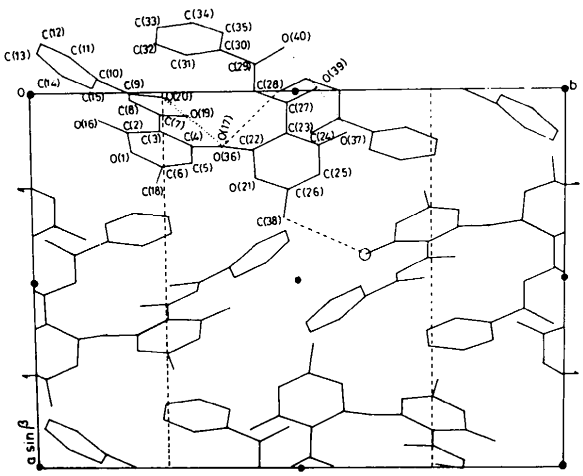

Fig. 2. Packing of the molecule viewed down the *c* axis. Dotted lines indicate intramolecular and dashed lines intermolecular hydrogen bonds. [The large open circle is O(16) twice translated on *z*.]

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# Structure of Antischistosome Compounds. II. Benzyltriphenylphosphonium Bromide

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**Abstract.** $C_{25}H_{22}P^+.Br^-$, $M_r = 433{\cdot}3$, monoclinic, $P2_1/c$, $a = 9{\cdot}761\,(1)$, $b = 20{\cdot}343\,(1)$, $c = 11{\cdot}544\,(1)$ Å, $\beta = 109{\cdot}17\,(1)°$, $V = 2165{\cdot}16$ Å$^3$, $Z = 4$, $D_m = 1{\cdot}315$, $D_x = 1{\cdot}329$ g cm$^{-3}$, graphite-monochromatized Cu $K\alpha$ radiation, $\lambda = 1{\cdot}5418$ Å, $\mu = 33{\cdot}4$ cm$^{-1}$, $F(000) = 888$, $T = 292$ K. Final $R = 0{\cdot}046$ for 2962 observed reflections. The four P—C distances are in the range 1·789 (4)–1·802 (4) Å with a mean of 1·795 (5) Å. The six C—P—C angles vary from 108·2 (2) to 110·4 (2)° with a mean of 109·5 (8)°. The dihedral angle of the phenylmethyl plane and the plane formed by the C atoms of the P—C(phenyl) bonds is 24·2°, which is in sharp contrast to the vertical orientation of the substituted group of the (2-aminoethyl)triphenylphosphonium compound.

**Introduction.** The crystal and molecular structure of the title compound have been determined as a part of a study of the triphenylphosphonium compounds which exhibit varying effects on the cholinergic nervous system of *Schistosoma mansoni* (McAllister, Dotson, Grim & Hillman, 1980). The biological effects of these compounds cannot be explained solely on the basis of chemical differences in the substituted moiety. The effects may also be due to the differences in the torsion angles in the substituted moieties.

**Experimental.** Sample provided by Professor G. Hillman, synthesized as described in McAllister *et al.* (1980); colorless crystals (from ethanol), 0·10 × 0·23 × 0·09 mm; Enraf–Nonius CAD-4 diffractometer, cell parameters from $2\theta$ angles for 22 reflections from least-squares refinement with $25 \leq \theta \leq 35°$; $\omega$–$2\theta$ scan, $\omega$ width $(0{\cdot}90 + 0{\cdot}14\tan\theta)°$, $(\sin\theta/\lambda)_{\max} = 0{\cdot}6092$ Å$^{-1}$, $h = -11$ to 11, $k = 0$ to 24 and $l = 0$ to 14; intensities of three standard reflections monitored every 3600 s showed a linear decline in intensity of −9·6%, correction applied; 3679 unique

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reflections measured, 2962 reflections with $I > 3\sigma(I)$; Lp corrections; structure solved by Patterson and Fourier methods; full-matrix least squares minimizing $w(F_o - F_c)^2$ with unit weights; min. and max. absorption correction of 0·826 and 1·201, respectively, using program *DIFABS* (Walker & Stuart, 1983); final $R$ = 0·046, $wR$ = 0·049; all H atoms from $\Delta F$ map and refined isotropically; 332 variables, $S$ = 1·47, max. $\Delta/\sigma$ = 0·02 for non-H atoms, 0·10 for H atoms; no significant features in final $\Delta F$ synthesis with $\Delta\rho$ = ±0·38 e Å$^{-3}$; atomic scattering factors, $f'$ and $f''$ from *International Tables for X-ray Crystallography* (1974); all calculations with a DEC PDP 11/44 computer using Enraf–Nonius *SDP-Plus* package (Frenz, 1984) and *ORTEP*II (Johnson, 1976).

**Discussion.** Table 1* lists the fractional atomic coordinates and isotropic thermal parameters. Fig. 1 shows the structure of the molecule with the thermal vibration ellipsoids of the non-H atoms. The packing of the molecules is shown in Fig. 2. Intermolecular distances correspond to normal van der Waals interactions. Bond lengths and angles of the non-H atoms and selected torsion angles are given in Table 2. The phenyl-ring numbers and atom numbers are assigned as previously described (Czerwinski, 1986).

In the cation, the P atom has a nearly perfect tetrahedral arrangement. All C—P—C angles are within the range of 108·2 (2) to 110·4 (2)° with a mean value of 109·5 (8)°. The average P—C distance is 1·795 (5) Å. The C(11)—C(12) bond length, 1·501 (5) Å, and the P—C(11)—C(12) angle, 113·5 (3)°, are similar to those found in benzyltriphenylphosphonium chloride (1·519 Å and 114·7°; Skapski & Stephens, 1974) and in benzyltriphenylphosphonium iodide (1·510 Å and 113·2°; Archer, Modro & Nassimbeni, 1981).

The Br$^-$ ion is face oriented with respect to the phosphonium center as seen in other similar-type structures (Archer *et al.*, 1981; Czerwinski, 1986). The closest C atom, C(11), is 3·709 (4) Å from the Br$^-$ ion. This distance is midway between the C(11)···Cl (3·45 Å) and the C(11)···I (3·96 Å) distances (Skapski & Stephens, 1974; Archer *et al.*, 1981), as expected from the van der Waals radii of these halide ions (Pauling, 1960).

The average C—C bond length of the four phenyl rings is 1·375 (2) Å. Least-squares-planes' calculations show that all four phenyl rings are planar with a maximum displacement of 0·010 (4) Å. The methylene atom [C(11)] is nearly in the plane of the substituted phenyl ring with a deviation of 0·010 (5) Å (Table 7, deposited).

Table 1. *Positional and isotropic thermal parameters and their e.s.d.'s*

| | $x$ | $y$ | $z$ | $B_{eq}/B_{iso}$(Å$^2$) |
|---|---|---|---|---|
| Br | 1·26847 (6) | −0·07266 (3) | 0·19808 (5) | 5·37 (1) |
| P | 1·1375 (1) | 0·13832 (6) | 0·1550 (1) | 3·49 (2) |
| C(11) | 1·0171 (4) | 0·0691 (2) | 0·1062 (4) | 3·9 (1) |
| C(12) | 0·9190 (5) | 0·0592 (2) | 0·1812 (4) | 3·9 (1) |
| C(13) | 0·7881 (5) | 0·0924 (3) | 0·1520 (5) | 5·5 (1) |
| C(14) | 0·6992 (5) | 0·0824 (4) | 0·2210 (5) | 6·8 (2) |
| C(15) | 0·7377 (6) | 0·0400 (3) | 0·3194 (5) | 6·3 (1) |
| C(16) | 0·8673 (6) | 0·0071 (3) | 0·3470 (5) | 5·9 (1) |
| C(17) | 0·9586 (5) | 0·0166 (3) | 0·2791 (5) | 4·9 (1) |
| C(21) | 1·2592 (4) | 0·1408 (3) | 0·0677 (4) | 3·9 (1) |
| C(22) | 1·2834 (6) | 0·0868 (3) | 0·0049 (5) | 6·2 (1) |
| C(23) | 1·3773 (6) | 0·0915 (4) | −0·0622 (5) | 7·2 (2) |
| C(24) | 1·4451 (5) | 0·1496 (4) | −0·0674 (5) | 6·6 (2) |
| C(25) | 1·4236 (6) | 0·2025 (3) | −0·0044 (5) | 7·0 (1) |
| C(26) | 1·3312 (5) | 0·1988 (3) | 0·0644 (5) | 5·7 (1) |
| C(31) | 1·0354 (4) | 0·2135 (2) | 0·1282 (4) | 3·9 (1) |
| C(32) | 0·9278 (6) | 0·2220 (3) | 0·0169 (5) | 5·4 (1) |
| C(33) | 0·8484 (6) | 0·2808 (3) | −0·0064 (6) | 7·0 (2) |
| C(34) | 0·8784 (6) | 0·3283 (3) | 0·0821 (6) | 7·2 (2) |
| C(35) | 0·9841 (6) | 0·3205 (3) | 0·1909 (5) | 6·2 (1) |
| C(36) | 1·0646 (5) | 0·2631 (3) | 0·2141 (5) | 5·0 (1) |
| C(41) | 1·2367 (4) | 0·1301 (2) | 0·3149 (4) | 3·54 (9) |
| C(42) | 1·1697 (5) | 0·1420 (3) | 0·4018 (4) | 4·1 (1) |
| C(43) | 1·2463 (5) | 0·1319 (3) | 0·5243 (4) | 4·6 (1) |
| C(44) | 1·3853 (6) | 0·1099 (3) | 0·5608 (4) | 5·2 (1) |
| C(45) | 1·4509 (5) | 0·0973 (3) | 0·4756 (5) | 5·7 (1) |
| C(46) | 1·3777 (5) | 0·1073 (3) | 0·3527 (4) | 4·9 (1) |
| H(111) | 0·962 (4) | 0·077 (2) | 0·016 (4) | 4 (1)* |
| H(112) | 1·079 (4) | 0·034 (2) | 0·119 (3) | 3·7 (9)* |
| H(13) | 0·758 (5) | 0·124 (3) | 0·080 (5) | 7 (1)* |
| H(14) | 0·614 (6) | 0·110 (3) | 0·199 (5) | 9 (2)* |
| H(15) | 0·681 (5) | 0·032 (3) | 0·365 (4) | 7 (1)* |
| H(16) | 0·894 (5) | −0·017 (3) | 0·412 (4) | 7 (1)* |
| H(17) | 1·049 (5) | −0·003 (2) | 0·300 (4) | 6 (1)* |
| H(22) | 1·238 (5) | 0·050 (3) | 0·014 (5) | 7 (1)* |
| H(23) | 1·386 (8) | 0·050 (4) | −0·103 (6) | 13 (2)* |
| H(24) | 1·511 (6) | 0·151 (3) | −0·111 (5) | 9 (2)* |
| H(25) | 1·462 (5) | 0·243 (3) | −0·002 (5) | 7 (1)* |
| H(26) | 1·318 (5) | 0·238 (3) | 0·109 (4) | 7 (1)* |
| H(32) | 0·913 (4) | 0·192 (2) | −0·035 (3) | 3·7 (9)* |
| H(33) | 0·774 (5) | 0·278 (2) | −0·091 (4) | 6 (1)* |
| H(34) | 0·809 (7) | 0·360 (4) | 0·060 (6) | 12 (2)* |
| H(35) | 1·002 (6) | 0·360 (3) | 0·253 (5) | 8 (2)* |
| H(36) | 1·137 (5) | 0·261 (2) | 0·283 (4) | 6 (1)* |
| H(42) | 1·074 (4) | 0·155 (2) | 0·376 (3) | 2·8 (8)* |
| H(43) | 1·206 (5) | 0·141 (2) | 0·582 (4) | 6 (1)* |
| H(44) | 1·441 (5) | 0·103 (3) | 0·651 (4) | 7 (1)* |
| H(45) | 1·541 (6) | 0·081 (3) | 0·502 (5) | 8 (2)* |
| H(46) | 1·416 (4) | 0·098 (2) | 0·298 (4) | 4 (1)* |

* Atoms refined isotropically. Anisotropically refined atoms are given in the form of the equivalent isotropic thermal parameter defined as: $\frac{4}{3}\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

A qualitative examination of the structures of the three halide salts of the benzyltriphenylphosphonium ion shows that the orientation of phenyl rings 2, 3 and 4 of the chloride structure (Skapski & Stephens, 1974) differs from those of the bromide and iodide (Archer *et al.*, 1981) structures. The angles between the phenyl-ring plane of the benzyl group of the bromide salt and the planes of rings 2, 3 and 4 are 65·4, 107·2 and 32·6°, respectively. Based on calculations from the published coordinates this arrangement is appreciably the same as that in the iodide structure (77·8, 105·0 and 27·5°), but different from that in the chloride structure (39·3, 40·9 and 69·1°) (Skapski & Stephens,

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* Lists of structure factors, anisotropic thermal parameters, bond lengths and angles involving H atoms, torsion angles and least-squares-planes' calculations have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42836 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

1974). The orientation of the phenyl rings is such that ring 2 makes angles of 91·3 and 91·7° to the normals of the planes of ring 3 and 4, respectively, whereas the corresponding angle of ring 3 to ring 4 is 128·1°. These values are similar to the previously reported values of 110·3, 78·9 and 123·7° for the (2-aminoethyl)triphenylphosphonium bromide hydrobromide (Czerwinski, 1986), and 89·2, 96·9 and 125·3° calculated for benzyltriphenylphosphonium iodide. However, the values 79·7, 80·8 and 59·6° for benzyltriphenylphosphonium chloride (Skapski & Stephens, 1974) are different, reflecting a different conformation, particularly at ring 4. The differences of the triphenyl-ring orientations with respect to the chloride structure are probably due to packing forces. The bromide and iodide structures crystallize in the same space group, $P2_1/c$, with similar cell parameters. The space group of the chloride structure is orthorhombic, *Pbca*, with different cell parameters.

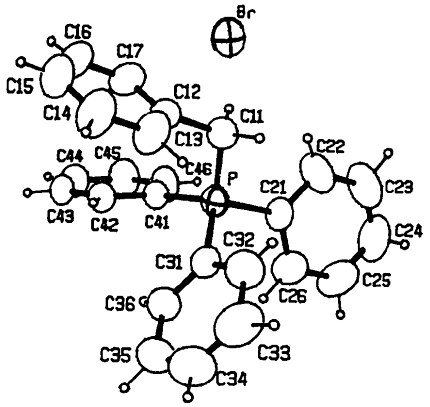

Fig. 1. A perspective view of the molecule showing the atom-labeling scheme. Thermal ellipsoids are drawn at the 50% probability level.

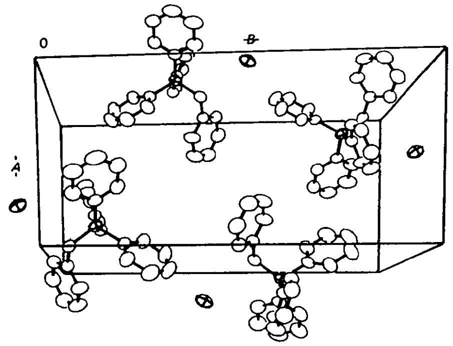

Fig. 2. The packing of the molecules in the unit cell along the *c* axis. Br and P atoms are drawn with the principal ellipses.

Table 2. *Bond distances* (Å), *bond angles* (°) *and selected torsion angles* (°)

Numbers in parentheses are e.s.d.'s in the least-significant digits.

| | | | | | |
|---|---|---|---|---|---|
| P | C(11) | 1·802 (4) | C(24) | C(25) | 1·353 (8) |
| P | C(21) | 1·793 (4) | C(25) | C(26) | 1·386 (6) |
| P | C(31) | 1·797 (4) | C(31) | C(32) | 1·378 (6) |
| P | C(41) | 1·789 (4) | C(31) | C(36) | 1·377 (6) |
| C(11) | C(12) | 1·501 (5) | C(32) | C(33) | 1·402 (7) |
| C(12) | C(13) | 1·385 (6) | C(33) | C(34) | 1·366 (9) |
| C(12) | C(17) | 1·374 (6) | C(34) | C(35) | 1·347 (8) |
| C(13) | C(14) | 1·371 (6) | C(35) | C(36) | 1·383 (7) |
| C(14) | C(15) | 1·376 (7) | C(41) | C(42) | 1·387 (5) |
| C(15) | C(16) | 1·373 (7) | C(41) | C(46) | 1·380 (5) |
| C(16) | C(17) | 1·381 (7) | C(42) | C(43) | 1·381 (6) |
| C(21) | C(22) | 1·378 (6) | C(43) | C(44) | 1·357 (6) |
| C(21) | C(26) | 1·381 (6) | C(44) | C(45) | 1·362 (6) |
| C(22) | C(23) | 1·385 (7) | C(45) | C(46) | 1·378 (6) |
| C(23) | C(24) | 1·366 (8) | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C(11) | P | C(21) | 109·3 (2) | C(23) | C(24) | C(25) | 120·1 (5) |
| C(11) | P | C(31) | 110·1 (2) | C(24) | C(25) | C(26) | 120·7 (6) |
| C(11) | P | C(41) | 109·1 (2) | C(21) | C(26) | C(25) | 119·6 (5) |
| C(21) | P | C(31) | 108·2 (2) | P | C(31) | C(32) | 118·5 (4) |
| C(21) | P | C(41) | 110·4 (2) | P | C(31) | C(36) | 121·9 (3) |
| C(31) | P | C(41) | 109·8 (2) | C(32) | C(31) | C(36) | 119·6 (4) |
| P | C(11) | C(12) | 113·5 (3) | C(31) | C(32) | C(33) | 119·3 (6) |
| C(11) | C(12) | C(13) | 120·5 (4) | C(32) | C(33) | C(34) | 119·4 (6) |
| C(11) | C(12) | C(17) | 119·9 (4) | C(33) | C(34) | C(35) | 121·6 (6) |
| C(13) | C(12) | C(17) | 119·7 (4) | C(34) | C(35) | C(36) | 119·5 (6) |
| C(12) | C(13) | C(14) | 119·7 (5) | C(31) | C(36) | C(35) | 120·5 (5) |
| C(13) | C(14) | C(15) | 121·2 (5) | P | C(41) | C(42) | 120·4 (3) |
| C(14) | C(15) | C(16) | 118·6 (5) | P | C(41) | C(46) | 120·2 (3) |
| C(15) | C(16) | C(17) | 121·1 (5) | C(42) | C(41) | C(46) | 119·2 (4) |
| C(12) | C(17) | C(16) | 119·7 (5) | C(41) | C(42) | C(43) | 119·3 (4) |
| P | C(21) | C(22) | 122·2 (4) | C(42) | C(43) | C(44) | 121·1 (4) |
| P | C(21) | C(26) | 118·5 (3) | C(43) | C(44) | C(45) | 119·8 (4) |
| C(22) | C(21) | C(26) | 119·3 (4) | C(44) | C(45) | C(46) | 120·5 (5) |
| C(21) | C(22) | C(23) | 120·0 (6) | C(41) | C(46) | C(45) | 120·0 (4) |
| C(22) | C(23) | C(24) | 120·2 (6) | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| C(21) | P | C(11) | C(12) | 175·0 (3) | P | C(11) | C(12) | C(13) | 86·3 (4) |
| C(31) | P | C(11) | C(12) | −66·3 (5) | P | C(11) | C(12) | C(17) | −94·2 (4) |
| C(41) | P | C(11) | C(12) | 54·3 (5) | | | | | |

The three C($n$1)(phenyl) atoms provide a convenient reference plane with which to compare the orientation of the substituted moiety to the triphenylphosphonium portion. The phenyl ring of the benzyl group has a dihedral angle of 24·2° with the plane formed by the C(21), C(31), and C(41) atoms. In the iodide structure this angle is calculated to be 24·8°, and 29·3° in the chloride structure. Thus the overall conformations of these benzyltriphenylphosphonium halides are not appreciably different. On the other hand, the extended 2-aminoethyl group is nearly vertical to its C(21)—C(31)—C(41) plane, having an angle of 106·6°. The amino group is 4·495 (5) Å from the C(21)–C(31)–C(41) plane, whereas the distance of the atom of the benzyltriphenylphosphonium bromide structure farthest from its C(21)–C(31)–C(41) plane, C(15) of the benzyl group, is only 4·126 (6) Å. This would indicate that the shape of the benzyltriphenylphosphonium compound is more compact than that of the (2-aminoethyl)-triphenylphosphonium compound. Whether this difference in overall shape is responsible or at least partially responsible for the differences in the biological activities of benzyltriphenylphosphonium bromide, (2-aminoethyl)triphenylphosphonium bromide hydrobromide and the other compounds of this series remains to be determined (McAllister *et al.*, 1980).

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*Acta Cryst.* (1986). C**42**, 1022–1024

# *N*-(1-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-prolinium–Hydrogen Maleate (1/1), Enalapril (MK-421)

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**Abstract.** $C_{20}H_{29}N_2O_5^+.C_4H_3O_4^-$, $M_r = 492{\cdot}5$, monoclinic, $P2_1$, $a = 11{\cdot}224\,(4)$, $b = 6{\cdot}645\,(2)$, $c = 17{\cdot}824\,(5)$ Å, $\beta = 105{\cdot}52\,(3)°$, $V = 1280{\cdot}9\,(7)$ Å$^3$, $Z = 2$, $D_x = 1{\cdot}27$ g cm$^{-3}$, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 1{\cdot}06$ cm$^{-1}$, $F(000) = 524$, $T = 293$ K, final $R = 0{\cdot}089$ for 1187 observed reflections. The title compound (MK-421) is a potent orally active inhibitor of angiotensin-converting enzyme. The molecule is observed with Ala $NH_2^+$ as a positively charged group. The backbone shows an extended conformation at Ala. The crystal-structure conformation is compared with the proposed biologically active conformation of enalapril and with the crystal conformation of captopril (SQ 14,225).

**Introduction.** Much attention focuses on the renin–angiotensin system in relation to mechanisms controlling blood pressure. The discovery of captopril (Ondetti, Rubin & Cushman, 1977) and enalapril (Patchett *et al.*, 1980) as potent orally active inhibitors of angiotensin-converting enzyme led to the development of novel molecules with similar biological activity (Condon *et al.*, 1982; Thorsett, Harris, Aster, Peterson, Taub & Patchett, 1983).

As yet, however, the only crystal-structure analysis of angiotensin-converting enzyme flexible inhibitor reported in the literature concerns captopril (Fujinaga & James, 1980).

The present study was undertaken to determine precise molecular and conformational parameters for MK-421 which may be of use in the understanding of conformational requirements for ACE (angiotensin-converting enzyme) inhibition. The observed crystal-structure conformation is compared with the biologically active conformation proposed by Andrews, Carson, Caselli, Spark & Woods (1985) and with the conformation of captopril.

**Experimental.** Crystals grown with vapour-diffusion technique with methanol as solvent and diethyl oxide as precipitating agent. Plate-like crystal, dimensions $0{\cdot}05 \times 0{\cdot}20 \times 0{\cdot}40$ mm; Enraf–Nonius CAD-4 diffractometer; Mo $K\alpha$ radiation, graphite monochromator. Lattice parameters from least-squares adjustment to setting angles of 25 reflections with $9 < 2\theta < 18°$. Correction for Lorentz and polarization effects; $\omega$–$2\theta$ scans. $\theta_{\max} = 25°$; range of $hkl$: $h$: $-12\rightarrow12$; $k$: $0\rightarrow7$; $l$: $0\rightarrow21$. Intensity variation of three standard reflections <2%. 2459 unique reflections measured; 1187 with $I > 2\sigma(I)$. Solution by direct methods (*MITHRIL*; Gilmore, 1984). Refinement on $F$ by block-diagonal least squares; anisotropic non-H atoms, fixed parameters for H atoms [located in $\Delta F$ map except at C(5) and at the carboxyl groups]. $R = 0{\cdot}089$, $wR = 0{\cdot}092$ (poor quality of crystal and hence of intensity data); $w = 1/\sigma^2(F_o)$ based on counting statistics; $S = 1{\cdot}10$; $\Delta/\sigma_{\max} = 0{\cdot}5$; $\Delta/\sigma_{\text{mean}} = 0{\cdot}1$. Max. and min. heights in final $\Delta\rho$ map $+0{\cdot}3$ and $-0{\cdot}2$ e Å$^{-3}$. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974)

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