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THE STRUCTURE OF *trans*-*O*-β-D-GLUCOPYRANOSYL METHYL ACETOACETATE, AND THE INTERPRETATION OF ITS OPTICAL ROTATIONS

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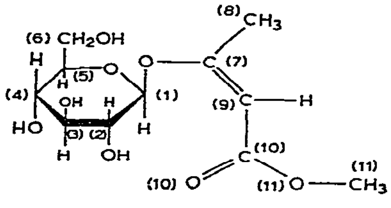
ABSTRACT

A crystal-structure determination of *trans*-*O*-β-D-glucopyranosyl methyl acetoacetate, $C_{11}H_{18}O_8$, m.p. 186°, confirmed the *trans* orientation deduced previously from physical properties. The conformation of the D-glucopyranosyl group is $^4C_1$, although the most symmetrical chair-conformer is actually ^3C_O. The glycosidic link is −*sc*, with a C–O anomeric bond of 1.428 Å (142.8 pm), *i.e.* longer than is normal in methyl β-glycopyranosides. All of the hydrogen bonding is intermolecular. The unusual optical rotations in solution can be interpreted in terms of rotameric populations that are derived from the solid-state conformers and are stabilized by intramolecular or solvent hydrogen-bonding.

INTRODUCTION

trans-*O*-β-D-Glucopyranosyl methyl acetoacetate (**1**) is one of a series of *cis,trans* enolic β-D-glycosides of methyl acetoacetate synthesized and studied by Ballou and Link[1], some of which have unusual optical properties in solution. Compound **1** in aqueous solution, for example, shows both an abnormally large change in $[\alpha]_D$ of 16° between temperatures of 3 and 73° and a reversal of $[M]_D$ from +12,100 for a 2% solution in water to −18,900 for a 0.3% solution in 1,4-dioxane[1]. The



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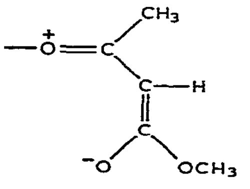
crystal-structure determination of **1** was undertaken in order to provide precise molecular dimensions as a basis for interpreting these optical rotation properties in terms of changes in conformational populations caused by steric hindrance or intramolecular association.

DESCRIPTION OF THE STRUCTURE

The atomic notations of the molecule and its structure, *i.e.*, bond lengths and valence and torsion angles, are given in Figs. 1 and 2 as they occur in the crystal structure. Although the D-glucopyranosyl group has the $^4C_1$ conformation, the ring torsion-angles show that the most symmetrical chair is ^3C_O, with C-3 and O-5 displaced by +0.62 Å (+62 pm) and −0.68 Å (−68 pm), respectively, from the C-1,C-2,C-4,C-5 reference plane. The primary alcohol side-chain is +*sc*, and the glycosidic linkage is −*sc*, as is usual in β-D-glycopyranoside crystal structures[3]. The bond lengths in the D-glucosyl group are normal, with the exception of C-1–O-5, which is 1.398 Å (139.8 pm). The C-1–O-1 (anomeric) bond has a normal, single-bond length, 1.428 Å (142.8 pm) as compared with a mean value of 1.383 Å (138.3 pm) in three methyl β-glycopyranosides[3].

The methyl acetoacetate group has the *trans*, planar orientation, as deduced by Ballou and Link[1] and as shown in formula **1**, but the group is not exactly planar, as shown by the torsion angles given in Fig. 1. The largest deviations from planarity are 20° about O-1–C-7, and 3° about C-9–C-10. The 20° twist appears to be related to the overcrowding of the C-8 methyl group, mainly with the ring-oxygen atom (O-5) of the D-glucosyl group, as shown by the nonbonding, intramolecular separations given in Table I.

The C–O and C–C bond-lengths in the acetoacetate group are intermediate between those usual for single and double bonds (see Fig. 1), reflecting π-bond conjugation, as represented by contributions to **1** of resonance forms, such as **2** and **3**. Of particular interest is the value of 1.369 Å (136.9 pm) for O-1–C-7, corresponding to about 20 percent of double-bond character. Contribution **2** is also consistent with the normal, single-bond length observed for the β-D-glycosidic bond, C-1–O-1. It implies competition for the delocalized, 2p-type, lone-pair electrons on O-1, thereby lessening the π-bond character of C-1–O-1, which was postulated by Jeffrey and coworkers[3], Romers *et al.*[4], and others, to account for the anomeric bond-shortening



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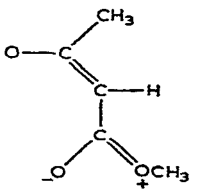

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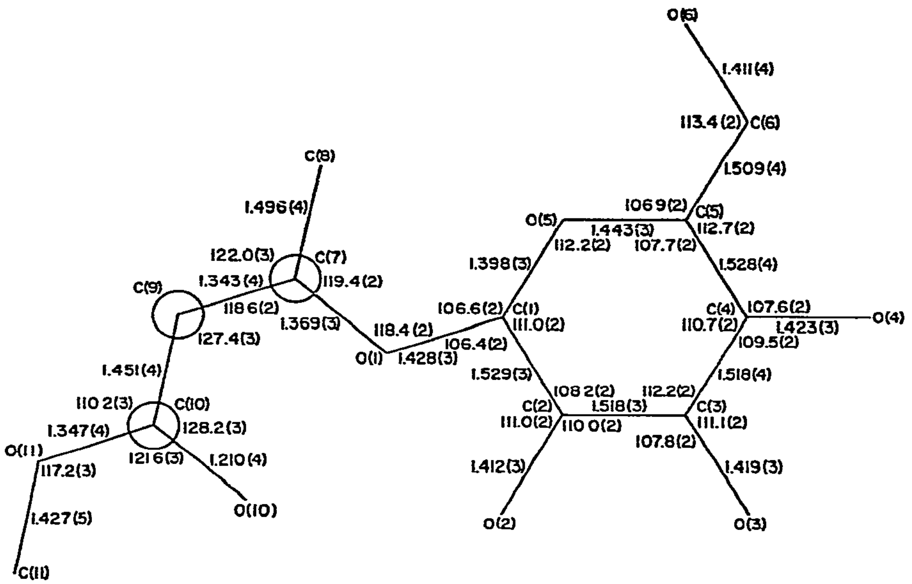

Fig. 1. Bond lengths and valence angles in *trans*-*O*-β-D-glucopyranosyl methyl acetoacetate. Numbers in parentheses are estimated standard deviations.

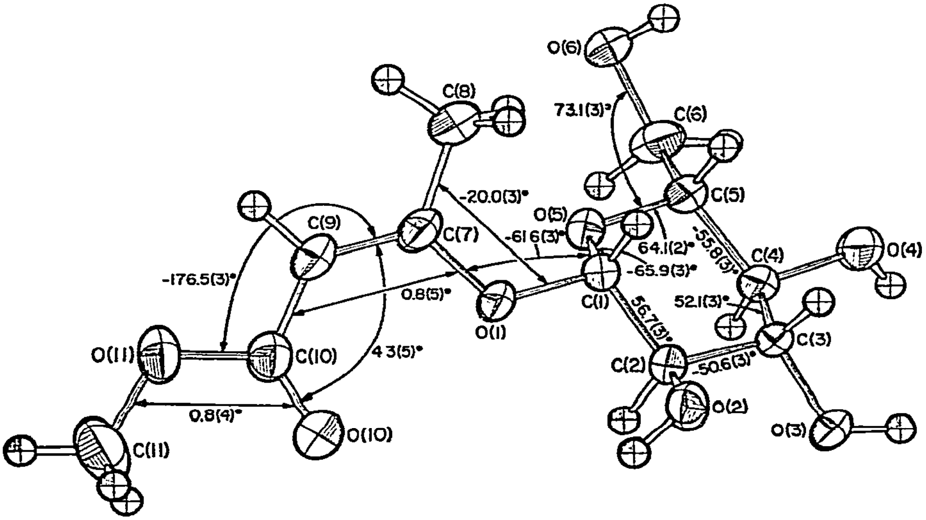

Fig. 2. Torsion angles and atomic thermal ellipsoids (at 50 percent probability level[2]) in the crystal structure of *trans*-*O*-β-D-glucopyranosyl methyl acetoacetate, with estimated standard deviations in parentheses.

TABLE I

SHORT NONBONDING AND HYDROGEN-BONDING DISTANCES IN *trans*-O-β-D-GLUCOPYRANOSYL METHYL ACETOACETATE[a]

Atoms involved			*Distances (D) in Å [picometers]*			*Angle (jik)*[b] *in degrees*
i	*j*	*k*	*D(ij)*	*D(ik)*	*D(jk)*	
Nonbonding, intramolecular distances involving the C-8-containing methyl group						
H-2(C-8)	O-5		2.22(3) [222(3)]			
H-1(C-8)	O-1		2.59(3) [259(3)]			
H-1(C-8)	H(C-1)		2.31(3) [231(3)]			
H-1(C-8)	H-2(C-6)		2.37(3) [237(3)]			
C-8	C-1		2.82(3) [282(3)]			
Intermolecular hydrogen-bonding distances and angles						
O-2	H–O-2	O-6	0.91(3) [91(3)]	2.706(3) [270.6(3)]	1.85(3) [185(3)]	15(1)
O-3	H–O-3	O-2	0.82(3) [82(3)]	2.797(3) [279.7(3)]	1.98(3) [198(3)]	5(2)
O-4	H–O-4	O-3	0.79(3) [79(3)]	2.840(3) [284.0(3)]	2.12(3) [212(3)]	21(2)
O-6	H–O-6	O-10	0.79(3) [79(3)]	2.733(3) [273.3(3)]	1.97(3) [197(3)]	12(2)

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[a] Numbers in parentheses are estimated standard deviations. [b] In X-ray structure determinations, the hydrogen atom attached to an oxygen atom generally appears closer to the oxygen atom than the nuclear separations, and O–H distances of 0.8 Å (80 pm), rather than 1.0 Å (100 pm), are often observed. For this reason, the deviation of the O···O–H angle from 0° is a better measure of the linearity of the hydrogen bond than the deviation of O···H–O from 180°.

effect widespread in glycopyranoses[5]. The shortening of the O-5–C-1 bond-length in the pyranoid ring to 1.398 Å (139.8 pm) suggests that the electron deficiency on O-1, as indicated by the formal charge in **2**, is further depopulating the C-1 2p orbital, so that the π-bonding normally associated with the anomeric, C-1–O-1 bond is transferred to the adjacent ring-bond (O-5–C-1).

In the crystal structure, the hydrogen bonding is all intermolecular, as shown in Table I and Fig. 3. It involves all of the hydroxyl groups and the carbonyl oxygen atom, but, interestingly, excludes the glycosidic, ring, and acetate oxygen atoms, O-1, O-5, and O-11. The hydrogen bonds constitute a finite chain originating in O-4–H and terminating in the carbonyl oxygen atom O-10, *i.e.*, the chain is O-4–H→O-3–H→O-2→H–O-6→H–O-10. These chains pack the molecules as shown in Fig. 3.

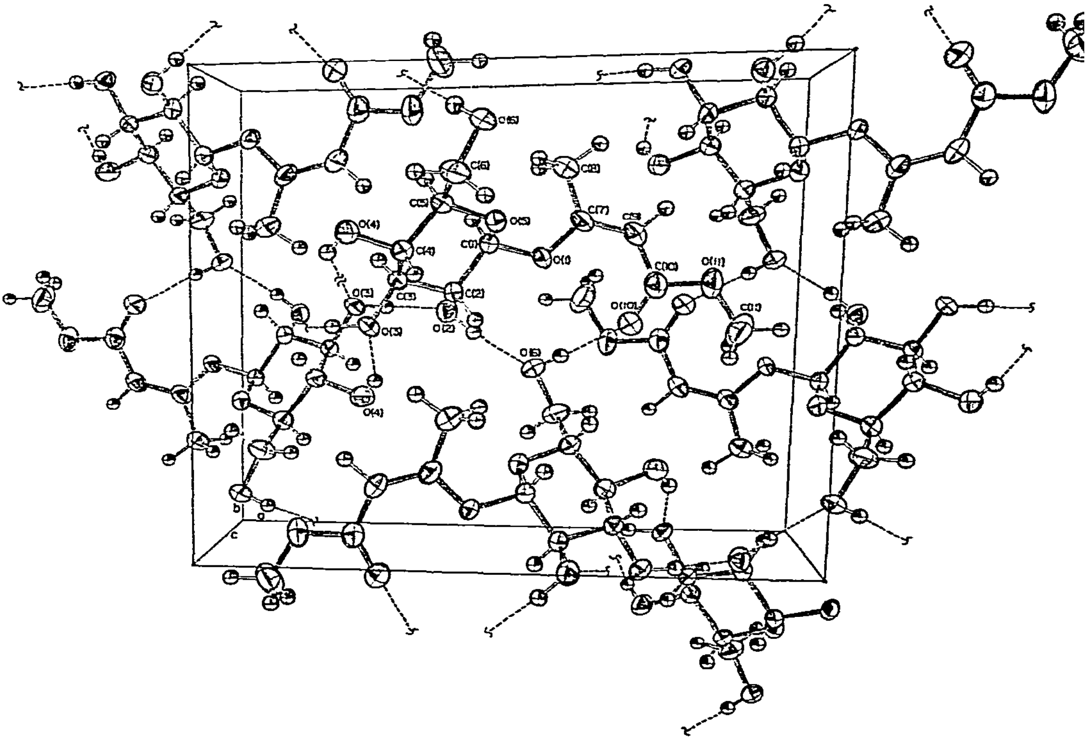


Fig. 3. Crystal structure of *trans*-*O*-β-D-glucopyranosyl methyl acetoacetate. The dotted lines are hydrogen bonds.

DISCUSSION OF THE OPTICAL PROPERTIES

What information does this structure determination provide that is relevant to the "anomalous" optical properties in solution? As shown by the intramolecular, nonbonding distances given in Table I, the almost planar disposition about O-1–C-7 due to the π-bonding implied in **2** leads to some steric interference between the

C-8-containing methyl group of the aglycon and the ring-oxygen atom; this is illustrated more quantitatively in the Ramachandran conformational map shown in Fig. 4, which contours the Van der Waals contact regions at the 90 and 80 percent levels against the two torsion angles, O-5–C-1–O-1–C-7 (θ) and C-1–O-1–C-7–C-9 (ψ), as variables. This map shows that the conformation having $\theta = 62°$, $\psi = 161°$ (observed in the crystal) is in a narrow region at the 80 percent level that lies between two broad regions of less, or no, steric interference at $\psi \sim \pm 100°$. Conformations in these favored regions would imply almost complete loss of the π-bond energy across C-1–O-7 from the resonance contribution **2**.

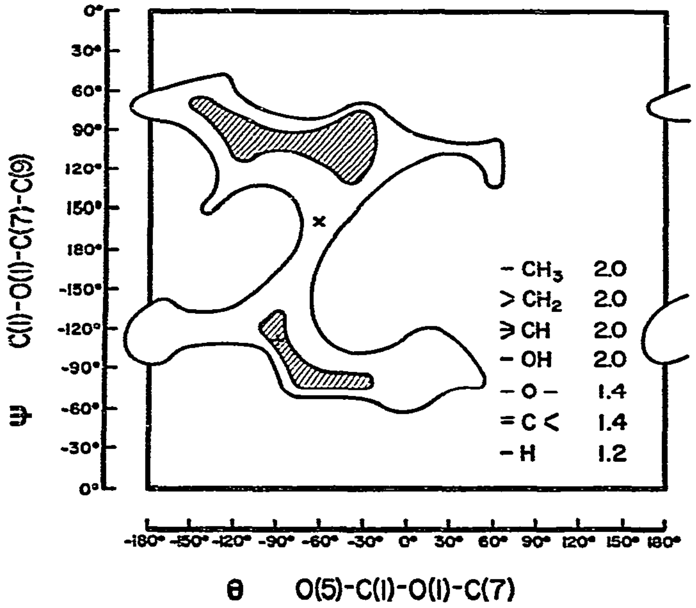
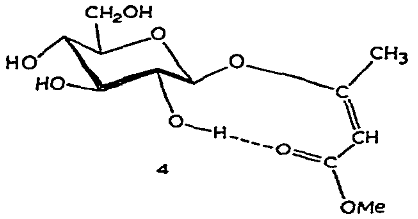


Fig. 4. Ramachandran conformational map for rotation about the linkage bonds in *trans*-*O*-β-D-glucopyranosyl methyl acetoacetate. The cross-hatched region corresponds to Van der Waals contacts of greater than 90 percent of the sum of the radii. The outer contour is at 80 percent of the sum of the radii. The Van der Waals radii used are given in the lower right-hand corner. × is for the angles of the observed conformer in the crystal structure, and + is for the angles corresponding to the intramolecular hydrogen-bonded conformer, **4**, discussed in the text.

If it is assumed that the unusual difference in optical rotation with solvent involves neither $\alpha \rightarrow \beta$ anomerization nor *cis-trans* isomerization, the only explanation remaining is that, in passing from the crystalline solid into solution, the molecules move into one or the other of the two favored conformational regions at $\psi \sim \pm 100°$. This would require that the solvation effects plus the release of the steric interactions, indicated in Table I, overcome the loss of π-bonding energy across O-1–C-7.

Ballou and Link[1] suggested that two intramolecular, hydrogen-bonded conformations, **4** and **5**, play a role in affording the optical rotations observed, and our results support this view. In *cis*-*O*-β-D-glucopyranosyl methyl acetoacetate (**6**),



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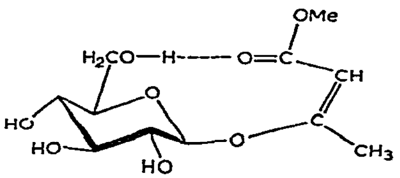

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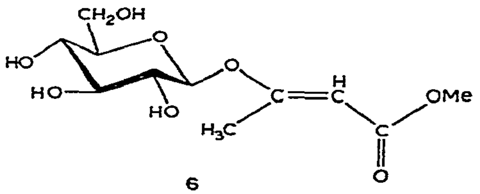

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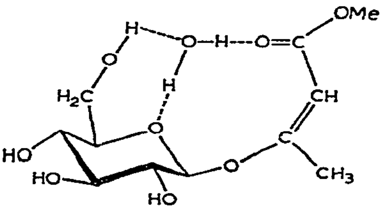

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which has the usual, negative, β-D-glucosidic rotation in both solvents, no such intramolecular interactions are possible. The CH_3 group containing C-8 is interposed between the D-glucosidic 2-hydroxyl group and the carbonyl oxygen atom (O-10) in all possible dispositions of the linkage bonds and would, therefore, prevent any intramolecular O–H····O bond-formation. In the *trans* structure, conformer **4**, having good linear geometry for the intramolecular hydrogen bond O-2–H···O-11 at 2.69 Å (269 pm), occurs with $\theta = -90°$, $\psi = -110°$. A rotameric population in the permitted regions of θ −60 to −110°, and ψ −80 to −140°, with such intramolecular hydrogen-bonding would, therefore, be favored in a non-hydrolytic solvent such as 1,4-dioxane, and would thus correspond to the negative optical rotation (in solution) usual for a β-D-glycoside.

The other intramolecular hydrogen-bonded conformation (**5**) cannot be formed within the other region permitted. At $\psi = +100°$, $\theta = -40$ to $-120°$, the separation between O-6 and O-11 is greater than 5 Å (500 pm). To obtain the hydrogen bonding approach indicated in **5**, rotation about the C-5–C-6 bond is necessary, so that the torsion angle O-5–C-5–C-6–O-6 is close to 0°. This is a sterically unfavorable orientation for a D-glucosidic primary alcohol group, because it brings the alcoholic oxygen atom too close to the ring-oxygen atom. However, hydrogen bonding by one or more water molecules, such as is shown in **7**, is geometrically compatible with all of the conformations within the favored region at $\psi = 100 \pm 15°$. It is, therefore, reasonable to postulate that, in aqueous solution, the rotameric population lies primarily in this region of $\theta = -30$ to $-120°$, and $\psi = +90$ to $+110°$, and this corresponds to the "abnormal" positive rotation for the β-D-glucoside. Furthermore, it is the effect of thermal motion *versus* the optimal arrangement for water hydrogen-bonding that could give rise to the unusually large temperature-dependence of optical rotation in aqueous solution reported by Ballou and Link[1].

EXPERIMENTAL

Crystals of *trans-O-β*-D-glucopyranosyl methyl acetoacetate (**1**) were provided by Professor C. E. Ballou, Department of Biochemistry, University of California at Berkeley. Unit-cell dimensions, space group, and intensity determinations were made on a Nonius CAD-4 diffractometer by $\theta-2\theta$ scan with graphite-monochromated CuKα radiation. A crystal of dimensions 0.4×0.2×0.2 mm gave 1,586 intensity measurements, of which 1,449 were greater than 1σ. The intensity data were reduced

TABLE II

FINAL ATOMIC COORDINATES FOR *trans-O-β*-D-GLUCOPYRANOSYL METHYL ACETOACETATE[a]

Atom	*X/A*	*Y/B*	*Z/C*
O-1	4484(1)	1223(1)	9430(3)
O-2	6066(1)	97(1)	10454(3)
O-3	7256(1)	−157(1)	7282(3)
O-4	7503(1)	1757(2)	5070(4)
O-5	5226(1)	1973(1)	6927(3)
O-6	5409(1)	3868(1)	4531(4)
O-10	3017(1)	−157(2)	9539(4)
O-11	1709(1)	690(2)	9686(4)
C-1	5352(2)	1525(2)	8753(4)
C-2	5906(2)	528(2)	8602(4)
C-3	6791(1)	789(2)	7622(4)
C-4	6658(2)	1390(2)	5751(4)
C-5	6057(2)	2336(2)	6089(4)
C-6	5818(2)	2891(2)	4230(5)
C-7	3848(2)	1981(2)	9695(5)
C-8	4139(2)	3088(2)	9915(6)
C-9	2980(2)	1700(2)	9782(5)
C-10	2614(2)	657(2)	9649(5)
C-11	1244(2)	−279(3)	9615(7)
H–O-2	562(2)	−35(2)	1079(5)
H–O-3	777(2)	−14(2)	685(5)
H–O-4	775(2)	140(2)	431(5)
H–O-6	581(2)	418(2)	500(5)
H–C-1	564(2)	199(2)	958(4)
H–C-2	554(2)	−5(2)	779(4)
H–C-3	716(2)	122(2)	859(4)
H–C-4	641(2)	93(2)	479(5)
H–C-5	637(2)	280(3)	694(4)
H–C-6	639(2)	288(3)	335(5)
H′–C-6	535(2)	242(2)	359(4)
H–C–8	457(2)	308(3)	1087(5)
H′–C-8	456(2)	326(2)	853(5)
H″–C-8	358(2)	357(2)	981(5)
H–C-9	249(2)	223(2)	1005(5)
H–C-11	58(2)	−29(3)	962(6)
H′–C-11	136(2)	−58(3)	1064(6)
H″–C-11	147(2)	−79(3)	838(6)

[a] Non-hydrogen coordinates $\times 10^4$; hydrogen coordinates $\times 10^3$. Estimated standard deviations are given in parentheses.

TABLE III

CRYSTAL DATA FOR *trans-O-β*-D-GLUCOPYRANOSYL METHYL ACETOACETATE

$C_{11}H_{18}O_8$, M.W. 278.27 daltons, m.p. 186°
Orthorhombic, Space Group $P2_12_12_1$
Cell dimensions a = 14.877(4) Å [1487.7 pm]
b = 12.866(4) Å [1286.6 pm]
c = 6.896(2) Å [689.6 pm]
Z = 4
D_x = 1.400 $g.cm^{-3}$
D_m = 1.436 $g.cm^{-3}$

to structure amplitudes and E-values, with no absorption corrections, by using programs by Shiono[6]. The structure was solved by direct methods by using a PDP-10 version of MULTAN[7]. Application of 196 amplitudes with $E \gtrsim 1.45$ gave five possible solutions. The five solutions were further refined by using the Hall tangent refinement program[8], to give an E-map which showed reasonable positions for the 19 carbon and oxygen atoms within the 22 highest peaks. Isotropic refinement by means of block-diagonal least-squares[9] gave an R = 0.076. Full matrix anisotropic refinement on $w_i(|F_o|-|F_c|)^2$, where $w_i = 1/\sigma F^2$, gave R = 0.052, with isotropic hydrogen thermal parameters*.

The final atomic coordinates are given in Table II. The atomic thermal parameters and the observed and calculated structure-factors are available**. The crystal data are given in Table III.

ACKNOWLEDGMENTS

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*$R = [\Sigma w(|F_o|-|F_c|)^2/\Sigma w|F_o|^2]^{1/2}$.

**Requests for these data should be sent to the Department of Crystallography, University of Pittsburgh, Pittsburgh, Pa. 15260, U. S. A.