Isolation and Structures of Dicyanide Derivatives, Epurpurins A to C, from *Emericella purpurea*

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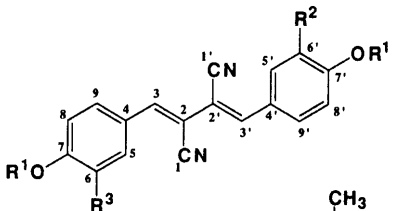
Three new yellow pigments, designated epurpurins A—C (1—3), were isolated along with variecolin and emindole PA from the dichloromethane extract of rice fermented with *Emericella purpurea*. Compounds of 1—3 were established as 2,3-dicyano-1,4-di(4-hydroxyphenyl)-1,3-butadiene derivatives by spectroscopic and chemical investigation and X-ray analysis of the dimethyl ether of epurpurin C (4).

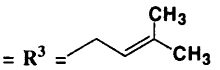
Key words *Emericella purpurea*; dicyanide; epurpurin A; epurpurin B; epurpurin C; emerin

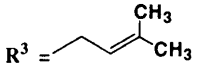
In the course of a search for indoloditerpenes by spraying van Urk's reagent,[1] we found that the dichloromethane extract of mycelium of *Emericella purpurea* SAMSON and MOUCHACCA, strain IFO 30849 (isolated from Egyptian dessert soil[2]), cultivated on potato-dextrose (PD) medium, contained a sesterterpene giving a bluish coloration, valiecolin,[3] and a new indoloditerpene giving a reddish coloration, emindole PA.[4] On further investigation, three new yellow pigments designated epurpurins A—C (**1**—**3**) were isolated along with variecolin and emindole PA from the dichloromethane extract of rice fermented with the above fungus. Compounds **1**—**3** were also obtained from the extract of mycelium cultivated on PD medium. The structure determination of **1**—**3** is reported in this paper.

The molecular formula of epurpurin A (**1**), mp 246.5—247 °C, was established as $C_{28}H_{28}N_2O_2$ from the mass spectrum (M^+, 424) and the elemental analysis. The ^{13}C-NMR spectrum of **1** showed 14 signals and the ^{1}H-NMR spectrum showed 9 signals whose total relative intensity indicated the existence of 14 hydrogens, whereas **1** had 28 carbon atoms and 28 hydrogen atoms in the molecule. These results indicated that **1** has a symmetrical system in the molecule. The UV absorption spectrum of **1** (250, 387, and 404 sh nm) resembled those of emerin (**4**)[5] and *O*-dimethylxanthocillin X (**5**).[6] The IR spectrum of **1** showed absorptions at 3390 and 2230 cm^{-1} indicating the hydroxyl group and the nitrile group,[7] respectively.

In the ^{1}H-NMR spectrum of **1**, three signals at δ 6.92 (2H, d, J=8.4 Hz), 7.60 (2H, dd, J=8.4, 2.1 Hz), and 7.74 (2H, d, J=2.1 Hz) were assigned to two sets of aromatic protons of a 1,2,4-trisubstituted benzene ring and the signals at δ 1.72 (6H, br s), 1.69 (6H, br s), 3.25 (4H, br d, J=7.0 Hz), and 5.31 (2H, br t, J=7.0 Hz) were assigned to the protons of two 3-methyl-2-butenyl groups. These results were also supported by analysis of the ^{1}H–^{1}H correlation spectroscopy (COSY) spectrum and by decoupling experiments in the ^{1}H-NMR spectrum. A broad signal at δ 10.32 (2H), which disappeared upon addition of D_2O, was assigned to two protons of two phenols, while a singlet at δ 7.46 (2H) was assigned to two olefinic protons. When the methylene protons at δ 3.25 were irradiated, 6.4% nuclear Overhauser enhancement (NOE) was observed on the aromatic protons at δ 7.74, in addition to the NOE's on the olefinic protons at δ 5.31 and the methyl protons at δ 1.72 in 3-methyl-2-butenyl groups. This suggested that the 3-methyl-2-butenyl groups are attached at the *ortho* position to the aromatic protons at

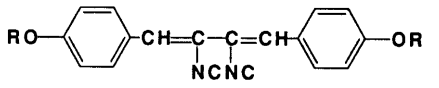


1 : R^1 = H, R^2 = R^3 = 

2 : R^1 = R^2 = H, R^3 = 

3 : R^1 = R^2 = R^3 = H

4 : R^1 = CH_3, R^2 = R^3 = H



5 : R = CH_3

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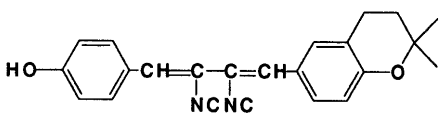

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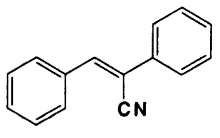

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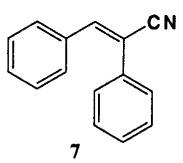

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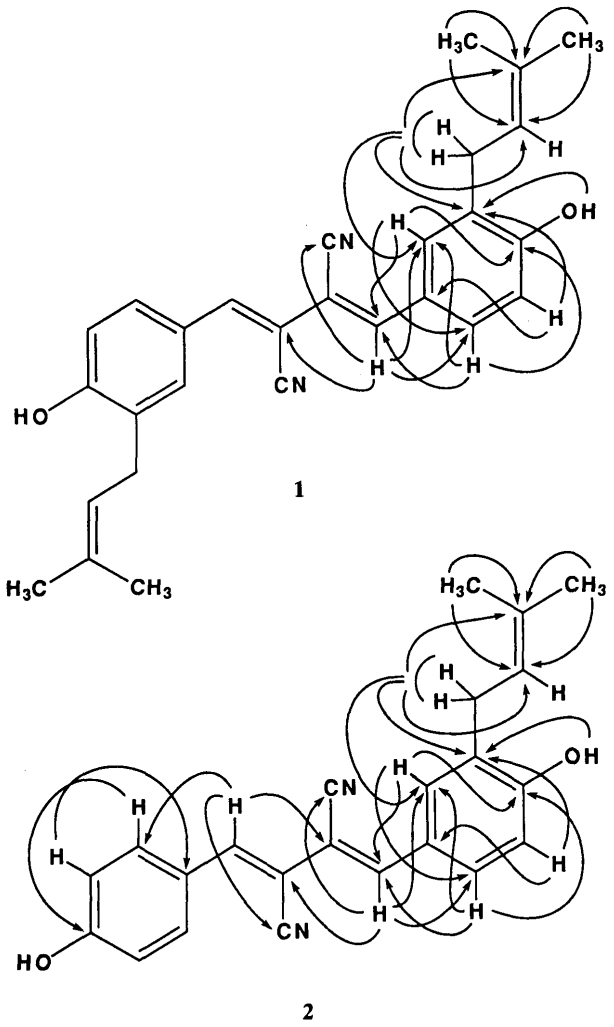

Fig. 1. Correlations in the COLOC Spectra of Epurpurins A (**1**) and B (**2**)

Arrows indicate the correlation from proton (H_A) to carbon (C_B): $H_A \rightarrow C_B$.

Table 1. ^{1}H- and ^{13}C-NMR Chemical Shifts of Epurpurins (**1**—**3**) in $(CD_3)_2SO$

Carbon No.	**1**		**2**		**3**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	116.1		116.1		116.0	
2	103.0		102.8		103.3	
3	142.9	7.46	143.2	7.48	143.0	7.53
4	123.6		123.6		123.6	
5	130.7	7.74	130.7	7.75	131.7	7.82
6	128.4		128.4		116.0	6.91
7	158.3		158.4		160.6	
7-OH		10.32		10.35		10.38
8	115.3	6.92	115.3	6.92	116.0	6.91
9	129.5	7.60	129.6	7.61	131.7	7.82
1′	116.1		116.1		116.0	
2′	103.0		103.4		103.3	
3′	142.9	7.46	142.7	7.51	143.0	7.53
4′	123.6		123.6		123.6	
5′	130.7	7.74	131.7	7.81	131.7	7.82
6′	128.4		116.0	6.91	116.0	6.91
7′	158.3		160.5		160.6	
7′-OH		10.32		10.35		10.38
8′	115.3	6.92	116.0	6.91	116.0	6.91
9′	129.5	7.60	131.7	7.81	131.7	7.82
1″	27.6	3.25	27.6	3.25		
2″	121.6	5.31	121.6	5.31		
3″	132.3		132.4			
4″	17.5	1.69	17.5	1.69		
5″	25.4	1.72	25.5	1.73		
1‴	27.6	3.25				
2‴	121.6	5.31				
3‴	132.3					
4‴	17.5	1.69				
5‴	25.4	1.72				

δ 7.74. NOE's of 14.8 and 12.9% were observed on the above aromatic protons at δ 7.74 and 7.60, respectively, in the difference NOE spectrum irradiated at the olefinic protons at δ 7.46. This result supported the view that the double bond bearing the proton at δ 7.46 was attached between the protons at δ 7.74 and 7.60 in the aromatic ring. It is concluded that the phenolic hydroxy groups were attached *ortho* to the aromatic protons at δ 6.92 from the chemical shifts and the above results. The remaining fragments were two nitrile groups and two olefinic quaternary carbons. So the structure of epurpurin A was presumed to be 1,4-di(4-hydroxy-3-(3-methyl-2-butenyl)phenyl)-2,3-dicyano-1,3-butadiene (**1**), though the stereochemistry of the double bonds was not established. This structure was confirmed by the analysis of the ^{1}H–^{13}C COSY spectrum and ^{1}H–^{13}C shift correlation *via* long-range coupling (COLOC) spectrum of **1**. The COLOC correlations of **1** are shown in Fig. 1 and the ^{1}H- and ^{13}C-NMR assignments of **1** are summarized in Table 1.

The ^{13}C- and ^{1}H-NMR spectrum of epurpurin C (**3**), mp >290 °C, $C_{18}H_{12}N_2O_2$, showed 7 carbon signals due to 9 carbons and 4 proton signals whose total relative intensity corresponded to 6 protons, respectively, but **3** has 18 carbon atoms and 12 hydrogen atoms in the molecule. These facts indicated that **3** has a symmetrical system in the molecule like **1**. The UV absorption spectrum of **3** (245, 312 sh, 379, and 395 sh nm) resembled those of emerin (**6**)[5] and **1**. The IR spectrum of **3** showed absorptions at 3360 and 2230 cm^{-1}, indicating the hydroxyl group and the nitrile group, respectively. The ^{1}H-NMR spectrum of **3** was closely similar to that of **6**,[5] except for the appearance of the phenolic protons at δ 10.38 in **3** instead of the methoxy protons at δ 3.87 in **6**. On methylation, **3** afforded a dimethyl ether (**4**), which was identical in terms of the spectroscopic data to emerin synthesized from succinonitrile and *p*-anisaldehyde according to the literature.[8] Therefore the structure of epurpurin C was determined as bisdemethylemerin (**3**), *i.e.*, 1,4-di(4-hydroxyphenyl)-2,3-dicyano-1,3-butadiene. This structure was confirmed by the analysis of the ^{1}H–^{1}H and ^{1}H–^{13}C COSY spectra and ^{1}H–^{13}C COLOC spectrum of **3**. The ^{1}H- and ^{13}C-NMR assignments of **3** are summarized in Table 1.

The UV (248, 384, 405 sh nm) and IR (3380 and 2230 cm^{-1}) spectra of epurpurin B (2), mp 238.5—239 °C, $C_{23}H_{20}N_2O_2$, were similar to those of epurpurins A (**1**) and C (**3**). The ^{1}H- and ^{13}C-NMR spectra of **2** were almost superimposable on the sum of those of **1** and **3** (Table 1). This fact indicated that **2** has non-symmetrical structure which consists of the halves of **1** and **3**. Therefore, the

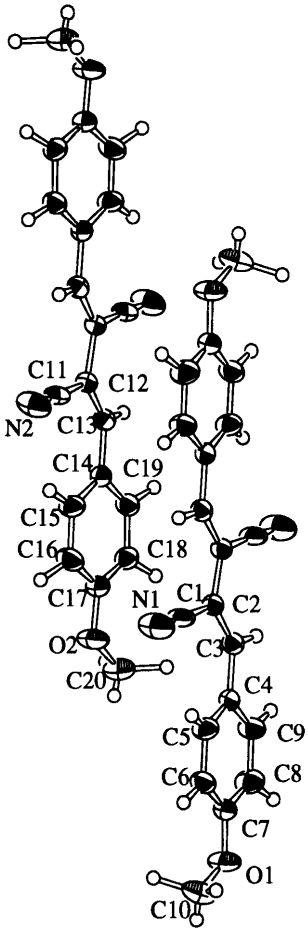

Fig. 2. Perspective View of the Crystal Structure of Epurpurin C Dimethyl Ether (**4**) with Thermal Ellipsoids at 50% Probability

structure of epurpurin B (**2**) was assumed to be 1-(4-hydroxy-3-(3-methyl-2-butenyl)phenyl)-4-(4-hydroxyphenyl)-2,3-dicyano-1,3-butadiene. This structure was confirmed by the analysis of the ^{1}H–^{13}C COSY and ^{1}H–^{13}C COLOC (Fig. 1) spectra of **2**. The ^{1}H- and ^{13}C-NMR assignments are summarized in Table 1.

The remaining problem was determination of the stereochemistry of the double bonds in epurpurins A (**1**) to C (**3**). Epurpurin C dimethyl ether (**4**) fortunately afforded yellow prisms with strong blue fluorescence, and a crystal suitable for X-ray single crystal analysis was grown from acetone solution. From the X-ray structure analysis, the crystal structure of **4** was established to be as shown in Fig. 2.[9] Two molecules of **4**, which have a symmetrical center in each molecule, existed independently in an asymmetric unit. The values of bond lengths and angles are not significantly different from the expected ones. The stereochemistry of the double bonds in **4** was confirmed as (*Z*). The structure of epurpurin C (**3**) was consequently established as (2*Z*,3*Z*)-1,4-di(4-hydroxyphenyl)-2,3-dicyano-1,3-butadiene.

The stereochemistry of the double bond in **1** and **2** was determined from the following data. From the proton coupled ^{13}C-NMR spectrum, the carbons of the nitrile group [δ 116.1, 116.1, and 116.0 (each 2C) in **1**, **2**, and **3**, respectively] were observed as a doublet with the coupling constants of 13.7, 14.1, and 15.3 Hz, respectively. It is clear that these carbons were coupled with the olefinic proton [δ 7.46 (2H), 7.48, 7.51 (each 1H), and 7.53 (2H) for **1**, **2**, and **3**, respectively), because there are no other protons within 3 bonds from the nitrile carbons. This was confirmed by the selective decoupling of the above protons. Kingsbury *et al.* reported[10] that the value of the coupling constant between the nitrile carbon and the olefinic proton depends on the stereochemistry of the double bond in trisubstituted alkenes *i.e.*, (*Z*)-isomer (*trans* between the allylic carbon and the olefinic proton) shows a coupling constant of 7.7—17 Hz (**6**, 14.2 Hz), whereas (*E*)-isomer (*cis* between the allylic carbon and the olefinic proton) shows a coupling constant of 4.3—10 Hz (**7**, 9.0 Hz). This indicated that the stereochemistry of the olefinic protons and the nitrile carbons in **1** and **2** was *trans*, as in **3**. The structures of epurpurins A and B were consequently confirmed to be (2*Z*,3*Z*)-1,4-di[4-hydroxy-3-(3-methyl-2-butenyl)phenyl]-2,3-dicyano-1,3-butadiene (**1**) and (2*Z*,3*Z*)-1-[4-hydroxy-3-(3-methyl-2-butenyl)phenyl]-4-(4-hydroxyphenyl)-2,3-dicyano-1,3-butadiene (**2**), respectively.

Epurpurins A to C (**1**—**3**) are the second reported examples of the isolation of 1,4-diphenyl-2,3-dicyano-1,3-butadiene derivatives from fungus. The first example was the isolation of emerin (**4**) from *Aspergillus nidulans* (Eidam) WINTER, the teleomorph of which is *Emericella nidulans* (Eidam) VUILL.[5] On the other hand, about 10 1,4-diphenyl-2,3-diisocyano-1,3-butadiene derivatives have already been isolated from fungi, *e.g.*, xanthocillin X (**8**) from *Penicillium nonatum* WESTLING,[11] *O*-dimethylxanthocillin X (**7**) from *Aspergillus* sp.,[6] and xanthoascin (**9**) from *Aspergillus candidus* LINK: Fr.[12] It is reported that the above diisocyanides had various biological activities, *e.g.*, antiviral activity of **7**,[6] and hepatotoxicity and cardiotoxicity of **9**.[13] The biological activities of epurpurins A (**1**) to C (**3**) will be investigated in the near future.

Experimental

General Procedures Melting points were determined on a Yanagimoto micro-melting point apparatus without correction. Electron impact (EI)-MS were taken with a JEOL JMS-D-300 spectrometer. UV and IR spectra were recorded on a Hitachi U-3210 spectrophotometer and a JASCO IR-810 spectrophotometer, respectively. The abbreviation sh is used to indicate a shoulder peak. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-GX-400 spectrometer at 399.78 and 100.43 MHz or JEOL Lambda-500 spectrometer at 500.00 and 125.65 MHz, respectively, using tetramethylsilane as an internal standard. The coupling patterns are indicated as follows: singlet = s, doublet = d, triplet = t, quartet = q, multiplet = m, and broad = br. Column chromatography was performed using Kieselgel 60 (Art. 7734, Merck). High-performance liquid chromatography (HPLC) was performed on a Senshu SSC-3160 pump with the flow rate of 5 ml/min using a Senshu Pak PEGASIL Silica 60-5 (10 i.d. × 250 mm) prepacked column, equipped with a Shimamura YRD-883 RI detector. Thin layer chromatography (TLC) was conducted on precoated Kieselgel 60 F_{254} plates (Art. 5715, Merck). Spots on TLC were detected under UV light at 254 nm and/or by fluorescence at 365 nm.

Isolation of Epurpurins A (1) to C (3) from *E. purpurea* *E. purpurea*, strain IFO 30849, was cultivated at 25 °C for 21 d using 10 Roux flasks containing 200 g of sterilized rice in each flask. The fermented rice was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and then evaporated *in vacuo*. The obtained residue (72 g) was chromatographed on silica gel with benzene to give variecolin and emindole PA, and with benzene–acetone (15 : 1) followed by repeated HPLC using the solvent system of hexane–benzene–acetone (2 : 1 : 1) to give epurpurin A (**1**) (91 mg), epurpurin B (**2**) (40 mg), and epurpurin C (**3**) (72 mg).

Epurpurin A (**1**): Yellow crystalline powder with greenish yellow

fluorescence, mp 246.5—247 °C (from acetone). EI-MS *m/z* (%): 424 (M^+, 100). *Anal.* Calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.19; H, 6.82; N, 6.50. UV λ_{max}^{MeOH} nm (log ε): 250 (4.09), 387 (4.65), 404 sh (4.58). IR ν_{max}^{KBr} cm^{-1}: 3390 (OH), 2230 (CN), 1600, 1585 (aromatic C=C). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.72 (6H, br s), 1.69 (6H, br s), 3.25 (4H, br d, J=7.0 Hz), 5.31 (2H, br t, J=7.0 Hz), 6.92 (2H, d, J=8.4 Hz), 7.46 (2H, s), 7.60 (2H, dd, J=8.4, 2.1 Hz), 7.74 (2H, d, J=2.1 Hz), 10.32 (2H, br). The assignments of ^{13}C-NMR signals are summarized in Table 1.

Epurpurin B (**2**): Yellow crystalline powder with greenish yellow fluorescence, mp 238.5—239 °C (from benzene–acetone). EI-MS *m/z* (%): 356.1519 (M^+, 356.1524 for $C_{23}H_{20}N_2O_2$, 100), 301 (34). UV λ_{max}^{MeOH} nm (log ε): 248 (4.09), 384 (4.72), 405 sh (4.59). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 2230 (CN), 1600, 1590 (aromatic C=C). ^{1}H-NMR [$(CD_3)_2CO$] δ: 1.74 (3H, br s), 1.76 (3H, d, J=1.4 Hz), 3.37 (2H, br d, J=7.4 Hz), 5.39 (1H, tqd, J=7.4, 1.4, 1.4 Hz), 6.99 (1H, d, J=8.6 Hz), 7.00 (2H, d, J=8.6 Hz), 7.53 (1H, s), 7.56 (1H, s), 7.71 (1H, dd, J=8.6, 2.3 Hz), 7.85 (1H, d, J=2.3 Hz), 7.90 (2H, d, J=8.6 Hz), 9.19 (1H, s) , 9.22 (1H, s). ^{1}H-NMR [$(CD_3)_2SO$] δ: 1.69 (3H, br s), 1.73 (3H, br s), 3.25 (2H, br d, J=7.4 Hz), 5.31 (1H, br t, J=7.4 Hz), 6.91 (2H, d, J=8.8 Hz), 6.92 (1H, d, J=8.6 Hz), 7.48 (1H, s), 7.51 (1H, s), 7.61 (1H, dd, J=8.6, 2.3 Hz), 7.75 (1H, d, J=2.3 Hz), 7.81 (2H, d, J=8.8 Hz), 10.35 (2H, s). The assignments of ^{13}C-NMR signals are summarized in Table 1.

Epurpurin C (**3**): Yellow crystalline powder with greenish yellow fluorescence, mp >290 °C (from acetone). EI-MS *m/z* (%): 288.0896 (M^+, 288.0897 for $C_{18}H_{12}N_2O_2$, 100). *Anal.* Calcd for $C_{18}H_{12}N_2O_2 \cdot 1/2\text{-}H_2O$: C, 72.72; H, 4.64; N, 9.21. Found: C, 73.18; H, 4.45; N, 9.19. UV λ_{max}^{MeOH} nm (log ε): 245 (4.12), 312 sh (3.98), 379 (4.71), 395 sh (4.62). IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 2230 (CN), 1610, 1595 (aromatic C=C). ^{1}H-NMR [$(CD_3)_2SO$] δ: 6.91 (4H, d, J=8.7 Hz), 7.53 (2H, s), 7.82 (4H, d, J=8.7 Hz), 10.38 (2H, br). The assignments of ^{13}C-NMR signals are summarized in Table 1.

Methylation of Epurpurin C (3) Epurpurin C (**3**) (20 mg) was methylated with diazomethane, which was prepared from nitrosomethylurea, in ether overnight at 0 °C. After the removal of ether by evaporation, the residue was purified by HPLC (benzene), followed by recrystallization from acetone to afford epurpurin C dimethyl ether (**4**) (8 mg).

Epurpurin C Dimethyl Ether (**4**): Yellow prisms with strong blue fluorescence, mp 226.5—227 °C (from acetone). EI-MS *m/z* (%): 316.1209 (M^+, 316.1211 for $C_{20}H_{16}N_2O_2$, 100), 209 ($C_{20}H_{16}N_2O_2$–$CH_3OC_6H_4$, 30), 158 ($C_{10}H_8NO$, 12), 108 ($CH_3OC_6H_5$, 62). *Anal.* Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 76.12; H, 5.15; N, 8.79. UV λ_{max}^{MeOH} nm (log ε): 250 (4.09), 301 sh (3.66), 380 (4.77), 395 (4.68). IR ν_{max}^{KBr} cm^{-1}: 2215 (CN), 1600, 1585 (aromatic C=C). ^{1}H-NMR ($CDCl_3$) δ: 3.87 (6H, s, 7-OMe), 6.97 (4H, d, J=9.0 Hz, 6-H, 8-H), 7.54 (2H, s, 3-H), 7.87 (4H, d, J=9.0 Hz, 5-H, 9-H). ^{13}C-NMR ($CDCl_3$) δ: 55.4 (2C, q, J=145 Hz), 105.3 (2C, d, J=8 Hz), 114.6 (4C, dd, J=161, 6 Hz), 115.9 (2C, d, J=13.7 Hz), 125.5 (2C, t, J=8 Hz), 131.7 (4C, dt, J=160, 6 Hz), 143.1 (2C, dt, J=156, 5 Hz), 162.1 (2C, m).

Synthesis of Epurpurin C Dimethyl Ether (4)[8] A solution of *p*-anisaldehyde (5.5 g) and succinonitrile (3.2 g) in NaOMe solution, which was prepared from 30 ml of methanol and 1 g of sodium metal, was left at room temperature overnight. Crystals that formed were collected by filtration and recrystallized from acetone to give emerin (**4**) (380 mg) as greenish yellow columnar crystals. This compound was identified as epurpurin C dimethyl ether by IR, UV, and ^{1}H-NMR spectral comparison and mixed fusion with an authentic sample.

X-Ray Crystallography of Epurpurin C Dimethyl Ether (4) Epurpurin C dimethyl ether (**4**) was grown from acetone as yellow prisms with strong blue fluorescence. Diffraction intensities were collected from a crystal of dimensions 0.60 × 0.30 × 0.20 mm on a Rigaku AFC7R four-circle diffractometer. Of the total of 2694 unique reflections (complete for $2\theta \leq 120°$), 1953 satisfied the criterion $F \geq 3\sigma(F)$ and only these were used in the solution and refinement of the structure.

Crystal data: $C_{20}H_{16}N_2O_2$, M.W. = 316.36, monoclinic, space group $P2_1/c$, a=13.314(1), b=6.687(1), c=18.773(1) Å, β=100.387(5)°, V=1644.0(3) $Å^3$, Z=4, D_c=1.278 g cm^{-3}, $F(000)$=664, CuK_α radiation, graphite-monochromated, λ=1.5418 Å.

Structure solution and refinement: The structure was solved by the direct method using SAPI91[14] and the final refinement was done by the full-matrix least-squares method with anisotropic thermal parameters for all non-hydrogen atoms and fixed isotropic thermal parameters for all hydrogen atoms. The final R value was 0.092.[9]

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