Articles

The Structure of 1-[2-[[(4-chlorophenyl)-methyl]thio]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole (Sulconazole) nitrate, $C_{18}H_{16}Cl_3N_3O_3S$

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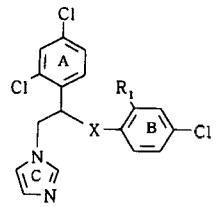
Sulconazole nitrate, $C_{18}H_{16}Cl_3N_3O_3S$, crystallizes in monoclinic, space group C2/c, with a=14.401(1), b=8.051(1), c=34.861(2) Å, β=95.9(1)°, μ=0.58 mm^{-1}, Dc=1.523 g/cm^3, Dm=1.522 g/cm^3, F(000)=1888.0, and z=8. Intensities for 2460 unique reflections were measured on a CAD4 diffractometer with graphited-monochromated Mo-Kα radiation. The structure was solved by direct method and refined by full matrix least squares to a final R=0.071 for 2182 reflections ($I_o>2\sigma I_o$). The bond lengths and angles are comparable with the values found in the analogues imidazole derivatives. The 2,4-dichlorophenyl ring(A) and the p-chlorophenyl ring(B) are almost planar with different heights [dihedral angle 17.3°] while the imidazole ring(C) is nearly perpendicular to the two phenyl rings[dihedral angles about the two rings A, B are 110.8° and 96.1°, respectively]. In order to understand the overall conformation we calculated the selected distances (l_1, l_2, l_3) among the center of the three rings and considered the imaginary plan D[C(7), C(9) and C(16)]. The two polar group S(8) and N(19) do not have gauche conformation and l_2 value (4.47 Å) is shorter than the other imidazole derivatives. One -NO_3 group are hydrogen bonded the two neighbored sulconazole molecules. The molecular crystal packing is also formed by two hydrogen bondings and van der Waals forces.

Introduction

Fungal cell membrane, due primarily to the presence of ergosterol, an integral and important sterol component of it, is very vulnerable to the action of some antifungal agents, such as imidazole derivatives. The initial members of this class were clotrimazole and miconazole.[1] The systemic administration of these compounds has proven effective in the treatment of some mycosis, but these agents are not ideal due to their poor bioavaility. Moreover, the initial azoles showed numerous side effects and more serious neurological and hematological effects. In medicinal chemistry research, it is believed that their antifungal activity was mainly caused by the disorganization of the fungal cytoplasmic membrane.[2] This is a consequence of hydrophobic interactions between these drugs and unsaturated fatty acid components of the fungal membrane. Change in membrane permeability and transportable functions leads to metabolic imbalance which results in the inhibition of growth or death of the fungal cell. It is suggested that the inhibitory mechanism of azoles may involve binding of nitrogen of the imidazole (or triazole) ring with the iron of the cytochrome P-450 isozyme.[3]



	X	R1
(1)	S	H
(2)	O	Cl
(3)	O	H
(4)	O	H

Scheme 1. Structure of imidazole derivatives.

Sulconazole nitrate(1) is a member of the imidazole derivatives with antifungal activity. Like its close analogue econazole nitrate, which differs in having a replaced S at O in the main chain, sulconazole nitrate has a wide antifungal spectrum.[4,5] The crystal structures of a number of imidazole derivatives have been determined by the X-ray diffraction method. These included miconazole(2),[6] econazole(3)[7] and econazole nitrate(4).[8] In this work, the crystal structure of sulconazole nitrate has been determined with the objective of determining the effect of the replaced S on the sterochemistry of imidazole derivatives in order to explain the difference in the biological activity of the different imidazole derivatives. Since many imidazole derivatives are antifungal agents, this work will also contribute to the basic understanding of the correlation between the pharmacological activity and the molecular structure of the imidazole derivatives.

Experimental

Crystals in the form of colorless rods elongated along b axis were prepared by slow evaporation of ethanol solution. The title compound was purchased from SIGMA chemicals. The unit cell constants were refined by a least-squares fit to 2θ values measured on a diffractometer. The density was measured by flotation in a benzene-carbon tetrachloride mixture. Crystal data are given in Table 1. Intensity data were measured on a CAD-4 automated diffractometer, using graphite-monochromated Mo-Kα radiation. A crystal of ap-

Table 1. The crystal data of sulconazole nitrate

Chemical formula : $C_{18}H_{16}Cl_3N_3O_3S$
Molecular weight : 470.89
Crystal system : Monoclinic
Cell Dimension : a=14.401(1), b=8.051(1), c=34.861(2) Å, β=95.9(1)°
Cell volume : V=4019.57 Å^3
Crystal density : Dc=1.523 g/cm^3, Dm=1.522 g/cm^3
Absorption coefficient : μ=0.58 mm^{-1}
Intensity control reflections : (0 0 −20), (0 −4 12), (−7 −1 10)
Total reflections : 2460
Observed reflections ($I_o>2\sigma I_o$) : 2182
Electron number in origin : F(0 0 0)=1888.0

proximate dimension of 0.27×0.32×0.12 mm was used in data collection. It was mounted with the b axis nearly parallel to the Φ axis of the diffractometer. Reflections were collected by the ω-2θ scan mode at a rate of 6° (2θ/min). 2460 independent reflections were measured for 1.5°<2θ<25° in indices range of $-17\le h\le 15$, $0\le k\le 9$, $0\le l\le 40$. Three standard reflections were checked after every 125 reflections; they showed no significant change in intensity. The intensity data were corrected for Lorentz and polarization factors, but not for absorption. The structure was solved by the direct method (SHELXS-86)[9] based on the 913 reflections with E≥1.2 and refined by full matrix least squares methods (SHELXL-93).[10] E map showed all non-hydrogen atoms, which led to an R_E index of 0.341 for 28 surviving atoms. After six cycles of full matrix least squares adjustment of the coordinates and isotropic temperature factors (R=0.17), a difference map indicated the locations of the hydrogen atoms. Final refinement cycles included in a single matrix 320 parameters. The final R index was 0.071, and GooF value was 1.126. The maximum parameter shift $(\Delta/\sigma)_{max}$ was 0.001. An extinction parameter ζ(0.001) is refined by least squares, where Fc is multiplied by: $k[1+0.001\times\zeta\times F\ c^2\times\lambda^3/\sin(2\theta)]^{0.25}$, where k is the overall scale factor. The maximum and minimum residual density in the final difference map were 0.48 and −0.41 eÅ^{-3}, respectively. These peaks were located nearly the Cl(1) atom. The atomic scattering factors were taken from *International Tables for Crystallography*.[11]

Results and Discussion

The final atomic coordinates and equivalent isotropic thermal parameters are listed in Table 2. The molecular structure of sulconazole nitrate by ORTEX[12] is presented in Figure 1. The comparison of selected bond lengths and angles in analogous imidazole derivatives with antifungal activity are given in Table 3. The C-C bond lengths vary from 1.363(12) to 1.399(8) Å in the two phenyl ring A, B. These values are similar to the values found in the other azoles. The C-N bond lengths in the imidazole ring vary from 1.325 to 1.380(7) Å and the C(21)-N(17) bond length [1.380(7) Å] is larger than 1.33(2) Å in the miconazole. But this value is in good agreement with those values in the pure imidazole, econazole and econazole nitrate. As shown in Table 4, in order to evaluate the effect of the replaced S at the position O(8) on the conformational changes of econazole and econa-

Table 2. Fractional atomic coordinates (×10^4) and equivalent isotropic thermal parameters (Å^2×10^3) for non-hydrogen atoms of sulconazole nitrate

Atom	x	y	z	Ueq
CL(1)	4912(1)	−2299(2)	4133(1)	57
CL(2)	2072(1)	1221(3)	4593(1)	63
CL(3)	6370(1)	−8456(4)	4681(1)	97
C(1)	3759(4)	−1619(7)	4034(2)	35
C(2)	3418(4)	−596(8)	4310(2)	39
C(3)	2517(4)	−22(8)	4246(2)	43
C(4)	1958(4)	−1421(8)	3915(2)	43
C(5)	2308(4)	−2070(7)	3648(2)	38
C(6)	3213(4)	−3246(7)	3704(2)	33
C(7)	3532(4)	−5118(2)	3408(2)	38
S(8)	2807(1)	−5789(1)	3354(1)	50
C(9)	2801(6)	−6363(8)	3862(3)	60
C(10)	3721(5)	−60941(0)	4051(2)	51
C(11)	3929(6)	−67941(1)	4442(2)	64
C(12)	4748(7)	−67541(1)	4633(2)	72
C(13)	5344(5)	−76531(0)	4435(2)	61
C(14)	5159(5)	−78891(1)	4055(2)	58
C(15)	4356(5)	−7271(9)	3864(2)	52
C(16)	3479(4)	−2551(8)	3004(2)	41
N(17)	4036(3)	−1027(6)	2985(1)	35
C(18)	3686(5)	455(8)	288(8)	45
N(19)	4398(4)	1508(7)	2894(2)	48
C(20)	5212(5)	689(9)	2999(2)	48
C(21)	4993(4)	−880(9)	3056(2)	44
N(22)	1048(3)	45(7)	2862(2)	42
O(23)	1363(3)	−1086(6)	2671(0)	61
O(24)	1500(3)	1329(6)	2928(2)	63
O(25)	283(3)	−163(6)	2999(2)	65

$$U_{eq}=\frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*a_i a_j$$

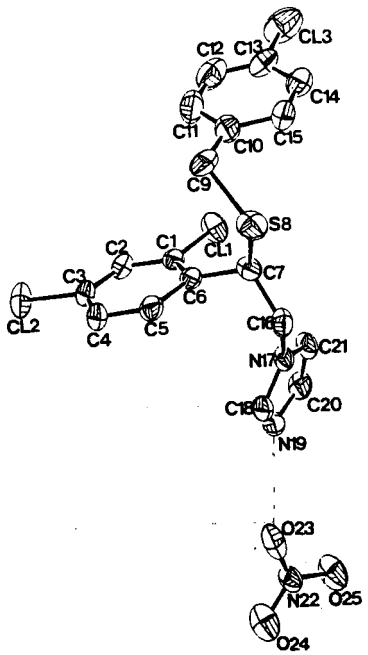
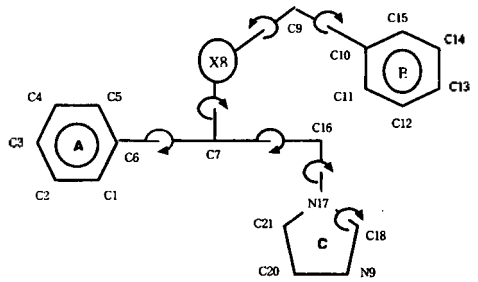


Figure 1. Molecular structure of sulconazole nitrate showing the atomic numbering and 45% thermal elipsoids. The hydrogen bonding is indicated by a dot line.

Table 3. The comparison of selected bond lengths(Å) and angles(°) in analogous imidazole derivatives with antifungal activity

Molecular Moiety	Bond Atoms	Miconazole · 1/2 H_2O		Econazole	Econazole Nitrate	
		Molecule A	Molecule B			
Benzene Ring A [C1, · · · , C6]	Average	1.37(2)	1.37(2)	1.381(6)	1.383(11)	1.383(9)
Benzene Ring B [C10, · · · , C15]	Average	1.36(2)	1.38(2)	1.376(2)	1.372(11)	1.374(11)
Imidazole Ring C [N17, · · · , N20]	Minimum	1.29(2)	1.30(2)	1.303(6)	1.308(10)	1.322(10)
	Maximum	1.35(2)	1.38(2)	1.372(6)	1.390(9)	1.380(7)
Main Chain D [C7, X8, C9, C16]	C6-C7	1.53(2)	1.57(2)	1.516(6)	1.474(10)	1.506(9)
	C7-X8	1.38(2)	1.38(1)	1.414(5)	1.421(8)	1.823(6)
	X8-C9	1.44(2)	1.45(2)	1.420(6)	1.443(7)	1.852(11)
	C9-C10	1.45(2)	1.47(2)	1.495(7)	1.489(9)	1.480(1)
Benzene Ring A [C1, · · · , C6]	Minimum	114.7(11)	116.6(11)	117.1(4)	116.2(6)	117.6(6)
	Maximum	122.2(11)	123.0(11)	125.5(4)	123.5(6)	122.1(6)
Benzene Ring B [C10, · · · , C15]	Minimum	114.6(12)	117.6(11)	117.3(4)	116.6(6)	116.7(7)
	Maximum	125.1(13)	123.1(12)	122.4(5)	124.0(7)	122.2(7)
Imidazole Ring C [N17, · · · , N20]	Minimum	106.6(12)	107.0(13)	104.8(4)	106.0(7)	106.9(6)
	Maximum	127.8(10)	127.3(11)	127.5(4)	126.4(6)	127.1(5)
Main Chain D [C7, X8, C9, C16]	N17-C16-C7	112.7(10)	111.4(10)	111.4(4)	112.1(5)	112.1(5)
	C16-C7-X8	106.8(10)	105.8(9)	106.2(4)	104.3(5)	103.6(4)
	C7-X8-C9	117.0(9)	115.2(9)	113.8(4)	113.7(4)	101.6(3)
	X8-C9-C10	110.0(10)	108.4(10)	114.7(4)	107.3(5)	115.2(6)

Table 4. The Comparison of selected torsion angles(°) for analogous imidazole derivatives with antifungal activity



Torsion angles	Miconazole · 1/2 H_2O		Econazole	Econazole Nitrate	Sulconazole Ntrate
	Molecule A	Molecule B			
τ_1=C16-N17-C18-N19	− 177.4(17)	177.9(17)	174.3(6)	177.4(6)	− 178.5(4)
τ_2=C7-C16-N17-C18	84.1(14)	− 76.2(13)	− 165.5(5)	− 77.7(7)	− 116.4(4)
τ_3=X8-C7-C16-N17	− 71.3(11)	− 66.6(10)	62.9(4)	70.1(5)	− 179.3(6)
τ_4=C16-C7-X8-C9	159.6(13)	158.1(12)	− 165.5(4)	− 158.5(6)	− 174.5(5)
τ_5=C7-X8-C9-C10	177.7(13)	− 178.1(13)	67.0(4)	168.5(6)	− 67.2(6)
τ_6=X8-C9-C10-C15	8.4(11)	0.9(10)	34.3(5)	− 77.5(4)	− 37.0(5)
τ_7=C5-C6-C7-X8	98.0(13)	− 17.9(10)	32.5(4)	13.7(5)	− 60.2(6)

*X8 indicates O8 in Miconazole · 1/2H_2O, Econazole, and Econazole nitrate, and S8 in Sulconazole nitrate.

zole nitrate, we examined the seven torsion angles (τ_1-τ_7). First we calculated two torsion angles τ_1[C(16)-N(17)-C(18)-N(19)] and τ_2[C(7)-C(16)-N(17)-C(18)] to understand the orientation of the imidazole ring C about the C(16)-N(17) axis. As compared to econazole molecule the replacement of S atom at O(8) position leads to several changes in the molecular conformation. The ring B is opposite rotated about the S(8)-C(9) bond in a 180°. This change confers a certain restriction on the degree of rotation of rings about the S(8)-C(9) bond which is observed in τ_5[C(7)-S(8)-C(9)-C(10)], − 67.2(6)°, and τ_6[S(8)-C(9)-C(10)-C(15)], − 37.0(5)°, when compared to the values of 67.0(4)° and 34.3(5)° found in econazole. As compared to econazole, the ring A is also opposite rotated about the C(6)-C(7) bond in about 93°. The imidazole ring C is found to be nearly perpendicular to the almost coplanar A, B ring system [dihedral angles about the two ring A, B are 110.8° and 96.1°, respectively]. The dihedral angles and overall geometric properties are com-

Table 5. The comparison of overall geometric properties for analogoue imidazole derivatives with antifungal activity

Bond Atoms		Miconazole · 1/2 H_2O		Econazole	Econazole Nitrate	Sulconazole Ntrate
		Molecule A	Molecule B			
Plane Distances	l_1	5.30	6.66	6.11	6.16	6.93
	l_2	6.21	6.21	6.21	6.18	4.47
	l_3	6.24	6.24	4.97	5.70	7.29
	l_4	4.28	4.28	4.12	4.21	6.09
Deviations of Plane D	X8	0.357(8)	0.357(8)	−0.279(3)	0.391(3)	−0.180(2)
	N19	−2.316(11)	−2.316(11)	2.101(3)	−2.275(6)	0.882(6)
Dihedral Angles	D ⊥ A	111.7	111.7	79.7	114.0	95.7
	D ⊥ B	154.9	154.9	85.1	121.9	95.2
	D ⊥ C	110.9	110.9	77.2	111.8	117.8
	A ⊥ B	81.0	90.7	123.8	10.4	17.3
	A ⊥ C	1.1	22.0	4.8	4.7	110.8
	B ⊥ C	82.1	95.2	119.3	10.6	96.1

*l_1: Distance between T1(the center of ring A) and T2(the center of ring B). l_2: Distance between T1(the center of ring A) and T3(the center of ring C). l_3: Distance between T2(the center of ring B) and T3(the center of ring C). l_4: Distance between N19 and X8. D: The least-square plane including C7, C9, and C16

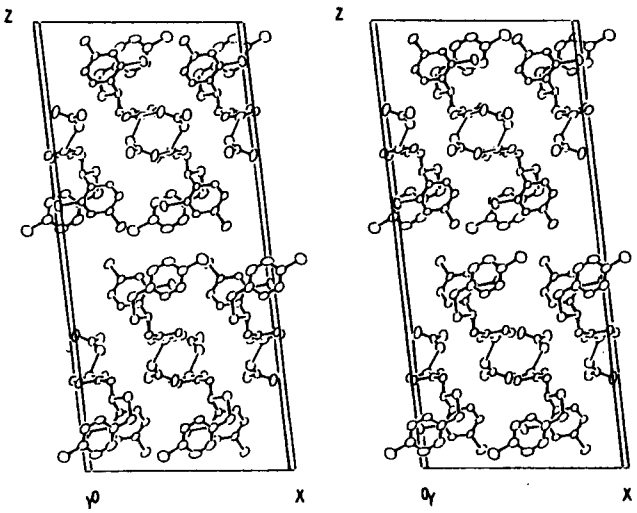


Figure 2. A Stereoscopic view of crystal packing of sulconazole nitrate. The hydrogen bondings are indicated by a thin line.

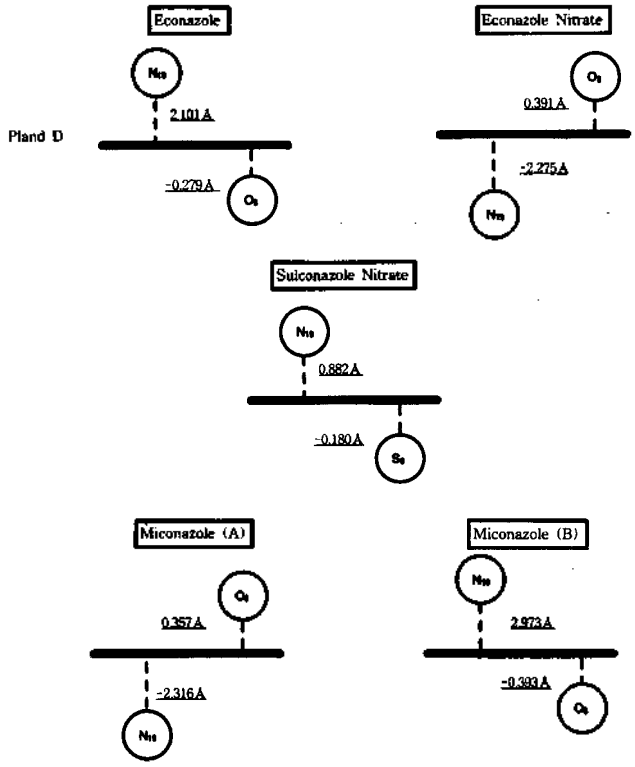


Figure 3. The deviation of N19 and X(O, S) from imaginary plane D (C7, C9 and C16).

pared in Table 5. In order to appreciate mechanism of drug action it is important to understand the forces of interaction and molecular conformation that the bind drugs to their receptors. It is generally believed that imidazole derivtives owe their antifungal activity mainly to the disorganization of the fungal cytoplasmic membrane. Recently Daha *et al.* have argued that the methylation at C(4) and C(14) of lanosterol, which results in a planar α face, renders the molecules more effective in interacting with hydrophobic present in the lipid bilayer of membrane.[13] The bulky 14-α methyl group destroys the planarity of the α face of sterol and hence the integrity of the membrane.[13] According to the docking model of diclobutazole and P-450 isozyme by Mashington,[14] in order to show the antifungal activity, the azoles have only the gauche conformation in between the polar group X (the tertiary hydroxyl group on diclobutrazole) and the triazole ring. They also suggested that the substituted phenyl ring can be fold on the side chain of the sterol molecule. Therefore, in order to estimated the common geometric conformation on the analougs imidazole derivatives, we carried out the geometry calculation on the selected distances (l_1, l_2, l_3) among the center of the three planar rings. As shown in Table 5, the distances l_1, l_3 on the title compound are longer than the other imidazole derivatives, while the distance l_2, is very shorter than we expected. This results indicate that the rotation of the rings about the C-C single bond is very freely changed. Also it is possible to confirm this effect on the difference of the torsion angle in the Table 4. According to a hypothesis by

Mashington,[14] in order to confirm that the analogous imidazole derivatives have only the gauche conformation in between the two polar group X(O,S) and the imidazole ring, N(19), we considered the imaginary plane D [C(7), C(9) and C(16)]. In most cases N(19) are deviated from the imaginary plane D about 2-3 Å, but in the sulconazole nitrate the deviation value is 0.88 Å. While the deviation values of the polar group X(O, S) from the plane D are about 0.18-0.39 Å expected for the miconazole A[2.316 Å]. As shown in Figure 3, in all cases we found that no the molecular conformation have gauche conformation. This result was a contrast to a hypothesis of Mashington *et al.*[14] Thus we examined the total deviations from the imaginary plane D for the two polar group, X(O, S) and N(19). Except for the title compound (about 1.6 Å), these deviation values ranges from about 2.3 to 3.3 Å. As stated above whether these subtle conformational differences, for example, the torsion angles, dihedral angles, the selected distances (*l*) and conformational type of two prlar groups, affect the pharmacological activity of the title compound is difficult to asses, because mainly activity data obtained from *in vitro* experiments are derived from a number of differing techinques and test organisms.

As shown in Figure 2, the unit cell contains independent eight molecule and one-NO_3 group are hydrogen bonded to the two neighbored sulconazole molecules [N(19)···O(23)(x, y, z): 2.896(7) Å, 136.9(6)°, N(19)···O(25)(x+0.5, y, z+0.5): 2.974(7) Å, 135.6(5)°]. The molecules are packed by two hydrogen bondings and van der Waals forces.

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A Structure-Based Activation Model of Phenol-Receptor Protein Interactions

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Data from structure/activity studies in *vir* gene induction system have led to evaluate the working hypothesis of interaction between phenolic inducers and phenol binding proteins. The primary specificity in the association of a phenolic inducer with its receptor in our system is hypothesized to be the hydrogen bonding interactions through the *ortho* methoxy substituents as well as the proton transfer between the inducer and the binding protein. In this paper the proposed working model for phenol-mediating signal transduction was evaluated in several ways. The importance of the general acid-base catalysis was first addressed by the presence of an acidic residue and a basic residue in the phenol binding protein. Series of compounds were tested for *vir* gene expression activity to confirm the generation of a strong nucleophile by an acidic residue and an involvement of a basic residue as a proton acceptor. An attempt was made to correlate the pK_a values of the phenolic compounds with *vir* gene induction activities as inducers to further support the proposed proton transfer mechanism. Finally, it was also observed that the regioselectively attached methoxy group on phenol compounds is required as the proper hydrogen bond accetptor.

Introduction

Agrobacterium tumefaciens causes crown gall tumors, transforming a wide range of gymnosperm and dicotyledonous angiosperms.[1] It initiates the expression of virulence genes in response to host-derived phenolic signals through two component regulatory proteins (VirA and VirG)[2] and putative phenol binding proteins.[3] Several investigations have been made to define structural requirements which confer on a compound inducing *vir* gene expression. Sys-