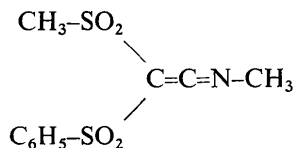


L'exemple de la *N*-méthyl-2-méthylsulfonyl-2-phénylsulfonyl-2-vinylidineaïne



étudiée par Bullough & Wheatley (1957) montre également une disposition stéréochimique où les interactions entre les liaisons S=O sont peu importantes. Là encore, la comparaison avec le bis(bromo-4-phénylsulfonyl)méthane n'est pas absolument rigoureuse puisque l'atome de carbone central est hybridé en sp^2 et les liaisons S-C (=) sont sensiblement plus courtes (1,73 Å).

En conclusion, la conformation moléculaire trouvée par diffraction des rayons X ne correspond pas à la conformation la plus stable prévue par l'étude des

moments dipolaires. On est donc conduit à admettre que le passage de l'état dissous à l'état solide entraîne un changement de conformation de la molécule (Pignat, Jeminet & Lumbroso, 1971).

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The Crystal and Molecular Structure of Xanthotoxin, $\text{C}_{12}\text{H}_8\text{O}_4$ *

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Xanthotoxin (8-methoxypsoralen or 8-methoxy-3',2':6,7-furocoumarin) is a naturally occurring drug used to treat the skin disease idiopathic vitiligo. The crystals are orthorhombic and belong to space group $Pna2_1$ with unit-cell dimensions $a = 12.911$ (6), $b = 15.804$ (8) and $c = 4.882$ (5) Å. The observed density, 1.440 g.cm^{-3} is consistent with 4 molecules per unit cell, $D_{\text{calc}} = 1.441 \text{ g.cm}^{-3}$. The structure was solved by direct methods using 731 independent reflections collected by counter techniques. The model was refined by conventional least-squares techniques to an R index of 0.046. The structure consists of a benzene ring to which is fused five and six-membered heterocyclic rings containing oxygen (a furan ring fused to a coumarin moiety). The ring system is almost planar, but the methoxy methyl is forced out of the plane due to steric interactions. The molecules are weakly held together and the packing arrangement facilitates cleavage along (100) and (010).

Introduction

Xanthotoxin (8-methoxypsoralen or 8-methoxy-3',2':6,7-furocoumarin) is a naturally occurring drug extracted from the fruits of *Fagara zanthoxylside* Lam., *Ammi majus* Lam., *Ruta chalepensis* Lam. and a few other species of subtropical shrubs and trees. It is used, in conjunction with ultraviolet light, to treat the skin disease idiopathic vitiligo. Krc (1951) reported the lattice parameters and other physical properties of the most stable crystalline form which he designated as xanthotoxin I. Lin (1963) began work on the crystal

structure using film data, but no structure solution was obtained. Recently, the data were recollected by counter techniques and the structure was solved by direct methods.

Experimental

A sample of xanthotoxin (marketed under the trade name 'Meloxine') was obtained from the Upjohn Company and was recrystallized from an ethanol-water solution. The crystals are prisms elongated along the crystallographic c axis. Precession and Weissenberg photographs confirmed the orthorhombic symmetry and the room temperature lattice parameters reported by Krc (1951).

* Contribution Number 7 from the FASTBIOS Laboratory.

C₁₂H₈O₄, molecular weight 216, $a=12.911(6)$, $b=15.804(8)$, $c=4.882(5)$ Å. Systematic absences: $h0l$ $h=2n$; $0kl$, $k+l=2n$. Space group: $Pna2_1$ (C_{2v}^2 , No. 33). $Z=4$; $F(000)=448$; $V=996$ Å³; $\mu=9.34$ cm⁻¹ (Cu $K\alpha$); D_{exp} (floatation)=1.440 g.cm⁻³; $D_{\text{calc}}=1.441$ g.cm⁻³; Cu $K\alpha=1.54178$ Å; graphite monochromator.

The errors in cell dimensions are standard deviations derived from the calculation of cell edges from a number of high angle reflections. The density was determined by the flotation method using a mixture of carbon tetrachloride and dioxane. The systematic extinctions observed in both the film and counter data were consistent with space groups $Pna2_1$ and $Pnam$. The molecular symmetry and unit-cell dimensions indicated that the more likely space group was $Pna2_1$ and subsequent refinement confirmed this choice.

A crystal of dimensions 0.1 × 0.2 × 1.0 mm ($a \times b \times c$) was selected for data collection and was mounted with the c axis coincident with the ω axis of a Phillips PAILRED diffractometer. Data were collected for layers $l=0$ to 4 using a scan rate of 1.0° per minute over an ω range of 4.0 to 7.2°, with the larger scan range used for lower angles and upper levels. A 10 sec background count was taken at the extremes of the scan range, and a reference reflection was monitored to check for crystal deterioration or instrument drift. A total of 1815 $I(hkl)$ and $I(\bar{h}kl)$ reflections were measured for $\sin \theta/\lambda < 0.55$. The exclusion of systematic extinctions and the averaging of space group equivalent reflections reduced the set to 731 independent reflections of which 648 were observed, $2\sigma(F_o) < F_o$. Standard deviations were assigned according to

$$\sigma(F_o)^2 = \frac{N_S + R^2 N_B + (0.05 I_o)^2}{4 L p I_o}$$

$$I_o = N_S - R N_B$$

where N_S is the total count obtained during a scan cycle, N_B is the total background count, R is a constant which relates the time of background count to the total scan time and I_o is the net integrated counts associated with each reflection.

The data were corrected for Lorentz and polarization factors, but no absorption corrections were made. A Wilson plot was used to estimate the scale and an overall temperature factor; structure factor magnitudes, $|F_o|$, and normalized structure factor magnitudes, $|E_h|$, were computed.

Structure determination

The set of 83 E 's with magnitudes greater than 1.5 was used to make a table of Σ_2 interactions. Three origin-defining reflections were selected on the basis of their magnitudes, number of contributions and the limitations imposed by linear independence (Hauptmann & Karle, 1956). Three additional reflections were selected and assigned symbolic phases a , b , and c , as shown in Table 1.

Table 1. Phase assignment for specifying the origin and implementing the symbolic addition process

H		Phases in degrees		
		Symbolic addition	Tangent refinement	Final structure
1	3 1	0	7	10
11	6 0	0	0	0
10	7 0	0	0	0
11	4 0	$a-180$	180	180
4	15 1	$b-45$	36	55
3	5 2	$c-45$	23	15

Four cycles of symbolic addition (Karle & Karle, 1964, 1966) phased 45 reflections from the set of 83. New phases were accepted if at least 80% of the contributing pairs gave an identical symbolic representation and the sum of the terms, $E_k \cdot E_{h-k}$, was greater than 8.0. An analysis of the unphased reflections indicated $a=\pi$ and $b=c$. The distribution of phases was more uniform if $b=45^\circ$ and three cycles of tangent refinement were calculated based upon this assignment. All 83 reflections were accepted. The set of E 's was increased to include all E 's greater than 1.0 and one cycle of tangent refinement was computed keeping all phases with $E > 1.5$ fixed. Of the 242 phases with E greater than 1.0, 235 were accepted.

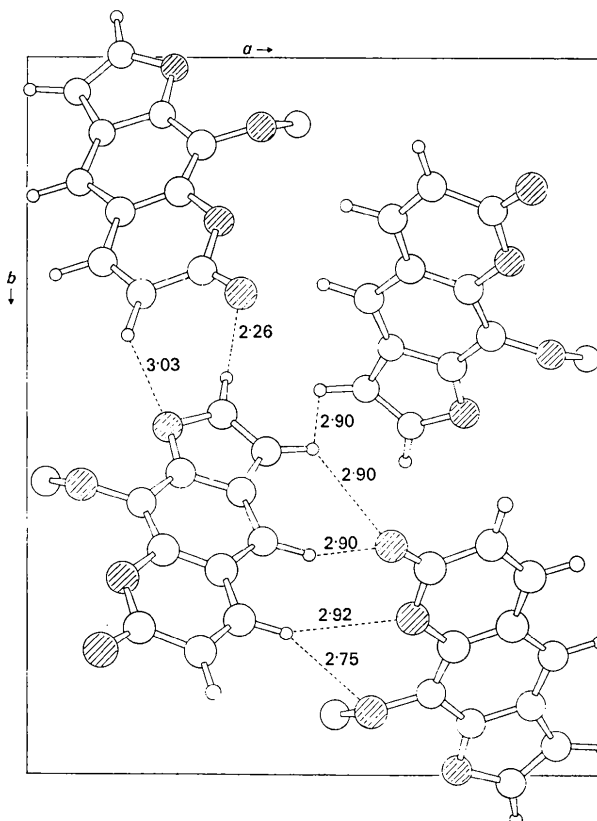


Fig. 1. Projection of the unit-cell contents onto the ab plane for xanthotoxin.

A three-dimensional E map was calculated using the 235 assigned phases. Only 16 large peaks appeared on the map, and they corresponded to the expected molecular structure of xanthotoxin. Structure factors calculated with these positions and an isotropic temperature factor of 3.0 yielded R=0.25. Three cycles of isotropic refinement using the 242 strongest reflections lowered R to 0.074. The function minimized in the refinement is \sum w(kF_o - F_c)^2 where w = [1/\sigma(F_o)]^2. The atomic scattering factors for carbon and oxygen atoms were taken from International Tables for X-ray Crystallography (1959) while those of Stewart, Davidson & Simpson (1965) were used for the hydrogen atoms.

At this stage of the refinement an error analysis program was run. A plot of Q = \sum(F_o - F_c)/\sigma(F_o) vs.

I_o indicated secondary extinction was important and a plot of Q vs. k indicated a strong vibrational anisotropy in the b direction. The data were corrected for secondary extinction by applying the equation F^2_{corr} = F^2_o / (1 + 2gI_{calc}) where 2g was found to be 1.3 \times 10^{-5}. Two cycles of full-matrix isotropic refinement with the corrected data gave an R index of 0.062 where R = \sum ||F_o| - |F_c|| / \sum |F_o|. Two cycles of full-matrix refinement using anisotropic temperature factors and all 648 observed reflections reduced R to 0.060 and R (wtd.) to 0.0598 where R (wtd.) = \sum w ||F_o| - |F_c|| / \sum w |F_o|. The coordinates of the five ring hydrogen atoms were calculated from the carbon atom parameters. The sixteen hydrogen atoms were refined anisotropically and the five hydrogen atoms isotropically for five additional cycles.

Table 2. Observed and calculated structure factors for xanthotoxin

Table with 4 columns of data, each representing a different set of structure factors (observed and calculated). Each column contains a grid of values for h, k, l, and phase. The table is organized into sections for different L values (0, 1, 2, 3).

The refinement converged to $R=0.046$ and $R(\text{wtd})=0.0461$. The addition of the five hydrogen atoms to the model was significant at the 0.99 confidence level. The methyl hydrogen atoms could not be located in the difference Fourier maps. All shifts in parameters were less than the estimated standard deviation of the parameter. The estimated standard deviations were calculated from the inverse of the normal equations matrix of the last least-squares cycle. The observed and calculated structure factors are given in Table 2 and the final parameters along with their estimated standard deviations are given in Table 3.

The error analysis program was run after the final least-squares refinement and only statistical fluctuations about $Q=0$ were observed. A final difference Fourier map indicated no peak as large as a hydrogen atom. All computations were made on an IBM 1800 computer using a program package developed by Stemple (1970).

Discussion

Fig. 1 shows a projection of the unit-cell contents onto the ab plane and Fig. 2 shows bond lengths, angles, and the numbering system used in the tables.

The central six-membered ring has equivalent bonds which are within 3σ of the average value of 1.395 Å. The two bonds C(3)–C(4) and C(12)–C(13) in the heterocyclic rings are distinctly double bond in character with lengths 1.338 (9) and 1.338 (10) Å respectively. The three bonds C(2)–C(3), C(4)–C(10) and C(6)–C(13) with distances 1.441 (9), 1.443 (8) and 1.434 (9) Å are shorter than normal C–C distances of 1.50 Å, but they are consistent with the values 1.44, 1.49, 1.43

and 1.43 Å observed in 4-hydroxy- and 3-bromo-4-hydroxycoumarin (Gaultier & Hauw, 1966).

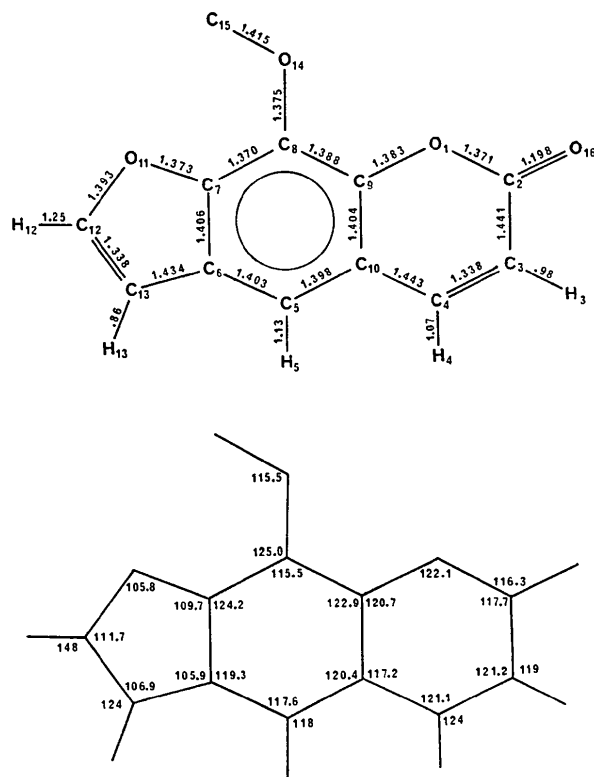


Fig. 2. Bond lengths, angles and numbering system for xanthotoxin. The average standard deviations of the bonds and angles involving only carbon and oxygen atoms are 0.008 Å and 0.5° respectively.

Table 3. Atomic and thermal parameters for xanthotoxin

Numbers in parentheses are estimated standard deviations of the last significant digit.

Anisotropic thermal parameters have the form

$$\exp[-0.25(B_{11}h^2a^*2 + B_{22}k^2b^*2 + B_{33}l^2c^*2 + 2B_{12}hka^*b^* + 2B_{13}hla^*c^* + 2B_{23}klb^*c^*)].$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> or <i>B</i> ₁₁	<i>B</i> ₂₂	<i>B</i> ₃₃	<i>B</i> ₁₂	<i>B</i> ₁₃	<i>B</i> ₂₃
O(1)	0.3326 (3)	0.2255 (3)	0.5320 (6)	3.54 (18)	5.62 (21)	4.55 (22)	0.02 (16)	−0.81 (20)	−0.86 (22)
C(2)	0.3043 (5)	0.2938 (4)	0.6879 (10)	5.00 (34)	5.15 (32)	4.51 (35)	−0.91 (27)	−0.46 (33)	−0.87 (33)
C(3)	0.1986 (5)	0.3224 (4)	0.6687 (10)	4.75 (33)	5.11 (33)	5.78 (41)	0.26 (27)	0.13 (33)	−1.61 (35)
C(4)	0.1302 (5)	0.2827 (4)	0.5078 (10)	4.12 (29)	5.07 (31)	4.94 (33)	0.44 (25)	−0.62 (30)	−0.30 (36)
C(5)	0.0915 (5)	0.1701 (4)	0.1656 (9)	3.73 (25)	5.15 (27)	3.84 (31)	−0.48 (21)	−0.23 (27)	0.04 (28)
C(6)	0.1295 (4)	0.1027 (4)	0.0082 (9)	4.16 (26)	4.81 (25)	3.45 (28)	−1.13 (22)	−0.32 (28)	0.82 (29)
C(7)	0.2335 (5)	0.0779 (3)	0.0385 (10)	5.07 (29)	3.86 (31)	3.54 (33)	0.10 (24)	0.41 (25)	0.19 (30)
C(8)	0.3027 (4)	0.1172 (4)	0.2089 (9)	3.68 (28)	4.56 (31)	4.13 (29)	0.37 (24)	−0.48 (27)	−0.24 (34)
C(9)	0.2639 (4)	0.1846 (4)	0.3597 (8)	3.36 (32)	4.36 (26)	3.37 (29)	−0.63 (23)	−0.23 (30)	0.11 (28)
C(10)	0.1605 (4)	0.2116 (4)	0.3404 (8)	3.34 (27)	4.48 (27)	3.51 (31)	0.00 (23)	−0.21 (26)	0.51 (30)
O(11)	0.2537 (4)	0.0101 (3)	−0.1289 (8)	6.05 (24)	5.21 (21)	5.12 (21)	0.09 (18)	−0.12 (23)	−1.06 (23)
C(12)	0.1610 (7)	−0.0079 (5)	−0.2626 (13)	5.77 (40)	6.10 (39)	4.28 (37)	−1.65 (35)	−0.42 (35)	−0.45 (33)
C(13)	0.0858 (7)	0.0456 (5)	−0.1886 (14)	7.51 (47)	5.36 (36)	4.46 (34)	−1.24 (32)	−0.08 (37)	−0.67 (33)
O(14)	0.4035 (3)	0.0918 (3)	0.2493 (7)	4.42 (23)	8.17 (29)	5.90 (28)	2.73 (20)	−0.24 (20)	−0.42 (26)
C(15)	0.4647 (6)	0.0867 (6)	0.0095 (12)	4.73 (37)	11.58 (58)	7.03 (45)	1.59 (40)	2.03 (40)	−0.06 (49)
O(16)	0.3705 (4)	0.3244 (3)	0.8287 (8)	5.90 (30)	7.54 (28)	8.31 (40)	−0.62 (22)	−2.33 (28)	−3.01 (35)
H(3)	0.178 (5)	0.373 (5)	0.768 (10)	6.2 (1.7)					
H(4)	0.054 (5)	0.305 (3)	0.469 (10)	4.9 (1.4)					
H(5)	0.010 (4)	0.197 (3)	0.147 (8)	4.5 (1.3)					
H(12)	0.190 (7)	−0.066 (6)	−0.417 (14)	13.0 (3)					
H(13)	0.025 (5)	0.045 (4)	−0.261 (10)	5.3 (1.8)					

The four C–O bonds in the two heterocyclic rings are within 2σ of the average value of 1.380 Å. The small differences are consistent with predictions based upon ring strain and electron delocalization. The C(8)–O(14) distance of 1.375 Å is similar to that found for many methoxyl groups attached to aromatic ring systems; however, the methoxyl group does not lie within the plane of the ring.

A unit weighted least-squares plane fitted to the six atoms comprising the benzene ring gives the equation $0.2515x + 0.6273y - 0.7370z = 1.4022$. The average deviation of the six ring atoms from the plane is 0.005 Å with a maximum deviation of 0.009 Å. The five-membered ring is slightly puckered with O(12) 0.006 Å above the plane of the benzene ring and O(11) and C(13) below. The atoms of the six-membered heterocyclic ring lie above the plane and there is a slight folding of the ring about the O(1)–C(4) axis. If a least-squares plane is fitted to the atoms comprising the three rings the equation $0.2517y + 0.6221y - 0.7414z = 1.3922$ is obtained. The maximum deviation from this plane is 0.02 Å indicating a reasonably planar system.

The methoxyl oxygen is 0.07 Å below the plane of the benzene ring while the methyl carbon is rotated to a position 0.94 Å above. The dihedral angle formed by the O(14)–C(15) bond with respect to the plane is 54.6°. If the methyl carbon lay in the plane of the ring, the electron pair of the oxygen would have the greatest overlap with the π orbitals of the aromatic ring system. This geometry is observed for most methoxyl groups attached to aromatic systems where there are no large substituents in the adjacent *ortho* positions, (Yonemitsu, Nakai, Kanaoka, Karle & Witkop, 1968; Corbin, Karle & Karle, 1970; Gilardi & Karle, 1971; Ting, Watson & Dominguez, 1972). If the methyl carbon in xanthotoxin lay within the plane the C(15)–O(11) or the C(15)–O(1) distance would be 2.60 Å or 2.16 Å. The methyl group is sterically forced out of the plane

and the angle of 54.6° is probably a compromise between steric repulsion and overlap of the oxygen electrons with the ring.

All intermolecular contact distances are greater than the sum of the van der Waals radii except for the O(16)–H(12) interaction distance of 2.26 Å. The C(12)–H(12)–O(16) angle is 141°. The easy cleavages along (100) and (010) are explained by molecular packing considerations. The perpendicular distance between molecular planes stacked along *c* is 3.58 Å, and the two molecules related by the *a* glide make an angle of 83°.

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The Crystal and Molecular Structure of α -*p*-Dimethylaminobenzaldoxime

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Crystals of α -*p*-dimethylaminobenzaldoxime, $(\text{CH}_3)_2\text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{CHNOH}$, are monoclinic, $a = 7.705$, $b = 6.190$, $c = 19.149$ Å, $\beta = 95.80^\circ$, space group $P2_1/c$, with four formula units in the unit cell. The structure was solved by Patterson and Fourier methods and refined by the full-matrix least-squares method, using 980 non-zero reflexions collected by the counter method, to a final *R* value of 0.059. Two centrosymmetrically related molecules interact through two O–H...N hydrogen bonds (2.784 Å), and the crystal is built up of discrete centrosymmetric quasi-planar dimers. The molecular structure is discussed on the basis of the observed bond lengths and angles.

The structure analysis of α -*p*-dimethylaminobenzaldoxime, $(\text{CH}_3)_2\text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{CHNOH}$, is part of a program

involving a systematic study of the structure of *para*-substituted benzaldoximes and their methyl derivatives.