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Studies on Antifungal Agents. 21. Structure of (±)-*cis*-3-(4-Chlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methyl-5-(4-chlorophenoxymethyl)isoxazolidine

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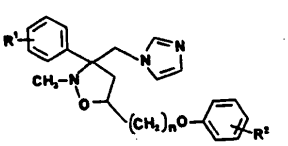
Abstract. $C_{21}H_{21}Cl_2N_3O_2$, $M_r = 418{\cdot}33$, monoclinic, $P2_1/n$, $a = 13{\cdot}547\ (4)$, $b = 7{\cdot}683\ (1)$, $c = 19{\cdot}740\ (2)$ Å, $\beta = 102{\cdot}26\ (2)°$, $V = 2007{\cdot}8$ Å^3, $Z = 4$, $D_x = 1{\cdot}384$ g cm^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}71073$ Å, $\mu = 3{\cdot}43$ cm^{-1}, $F(000) = 872$, $T = 297$ K, final $R = 0{\cdot}051$ for 3212 unique observed reflections. The X-ray analysis confirms the molecular geometry of the title *cis* compound, which is a more potent antifungal agent than the *trans* diastereomer. The individual aromatic rings are planar. The title compound has normal bond lengths and angles.

Introduction. Recently (Mullen, Maryniak, Swift, Allen, Mitchell, Kinsolving & Georgiev, 1987), we reported the synthesis of a series of a novel class of potent antifungal agents, the 5-phenoxyalkyl-3-phenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidines (1), *via* a 1,3-dipolar cycloaddition reaction of α-substituted ketonitrones with 1-alkenyl phenyl ethers. The resulting products comprised the *cis* and *trans* diastereomers of (1) which were conveniently separated by flash chromatography on silica gel. The initial stereochemical assignment of both diastereomers was accomplished by interpretation of their NMR spectra. In general, *cis* analogs were more potent antifungal agents *in vitro* than their *trans* counterparts.

The title compound, (±)-*cis*-3-(4-chlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methyl-5-(4-chlorophenoxymethyl)isoxazolidine (2), demonstrated potent *in vitro* antifungal activity against a broad spectrum of yeast and systemic mycoses and dermatophytes. An X-ray crystal-structure determination of compound (2) was undertaken in order to define unambiguously the stereochemistry of the *cis* derivatives and allow for a consistent differentiation between the *cis* and *trans* diastereomers by NMR techniques.



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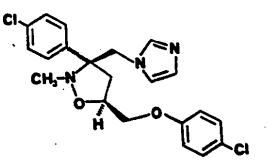

(2)

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Table 1. *Refined positional parameters*

	x	y	z	B_{eq}(Å²)
Cl(1)	0·88758 (7)	0·2858 (1)	−0·27530 (4)	6·09 (2)
Cl(2)	0·51091 (7)	0·8612 (1)	0·35247 (4)	6·47 (2)
C(1)	0·8305 (2)	2·2930 (4)	−0·2042 (2)	4·30 (6)
C(2)	0·8872 (2)	0·2641 (4)	−0·1391 (2)	4·44 (6)
C(3)	0·8419 (2)	0·2758 (4)	−0·0825 (1)	3·94 (6)
C(4)	0·7403 (2)	0·3143 (3)	−0·0909 (1)	3·51 (5)
C(5)	0·6850 (2)	0·3427 (4)	−0·1579 (2)	4·38 (6)
C(6)	0·7294 (2)	0·3315 (4)	−0·2149 (2)	4·72 (7)
C(7)	0·6895 (2)	0·3383 (4)	−0·0300 (1)	3·44 (5)
C(8)	0·7475 (2)	0·2713 (4)	0·0406 (1)	3·84 (6)
C(9)	0·6648 (2)	0·2007 (4)	0·0750 (2)	4·24 (6)
C(10)	0·6567 (2)	0·2740 (4)	0·1448 (2)	4·49 (6)
C(11)	0·6288 (2)	0·5474 (4)	0·1949 (1)	3·99 (6)
C(12)	0·6066 (2)	0·7217 (4)	0·1834 (2)	4·52 (6)
C(13)	0·5733 (2)	0·8198 (4)	0·2324 (2)	4·88 (7)
C(14)	0·5605 (2)	0·7409 (4)	0·2930 (2)	4·44 (6)
C(15)	0·5848 (2)	0·5702 (4)	0·3059 (2)	4·66 (7)
C(16)	0·6195 (2)	0·4715 (4)	0·2570 (2)	4·55 (6)
C(17)	0·6591 (2)	0·5317 (4)	−0·0254 (2)	3·91 (6)
C(18)	0·7881 (2)	0·7208 (4)	0·0510 (2)	4·73 (7)
C(19)	0·8725 (3)	0·8158 (4)	−0·0199 (2)	5·12 (7)
C(20)	0·8009 (2)	0·7096 (4)	−0·0567 (2)	4·50 (6)
C(21)	0·6016 (3)	0·0597 (4)	−0·0631 (2)	4·96 (7)
N(1)	0·5915 (2)	0·2419 (3)	−0·0422 (1)	4·02 (5)
N(2)	0·7461 (2)	0·6489 (3)	−0·0109 (1)	3·84 (5)
N(3)	0·8640 (2)	0·8225 (4)	0·0480 (1)	5·29 (6)
O(1)	0·6579 (2)	0·4597 (3)	0·1419 (1)	4·71 (4)
O(2)	0·5708 (1)	0·2398 (3)	0·0268 (1)	4·40 (4)
H(9)	0·677 (2)	0·066 (4)	0·083 (2)	6·0*
H(2)	0·959 (2)	0·238 (4)	−0·131 (2)	6·0*
H(3)	0·883 (2)	0·261 (4)	−0·038 (2)	6·0*
H(5)	0·616 (2)	0·381 (4)	−0·165 (2)	6·0*
H(6)	0·692 (2)	0·344 (4)	−0·259 (2)	6·0*
H(8)	0·793 (2)	0·185 (4)	0·035 (2)	6·0*
H'(8)	0·787 (2)	0·358 (4)	0·067 (2)	6·0*
H(10)	0·589 (2)	0·235 (4)	0·155 (2)	6·0*
H'(10)	0·714 (2)	0·235 (4)	0·182 (2)	6·0*
H(12)	0·607 (2)	0·761 (4)	0·142 (2)	6·0*
H(13)	0·550 (2)	0·943 (4)	0·224 (2)	6·0*
H(15)	0·577 (2)	0·522 (4)	0·345 (2)	6·0*
H(16)	0·638 (2)	0·358 (4)	0·265 (2)	6·0*
H(17)	0·619 (2)	0·571 (4)	−0·069 (2)	6·0*
H'(17)	0·622 (2)	0·547 (4)	0·013 (2)	6·0*
H(18)	0·760 (2)	0·694 (4)	0·088 (2)	6·0*
H(19)	0·923 (2)	0·888 (4)	−0·035 (2)	6·0*
H(20)	0·786 (2)	0·668 (4)	−0·103 (2)	6·0*
H(21)	0·537 (2)	−0·002 (4)	−0·057 (2)	6·0*
H'(21)	0·660 (2)	0·001 (4)	−0·035 (2)	6·0*
H''(21)	0·602 (2)	0·061 (4)	−0·114 (2)	6·0*

$B_{eq} = \frac{4}{3}[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$.

* Temperature factors not refined.

Experimental. Clear colorless crystal (0·22 × 0·28 × 0·36 mm); Enraf–Nonius CAD-4 diffractometer with graphite-monochromated Mo $K\alpha$ radiation. Lattice parameters from 23 reflections with $21 \le 2\theta \le 28°$. 5085 reflections measured using the ω-2θ scan technique within ranges $4 \le 2\theta \le 55°$, $-17 \le h \le 17$, $0 \le k \le 9$, $0 \le l \le 25$, systematic absences $0k0$: $k = 2n$ and $h0l$: $h + l = 2n$. Intensities of two standard reflections (206, 132) recorded every 2500 s of X-ray exposure showed no significant decay. 3212 unique observed reflections [$I > 3\sigma(I)$], $R_{int} = 6·2\%$. Data corrected for Lorentz and polarization effects, not for absorption. Structure solved by *MULTAN*11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982) in the centrosymmetric space group $P2_1/n$, which revealed 27 non-H atoms. The remaining atom was found from a subsequent Fourier synthesis. H atoms found from difference Fourier syntheses after anisotropic refinement. Refinement by full-matrix least squares to minimize $\sum w(|F_o| - |F_c|)^2$ led to $R = 0·051$ and $wR = 0·054$ for 316 variables with $w = 1/\sigma^2(F_o)$ and $S = 2·29$ (σ estimated from counting statistics). Non-H atoms were refined with anisotropic thermal parameters; H-atom positions were refined. Maximum least-squares shift to e.s.d. ratio 0·12 in final refinement cycle for one of the H atoms; ratios for all heavy atoms were less than 0·05. Largest residual electron density in final difference Fourier synthesis 0·55 e Å^{-3}. Atomic scattering factors from Cromer & Waber (1974); anomalous-dispersion terms from Ibers & Hamilton (1964). All computer programs from Enraf–Nonius *SDP* package (Frenz, 1978).

Discussion. Final positional parameters and equivalent isotropic thermal parameters are given in Table 1.* An *ORTEP* representation of the molecule appears in Fig. 1 and an *ORTEP* drawing of the unit cell in Fig. 2. The results of the structure determination confirm the molecular geometry of the title compound as the *cis*

* Tables of anisotropic thermal parameters, bond distances, bond angles and observed and calculated structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44843 (21 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

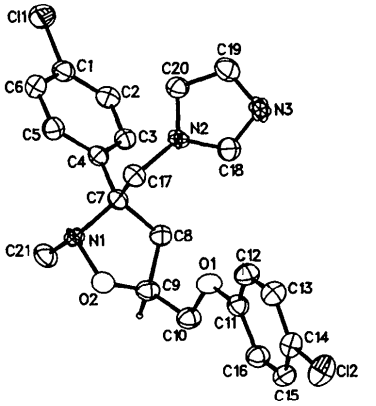

Fig. 1. *ORTEP* (Johnson, 1965) drawing (30% probability thermal ellipsoids) showing atom-numbering scheme.

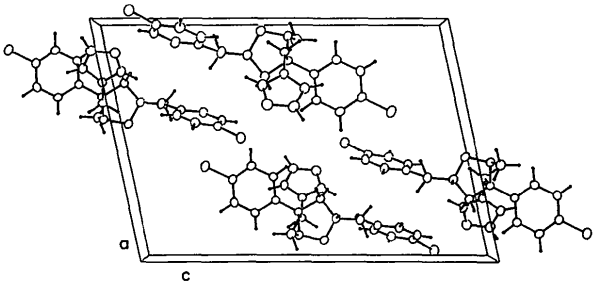

Fig. 2. *ORTEP* view of unit cell along the *b* axis.

diastereomer. The phenyl ring defined by C(1), C(2), C(3), C(4), C(5), C(6) is planar within 0·003 Å; phenyl ring C(11), C(12), C(13), C(14), C(15), C(16) is planar within 0·02 Å; the imidazole ring defined by C(18), C(19), C(20), N(2), N(3) is planar within 0·003 Å.

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Structure of 6-(Iodomethyl)-2-oxo-2-phenoxy-1,2-oxaphosphorinane

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Abstract. $C_{11}H_{14}IO_3P$, M_r=352·11, monoclinic, $P2_1/n$, a=8·300 (3), b=14·081 (2), c=11·326 (4) Å, β=104·32 (3)°, V=1282·6 (13) Å^3, Z=4, D_x=1·823 Mg m^{-3}, λ(Mo $K\alpha$)=0·71073 Å, μ=25·8 cm^{-1}, $F(000)$=688, R=0·035 for 2364 observed reflections. The six-membered ring O(1), P(2), C(3), C(4), C(5), C(6) is in a chair conformation with phenoxy and iodomethyl groups adopting axial and equatorial orientations, respectively. The bond distances and angles are unexceptional.

Introduction. The phosphonate ester 6-(aminomethyl)-2-oxo-2-phenoxy-1,2-oxaphosphorinane was synthesized to resemble a product-like intermediate for the cyclization of phenyl 6-acetamido-5-hydroxyhexanoate. The phosphonate ester was used as a hapten to generate a series of monoclonal antibodies that were then screened for their ability to act as abzyme catalysts for the cyclization reaction (Napper, Benkovic, Tramontano & Lerner, 1987).

The synthesis of the phosphonate ester was accomplished by a stereospecific cyclization of phenyl isopropyl-4-pentenylphosphonate induced by iodine (Zhao & Yan, 1985) followed by conversion of the iodomethyl derivative to the desired compound. Definitive evidence for a 1,3-*trans* orientation (axial–equatorial) of the phenoxy and aminomethyl substituents was sought by obtaining the X-ray crystal structure of the precursor iodo compound. The results of that study are presented herein.

Experimental. A large crystal of the title compound, (1), from a hot acetone solution by slow cooling was cut to an approximate size 0·54 × 0·70 × 0·70 mm and was used for data collection.

Accurate cell constants and a crystal orientation matrix were determined on an Enraf–Nonius CAD-4 diffractometer by a least-squares refinement of the setting angles of 25 reflections with θ in the range 10–15°. Intensity data were collected by the $\omega/2\theta$-scan method and variable scan speed using monochromatized radiation in the range $2 < \theta < 27°$. The intensities of three reflections, chosen as standards, were monitored at 2 h exposure intervals and decreased in a linear fashion by 2·4% over the course of data collection; this decay was corrected for by appropriate scaling. Intensities of 2788 independent reflections (h 0→10, k 0→17, l −14→14) were measured, of which 2364 had $I > 3\sigma(I)$ and were used in the structure solution and refinement. The data were corrected for Lorentz–polarization effects and for empirical absorption (North, Phillips & Mathews, 1968); minimum and maximum correction factors were 0·854 and 1·000, respectively.

The structure was solved by the heavy-atom method and refined by full-matrix least-squares calculations on F's, initially with isotropic and finally with anisotropic temperature factors for the non-H atoms. At an intermediate stage in the refinement, a difference map revealed all H atoms which were included in the subsequent cycles in geometrically idealized positions

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