The Absolute Configuration of Econazole, an Antifungal Agent. The Crystal Structure of (*R*)-(−)-Econazole Hydrobromide

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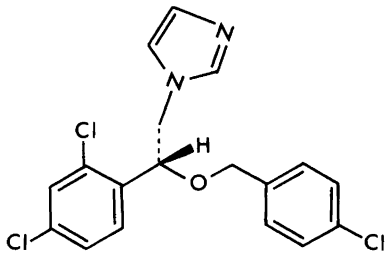
Racemic econazole nitrate has been resolved employing (*R,R*)- and (*S,S*)-tartaric acid as resolving agents. The absolute stereochemistry of the enantiomers has been established as (*R*)-(−) and (*S*)-(+) by determination of the crystal structure of (*R*)-(−)-econazole hydrobromide.

Econazole nitrate {(±)-**1**; (±)-1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole} is a member of a group of imidazole derivatives which exhibit antimycotic activity.[1,2] Econazole nitrate, which is used in the racemic form, has a wide spectrum of antifungal activity and is a powerful drug in the topical treatment of superficial mycoses.[3] Optical resolution of racemic econazole nitrate has previously been achieved (unpublished),[4] and Yamasaki *et al.*[5] have examined the antimicrobial activity of (+)- and (−)-econazole nitrate against *Candida albicans, Trichophyton mentagrophytes, Staphylococcus aureus* and *Escherichia coli.* The stereoisomers did not display any difference in activity.



(*R*)-(−)-**1**

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Optical resolution and assignment of the absolute stereochemistry of econazole nitrate constitute the subject of the present communication.

Experimental

Melting points were determined on a Reichert melting point apparatus and are uncorrected. Optical rotations and mass spectra were recorded on Carl Zeiss or Perkin-Elmer 241, and Micromass 7070F instruments, respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded at 270 MHz and 68 MHz, respectively, on a Jeol JNM GX 270 instrument. TMS, or the central solvent peaks (^{13}C) of $CDCl_3$ (δ 77.08) or CD_3OD (δ 49.04) were used as internal references. Elemental analyses were performed at Novo Microanalytical Laboratory, Bagsværd, Denmark.

Optical resolution of (±)-econazole nitrate {(±)-**1** nitrate; (±)-1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl)]-1*H*-imidazole nitrate}. Optical resolution of (±)-econazole nitrate has been achieved independently by Funato,[4] who also employed the tartaric acids as resolving agents.

(−)-Econazole (R,R)*-(+)-tartrate.* (±)-Econazole base (3.53 g; 9.24 mmol) and (*R,R*)-(+)-tartaric acid (1.39 g; 9.25 mmol) were dissolved

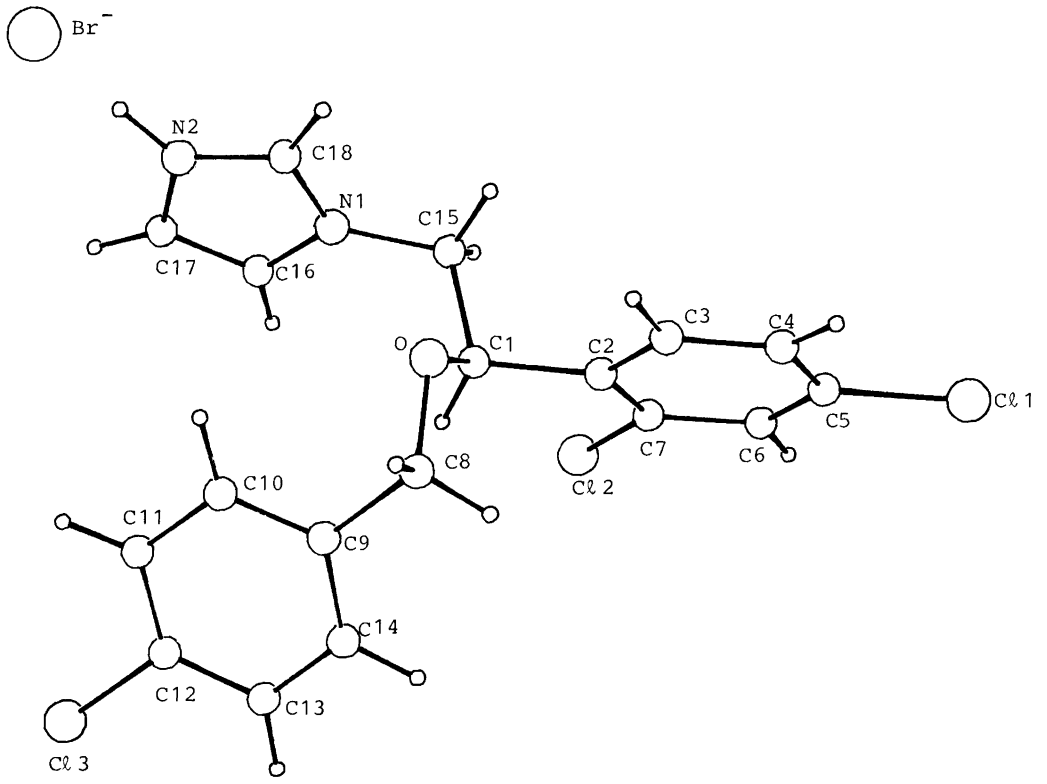

Fig. 1. Perspective drawing of (*R*)-(−)-econazole hydrobromide [(*R*)-(−)-**1**] showing the numbering of atoms.

in hot EtOH (125 ml) and the solution left at room temperature overnight. The solid precipitate (3.25 g) was collected by filtration and recrystallized thrice from EtOH (ca. 100 ml each time) at ambient temperature, furnishing 1.80 g (73 %) of the salt. M.p. 188–190 °C (decomp.). Anal. $C_{22}H_{21}Cl_3N_2O_7$: C, H, N.

(R)-(−)-Econazole [(*R*)-(−)-**1**]. (−)-Econazole (*R,R*)-(+)-tartrate (715 mg) was dissolved in water (50 ml), pH was adjusted to ca. 10 with 2N NaOH, and the solution was extracted with ethyl acetate, furnishing (−)-econazole [(*R*)-(−)-**1**] as an oil (518 mg). $[\alpha]_D^{26}$ −83.7° (*c* 8.6, MeOH). ^{1}H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$) and mass spectra were virtually identical with those of racemic econazole [(±)-**1**].

(R)-(−)-Econazole nitrate [(*R*)-(−)-**1** nitrate]. Concentrated HNO_3 (5 drops) was added to a solution of (*R*)-(−)-econazole base [(*R*)-(−)-**1**; 166 mg] in 2-propanol (2 ml). Diethyl ether was added until cloudiness appeared and the mixture was left at −18 °C overnight. The crystalline precipitate was recrystallized twice from 2-propanol, giving 137 mg of (*R*)-(−)-econazole nitrate as colourless crystals. M.p. 166–168 °C (decomp.?); lit.[4] m.p. 162–164 °C; $[\alpha]_D^{21}$ −82.0°, $[\alpha]_{578}^{21}$ −85.8°, $[\alpha]_{546}^{21}$ −97.7°, $[\alpha]_{436}^{21}$ −171.6°, $[\alpha]_{365}^{21}$ −282.9° (*c* 1.3, MeOH); lit.[4] $[\alpha]_D^{20}$ −81.5° (*c* 4, MeOH). ^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) spectra were in agreement with those of racemic econazole nitrate [(±)-**1** nitrate].

(R)-(−)-Econazole hydrobromide [(*R*)-(−)-**1** hydrobromide]. To a solution of (*R*)-(−)-econazole base [(*R*)-(−)-**1**; 55 mg] in 2-propanol (2 ml) was added 40 % aqueous HBr. The solution was concentrated to dryness and the residual oil treated with diethyl ether, which effected crystallization. Recrystallization twice from 2-propanol/diethyl ether (in about 1:1 ratio) furnished the hydrobro-

Table 1. Final fractional coordinates and equivalent temperature factors with estimated standard deviations for non-hydrogen atoms.

Atom	*x*	*y*	*z*	U_{eq}[a]/Å^2
Br	0.31790(9)	0.40928	1.02827(6)	0.081
Cl1	1.3166(5)	−0.3845(4)	0.7435(3)	0.168
Cl2	1.2989(3)	0.1939(4)	0.7769(2)	0.116
Cl3	0.7537(4)	0.7737(4)	0.5011(2)	0.144
O	0.7558(6)	0.1405(5)	0.7363(4)	0.070
N1	0.8444(8)	0.3069(7)	0.9058(6)	0.056
N2	0.6382(7)	0.4208(13)	0.9371(4)	0.078
C1	0.9298(9)	0.1607(8)	0.7770(6)	0.059
C2	1.0290(12)	0.0214(10)	0.7664(7)	0.064
C3	0.9543(9)	−0.1123(11)	0.7599(6)	0.080
C4	1.0437(17)	−0.2366(10)	0.7524(9)	0.093
C5	1.2098(17)	−0.2239(15)	0.7543(10)	0.096
C6	1.2875(9)	−0.0973(19)	0.7608(6)	0.091
C7	1.1973(14)	0.0319(11)	0.7679(7)	0.071
C8	0.7088(11)	0.1558(11)	0.6304(8)	0.092
C9	0.7209(13)	0.3106(13)	0.5974(9)	0.082
C10	0.6438(10)	0.4157(18)	0.6355(6)	0.093
C11	0.6554(13)	0.5629(14)	0.6076(9)	0.098
C12	0.7440(13)	0.5918(13)	0.5386(9)	0.093
C13	0.8226(18)	0.4894(22)	0.4992(10)	0.114
C14	0.8103(16)	0.3484(18)	0.5300(10)	0.107
C15	0.9488(8)	0.1851(9)	0.8878(6)	0.063
C16	0.8738(11)	0.4499(9)	0.8967(7)	0.069
C17	0.7417(14)	0.5225(11)	0.9144(9)	0.081
C18	0.7010(12)	0.2900(11)	0.9305(9)	0.070

[a] $U_{eq} = (U_{11} + U_{22} + U_{33})/3$.

mide of (*R*)-(−)-**1** as prisms (ca. 35 mg). M.p. 180.5–181.5 °C. $[\alpha]_D^{21}$ −80.6°, $[\alpha]_{578}^{21}$ −83.7°, $[\alpha]_{546}^{21}$ −95.4°, $[\alpha]_{436}^{21}$ −167.9°, $[\alpha]_{365}^{21}$ −276.6° (*c* 0.8, MeOH). Anal. $C_{18}H_{16}BrCl_3N_2O$: C, H, N. The ^{1}H NMR spectrum (CD_3OD) was indistinguishable from that of (*R*)-(−)-**1** nitrate.

(+)-Econazole (S,S)-(−)-tartrate. (+)-Enriched econazole base (2.17 g; 5.69 mmol), recovered from the mother liquors collected during the purification of (−)-econazole (*R,R*)-(+)-tartrate, and (*S,S*)-(−)-tartaric acid (0.85 g; 5.69 mmol) were dissolved in hot EtOH (120 ml) and the solution left at room temperature overnight. The solid precipitate (2.23 g) was recrystallized twice from EtOH (95 ml and 75 ml, respectively; ambient temperature) yielding (+)-econazole (*S,S*)-(−)-tartrate (1.76 g). M.p. 189–191 °C (decomp.). Anal. $C_{22}H_{21}Cl_3N_2O_7$: C, H, N.

(S)-(+)-Econazole [(*S*)-(+)-**1**]. (*S*)-(+)-Econazole (491 mg; oil) was obtained on decomposition of the corresponding (*S,S*)-(−)-tartrate (ca. 700 mg) as described above for the (*R,R*)-(+)-tartrate. $[\alpha]_D^{27}$ +86.4° (*c* 8.2, MeOH). ^{1}H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$) and mass spectra were in good agreement with those of racemic econazole base [(±)-**1**].

(S)-(+)-Econazole nitrate [(*S*)-(+)-**1** nitrate]. (*S*)-(+)-Econazole nitrate (505 mg) was prepared from the corresponding base (491 mg) as described above for the enantiomeric salt. M.p. 166.5–167.5 °C; lit.[4] m.p. 161.5–163.5 °C; $[\alpha]_D^{20}$ +83.3°, $[\alpha]_{578}^{20}$ +87.4°, $[\alpha]_{546}^{20}$ +99.6°, $[\alpha]_{436}^{20}$ +175.1°, $[\alpha]_{365}^{20}$ +288.4° (*c* 0.6, MeOH); lit.[4] $[\alpha]_D^{20}$ +81.5° (*c* 4, MeOH). ^{1}H NMR (CD_3OD) and ^{13}C NMR (CD_3OD) spectra were virtually identical with those of racemic econazole nitrate [(±)-**1** nitrate].

Table 2. Bond distances (Å) and bond angles (°) with estimated standard deviations.

Distance		Distance	
Cl1–C5	1.75(2)	Cl2–C7	1.71(2)
Cl3–C12	1.77(2)	O–C1	1.43(1)
O–C8	1.43(2)	N1–C15	1.47(1)
N1–C16	1.35(2)	N1–C18	1.32(2)
N2–C17	1.36(2)	N2–C18	1.33(2)
C1–C2	1.55(2)	C1–C15	1.52(2)
C2–C3	1.37(2)	C2–C7	1.39(2)
C3–C4	1.38(2)	C4–C5	1.37(2)
C5–C6	1.33(3)	C6–C7	1.42(2)
C8–C9	1.51(2)	C9–C10	1.34(2)
C9–C14	1.37(2)	C10–C11	1.42(3)
C11–C12	1.36(2)	C12–C13	1.34(3)
C13–C14	1.38(3)	C16–C17	1.35(2)
Angle		**Angle**	
C1–O–C8	113.2(6)	C15–N1–C16	127.1(7)
C15–N1–C18	123.4(8)	C16–N1–C18	109.4(8)
C17–N2–C18	109.7(8)	O–C1–C2	111.0(7)
O–C1–C15	105.7(6)	C2–C1–C15	106.8(7)
C1–C2–C3	120.9(8)	C1–C2–C7	119.3(9)
C3–C2–C7	119.8(9)	C2–C3–C4	120.8(9)
C3–C4–C5	118.5(9)	Cl1–C5–C4	116.6(9)
Cl1–C5–C6	120.5(9)	C4–C5–C6	122.8(9)
C5–C6–C7	119.4(9)	Cl2–C7–C2	122.4(9)
Cl2–C7–C6	119.0(9)	C2–C7–C6	118.6(9)
O–C8–C9	112.5(9)	C8–C9–C10	119.7(9)
C8–C9–C14	122.3(9)	C10–C9–C14	118.1(9)
C9–C10–C11	121.2(9)	C10–C11–C12	117.4(9)
Cl3–C12–C11	117.6(9)	Cl3–C12–C13	119.5(9)
C11–C12–C13	122.9(9)	C12–C13–C14	117.6(9)
C9–C14–C13	122.9(9)	N1–C15–C1	111.1(7)
N1–C16–C17	107.2(8)	N2–C17–C16	106.2(9)
N1–C18–N2	107.4(9)		

Results and discussion

Crystal and intensity data. Crystal data for (−)-econazole hydrobromide [(−)-**1**], $C_{18}H_{16}Cl_3N_2O^+ \cdot Br^-$ are: $a = 8.256(4)$, $b = 9.236(4)$, $c = 13.879(8)$ Å; $\beta = 103.82(4)°$, space group $P2_1$, $Z = 2$, $D_x = 1.49$ g cm^{-3}, $V = 1027.8(8)$ Å^3, μ(Mo$K\alpha$) = 25.15 cm^{-1}, λ(Mo$K\alpha$) = 0.71069 Å. Data were collected on a Syntex P1 automatic four-circle diffractometer at room temperature by the ω-scan technique (2θ max = 50°) with Mo$K\alpha$-radiation and scan rate 6° min^{-1}. The intensities of two test reflections remeasured after every 100 reflections showed no significant changes during data collection. The intensities were corrected for Lorentz and polarization effects and for absorption[6] (crystal size 0.3×0.5×0.8 mm). The minimum and maximum empirical absorption corrections were 0.51 and 1.42, respectively. With an observed–unobserved cut-off at 2.5$\sigma(I)$, 1843 reflections were regarded as observed [$(h,-k,l)$-reflections included].

Determination and refinement of the structure. The structure was solved by direct methods[7] and refined by the full-matrix least-squares technique.[8] Anisotropic temperature factors were used for non-hydrogen atoms. Hydrogen atoms, the positions of which were calculated, were included in structure factor calculations but not refined. Weights in least-squares were calculated from the standard deviations in intensities, $\sigma(I)$,

taken as $\sigma(I) = [C_1 + (0.02C_2)^2]^{1/2}$, where C_1 is the total number of counts and C_2 the net count. The maximum r.m.s. amplitudes of thermal vibration range from 0.27 to 0.53 Å. The anomalous scattering factors for Br with Mo$K\alpha$ radiation are: $\Delta f' = -0.374$ and $\Delta f'' = 2.456$ (corresponding values for Cl are 0.132 and 0.159). The refinement without anomalous dispersion converged at $R = 0.0494$ ($R_w = 0.0437$) for 1843 observed reflections. With these parameters and $+\Delta f''$, the R-values decreased to $R = 0.0444$ and $R_w = 0.0368$, respectively. The effect of changing the sign of $\Delta f''$ was an increase in the R-values to $R = 0.0643$ and $R_w = 0.0662$. Furthermore, 86 Bijvoet pairs with $P_o = F_o(h,k,l)/F_o(h,-k,l) > 1.2$ or $P_o < 0.8$ were compared with the corresponding ratios for the calculated structure factors, $P_c = F_c(h,k,l)/F_c(h,-k,l)$. The mean value $<|P_o - P_c|>$ was 0.181 for $+\Delta f''$ and 0.390 for $-\Delta f''$. A final cycle of least-squares refinement with anomalous dispersion included reduced the R-factors to $R = 0.0431$ and $Rw = 0.0349$.

These findings uniquely determine the absolute configuration of the (−)-enantiomer to be (*R*) (Fig. 1). Final fractional coordinates with estimated standard deviations for non-hydrogen atoms are given in Table 1. Bond distances and angles with estimated standard deviations may be found in Table 2. Within the large estimated limits of error there are no significant deviations from corresponding bond distances and angles found in the crystals of racemic econazole base [(±)-**1**].[9]

Lists of thermal parameters, hydrogen atom parameters, and observed and calculated structure factors are obtainable from one of the authors (P.G.) on request.

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