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The isomeric compounds nimbolide and isonimbolide

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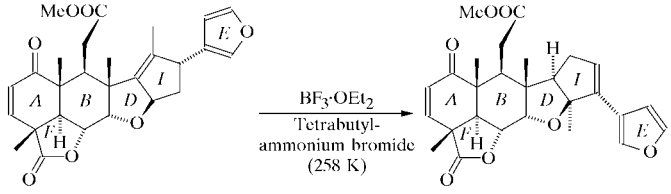
Nimbolide [systematic name: (4α,5α,6α,7α,15β,17α)-7,15:-21,23-diepoxy-6-hydroxy-4,8-dimethyl-1-oxo-18,24-dinor-11,-12-secochola-2,13,20,22-tetraene-4,11-dicarboxylic acid γ-lactone methyl ester], $C_{27}H_{30}O_7$, was isolated from the leaves of *Azadirachta indica*, and its isomer, isonimbolide [systematic name: (4α,5α,6α,7α,15α)-7,15:21,23-diepoxy-6-hydroxy-4,8-dimethyl-1-oxo-18,24-dinor-11,12-secochola-2,16,20,22-tetraene-4,11-dicarboxylic acid γ-lactone methyl ester], was prepared from a novel rearrangement reaction of nimbolide, using boron trifluoride etherate and tetrabutylammonium bromide. The reaction conditions are probably responsible for the ether cleavage, double-bond rearrangement and reformation of the ether linkage. As a result, there are conformational changes in two cyclopentane rings and the side-chain –CH_2COOMe group. In isonimbolide, an $R_4^4(24)$ hydrogen-bond motif is observed.

Comment

Neem (*Azadirachta indica*) and its constituents have been shown to possess bioinsecticidal activity at different levels (Chawla *et al.*, 1996; Govindachari, 1992; Govindachari, Narasimhan *et al.*, 1996; Govindachari & Geetha Gopalakrishnan, 1998). More than 300 limonoids have been isolated and many of them belong to the class of tetranortriterpenoids, the crystal structures of many of which have been established (Govindachari *et al.*, 1994; Govindachari, Geetha Gopalakrishnan *et al.*, 1996; Kabaleeswaran *et al.*, 1994, 1997, 1999; Malathi *et al.*, 2003). It has also been shown that the bioinsecticidal activity can be enhanced by photo-oxidation and microwave-induced oxidation (Suresh *et al.*, 2002; Gopalakrishnan *et al.*, 2001; Geetha Gopalakrishnan *et al.*, 2000). The present paper reports the structures of two compounds, namely nimbolide, (I), a tetranortriterpenoid isolated from the leaves of *Azadirachta indica*, and a novel rearranged product, isonimbolide, (II). The rearranged product was synthesized with a view to enhancing the activity of the native compound through the reaction of nimbolide with a Lewis acid, $BF_3{\cdot}OEt_2$, in the presence of tetrabutylammonium bromide.



(I) (II)

The chemical modification brought about the cleavage of the ether linkage between atoms C7 and C15. Due to stability constraints, there is a rearrangement of the double bond, from C13═C14 in nimbolide to C16═C17 in isonimbolide, along with ring closure between C7 and C13, resulting in the reformation of the ether linkage. Hence, chemically, nimbolide and its isomer differ in the ether linkage, which is between C7

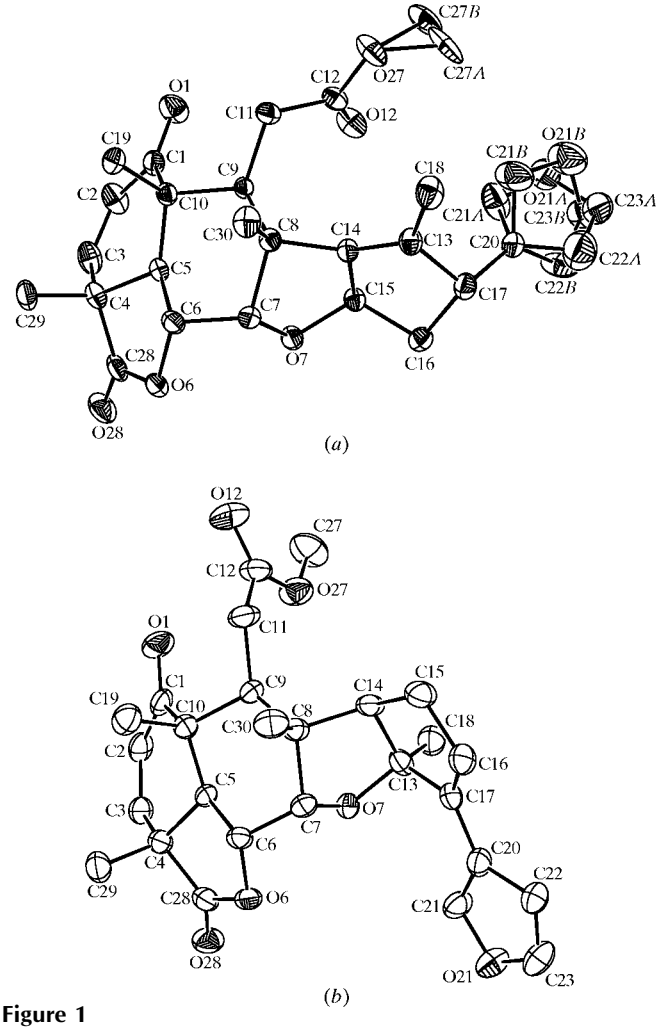


Figure 1
The molecular structures of (*a*) nimbolide, (I), and (*b*) isonimbolide, (II), with the atom-numbering schemes. Displacement ellipsoids are drawn at the 30% probability level and H atoms have been omitted.

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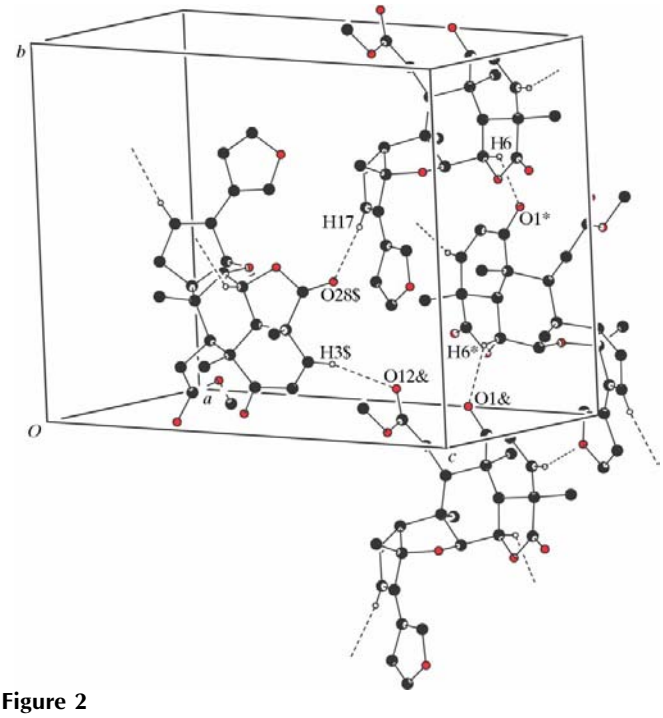

Figure 2
A view of the supramolecular structure of isonimbolide, showing the $R_4^4(24)$ motif. The suffixes *, $ and & denote symmetry positions $(1-x, y+\frac{1}{2}, \frac{1}{2}-z)$, $(\frac{3}{2}-x, 1-y, z-\frac{1}{2})$ and $(x, y-1, z)$, respectively.

and C15 in nimbolide, and C7 and C13 in isonimbolide (scheme and Fig. 1). Nimbolide and isonimbolide thus differ primarily in the orientation of the $-CH_2COOMe$ group attached to C9. The orientation of this group can be defined by the C8—C9—C11—C12 torsion angle, which is 91.1 (5)° in nimbolide and 132.5 (6)° in isonimbolide. The orientation of the methoxycarbonyl group (C9—C11—C12—O27) is *−ac* [−148.8 (5)°] and *sp* [−29.0 (9)°] (Klyne & Prelog, 1960) in nimbolide and isonimbolide, respectively. These differences in the side-chain conformation arise due to the change in the orientation of ring *I* and the methyl group attached to C13 between nimbolide and isonimbolide. The migration of the double bond in ring *I* of isonimbolide accompanies a difference in the fusion of rings *I*/*D*, which is quasi-*trans* in nimbolide and *trans* in isonimbolide.

The ring junctions *A*/*B*, *A*/*F*, *B*/*F* and *B*/*D* in both structures are *trans*, *trans*, *trans* and *cis*, respectively. In isonimbolide, atom C13 is sp^3 hybridized and the C18 methyl group attached to this atom is in an α conformation. There are considerable variations in the torsion angles involving the atoms of rings *D* and *I*, which indicates that the reaction centre would have been atom O7, which is a potential centre for the coordination of the Lewis acid. In both structures, rings *A*, *B* and *F* have sofa, chair and half-chair conformations, respectively (Cremer & Pople, 1975), and the methyl atoms C19, C29 and C30 are in β conformations. In nimbolide, the furan ring at C17 shows rotational disorder about the C17—C20 bond. This rotational flexibility results in disorder of all the atoms of the furan ring except C20, and these atoms show split positions, *viz*. C21*A*, O21*A*, C22*A* and C23*A*, and C21*B*, O21*B*, C22*B* and C23*B*. However, the furan ring of isonimbolide shows no disorder (Fig. 1*b*). The orientation of this furan ring is described by the C16—C17—C20—C22 torsion angles, which are −101.2 (14) and −55.3 (13)° for the congeners *A* and *B*, respectively, in nimbolide, and −12.1 (10)° in isonimbolide. The angles between the least-squares planes of ring *A* and furan ring *E* are 123.0 (7) and 95.6 (9)° for disorder components *A* and *B*, respectively, in nimbolide, and 151.4 (2)° in isonimbolide.

No significant hydrogen-bonding interactions are seen in nimbolide, but an interesting hydrogen-bonding pattern is present in isonimbolide, for which three hydrogen-bonded chain motifs (Bernstein *et al.*, 1995) are observed (Table 1). The first, C3···O12$(\frac{3}{2}-x, -y, \frac{1}{2}+z)$, produces a *C*(9) chain parallel to the *z* axis. The second chain, a *C*(6) motif mediated by C6···O1$(1-x, \frac{1}{2}+y, \frac{1}{2}-z)$, runs parallel to the *y* axis. The third, linked by C16···O28$(\frac{3}{2}-x, 1-y, z-\frac{1}{2})$, forms a *C*(9) chain along the *z* axis. These combine to generate a ring with an $R_4^4(24)$ motif (Fig. 2).

Experimental

Nimbolide, (I), was isolated from the the fresh uncrushed leaves of *Azadirachta indica* following the procedure described by Govindachari *et al.* (1999). To prepare isonimbolide, (II), nimbolide (200 mg) was dissolved in chloroform (analytical reagent, 200 ml) at 258 K. To this solution, tetrabutylammonium bromide (145 mg) and boron triflouride etherate (0.3 ml) were added. The reaction mixture was allowed to reach room temperature and was then stirred for 6 h. On completion (monitored by thin-layer chromatography), the reaction was quenched with solid sodium bicarbonate. The organic layer was filtered and concentrated under reduced pressure to yield crude isonimbolide. Flash column chromatography of the product over silica gel using hexane–ethyl acetate (3:2) as eluant furnished pure isonimbolide (final yield 52%).

Compound (I)

Crystal data

$C_{27}H_{30}O_7$
M_r = 466.51
Orthorhombic, $P2_12_12_1$
a = 12.115 (3) Å
b = 12.225 (4) Å
c = 15.710 (3) Å
V = 2326.8 (10) Å^3
Z = 4
D_x = 1.332 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 15–30°
μ = 0.79 mm^{-1}
T = 293 (2) K
Rod, colourless
0.40 × 0.25 × 0.15 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Non–profiled $\omega/2\theta$ scans
2806 measured reflections
2695 independent reflections
1958 reflections with $I > 2\sigma(I)$
R_{int} = 0.119
θ_{max} = 75.2°
$h = -15 \rightarrow 15$
$k = -5 \rightarrow 15$
$l = -10 \rightarrow 19$
3 standard reflections
every 200 reflections
intensity decay: 4%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.059
$wR(F^2)$ = 0.183
S = 1.00
2695 reflections
355 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1148P)^2 + 0.6918P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.015
$\Delta\rho_{max}$ = 0.41 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0029 (6)

Compound (II)

Crystal data

$C_{27}H_{30}O_7$	D_x = 1.325 Mg m^{-3}
M_r = 466.51	Mo $K\alpha$ radiation
Orthorhombic, $P2_12_12_1$	Cell parameters from 25 reflections
a = 9.026 (2) Å	θ = 5–12°
b = 14.009 (18) Å	μ = 0.10 mm^{-1}
c = 18.495 (5) Å	T = 293 (2) K
V = 2339 (3) Å^3	Rod, colourless
Z = 4	0.40 × 0.25 × 0.20 mm

Data collection

Enraf-Nonius CAD-4 diffractometer	θ_{max} = 30.6°
Non–profiled $\omega/2\theta$ scan	$h = 0 \rightarrow 12$
3895 measured reflections	$k = 0 \rightarrow 19$
3864 independent reflections	$l = 0 \rightarrow 26$
1434 reflections with $I > 2\sigma(I)$	3 standard reflections
R_{int} = 0.019	every 200 reflections
	intensity decay: 3%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0844P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.066	$(\Delta/\sigma)_{max}$ = 0.001
$wR(F^2)$ = 0.198	$\Delta\rho_{max}$ = 0.23 e Å^{-3}
S = 0.98	$\Delta\rho_{min}$ = −0.23 e Å^{-3}
3864 reflections	Extinction correction: *SHELXL97* (Sheldrick, 1997)
308 parameters	Extinction coefficient: 0.015 (2)
H-atom parameters constrained	

Table 1
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
C3—H3···O12^{i}	0.93	2.56	3.466 (8)	163
C6—H6···O1^{ii}	0.98	2.50	3.244 (7)	132
C16—H17···O28^{iii}	0.93	2.47	3.387 (8)	169

Symmetry codes: (i) $-x+\frac{3}{2}, -y, z+\frac{1}{2}$; (ii) $-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$; (iii) $-x+\frac{3}{2}, -y+1, z-\frac{1}{2}$.

In the absence of suitable anomalous scatters, Friedel equivalents could not be used to determine the absolute structure. Refinement of the Flack (1983) parameter led to inconclusive values (Flack & Bernadinelli, 2000) [−0.8 (7) for nimbolide and −1 (3) for isonimbolide]. Therefore, the 103 and 34 Friedel equivalents of nimbolide and isonimbolide, respectively, were merged before the final refinements. The enantiomer employed in the refined model was chosen to agree with the accepted configuration of triterpenoids (Henderson *et al.*, 1968; Narayanan *et al.*, 1964; Harris *et al.*, 1968). The methyl and hydroxyl H atoms were constrained to an ideal geometry (C—H = 0.96 Å and O—H = 0.82 Å), with U_{iso}(H) = 1.5U_{eq}(parent atom), but were allowed to rotate freely about their C—C and C—O bonds, respectively; difference-map plots show that methyl H atoms at C18, C27 and C27*A* in (I) are not as well resolved. All remaining H atoms were placed in geometrically idealized positions (C—H = 0.97–0.98 Å) and constrained to ride on their parent atom, with U_{iso}(H) = 1.2U_{eq}(C). All the disordered atoms were restrained using SAME, SADI and DFIX restraints. A SIMU restraint was used for the chemically equivalent disordered congeners.

For both compounds, data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo, 1995); structure solution: *SHELXS97* (Sheldrick, 1997); structure refinement: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996); publication software: *SHELXL97* and *PARST97* (Nardelli, 1995).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA1106). Services for accessing these data are described at the back of the journal.

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