

# The Crystal Structure of Tetronic Acid Derivatives. I. $\alpha$ -Methyltetronic Acid

By S. G. G. MACDONALD AND A. B. ALLEYNE

Physics Department, University of the West Indies, Kingston 7, Jamaica

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The structure of  $\alpha$ -methyltetronic acid  $C_5H_6O_3$ , has been determined and refined by the use of Fourier and difference syntheses in two principal projections. The molecule is planar and the bond lengths indicate that resonance is taking place across the  $OH-C=C-CO$  chain. Strong hydrogen bonding exists linking the molecules into long chains in the crystal.

## Introduction

Tetronic-acid derivatives are obtained by substitution in the  $\alpha$  or  $\gamma$  positions of the parent acid (Fig. 1(a)). They occur in a wide range of natural products, the most important member of the group being vitamin C, which is a  $\gamma$ -substituted  $\alpha$ -hydroxytetronic acid. A survey of the tetronic acids may be found in the literature (Haynes & Plimmer, 1960).

The tetronic acids exhibit aromatic properties, indicating that resonance may be taking place across the  $OH-C=C-CO$  system. An investigation of the structures of tetronic acid derivatives to determine the partial bond character of the bonds in the tetronic acid nucleus is therefore of considerable interest.

Further, tetronic acids are probably the most strongly hydrogen-bonded group of compounds known from the evidence of infra-red spectral measurements (Duncanson, 1953). The OH bonds in most tetronic acids in the solid state have very low stretching frequencies ( $2530-2650\text{ cm}^{-1}$ ). How the hydrogen bonding is taking place is, however, the subject of speculation and a determination of several structures should settle the point finally.

Recent researches (Dickens & Jones, 1961) have given rise to the belief that some  $\alpha\beta$ -unsaturated lactones possess weak carcinogenic properties. A knowledge of the structures of tetronic acid derivatives may therefore help in the attempt to link structure with carcinogenic potency.

The first tetronic-acid derivative prepared was

$\alpha$ -methyltetronic acid (De Marçay, 1879) and, as this is also one of the simplest derivatives, it was investigated first. The crystals of tetronic acid derivatives so far studied have shown that they suffer, in most cases badly, from twinning, and one further advantage of  $\alpha$ -methyltetronic acid was that it could be produced in crystals where, though twinning was still present, it was not too serious.

## Experimental

The crystals of  $\alpha$ -methyltetronic acid used were kindly supplied by the Natural Products Unit attached to the Chemistry Department of the University of the West Indies. It was impossible to find a crystal which did not exhibit at least slight twinning and the specimens finally used were selected only after careful examination under the polarizing microscope.

Using  $Cu\ K\alpha$  radiation, oscillation and equi-inclination Weissenberg photographs of the  $a$  and  $c$  axis zero layers and  $b$  axis zero and upper layers were taken. Multiple-film techniques were employed and the relative intensities were estimated visually with the aid of a calibration strip produced with the X-ray set under carefully controlled conditions. These intensities were corrected for Lorentz and polarization factors and the factors applicable to upper layers, sets of intensities being correlated by common spots. The totality of intensities was put on an approximately absolute basis by the use of Wilson's statistical method (Wilson, 1942).

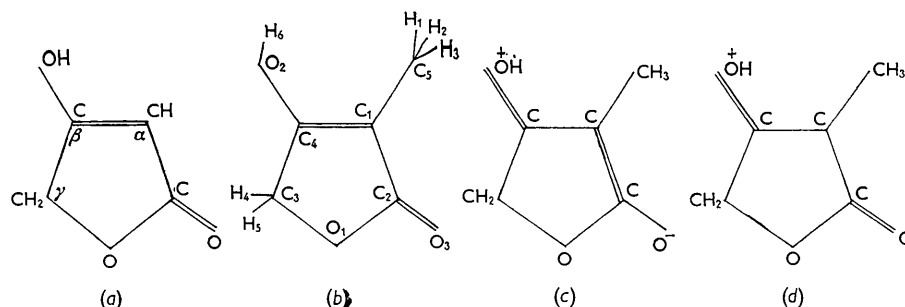


Fig. 1. (a) The tetronic acid molecule. (b) The classical structure of  $\alpha$ -methyltetronic acid showing the numbering of the atoms. (c) and (d) Other possible structures for  $\alpha$ -methyltetronic acid.

The unit-cell parameters were calculated from zero-layer Weissenberg photographs by analytical extrapolation.

### Unit cell and space group

The unit cell has the dimensions

$$a = 4.00 \pm 0.01, \quad b = 21.57 \pm 0.03, \quad c = 6.30 \pm 0.01 \text{ \AA}, \\ \beta = 107^\circ 36' \pm 20'$$

and contains four molecules of  $C_5H_6O_3$ . The space group is  $P2_1/c (C_{2h}^5)$ . The calculated density is  $1.461 \text{ g.cm}^{-3}$ ; the experimentally obtained value is  $1.460 \text{ g.cm}^{-3}$ .

### Determination of the structure

With the relatively small number of atoms in the asymmetric unit, it was felt that the application of inequality and probability relations to the unitary structure factors might well produce a satisfactory trial structure. In practice it was found that the signs of the structure factors obtained in this way led to electron density maps for the projections on (100) and (001) which were difficult to interpret.

The molecule of  $\alpha$ -methyltetronic acid was expected to be planar and thus Fourier-transform techniques could also be applied. The small number of atoms per molecule and the fairly regular molecular shape led, however, to considerable pseudo-symmetry in the molecular transform and the task of fitting the reciprocal axes in their correct positions was difficult. On the assumption that the majority of the signs of the largest unitary structure factors obtained by the use of probability relations were correct, it was, however, possible to eliminate many of the theoret-

ically possible orientations of the  $b^*$  and  $c^*$  axes. The most likely trial structure was selected and refined by successive Fourier syntheses. When the structure refused to refine from the position where its reliability index, defined as  $R = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$ , was around 0.25, a difference synthesis was performed which showed clearly that, although the typical molecule occupied approximately the correct position, it was incorrectly orientated. Rectifying this fault allowed continued refinement by successive Fourier and difference syntheses.

In putting the intensities on an absolute basis, the atomic scattering factors used had been those of McWeeny (1951). It now became obvious that the scale factor and temperature factor obtained by the use of Wilson's method were not correct, and  $\log F_o^2/F_c^2$  was plotted against  $\sin^2 \theta$  yielding the correct scale factor and showing that the temperature factor applicable to McWeeny's atomic scattering factors was such that  $B$  had the value  $1.273 \text{ \AA}^2$ . With these

Table 1. Atomic coordinates

	$x/a$	$y/b$	$z/c$
$C_1$	0.4722	0.1068	0.1329
$C_2$	0.7000	0.1590	0.2336
$C_3$	0.4278	0.1924	-0.1208
$C_4$	0.3000	0.1246	-0.0814
$C_5$	0.4222	0.0447	0.2500
$O_1$	0.6778	0.2056	0.0853
$O_2$	0.0833	0.0941	-0.2250
$O_3$	0.9056	0.1619	0.4181
$H_1$	0.1528	0.0447	0.2500
$H_2$	0.6806	0.0708	0.3708
$H_3$	0.6667	0.0250	0.1333
$H_4$	0.1528	0.2167	-0.2250
$H_5$	0.1528	0.1833	-0.2500
$H_6$	-0.0278	0.1194	-0.3583

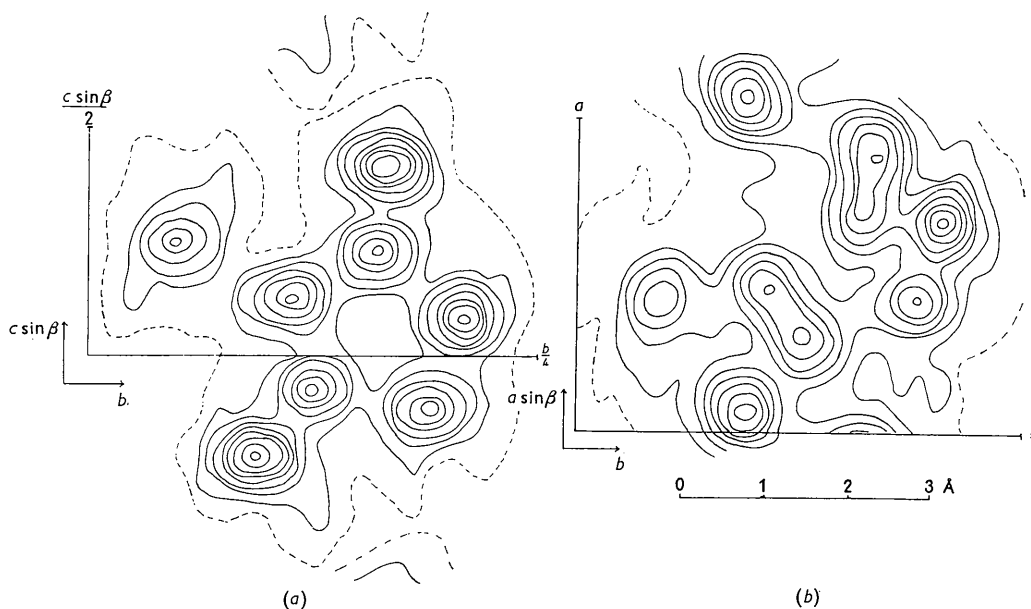


Fig. 2. Projections of the electron density ( $\alpha$ ) on (100) and ( $\beta$ ) on (001). Contours are at intervals of  $1 \text{ e.}\text{\AA}^{-2}$ , the broken line being the  $1 \text{ e.}\text{\AA}^{-2}$  contour.



synthesis were performed. The latter is shown in Fig. 2(a) and it will be seen that the approximate positions of the hydrogen atoms are appearing. These were confirmed in the difference synthesis and the hydrogen atoms were included in the final  $F_c$  calculation, the reliability index being then 0.146.

The techniques used in the first zone were applied to the projection of the electron density on (001) but produced ambiguous results. Even with the  $y$  coordinates of the atoms in the typical molecule known, it was found that there were at least seven different possible positions and orientations for the molecule which produced trial structures all *a priori* equally likely. The symmetrical nature of the molecule and the small number of atoms it possessed were, of course, responsible and it appeared at first sight that there was no simple method of deciding unambiguously between the various possible alternatives.

It was at this point that the method described in an earlier paper (MacDonald, 1963) was devised. It provided a rapid and simple means of determining the signs of the majority of the  $F(h, k, 0)$ s and with these signs an electron-density map was obtained which showed clearly the position and orientation of the molecule in this projection. Only a few successive difference syntheses were needed to refine completely the structure in this zone. The temperature factor used in the first projection also applied to this one and the three largest intensities required to be corrected for extinction. The hydrogen atoms did not show up as clearly as before and their effect was included by assuming a C-H bond length of 1.08 Å and an O-H bond length of 1.00 Å. The final reliability index in this zone was 0.143. The projection of the electron density on (001) is shown in Fig. 2(b).

For the projection on (010), the reliability index was 0.151 and for all the reflexions measured it was 0.145. These values would presumably have been lower if an untwinned crystal had been obtainable. Table 2 gives the  $F$ 's calculated from the final atomic coordinates compared with those experimentally observed.

### Discussion of the structure

Fig. 1(b) shows the numbering of the atoms of  $\alpha$ -methyltetronic acid adopted in this investigation and Table 1 gives the final coordinates of the atoms of the typical

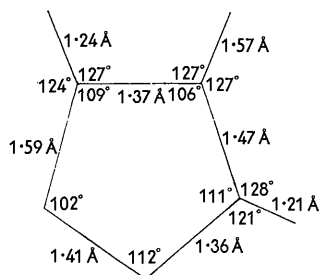


Fig. 3. Bond lengths and bond angles.

molecule in fractions of the cell edge. Fig. 3 shows the bond lengths and bond angles in the molecule.

The accuracy of the atomic coordinates was estimated by applying Cruickshank's formula (Cruickshank, 1949). For a carbon atom,  $\sigma(x_r)$  and  $\sigma(y_r)$  are given as  $1.0 \times 10^{-3}$  Å, while  $\sigma(z_r)$ , since the  $z$  coordinates were obtained from the second projection, is  $1.2 \times 10^{-3}$  Å. The values for the oxygen atoms are correspondingly smaller. Bond lengths should thus be accurate to within 0.02 Å and bond angles to 1°.

The  $\alpha$ -methyltetronic acid molecule is planar (apart from H atoms), no C or O atom lying further than  $\pm 0.02$  Å, which is within the experimental error, from the plane

$$-0.7830x + 0.3701y + 0.5000z = -0.2023$$

$x$ ,  $y$  and  $z$  being measured in Angström units.

It is clear that the classical structure, Fig. 1(b), does not represent the molecule correctly. C<sub>1</sub>-C<sub>4</sub> and C<sub>2</sub>-O<sub>3</sub> are not pure double bonds and C<sub>4</sub>-O<sub>2</sub> and C<sub>1</sub>-C<sub>2</sub> are not pure single bonds. Resonance is probably taking place between the structures shown in Figs. 1(b), (c) and (d). This would explain the partial bond character of the bonds mentioned if one assumes that the percentage participation of the three structures is 56%, 28% and 16% respectively.

All intermolecular distances are greater than 3 Å with the exception of the distances from atoms O<sub>2</sub> and O<sub>3</sub> to adjacent molecules, where it is clear that the H bonding is taking place. Atom O<sub>3</sub> of the molecule at  $(x, y, z)$  is 2.60 Å from atom O<sub>2</sub>' of the molecule at  $(a+x, y, c+z)$  and atom O<sub>2</sub> of the molecule at  $(x, y, z)$

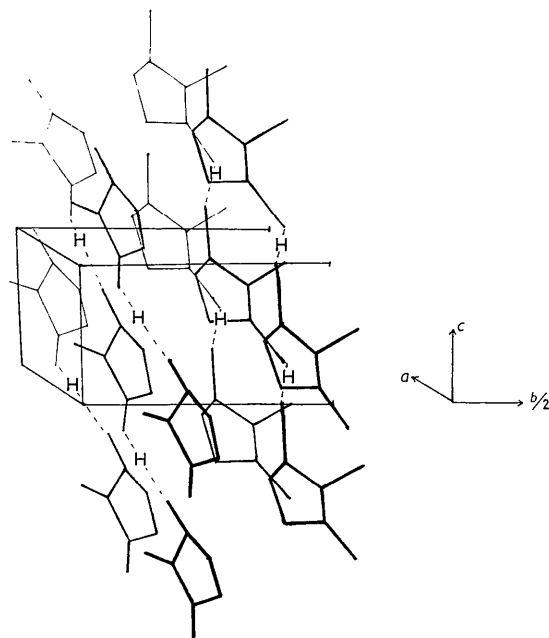


Fig. 4. A three-dimensional diagram of the crystal showing the hydrogen bonding.

is at a similar distance from atom  $O_3'$  of the molecule at  $(x-a, y, z-c)$ . The molecules are thus linked by the H bonding into long chains, the shortness of the O-H-O distance showing that the bonding is very strong as has already been indicated by the infra-red spectral data. The binding between chains is much weaker since no H-bonding is then involved. A diagrammatic picture of the bonding is shown in Fig. 4.

We wish to express our thanks to Prof. L. J. Haynes of the Department of Chemistry for suggesting this investigation of the tetronic acids to us, and to Dr J. R. Plimmer of the Natural Products Unit for

supplying the crystals. To both of them we are also indebted for most helpful discussions.

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## The Direct Determination of Molecular Structure: The Crystal Structure of the Bromodilactone from Jacobine at $-150^\circ\text{C}$

By A. McL. MATHIESON

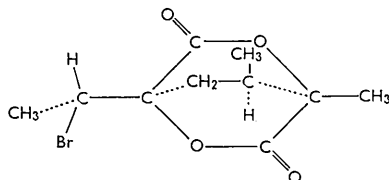
*Division of Chemical Physics, C.S.I.R.O. Chemical Research Laboratories, Melbourne, Australia*

AND J. C. TAYLOR

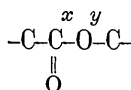
*Department of Chemistry, University of New South Wales, Sydney, Australia*

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The bromodilactone from jacobine,  $C_{10}H_{13}O_4Br$ , crystallizes in the monoclinic space group  $P2_1$  with cell dimensions,  $a = 8.70$ ,  $b = 6.34$ ,  $c = 10.44$  Å,  $\beta = 98.2^\circ$  at  $-150^\circ\text{C}$ . The structure was determined by use of the heavy atom to obtain the projected distributions  ${}_1\rho_0(x, z)$  and the generalized projection  ${}_1C_1(x, z)$ . With the available range of data, up to  $k = 4$ , least-squares refinement, with two different weighting schemes, one a function of  $|F|$  and the other of  $\sin \theta$ , has reduced the overall reliability index,  $R$ , to 0.12.



Bond lengths and angles in the absolute structure (above) are normal, the lactone group containing certain features of interest. Both groups



are planar within experimental error, the bond  $y$  being longer than bond  $x$  by approximately 0.1 Å.

The analysis, together with that of jacobine bromhydrin, provides clarification of the structural and configurational aspects of the pyrrolizidine alkaloids of the jacobine group.

### Introduction

From *Senecio jacobaea* L., several alkaloids have been isolated and studied (for earlier work, see Bradbury & Culvenor (1954) and Adams, Gianturco & van

Duuren (1956)). Three of these, jacobine, jaconine and jacoline, are closely related as epoxide-chlorhydrin-glycol. The alkaloids can all be hydrolysed into a pyrrolizidine base, retronecine, and a dibasic acid, indicating a di-ester structure. In 1958, the dibasic