B

1 g isatin was dissolved 30 ml DMF, 3 g K_2CO_3 and 1.2 g bromoethane were added. The mixture was stirred over night, and the crude product was extracted by ethyl acetate. Then the solvent was removed *in vacuo* and the residue was separated by column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1), giving 1-ethyl isatin in the yield of 98%. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.57 (2H, m), 7.09 (1H, t, *J* = 7.6 Hz), 6.89 (1H, d, *J* = 7.6 Hz), 3.76 (2H, q, *J* = 7.6 Hz), 1.29 (3H, t, *J* = 7.6 Hz). MS (EI) *m/z*: 175 (M^+). Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.55; H, 5.22; N, 8.05 %.

1 g 1-ethyl isatin and 0.2 g DBU were dissolved in 20 ml nitromethane, stirred over night. The solvent was removed *in vacuo* and the residue was dissolved in 20 ml dichlormethane, then 1 ml TEA was added in. Cool to 0℃ with water-ice bath, and then 1 g mesyl chloride was added by dropwise. The mixture was stirred over night at 0℃, and the residue was separated by column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) after the solvent was removed *in vacuo*, providing 1-ethyl-3- nitromethylene-indol-2-one in the yield of 53%. ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 11.6 (1H, b), 8.12 (1H, d, *J* = 7.6 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.07 (1H, t, *J* = 7.6 Hz), 6.85 (1H, d, *J* = 7.6 Hz), 3.81 (2H, q, *J* = 7.2 Hz), 1.29 (3H, t, *J* = 7.2 Hz). MS (EI) *m/z*: 218 (M^+). Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.50; H, 4.61; N, 12.89 %.

A suspension of iron powder (120 mmol) in acetic acid (1.2 mL) and acetic anhydride (12 mL) was heated to reflux for 30 min under a nitrogen atmosphere, then the 1-ethyl-3-nitromethylene-indol-2-one (6 mmol) was added to the mixture in half hour and the reaction system was kept refluxing for another 4 h until the disappearance of starting material monitored by TLC check. The mixture was then cooled and poured to ice cooled water. After filtration, the filtrate was evaporated to give a residue which was purification on silica gel chromatography afforded the target compounds (**A** and **B**). (3H, t, J = 7.2 Hz); ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 7.67 (1H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.11 (1H, t, J = 7.6 Hz), 7.01 (1H, b), 6.72 (1H, d, J = 7.6 Hz), 3.83 (2H, q, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz). MS (EI) *m/z*: 188 (M^+). Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.15; H, 6.48; N, 14.86.

30 mg compounds **A** and **B** were dissolved in 30 ml ethanol and were kept at room temperature for 4 d, natural evaporation gave yellow single crystals of compound **A** and **B** suitable for X-ray analysis.

X-Ray Data Collection and Structure Refinement

All H atoms were positioned geometrically, with C–H = 0.93–0.98 Å, and refined with a riding model, with $U_{iso}(H) = 1.2U_{eq}$(carrier). Data collection: SMART (Bruker, 2002); cell refinement: SAINT (Bruker, 2002); data reduction: SAINT (Bruker, 2002); program (s) used to solve structure: SHELXS97 (Sheldrick, 1997); program (s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: Ortep-3 for Windows (Farrugia, 1997); software used to prepare material for publication: WinGX (Farrugia, 1999).

The experimental data is reported in **Table 2-4**. The main information of the crystal was shown in **Table 5**.

Table 2 The crystal data.

Crystal data	
$C_{22}H_{24}N_4O_2$	$Z = 4$
$M_r = 376.46$	$F_{000} = 836$
Monoclinic, $P2_1/c$	$D_x = 1.312$ Mg m^{-3}
Hall symbol: -P 2ybc	Melting point: 396 K
$a = 8.7193$ (5) Å	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$b = 9.2507$ (5) Å	Cell parameters from 3113 reflections
$c = 23.6462$ (15) Å	$\theta = 1.9–27.1°$
$\alpha = 92.340$ (4)°	$\mu = 0.09$ mm^{-1}
$\beta = 90.114$ (4)°	$T = 273$ (2) K
$\gamma = 90.033$ (4)°	Block, yellow
$V = 1905.70$ (19) Å^3	0.22 × 0.20 × 0.15 mm

Table 3 The data collection of the analyis.

Data collection	
Bruker CCD Area Detector diffractometer	Radiation source: fine-focus sealed tube
Monochromator: graphite	3212 reflections with $I > 2\sigma(I)$
$T = 273(2)$ K	$R_{int} = 0.028$
φ and ω scan	$\theta_{max} = 27.5°$
Absorption correction: multi-scan SADABS (Sheldrick 2005)	$\theta_{min} = 2.5°$
$T_{min} = 0.941$, $T_{max} = 0.962$	$h = -11$ 11
17183 measured reflections	$k = -11$ 11

4313 independent reflections	$l = -30$ 30

Table 4 The refinement of the structure.

Refinement	
Refinement on F^2	Least-squares matrix: full
Secondary atom site location: difference Fourier map	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.094$	$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.123$	$(\Delta/\sigma)_{max} < 0.001$
$S = 3.14$	$\Delta\rho_{max} = 0.80$ e Å^{-3}
8179 reflections	$\Delta\rho_{min} = -0.80$ e Å^{-3}
Primary atom site location: structure-invariant direct methods	Extinction correction: SHELXL, $Fc^{*}=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
254 parameters	Extinction coefficient: 3.7 (9)

Table 5 Geometric parameters

Geometric parameters (Å, °)			
O1'—C1'	1.24 (2)	C6'—H6'A	0.9300
N1'—C7'	1.43 (3)	N2'—H2'A	0.8600
N1'—C9'	1.52 (2)	N2'—H2'B	0.8600
N1'—C1'	1.53 (2)	C3'—C4'	1.29 (4)
O1—C1	1.35 (3)	C3'—H3'A	0.9300
C7'—C6'	1.40 (4)	C3—C4	1.50 (3)
C7'—C8'	1.46 (3)	C3—H3A	0.9300
C8—C3	1.37 (3)	C6—C5	1.28 (3)
C8—C7	1.27 (3)	C6—H6A	0.9300
C8—C2	1.47 (2)	C9'—C10'	1.58 (4)
N2—C11	1.43 (2)	C9'—H9'A	0.9700
N2—H2A	0.8600	C9'—H9'B	0.9700
N2—H2B	0.8600	C5—C4	1.54 (3)
N1—C1	1.24 (4)	C5—H5A	0.9300
N1—C7	1.44 (3)	C4—H4A	0.9300
N1—C9	1.41 (2)	C5'—C4'	1.30 (4)
C11—C2	1.31 (2)	C5'—H5'A	0.9300
C11—H11A	0.9300	C9—C10	1.66 (3)
C8'—C3'	1.43 (3)	C9—H9A	0.9700
C8'—C2'	1.63 (3)	C9—H9B	0.9700
C1'—C2'	1.35 (3)	C4'—H4'A	0.9300
C2'—C11'	1.31 (3)	C10'—H10A	0.9600
C11'—N2'	1.32 (3)	C10'—H10B	0.9600
C11'—H11B	0.9300	C10'—H10C	0.9600
C2—C1	1.53 (4)	C10—H10D	0.9600
C7—C6	1.53 (4)	C10—H10E	0.9600

C6'—C5'	1.29 (3)	C10—H10F	0.9600
C7'—N1'—C9'	125.2 (15)	C4'—C3'—C8'	108 (2)
C7'—N1'—C1'	109.9 (16)	C4'—C3'—H3'A	125.9
C9'—N1'—C1'	123.3 (14)	C8'—C3'—H3'A	126.0
C6'—C7'—N1'	135.4 (19)	C8—C3—C4	116.9 (18)
C6'—C7'—C8'	117.0 (17)	C8—C3—H3A	121.6
N1'—C7'—C8'	107.5 (19)	C4—C3—H3A	121.5
C3—C8—C7	119 (2)	C5—C6—C7	106 (2)
C3—C8—C2	132 (2)	C5—C6—H6A	126.8
C7—C8—C2	108 (2)	C7—C6—H6A	127.2
C11—N2—H2A	120.2	N1'—C9'—C10'	110 (2)
C11—N2—H2B	119.8	N1'—C9'—H9'A	109.5
H2A—N2—H2B	120.0	C10'—C9'—H9'A	109.6
C1—N1—C7	111 (2)	N1'—C9'—H9'B	109.5
C1—N1—C9	122 (2)	C10'—C9'—H9'B	109.8
C7—N1—C9	127.0 (18)	H9'A—C9'—H9'B	108.1
C2—C11—N2	99.4 (17)	C6—C5—C4	129 (2)
C2—C11—H11A	130.3	C6—C5—H5A	115.7
N2—C11—H11A	130.3	C4—C5—H5A	115.6
C3'—C8'—C7'	118.7 (16)	C3—C4—C5	114.8 (17)
C3'—C8'—C2'	134.8 (18)	C3—C4—H4A	122.5
C7'—C8'—C2'	104.7 (16)	C5—C4—H4A	122.7
O1'—C1'—C2'	132.4 (18)	C4'—C5'—C6'	118 (3)
O1'—C1'—N1'	119.4 (17)	C4'—C5'—H5'A	120.8
C2'—C1'—N1'	107.8 (16)	C6'—C5'—H5'A	121.0
C11'—C2'—C1'	132 (2)	N1—C9—C10	112.6 (17)
C11'—C2'—C8'	119.9 (18)	N1—C9—H9A	109.0
C1'—C2'—C8'	108.4 (18)	C10—C9—H9A	109.1
C2'—C11'—N2'	121 (2)	N1—C9—H9B	109.1
C2'—C11'—H11B	119.7	C10—C9—H9B	109.2
N2'—C11'—H11B	119.7	H9A—C9—H9B	107.8
C11—C2—C1	119 (2)	C3'—C4'—C5'	132 (3)
C11—C2—C8	132.6 (17)	C3'—C4'—H4'A	113.8
C1—C2—C8	102.5 (18)	C5'—C4'—H4'A	114.0
C8—C7—C6	133 (2)	C9'—C10'—H10A	109.3
C8—C7—N1	110 (2)	C9'—C10'—H10B	109.4
C6—C7—N1	117 (2)	H10A—C10'—H10B	109.5
C5'—C6'—C7'	118 (3)	C9'—C10'—H10C	109.7
C5'—C6'—H6'A	121.0	H10A—C10'—H10C	109.5
C7'—C6'—H6'A	121.0	H10B—C10'—H10C	109.5
O1—C1—N1	123 (3)	C9—C10—H10D	109.4
O1—C1—C2	130 (3)	C9—C10—H10E	109.4
N1—C1—C2	106 (2)	H10D—C10—H10E	109.5
C11'—N2'—H2'A	120.1	C9—C10—H10F	109.5
C11'—N2'—H2'B	119.9	H10D—C10—H10F	109.5

H2'A—N2'—H2'B	120.0	H10E—C10—H10F	109.5

lementary Material

ystallographic data for the structure reported in this paper has been deposited at the Cambridge Crystallographic Center. Copies of the data (CCDC 721787) can be obtained free of charge upon application to CCDC, 12 Union , Cambridge CB2 1EZ, UK [E-mail: deposit@ccdc.cam.ac.uk].

ACKNOWLEDGMENTS

iis work was financially supported by the grants from the Ministry of Science and Technology of China)CB522303 and 2009CB940900) and Natural Science Research Plan Projects of Shaanxi Science and Technology rtment (SJ08B20).

REFERENCES

'. Glover, J. Halket, P. J. Watkins, A. Clow and B. L. Goodwin, *J. Neurochem.*, 1988, **51**, 656.

.. Sun, N. Tran, T. Tang, H. App, P. Hirth, G. McMahon and C. Tang, *J. Med. Chem.*, 1998, **41**, 2588.

. N. Pandeya, D. Sriram, G. Nath and E. DeClercq, Eur. *J. Med. Chem.*, 2000, **35**, 249.

'. M. Li, Z. K. Zhang, Y. T. Jia, Y. M. Shen, H. P. He, R. X. Fang, X. Y. Chen and X. J. Hao, *Plant. Biotechnol. J.*, 2008, **6**, 301.

`. R. Jr Burke, M. R. Fesen, A. Mzaumder, J. Wang, A. M. Carothers, D. Grunberger, J. Driscoll, K. Kohn and Y. J. Pommier, *Med. Chem.*, 1995, **38**, 4171.

V. Hassan, R. Edrada, R. Ebel, V. Wray and P. Proksh, *Mar. Drugs*, 2004, **2**, 88.

;. Suksamrarn, N. Suwannapoch, N. Aunchai, M. Kano, P. Ratananukul, R. Haritakun, C. Jansakul and S. Ruchirawat, *Tetrahedron*, 2005, **61**, 1175.

'. Cheng, Z. Y. Jiang, R. R Wang, X. M. Zhang, Q. Wang, Y. T. Zheng, J. Zhou, and J. J. Chen, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4476.

'. Giovanni, A. Rita, P. Gianluca and S. Massimo, *Tetrahedron: Asymmetry*, 1996, **7**, 1.

Received on June 23,2009.