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Structure of the Aromatic Glutarimide Antibiotic Actiphenol, 4-[2-(2-Hydroxy-3,5-dimethylphenyl)-2-oxoethyl]-2,6-piperidinedione, $C_{15}H_{17}NO_4$

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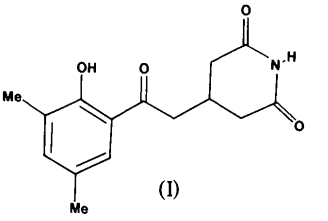
Abstract. $M_r = 275{\cdot}3$, monoclinic, $P2_1/n$, $a = 10{\cdot}772$ (2), $b = 6{\cdot}594$ (1), $c = 20{\cdot}185$ (3) Å, $\beta = 100{\cdot}60$ (1)°, $U = 1409{\cdot}3$ (4) Å^3, $Z = 4$, D_m(flotation) $= 1{\cdot}29$, $D_x = 1{\cdot}297$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 7{\cdot}90$ cm^{-1}, $F(000) = 584$, room temperature, final $R = 0{\cdot}068$ over 1443 reflections. Actiphenol has been shown to be a major product from a deteriorating culture of *Streptomyces gelaticus*. The molecule possesses an —OH···O=C— intramolecular hydrogen bond with an O···O separation of 2·573 (4) Å and an O—H···O angle of 151 (5)°. The glutarimide ring adopts a 1,2-diplanar, or sofa, conformation and the bond lengths and angles agree with those of similar compounds. The molecules form N—H···O hydrogen-bonded dimers, which are held together by van der Waals interactions.

Introduction. The actinomycete *Streptomyces gelaticus* is known to produce the antibiotic elaiomycin (Ehrlich *et al.*, 1954; Haskell, Ryder & Bartz, 1954; Stevens, Gillis, French & Haskell, 1956, 1958; Stevens, Gillis & Haskell, 1959; Taylor & Riehl, 1972). During the course of investigations of the biosynthesis of this compound, it was noted that a gradual deterioration of the cultures which led to decreased elaiomycin production also led to an increase in the concentration of an unknown substance in the ethyl acetate extract of the fermentation broth. Isolation of the unknown yielded a crystalline substance, m.p. 478–479 K, whose spectral characteristics indicated that it bore no relationship to elaiomycin. Since the structure of the unknown was not apparent from the spectral data, an X-ray analysis was carried out on a single crystal obtained from ethyl acetate and tetrahydrofuran. The X-ray data revealed that the unknown compound is actiphenol (C-73). Actiphenol, (I), was first isolated by Highet & Prelog (1959) from an *Actinomyces* culture (ETH 7796) and has subsequently been obtained from *S. albulus, S. noursei, S. pulverascens* and *S. griseus* (Bardy, Aszalos, Bostian & McNitt, 1981). Actiphenol exhibits weak biological activity in comparison with the more saturated members of the series (Ennis, 1968), and is the only member of the family of glutarimide antibiotics that contains an aromatic ring (Johnson, 1971).



(I)

Experimental. *Streptomyces gelaticus* obtained from Warner-Lambert Co. (PD No. 04942) was cultivated according to published procedures (Ehrlich *et al.*, 1954; Haskell *et al.*, 1954; Stevens *et al.*, 1956, 1958, 1959; Taylor & Riehl, 1972). The ethyl acetate extract of 2 L of 4 d old fermentation broth was evaporated *in vacuo* and the residue chromatographed on two preparative silica TLC plates using 1:1 benzene–ethyl acetate. In this system, elaiomycin had an R_f of *ca* 0·60 while actiphenol had an R_f of *ca* 0·50. The crude actiphenol (15 mg) was recrystallized from ethyl acetate–ether to yield 5 mg of colorless crystals, m.p. 478–479 K; lit. m.p. 472 K (Highet & Prelog, 1959), $[\alpha]_D = 0°$ (EtOH). The crystal used in the X-ray analysis had dimensions of *ca* 0·05 × 0·05 × 0·40 mm.

Accurate cell dimensions by least-squares refinement of 2θ values of 15 reflections with $44 \le 2\theta \le 77°$, Syntex $P2_1$ automated diffractometer, Cu $K\alpha$ radiation. Intensities with $4 \le 2\theta \le 130°$ collected by $\theta/2\theta$ scan with variable-speed scans (2·0 to 29·3° min^{-1}). Two check reflections, no significant variation in intensity, measured every 98 reflections. 2421 independent reflections, 1443 with $I \ge 2\sigma(I)$ considered observed, corrected for Lorentz and polarization factors. Empirical absorption correction applied; transmission factors from 0·911 to 0·961. Structure solved by direct methods (*MULTAN*; Germain, Main & Woolfson,

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1971). After several cycles of full-matrix least-squares refinement (program based on that by P. K. Gantzel, R. A. Sparks & K. N. Trueblood, modified by A. T. McPhail), hydrogen atoms placed at geometrically reasonable positions. Non-hydrogen atoms refined anisotropically, hydrogen atoms isotropically. $\sum w(|F_o|-|F_c|)^2$ minimized with $w^{1/2}=1$ for $|F_o|\le 8{\cdot}0$ and $w^{1/2}=8{\cdot}0/|F_o|$ for $|F_o|>8{\cdot}0$. Six low-angle reflections discarded because of probable secondary-extinction effects ($10\bar{3}$, 101, 105, $20\bar{4}$, $20\bar{2}$, 202). Convergence at $R=0{\cdot}068$, $wR=0{\cdot}072$, $S=0{\cdot}75$. Mean e.s.d. in parameters of non-hydrogen atoms >15 times av. Δ; max. Δ/σ 0·36 for z coordinate of C(16). Final difference map smooth, max. residual electron density $\sim 0{\cdot}5$ e Å^{-3}. Neutral-atom scattering factors from Cromer & Waber (1965) for C, N, O and from Stewart, Davidson & Simpson (1965) for H. Illustrations drawn using *ORTEP* (Johnson, 1965).

Discussion. A view of the molecular conformation adopted by actiphenol is shown in Fig. 1. Final atomic coordinates for the non-hydrogen atoms are listed in Table 1 and interatomic bond lengths and valency angles are in Table 2.*

The benzene ring is planar to within ±0·009 Å. Two of the substituents, O(15) and C(17), are significantly displaced [0·039 (3) and 0·049 (4) Å, respectively] to the same side of the plane while substituents C(7) and C(16) are very nearly in the plane. The carbonyl moiety of the two-carbon chain linking the two rings lies nearly coplanar with the benzene ring with a C(2)–C(1)–C(7)–O(18) torsion angle of −3·5 (4)° and a C(6)–C(1)–C(7)–C(8) angle of −4·4 (4)°. This allows a delocalization of the electrons into the carbonyl group.

* Lists of structure factors, anisotropic thermal parameters, hydrogen-atom parameters, various mean planes and a complete table of torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39865 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

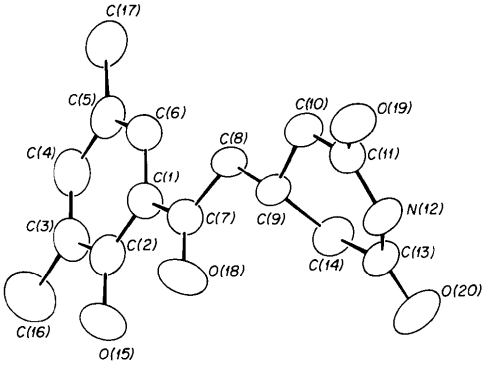


Fig. 1. A view of the molecular conformation and crystallographic numbering scheme of actiphenol (50% probability ellipsoids).

Table 1. *Fractional atomic coordinates* (×10⁴) *for the non-hydrogen atoms and equivalent isotropic temperature factors* (Å² ×10⁴), *with e.s.d.'s in parentheses*

$U_{eq}=\frac{1}{3}|U_{11}(1/\sin^2\beta)+U_{22}+U_{33}(1/\sin^2\beta)+2U_{13}\cos\beta/\sin^2\beta|$.

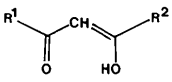
	x	y	z	U_{eq}
C(1)	−372 (3)	1964 (6)	3603 (2)	456
C(2)	−1078 (4)	996 (6)	4032 (2)	518
C(3)	−1739 (4)	−790 (6)	3819 (2)	569
C(4)	−1697 (4)	−1522 (6)	3190 (2)	598
C(5)	−1026 (3)	−590 (5)	2742 (2)	498
C(6)	−360 (3)	1158 (6)	2962 (2)	486
C(7)	337 (3)	3838 (6)	3835 (2)	472
C(8)	1158 (4)	4818 (6)	3402 (2)	465
C(9)	1931 (3)	6600 (5)	3751 (2)	408
C(10)	2496 (3)	7822 (6)	3248 (2)	490
C(11)	3271 (3)	9561 (6)	3570 (2)	478
N(12)	3884 (3)	9285 (5)	4218 (1)	485
C(13)	3843 (3)	7579 (6)	4612 (2)	484
C(14)	2998 (4)	5896 (5)	4306 (2)	508
O(15)	−1167 (3)	1696 (5)	4649 (1)	666
C(16)	−2480 (5)	−1822 (8)	4284 (3)	929
C(17)	−1044 (4)	−1428 (7)	2047 (2)	675
O(18)	262 (3)	4590 (5)	4377 (1)	751
O(19)	3379 (3)	11169 (4)	3283 (1)	672
O(20)	4479 (3)	7495 (4)	5171 (1)	654

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

C(1)–C(2)	1·406 (5)	C(7)–O(18)	1·218 (4)
C(1)–C(6)	1·400 (5)	C(8)–C(9)	1·535 (5)
C(1)–C(7)	1·483 (5)	C(9)–C(10)	1·510 (5)
C(2)–C(3)	1·402 (6)	C(9)–C(14)	1·522 (5)
C(2)–O(15)	1·348 (5)	C(10)–C(11)	1·494 (5)
C(3)–C(4)	1·368 (6)	C(11)–N(12)	1·364 (5)
C(3)–C(16)	1·502 (7)	C(11)–O(19)	1·225 (5)
C(4)–C(5)	1·399 (6)	N(12)–C(13)	1·383 (5)
C(5)–C(6)	1·387 (5)	C(13)–C(14)	1·495 (5)
C(5)–C(17)	1·504 (6)	C(13)–O(20)	1·208 (4)
C(7)–C(8)			
C(2)–C(1)–C(6)	119·7 (3)	C(1)–C(7)–O(18)	120·5 (3)
C(2)–C(1)–C(7)	119·3 (3)	C(8)–C(7)–O(18)	119·5 (3)
C(6)–C(1)–C(7)	121·1 (3)	C(7)–C(8)–C(9)	113·0 (3)
C(1)–C(2)–C(3)	119·6 (4)	C(8)–C(9)–C(10)	110·6 (3)
C(1)–C(2)–O(15)	123·5 (3)	C(8)–C(9)–C(14)	112·1 (3)
C(3)–C(2)–O(15)	116·9 (3)	C(10)–C(9)–C(14)	108·3 (3)
C(2)–C(3)–C(4)	118·6 (4)	C(9)–C(10)–C(11)	112·2 (3)
C(2)–C(3)–C(16)	119·2 (4)	C(10)–C(11)–N(12)	116·6 (3)
C(4)–C(3)–C(16)	122·2 (4)	C(10)–C(11)–O(19)	123·5 (3)
C(3)–C(4)–C(5)	123·7 (4)	N(12)–C(11)–O(19)	119·9 (3)
C(4)–C(5)–C(6)	117·1 (4)	C(11)–N(12)–C(13)	126·7 (3)
C(4)–C(5)–C(17)	121·4 (3)	N(12)–C(13)–C(14)	116·6 (3)
C(6)–C(5)–C(17)	121·4 (3)	N(12)–C(13)–O(20)	120·1 (3)
C(1)–C(6)–C(5)	121·3 (3)	C(14)–C(13)–O(20)	123·3 (3)
C(1)–C(7)–C(8)	120·0 (3)	C(9)–C(14)–C(13)	113·4 (3)

This conformation, coupled with the presence of a methyl group at C(3), also promotes an intramolecular hydrogen bond between the hydroxyl group at C(2) and the carbonyl oxygen O(18) [O···O 2·573 (4) Å]. Short hydrogen bonds, where the O···O separation is 2·4–2·6 Å, have attracted considerable attention (*e.g.* Joswig, Fuess & Ferraris, 1982, and references therein; Ichikawa, 1978, and references therein), but most are intermolecular. There have been, however, neutron diffraction studies carried out on two simple molecules incorporating β-keto enol units, 1-phenyl-1,3-

butanedione (II) (Jones, 1976*b*) and 1,3-diphenyl-1,3-propanedione (III) (Jones, 1976*a*). A comparison of bond lengths shows the hydrogen bond in (I) to be more asymmetric than those in either (II) or (III). The O···O, O–H, H···O and O–H···O values for the three compounds are: (I) 2·573 (4), 1·09 (6), 1·56 (6) Å, 151 (5)°; (II) 2·489 (5), 1·238 (11), 1·322 (12) Å, 153·2 (7)°; and (III) 2·463 (4), 1·161 (9), 1·360 (9) Å, 154·7 (5)°. The dimensions observed in (I) are, in part, a result of the opening of the C(1)–C(2)–O(15) angle to 123·5 (3)°. No such strain relief is displayed by either (II) or (III).

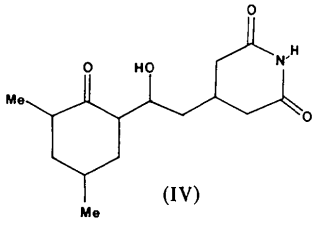


(II) R^1 = Me, R^2 = Ph
(III) $R^1 = R^2$ = Ph

Jeffrey & Takagi (1978) have suggested that, in order to compare X-ray and neutron diffraction data, the O–H bond lengths of X-ray studies should be normalized to 0·97 Å. Contraction of the O(15)–H(15) bond results in parameters that make the asymmetry of (I) appear even more marked.

The actual H···O separation in (I) may be longer than that determined crystallographically since the thermal ellipsoids of both O(15) and O(18) are elongated in a direction perpendicular to the plane of the benzene ring and H(15) assumes a rather large isotropic thermal parameter (B = 9·7 Å^2).

Cycloheximide, (IV), another glutarimide antibiotic whose solid-state conformation has been determined, crystallizes with two independent molecules in the asymmetric unit (Sayers, Schindler & Sundaralingam, 1977). In (IV) an intramolecular –C=O···H–O– hydrogen bond is geometrically possible but in neither molecule is it realized.

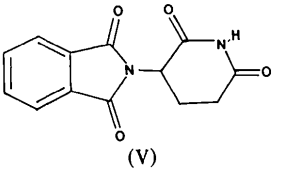


(IV)

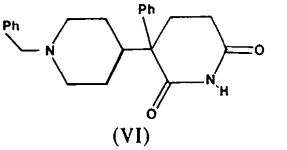
The endocyclic bond angles in the benzene ring [range 117·1 (4) to 123·7 (4)°] show small deformations, which can be explained by the cumulative inductive effects of the substituents. The electron-releasing effect of a methyl group decreases the internal angle at the site of substitution and increases the internal angles next to it. Because the methyl groups are *meta* to one another the angle at C(4) is particularly large.

The glutarimide ring in actiphenol adopts a 1,2-diplanar, or sofa, conformation in which C(9) lies 0·659 (4) Å from the plane of the rest of the moiety. The two independent molecules of cycloheximide differ conformationally. The glutarimide moiety of one closely approximates a 1,2-diplanar form with C(9) lying 0·645 Å from the plane of the rest of the ring; in the other molecule, though a C_s axis is maintained, the ring is much more puckered and C(9) lies 0·604 Å from the plane of the ring. Thalidomide, (V) (Allen & Trotter, 1971), also possesses a glutarimido unit but it is substituted at a position β (not γ) to the nitrogen, which may explain why it is less symmetrical. The conformation adopted is intermediate between a sofa and a half-chair.

In actiphenol the bond lengths and angles in the glutarimide ring compare well with those in cycloheximide (IV), thalidomide (V), benzitimide [3-(1-benzyl-4-piperidyl)-3-phenyl-2,6-piperidinedione] (VI) (Koch & Dideberg, 1973) and 4,4-dimethyl-2,6-piperidinedione (Bocelli & Grenier-Loustalot, 1981). In each, the endocyclic angle at the position bearing the alkyl substituent is *ca* 108°, the other C–C–C angles are *ca* 113°, the C–C(=O)–N angles are *ca* 117° and the C(=O)–N–C(=O) angle is large (>125°). That a large C–N–C angle results when nitrogen bears an extra-annular substituent was first noted by Singh (1965) for pyrimidines and was generalized by Ringertz (1972). This observation has been corroborated by many studies, *e.g.* in uracil derivatives (Neugebauer & Lippert, 1982), in 8-azapurines (Wilson, Wilson, Shoemaker, Wooldridge & Hodgson, 1982) and in barbiturates (Dideberg, Dupont & Pyzalska, 1975).



(V)



(VI)

The mean N–C distance in (I) is 1·374 Å, a value very close to those observed for barbiturates (*e.g.* Dideberg *et al.*, 1975; Hsu, Lesser & Craven, 1975; Escobar, 1975), and for (IV), (V) and (VI). However, though the sum of the C(11)–O(19) and C(11)–N(12) lengths in (I) is equal to the sum of the C(13)–O(20) and N(12)–C(13) lengths, the C(11)–O(19) bond is *ca* 4σ longer than the C(13)–O(20) bond and the C(11)–N(12) bond is *ca* 4σ shorter than the N(12)–C(13) bond. It might be expected, because O(20) is involved in hydrogen bonding and O(19) is not, that the C(13)–O(20) length should be the longer. Bond lengths in one of the cycloheximide molecules show the same pattern as those observed in (I) (Sayers *et al.*, 1977).

The molecules pack (Fig. 2) in characteristic fashion (Allen & Trotter, 1971; Dideberg *et al.*, 1975). Centrosymmetrically related molecules form dimers linked by N–H to O(20) hydrogen bonds with O···N separations of 2·887 (4) Å; O(19) does not take part in

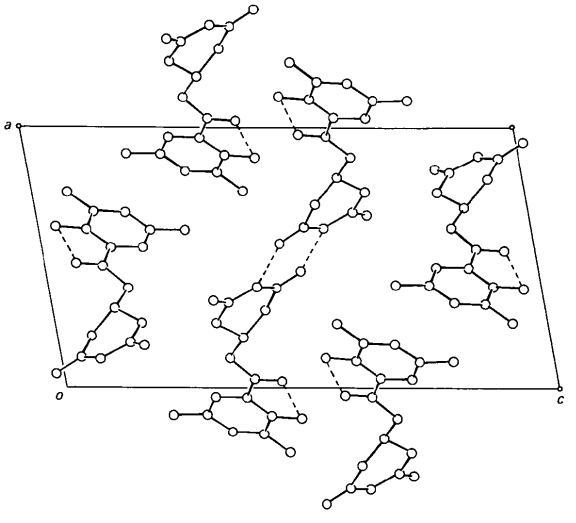


Fig. 2. Unit-cell contents projected down **b**. Hydrogen bonds are indicated by dashed lines.

hydrogen bonding. The O···N separation compares well with those observed for compounds with similar molecular fragments. The C=O···H and O···H–N angles are typical at 122 (1) and 172 (3)°. Contact between dimers corresponds to normal van der Waals interactions.

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2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose, $C_{12}H_{20}O_6$

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Abstract. $M_r = 260{\cdot}29$, orthorhombic, $P2_12_12_1$, $a = 6{\cdot}665$ (1), $b = 10{\cdot}816$ (1), $c = 18{\cdot}891$ (3) Å, $V = 1362$ Å^3, $Z = 4$, $D_x = 1{\cdot}269$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 0{\cdot}766$ mm^{-1}, $F(000) = 560$, $T = 293$ K, final $R = 0{\cdot}0437$ for 1353 unique observed reflections. The fused five-membered rings have envelope configurations with maximum distances from the best planes of −0·205 (4) Å [C(7)] and 0·247 (2) Å [O(4)]

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