Crystal structure of diethyl 4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate, $C_{19}H_{21}NO_4$, *an multidrug resistance reversal agent from Jatropha elliptica*

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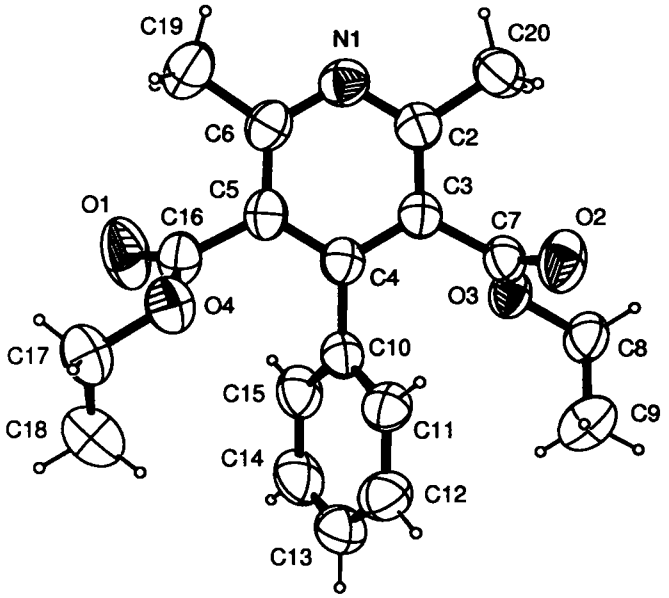

Abstract

$C_{19}H_{21}NO_4$, monoclinic, $P12_1/n1$ (no. 14), $a = 11.204(5)$ Å, $b = 8.368(5)$ Å, $c = 18.817(5)$ Å, $\beta = 99.366(5)°$, $V = 1740.7$ Å^3, $Z = 4$, $R_{gt}(F) = 0.054$, $wR_{ref}(F^2) = 0.154$, $T = 293$ K.

Source of material

For the extraction and identification of the title compound, the rhizomes of *Jatropha elliptica* (2.5 kg) were collected, dried and powdered and extracted by percolation with ethanol (90 %). The solvent was removed by distillation under reduced pressure, giving 313.1 g of crude ethanol extract. A sample of 183.4 g of crude extract was incorporated into silica gel (300 g) and extracted successively with hexane (3 l), chloroform (3 l), ethyl acetate (3 l), ethanol (3 l) and ethanol/acetic acid (1 %) (3 l) giving, respectively, the hexane (52.9 g), chloroform (33.7 g), ethyl acetate (18.8 g), ethanol (50.2 g) and the ethanol/acetic acid (9.30 g) fractions after removal of the solvents. The ethyl acetate fraction (18.8 g) was submitted to chromatography on a silica gel column (380 g). Fractions F-(16-21) eluted with ethyl acetate showed the same characteristics when compared by TLC and were put together (2.50 g). Recrystallization from hot hexane furnished a white crystal (1.5 g, m.p. 60-61 °C).

Discussion

Jatropha elliptica Muell. Arg. (Euphorbiaceae), a shrub annual herb distributed throughout the North and the West of Brazil and has been reported to possess several medicinal properties [1-3]. *Jatropha elliptica* is used in the folk medicine for the treatment of neoplasia, inflammation, ulcers and diuretic diseases among others [2]. The ethanolic extract of root has shown molluscicidal activity. As part of an ongoing project to identify plant natural products with antibacterial activity, bioassay guided isolation of an extract of *Jatropha elliptica* led to a penta-substituted pyridine, namely diethyl 4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate. This compound was assayed for *in vitro* antibacterial and resistance-modifying activity against strains of *Staphylococcus aureus* possessing the MsrA and NorA resistance efflux mechanisms. Antibiotic efflux studies indicated that the title compound acts as an inhibitor of the NorA efflux pump and restores the level of intracellular drug concentration [4].

In the crystal structure of the title compound, the conformation of the piperidine ring is planar and the main deviation of the atoms to the average least squares plane is 0.010 Å. The puckering parameters for this conformation are: $q_2 = 0.413$ Å, $q_3 = 0.211$ Å, $Q = 0.464$ Å, $\tau = 62.9°$ and $\varphi = 7.9°$ [5]. C7, C16, C19 and C20 atoms are on the same average plane of the piperidine ring. The ethyl acetate groups are in opposite sides related to the plane of the heterocyclic ring. The dihedral angle between the mean least-squares plane passing through the atoms of the aromatic ring and the other averaged plane passing through the piperidine ring is 57.4°. Neighbored molecules are held together through one weak hydrogen interaction: C–H···N, where d(C8···N^i) = 3.370(2) Å, d(H8B···N^i) = 2.566(2) Å, d(C8—H8B) = 0.97 Å, ∠C8–H8B···N^i = 140° (symmetry operation i: x,y+1,z).

Table 1. Data collection and handling.

Crystal:	colorless prism, size 0.08 × 0.12 × 0.18 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	0.88 cm^{-1}
Diffractometer, scan mode:	Nonius 95mm KappaCCD, ω/φ
$2\theta_{max}$:	54.96°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	7043, 3940
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 2815
$N(param)_{refined}$:	218
Programs:	SHELXS-97 [6], SHELXL-97 [7], ORTEP-3 [8], WinGX [9]

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Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{iso}
H(20A)	4e	0.8358	-0.0882	1.0845	0.102
H(20B)	4e	0.8343	0.0991	1.0831	0.102
H(20C)	4e	0.9151	0.0047	1.0368	0.102
H(9A)	4e	0.8743	0.7120	0.9096	0.125
H(9B)	4e	0.7470	0.6421	0.8779	0.125
H(9C)	4e	0.8643	0.5433	0.8729	0.125
H(17A)	4e	0.3350	-0.1613	0.7044	0.092
H(17B)	4e	0.4366	-0.1447	0.6565	0.092
H(8A)	4e	0.9000	0.5162	0.9975	0.077
H(8B)	4e	0.7826	0.6151	1.0024	0.077
H(15)	4e	0.4276	0.2924	0.8444	0.079
H(11)	4e	0.7596	0.2313	0.7950	0.069
H(12)	4e	0.7204	0.4259	0.7078	0.082
H(14)	4e	0.3913	0.4890	0.7567	0.095
H(13)	4e	0.5371	0.5559	0.6892	0.091
H(19A)	4e	0.5230	-0.3467	0.9806	0.116
H(19B)	4e	0.4971	-0.3490	0.8962	0.116
H(19C)	4e	0.4103	-0.2561	0.9391	0.116
H(18A)	4e	0.2880	0.0447	0.6228	0.137
H(18B)	4e	0.4100	0.1304	0.6534	0.137
H(18C)	4e	0.3084	0.1139	0.7012	0.137

Table 3. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(3)	4e	0.7478(1)	0.3941(1)	0.96434(7)	0.0498(6)	0.0452(7)	0.0703(8)	-0.0020(5)	0.0087(6)	-0.0061(6)
O(4)	4e	0.4890(1)	-0.0696(2)	0.75790(7)	0.0584(7)	0.0726(9)	0.0602(8)	-0.0007(6)	0.0060(6)	-0.0111(6)
C(3)	4e	0.7188(1)	0.1213(2)	0.94054(9)	0.0433(8)	0.0439(9)	0.058(1)	0.0042(7)	0.0064(7)	-0.0045(7)
C(20)	4e	0.8398(2)	0.0045(3)	1.0549(1)	0.065(1)	0.068(1)	0.066(1)	0.006(1)	-0.0039(9)	0.003(1)
N(1)	4e	0.6614(1)	-0.1233(2)	0.99116(8)	0.0636(9)	0.0495(8)	0.0611(9)	0.0019(7)	0.0108(7)	-0.0016(7)
C(9)	4e	0.8269(2)	0.6162(3)	0.9020(1)	0.097(2)	0.064(1)	0.094(2)	-0.013(1)	0.031(1)	-0.001(1)
O(2)	4e	0.9073(1)	0.2551(2)	0.9404(1)	0.0424(7)	0.0669(9)	0.121(1)	0.0020(6)	0.0113(7)	-0.0040(8)
C(5)	4e	0.5469(2)	-0.0241(2)	0.8815(1)	0.0445(8)	0.056(1)	0.060(1)	-0.0031(7)	0.0094(7)	-0.0079(8)
C(4)	4e	0.6214(1)	0.1110(2)	0.88377(9)	0.0416(8)	0.0487(9)	0.057(1)	0.0026(7)	0.0083(7)	-0.0042(7)
C(10)	4e	0.5979(1)	0.2389(2)	0.8284(1)	0.0469(9)	0.0472(9)	0.057(1)	0.0007(7)	0.0009(7)	-0.0057(8)
C(7)	4e	0.8028(1)	0.2618(2)	0.9475(1)	0.0417(8)	0.051(1)	0.062(1)	0.0023(7)	0.0003(7)	-0.0012(8)
C(2)	4e	0.7363(2)	0.0012(2)	0.9927(1)	0.0525(9)	0.0470(9)	0.058(1)	0.0060(8)	0.0064(7)	-0.0054(8)
C(17)	4e	0.3991(2)	-0.0925(3)	0.6933(1)	0.077(1)	0.086(2)	0.063(1)	-0.003(1)	0.000(1)	-0.016(1)
O(1)	4e	0.3420(1)	-0.0601(3)	0.82460(9)	0.0495(8)	0.171(2)	0.079(1)	-0.029(1)	0.0104(7)	-0.015(1)
C(16)	4e	0.4467(2)	-0.0518(2)	0.8197(1)	0.052(1)	0.066(1)	0.063(1)	-0.0119(9)	0.0078(8)	-0.0077(9)
C(6)	4e	0.5683(2)	-0.1373(2)	0.9365(1)	0.058(1)	0.052(1)	0.062(1)	-0.0043(8)	0.0158(8)	-0.0069(8)
C(8)	4e	0.8191(2)	0.5404(2)	0.9729(1)	0.065(1)	0.050(1)	0.077(1)	-0.0089(8)	0.0057(9)	-0.0066(9)
C(15)	4e	0.4869(2)	0.3183(3)	0.8170(1)	0.0466(9)	0.066(1)	0.082(1)	0.0042(9)	0.0019(8)	-0.003(1)
C(11)	4e	0.6847(2)	0.2820(2)	0.7874(1)	0.056(1)	0.051(1)	0.067(1)	0.0033(8)	0.0095(8)	0.0005(8)
C(12)	4e	0.6615(2)	0.3992(2)	0.7354(1)	0.083(1)	0.057(1)	0.065(1)	-0.006(1)	0.011(1)	0.002(1)
C(14)	4e	0.4654(2)	0.4365(3)	0.7645(1)	0.061(1)	0.066(1)	0.101(2)	0.015(1)	-0.017(1)	0.005(1)
C(13)	4e	0.5522(2)	0.4766(3)	0.7241(1)	0.085(2)	0.060(1)	0.075(1)	-0.002(1)	-0.012(1)	0.009(1)
C(19)	4e	0.4928(2)	-0.2857(3)	0.9383(1)	0.080(1)	0.067(1)	0.087(2)	-0.022(1)	0.019(1)	-0.004(1)
C(18)	4e	0.3467(2)	0.0629(3)	0.6652(1)	0.087(2)	0.108(2)	0.073(2)	0.014(2)	-0.001(1)	0.000(1)

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