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XANTHONES OF THE GENTIANACEAE—III

THE CRYSTAL AND MOLECULAR STRUCTURE OF 2-HYDROXY-1,3,4,7-TETRAMETHOXYXANTHONE[1,2]

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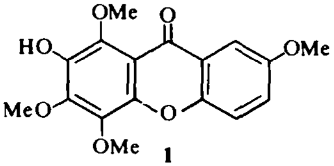
Abstract—One of the xanthones isolated from *Frasera albicaulis* Dougl. *ex* Griesb. is shown to have the structure 2-hydroxy-1,3,4,7-tetramethoxyxanthone (1) by X-ray crystallographic analysis using the symbolic addition method.

Among the products isolated from the roots of *Frasera albicaulis* Dougl. *ex* Griesb. was a hydroxytetramethoxyxanthone (xanthone J[1]) which is unusual in lacking an OH group at C-1. Methylation yielded 1,2,3,4,7-pentamethoxyxanthone, defining the oxygenation pattern but leaving the location of the OH group uncertain. To determine this unambiguously and to obtain further information about this heavily substituted aromatic system, we undertook an X-ray structural investigation of the compound.

DISCUSSION

Solution of the structure of the natural product by direct phase determination showed that the crystal consists of molecules of 2-hydroxy-1,3,4,7-tetramethoxyxanthone (1) (chemical numbering; see Fig. 1 for that used in the X-ray analysis) linked in chains by intermolecular H-bonds between the OH and CO groups. This structure is entirely consistent with the chemical and physical properties of the molecule.



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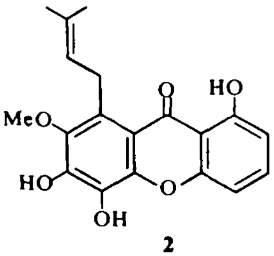

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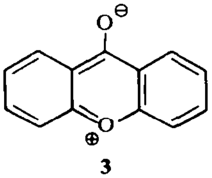

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The bond lengths and angles found from the atomic parameters of Table 3 are listed in Table 1. These are generally normal and show similarities to those reported for celebixanthone (2), another xanthone with one ring entirely substituted.[3] One

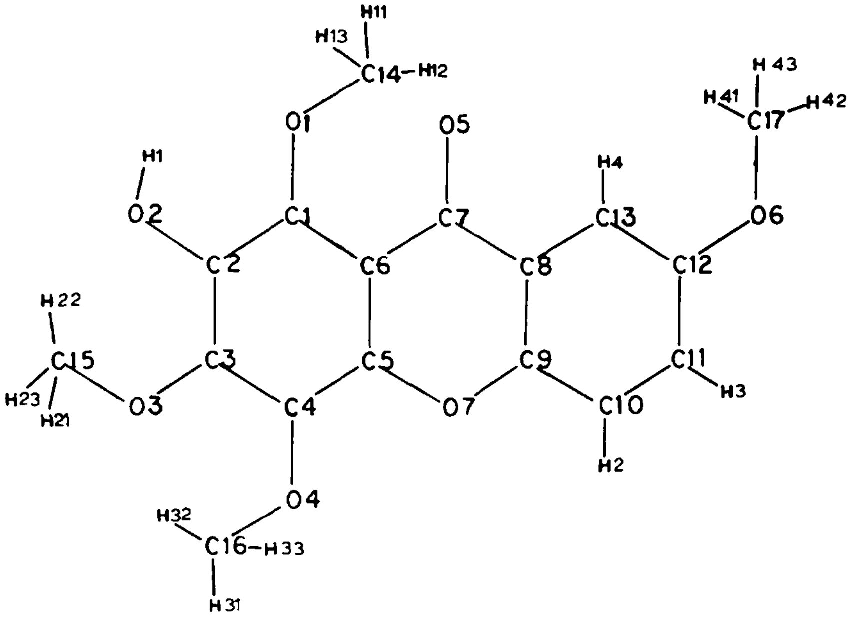

Fig. 1 Crystallographic numbering. The molecular conformation is approximately as seen normal to the ring system.

Table 1. Bond lengths and bond angles

C1	C2	1·389 (2) Å	C2	C1	C6	120·8 (2)°
C1	C6	1·417 (2)	C2	C1	O1	115·3 (1)
C2	C3	1·401 (3)	C6	C1	O1	123·8(1)
C3	C4	1·386 (3)	C1	C2	C3	120·3 (2)
C4	C5	1·404 (2)	C1	C2	O2	122·3 (2)
C5	C6	1·399 (2)	C3	C2	O2	117·4 (1)
C8	C13	1·399 (2)	C2	C3	C4	120·3 (2)
C8	C9	1·390 (3)	C2	C3	O3	121·8 (2)
C9	C10	1·395 (2)	C4	C3	O3	117·7 (2)
C10	C11	1·369 (3)	C3	C4	C5	118·8 (2)
C11	C12	1·403 (3)	O4	C4	C3	121·5 (1)
C12	C13	1·380 (3)	O4	C4	C5	119·6 (2)
C6	C7	1·470 (2)	C4	C5	C6	122·4 (1)
C7	C8	1·470 (2)	C4	C5	O7	113·8 (2)
C5	O7	1·369 (2)	C6	C5	O7	123·8 (1)
C9	O7	1·363 (2)	C5	C6	C1	117·3 (1)
C1	O1	1·372 (2)	C1	C6	C7	124·2 (1)
C2	O2	1·360 (2)	C5	C6	C7	118·5 (1)
C3	O3	1·367 (2)	C6	C7	O5	124·2 (1)
C4	O4	1·368 (2)	C6	C7	C8	115·3 (1)
C12	O6	1·370 (3)	C8	C7	O5	120·5 (1)
C7	O5	1·226 (2)	C7	C8	C9	120·1 (1)
O1	C14	1·436 (2)	C9	C8	C13	120·2 (2)
O3	C15	1·431 (3)	C7	C8	C13	119·6 (2)

TABLE 1—*continued*

O4	C16	1·420(3)	C8	C9	O7	122·6(1)
O6	C17	1·427(4)	C8	C9	C10	120·3(2)
			O7	C9	C10	117·0(2)
C14	H11	0·982(32)	C9	C10	C11	119·8(2)
C14	H12	0·903(30)	C9	C10	H2	117·1(6)
C14	H13	0·941(43)	C11	C10	H2	123·0(16)
C15	H21	1·020(35)	C10	C11	H3	118·3(18)
C15	H22	1·122(51)	C10	C11	C12	120·4(2)
C15	H23	1·018(42)	C12	C11	H3	121·3(18)
C16	H31	1·081(39)	C13	C12	C11	120·0(2)
C16	H32	0·983(37)	C13	C12	O6	125·0(2)
C16	H33	1·113(66)	C11	C12	O6	114·9(2)
C17	H41	1·059(30)	C8	C13	H4	117·4(14)
C17	H42	0·987(29)	C8	C13	C12	119·8(2)
C17	H43	1·112(33)	C12	C13	H4	122·9(14)
C10	H2	0·942(29)	O1	C14	H11	98·9(17)
C11	H3	0·964(30)	O1	C14	H12	114·2(20)
C13	H4	0·932(26)	O1	C14	H13	117·5(22)
O2	H1	0·867(36)	O3	C15	H21	103·0(17)
			O3	C15	H22	107·1(22)
			O3	C15	H23	109·5(21)
			O4	C16	H31	107·2(18)
			O4	C16	H32	115·4(24)
			O4	C16	H33	96·0(34)
			O6	C17	H41	117·5(16)
			O6	C17	H42	105·0(19)
			O6	C17	H43	115·4(17)
			C14	O1	C1	116·5(1)
			C2	O2	H1	109·7(21)
			C3	O3	C15	116·2(2)
			C4	O4	C16	114·8(2)
			C12	O6	C17	116·4(2)
			C5	O7	C9	118·9(1)

significant feature is the repulsion between O1 and O5. This is shown by the opening of the angles O1—C1—C6 and O5—C7—C6 from their nominal value of 120° and serves to increase the O1—O5 distance to 2·84 Å, as compared with 2·55 Å for C1—C7. This distortion appears to be transmitted, with diminishing effect, around the ring, since the substituents at C2, C3, and C4 are all bent away from C1.

The precision of the bond lengths as calculated from the atomic standard deviations is remarkably high, perhaps optimistically so in view of the partial block character of the least squares refinement. Comparison of the four Ar—OMe bonds, however, provides an esd of 0·002 Å, while the four O—Me bonds give 0·007. The latter figure is certainly too high since the observed bond lengths include varying contributions from shortening caused by rotary oscillation (note that the order of O—Me bond lengths is the inverse of the order of the average B_{ii} of the Me carbons). Thus the best estimate of the standard deviations probably lies between these values and 0·004 would appear a reasonably conservative value.

On this basis the apparent shortening of the αβ bonds of the xanthone ring (C1–C2, C3–C4, C10–C11, and C12–C13), which are between 0·012 and 0·037 Å shorter than the adjacent C—C bonds, is clearly significant. This shortening implies increased bond order and bond localization at these positions and indicates that the aromatic system tends toward the canonical form shown as **1**. A similar effect should appear at C5–C6 and C8–C9 but, although suggested by the data, is much less marked. This difference may reflect additional contributions from the zwitterionic forms **3**, which would serve to lengthen these bonds.

Least squares planes calculated for the two benzene rings are given in Table 2, together with the distances of some neighbouring atoms from them. The deviations of the C atoms forming the rings from their L. S. planes, compared to the estimated standard deviations in the positional parameters, suggest that the rings are not rigorously planar although they approach planarity closely. This is confirmed by a χ^2 test.[4] As might be expected, the average deviation from planarity in the less substituted ring is smaller than that of the other.

TABLE 2. DEVIATIONS (IN Å) FROM LEAST SQUARES PLANES

	A	B	C
C1	**−0·011**		**−0·022**
C2	**0·018**		**−0·081**
C3	**−0·008**		**−0·011**
C4	**−0·009**		**0·064**
C5	**0·016**		**0·067**
C6	**−0·006**		**0·048**
C7	−0·045	−0·107	**0·123**
C8		**−0·013**	**0·008**
C9		**0·014**	**0·039**
C10		**−0·002**	**0·035**
C11		**−0·010**	**−0·033**
C12		**0·012**	**−0·113**
C13		**0·000**	**−0·082**
C14	1·078		
C15	−1·002		
C16	−1·221		
C17		0·137	
O1	−0·099		**0·018**
O2	0·079		**−0·213**
O3	0·059		**−0·105**
O4	0·037		**0·061**
O5	−0·220	−0·301	**0·267**
O6		0·006	**−0·181**
O7	0·046	0·019	0·110

Bold face numbers represent atoms used in calculating the plane.

The planes A and B intersect at an angle of 174·9°, causing the molecule to be slightly butterfly-shaped, although less so than is implied by models. The considerable deviations of O5 from A and B show that the CO group is twisted somewhat out of the molecular plane, and altho O5 and O7 are on opposite sides of these planes the heterocyclic ring assumes a very flattened boat form. The deviations from a plane (C) calculated through the entire aromatic system show that O5 appears, as would be expected, on the side opposite to that toward which the rings are bent.

The OMe groups attached to plane A are rotated so that C14, C15, and C16 are well out of the aromatic planes. The rotation about C1–O1 is 72·0°, that around C3–O3 is 58·1°, and that around C4–O4 is 83·0°. These results are in accord with those for celebixanthone, in which the OMe group, similarly hindered by adjacent alkyl and OH groups, is rotated by 72·8° from the L. S. plane of the phenyl ring. In contrast, however, C17 is only slightly out of plane B and rotation about C12–O6 is only 5·1°. This preferred, nearly coplanar conformation that allows maximum overlap of the unshared oxygen electrons with the aromatic π cloud is assumed despite the close approach of C17 and C13 (2·80 Å) that it produces. The opening of the C13–C12–O6 bond angle presumably reflects an attempt to relieve the resulting strain.

In the same way, H1 lies close (0·18 Å) to plane A and the rotation of the OH group about C2–O2 is only 6·6°. It is possible that there is some H-bond interaction between H1 and O1 (H1···O1 2·27 Å, O2—H1···O1 112°), but it is unlikely that this is as important as the advantages of coplanarity in determining the OH orientation.

An H-bond clearly exists, however, between O2 and O5′ of a molecule related by the two-fold screw plus unit translation along a $(1 - x, y + \frac{1}{2}, \frac{1}{2} - z)$. The O2···O5′ distance is 2·73 Å, the H1···O5′ distance 1·98 Å, and the O2—H1···O5′ angle 144°. This bond serves to link the molecules into chains running along the b axis, the chains consisting of alternate molecules in the planes x and $1 - x$. To show this chain, Fig. 2 includes the CO group of $1 - x$, $y + \frac{1}{2}$, $\frac{1}{2} - z$ and the OH of $1 - x$, $y - \frac{1}{2}$,

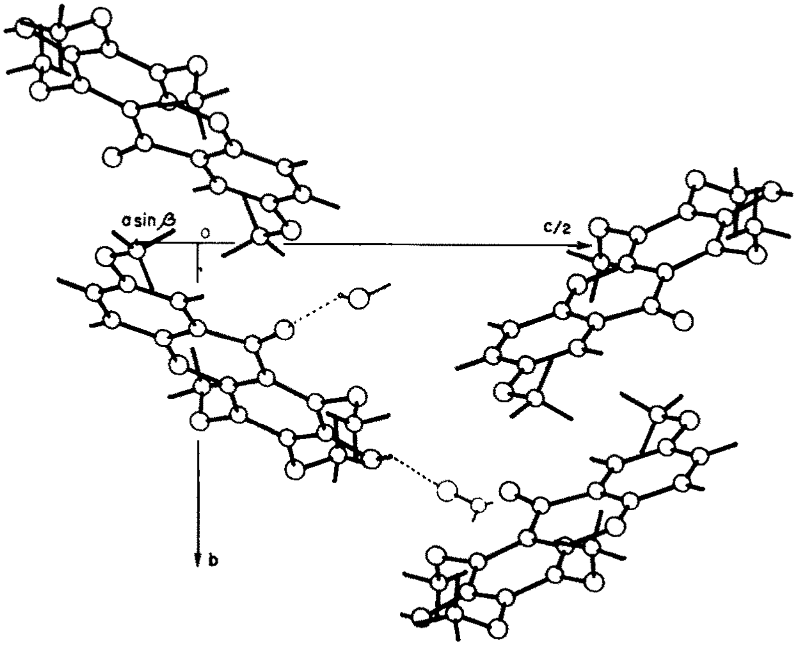

FIG. 2 Four molecules in projection along a^*. Dotted lines show the hydrogen bond system from the molecule at x, y, z to those at $1 - x$.

TABLE 3

Positional parameters (× 10^4) and thermal parameters (× 10^2)

Atom	x/a	y/b	z/c	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C1	6404(2)	4941(2)	1978(1)	238(6)	274(6)	224(6)	018(5)	066(5)	−002(6)
C2	7596(2)	5901(2)	2196(1)	260(6)	321(7)	256(6)	006(5)	044(5)	−045(7)
C3	8655(2)	6069(2)	1799(1)	248(6)	296(7)	306(7)	−022(5)	044(5)	−026(7)
C4	8495(2)	5333(2)	1175(1)	259(6)	290(7)	264(6)	004(5)	084(5)	025(6)
C5	7258(2)	4421(2)	0949(1)	286(6)	258(6)	217(6)	022(5)	064(5)	005(6)
C6	6203(2)	4178(2)	1342(1)	260(6)	240(6)	210(6)	014(5)	048(4)	016(6)
C7	4978(2)	3135(2)	1076(1)	287(6)	255(6)	233(6)	000(5)	044(5)	003(6)
C8	4882(2)	2646(2)	0373(1)	325(7)	255(6)	223(6)	022(5)	018(5)	017(6)
C9	6005(2)	2960(2)	0035(1)	359(7)	249(6)	219(6)	026(5)	045(5)	021(6)
C10	5965(2)	2386(2)	−0615(1)	525(10)	300(7)	223(6)	018(7)	084(6)	−006(7)
C11	4798(3)	1545(3)	−0928(1)	586(11)	328(8)	240(7)	035(8)	003(7)	−014(7)
C12	3636(2)	1274(2)	−0601(1)	462(7)	278(7)	283(7)	011(6)	−065(6)	−007(7)
C13	3683(2)	1810(2)	0048(1)	360(7)	284(7)	296(7)	−007(6)	−020(6)	−009(7)
C14	4169(2)	5610(3)	2290(1)	277(7)	411(8)	347(8)	044(6)	090(6)	−009(8)
C15	0714(2)	6586(3)	2599(1)	301(8)	573(12)	500(10)	−036(8)	−022(7)	−106(11)
C16	0655(2)	4458(4)	0884(1)	376(9)	745(15)	474(11)	136(10)	207(8)	1125(13)
C17	1288(3)	0242(3)	−0669(1)	541(12)	491(12)	526(12)	−152(10)	−106(10)	−036(12)
O1	5498(1)	4746(2)	2431(1)	268(5)	371(5)	242(4)	039(4)	098(4)	028(5)
O2	7788(1)	6715(2)	2790(1)	322(5)	568(8)	348(6)	−084(5)	094(4)	−222(7)
O3	9822(1)	7042(2)	1989(1)	313(5)	443(7)	420(6)	−116(5)	049(5)	−048(7)
O4	9476(1)	5550(2)	0763(1)	326(5)	415(6)	346(5)	−007(5)	159(4)	056(6)
O5	4077(1)	2680(2)	1402(1)	388(6)	481(7)	316(5)	−166(5)	118(4)	−047(6)
O6	2531(2)	0426(2)	−0966(1)	569(8)	443(7)	394(6)	−099(6)	−104(6)	−101(7)
O7	7197(1)	3784(2)	0320(1)	362(5)	328(5)	213(4)	−027(4)	091(4)	−018(5)

Positional parameters ($\times 10^3$) and isotropic thermal parameter

H1	703(3)	663(4)	297(2)	7·1(8)
H2	678(3)	255(3)	−081(1)	4·8(6)
H3	480(3)	115(4)	−137(1)	5·5(6)
H4	294(2)	165(3)	028(1)	3·9(5)
H11	379(3)	533(4)	270(1)	5·6(7)
H12	360(3)	526(4)	192(2)	6·1(7)
H21	154(4)	739(4)	262(1)	6·7(7)
H13	419(4)	678(5)	231(1)	8·9(10)
H22	010(5)	685(6)	301(2)	11·8(13)
H23	098(4)	537(5)	258(2)	8·9(10)
H31	135(4)	478(4)	054(2)	7·4(8)
H32	105(4)	428(5)	136(2)	8·7(10)
H33	005(7)	331(8)	072(3)	18·1(21)
H41	139(3)	−039(4)	−021(1)	5·8(6)
H42	060(3)	−032(4)	−101(1)	6·1(7)
H43	083(3)	142(4)	−051(1)	6·2(7)

The thermal parameters are of the form

$$\exp -\tfrac{1}{4} \sum_{i=1}^{3} \sum_{j=1}^{3} B_{ij} h_i h_j a_i^* a_j^*$$

$\frac{1}{2} - z$ as well as the molecules $x, y, z/-x, \frac{1}{2}+y, \frac{1}{2}-z/x, \frac{1}{2}-y, \frac{1}{2}+z/-x, -y, -z$ seen in perpendicular projection onto the *bc* plane.

Aside from the close O···O and H···O approaches characteristic of the H-bond, all of the intermolecular distances in the crystal are greater than or only slightly less than the sum of the van der Waals radii. These close approaches can all be attributed to imprecision in hydrogen positions, to the anisotropic van der Waals radius of Me groups, or to uncertainties in the radius of hydrogen, here taken as 1·2 Å.[5]

EXPERIMENTAL

The sample of xanthone J, m.p. 144·5–145·5°, $C_{17}H_{16}O_7$, MW 332, was obtained from *Frasera albicaulis* Dougl. *ex* Griesb. as described earlier.[1] A rounded cube of approximately 0·3 mm thickness was cut from a large crystal using a solvent lathe,[6] and mounted along the *b* axis. After preliminary oscillation and equi-inclination photographs, the lattice parameters were measured by carrying out a least-squares fit to 16 2θ values measured on a Picker handset diffractometer fitted with a General Electric goneostat.[7] Intensity data were obtained on this same instrument, using a 2θ scan and stationary background counts with Ni filtered CuK_α radiation (K_{α_1} 1·540510, K_{α_2} 1·54433 Å).

Crystal data. Monoclinic
$a = 9{\cdot}564 \pm 0{\cdot}0023$ $b = 8{\cdot}059 \pm 0{\cdot}0015$ $c = 20{\cdot}316 \pm 0{\cdot}0025$ Å
$\beta = 99{\cdot}499 \pm 0{\cdot}017°$
$V = 1544$ Å^3 $F(000) = 696$
$D_{(meas)} = 1{\cdot}430$ g cm^{-3} (flotation in CCl_4/hexane)
$D_{(calc)} = 1{\cdot}427$ g cm^{-3} for $Z = 4$
Space group $P2_1/c$.

The intensities of 3330 reflections to the limit of $2\theta = 160°$ were measured and scaled together on the basis of three standard reflections that were remeasured twice a day. There was a slow decrease in intensity with time, reaching -15% by the end of the data collection.

The data were reduced with the usual $1/Lp$ corrections, but without absorption corrections, and standard deviations were determined based on counting statistics. Those reflections (156) which differed from zero by less than their standard deviation were coded as unobserved. The small fraction of unobserved reflections undoubtedly arises from the size of the crystal used and contributes to the high precision of the results, although at the cost of possible systematic errors from absorption and Renninger effects.

During the data collection intensities were measured for both 0*kl* and 0*kl* reflections (201 each). Calculation of the usual *R* value (here

$$R = \frac{\sum \| F_{0kl}| - |F_{0kl}\|}{\sum |F_{0kl}|}$$

gave 3·6%.

All calculations were carried out on an IBM 7094. The data reduction, Fourier, and structure factor programs were those of the X-RAY 63 crystallographic system of Stewart *et al.*[8] Scattering factors for carbon,[9] oxygen,[10] and hydrogen[11] were taken from the literature. The full matrix least-squares refinement used a version of the ORFLS program of Busing *et al.*[12] modified for the X-RAY 63 system. This program minimizes $\sum w(|F_0| - |F_c|)^2$. The residual index *R* is defined throughout as

$$\frac{\sum \| F_0| - |F_c\|}{\sum |F_0|}$$

where the summation is over the unique observed reflections only. Fig. 2 was prepared largely by the illustrative program ORTEP.[13]

Structure determination. The structure was obtained by direct phase determination using the "symbolic addition" method and programs written by ourselves.[14] The phases of 242 reflections ($E \geqslant 1{\cdot}5$) were obtained in this way in terms of three variables. Examination of three-dimensional Fourier maps corresponding to the possible sign combinations of these variables yielded one which revealed the location of 19 atoms forming three rings with 5 attached atoms.

Structure factors were calculated for this model for the set of data to $(\sin\theta)/\lambda$ 0·45 (1182 refl) and another Fourier map showed the remaining five atoms. With these included *R* for the limited data was 41% and three cycles of difference Fourier syntheses reduced it to 22%. Individual isotropic temperature factors were introduced and two cycles of least squares refinement gave $R = 15{\cdot}5\%$ for the full data.

The thermal parameters were changed to individual anistropic, and one cycle of refinement using the full data lowered R to 11·3%. Because of the large number of parameters now involved, the refinement was performed in two blocks, C9 through C15 appearing in both to provide an overlap. Eighteen reflection which had very bad ΔF values were removed from the data set and another cycle of anisotropic refinement gave $R = 8{\cdot}3\%$.

A difference Fourier map at this point showed all 16 H atoms and these were added to the model. One cycle of refinement on these and their individual isotropic temperature factors brought R to 6·8%.

The 18 reflections previously rejected were remeasured using a smaller crystal and MoK$_\alpha$ radiation. Sixty other reflections were also remeasured to provide scaling. The new $|F_0|$'s showed good agreement with the $|F_c|$'s and were added to the data.

Four complete cycles of least-squares refinement were carried out, each cycle consisting of three passes, two covering the carbon and O atoms and the third the hydrogens. The weights for these refinements were

$$w = \frac{1}{\text{MAXF}\,(0{\cdot}70 + 0{\cdot}07\,|F_0|, \sigma_{F_0})}$$

where $\underline{\text{MAXF}}$ means "the greater of", σ_{F_0} was obtained from counting statistics, and the constants from a plot of $\overline{|\Delta F|}$ against $\overline{|F_0|}$.[15] The final value of R was 5·4%, and the maximum change in the positional parameters during the last cycle of refinement was 0·4 σ. The values of the atomic coordinates and the thermal parameters are given in Table 1, in which the numbers in parentheses are the standard deviations obtained from the final inverse matrix.[16]

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