

cis-1-Acetyl-4-(4-{[2-(2,4-dichlorophenyl)-2-(1*H*-1-imidazolylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazine: Ketoconazole. A Crystal Structure with Disorder

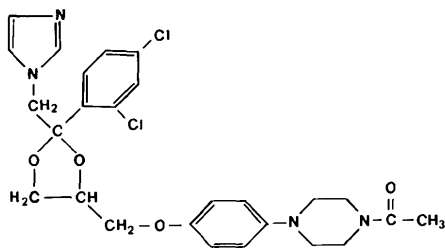
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Abstract. $C_{26}H_{28}Cl_2N_4O_4$, $M_r = 531.43$, triclinic, $P\bar{1}$, $a = 10.843$ (4), $b = 13.221$ (3), $c = 10.395$ (3) Å, $\alpha = 100.36$ (2), $\beta = 114.12$ (2), $\gamma = 68.02$ (2)°, $Z = 2$, $V = 1260.5$ Å³, $F(000) = 556.0$, $\mu(\text{Mo } K\alpha) = 0.290$ mm⁻¹, $D_c = 1.40$, $D_m = 1.39$ Mg m⁻³. The structure was solved by direct methods. Because of disorder in the crystal structure two models, responsible for two different conformations, with 0.50 occupancy factors, were accepted. The structure refined to an R of 0.060.

Introduction. The title compound, ketoconazole, is a novel product in a series of substituted imidazole derivatives and is reported to show broad-range activity against yeasts and fungi (Thienpont, Van Cutsem, Van Gerven & Janssen, 1979; Borgers, De Brabander, Van den Bossche & Van Cutsem, 1979).



The starting material was racemic with a melting range of 418–422 K. Transparent, colourless single crystals were grown at room temperature by slow evaporation from a solution in 2-propanol. The single crystal used for data collection melted at 421–422 K, which indicated that the compound had crystallized as a racemate. The final structure analysis confirmed this. From rotation and Weissenberg photographs the space group was found to be triclinic. The cell constants were obtained by least-squares refinement of the setting angles of 24 reflections with $20^\circ < 2\theta < 30^\circ$. Intensities were collected out to $2\theta = 50^\circ$ on a Syntex $P2_1$ computer-controlled diffractometer operating in the ω scan mode, with graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.71069$ Å). Of 4436 measured intensities, 3530 unique observed reflections [$I >$

$2.0\sigma(I)$] were employed in the analysis. The data were corrected for Lorentz–polarization effects but not for absorption. The structure was solved in space group $P\bar{1}$ with *MULTAN* (Main, Woolfson, Lessinger, Germain & Declercq, 1974) and 499 reflections with $E > 1.56$ were used for phase generation. The phase set with the highest combined figure of merit yielded the complete molecular structure, but contained two possibilities for the link [C(20)] between the dioxolane ring and the benzene ring, corresponding respectively to the *cis*-[(2*R*,4*S*)-1,3-dioxolane] (conformer *A*) and to the *cis*-[(2*S*,4*R*)-1,3-dioxolane] configurations (conformer *B*). Refinement in $P\bar{1}$ of either conformer *A* or conformer *B* did not result in a sufficiently accurate chemical structure, although the R values obtained in both refinements were about 0.10. For instance, the bond distances C(9)–C(20) (conformer *A*) and C(10)–C(20) (conformer *B*) deviated by up to 0.20 Å from the expected value and the thermal parameters of C(9), C(10), C(20), O(21), C(22), C(23) and C(24) were abnormally high.

Difference Fourier syntheses at this stage showed one peak of about $3 \text{ e } \text{Å}^{-3}$ at the position of the non-loaded C(20) possibility from the direct-methods solution.

To solve the problem, two possibilities were considered: the space group is either $P\bar{1}$ in which case both conformers must be present with partial occupancy or it is $P1$ with both conformers present as an enantiomorphic pair in the same unit cell. The latter possibility was tested with two noncentrosymmetric phasing models. In the first model conformer *A* and the inverted molecule of conformer *B* as found in the solution from direct methods were used; in the second model the opposite combination of conformers *A* and *B* was taken. Two cycles of isotropic refinement reduced the R value to 0.189 for both models. A similar two cycles of isotropic refinement in $P\bar{1}$, but with the two conformers in the asymmetric unit and 0.50 occupancy factors for the C(20) atoms, resulted in an R value of 0.197. Nevertheless, the latter gave the most consistent chemical structure. Therefore the structure was further refined in $P\bar{1}$ restarting from the result at $R = 0.10$. C(20) was given the position from the direct-

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Table 1. Atomic coordinates ($\times 10^4$) and temperature factors (\AA^2), with e.s.d.'s of the refined parameters in parenthesesAtoms denoted *A* or *B* were assigned population parameters of 0.50.

	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}		<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}
N(1)	1456 (2)	1351 (2)	2498 (2)	2.71 (7)	O(21 <i>B</i>)	1167 (8)	2841 (7)	-1438 (9)	3.91 (24)
C(2)	28 (3)	1532 (3)	1848 (4)	3.73 (11)	C(22 <i>B</i>)	-78 (15)	3668 (15)	-1829 (18)	2.48 (40)
N(3)	-738 (3)	2567 (2)	1905 (3)	4.07 (9)	C(23 <i>B</i>)	-789 (11)	4285 (8)	-965 (10)	4.56 (30)
C(4)	246 (4)	3070 (3)	2634 (4)	4.24 (12)	C(24 <i>B</i>)	-2066 (11)	5138 (9)	-1497 (11)	4.64 (32)
C(5)	1602 (3)	2347 (3)	3014 (4)	3.89 (11)	H(2)	-284	838	1378	3.71
C(6)	2575 (3)	304 (2)	2592 (3)	2.90 (9)	H(4)	0	3838	2832	4.23
C(7)	3084 (3)	52 (2)	1375 (3)	2.40 (8)	H(5)	2642	2387	3470	3.86
O(8)	1890 (2)	130 (1)	84 (2)	2.88 (6)	H(6)	3442	350	3467	2.85
C(9 <i>A</i>)	1965 (25)	920 (12)	-764 (20)	3.36 (40)	H(106)	2265	-262	2692	2.85
C(10 <i>A</i>)	3457 (13)	1005 (15)	-10 (21)	4.34 (40)	H(9 <i>A</i>)	2003	881	-1613	3.64
O(11)	3670 (2)	827 (1)	1340 (2)	3.29 (7)	H(10 <i>A</i>)	4117	296	-322	4.15
C(12)	4161 (3)	-1124 (2)	1511 (3)	2.48 (8)	H(110 <i>A</i>)	3693	1657	-265	3.85
C(13)	5553 (3)	-1444 (2)	2487 (3)	2.67 (9)	H(14)	7457	-2699	3331	2.97
C(14)	6440 (3)	-2522 (2)	2632 (3)	2.93 (10)	H(16)	4139	-3694	0	3.66
C(15)	5908 (4)	-3312 (2)	1784 (4)	3.63 (11)	H(17)	2587	-1699	0	3.26
C(16)	4518 (4)	-3040 (2)	815 (4)	3.64 (11)	H(20 <i>A</i>)	5	1661	-960	3.49
C(17)	3668 (3)	-1961 (2)	686 (3)	3.22 (10)	H(120 <i>A</i>)	1094	2189	225	3.49
Cl(18)	6312 (1)	-501 (1)	3610 (1)	3.97 (3)	H(23 <i>A</i>)	-1119	3597	-322	4.04
Cl(19)	7003 (1)	-4675 (1)	1963 (1)	5.50 (3)	H(24 <i>A</i>)	-3363	5220	-1290	3.56
C(20 <i>A</i>)	725 (7)	1966 (5)	-788 (7)	3.40 (20)	H(26)	-2283	5001	-4729	3.92
O(21 <i>A</i>)	608 (8)	2615 (7)	-1826 (9)	3.88 (23)	H(27)	-144	3651	-4013	4.00
C(22 <i>A</i>)	-635 (15)	3558 (14)	-2198 (18)	2.15 (35)	H(29)	-5742	5859	-3464	4.65
C(23 <i>A</i>)	-1510 (9)	3931 (7)	-1443 (10)	4.07 (28)	H(129)	-4832	6417	-1875	4.65
C(24 <i>A</i>)	-2726 (10)	4856 (7)	-1917 (10)	3.38 (27)	H(30)	-7063	7781	-2815	4.70
C(25)	-2879 (4)	5415 (2)	-2985 (4)	3.78 (11)	H(130)	-5695	8210	-2526	4.70
C(26)	-2025 (4)	4918 (3)	-3753 (3)	3.85 (11)	H(32)	-6492	7821	-6432	4.11
C(27)	-778 (4)	4030 (2)	-3276 (4)	4.02 (11)	H(132)	-5279	8281	-4814	4.11
N(28)	-4120 (3)	6356 (2)	-3435 (2)	3.47 (11)	H(33)	-5275	5916	-5460	3.95
C(29)	-5234 (4)	6527 (3)	-2890 (4)	4.66 (12)	H(133)	-4011	6531	-5242	3.95
C(30)	-6301 (4)	7669 (3)	-3151 (4)	4.75 (13)	H(136)	-9286	8026	-4352	5.61
N(31)	-6925 (3)	7898 (2)	-4654 (3)	4.00 (9)	H(236)	-9279	9176	-3923	5.61
C(32)	-5827 (4)	7708 (3)	-5238 (4)	4.18 (11)	H(336)	-10360	8756	-5432	5.61
C(33)	-4782 (4)	6555 (2)	-4955 (4)	4.02 (11)	H(9)	2695	-139	-1233	3.92
C(34)	-8305 (4)	8430 (3)	-5390 (4)	3.86 (11)	H(109 <i>B</i>)	1243	592	-1934	3.92
O(35)	-8691 (2)	8777 (2)	-6552 (3)	5.31 (9)	H(10 <i>B</i>)	3507	1347	-542	3.85
C(36)	-9367 (4)	8594 (3)	-4743 (4)	5.46 (14)	H(20 <i>B</i>)	1094	2189	225	3.82
C(9 <i>B</i>)	2082 (27)	465 (11)	-959 (24)	4.00 (41)	H(120 <i>B</i>)	1992	2918	644	3.82
C(10 <i>B</i>)	2819 (14)	1278 (14)	-132 (18)	3.10 (38)	H(23 <i>B</i>)	-326	4287	254	4.35
C(20 <i>B</i>)	1709 (8)	2407 (5)	-83 (8)	4.04 (22)	H(24 <i>B</i>)	-2319	5490	-644	4.06

methods solution and the atoms with high thermal motion, as mentioned above, were split up in the direction of their highest anisotropic thermal motion. All these atom positions were assigned population parameters of 0.50 based on peak heights. Anisotropic block-diagonal least-squares analysis reduced the *R* value to 0.090.

At this stage all H atoms, even those with population parameters of 0.50, were found in a difference map. In the further refinement they were included with fixed positions and the isotropic temperature factors of their parent atoms. In a final four blocks of least-squares analysis with $w = \sigma^{-2}(F_{\text{ref}})$ the refinement converged to *R* = 0.060. The maximum electron density remaining in the final difference map was 0.31 e \AA^{-3} . The final

positional parameters are given in Table 1.* All calculations were performed with the XRAY system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) on the KU Leuven IBM 370/158 computer.

Discussion. Bond lengths, angles and the numbering of the atoms of the title compound are shown in Fig. 1. Stereoviews of both conformers are in Fig. 2. As a result of the disorder, the bond lengths and angles in the

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34572 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

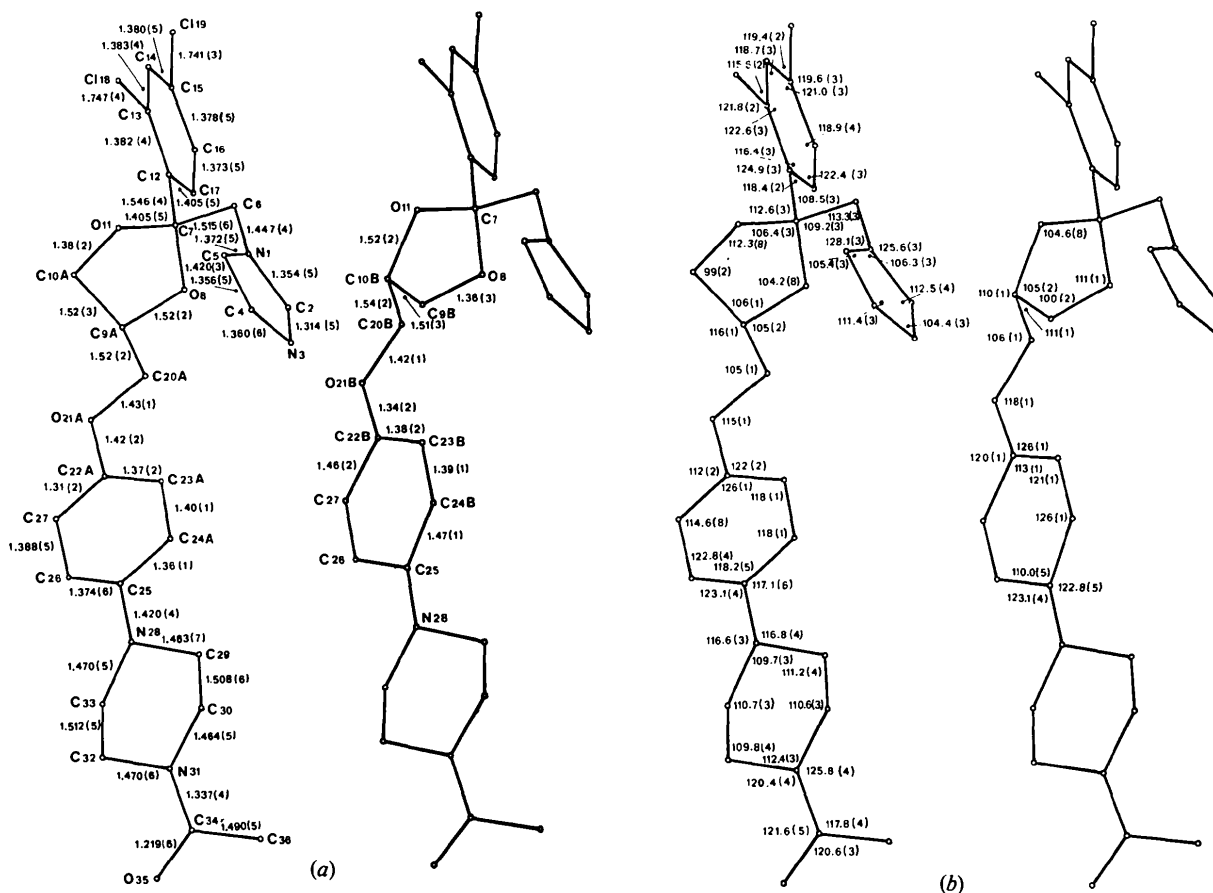


Fig. 1. (a) Atom numbering and bond distances (Å). (b) Bond angles (°). E.s.d.'s are in parentheses.

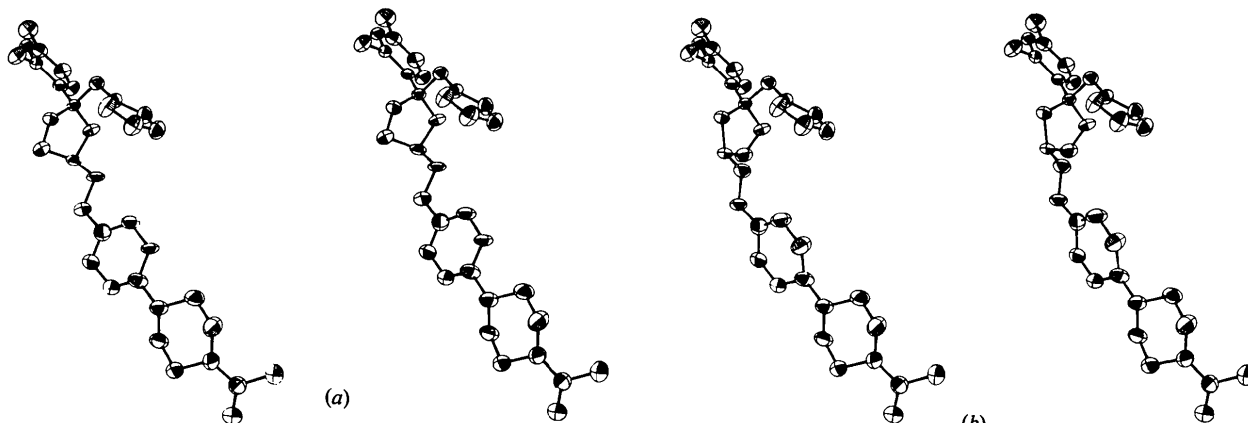


Fig. 2. Stereoviews of (a) conformer A and (b) conformer B. Ellipsoids of 50% probability are shown.

(1,3-dioxolan-4-yl)methoxyphenyl moiety are unreliable. All other bonds and angles have expected values. The molecule contains five rings. The imidazole and the 2,4-dichlorobenzene rings are planar. The dioxolane ring adopts the envelope conformation with the unsubstituted C atom as the flap of the envelope. The distance of the unsubstituted C atom to the mean plane

through the four remaining atoms of the dioxolane ring (0.497, 0.511 Å) is in accordance with that in similar ring compounds (*e.g.* Ružić-Toros & Leban, 1978). The benzene ring is distorted in both conformers because only three atoms of the ring were split on the basis of their thermal parameters. The largest deviations from the mean planes are 0.074, -0.101 Å

Table 2. Least-squares planes and distances (Å) of atoms from these planes

E.s.d.'s of the atom deviations for atoms with population parameters 1.00 and 0.50 are respectively *ca* 0.005 and 0.025 Å. The equations of the planes in direct space are expressed as $PX + QY + RZ = S$. Atoms not included in the calculations of the least-squares planes are denoted by asterisks.

Plane I: imidazole ring

$$-5.26463X - 4.50685Y + 10.24225Z = 1.18489$$

N(1)	-0.001	C(4)	0.000
C(2)	0.002	C(5)	0.001
N(3)	-0.001	C(6)*	-0.023

Plane II: 2,4-dichlorobenzene ring

$$-7.76138X - 5.00883Y + 9.60016Z = -1.20734$$

C(12)	-0.008	C(17)	0.001
C(13)	0.008	C(7)*	0.107
C(14)	-0.000	Cl(18)*	0.025
C(15)	-0.006	Cl(19)*	-0.000
C(16)	0.005		

Plane IIIA: 1,3-dioxolane ring (conformer A)

$$0.59048X - 5.94853Y - 5.68270Z = 1.12189$$

C(7)	0.039	C(10A)*	0.499
O(8)	-0.037	C(6)*	-1.126
C(9A)	0.023	C(12)*	1.352
O(11)	-0.025	C(20A)*	-1.378

Plane IIIB: 1,3-dioxolane ring (conformer B)

$$6.36457X - 5.89862Y - 5.82486Z = 1.09805$$

C(7)	0.032	C(9B)*	0.511
O(8)	-0.021	C(6)*	-1.148
C(10B)	0.019	C(12)*	1.333
O(11)	-0.030	C(20B)*	-1.381

Plane IVA: benzene ring (conformer A)

$$6.48853X + 9.51408Y + 2.95591Z = 2.32673$$

C(22A)	-0.002	C(26)	-0.070
C(23A)	0.007	C(27)	0.034
C(24A)	-0.041	O(21A)*	0.016
C(25)	0.074	N(28)*	0.031

Plane IVB: benzene ring (conformer B)

$$7.87785X + 11.53963Y - 1.11577Z = 4.41531$$

C(22B)	-0.039	C(26)	0.083
C(23B)	0.016	C(27)	-0.012
C(24B)	0.053	O(21B)*	-0.056
C(25)	-0.101	N(28)*	0.057

Plane V: piperazine ring

$$6.78993X + 10.64785Y + 1.68866Z = 3.13968$$

N(28)	0.250	N(31)	-0.217
C(29)	-0.231	C(32)	0.226
C(30)	0.215	C(33)	-0.243

for C(25) and -0.070, 0.083 Å for C(26) (Table 2). The piperazine ring shows the normal chair conformation.

There are no intermolecular contacts that are significantly shorter than the sum of the corresponding van der Waals radii.

The two conformers present in the disordered crystal are optical antipodes (Table 3). Conformer A has the

Table 3. Selected torsion angles (°) describing the conformations of the dioxolane rings

Conformer A

O(11)-C(7)-O(8)-C(9A)	6.8 (8)
C(7)-O(8)-C(9A)-C(10A)	14.5 (13)
C(7)-O(8)-C(9A)-C(20A)	-108.4 (9)
O(8)-C(9A)-C(10A)-O(11)	-29.9 (14)
C(20A)-C(9A)-C(10A)-O(11)	86.0 (18)
C(9A)-C(10A)-O(11)-C(7)	36.9 (11)
O(8)-C(9A)-C(20A)-O(21A)	-167.9 (8)
C(10A)-O(11)-C(7)-O(8)	-29.6 (7)

Conformer B

O(8)-C(7)-O(11)-C(10B)	-5.6 (6)
C(7)-O(11)-C(10B)-C(9B)	-15.9 (15)
C(7)-O(11)-C(10B)-C(20B)	102.8 (11)
O(11)-C(10B)-C(9B)-O(8)	31.7 (15)
C(20B)-C(10B)-C(9B)-O(8)	-86.9 (15)
C(10B)-C(9B)-O(8)-C(7)	-37.6 (12)
O(11)-C(10B)-C(20B)-O(21B)	169.3 (10)
O(11)-C(7)-O(8)-C(9B)	29.1 (7)

cis-(2*R*,4*S*)-1,3-dioxolane and conformer B the *cis*-(2*S*,4*R*)-1,3-dioxolane configuration. Their mutual substitution in the crystal is possible, for the similarity of both conformers is such that no appreciable changes in the number of contacts and no drastic modifications in intermolecular distances occur.

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