Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

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

	x	y	z	U_{eq}
O1	0.37829 (5)	0.0838 (2)	0.85350 (11)	0.0313 (3)
O2	0.32206 (7)	0.4750 (2)	0.88946 (13)	0.0447 (4)
O3	0.27026 (7)	0.5054 (2)	0.67691 (14)	0.0448 (4)
O4	0.46017 (7)	−0.4518 (3)	0.83946 (13)	0.0461 (4)
O5	0.46085 (6)	−0.2286 (3)	1.01629 (12)	0.0439 (4)
N1	0.30843 (7)	0.4061 (3)	0.77363 (14)	0.0338 (4)
C1	0.44395 (8)	−0.2734 (3)	0.8913 (2)	0.0331 (4)
C2	0.40099 (8)	−0.1051 (3)	0.8002 (2)	0.0321 (4)
C3	0.37659 (9)	−0.1025 (4)	0.6649 (2)	0.0382 (5)
C4	0.33612 (9)	0.0977 (4)	0.6292 (2)	0.0370 (5)
C5	0.33927 (8)	0.2000 (3)	0.7461 (2)	0.0307 (4)

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

O1—C5	1.343 (2)	N1—C5	1.414 (2)
O1—C2	1.365 (2)	C1—C2	1.451 (3)
O2—N1	1.222 (2)	C2—C3	1.351 (3)
O3—N1	1.222 (2)	C3—C4	1.401 (3)
O4—C1	1.244 (2)	C4—C5	1.341 (3)
O5—C1	1.272 (3)		
C5—O1—C2	104.12 (14)	C3—C2—C1	130.9 (2)
O2—N1—O3	124.7 (2)	O1—C2—C1	118.2 (2)
O2—N1—C5	119.00 (15)	C2—C3—C4	106.9 (2)
O3—N1—C5	116.3 (2)	C5—C4—C3	104.8 (2)
O4—C1—O5	125.8 (2)	C4—C5—O1	113.4 (2)
O4—C1—C2	116.4 (2)	C4—C5—N1	130.7 (2)
O5—C1—C2	117.8 (2)	O1—C5—N1	115.88 (15)
C3—C2—O1	110.8 (2)		
O5—C1—C2—C3	178.2 (2)	O3—N1—C5—O1	−176.23 (14)
O4—C1—C2—O1	175.27 (15)		

The temperature of the crystal was controlled using the Oxford Cryosystems Cryostream Cooler (Cosier & Glazer, 1986). H atoms were added from difference density maps. Anisotropic displacement parameters were used for all non-H atoms; H atoms were given isotropic displacement parameters equal to 1.2 times the equivalent isotropic displacement parameter of the atom to which they are attached.

Data collection: Siemens *P3R3* system. Cell refinement: Siemens *P3R3* system. Data reduction: *SHELXTL-Plus* (Sheldrick, 1991). Program(s) used to solve structure: *SHELXTL-Plus*. Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993).

We wish to acknowledge the use of the Cambridge Structural Database (Allen *et al.*, 1991) through the EPSRC's Chemical Database Service at Daresbury. One of us (JL) wishes to thank the Department of Chemistry at the University of Warwick for its hospitality.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, torsion angles and complete geometry have been deposited with the IUCr (Reference: CF1029). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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1-Trityl-4-nitroimidazole

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Abstract

X-ray analysis confirmed the configuration of the title N1-alkylated C4-nitroimidazole inhibitor. The plane of the imidazole ring, sitting on an axis of the trityl propeller, bisects the angle between two phenyl rings, while the nitro group extends over the third. Modeling of the interactions between the cytochrome P450 and the title compound ($C_{22}H_{17}N_3O_2$) has been performed on the basis of the crystal structures of 1-trityl-4-nitroimidazole and bacterial cytochrome $P450_{BM-3}$. The replacements and deletions in the sequence of the latter has been performed to match mammalian cytochrome P450-IIIA1. The modeling explained why inhibitors with a C4-substituted imidazole ring showed lower effectivity than those without substituents, as an additional group of atoms at C4 prevents close interactions of the imidazole ring with the heme Fe atom.

Comment

Tritylimidazoles are used clinically as topical antifungal agents (von Buchel, Draber, Regel & Pempel, 1972). The antifungal activity is thought to be due to inhibition of a fungal cytochrome P450 mixed-function oxidase, which catalyses 14-α-dimethylation of sterols in the conversion of lanosterol to ergosterol. Tritylimidazoles also selectively inhibit certain mammalian cytochrome P450 isozymes (Rodrigues, Gibson, Ioannides & Parke, 1987). The structures of substituted tritylimidazoles such

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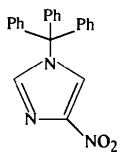
as the title compound, (I), are, therefore, important for understanding and predicting the interactions of these compounds with mammalian and microbial cytochrome P450 isozymes (Lewis, Rodrigues, Ioannides & Parke, 1989).



(I)

It has been well established that clotrimazole and similar compounds (Rodrigues *et al.*, 1987) are the potent inhibitors of oxidative metabolism in fungi. In contrast to clotrimazole, 1-trityl-4-nitroimidazoles and 4-aminoimidazoles show very poor inhibitory activity toward cytochrome P450. To understand the nature of the interaction of substrates in the P450 active sites, computer-modeling studies were performed using the crystal structure of 1-trityl-4-nitroimidazole (Fig. 1) as inhibitor and the recently determined structure of $P450_{BM-3}$ (Ravichandran, Boddupalli, Hasemann, Peterson & Deisenhofer, 1993) as the cytochrome model. This bacterial enzyme displays 25–30% amino-acid sequence identity with eukariotic microsomal cytochromes P450. It also resembles them in the nature of the interaction with the electron-donating redox partner. Thus, the structure of $P450_{BM-3}$ represents a good model for understanding the structure–function relationship of the eukariotic cytochromes P450.

An optimal alignment of the amino-acid sequences of $P450_{BM-3}$ and rat P450-IIIA1, a microsomal enzyme, reveals *ca* 30% sequence identity. There is a close homology between P450-IIIA1, rat P450-IIIA2 and human P450-IIIA4 (Lewis & Moereels, 1992) that allows us to make reasonable predictions concerning the human enzyme. Some differences between bacterial and mammalian cytochromes P450 occur in deletions close to the active site. The sequence of $P450_{BM-3}$ was changed in the vicinity of the active site to reflect that of P450-IIIA1 (Gonzales, Nebert, Hardwick & Kasper, 1985). One of the major differences was near the β4 region, where P450-IIIA1 has a deletion of four residues. This deletion is also present in most of the steroid-binding cytochromes P450. As a result of this deletion the active site and the substrate-binding site become more open. This might be necessary in order to accommodate a bulky substrate such as a steroid molecule (while $P450_{BM-3}$ hydroxylates long-chain fatty acids).

1-Trityl-4-nitroimidazole was docked into the altered structure of $P450_{BM-3}$ using the program *INSIGHT*II (Biosym Technologies, 1993). The most favorable orientation was with the NO_2 substituent of the imidazole ring interacting with the heme group of the cytochrome. This substituent does introduce some steric overcrowding and prevents the imidazole ring from interacting directly with Fe from the heme moiety, while in the case of clotrimazole, the imidazole ring (which is not substituted) would be closer to the heme moiety. This probably explains the poor inhibitory effect of C4-substituted 1-tritylimidazoles on the metabolism of microsomal cytochromes P450.

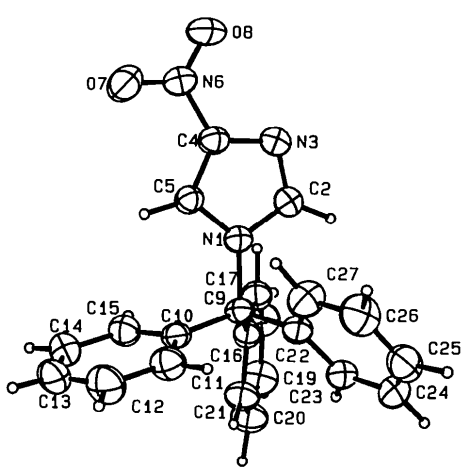


Fig. 1. View of a molecule of 1-trityl-4-nitroimidazole (clotrimazole has an unsubstituted imidazole ring and a Cl atom at the *ortho* position in one phenyl ring). Ellipsoids are shown at the 50% probability level.

Experimental

The title compound was crystallized from benzene.

Crystal data

$C_{22}H_{17}N_3O_2$
M_r = 355.40
Monoclinic
$P2_1/c$
a = 9.830 (2) Å
b = 9.239 (2) Å
c = 19.654 (2) Å
β = 96.11 (1)°
V = 1775 (1) Å^3
Z = 4
D_x = 1.33 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 10–14°
μ = 0.081 mm^{-1}
T = 294 K
Prism
0.41 × 0.40 × 0.29 mm
Transparent

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
3942 measured reflections
3720 independent reflections
2595 observed reflections [$I > 3.0\sigma(I)$]
R_{int} = 0.013
θ_{max} = 25.97°
h = 0 → 12
k = 0 → 11
l = −24 → 24
3 standard reflections
frequency: 60 min
intensity decay: 1.55%

Refinement

Refinement on F
$R = 0.039$
$wR = 0.054$
$S = 1.800$
2595 reflections
244 parameters
H atoms riding
$w = 4F_o^2/[\sigma^2(F_o^2) + 0.0016F_o^4]$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.168$ e Å^{-3}
$\Delta\rho_{min} = -0.102$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

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

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

	x	y	z	U_{eq}
N1	0.6578 (1)	0.2057 (1)	0.11484 (6)	0.0358 (3)
C2	0.5314 (2)	0.2303 (2)	0.08069 (8)	0.0449 (4)
N3	0.4551 (1)	0.3157 (1)	0.11365 (7)	0.0448 (3)
C4	0.5381 (1)	0.3474 (2)	0.17163 (7)	0.0381 (4)
C5	0.6627 (1)	0.2827 (2)	0.17407 (7)	0.0364 (3)
N6	0.4952 (1)	0.4443 (2)	0.22220 (7)	0.0461 (3)
O7	0.5812 (1)	0.4804 (2)	0.26863 (6)	0.0698 (4)
O8	0.3771 (1)	0.4862 (1)	0.21678 (7)	0.0686 (4)
C9	0.7680 (1)	0.1155 (2)	0.08808 (7)	0.0351 (3)
C10	0.9015 (1)	0.1378 (2)	0.13590 (7)	0.0363 (3)
C11	1.0100 (2)	0.2193 (2)	0.11782 (9)	0.0473 (4)
C12	1.1259 (2)	0.2397 (2)	0.1636 (1)	0.0603 (5)
C13	1.1346 (2)	0.1793 (2)	0.2278 (1)	0.0604 (5)
C14	1.0287 (2)	0.0947 (2)	0.24584 (9)	0.0570 (5)
C15	0.9134 (2)	0.0732 (2)	0.20012 (8)	0.0464 (4)
C16	0.7284 (1)	−0.0457 (2)	0.08935 (7)	0.0361 (3)
C17	0.6024 (1)	−0.0945 (2)	0.10579 (8)	0.0425 (4)
C18	0.5734 (2)	−0.2418 (2)	0.10536 (9)	0.0524 (4)
C19	0.6683 (2)	−0.3402 (2)	0.0880 (1)	0.0566 (5)
C20	0.7954 (2)	−0.2938 (2)	0.0730 (1)	0.0545 (5)
C21	0.8253 (1)	−0.1476 (2)	0.07450 (8)	0.0456 (4)
C22	0.7792 (1)	0.1710 (2)	0.01466 (7)	0.0372 (3)
C23	0.7845 (2)	0.0805 (2)	−0.04121 (8)	0.0439 (4)
C24	0.7979 (2)	0.1381 (2)	−0.10557 (8)	0.0543 (5)
C25	0.8049 (2)	0.2850 (2)	−0.11542 (9)	0.0610 (5)
C26	0.7965 (2)	0.3762 (2)	−0.0606 (1)	0.0613 (5)
C27	0.7844 (2)	0.3192 (2)	0.00363 (9)	0.0520 (4)

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

N1—C2	1.367 (2)	C12—C13	1.373 (3)
N1—C5	1.361 (2)	C13—C14	1.378 (3)
N1—C9	1.505 (2)	C14—C15	1.384 (2)
C2—N3	1.307 (2)	C16—C17	1.389 (2)
N3—C4	1.361 (2)	C16—C21	1.392 (2)
C4—C5	1.359 (2)	C17—C18	1.391 (2)
C4—N6	1.434 (2)	C18—C19	1.372 (2)
N6—O7	1.222 (2)	C19—C20	1.382 (3)
N6—O8	1.218 (2)	C20—C21	1.382 (2)
C9—C10	1.545 (2)	C22—C23	1.386 (2)
C9—C16	1.540 (2)	C22—C27	1.388 (2)
C9—C22	1.546 (2)	C23—C24	1.391 (2)
C10—C11	1.382 (2)	C24—C25	1.374 (3)
C10—C15	1.390 (2)	C25—C26	1.378 (3)
C11—C12	1.387 (2)	C26—C27	1.384 (3)
C2—N1—C5	106.3 (1)	C10—C11—C12	120.6 (2)
C2—N1—C9	124.8 (1)	C11—C12—C13	120.5 (2)
C5—N1—C9	128.8 (1)	C12—C13—C14	119.5 (2)
N1—C2—N3	113.4 (1)	C13—C14—C15	120.2 (2)
C2—N3—C4	102.7 (1)	C10—C15—C14	120.8 (1)
N3—C4—C5	113.1 (1)	C9—C16—C17	123.4 (1)
N3—C4—N6	121.4 (1)	C9—C16—C21	118.1 (1)
C5—C4—N6	125.5 (1)	C17—C16—C21	118.5 (1)
N1—C5—C4	104.5 (1)	C16—C17—C18	120.2 (1)
C4—N6—O7	117.2 (1)	C17—C18—C19	120.4 (2)
C4—N6—O8	119.1 (1)	C18—C19—C20	120.2 (2)
O7—N6—O8	123.7 (1)	C19—C20—C21	119.5 (2)
N1—C9—C10	108.1 (1)	C16—C21—C20	121.2 (1)
N1—C9—C16	109.7 (1)	C9—C22—C23	123.5 (1)
N1—C9—C22	105.5 (1)	C9—C22—C27	118.7 (1)
C10—C9—C16	108.6 (1)	C23—C22—C27	117.8 (1)
C10—C9—C22	112.5 (1)	C22—C23—C24	120.3 (2)
C16—C9—C22	112.3 (1)	C23—C24—C25	121.1 (2)
C9—C10—C11	123.0 (1)	C24—C25—C26	119.1 (2)
C9—C10—C15	118.6 (1)	C25—C26—C27	119.9 (2)
C11—C10—C15	118.4 (1)	C22—C27—C26	121.7 (2)

Backgrounds were obtained from analysis of the scan profile (Blessing, Coppens & Becker, 1974). H atoms were located in the difference map and refined isotropically.

Data collection: *CAD*-4 software (Enraf–Nonius, 1977). Cell refinement: *CAD*-4 software. Data reduction: *MolEN PROCESS* (Fair, 1990). Program(s) used to solve structure: *MULTAN* (direct methods) (Main *et al.*, 1980). Program(s) used to refine structure: *MolEN LSFM* (Fair, 1990). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *MolEN CIF IN* (Fair, 1990).

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Lists of structure factors, torsion angles, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: SZ1038). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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