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Structural analysis of pyrrolidinones

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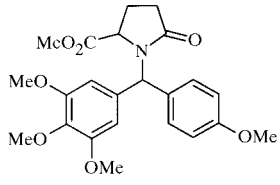
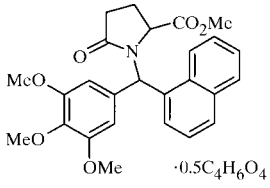
In the course of a study on pyrrolidinones, the crystal structures of four compounds, namely, methyl *N*-[(4-methoxyphenyl)(3,4,5-trimethoxyphenyl)methyl]pyroglutamate, $C_{23}H_{27}NO_7$, methyl *N*-[naphthyl-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamate diacetyl peroxide, $C_{26}H_{27}NO_6\cdot 0.5C_4H_6O_4$, 5-(3,4,5-trimethoxyphenyl)-1,2,3,11b-tetrahydro-5*H*-naphtho[1,8-*f*,*g*]indolizin-3-one, $C_{24}H_{23}NO_4$, and 5-(3,4,5-trimethoxyphenyl)-1,2,3,5,12,12a-hexahydronaphtho[1,2-*f*]indolizine-3,12-dione, $C_{25}H_{23}NO_5$, are presented, compared and discussed.

Comment

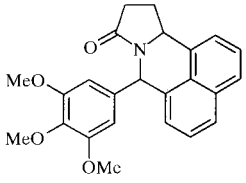
Azatoxin, an anti-cancer drug, is an inhibitor of both the topoisomerase II and the tubulin polymerization (Leteurtre *et al.*, 1995). Methyl *N*-[naphthyl-(3,4,5-trimethoxyphenyl)-methyl]pyroglutamate, is the precursor of 5-(3,4,5-trimethoxyphenyl)-1,2,3,11b-tetrahydro-5*H*-naphtho[1,8-*f*,*g*]-



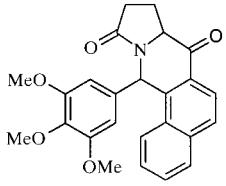
(I)



(II)



(III)



(IV)

indolizin-3-one, (III), and 5-(3,4,5-trimethoxyphenyl)-1,2,3,5,12,12a-hexahydronaphtho[1,2-*f*]indolizine-3,12-dione, (IV), two azatoxin analogues. Methyl *N*-[(4-methoxyphenyl)(3,4,5-trimethoxyphenyl)methyl]pyroglutamate, (I), is an aryl derivative of methyl *N*-[naphthyl-(3,4,5-trimethoxyphenyl)methyl]pyroglutamate diacetyl peroxide (II). Discussion of the geometry is based on the *SS* enantiomer.

A comparison of the molecular geometries shows the similarity of all bond lengths among the four compounds (Tables 1–4). In all cases (Fig. 1*a*–*d*), N18 is found to be clearly of sp^2 geometry [sums of bond angles around N18 are 360.0 (1), 359.6 (2), 359.9 (1) and 360.0 (2)° for compounds (I), (II), (III) and (IV), respectively (Tables 1–4)]. In compound (I), an π–π interaction orients the methyl ester group just above the trimethoxyphenyl ring, imposing a torsion angle C2—C1—N18—C19 close to 130° (Table 1) which is different from the one obtained in compound (II) where the intramolecular forces orient the methyl ester group just above the naphthyl ring [torsion angle close to 106.0 (2)° (Table 2)]. This observation is in agreement with NMR results (Legrand *et al.*, 1999). The formation of the covalent bond to obtain compounds (III) and (IV) does not modify significantly this torsion angle which lies close to 97° (Tables 3 and 4). Moreover, the formation of the covalent bond tends to make the bridged molecules nearly coplanar [N18—C1—C8—C17 for (III) (Table 3) and N18—C1—C8—C9 for (IV) (Table 4)] in comparison with compound (II). The C8—C1—C2—C3 torsion angle varies according to whether the molecule is bridged or not (Tables 1–4). In all compounds, the two *meta*-methoxy groups lie in the same plane as the aromatic ring (torsion angles near 0 or 180°, see Tables 1–4) and the *para*-methoxy group is out of plane. For the four compounds, the torsion angle of the *para*-methoxy group is close to 85° (Tables 1–4). The study of the packing of compound (II) shows the presence of a planar diacetyl peroxide co-crystallization molecule (torsion angles close to 180°) stacked between two naphthyl rings and situated near an inversion centre generating the other half of the molecule by symmetry (Table 2). A similar case of a planar peroxide molecule stacked between two aromatic rings has already been cited in the literature (Walter & McBride, 1981).

Experimental

The syntheses of compounds (I)–(IV) have been reported elsewhere (Legrand *et al.*, 2000). Crystals were obtained by slow evaporation of an ethanol solution [compounds (I), (III) and (IV)] or an ethyl acetate–diethyl ether solution [compound (II)] at room temperature.

Compound (I)

Crystal data

$C_{23}H_{27}NO_7$
M_r = 429.46
Monoclinic, $P2_1/n$
a = 8.481 (1) Å
b = 14.206 (1) Å
c = 18.273 (1) Å
β = 90.538 (4)°
V = 2201.5 (3) Å^3
Z = 4
D_x = 1.296 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 30–42°
μ = 0.797 mm^{-1}
T = 293 (2) K
Prism, colourless
0.30 × 0.30 × 0.20 mm

Table 1
Selected geometric parameters (Å, °) for (I).

C1—N18	1.464 (2)	N18—C22	1.456 (2)
C1—C8	1.521 (2)	C19—C20	1.512 (2)
C1—C2	1.527 (2)	C20—C21	1.514 (2)
N18—C19	1.357 (2)	C21—C22	1.546 (2)
C19—N18—C22	113.7 (1)	C22—N18—C1	124.2 (1)
C19—N18—C1	122.1 (1)		
C8—C1—C2—C3	−49.0 (2)	C6—C5—O25—C26	87.9 (2)
C2—C1—N18—C19	129.2 (1)	C7—C6—O27—C28	−0.8 (2)
C5—C4—O23—C24	168.4 (2)		

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.796, T_{max} = 0.857
6885 measured reflections
4331 independent reflections
3939 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 71.91°
$h = -10 \rightarrow 10$
$k = 0 \rightarrow 17$
$l = 0 \rightarrow 22$
3 standard reflections
every 200 reflections
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.122
S = 1.058
4331 reflections
$w = 1/[\sigma^2(F_o^2) + (0.0648P)^2 + 0.5599P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
283 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0104 (5)

Compound (II)

Crystal data

$C_{26}H_{27}NO_6{\cdot}0.5C_4H_6O_4$
M_r = 508.55
Triclinic, $P\overline{1}$
a = 9.190 (1) Å
b = 11.333 (1) Å
c = 14.756 (1) Å
α = 89.292 (7)°
β = 73.923 (5)°
γ = 66.722 (7)°
V = 1348.3 (2) Å^3
Z = 2
D_x = 1.253 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 30–42°
μ = 0.763 mm^{-1}
T = 293 (2) K
Prism, colourless
0.40 × 0.30 × 0.30 mm

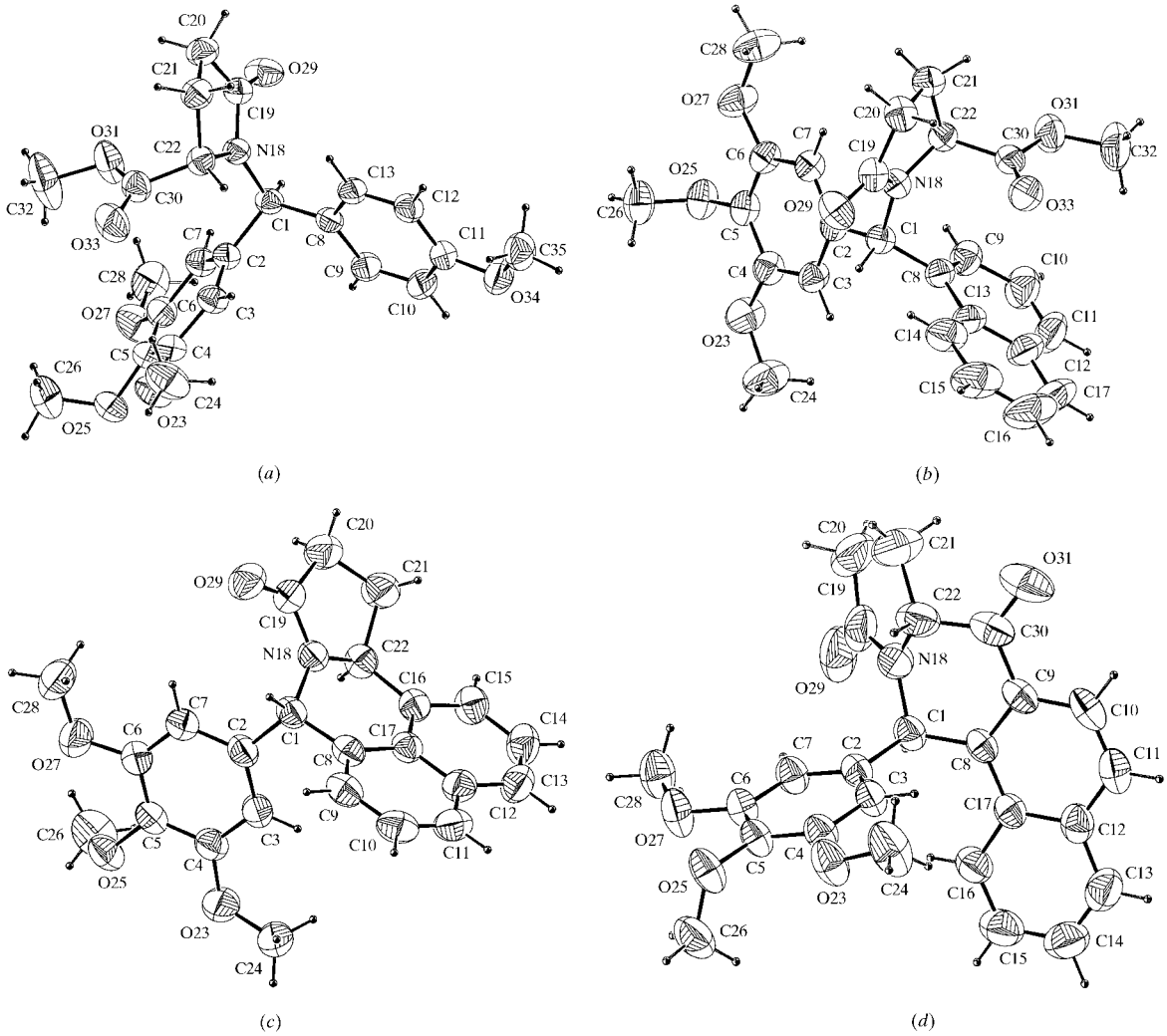


Figure 1
*ORTEP*II (Johnson, 1976) representation of (*a*) (I), (*b*) (II) (without the diacetyl peroxide moiety), (*c*) (III) and (*d*) (IV), with displacement ellipsoids shown at the 50% probability level.

Data collection

Enraf–Nonius CAD-4 diffractometer	R_{int} = 0.008
$\theta/2\theta$ scans	θ_{max} = 71.96°
Absorption correction: ψ scan (North *et al.*, 1968)	$h = 0 \rightarrow 11$
T_{min} = 0.750, T_{max} = 0.804	$k = -12 \rightarrow 13$
5621 measured reflections	$l = -17 \rightarrow 18$
5274 independent reflections	3 standard reflections every 200 reflections
4947 reflections with $I > 2\sigma(I)$	intensity decay: 8%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.1495P)^2 + 0.3694P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.065	$\Delta\rho_{max}$ = 0.35 e Å^{-3}
$wR(F^2)$ = 0.210	$\Delta\rho_{min}$ = −0.60 e Å^{-3}
S = 1.002	Extinction correction: *SHELXL*97 (Sheldrick, 1997)
5274 reflections	Extinction coefficient: 0.0127 (15)
311 parameters	
H-atom parameters constrained	

Table 2
Selected geometric parameters (Å, °) for (II).

C1—N18	1.458 (2)	C19—C20	1.510 (2)
C1—C8	1.521 (2)	C20—C21	1.510 (3)
C1—C2	1.532 (2)	C21—C22	1.550 (2)
N18—C19	1.360 (2)	O41—O41^{i}	1.424 (6)
N18—C22	1.454 (2)		
C19—N18—C22	113.3 (1)	C22—N18—C1	124.4 (1)
C19—N18—C1	122.0 (1)		
C8—C1—C2—C3	56.2 (2)	C6—C5—O25—C26	−87.3 (2)
N18—C1—C8—C13	86.5 (2)	C7—C6—O27—C28	1.1 (3)
C2—C1—N18—C19	106.0 (2)	O41^{i}—O41—C43—O42	−0.6 (1)
C5—C4—O23—C24	−177.1 (2)	O41^{i}—O41—C43—C44	178.4 (5)

Symmetry code: (i) $2-x, 2-y, -z$.

Compound (III)

Crystal data

$C_{24}H_{23}NO_4$	D_x = 1.301 Mg m^{-3}
M_r = 389.43	Cu $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 25 reflections
a = 9.909 (1) Å	θ = 30–42°
b = 8.519 (1) Å	μ = 0.716 mm^{-1}
c = 23.793 (1) Å	T = 293 (2) K
β = 98.104 (4)°	Prism, colourless
V = 1988.4 (3) Å^3	0.40 × 0.40 × 0.30 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 diffractometer	R_{int} = 0.012
$\theta/2\theta$ scans	θ_{max} = 71.90°
Absorption correction: ψ scan (North *et al.*, 1968)	$h = -12 \rightarrow 12$
T_{min} = 0.763, T_{max} = 0.814	$k = 0 \rightarrow 10$
5132 measured reflections	$l = 0 \rightarrow 29$
3899 independent reflections	3 standard reflections every 200 reflections
3676 reflections with $I > 2\sigma(I)$	intensity decay: 7%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0607P)^2 + 0.4150P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.042	$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$wR(F^2)$ = 0.121	$\Delta\rho_{min}$ = −0.23 e Å^{-3}
S = 1.076	Extinction correction: *SHELXL*97 (Sheldrick, 1997)
3899 reflections	Extinction coefficient: 0.0041 (4)
263 parameters	
H-atom parameters constrained	

Table 3
Selected geometric parameters (Å, °) for (III).

C1—N18	1.460 (2)	N18—C22	1.460 (2)
C1—C8	1.508 (2)	C19—C20	1.511 (2)
C1—C2	1.536 (2)	C20—C21	1.507 (2)
N18—C19	1.343 (2)	C21—C22	1.538 (2)
C19—N18—C22	114.4 (1)	C22—N18—C1	121.3 (1)
C19—N18—C1	124.3 (1)		
C8—C1—C2—C3	−13.1 (2)	C5—C4—O23—C24	−167.0 (1)
N18—C1—C8—C17	−26.4 (2)	C6—C5—O25—C26	79.5 (2)
C2—C1—N18—C19	97.7 (2)	C7—C6—O27—C28	−2.8 (2)

Compound (IV)

Crystal data

$C_{25}H_{23}NO_5$	D_x = 1.318 Mg m^{-3}
M_r = 417.44	Cu $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 25 reflections
a = 10.868 (1) Å	θ = 30–42°
b = 12.937 (1) Å	μ = 0.752 mm^{-1}
c = 15.049 (1) Å	T = 293 (2) K
β = 96.009 (4)°	Prism, colourless
V = 2104.3 (3) Å^3	0.30 × 0.30 × 0.15 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 diffractometer	R_{int} = 0.019
$\theta/2\theta$ scans	θ_{max} = 71.90°
Absorption correction: ψ scan (North *et al.*, 1968)	$h = 0 \rightarrow 13$
T_{min} = 0.806, T_{max} = 0.896	$k = 0 \rightarrow 15$
7065 measured reflections	$l = -18 \rightarrow 18$
4129 independent reflections	3 standard reflections every 200 reflections
3427 reflections with $I > 2\sigma(I)$	intensity decay: 2%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0553P)^2 + 0.3806P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.040	$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$wR(F^2)$ = 0.118	$\Delta\rho_{min}$ = −0.15 e Å^{-3}
S = 1.051	Extinction correction: *SHELXL*97 (Sheldrick, 1997)
4129 reflections	Extinction coefficient: 0.0046 (4)
281 parameters	
H-atom parameters constrained	

Table 4
Selected geometric parameters (Å, °) for (IV).

C1—N18	1.454 (2)	N18—C22	1.454 (2)
C1—C8	1.512 (2)	C19—C20	1.517 (3)
C1—C2	1.533 (2)	C20—C21	1.497 (4)
N18—C19	1.343 (2)	C21—C22	1.535 (3)
C19—N18—C22	115.4 (2)	C22—N18—C1	120.4 (1)
C19—N18—C1	124.3 (2)		
C8—C1—C2—C3	−17.7 (2)	C5—C4—O23—C24	169.2 (2)
N18—C1—C8—C9	−12.8 (2)	C6—C5—O25—C26	−80.5 (2)
C2—C1—N18—C19	95.6 (2)	C7—C6—O27—C28	9.0 (2)

For all compounds, data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1992); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1990); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GS1054). Services for accessing these data are described at the back of the journal.

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