B(4)	0.2716 (5)	0.1468 (2)	0.4300 (4)	0.053 (2)
B(5)	0.1455 (5)	0.2039 (2)	0.3737 (4)	0.056 (2)
B(6)	0.1798 (4)	0.2197 (2)	0.2125 (4)	0.048 (2)
B(7)	0.4699 (5)	0.2043 (2)	0.2613 (4)	0.051 (2)
B(8)	0.4347 (5)	0.1857 (2)	0.4214 (4)	0.059 (2)
B(9)	0.2873 (5)	0.2328 (2)	0.4648 (5)	0.063 (2)
B(10)	0.2298 (5)	0.2779 (2)	0.3309 (5)	0.060 (2)
B(11)	0.3424 (5)	0.2609 (2)	0.2058 (4)	0.053 (2)
B(12)	0.4092 (5)	0.2680 (2)	0.3620 (4)	0.061 (2)
C(13)	0.3453 (3)	0.1515 (2)	0.0437 (3)	0.046 (1)
C(14)	0.2772 (4)	0.1812 (2)	−0.0567 (4)	0.069 (2)
C(15)	0.2961 (5)	0.1589 (3)	−0.1780 (4)	0.087 (2)
C(16)	0.3820 (6)	0.1069 (3)	−0.2026 (4)	0.085 (2)
C(17)	0.4512 (5)	0.0774 (2)	−0.1044 (4)	0.080 (2)
C(18)	0.4339 (4)	0.0996 (2)	0.0187 (4)	0.062 (2)
C(19)	0.1088 (4)	0.0046 (2)	0.3308 (3)	0.058 (1)
C(20)	0.2495 (5)	−0.0277 (2)	0.3505 (4)	0.085 (2)
C(21)	0.0054 (5)	−0.0494 (2)	0.2870 (4)	0.087 (2)
C(22)	−0.0737 (4)	0.1039 (2)	0.2065 (4)	0.065 (2)
C(23)	−0.1547 (5)	0.0741 (3)	0.0929 (4)	0.103 (2)
C(24)	−0.1560 (4)	0.0988 (2)	0.3277 (4)	0.090 (2)

Table 2. *Selected geometric parameters (Å, °)*

P—C(1)	1.879 (3)	C(1)—B(6)	1.731 (5)
P—C(19)	1.866 (4)	C(2)—C(13)	1.501 (5)
P—C(22)	1.881 (4)	C(19)—C(20)	1.519 (6)
C(1)—C(2)	1.769 (4)	C(19)—C(21)	1.540 (6)
C(1)—B(3)	1.730 (5)	C(22)—C(23)	1.544 (6)
C(1)—B(4)	1.710 (5)	C(22)—C(24)	1.522 (6)
C(1)—P—C(19)	104.4 (2)	B(6)—C(2)—C(13)	118.4 (3)
C(1)—P—C(22)	101.5 (2)	B(7)—C(2)—C(13)	120.7 (3)
C(19)—P—C(22)	104.0 (2)	B(11)—C(2)—C(13)	120.4 (3)
P—C(1)—C(2)	113.5 (2)	C(2)—C(13)—C(14)	120.9 (3)
P—C(1)—B(3)	116.6 (2)	C(2)—C(13)—C(18)	120.9 (3)
P—C(1)—B(4)	127.3 (2)	P—C(19)—C(20)	113.1 (3)
P—C(1)—B(5)	127.6 (2)	P—C(19)—C(21)	106.7 (3)
P—C(1)—B(6)	116.3 (2)	P—C(22)—C(23)	108.8 (3)
C(1)—C(2)—C(13)	120.5 (3)	P—C(22)—C(24)	118.7 (3)
B(3)—C(2)—C(13)	119.5 (3)		

C(19)—P—C(1)—C(2)	134.9 (2)
C(22)—P—C(1)—C(2)	−117.2 (2)
P—C(1)—C(2)—C(13)	0.7 (4)
C(1)—C(2)—C(13)—C(14)	95.6 (4)
C(1)—C(2)—C(13)—C(18)	−88.0 (4)

The non-H atoms were refined with anisotropic displacement parameters and H(B) atoms with fixed isotropic displacement parameters. H(C) atoms were placed at fixed positions (C—H = 0.95 Å) and not refined.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1989*a*). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1989*b*). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *CRYLSQ* in *Xtal*3.0 (Hall & Stewart, 1990). Molecular graphics: *ORTEP*II (Johnson, 1976) in *Xtal*3.0. Software used to prepare material for publication: *ATABLE* and *BONDLA* in *Xtal*3.0.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry, including torsion angles and contact distances, have been deposited with the IUCr (Reference: AB1350). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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cis-2-*sec*-Butyl-4-{4-[4-(4-{[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)-1-piperazinyl]phenyl}-2,4-dihydro-3*H*-1,2,4-triazol-3-one (Itraconazole†)

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Abstract

The molecular structure of itraconazole, $C_{35}H_{38}Cl_2N_8O_4$, has been determined from single-crystal X-ray diffraction data. The two molecules in the asymmetric unit differ mainly in the conformation of the methoxy-

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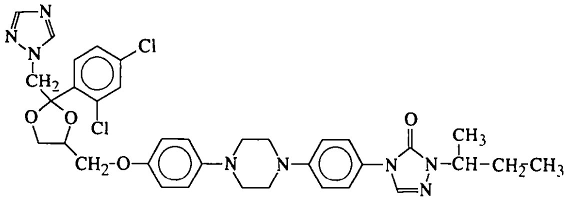
† Internal code of the Janssen Research Foundation: R51211.

phenylpiperazine moiety. Apart from a 180° rotation of the triazole ring, the geometry of the dichlorophenylethoxytriazole moiety is almost the same as the dichlorophenylethoxyimidazole geometry found in miconazole, econazole and ketoconazole.

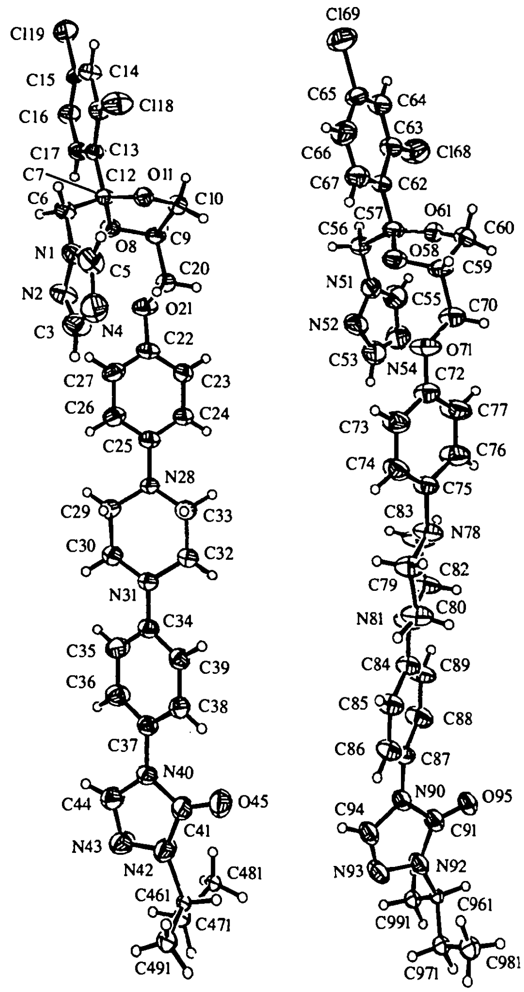
Comment

Itraconazole, (I), is an oral antifungal triazole registered in most countries of the world. In comparison with miconazole and ketoconazole, itraconazole is essentially a more potent antifungal agent with a wider spectrum, a slower clearance and reduced toxicity.



(I)

All antifungal azoles probably act by an identical mechanism of inhibition of the fungal cytochrome P-450 enzymes. The potency seems to be determined by the affinity and geometric orientation of the nitrogen heterocycle to the heme iron ion, by protonation of the N3 or N4 atom in the imidazole or triazole ring, and by the affinity of the non-ligand portion for the apoprotein of cytochrome P-450 (Vanden Bossche, Marichal, Gorrens, Geerts & Janssen, 1988). The crystal structure of itraconazole has been determined for comparison with the structures of ketoconazole (Peeters, Blaton & De Ranter, 1979*a*), miconazole (Peeters, Blaton & De Ranter, 1979*b*) and econazole (Freer, Pearson & Salole, 1986). The asymmetric unit contains two molecules (*A* and *B*) partly related by a pseudo-inversion centre at *ca* 0.25,0.49,0.25 (Fig. 1). The *sec*-butyl side chain is statistically disordered in both molecules implying that both the *R* and *S* configurations are present. The main difference between the two molecules is the orientation of the methoxyphenylpiperazine moiety. In molecule *A*, the methoxy group is almost perpendicular to the phenyl ring, whereas in molecule *B*, it is almost coplanar with the phenyl ring. As a consequence, the C70—O71—C72 and O71—C72—C77 angles are enlarged by *ca* 4°.



Molecule *A* Molecule *B*

Fig. 1. Perspective view of molecules *A* and *B* of (I) with the atomic numbering schemes. For clarity, only one configuration of the disordered *sec*-butyl moieties is shown in each case. Displacement ellipsoids are drawn at the 40% probability level.

Each molecule contains seven rings of which the triazole and benzene rings are essentially planar with a maximum deviation of 0.014 (5) Å. The dioxolane rings have conformations close to envelope, with the flap at atoms O11 and O61 [puckering parameters q_2 = 0.326 (4) and 0.350 (5) Å, and φ_2 = −41.4 (8) and 134.3 (8)° for molecules *A* and *B*, respectively]. The piperazine rings have chair conformations although that of molecule *B* is markedly flattened [Q = 0.421 (6) Å] with shorter bond lengths, enlarged internal angles and smaller torsion angles. All other bond lengths and angles agree within 3σ and are close to accepted values. There are no intermolecular contacts significantly shorter than the sum of the corresponding van der Waals radii. R.m.s. fits (Hypercube, 1993) of the dichlorophenylethoxytriazole moiety of itraconazole with the dichlorophenylethoxyimidazole moiety of miconazole, econazole and ketoconazole give r.m.s. error values of 0.23, 0.12 and 0.14 Å, respectively. Apart from the 180° rotation of the triazole ring in itraconazole, the orientation of the nitrogen heterocycle is almost the same in the crystal structures of all four antifungal drugs. This suggests that the differentation in potency is not due to a different orientation of the nitrogen heterocycle.

Experimental

Crystals of the title compound were obtained from the Janssen Research Foundation, Beerse, Belgium. The density D_m was measured by flotation in aqueous KI solution.

Crystal data

$C_{35}H_{38}Cl_2N_8O_4$
$M_r = 705.64$
Triclinic
$P\overline{1}$
$a = 8.6202\,(3)$ Å
$b = 20.154\,(1)$ Å
$c = 21.0425\,(9)$ Å
$\alpha = 73.497\,(4)°$
$\beta = 89.067\,(3)°$
$\gamma = 79.781\,(4)°$
$V = 3447.3\,(3)$ Å^3
$Z = 4$
$D_x = 1.360$ Mg m^{-3}
$D_m = 1.356$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.54184$ Å
Cell parameters from 40 reflections
$\theta = 22\text{–}56°$
$\mu = 2.120$ mm^{-1}
$T = 293$ K
Plate
$0.36 \times 0.18 \times 0.04$ mm
Colourless

Data collection

Siemens *P*4 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: empirical *via* ψ scans (*XEMP*; Siemens, 1989)
$T_{\min} = 0.383$, $T_{\max} = 0.554$
11 393 measured reflections
9215 independent reflections

5083 observed reflections $[I > 3.0\sigma(I)]$
$R_{\rm int} = 0.0286$
$\theta_{\max} = 57.06°$
$h = -1 \rightarrow 9$
$k = -20 \rightarrow 20$
$l = -22 \rightarrow 22$
3 standard reflections monitored every 100 reflections intensity decay: 17.0%

Refinement

Refinement on F^2
$R(F) = 0.0594$
$wR(F^2) = 0.2000$
$S = 1.020$
9213 reflections
886 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.0777P)^2 + 6.1836P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.001$

$\Delta\rho_{\max} = 0.44$ e Å^{-3}
$\Delta\rho_{\min} = -0.43$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.00058 (9)
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Tables 2.2B and 2.3.1)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	$U_{\rm eq}$
N1	0.2817 (5)	0.1063 (2)	0.3690 (2)	0.050 (2)
N2	0.3469 (5)	0.1625 (3)	0.3373 (2)	0.064 (2)
C3	0.4573 (7)	0.1600 (4)	0.3811 (4)	0.075 (3)
N4	0.4692 (6)	0.1075 (4)	0.4371 (3)	0.082 (3)
C5	0.3553 (7)	0.0746 (4)	0.4275 (3)	0.068 (3)
C6	0.1487 (5)	0.0880 (3)	0.3399 (3)	0.048 (2)
C7	−0.0103 (6)	0.1251 (2)	0.3572 (2)	0.040 (2)
O8	−0.0262 (4)	0.1984 (2)	0.3283 (2)	0.046 (1)
C9	−0.0933 (6)	0.2322 (3)	0.3770 (3)	0.046 (2)
C10	−0.1220 (6)	0.1719 (3)	0.4357 (3)	0.052 (2)
O11	−0.0145 (4)	0.1138 (2)	0.4256 (2)	0.045 (1)
C12	−0.1411 (6)	0.0965 (2)	0.3297 (2)	0.038 (2)
C13	−0.1869 (6)	0.0328 (3)	0.3613 (2)	0.046 (2)
C14	−0.3078 (6)	0.0103 (3)	0.3342 (3)	0.053 (2)
C15	−0.3804 (6)	0.0506 (3)	0.2752 (3)	0.048 (2)
C16	−0.3337 (6)	0.1126 (3)	0.2413 (3)	0.053 (2)
C17	−0.2158 (6)	0.1346 (3)	0.2691 (2)	0.048 (2)
Cl18	−0.0971 (2)	−0.02376 (7)	0.43381 (7)	0.0711 (6)
Cl19	−0.5325 (2)	0.02357 (9)	0.24243 (8)	0.0764 (7)
C20	0.0202 (7)	0.2736 (3)	0.3945 (3)	0.054 (2)
O21	0.0413 (5)	0.3287 (2)	0.3370 (2)	0.062 (1)
C22	0.1620 (7)	0.3638 (3)	0.3465 (3)	0.053 (2)
C23	0.1348 (6)	0.4160 (3)	0.3784 (3)	0.052 (2)
C24	0.2532 (6)	0.4531 (3)	0.3816 (3)	0.053 (2)
C25	0.3991 (6)	0.4387 (3)	0.3549 (3)	0.049 (2)
C26	0.4230 (7)	0.3850 (3)	0.3249 (3)	0.069 (3)
C27	0.3042 (7)	0.3490 (3)	0.3201 (3)	0.064 (3)
N28	0.5129 (5)	0.4821 (2)	0.3553 (2)	0.048 (2)
C29	0.6531 (7)	0.4712 (3)	0.3176 (3)	0.067 (3)
C30	0.7419 (7)	0.5316 (3)	0.3087 (3)	0.065 (3)
N31	0.7843 (5)	0.5383 (2)	0.3726 (2)	0.051 (2)
C32	0.6447 (7)	0.5489 (3)	0.4104 (3)	0.063 (3)
C33	0.5524 (7)	0.4895 (3)	0.4185 (3)	0.062 (3)
C34	0.8977 (6)	0.5815 (3)	0.3730 (3)	0.048 (2)
C35	0.9610 (7)	0.6184 (3)	0.3152 (3)	0.064 (3)
C36	1.0796 (7)	0.6559 (3)	0.3184 (3)	0.063 (3)
C37	1.1378 (6)	0.6572 (3)	0.3776 (3)	0.047 (2)
C38	1.0760 (6)	0.6206 (3)	0.4356 (3)	0.053 (2)
C39	0.9574 (6)	0.5840 (3)	0.4324 (3)	0.051 (2)
N40	1.2604 (5)	0.6959 (2)	0.3794 (2)	0.052 (2)
C41	1.2974 (7)	0.7205 (3)	0.4316 (3)	0.064 (3)
N42	1.4146 (6)	0.7567 (3)	0.4074 (2)	0.080 (3)
N43	1.4502 (7)	0.7568 (3)	0.3438 (2)	0.086 (3)
C44	1.3574 (7)	0.7197 (3)	0.3287 (3)	0.068 (3)
O45	1.2403 (6)	0.7126 (3)	0.4858 (2)	0.088 (2)
C461†	1.532 (1)	0.7757 (6)	0.4481 (6)	0.048 (4)
C471†	1.527 (2)	0.8515 (7)	0.4109 (7)	0.072 (5)
C481†	1.356 (2)	0.8906 (8)	0.418 (1)	0.058 (5)
C491†	1.688 (2)	0.730 (1)	0.468 (1)	0.085 (6)
C462†	1.456 (1)	0.8131 (5)	0.4367 (5)	0.050 (3)
C472†	1.633 (1)	0.8094 (6)	0.4284 (6)	0.075 (4)
C482†	1.731 (2)	0.7400 (8)	0.4487 (8)	0.093 (5)
C492†	1.377 (2)	0.8881 (6)	0.3989 (8)	0.080 (5)
N51	0.2556 (6)	0.8512 (3)	0.1432 (2)	0.063 (2)
N52	0.1978 (6)	0.7929 (3)	0.1776 (3)	0.075 (3)
C53	0.0910 (8)	0.7899 (4)	0.1353 (4)	0.085 (3)
N54	0.0745 (7)	0.8409 (4)	0.0777 (3)	0.087 (3)
C55	0.1811 (8)	0.8783 (4)	0.0851 (3)	0.078 (3)
C56	0.3861 (6)	0.8731 (3)	0.1706 (3)	0.058 (2)
C57	0.5449 (6)	0.8412 (3)	0.1491 (3)	0.050 (2)
O58	0.5653 (4)	0.7668 (2)	0.1733 (2)	0.060 (2)
C59	0.6247 (7)	0.7384 (3)	0.1212 (3)	0.061 (3)
C60	0.6537 (7)	0.8019 (3)	0.0660 (3)	0.065 (3)
O61	0.5435 (4)	0.8573 (2)	0.0800 (2)	0.056 (2)
C62	0.6769 (6)	0.8676 (3)	0.1778 (3)	0.051 (2)
C63	0.7219 (7)	0.9316 (3)	0.1483 (3)	0.060 (3)
C64	0.8434 (7)	0.9522 (4)	0.1761 (3)	0.070 (3)
C65	0.9184 (7)	0.9098 (4)	0.2335 (3)	0.065 (3)
C66	0.8738 (7)	0.8464 (4)	0.2651 (3)	0.071 (3)
C67	0.7547 (7)	0.8255 (3)	0.2367 (3)	0.063 (2)
Cl68	0.6279 (2)	0.99237 (9)	0.07767 (9)	0.0938 (8)
Cl69	1.0712 (2)	0.9357 (1)	0.2670 (1)	0.104 (1)
C70	0.5038 (7)	0.7033 (3)	0.0979 (3)	0.065 (3)
O71	0.4723 (5)	0.6474 (2)	0.1530 (2)	0.073 (2)
C72	0.3502 (7)	0.6145 (3)	0.1441 (3)	0.060 (3)
C73	0.3085 (7)	0.5675 (3)	0.1991 (3)	0.067 (3)
C74	0.1891 (7)	0.5304 (3)	0.1949 (3)	0.068 (3)
C75	0.1090 (7)	0.5412 (3)	0.1354 (3)	0.057 (2)
C76	0.1525 (8)	0.5893 (3)	0.0807 (3)	0.082 (3)
C77	0.2739 (8)	0.6257 (3)	0.0847 (3)	0.087 (3)
N78	−0.0098 (6)	0.5024 (2)	0.1283 (2)	0.065 (2)
C79	−0.0096 (7)	0.4373 (3)	0.1778 (3)	0.065 (3)
C80	−0.1232 (7)	0.3959 (3)	0.1637 (3)	0.070 (3)
N81	−0.2768 (5)	0.4348 (2)	0.1421 (2)	0.064 (2)
C82	−0.2790 (7)	0.5017 (3)	0.0932 (3)	0.068 (3)
C83	−0.1620 (8)	0.5417 (3)	0.1076 (4)	0.082 (3)
C84	−0.3971 (6)	0.3974 (3)	0.1387 (3)	0.051 (2)
C85	−0.4003 (7)	0.3325 (3)	0.1856 (3)	0.057 (2)
C86	−0.5196 (6)	0.2957 (3)	0.1836 (3)	0.056 (2)
C87	−0.6382 (6)	0.3220 (3)	0.1361 (3)	0.049 (2)
C88	−0.6407 (7)	0.3861 (3)	0.0908 (3)	0.072 (3)
C89	−0.5202 (7)	0.4230 (3)	0.0924 (3)	0.074 (3)
N90	−0.7611 (5)	0.2826 (2)	0.1350 (2)	0.051 (2)
C91	−0.8193 (7)	0.2702 (3)	0.0791 (3)	0.055 (2)

N92	−0.9180 (6)	0.2246 (3)	0.1045 (2)	0.068 (2)
N93	−0.9247 (7)	0.2081 (3)	0.1730 (2)	0.076 (3)
C94	−0.8301 (7)	0.2437 (3)	0.1890 (3)	0.062 (3)
O95	−0.7890 (5)	0.2945 (2)	0.0215 (2)	0.071 (2)
C961†	−1.030 (1)	0.2007 (4)	0.0677 (4)	0.048 (3)
C971†	−0.996 (1)	0.1209 (5)	0.0932 (5)	0.070 (3)
C981†	−0.836 (2)	0.0881 (9)	0.085 (1)	0.100 (6)
C991†	−1.200 (1)	0.2298 (6)	0.0743 (6)	0.068 (3)
C962†	−0.949 (2)	0.1715 (8)	0.0694 (7)	0.041 (5)
C972†	−1.108 (2)	0.153 (1)	0.089 (1)	0.077 (7)
C982†	−1.237 (3)	0.216 (2)	0.068 (2)	0.18 (2)
C992†	−0.829 (4)	0.101 (2)	0.090 (3)	0.15 (2)

† Partial occupancies (see below).

Table 2. *Geometric parameters (Å, °)*

N1—N2	1.353 (7)	N51—N52	1.365 (8)
N1—C5	1.326 (7)	N51—C55	1.315 (8)
N1—C6	1.458 (7)	N51—C56	1.461 (8)
N2—C3	1.320 (9)	N52—C53	1.31 (1)
C3—N4	1.333 (8)	C53—N54	1.339 (9)
N4—C5	1.33 (1)	N54—C55	1.32 (1)
C6—C7	1.531 (7)	C56—C57	1.524 (7)
C7—O8	1.411 (5)	C57—O58	1.420 (6)
C7—O11	1.392 (6)	C57—O61	1.398 (6)
C7—C12	1.543 (8)	C57—C62	1.536 (9)
O8—C9	1.444 (7)	O58—C59	1.424 (8)
C9—C10	1.518 (7)	C59—C60	1.520 (8)
C9—C20	1.507 (9)	C59—C70	1.52 (1)
C10—O11	1.423 (6)	C60—O61	1.428 (7)
C12—C13	1.390 (7)	C62—C63	1.384 (8)
C12—C17	1.387 (6)	C62—C67	1.390 (7)
C13—C14	1.395 (8)	C63—C64	1.39 (1)
C13—Cl18	1.722 (5)	C63—Cl68	1.737 (5)
C14—C15	1.366 (7)	C64—C65	1.360 (8)
C15—C16	1.377 (8)	C65—C66	1.38 (1)
C15—Cl19	1.729 (6)	C65—Cl69	1.729 (8)
C16—C17	1.378 (8)	C66—C67	1.38 (1)
C20—O21	1.426 (6)	C70—O71	1.430 (7)
O21—C22	1.404 (8)	O71—C72	1.381 (8)
C22—C23	1.384 (9)	C72—C73	1.360 (8)
C22—C27	1.358 (8)	C72—C77	1.363 (9)
C23—C24	1.382 (9)	C73—C74	1.39 (1)
C24—C25	1.386 (8)	C74—C75	1.382 (8)
C25—C26	1.384 (9)	C75—C76	1.373 (8)
C25—N28	1.427 (8)	C75—N78	1.427 (8)
C26—C27	1.38 (1)	C76—C77	1.40 (1)
N28—C29	1.452 (7)	N78—C79	1.425 (7)
N28—C33	1.434 (8)	N78—C83	1.411 (7)
C29—C30	1.52 (1)	C79—C80	1.479 (9)
C30—N31	1.447 (8)	C80—N81	1.423 (7)
N31—C32	1.449 (7)	N81—C82	1.442 (6)
N31—C34	1.421 (8)	N81—C84	1.400 (8)
C32—C33	1.521 (9)	C82—C83	1.48 (1)
C34—C35	1.392 (7)	C84—C85	1.401 (7)
C34—C39	1.377 (8)	C84—C89	1.376 (8)
C35—C36	1.388 (9)	C85—C86	1.379 (9)
C36—C37	1.360 (8)	C86—C87	1.365 (7)
C37—C38	1.388 (7)	C87—C88	1.367 (7)
C37—N40	1.428 (8)	C87—N90	1.436 (8)
C38—C39	1.376 (8)	C88—C89	1.39 (1)
N40—C41	1.390 (9)	N90—C91	1.389 (8)
N40—C44	1.374 (7)	N90—C94	1.378 (7)
C41—N42	1.360 (9)	C91—N92	1.357 (8)
C41—O45	1.213 (8)	C91—O95	1.214 (6)
N42—N43	1.368 (7)	N92—N93	1.387 (6)
N42—C461	1.50 (1)	N92—C961	1.47 (1)
N42—C462	1.53 (1)	N92—C962	1.52 (2)
N43—C44	1.29 (1)	N93—C94	1.284 (9)
C461—C471	1.50 (2)	C961—C971	1.52 (1)
C461—C491	1.48 (2)	C961—C991	1.49 (1)
C471—C481	1.56 (2)	C971—C981	1.45 (2)
C462—C472	1.52 (1)	C962—C972	1.50 (2)
C462—C492	1.53 (1)	C962—C992	1.56 (3)
C472—C482	1.45 (2)	C972—C982	1.50 (4)

C5—N1—C6	128.5 (5)	N42—C461—C471	100.5 (9)
N2—N1—C6	121.8 (4)	C471—C461—C491	118 (1)
N2—N1—C5	109.6 (5)	C461—C471—C481	106 (1)
N1—N2—C3	101.5 (5)	N42—C462—C492	113.4 (9)
N2—C3—N4	116.4 (6)	N42—C462—C472	104.9 (8)
C3—N4—C5	101.6 (6)	C472—C462—C492	106.8 (9)
N1—C5—N4	110.9 (5)	C462—C472—C482	117 (1)
N1—C6—C7	112.4 (4)	C55—N51—C56	129.4 (5)
C6—C7—C12	107.7 (4)	N52—N51—C56	121.0 (5)
C6—C7—O11	109.3 (4)	N52—N51—C55	109.5 (5)
C6—C7—O8	109.7 (4)	N51—N52—C53	101.7 (5)
O11—C7—C12	112.9 (4)	N52—C53—N54	115.8 (6)
O8—C7—C12	110.4 (4)	C53—N54—C55	102.1 (6)
O8—C7—O11	106.8 (4)	N51—C55—N54	111.0 (6)
C7—O8—C9	107.4 (3)	N51—C56—C57	111.6 (5)
O8—C9—C20	109.9 (4)	C56—C57—C62	109.2 (4)
O8—C9—C10	104.4 (4)	C56—C57—O61	109.3 (4)
C10—C9—C20	112.2 (4)	C56—C57—O58	108.9 (4)
C9—C10—O11	102.3 (4)	O61—C57—C62	113.2 (4)
C7—O11—C10	106.1 (3)	O58—C57—C62	110.0 (4)
C7—C12—C17	119.2 (4)	O58—C57—O61	106.2 (4)
C7—C12—C13	123.8 (4)	C57—O58—C59	108.0 (4)
C13—C12—C17	117.0 (4)	O58—C59—C70	110.7 (5)
C12—C13—Cl18	122.9 (4)	O58—C59—C60	104.3 (5)
C12—C13—C14	121.0 (5)	C60—C59—C70	110.1 (5)
C14—C13—Cl18	116.1 (4)	C59—C60—O61	101.8 (5)
C13—C14—C15	119.8 (5)	C57—O61—C60	105.2 (4)
C14—C15—Cl19	119.8 (4)	C57—C62—C67	118.7 (5)
C14—C15—C16	120.7 (5)	C57—C62—C63	123.3 (5)
C16—C15—Cl19	119.5 (4)	C63—C62—C67	118.0 (5)
C15—C16—C17	118.8 (5)	C62—C63—Cl68	123.5 (4)
C12—C17—C16	122.6 (5)	C62—C63—C64	120.7 (6)
C9—C20—O21	108.7 (4)	C64—C63—Cl68	115.7 (5)
C20—O21—C22	112.3 (4)	C63—C64—C65	120.0 (6)
O21—C22—C27	118.7 (5)	C64—C65—Cl69	119.5 (5)
O21—C22—C23	121.1 (5)	C64—C65—C66	120.7 (6)
C23—C22—C27	120.1 (5)	C66—C65—Cl69	119.8 (5)
C22—C23—C24	118.9 (5)	C65—C66—C67	119.1 (6)
C23—C24—C25	121.8 (5)	C62—C67—C66	121.4 (6)
C24—C25—N28	119.4 (5)	C59—C70—O71	107.7 (5)
C24—C25—C26	117.5 (5)	C70—O71—C72	116.4 (4)
C26—C25—N28	122.9 (5)	O71—C72—C77	124.3 (5)
C25—C26—C27	120.9 (6)	O71—C72—C73	116.0 (5)
C22—C27—C26	120.7 (6)	C73—C72—C77	119.8 (6)
C25—N28—C33	116.3 (4)	C72—C73—C74	120.3 (5)
C25—N28—C29	116.6 (4)	C73—C74—C75	121.0 (6)
C29—N28—C33	111.1 (4)	C74—C75—N78	122.9 (5)
N28—C29—C30	110.2 (5)	C74—C75—C76	117.6 (6)
C29—C30—N31	110.4 (5)	C76—C75—N78	119.5 (5)
C30—N31—C34	116.6 (4)	C75—C76—C77	121.4 (6)
C30—N31—C32	110.5 (4)	C72—C77—C76	119.9 (6)
C32—N31—C34	116.6 (4)	C75—N78—C83	116.6 (5)
N31—C32—C33	111.0 (5)	C75—N78—C79	116.7 (5)
N28—C33—C32	110.9 (4)	C79—N78—C83	113.9 (5)
N31—C34—C39	119.9 (5)	N78—C79—C80	114.1 (5)
N31—C34—C35	122.6 (5)	C79—C80—N81	115.1 (5)
C35—C34—C39	117.3 (5)	C80—N81—C84	118.1 (5)
C34—C35—C36	120.5 (5)	C80—N81—C82	114.5 (5)
C35—C36—C37	121.2 (5)	C82—N81—C84	118.3 (5)
C36—C37—N40	119.9 (5)	N81—C82—C83	113.7 (5)
C36—C37—C38	119.0 (5)	N78—C83—C82	115.8 (5)
C38—C37—N40	121.0 (4)	N81—C84—C89	122.8 (5)
C37—C38—C39	119.7 (5)	N81—C84—C85	120.2 (5)
C34—C39—C38	122.2 (5)	C85—C84—C89	116.9 (5)
C37—N40—C44	126.8 (4)	C84—C85—C86	120.9 (5)
C37—N40—C41	126.1 (4)	C85—C86—C87	120.6 (5)
C41—N40—C44	107.0 (5)	C86—C87—N90	119.6 (5)
N40—C41—O45	129.5 (6)	C86—C87—C88	119.9 (5)
N40—C41—N42	103.0 (5)	C88—C87—N90	120.5 (5)
N42—C41—O45	127.5 (6)	C87—C88—C89	119.6 (6)
C41—N42—C461	125.8 (6)	C84—C89—C88	122.1 (6)
C41—N42—C462	121.9 (6)	C87—N90—C94	126.9 (4)
C41—N42—N43	113.1 (5)	C87—N90—C91	125.6 (4)
N43—N42—C461	118.4 (6)	C91—N90—C94	107.1 (4)
N43—N42—C462	121.3 (6)	N90—C91—O95	128.3 (5)
N42—N43—C44	104.4 (5)	N90—C91—N92	103.1 (4)
N40—C44—N43	112.5 (5)	N92—C91—O95	128.6 (5)
N42—C461—C491	121 (1)	C91—N92—C961	127.4 (5)
C91—N92—C962	120.8 (7)	N92—C961—C971	105.3 (6)
C91—N92—N93	113.2 (5)	C971—C961—C991	111.7 (8)

N93—N92—C961	118.8 (5)	C961—C971—C981	115.2 (9)
N93—N92—C962	119.6 (7)	N92—C962—C992	114 (2)
N92—N93—C94	103.8 (4)	N92—C962—C972	108 (1)
N90—C94—N93	112.8 (4)	C972—C962—C992	106 (2)
N92—C961—C991	114.6 (7)	C962—C972—C982	112 (2)
N2—N1—C6—C7	−88.5 (6)	N52—N51—C56—C57	91.8 (6)
N1—C6—C7—O8	65.2 (5)	N51—C56—C57—O58	−61.3 (6)
N1—C6—C7—O11	−51.6 (5)	N51—C56—C57—O61	54.2 (6)
N1—C6—C7—C12	−174.6 (4)	N51—C56—C57—C62	178.5 (4)
C6—C7—C12—C13	80.3 (6)	C56—C57—C62—C63	−83.1 (6)
O8—C9—C20—O21	64.0 (5)	O58—C59—C70—O71	−60.9 (6)
C9—C20—O21—C22	−171.7 (4)	C59—C70—O71—C72	172.2 (5)
C20—O21—C22—C27	102.7 (6)	C70—O71—C72—C77	8.8 (8)
C36—C37—N40—C41	158.5 (6)	C86—C87—N90—C91	−133.9 (6)

The *sec*-butyl moieties are statistically disordered. Both *R* and *S* configurations are present at the same location and were refined isotropically with geometric restraints. The sum of the occupancy factors was constrained to 1. The refined occupancy factors for atoms C461–C491 and C961–C991 are 0.43 (1) and 0.68 (1), respectively.

Data collection: *XSCANS* (Siemens, 1994). Cell refinement: *XSCANS*. Data reduction: *XSCANS*. Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEX*2.1 (McArdle, 1994). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: NA1232). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Lupulin D

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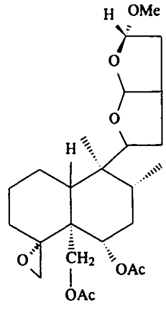
Abstract

In the title compound, 3-deoxy-14,15-dihydro-15-methoxycaryoptinol, $C_{25}H_{38}O_8$, the conformation of the 15-methoxy group has been determined by X-ray analysis. The structure is stabilized by van der Waals interactions.

Comment

Most clerodane diterpenes from *Clerodandron* and *Ajuga* plants possess insect antifeedant activity (Camps & Coll, 1993). Extensive research indicates that the antifeedant activity of clerodane diterpenes may be related to a synergistic action of the furanofuran ring and the epoxy diacetate groups of the *trans*-decalin moiety (Belles, Camps, Coll & Piulachs, 1985). Recently, we obtained lupulin D, a clerodane diterpene from the whole plants of *Ajuga lupulina* Maxim, in crystal form. This compound, first isolated from the leaves of *Clerodandron brachyanthum* by Lin, Kuo & Chen (1989), was the first reported clerodane diterpene with a methoxy group at C17. Its structure was established by spectral methods and chemical correlation; however, the determination of the conformation of the methoxy group at C17 was difficult. Lin *et al.* (1989) presumed that the methoxy group at C17 has an α orientation. In order to confirm this presumption, the X-ray analysis was undertaken. The two six-membered rings of the *trans*-fused decalin ring system are in normal chair conformations while the furan rings of the *cis*-fused hexahydrofuranofuran system are in envelope conformations. The re-



Lupulin D