

# The Crystal Structure of One Natural Compound Cyclo-(1,10-Docandiamino-11,20-Docanedioic) Amide (1,12-Diazacyclodocosane-2,11-Dione)

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1,12-diazacyclodocosane-2,11-dione was first isolated from a plant *Phyllanthus niruri* Linn. Its structure has been determined by means of spectroscopy methods and X-ray crystallography. Two peptide groups in the big ring (lactam) are the main factors influencing intermolecular contacts. The hydrogen-bond interaction of these hydrophilic groups is observed in the crystal structure. Meanwhile, C-H...O hydrogen bonds in molecules contribute to the formation of the whole crystal. These two kinds of hydrogen-bond form six-member rings among molecules. This compound crystallizes in the triclinic space group P-1 with  $a = 9.588(1) \text{ \AA}$ ,  $b = 9.850(1) \text{ \AA}$ ,  $c = 11.810(1) \text{ \AA}$ ,  $\alpha = 68.18(1)^\circ$ ,  $\beta = 84.98(1)^\circ$ ,  $\gamma = 86.03(1)^\circ$ ,  $V = 1030.66(17) \text{ \AA}^3$ ,  $Z = 2$ . A disorder of five-member carbon chain in the whole ring is observed in the title compound. The bond angle  $105.8(4)^\circ$  is determined for a extreme configuration C(14)-C(15)-C(16), and  $117.7(10)^\circ$  for another extreme configuration C(14')-C(15')-C(16'). In this crystal, two molecules are tied each other by short intermolecular hydrogen bonds, the oxygen atom being tied by hydrogen bond to nitrogen atom of another two molecules. The NMR and IR spectral data coincides to the structure of the compound.

**Key Words :** 1,12-Diazacyclodocosane-2,11-dione, Cyclo(1,10-docandiamino-11,20-docanedioic) amide, Crystal structure, *Phyllanthus niruri* Linn

## Introduction

1,12-Diazacyclodocosane-2,11-dione was first isolated from *phyllanthus niruri* linn, a plant was used as medicine in China and Indian.<sup>1,2</sup> Many other studies on this plant showed that it has many bioactivities.<sup>3-12</sup> The bioactivity of this plant proposed us to investigate its chemical components. We have obtained phyllanthin, hypophyllanthin and neonirtetralin in previous work.<sup>13</sup> In recent work we obtained 1,12-Diazacyclodocosane-2,11-dione (**1**) along with dihexylbenzene-1,2-dicarboxylate (**2**), 2,3,7,8-tetrahydrochromeno[5,4,3-cde]chromene-5,10-dione (ellagic acid **3**), 3,4,5-trihydroxy benzoic acid (**4**) from this plant. Compound (**1**) was first got from plants. So far, few studies on compound (**1**) have been reported.<sup>14</sup>

Structures of compound (**2**), compound (**3**) and compound (**4**) were elucidated by means of spectroscopy NMR, IR, MS. We reported the structure elucidation of compound (**1**) by means of spectroscopy and X-ray single crystallography.

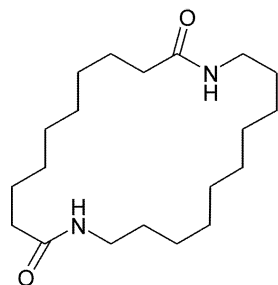


Figure 1. diagram of compound 1.

## Experimental Section

*Phyllanthus niruri* L. was collected from Longan county, Guangxi province and was identified by Dr. Shifeng Ni. A voucher specimen is kept in our lab.

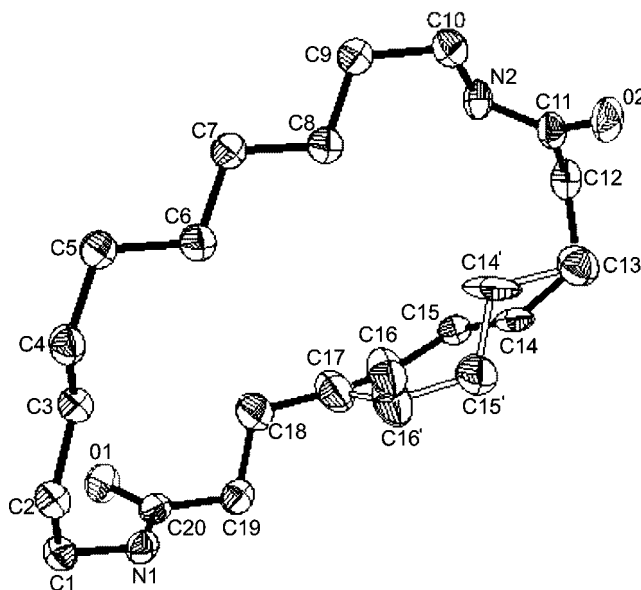


Figure 2. View of the title compound showing the atomic numbering scheme.

*P. niruri* plant (3.5 kg) was powdered and then was extracted with ethanol and all extracts were distilled in *vacuo*. The residue was dissolved in water and successively extracted with petroleum ether and ethyl acetate. The petro-

leum ether extracts and ethyl acetate extracts were dried and the two residues were combined (105 g). The gradient chromatography of this 105 g residue was applied in silica gel (40-60 nm) column with petroleum ether to ethyl acetate. The polarities of solvents were increased stepwise to increase the proportion of ethyl acetate until the ratio reached 100 ethyl acetate and finally with methanol. The fraction obtained at a ratio of 3 : 1 of petroleum and ethyl acetate gave 0.15 g liquid residues and purified with silica gel column chromatography, obtained 25 mg compound (1). The fraction obtained at a ratio of 1.4 : 1 of petroleum and ethyl acetate gave 1.4 g solid residues and purified with silica gel column chromatography, obtained 110 mg compound (3) and 65 mg compound (4).

$^1\text{H-NMR}$  (500 MHz) and  $^{13}\text{C-NMR}$  (125 MHz) were recorded on a Bruker AM-500 spectrometer. Sample dissolved in  $\text{CDCl}_3$  for NMR studies. Chemical shifts were reported in ppm. Coupling constants ( $J$ -Values) were given in Hertz (Hz). IR data was recorded on Thermo Nicolet nexus 470 infrared spectrometer.

As mostly perfect in shape, a single crystal obtained from solution of compound (1) in methanol was mounted on the diffractometer for X-ray data collection. The structure was solved by *SHELXS-97* (sheldrick, 1990),<sup>15</sup> and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropy. The hydrogen atoms involved in hydrogen bonding of NHO were deduced from difference Fourier maps, their position and  $U_{eq}$  were involved in the refinement

procedure; while the others were placed in calculated positions, their  $U_{eq}$  are 20% larger than that of parent atoms. The weighting scheme used at the final stage was  $W = [(\sigma_c^2) + (0.0477P)^2]^{-1}$ , where  $P = (F_o^2 + 2F_c^2)/3$ . Atomic scattering facts used were taken from international Table for X-ray Crystallography.<sup>16</sup>

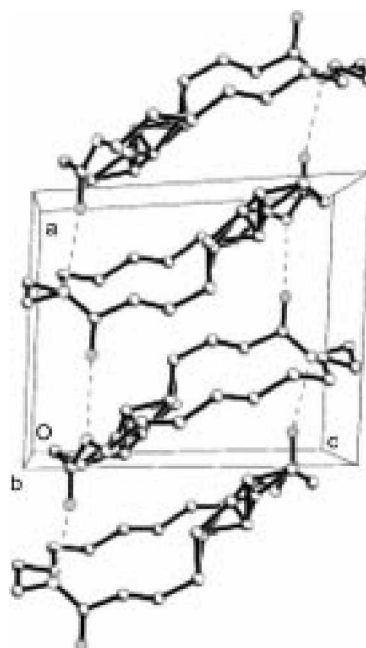
## Results and Discussion

Compound (2), compound (3) and compound (4) was elucidated as dihexylbenzene-1,2-dicarboxylate (2), 2,3,7,8-tetrahydrochromeno[5,4,3-*cde*]chromene-5,10-dione (ellagic acid 3), 3,4,5-trihydroxybenzoic acid (4) ellagic acid respectively based on the spectroscopy data s. The diagram of compound (1) was showed in Figure 1. Data of NMR of compound (1) was showed in Table 4. H-H COSY spectrum showed that proton signal at 3.24(H1) correlate to proton signal at 1.53(H2), proton signal at 1.35(H3) correlates to (H2) proton signal at 2.21(H12) correlates to proton signal at 1.66(H13), proton signal at 1.66 (H13) correlates to the proton signal at 1.37(H14). Meanwhile C-H COSY spectrum showed that proton signal at 3.24(H1) correlates to the carbon signal at 39.95(C1), proton signal at 2.21(H12) correlates to carbon signal at 36.97(C12), the proton signal at 1.65(H13) correlates the carbon signal at 27.07(C13), proton signal at 1.37(H14) correlates to the carbon signal at 30.16 (C14), the proton signal at 1.37(H15,16) correlates to the carbon signal at 29.93(C15,16), the proton signal at 1.35(H4) correlates to the carbon signal at 30.15(C4), the proton signal at 1.53(H2) correlates to the carbon signal at 30.54(C2).

The IR spectra showed the function group amide, signal at  $3288\text{ cm}^{-1}$  and  $3086\text{ cm}^{-1}$  are the absorption of stretching vibration of bond N-H on amide group. Signal at  $1638.4\text{ cm}^{-1}$

**Table 1.** Crystal data and structure refinement

Empirical formula	C20 H38 N2 O2
Formula weight	338.52
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	$a = 9.588(1)\text{ Å}$ $\alpha = 68.18(1)^\circ$ $b = 9.850(1)\text{ Å}$ $\beta = 84.98(1)^\circ$ $c = 11.810(1)\text{ Å}$ $\gamma = 86.03(1)^\circ$
Volume, Z	1030.66(17) Å <sup>3</sup> , 2
Density (calculated)	1.091 g m <sup>-3</sup>
Absorption coefficient	0.069 mm <sup>-1</sup>
F(000)	376
Crystal size	0.50 × 0.42 × 0.40 mm
Theta range for data collection	1.86-25.00°
Limiting indices	$0 \leq h \leq 11$ , $-10 \leq k \leq 10$ , $-13 \leq l \leq 14$
Reflections collected	3902
Independent reflections	3553 [R(int) = 0.0122]
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints parameters	3553 / 7 / 248
Goodness-of-fit on F <sup>2</sup>	1.017
Final R indices [I > 2(I)]	R1 = 0.0554, wR2 = 0.1485
R indices (all data)	R1 = 0.0928, wR2 = 0.1655
Extinction coefficient	0.029(6)
Largest diff. peak and hole	0.397 and -0.343 e.Å <sup>-3</sup>



**Figure 3.** A stereoscopic illustration of the unit cell packing of the title compound.

**Table 2.** Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $10^3 \times \text{\AA}^2$ ).  $U_{\text{eq}}$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor

Atom	<i>x a</i>	<i>y b</i>	<i>z c</i>	$U_{\text{eq}}$
O(1)	4069(2)	3093(2)	2007(2)	72(1)
O(2)	10988(2)	-4126(2)	8473(2)	73(1)
N(1)	6252(2)	3377(2)	1125(2)	53(1)
N(2)	8800(2)	-4263(2)	8033(2)	53(1)
C(1)	5935(3)	3120(3)	43(2)	59(1)
C(2)	6652(3)	1710(3)	-6(2)	58(1)
C(3)	6300(3)	353(2)	1092(2)	55(1)
C(4)	7016(3)	-1038(3)	1016(2)	60(1)
C(5)	6803(3)	-2410(3)	2154(2)	62(1)
C(6)	7562(3)	-2417(3)	3235(2)	61(1)
C(7)	7425(3)	-3815(3)	4360(2)	57(1)
C(8)	8275(3)	-3837(3)	5398(2)	59(1)
C(9)	8175(3)	-5238(3)	6507(2)	57(1)
C(10)	9139(3)	-5354(3)	7492(2)	60(1)
C(11)	9740(2)	-3725(3)	8488(2)	54(1)
C(12)	9244(3)	-2562(3)	8986(2)	66(1)
C(13)	9805(4)	-1077(3)	8209(3)	88(1)
C(14)	9481(6)	-259(7)	6888(4)	66(2)
C(15)	7989(5)	315(7)	6864(5)	64(2)
C(16)	7655(7)	901(13)	5528(6)	115(4)
C(17)	6229(4)	1669(4)	5425(3)	104(1)
C(13')	9805(4)	-1077(3)	8209(3)	88(1)
C(14')	8897(13)	-715(8)	7127(7)	112(5)
C(15')	8847(13)	893(7)	6333(9)	113(3)
C(16')	7804(6)	1420(20)	5343(10)	115(4)
C(17')	6229(4)	1669(4)	5425(3)	104(1)
C(18)	5556(4)	1899(3)	4258(3)	89(1)
C(19)	5867(2)	3314(3)	3187(2)	59(1)
C(20)	5317(2)	3273(2)	2048(2)	50(1)

is the absorption of stretching vibration of bond C=O. The absorption of carboxyl group shifted from normal absorption of carboxyl group due to intermolecular hydrogen bond N-H...O=C. The intermolecular hydrogen bond N-H...O=C also affected the absorption of bending vibration of bond N-H.

A summary of data collection and structure refinement is listed in Table 1. The final atomic parameters are given in Table 2. Selected bond lengths and bond angles are presented in Table 3. Crystal structure of title compound was showed in Figure 2. A stereoscopic illustration of the unit cell packing of the title compound was showed in Figure 3.

A disorder is observed in a block, C13 → C14 → C17, which is embedded in chain C11-C20. The angles of C-C bonds in this block are showed in Table 3. In the two alternative blocks, carbon-carbon angles are different. The angle of C(14)-C(15)-C(16) is 105.8(4)°, and C(14')-C(15')-C(16') 117.7(10)°. Intermolecular hydrogen bonds N-H...O is the main contribution to crystal formation. Bond length 2.920 Å and bond angle 173° is determined for N1-H1...O2. 2.905 Å and 180° is for N2-H2...O1. Meanwhile another kind of intermolecular hydrogen bond C-H...O appear in the crystal. Bond length 3.614 Å is calculated for C1-H...O.

**Table 3.** Selected bonds [Å] and angles [°]

O(1)-C(20)	1.229(2)	C(11)-N(2)-C(10)	123.3(2)
O(2)-C(11)	1.235(3)	C(1)-N(2)-H(2)	118.5(18)
N(1)-C(20)	1.327(3)	C(10)-N(2)-H(2)	118.0(18)
N(1)-C(1)	1.452(3)	N(1)-C(1)-C(2)	111.84(18)
N(1)-H(1)	0.82(2)	C(3)-C(4)-C(5)	115.4(2)
N(2)-C(11)	1.321(3)	N(2)-C(10)-C(9)	112.8(2)
N(2)-C(10)	1.447(3)	O(2)-C(11)-N(2)	121.5(2)
N(2)-H(2)	0.83(3)	O(2)-C(11)-C(12)	121.0(2)
C(1)-C(2)	1.524(3)	N(2)-C(11)-C(12)	117.5(2)
C(2)-C(3)	1.510(3)	C(11)-C(12)-C(13)	112.4(2)
C(3)-C(4)	1.519(3)	C(14)-C(13)-C(12)	123.6(3)
C(7)-C(8)	1.523(3)	C(14)-C(15)-C(16)	105.8(4)
C(8)-C(9)	1.511(3)	C(17)-C(16)-C(15)	108.3(4)
C(9)-C(10)	1.516(3)	C(18)-C(17)-C(16)	114.5(4)
C(15)-C(16)	1.521(4)	C(14')-C(15')-C(16')	117.7(10)
C(14')-C(15')	1.512(4)	H(16C)-C(16')-H(16D)	105.7
C(15')-C(16')	1.522(4)	C(17)-C(18)-C(19)	116.5(3)
C(18)-C(19)	1.520(4)	C(20)-C(19)-C(18)	110.0(2)
C(19)-C(20)	1.502(3)	O(1)-C(20)-N(1)	122.5(2)
C(20)-N(1)-C(1)	123.3(2)	O(1)-C(20)-C(19)	120.8(2)
C(20)-N(1)-H(1)	117.9(17)	O(1)-C(20)-C(19)	116.6(2)
C(1)-N(1)-H(1)	118.7(17)		

**Table 4.** NMR data of compound 1

Atoms	$^1\text{H}$	$^{13}\text{C}$	HMBC
1.10	3.23	39.95	3.8,2.9
2.9	1.53	30.53	
3.8	1.35	27.66	
4.7	1.35	30.15	
5.6	1.35	29.93	
11.20		176.28	
12.19	2.21	36.97	13.18,14.17
13.18	1.65	27.07	14.17,12.19
14.17	1.37	30.16	12.19,13.18,15.16
15.16	1.37	29.93	11.19,13.18

3.422 Å for C19-H...O, 3.616 Å for C12-H...O, and 3.641 Å for C14'-H...O. Those two kinds of intermolecular hydrogen bond, N-H...O and C-H...O formed six-member rings between two molecules. Because of those six-member rings, the chain block C11 → C14 → C17 → C19 has to adopt a limited bond rotating degrees of freedom, and has to be in a strictly tough situation and cause angle strain. The effects of the angle strain contributed to many C-C-C angles shifting off 109.5°. There are not any intramolecular hydrogen-bonds in the crystal just as other lactams.<sup>17,18</sup> The limited bond rotation caused limitation of chain flexibility. Those limitations made atoms at this block not to adopt stably low energy states. The limited flexibility caused the disorder of some atoms then brought about multiple conformations that decreased the symmetry of molecules in crystal cells. That decreasing symmetry of array of atoms and limited flexibility in this block caused multiple conformations in molecular resulted partial disorder in crystal cell units.

### Conclusion

Compound (1) 1,12-diazacyclodocosane-2,11-dione was elucidated by spectroscopy methods and X-ray signal crystal crystallography. The structure of the title compound showed a disorder block. In the disorder block, C-C-C bond angles are different in two conformations meanwhile there aren't differences among H-C-H angles. C-H...O bonds formed among C1-H, C19-H, C12-H, C14'-H and O in other molecules limited flexibility of this block. The main cause of disorder in the crystal structure was due to limited flexibility and decreasing symmetry of array of atoms of block C11 → C14 → C17 → C19.

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### References

1. Thyagarajan, S. P. *et al. The Lancet*. **1988**, *1*, 764.
2. Wan, L.; Jiang, Z.-Z.; Huang, B. *Z. Xinzhongyi*. **1997**, *29*(5), 39 (China).
3. Ogata, T.; Higuchi, H. *et al. AIDS Res. Hum. Retroviruses*. **1992**, *8*(11), 1937.
4. Calixto, J. B.; Santos, R. S. A.; Paulino, N. *Cient. Cult.* **1997**, *49*(5/6), 422.
5. Joy, K. L.; Kuttan, R. *J. Clin. Biochem. Nutr.* **1998**, *24*(3), 133.
6. Ott, M.; Thyagarajan, S. P.; Gupta, S. *Eur. J. Clin. Invest.* **1997**, *27*(1), 908.
7. Lee, C. D.; Ott, M.; Thyagarajan, S. P. *Eur. J. Clin. Invest.* **1996**, *26*(12), 1069.
8. Syamasundar, K. V.; Bikram Singh; Thakur, R. S. *J. Ethnopharmacol.* **1985**, *14*(1), 41.
9. Hussain, R. A.; Dickey, J.K.; Rosser, M. P. *J. Nat. Prod.* **1995**, *58*(10), 1515.
10. Polya, G. M.; Wang, B. H. *et al. Phytochemistry* **1995**, *38*(2), 307.
11. Eur. Pat. Appl. *EP199*, 429, 1986.
12. Rajeshkumar, N. V.; Kuttan, R. *Journal of Ethnopharmacology* **2000**, *73*, 215.
13. Wei, W. X.; Gong, X. G.; Ishrud, O.; Pan, Y. J. *Bull. Korean Chem. Soc.* **2002**, *23*(6), 896.
14. Gutman, A. I.; Meyer, E.; Xu, Y.; Abell, C. *Tetrahedron Letter* **1992**, *33*(27), 3943.
15. Sheldrick, G. M. *SHELXTL-Plus, Structure Determination Software Programs, Siemens Analytical X-Ray Instruments*, Madison, WI, 1990.
16. *International Tables for X-ray Crystallography*; VOL. IV, Table 2.2A, Kynoch Press: Birmingham, England, 1974.
17. Suetton, P. W.; Bradley, A.; Mark, R. J.; Elsegood, M. R. J.; Farras, J.; Jackson, R. F. W. *Tetrahedron Letters* **1999**, *40*, 2629.
18. Wawrzycka, I.; Stepniak, K.; Awomir, M. S.; Kozioladeusz Lis Anna E.; Abboud, K. A. *Journal of Molecular Structure* **1999**, *474*, 157.