Acta Cryst. (1988). C44, 1782–1784

Structure of Ergosterol Biosynthesis Inhibitors. II. Structure of Fenarimol, α-(2-Chlorophenyl)-α-(4-chlorophenyl)-5-pyrimidinemethanol

By Alberto Albinati

Istituto di Chimica Farmaceutica, Università di Milano, Viale Abruzzi 42, 20131 *Milano, Italy*

Stefano V. Meille*

Dipartimento di Chimica, Politecnico di Milano, Piazza L. da Vinci 32, 20133 *Milano, Italy*

and Anna Arnoldi and Lucio Merlini

Istituto di Biochimica e di Chimica, Università di Milano, Via Celoria 2, 20133 *Milano, Italy*

(*Received* 24 *November* 1987; *accepted* 11 *April* 1988)

Abstract. $C_{17}H_{12}Cl_2N_2O$, $M_r = 331{\cdot}204$, triclinic, $P\bar{1}$, $a = 13{\cdot}527\,(3)$, $b = 8{\cdot}525\,(2)$, $c = 7{\cdot}226\,(2)$ Å, $\alpha = 98{\cdot}50\,(3)$, $\beta = 82{\cdot}54\,(3)$, $\gamma = 74{\cdot}68\,(4)°$, $V = 782{\cdot}3\,(4)$ Å^3, $Z = 2$, D_m(flotation) = 1·40, $D_x = 1{\cdot}406$ g cm^{-3}, λ(Mo $K\bar{\alpha}$) = 0·71069 Å, $\mu = 4{\cdot}159$ cm^{-1}, $F(000) = 340$, room temperature, $R = 0{\cdot}056$ (1525 observed reflections). The product, a commercial fungicide acting as an ergosterol biosynthesis inhibitor, shows dihedral angles between the pyrimidinyl plane and the *o*-Cl-phenyl and the *p*-Cl-phenyl planes, respectively, of 91·2 (2), and 82·4 (2)°: the dihedral angle between the two phenyl planes is 84·8 (2)°. An intramolecular hydrogen bond is observed between the hydroxyl H atom and the *ortho* Cl atom of the adjacent phenyl.

Introduction. In the last few years there has been increasing interest in ergosterol biosynthesis inhibitors as fungicides. A particular feature of this class of compounds is that species with very different chemical structure share the same mechanism of action. For example, some triazoles, imidazoles, pyrimidines, pyridines and piperazines were shown to inhibit a cytochrome P-450 dependent 14α-methylsterol-14α-methyldemethylase (Mercer, 1984). A number of structural studies particularly of imidazole and triazole derivatives were undertaken in order to clarify some aspects of their mechanism of action, while pyrimidine derivatives have been less studied. We report here the crystal structure of the pyrimidine derivative fenarimol (Buchenauer, 1977).

Experimental. Colourless transparent prismatic crystals (0·3 × 0·2 × 0·2 mm) obtained from 2:1 *n*-hexane–ethyl acetate solution. Crystal mounted on a glass fibre in a general orientation on a PW 1100 diffractometer. Monochromated Mo $K\bar{\alpha}$ radiation. Cell constants refined from $\pm 2\theta$ values of 20 reflections with $2\theta \geq 18°$. 2747 independent reflections measured, ω-scan mode, constant speed 0·05° s^{-1}, constant scan width 1·10°, $5{\cdot}0 \leq 2\theta \leq 50{\cdot}0°$, $\pm h$, $\pm k$, l, 1525 observed reflections [$I \geq 3\sigma(I)$] used for all calculations. Index range $|h| \leq 16$, $k \leq 10$, $l \leq 9$. Two standard reflections monitored every 90 min; no absorption correction. Structure solved using *MULTAN*76 (Main, Lessinger, Woolfson, Germain & Declercq, 1976); atomic scattering factors from *International Tables for X-ray Crystallography* (1974); correction for the real part of anomalous dispersion; refinement using block-diagonal least squares; Cruickshank (1970) weighting scheme; function minimized $\sum w(|F_o| - |F_c|)^2$. Anisotropic temperature factors for all non-H atoms; H atoms located on difference Fourier map and refined. $R = 0{\cdot}056$, $wR = 0{\cdot}061$, $S = 0{\cdot}68$, maximum residual Fourier peak 0·3 e Å^{-3}. Maximum $\Delta/\sigma = 0{\cdot}2$. Geometrical calculations using *PARST* (Nardelli, 1983). Final positional parameters and equivalent isotropic temperature factors in Table 1.†

Discussion. In Fig. 1 a *PLUTO* (Motherwell, 1978) view of the fenarimol molecule with the atom-numbering scheme is shown. Bond lengths and angles are listed in Table 2.

The bond lengths for C(1)—O(1), 1·447 (6) Å, and for the two phenyl and pyrimidine rings are in the expected range, as well as those involving C—C(1) [av.

---

* To whom correspondence should be addressed.

† H-atom positional parameters, selected torsion angles, lists of structure factors, anisotropic thermal parameters, details of least-squares-planes calculations and short intra- and intermolecular distances have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44958 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

0108-2701/88/101782-03$03.00

Table 1. *Final positional parameters with e.s.d. on last significant figure in parentheses and equivalent isotropic temperature factors* B_{eq} (Å^2) (*Hamilton*, 1959)

	x	y	z	B_{eq}
Cl(1)	0·4159 (1)	0·6800 (2)	0·6602 (2)	4·43
Cl(2)	−0·0357 (2)	1·2896 (3)	0·0221 (4)	7·16
O(1)	0·2840 (3)	0·9943 (4)	0·5653 (5)	2·85
N(1)	0·5552 (4)	0·9401 (6)	0·1919 (7)	3·59
N(2)	0·5500 (4)	0·6759 (6)	0·0456 (7)	3·44
C(1)	0·2950 (4)	0·8840 (6)	0·3863 (7)	2·49
C(2)	0·4050 (4)	0·8507 (6)	0·2730 (7)	2·28
C(3)	0·4587 (5)	0·9664 (7)	0·2887 (8)	3·21
C(4)	0·5940 (4)	0·7952 (7)	0·0763 (9)	3·25
C(5)	0·4555 (4)	0·7055 (7)	0·1457 (8)	3·07
C(6)	0·2743 (4)	0·7207 (7)	0·4192 (8)	2·66
C(7)	0·3228 (5)	0·6236 (7)	0·5385 (8)	3·26
C(8)	0·3031 (6)	0·4766 (8)	0·5650 (10)	5·05
C(9)	0·2354 (6)	0·4205 (8)	0·4685 (12)	5·32
C(10)	0·1864 (5)	0·5105 (8)	0·3457 (11)	4·74
C(11)	0·2068 (5)	0·6574 (8)	0·3215 (9)	3·81
C(12)	0·2121 (4)	0·9836 (6)	0·2882 (8)	2·73
C(13)	0·1160 (5)	1·0713 (8)	0·3952 (9)	3·58
C(14)	0·0385 (5)	1·1642 (8)	0·3138 (10)	4·08
C(15)	0·0598 (5)	1·1672 (8)	0·1231 (10)	4·12
C(16)	0·1530 (5)	1·0796 (9)	0·0131 (10)	4·66
C(17)	0·2294 (4)	0·9865 (8)	0·0959 (8)	3·35

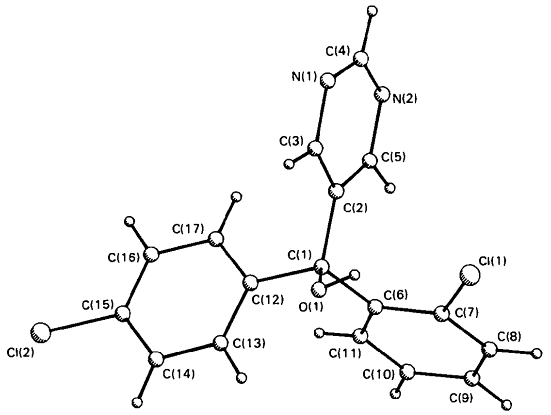

Fig. 1. A *PLUTO* view of fenarimol showing the atom-numbering scheme.

Table 2. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

Cl(1)–C(7)	1·754 (7)	C(6)–C(11)	1·392 (10)
Cl(2)–C(15)	1·746 (7)	C(7)–C(8)	1·383 (10)
O(1)–C(1)	1·447 (6)	C(8)–C(9)	1·361 (12)
N(1)–C(3)	1·344 (8)	C(9)–C(10)	1·379 (12)
N(1)–C(4)	1·318 (7)	C(10)–C(11)	1·382 (11)
N(2)–C(4)	1·314 (9)	C(12)–C(13)	1·379 (7)
N(2)–C(5)	1·325 (8)	C(12)–C(17)	1·384 (8)
C(1)–C(2)	1·534 (7)	C(13)–C(14)	1·390 (9)
C(1)–C(6)	1·537 (8)	C(14)–C(15)	1·376 (10)
C(1)–C(12)	1·537 (8)	C(15)–C(16)	1·358 (8)
C(2)–C(3)	1·371 (9)	C(16)–C(17)	1·388 (9)
C(2)–C(5)	1·378 (7)	O(1)–H(O1)	0·83 (8)
C(6)–C(7)	1·389 (9)	⟨C–H⟩	0·98 (3)*

C(3)–N(1)–C(4)	114·8 (5)	Cl(1)–C(7)–C(6)	121·1 (5)
C(4)–N(2)–C(5)	115·4 (5)	Cl(1)–C(7)–C(8)	116·2 (5)
O(1)–C(1)–C(2)	109·3 (4)	C(6)–C(7) C(8)	122·7 (6)
O(1)–C(1)–C(6)	110·9 (4)	C(7)–C(8)–C(9)	119·7 (7)
O(1)–C(1)–C(12)	103·0 (4)	C(8)–C(9)–C(10)	120·0 (7)
C(2)–C(1)–C(6)	110·5 (4)	C(9)–C(10)–C(11)	119·4 (7)
C(2)–C(1)–C(12)	111·3 (4)	C(6)–C(11)–C(10)	122·5 (6)
C(6)–C(1)–C(12)	111·6 (5)	C(1)–C(12)–C(13)	118·8 (5)
C(1)–C(2)–C(3)	121·8 (5)	C(1)–C(12)–C(17)	122·6 (5)
C(1)–C(2)–C(5)	122·8 (5)	C(13)–C(12)–C(17)	118·6 (6)
C(3)–C(2)–C(5)	115·4 (5)	C(12)–C(13)–C(14)	121·1 (6)
N(1)–C(3)–C(2)	123·0 (5)	C(13)–C(14)–C(15)	118·4 (6)
N(1)–C(4)–N(2)	128·0 (6)	Cl(2)–C(15)–C(14)	118·6 (5)
N(2)–C(5)–C(2)	123·4 (6)	Cl(2)–C(15)–C(16)	119·5 (5)
C(1)–C(6)–C(7)	123·8 (5)	C(14)–C(15)–C(16)	121·9 (7)
C(1)–C(6)–C(11)	120·6 (5)	C(15)–C(16)–C(17)	119·1 (6)
C(7)–C(6)–C(11)	115·6 (5)	C(12)–C(17)–C(16)	120·8 (6)

* Standard deviation from the mean according to:

$$\sigma(\bar{x}) = [\textstyle\sum(x_i - \bar{X})^2/(n-1)]^{1/2}.$$

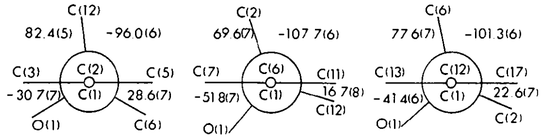

Fig. 2. Newman projections along bonds C(1)–C(2), C(1)–C(6) and C(1)–C(12) with relevant dihedral angles (°), e.s.d.'s in parentheses.

1·536 (2) Å] (Sutton, 1958). The only bond angle at C(1) significantly distorted from the tetrahedral value is O(1)–C(1)–C(12), 103·0 (4)°, probably to relieve steric strain, while systematic phenyl bond-angle deformations caused by the substitution pattern (Domenicano, Murray-Rust & Vaciago, 1983, and references quoted therein) are observed. While the values of 118·6 (6)° for C(13)–C(12)–C(17) and 121·9 (7)° for C(14)–C(15)–C(16) show distortions of borderline significance, the C(7)–C(6)–C(11) and C(6)–C(7)–C(8) bond-angle values of 115·6 (5) and 122·7 (6)° follow more clearly the expected trend. These large deviations are possibly due to the steric factors which also determine the dissymmetry in the exocyclic bond angles at C(2) and C(6). The largest deviations correspond to the most severe non-bonded interactions: the distance of 2·904 (8) Å between C(5) and C(6) results in a C(5)–C(2)–C(1) angle of 122·8 (5)°, 2·896 (8) Å between C(2) and C(17) gives a C(17)–C(12)–C(1) angle of 122·6 (5)°; the Cl(1)···O(1) distance of 3·028 (4) Å corresponds to a C(1)–C(6)–C(7) angle of 123·8 (5)°. This effect is also reflected in the torsion angles C(7)–C(6)–C(1)–O(1) [−51·8 (7)°] and C(11)–C(6)–C(1)–C(12) [16·7 (8)°]. The planarity required by the sp^2 hybridization of C(6), together with the already discussed values of C(7)–C(6)–C(1) and C(7)–C(6)–C(11), does not allow expansion of the angle C(11)–C(6)–C(1) beyond 120·6 (5)°, notwithstanding the distance of 2·845 (9) Å between C(11) and C(12).

The overall conformation of the fenarimol molecule can be conveniently described by the values of the dihedral angles between the aromatic rings: 91·2 (2) and 82·4 (2)° between the pyrimidinyl ring and the *o*-chlorophenyl and the *p*-chlorophenyl rings, respectively, and 84·8 (2)° between the two phenyl planes. Thus each ring is approximately orthogonal to the other two. We note that the conformations at the C(1)—C(2), C(1)—C(6) and C(1)—C(12) bonds are similar which is different from the closely related α,α-bis(p-chlorophenyl)-3-pyridinemethanol (parinol) (Kennard, Smith & Palm, 1981). For clarity, Newman projections along the three bonds in fenarimol are shown in Fig. 2. While in parinol the two phenyl rings are nearly symmetrically oriented with respect to the heterocyclic ring plane, this is not the case in fenarimol.

Short H-bond interactions (Taylor & Kennard, 1982) are intramolecular Cl(1)···H(O1) [2·37 (8) Å] and intermolecular O(1)···H(C16) [2·48 (8) Å] and N(2)···H(C5) [2·54 (8) Å]; all other packing distances are in the normal range.

Research work supported by the CNR, Italy. Special Grant IPRA, Subproject 1, Paper No. 1804.

References

BUCHENAUER, H. (1977). *Pestic. Biochem. Physiol.* **7**, 309–320.

CRUICKSHANK, D. W. J. (1970). *Crystallographic Computing*, edited by F. R. AHMED, pp. 187–197. Copenhagen: Munksgaard.

DOMENICANO, A., MURRAY-RUST, P. & VACIAGO, A. (1983). *Acta Cryst.* B**39**, 457–468.

HAMILTON, W. C. (1959). *Acta Cryst.* **18**, 609–610.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

KENNARD, C. H. L., SMITH, G. & PALM, T. B. (1981). *Acta Cryst.* B**37**, 1796–1798.

MAIN, P., LESSINGER, L., WOOLFSON, M. M., GERMAIN, G. & DECLERCQ, J.-P. (1976). *MULTAN76. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

MERCER, E. I. (1984). *Pestic. Sci.* **15**, 133–155.

MOTHERWELL, W. D. S. (1978). *PLUTO78.* Program for plotting molecular and crystal structures. Univ. of Cambridge, England.

NARDELLI, M. (1983). *Comput. Chem.* **7**, 95–98.

SUTTON, L. E. (1958). Editor. *Tables of Interatomic Distances and Configuration in Molecules and Ions.* Spec. Publ. No. 11. London: The Chemical Society.

TAYLOR, R. & KENNARD, O. (1982). *J. Am. Chem. Soc.* **104**, 5063–5070.

Acta Cryst. (1988). C**44**, 1784–1786

Structure of Dimethyl 2,3,4,5-Tetrahydro-2-oxo-5α-(3,4,5-trimethoxyphenyl)-3α,4β-furandicarboxylate

BY JOHN R. PETERSON,* ROBIN D. ROGERS* AND HOANG D. DO

The Michael Faraday Laboratories, Department of Chemistry, Northern Illinois University, DeKalb, IL 60115, USA

(*Received* 11 *April* 1988; *accepted* 1 *June* 1988)

Abstract. $C_{17}H_{20}O_9$, $M_r = 368{\cdot}3$, triclinic, $P\bar{1}$, $a = 5{\cdot}687$ (4), $b = 12{\cdot}367$ (3), $c = 12{\cdot}830$ (3) Å, $\alpha = 106{\cdot}24$ (2), $\beta = 92{\cdot}34$ (5), $\gamma = 90{\cdot}39$ (5)°, $V = 865{\cdot}5$ Å^3, $Z = 2$, $D_x = 1{\cdot}41$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0{\cdot}73$ cm^{-1}, $F(000) = 388$, $T = 293$ K, final $R = 0{\cdot}091$ for 1482 observed $[F_o \geq 5\sigma(F_o)]$ reflections. The observed structure confirms the stereochemistry as the all-*trans* isomer. There is no crystallographically imposed symmetry. High thermal motion was noted for one of the methoxycarbonyl groups, but a disorder model could not be developed.

Introduction. In the course of our work on the total synthesis of naturally occurring, antimitotic lignan lactones, we have determined the X-ray structure of the title compound. The assignment of substituent stereochemistry on a γ-lactone moiety by ^{1}H NMR coupling-constant analysis is sometimes problematic. Vicinal hydrogen coupling constants for *trans*-substituted compounds have generally been larger than those of the *cis* isomer; however, several exceptions have been noted (Bystrom, Hogberg & Norin, 1981; Fristad & Peterson, 1985). The preparation of the title compound provided two isomers that we felt were simply epimeric at the 3-position due to ^{1}H NMR chemical shifts and coupling constants. As our projected conversion of this mixture to a *cis*-fused dicinnamic acid dilactone necessitated a *trans* disposition of the 4-methoxycarbonyl and 5-aryl groups, we felt compelled to establish firmly this stereorelationship for the major isomer at an early stage.

Experimental. Crystals (m.p. 380–382 K) were obtained by slow evaporation of an ethyl acetate–petroleum ether solution of the title compound. The X-ray structure was in full agreement with IR, ^{1}H and ^{13}C NMR and analytical data. The compound was

---

* Authors to whom correspondence should be addressed.

0108-2701/88/101784-03$03.00