

The Chemistry of Fungi. Part LXVIII.¹ The Absolute Configuration of (+)-Sclerotiorin and of the Azaphilones

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X-Ray crystallographic examination of *N*-methylsclerotioramine, derived from (+)-sclerotiorin, has defined the absolute stereochemistry of the derivative and hence that of (+)-sclerotiorin and of the other members of the azaphilone group of fungal metabolites.

WE have previously² deduced the relative stereochemistry of the azaphilone group of fungal metabolites.

¹ P. S. Manchand, W. B. Whalley, and Fa-ching Chen, *Phytochemistry*, 1973, **12**, 2531 is regarded as Part LXVII of this series.

From an X-ray crystallographic examination we have now defined the absolute stereochemistry of *N*-methyl-

² F. C. Chen, P. S. Manchand, and W.B. Whalley, *J. Chem. Soc. (C)*, 1971, 3677.

sclerotioramine³ as illustrated in formula (1; R = Ac, X = NMe). The course of the analysis is described in the Experimental section and a view of the molecule, giving the crystallographic numbering scheme, is shown in Figure 1. A view of the molecular packing viewed along the *b* axis is given in Figure 2. Because of the

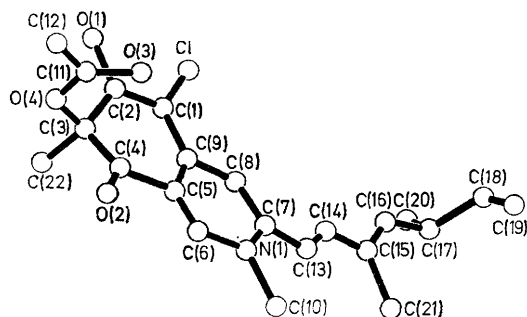


FIGURE 1 View of *N*-methylsclerotioramine showing the crystallographic numbering scheme

relatively large estimated standard deviation of the bond lengths, a result in part of the fairly high thermal motion, especially in the heptadiene side chain, none of the observed bond lengths or angles listed in Table 2 differs significantly from expected values.⁴ The intra-annular torsion angles in Table 3 reveal that ring A adopts a conformation close to a half-chair, and ring B is essentially planar. The bond lengths and angles involving N(1) (Figure 1) indicate that this atom is *sp*²-hybridized and takes part in the extensive conjugated system. These conformational conclusions are similar to those deduced

TABLE 1

Fractional co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
Cl(1)	-0 506(3)	0 *	2 138(1)
O(1)	2 238(7)	-1 027(12)	3 087(4)
O(2)	1 990(7)	4 764(13)	4 542(3)
O(3)	1 232(7)	0 096(13)	4 584(3)
O(4)	3 434(6)	1 173(10)	4 184(3)
N(1)	-1 948(7)	6 987(12)	3 440(4)
C(1)	0 272(9)	1 508(16)	2 815(4)
C(2)	1 629(11)	0 718(18)	3 165(5)
C(3)	2 506(9)	2 332(15)	3 662(4)
C(4)	1 547(9)	3 925(15)	3 991(5)
C(5)	0 104(8)	4 574(14)	3 597(4)
C(6)	-0 667(10)	6 292(15)	3 786(5)
C(7)	-2 498(9)	5 945(16)	2 850(5)
C(8)	-1 796(10)	4 156(16)	2 653(5)
C(9)	-0 445(9)	3 353(16)	3 010(4)
C(10)	-2 721(14)	8 867(21)	3 708(7)
C(11)	2 649(11)	0 077(18)	4 636(4)
C(12)	3 615(11)	-1 087(19)	5 155(5)
C(13)	-3 816(10)	6 890(18)	2 425(5)
C(14)	-4 478(11)	5 998(21)	1 873(5)
C(15)	-5 728(10)	6 849(18)	1 401(5)
C(16)	-6 304(10)	5 587(20)	0 898(7)
C(17)	-7 529(14)	6 047(31)	0 338(8)
C(18)	-8 908(18)	4 595(28)	0 439(9)
C(19)	-9 700(24)	5 098(49)	1 074(11)
C(20)	-6 934(23)	5 689(49)	-0 385(9)
C(21)	-6 277(17)	8 979(27)	1 539(8)
C(22)	3 650(13)	3 513(22)	3 233(6)

* Fixed to specify the origin in space group *P*₂₁.

less than 3.5 Å are listed in Table 4 and correspond to van der Waals interactions.

It thus follows that (+)-sclerotiorin, from which our specimen of *N*-methylsclerotioramine was derived, has

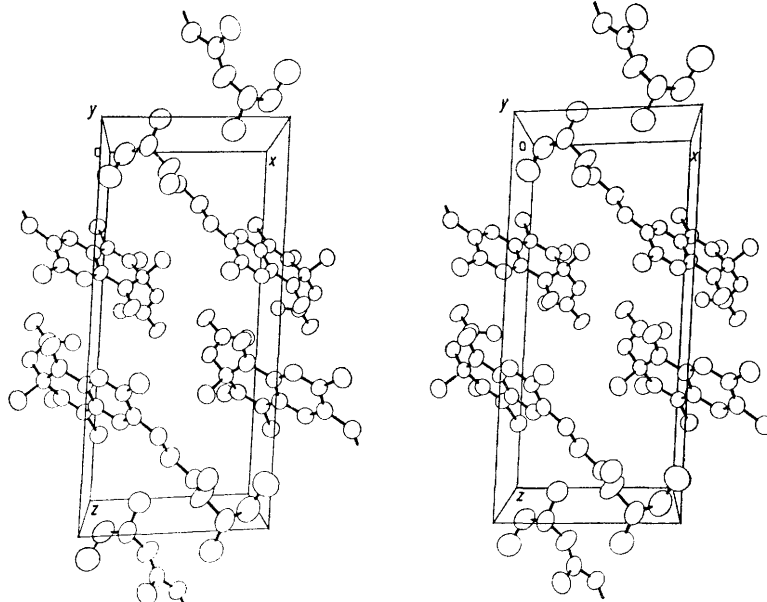


FIGURE 2 View of the molecular packing of *N*-methylsclerotioramine

earlier⁵ on the basis of other spectroscopic and chemical data.

There are no unusual intermolecular contacts. Those

³ R. A. Eade, H. Page, A. Robertson, K. Turner, and W. B. Whalley, *J. Chem. Soc.*, 1957, 4913.

⁴ L. E. Sutton, *Chem. Soc. Special Publ.*, No. 18, 1965.

the absolute configuration shown in formula (1; R = Ac, X = O). Hence (+)-deacetylsclerotiorin (1; R = H, X = O), rotiorin (2; R = H), 5-chlororotiorin (2; R =

⁵ F. M. Dean, J. Staunton, and W. B. Whalley, *J. Chem. Soc.*, 1959, 3004.

TABLE 2

Bond lengths (Å) and valency angles (°) with estimated standard deviations in parentheses

C(1)—Cl(1)	1.720(9)	C(7)—C(13)	1.49(1)
C(1)—C(2)	1.42(1)	C(8)—C(9)	1.42(1)
C(1)—C(9)	1.39(1)	N(1)—C(10)	1.48(1)
C(2)—O(1)	1.24(1)	C(13)—C(14)	1.31(1)
C(2)—C(3)	1.56(1)	C(14)—C(15)	1.47(1)
C(3)—O(4)	1.45(1)	C(15)—C(16)	1.33(2)
C(3)—C(4)	1.49(1)	C(15)—C(21)	1.46(2)
C(3)—C(22)	1.54(2)	C(16)—C(17)	1.50(2)
C(4)—O(2)	1.23(1)	C(17)—C(18)	1.54(2)
C(4)—C(5)	1.48(1)	C(17)—C(20)	1.55(2)
C(5)—C(6)	1.35(1)	C(18)—C(19)	1.49(3)
C(5)—C(9)	1.43(1)	C(11)—O(3)	1.24(1)
C(6)—N(1)	1.34(1)	C(11)—O(4)	1.35(1)
C(7)—N(1)	1.37(1)	C(11)—C(12)	1.46(1)
C(7)—C(8)	1.36(1)		
C(6)N(1)C(7)	119.2(8)	N(1)C(7)C(8)	119.8(8)
C(6)N(1)C(10)	118.4(8)	N(1)C(7)C(13)	118.4(8)
C(7)N(1)C(10)	122.4(8)	C(8)C(7)C(13)	121.8(9)
Cl(1)C(1)C(2)	116.1(7)	C(7)C(8)C(9)	122.7(8)
Cl(1)C(1)C(9)	120.8(6)	C(1)C(9)C(5)	122.6(7)
C(2)C(1)C(9)	123.1(8)	C(1)C(9)C(8)	123.0(8)
O(1)C(2)C(1)	127.5(9)	C(5)C(9)C(8)	114.4(8)
O(1)C(2)C(3)	117.5(8)	O(3)C(11)O(4)	120.0(8)
C(1)C(2)C(3)	114.8(9)	O(3)C(11)C(12)	125.9(9)
O(4)C(3)C(2)	108.8(7)	O(4)C(11)C(12)	114.2(8)
O(4)C(3)C(4)	110.5(7)	C(7)C(13)C(14)	123.9(10)
O(4)C(3)C(22)	105.6(7)	C(13)C(14)C(15)	127.8(11)
C(2)C(3)C(4)	116.1(7)	C(14)C(15)C(16)	117.2(11)
C(2)C(3)C(22)	107.2(7)	C(14)C(15)C(21)	117.5(10)
C(4)C(3)C(22)	108.2(8)	C(16)C(15)C(21)	125.2(11)
O(2)C(4)C(3)	120.9(8)	C(15)C(16)C(17)	128.8(14)
O(2)C(4)C(5)	121.9(8)	C(16)C(17)C(18)	108.5(14)
C(3)C(4)C(5)	117.0(8)	C(16)C(17)C(20)	110.9(13)
C(4)C(5)C(6)	120.6(8)	C(18)C(17)C(20)	110.3(15)
C(4)C(5)C(9)	118.8(8)	C(17)C(18)C(19)	113.3(16)
C(6)C(5)C(9)	120.6(7)	C(3)O(4)C(11)	115.3(6)
N(1)C(6)C(5)	123.2(8)		

TABLE 3

Intra-annular torsion angles with estimated standard deviations in parentheses

C(9)C(1)—C(2)C(3)	-15.2(13)	C(6)C(5)—C(9)C(8)	2.0(12)
C(1)C(2)—C(3)C(4)	30.8(11)	C(9)C(5)—C(6)N(1)	-1.5(13)
C(2)C(3)—C(4)C(5)	-29.8(11)	C(6)N(1)—C(6)C(5)	-1.7(13)
C(3)C(4)—C(5)C(9)	13.1(11)	C(6)N(1)—C(7)C(8)	4.2(13)
C(4)C(5)—C(9)C(1)	3.7(13)	N(1)C(7)—C(8)C(9)	-3.6(14)
C(2)C(1)—C(9)C(5)	-2.1(14)	C(7)C(8)—C(9)C(5)	0.5(13)

TABLE 4

Intermolecular contacts less than 3.5 Å

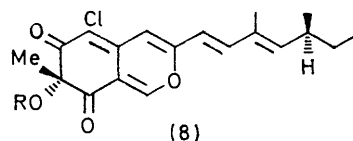
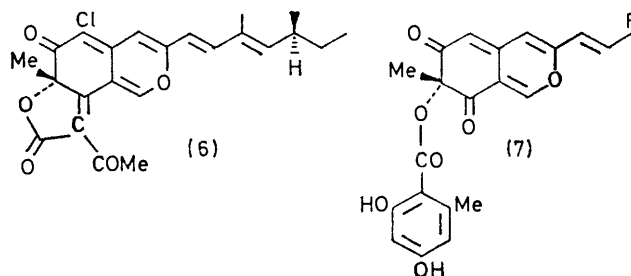
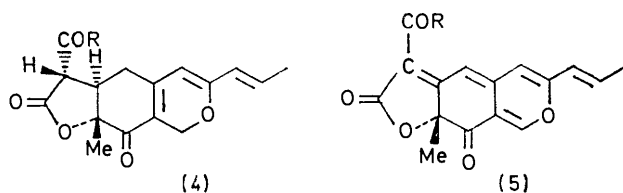
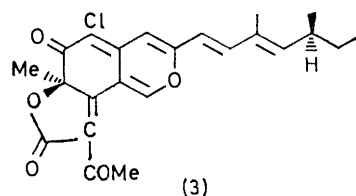
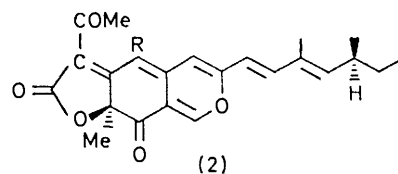
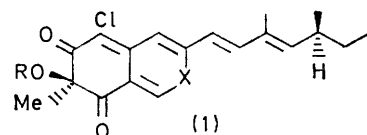
O(1) ... C(21 ^{II})	3.36(2)	C(6) ... O(3 ^{III})	3.25(1)
N(1) ... Cl(1 ^{III})	3.473(8)	Cl(1) ... C(7 ^{III})	3.45(1)
O(2) ... C(11 ^{III})	3.42(1)	O(4) ... C(12 ^{IV})	3.29(1)
O(2) ... O(3 ^{III})	3.44(1)	C(10)—O(2 ^V)	3.45(1)
O(2) ... C(12 ^{III})	3.18(1)	O(2) ... O(3 ^V)	3.40(1)
C(6) ... O(1 ^{III})	3.42(1)		

Roman numerals as superscripts refer to the following transformations relative to the reference molecule at x, y, z : I ($1 + x, -1 + y, z$); II ($x, 1 + y, z$); III ($x, -1 + y, z$); IV ($1 - x, \frac{1}{2} + y, 1 - z$); V ($-x, \frac{1}{2} + y, 1 - z$).

Cl), 5-chlorisorotiorin (3), and (+)-deacetylsclerotiorin orsellinate (1; R = orsellinyl), have the absolute configurations shown. Similarly, ankaflavin (4; R = n-C₇H₁₅), monascin (4; R = n-C₅H₁₃), rubropunctatin (5; R = n-C₅H₁₃), monascorubrin (5; R = n-C₇H₁₅), rubrorotiorin (6), mitorubrin (7; R = H),* mitorubrinol (7; R = OH), mitorubrinic acid (7; R = CO₂H), (-)-sclero-

* The orsellinyl residue in structures (6) and (7) in ref. 2 is incorrectly formulated.

tiorin (8; R = Ac), and (-)-deacetylsclerotiorin (8; R = H) have the absolute configuration shown.



EXPERIMENTAL

X-Ray Crystal Structure Analysis of N-Methylsclerotioramine.—Crystals of N-methylsclerotioramine are deep red needles elongated along the b axis. Preliminary cell parameters and space group data were obtained from various rotation, precession, and Weissenberg photographs; accurate cell parameters were obtained by a least-squares procedure applied to 12 general reflections measured on a Hilger and Watts diffractometer.

Crystal data. C₂₂H₂₆ClNO₄, $M = 403.9$. Monoclinic, $a = 8.756(2)$, $b = 6.330(1)$, $c = 19.367(6)$ Å, $\beta = 94.27(2)^\circ$, $U = 1070.4$ Å³, $Z = 2$, $D_o = 1.253$ g cm⁻³, $F(000) = 428$ (20 °C; Cu-K α ; $\lambda = 1.5418$ Å, $\mu = 18.1$ cm⁻¹). Space

group $P2_1/m (C_{2h}^2)$ or $P2_1 (C_2)$ from absent reflections: $0k0$, $k = 2n + 1$; $P2_1$ from structure analysis.

The intensities of all reflections with $2\theta(\text{Cu-K}\alpha) \leq 140^\circ$ were measured on a PDP8-I controlled Hilger and Watts four-circle diffractometer with a scintillation counter and approximate monochromatic radiation (Ni filter and pulse height analyser). A θ/ω step scan was employed with 0.01° steps, a counting time of 1 s per step, and a scan width of 0.7° in θ . Background counts of 17.5 s were made at the beginning and end of each scan. The intensities of 3 standard reflections, measured after every 50 reflections, decreased over the course of the data collection to values which were 90% of the starting intensities, indicating some crystal decomposition. The data were corrected for the decomposition (assumed linear between standards), Lorentz and polarization factors were applied, and the structure amplitudes were derived. Of the 1920 unique data, 786 reflections had a net count of less than 3σ above background, [where $\sigma(I)$ is defined by $\sigma^2(I) = S + 4(B_1 + B_2) + (0.05 S)^2$ where S is the scan count and B_1 and B_2 are the background counts] and were excluded from the refinement.

Structure analysis. The structure was solved in a straightforward manner, by using the multiple solution program MULTAN.⁶ The E -map revealed almost the entire molecule except for six atoms which were subsequently located from an $(F_o - F_c)$ synthesis. Refinement proceeded smoothly. Isotropic full-matrix followed by block-diagonal anisotropic least-squares refinement gave an R value of

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

⁶ G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

0.075. At this stage a difference map revealed the presence of 23 of the 26 hydrogen atoms. The C(12) methyl group appeared to be rotationally disordered. Inclusion of the hydrogen atoms in the structure factor calculation, but not in the refinement, gave a final R value of 0.058 for the 1134 observed reflections. The scattering factors for the non-hydrogen atoms, including the anomalous dispersion corrections for chlorine, were taken from ref. 7; those for the hydrogen atoms were from ref. 8. The weighting scheme employed in the final stages of refinement was that of Hughes⁹ with $\omega = 1.0$ for $F_o < 8.0$ and $\omega = (8.0/F_o)^2$ for $F_o > 8.0$. The relative validity of the weighting scheme, as judged by the variation of $\omega(F_o - F_c)^2$ over ranges of $|F_o|$ and $\sin \theta/\lambda$, was satisfactory. Final positional parameters appear in Table 1. The observed and final calculated structure amplitudes as well as the thermal parameters are listed in Supplementary Publication No. SUP 21739 (16 pp.).* A structure factor calculation on the other enantiomorph yielded an R value of 0.060.

The difference in the R value is small, and we would be hesitant to argue strongly in favour of the configuration giving $R = 0.058$ on this basis alone; however, this configuration, corresponding to the co-ordinates listed in Table 1, follows from the absolute configuration already known¹⁰ of the asymmetric centre in the side-chain.

[5/2265 Received, 19th November, 1975]

⁷ 'International Tables for X-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1968.

⁸ R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3178.

⁹ E. W. Hughes, *J. Amer. Chem. Soc.*, 1941, **63**, 1737.

¹⁰ G. A. Ellestad and W. B. Whalley, *J. Chem. Soc.*, 1965, 7260.