

에코나졸 나이트레이트의 구조

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The Structure of Econazole Nitrate

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요 약

Abstract

Econazole nitrate, 1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole mono-nitrate, $C_{18}H_{16}Cl_3N_3O_4$ 의 단위 세포 상수는 $a=19.337(4)\text{\AA}$, $b=15.191(5)\text{\AA}$, $c=7.601(3)\text{\AA}$, $\beta=91.72(2)^\circ$, $V=2000.0\text{\AA}^3$, $D_o=1.49\text{g/ml}$, $D_m=1.47\text{g/ml}$, $M=4.31\text{cm}^{-3}$, $F(000)=912.0$, $2\theta=298\text{K}$, 공간군은 $P2_1/c$ 이고 단사 정계이며 $Z=4$ 이다. $\lambda(\text{Mo-K}\alpha)=0.7107\text{\AA}$ 을 사용한 1330개의 Intensity data에 대해 최종 R값은 0.061이다.

Econazole nitrate의 각 세 ring은 각각 평면이며 B, A, C ring 순서로 층계를 이루고 있다. 반면에 Econazole의 A와 C ring은 거의 같은 평면에 누워 있으나 B ring과는 약 60° 의 평면각을 이루고 있다.

Nitrate의 O(*3)와 Imidazole의 N(2) 사이의 수소결합은 Econazole salt의 안정화에 기여한다.

Econazole nitrate, 1-[2-(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole mono-nitrate, $C_{18}H_{16}Cl_3N_3O_4$, $M_w=444.7$, Monoclinic. $P2_1/c$, $a=17.337(4)\text{\AA}$, $b=15.191(5)\text{\AA}$, $c=7.601(3)\text{\AA}$, $\beta=91.72(2)^\circ$, $V=2000.9\text{\AA}^3$, $Z=4$, $D_c=1.49\text{g/cm}^3$, $D_m=1.45\text{g/cm}^3$, $(\text{mo-K}\alpha)=0.7107\text{\AA}$, $\mu=4.31\text{cm}^{-1}$, $F(000)=912.0$, $T=298\text{K}$, final $R=0.061$ for 1330 unique observed reflections. Each of the three ring system of this compound is essentially planar and consists of the stairs with B, A and C rings in order whilst A and C rings of econazole lie close to the same plane which is nearly 60° with B ring.

The hydrogen bonding between nitrogen of C ring and oxygen of nitrate contributes to stabilization of econazole nitrate. Intr and intermolecular distances and angles are within the values recorded for similar compounds.

INTRODUCTION

Econazole and econazole nitrate are prime members of the group of imidazole derivatives (Godefroi, Heers, Van Cutsen, and Janssen, 1969) which have achieved prominence as antimycotic agents (Drouhet, 1978). Econazole and econazole nitrate have a wide antifungal spectrum (Thienpond, Van Cutsen, Van Nueten, Niemegeers and Marsboom, 1975) and are of clinical use in the topical treatment of superficial mycoses. As the racemic free-base forms of both econazole and econazole nitrate are poorly soluble in aqueous system, they were selected as models for a study of crystal growth in pharmaceutical semi-solid formulations (Pearson, Shankland, Salole & Johnson, 1985). Since the crystallographic structure of econazole (Pearson and Salole, 1986) had been elucidated, it was considered of interest to determine the structure of econazole nitrate.

EXPERIMENTAL DETAILS

Colourless, thin needle-shaped crystals grown by slow evaporation from aqueous acetone, crystal size 1.3x0.5x0.2 mm used in data collection, Enraf-Nonius CAD-4 diffractometer. Preliminary Weissenberg photographs indicated crystals to be monoclinic $P2_1/c$, Dm by flotation. Least-squares technique based on 17 reflections, $11.44^\circ < \theta < 15.17^\circ$, used to refine lattice parameters. 1330 independent intensities measured for $2^\circ < 2\theta < 38^\circ$, $0 < h < 14$, $0 < k < 13$, $-6 < l < 6$, θ - 2θ scan mode, scanning rate $6^\circ (2\theta)/\text{min}$. Three standard intensities were used to monitor variations in intensity data: $< 3\%$ variation observed. Structure solution by direct methods with SHELXS-86 (Sheldrick, 1986). Full-matrix least-squares refinement on F of coordinates and anisotropic thermal parameters for non-H atoms converged to R and R_w of 0.061 and 0.057 with unit weight. Coordinates of H-atoms determined from difference Fourier synthesis (SHELXS-76, 1976) and subse-

quently refined isotropically in final two cycles of least-squares. Max. and min. heights in final difference Fourier synthesis = 0.17 and -0.73 eA^{-3} . Scattering factors from International Tables for X-ray Crystallography (1974).

Table 1. Final positional parameters and equivalent isotropic thermal parameters ($\text{Å}^2 \times 10^3$) with e. s. d. s in parentheses.

$$U = 1/3(U_{11} + U_{22} + U_{33})$$

atom	x	y	z	Ueq
CL(1)	3666(1)	1797(1)	1707(2)	·073
CL(2)	1288(1)	3599(1)	4223(2)	·090
CL(3)	505(1)	-4364(1)	2611(3)	·097
O(1)	2370(2)	-602(3)	3166(4)	·050
N(1)	4024(3)	-719(4)	3746(6)	·049
N(2)	4443(4)	-2050(4)	3213(7)	·063
C(1)	2786(3)	1797(5)	2754(7)	·050
C(2)	2444(5)	2587(4)	3063(8)	·055
C(3)	1725(5)	2590(5)	3877(9)	·061
C(4)	1412(4)	1820(6)	4418(8)	·061
C(5)	1765(4)	1034(4)	4128(7)	·053
C(6)	2482(4)	998(4)	3274(7)	·045
C(7)	2853(4)	143(5)	2946(7)	·050
C(8)	3540(4)	-11(4)	4273(7)	·056
C(9)	3894(4)	-1583(6)	3896(8)	·058
C(10)	4959(4)	-1454(6)	2552(9)	·073
C(11)	4713(4)	-644(5)	2870(9)	·062
C(12)	1857(4)	-772(4)	1675(7)	·059
C(13)	1513(4)	-1659(4)	1935(7)	·044
C(14)	1931(4)	-2400(6)	1609(8)	·060
C(15)	1655(5)	-3247(5)	1814(8)	·061
C(16)	905(5)	-3328(4)	2365(8)	·054
C(17)	475(4)	-2607(6)	2708(8)	·057
C(18)	766(4)	-1784(5)	2489(8)	·057
N(*3)	3852(4)	4095(5)	5905(7)	·065
O(*2)	4425(3)	6193(3)	2892(6)	·086
O(*3)	3699(3)	5126(4)	3759(6)	·097
O(*4)	3487(3)	6428(6)	4558(9)	·106

Table 2. Bond distance (Å) °

CL(1)-C(1)	1.742(5)	CL(2)-C(3)	1.733(8)
CL(3)-C(16)	1.732(7)	O(1) -C(7)	1.421(8)
O(1) -C(12)	1.443(7)	N(1) -C(8)	1.429(8)
N(1) -C(9)	1.337(11)	N(1) -C(11)	1.390(9)
N(2) -C(9)	1.308(10)	N(2) -C(10)	1.378(10)
C(1) -C(2)	1.362(10)	C(1) -C(6)	1.386(9)
C(2) -C(3)	1.408(12)	C(3) -C(4)	1.358(12)
C(4) -C(5)	1.363(11)	C(5) -C(6)	1.421(9)
C(6) -C(7)	1.474(10)	C(7) -C(8)	1.555(9)
C(10)-C(11)	1.327(12)	C(12)-C(13)	1.489(9)
C(13)-C(14)	1.365(11)	C(13)-C(18)	1.387(10)
C(14)-C(15)	1.383(12)	C(15)-C(16)	1.383(12)
C(16)-C(17)	1.355(11)	C(17)-C(18)	1.360(12)
N(*3)-O(*2)	1.256(8)	N(*3)-O(*3)	1.215(10)
N(*3)-O(*4)	1.683(11)		

DISCUSSION

Final positional and equivalent isotropic thermal parameters are given in Table 1. Bond lengths, bond angles, and selected torsion angles and dihedral angles are given in Tables 2–5. An ORTEP (Johnson, 1976) diagram, Fig. 1, illustrates the numbering scheme for the molecule and a comparison of econazole nitrate and econazole. Each of the three ring systems in the molecule is almost planar with maximum deviation $-0.016(7)\text{Å}$ from the least-squares plane. 2,4-dichlorophenyl ring A, P-chlorophenyl ring B, and imidazole ring C, are planar with different heights (maximum dihedral angle 11.0°), but in econazole, A and C rings lie close to the same plane (dihedral angle, 4.4°) whilst B ring is at the angle of $60.7(4)^\circ$ to that plane. The hydrogen bonding ($O(*4)-N(2):2.521\text{Å}$, 143°) contributes to stabilization of econazole nitrate. This bonding, compared to econazole, induces

Table 3. Bond angle ($^\circ$)

N(2) -C(9) -N(1)	111.8(6)	C(2) -C(1) -CL(1)	118.1(6)
C(2) -C(3) -CL(2)	117.8(6)	C(3) -C(2) -C(1)	118.3(6)
C(4) -C(3) -CL(2)	122.4(6)	C(4) -C(3) -C(2)	119.8(7)
C(5) -C(4) -C(3)	121.3(7)	C(5) -C(6) -C(1)	116.2(6)
C(6) -C(1) -CL(1)	118.4(5)	C(6) -C(1) -C(2)	123.5(6)
C(6) -C(5) -C(4)	120.7(6)	C(6) -C(7) -O(1)	114.8(5)
C(7) -C(6) -C(1)	123.5(6)	C(7) -C(6) -C(5)	120.2(6)
C(7) -C(8) -N(1)	112.1(5)	C(8) -C(7) -O(1)	104.3(5)
C(8) -C(7) -C(6)	110.6(5)	C(9) -N(1) -C(8)	127.8(5)
C(10) -N(2) -C(9)	106.0(7)	C(10) -C(11) -N(1)	107.3(6)
C(11) -N(1) -C(8)	126.4(6)	C(11) -N(1) -C(9)	105.7(6)
C(11) -C(10) -N(2)	109.1(6)	C(12) -O(1) -C(7)	113.7(4)
C(13) -C(12) -O(1)	107.3(5)	C(14) -C(13) -C(12)	120.3(6)
C(15) -C(14) -C(13)	124.0(7)	C(15) -C(16) -CL(3)	119.8(5)
C(16) -C(15) -C(14)	116.6(7)	C(17) -C(16) -CL(3)	119.3(6)
C(17) -C(16) -C(15)	120.9(7)	C(17) -C(18) -C(13)	121.1(7)
C(18) -C(13) -C(12)	123.1(6)	C(18) -C(13) -C(14)	116.6(6)
C(18) -C(17) -C(16)	120.7(7)	O(*3) -N(*3) -O(*2)	122.5(6)
O(*4) -N(*3) -O(*2)	102.2(6)	O(*4) -N(*3) -O(*3)	135.3(6)

Table 4. Comparison of selected torsion angles for econazole nitrate and econazole.

atom				econazole nitrate	econazole
C(12)	-O(1)	-C(7)	-C(6)	-80.3(6)	75.2(4)
C(12)	-O(1)	-C(7)	-C(8)	158.5(6)	-165.5(3)
C(7)	-O(1)	-C(12)	-C(13)	-168.5(6)	66.9(4)
C(9)	-N(1)	-C(8)	-C(7)	77.7(7)	-87.0(5)
C(11)	-N(1)	-C(8)	-C(7)	-98.2(8)	85.9(5)
C(1)	-C(6)	-C(7)	-C(8)	-77.5(7)	-92.2(5)
C(5)	-C(6)	-C(7)	-C(8)	104.0(7)	-85.0(5)
O(1)	-C(7)	-C(8)	-N(1)	-70.1(5)	63.0(4)
C(6)	-C(7)	-C(8)	-N(1)	165.9(7)	-175.9(5)
O(1)	-C(12)	-C(13)	-C(14)	77.5(7)	34.2(4)
O(1)	-C(12)	-C(13)	-C(18)	-103.2(7)	-146.8(6)

The Structure of Econazole Nitrate

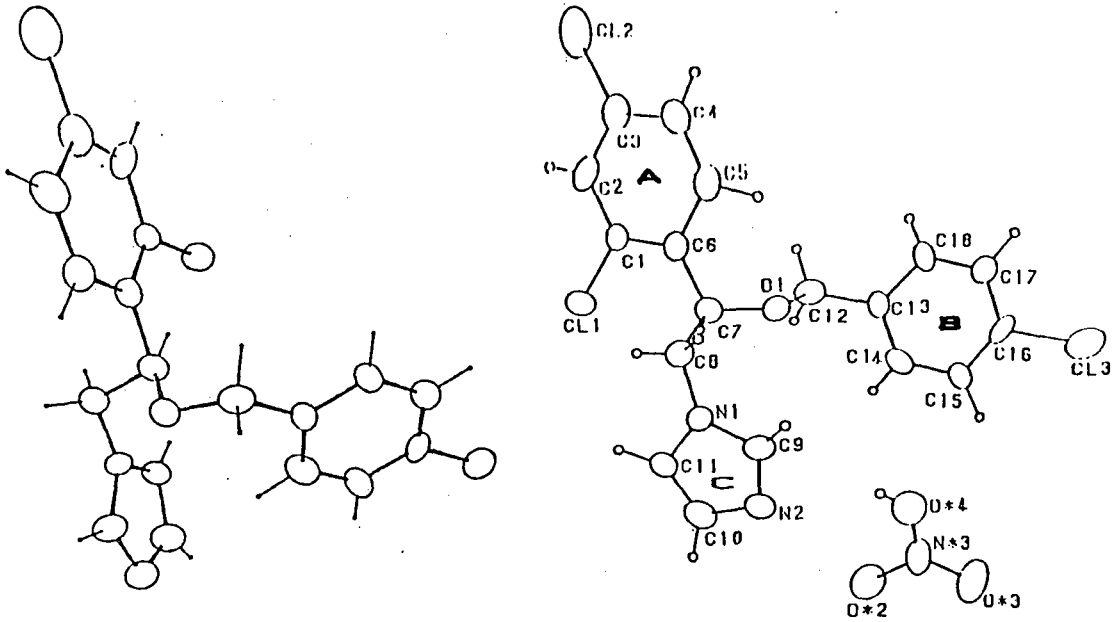


Fig. 1. ORTEP figures of econazole and econazole nitrate (45% probability).

several changes in conformation whereby rings A and C rotate about 180° such that nitrate and C ring have hydrogen bonding, B ring approaches to

nitrate and the interaction between C11 and P-chlorophenyl ring disappears. These situations confer certain restrictions on the degree of rotation

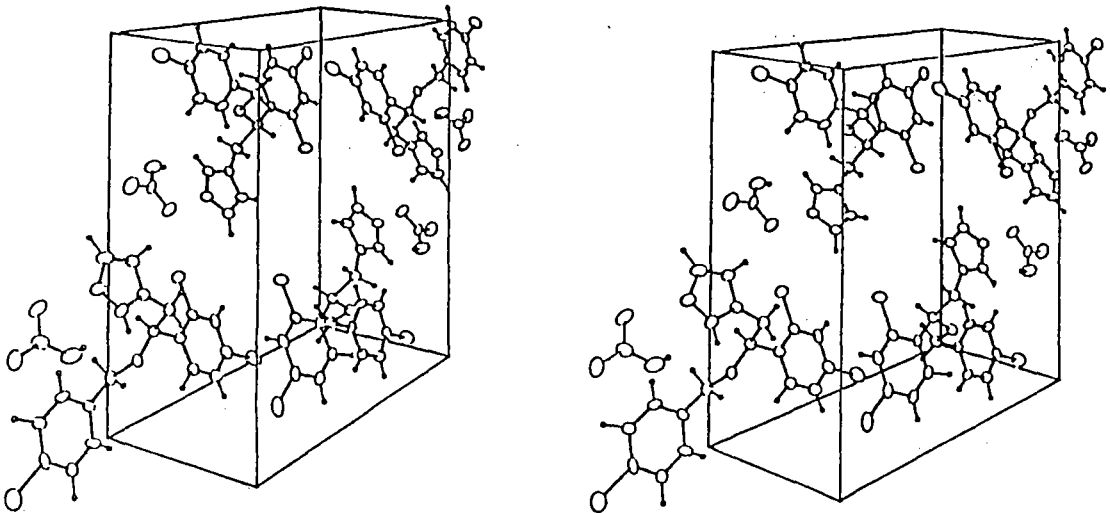


Fig. 2. Stereoscopic drawing of the crystal packing of Econazole nitrate.

Table 5. Comparison of dihedral angles for econazole nitrate and econazole.

	econazole nitrate	econazole
A and B ring	4.9°	56.4°
A and C ring	10.9°	4.6°
B and C ring	11.0°	60.7°

of B ring about O1-C12 bond and C ring about C7-C8 bond which is observed in torsion angle. In the O1-C12 bond, torsion angles of the C7-O1-C12-C13 are $-160.5(6)^\circ$ and O1-C12-C13-C14, $77.5(7)^\circ$, whereas the values of $34.2(4)^\circ$ and $66.9(4)^\circ$ are found in econazole. In the C7-C8 bond, $C7-C7-C8-N1; 165.9(7)^\circ$ and $C9-N1-C8-C7; 77.7(7)^\circ$ are compared to $-175.^\circ$, $-87.0(5)^\circ$ of econazole.

It is difficult to assess whether these subtle conformational differences affect pharmacological activity of the compound, mainly because data obtained from in vitro experiments are derived from a number of different techniques and test organisms.

The crystal structure is shown in Fig. 2. The molecule lies to a b plane and is made up of stairs shape to c axis.

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