THE CRYSTAL STRUCTURE OF FUSIDIC ACID METHYL ESTER 3-p-BROMOBENZOATE

A. COOPER

Chemical Crystallography Laboratory, Oxford

Abstract—Crystals of fusidic acid methyl ester 3-p-bromobenzoate are monoclinic, space group $P2_1$, with unit cell dimensions a = 10·310 Å, b = 7·935 Å, c = 22·06 Å, and β = 91°36'. The intensities of 3,314 reflections, observed with copper $K\alpha$ X radiation, were measured, partly photographically, partly on a linear diffractometer. The structure was solved from calculated three dimensional Patterson and electron density distributions and partly refined by least squares calculations. The atomic positions found establish the chemical structure of fusidic acid proposed by Godtfredsen and Arrigoni (compare preceding paper).

THE crystal structure of the 3-p-bromobenzoate of fusidic acid methyl ester has been determined by 3-dimensional X-ray methods. The results of this examination are shown in Figs. 1 and 2 and these confirm the stereochemistry of the steroid as proposed by Godtfredsen *et al.* (compare the previous article).

Three heavy-atom derivatives of fusidic acid were provided by Godtfredsen: the iodolactone, the dibromo derivative and the 3-p-bromobenzoate methyl ester. Of these, the last named was found to be the most suitable for X-ray analysis.

Crystal data

Iodolactone of fusidic acid. The crystals appeared to be losing solvent and new crystals were grown from an ether–n-hexane mixture. These were monoclinic plates on (001), elongated along *b*. From the X-ray photographs taken, the spacegroup is probably A2 with a = 16·4 × 2? Å, b = 14·7 Å, c = 16·4 Å, β = 110°. The observed density was 1·14 g cm^{-3} from which it is likely that there are two molecules in the asymmetric unit.

Dibromofusidic acid. The crystals were plates on (001) and were multiple, giving diffuse reflections which suggested that the crystals were losing solvent. Photographs at first sight indicated an orthorhombic, C-face centred cell with a = 22·75 Å, b = 22·03 Å, c = 13·3 Å and with 8 molecules in the unit-cell. However a closer examination of the photographs revealed that some reflections were doubled and it is likely that the crystals were twinned and that the true lattice is monoclinic.

Fusidic acid methyl ester 3-p-*bromobenzoate.* The crystals were plates with (001) dominating and elongated along *b*. They appeared to be quite stable but had a tendency to split after several day's exposure to X-rays. Cell dimensions were measured on a linear diffractometer: a = 10·310 Å, b = 7·935 Å, c = 22·066 Å, β = 91°36'. The spacegroup is $P2_1$ with two molecules in the unit-cell.

Collection of data and solution of the structure

X-ray data were collected in three batches. Those *b*-axis reflections with Bragg angle (2θ) less than 60° were collected on a linear diffractometer and the remainder
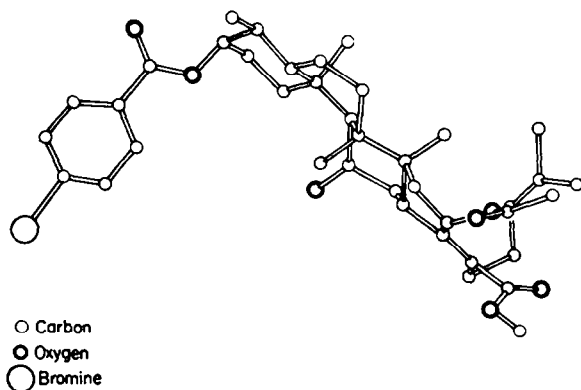
FIG. 1. Fusidic acid methyl ester 3-*p*-bromobenzoate.
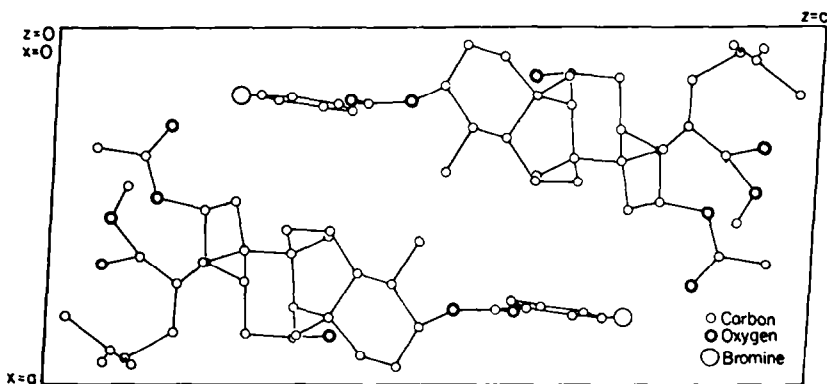Projection of one molecule onto (100).

FIG. 2. Fusidic acid methyl ester 3-*p*-bromobenzoate.
Projection down the *b*-axis of the unitcell.

of the *b*-axis data were recorded photographically on a Weissenberg goniometer, copper K_α radiation being used in both cases. The remainder of the reciprocal lattice available in the copper K_α sphere was collected by *a*-axis Weissenberg photography. In all, 3314 independent reflections were recorded. Lorentz and polarization corrections only, were applied to the observed intensities.

A 3-dimensional Patterson function in which the Fourier coefficients were modified to represent approximately, point atoms at rest, was computed and from the Harker section $(x\frac{1}{2}z)$, the (xz) co-ordinates of the bromine atom were determined. The bromine *y* co-ordinate was set at 0·25 so that the phases contributed by this atom to the general structure factor expression were 0 or π. Using these (xz) co-ordinates, a 2-dimensional Fourier projection down the *b*-axis, phased on the bromine atom alone, was computed. This showed the orientation of the molecule in the unitcell and a comparison of this projection with the 3-dimensional Patterson function allowed the assignment of (xyz) co-ordinates to the atoms of the bromobenzoate group. Three successive structure factor and Fourier calculations based initially on these co-ordinates brought forth a further 12 atoms then 3 atoms and finally the full molecule.

(These three cycles were performed using a programme written by J. S. Rollett which automatically scanned the calculated map and output positions corresponding to the centres of electron density—"FATAL".) After three cycles of isotropic least squares refinement, the individual layer-scalefactors were adjusted and a 3-dimensional Fourier difference calculation showed that apart from shifts of atomic positional and thermal parameters, the structure was essentially correct. Five further cycles of both isotropic and anisotropic least squares refinement gave R factors of 0·224 and 0·177 respectively. The refinement of atomic positional and thermal parameters is continuing.

DISCUSSION

Inherent in the preliminary stages of the structure solution is the introduction of a mirror plane through the bromine atom, parallel to the xz plane. This necessitates the unravelling of the true structure from its superposed mirror image, and consequently introduces a degree of uncertainty in the atomic co-ordinates, especially if for an atom at (xyz), there is another close to $(x \frac{1}{2} - y z)$. For this reason it is not intended to describe the exact geometry of the molecule until the refinement process has been satisfactorily concluded. At the present stage of refinement, the bond lengths of the steroid and its side chains are all within 0·1 Å of their expected values. Rings A, C and D in the steroid ring system appear to have normal chair-shaped stereochemistry and ring B is boat-shaped and appears to be severely strained.