Crystal and Molecular Structure of Compactin, a New Antifungal Metabolite from *Penicillium brevicompactum*

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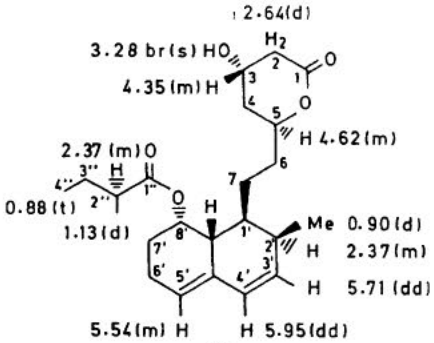
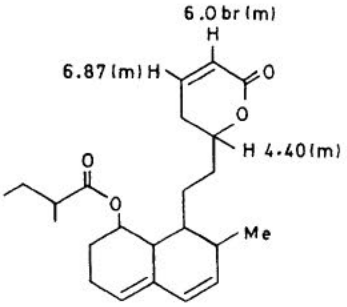
The structure of compactin (I) {7-[1,2,6,7,8,8a-hexahydro-2-methyl-8-(2-methylbutyryloxy)naphthyl]-3-hydroxyheptan-5-olide}, a metabolite isolated from cultures of *Penicillium brevicompactum*, has been determined by a combination of spectroscopic, chemical, and *X*-ray crystallographic methods.

METABOLITES isolated previously from strains of *Penicillium brevicompactum* [1] include mycophenolic acid and related compounds, the pebrolide sesquiterpenes, and the brevianamides. We describe here a new compound, compactin (I), which was isolated from a culture believed to be *Penicillium brevicompactum* and was detected by its antifungal activity.[2]

Compactin, $C_{23}H_{34}O_5$, is optically active and shows u.v. absorption typical of a *transoid* conjugated diene. The i.r. spectrum shows hydroxy and lactone absorption, consistent with the formation of a benzoate, and the solubility of compactin, which is neutral, in aqueous sodium hydroxide and its recovery on acidification. The carbonyl band at 1 710 cm^{-1} (in KBr) is shifted to 1 724 cm^{-1} in chloroform solution, and later work (see below) showed that this must arise from an ester group. The five oxygen atoms in compactin are thus identified.



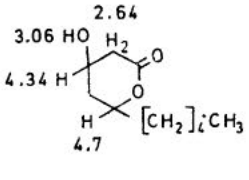
(I)



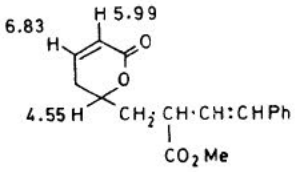
(II)

The δ-lactone system in (I) was identified from the ^{1}H n.m.r. assignments shown and appropriate decoupling and exchange experiments, and by dehydration to the αβ-unsaturated lactone (II) in the i.r. spectrum of which the carbonyl absorption had moved to 1 730 cm^{-1}. The anhydro-compound (II) was first obtained in an attempt to prepare a *p*-bromophenylsulphonyl derivative, and was also made by heating compactin with potassium hydrogen sulphate in dimethylformamide. The relevant spectroscopic data for (I) and (II) agree well with those for the δ-lactone (III), from *Cephalosporium recifei*,[3] and cryptocaryalactone (IV), from the roots of *Cryptocarya bourdilloni*,[4] respectively.

The ^{1}H n.m.r. spectrum of compactin (I) at high field shows two methyl doublets at δ 1.13 and 0.90 (each with *J* 7 Hz) and a methyl triplet at δ 0.88 (*J* 7.5 Hz) ascribed to the ethyl group. Both doublets collapse to singlets on irradiation at δ 2.37, indicating the presence of either an isopropylidene (Me_2CH) group with non-equivalent methyls or two ethylidene ($CH_3{\cdot}CH{<}$) groups, the methine carbon atom(s) being adjacent to a carbonyl group or a carbon–carbon double bond. A study of the 60 and 100 MHz n.m.r. spectra revealed that the methylene protons of the ethyl group are strongly coupled to another adjacent group; thus the unit $CH_3{\cdot}CH_2{\cdot}CH_2{-}$ or $CH_3{\cdot}CH_2{\cdot}CH{<}$ must be present. Combining the latter with an ethylidene group next to a carbonyl gives the fragment $CH_3{\cdot}CH_2{\cdot}CHMe{\cdot}CO{-}$. That this is derived



(III)



(IV)

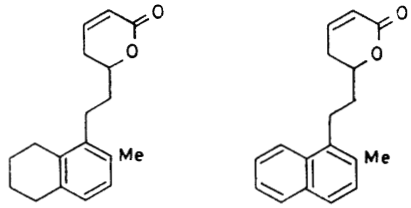
[1] W. B. Turner, 'Fungal Metabolites,' Academic Press, London, 1971.
[2] M. Richards, A. R. Clare, C. Reading, and M. S. Verrall, in preparation.
[3] R. F. Vesonder, F. H. Stodola, and W. K. Rohwedder, *Canad. J. Biochem.*, 1972, **50**, 363.
[4] R. T. Govindachari and P. C. Parthasarathy, *Tetrahedron Letters*, 1971, 3401.

from a 2-methylbutyric acid unit, as suggested by the mass spectrum, was subsequently confirmed by an acid-catalysed elimination reaction from which it was isolated. Hence compactin contains the ester group shown in (I).

The presence of a *transoid* diene system was confirmed by extensive n.m.r. evidence, and decoupling experiments established its relationship to the rest of the molecule, but were difficult to interpret. The problem was resolved by the ^{13}C n.m.r. spectrum, which confirmed the presence of four vinylic carbon atoms in compactin, the signals from three of which (at 132, 128, and 123 p.p.m.) are doublets in the off-resonance decoupled spectrum whereas the fourth (at 133 p.p.m.) is a singlet. The ^{13}C n.m.r. spectrum also confirmed the presence of two carbonyl carbon atoms (176 and 170 p.p.m.), and revealed the existence of three sp^3 carbon atoms attached to oxygen (76, 67, and 62 p.p.m.) which appeared as doublets in the off-resonance decoupled spectrum. Two of these >CH·O− groups have already been identified in the lactone system, and the third must carry the ester side chain. Irradiation at 3 038 Hz (δ 5.33) caused collapse of the signal at 67 p.p.m. to a sharp singlet, at the same time reducing the vinylic signal at 123 p.p.m. to a broad singlet. It follows that the broad 'singlet' at δ 5.33 in the ^1H n.m.r. spectrum arises from the proton attached to the carbon atom bearing the ester group; this δ value is unusually low. The other signal which collapses on irradiation at 3 038 Hz must be that of the vinyl carbon atom attached to the proton which resonates at 3 061 Hz, *i.e.* the proton which gives the broad 'singlet' at δ 5.54, namely H-5′.

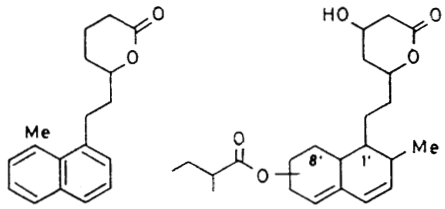
Significant peaks in the mass spectrum of compactin are seen at *m/e* 390 (M^+), 372 ($M - H_2O$), 288 ($M - C_5H_{10}O_2$), and 270 ($M - H_2O - C_5H_{10}O_2$), which support the presence of a C_5 ester unit as discussed above, and further major peaks at *m/e* 159 ($C_{12}H_{15}$), 158 ($C_{12}H_{14}$), 155 ($C_{12}H_{11}$), 145 ($C_{11}H_{13}$), and 143 ($C_{11}H_{11}$) (100%) suggested a reduced naphthalene system. More convincing evidence was derived from the following chemical reactions.

Heating compactin in toluene with toluene-*p*-sulphonic acid gave a viscous liquid, identified as a tetralin derivative, $C_{18}H_{22}O_2$. From spectroscopic evidence it was seen that the lactone ring had been dehydrated, and the 2-methylbutyric ester group eliminated; the chromophore was now benzenoid and there was a methyl group attached to the benzene ring. Owing to overlapping signals from the vinyl and aromatic protons in the ^1H n.m.r. spectrum, the substitution pattern was not easily discernible but this problem was resolved by converting the tetralin into a naphthalene derivative by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In the n.m.r. spectrum of this compound the pattern of aromatic signals is identical with that of 1,2-dimethylnaphthalene (and different from those of the other isomers), showing that it is a 1,2-dialkylated naphthalene. The chemical shift of the methyl group (δ 2.50) is normal for β-methylated naphthalenes, and the other side chain, containing the αβ-unsaturated lactone (in agreement with the n.m.r. spectrum and the molecular formula), occupies the adjacent α-position. Thus the naphthalene derivative has structure (VI), and the tetralin is (V). Some support for this was obtained by



(V) (VI)

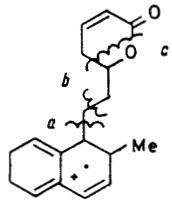
synthesis of the lactone (VII) and its 6-methyl-2-naphthyl isomer, by condensing the appropriate methylnaphthaldehydes with 4-acetylbutyric acid followed by hydrogenation. The n.m.r. spectra of these lactones, at high field, showed a close resemblance to that of the dihydro-derivative of (VI).



(VII) (VIII)

There remains the structure of compactin itself. Combination of all the evidence cited leads to the indefinite structure (VIII). As we did not have evidence to locate the ester grouping unambiguously, compactin was submitted to *X*-ray analysis (see Experimental section and Tables 1—3), which established the structure and relative stereochemistry as in (I).

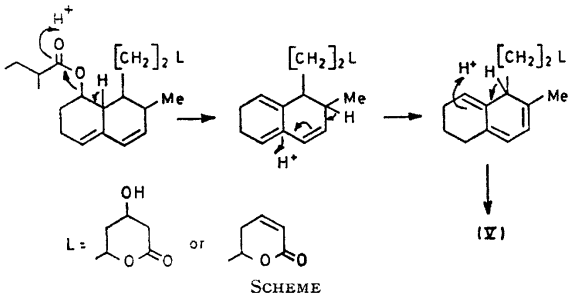
The main modes of fragmentation of compactin under electron impact are now evident. The $M - H_2O - C_5H_{10}O_2$ ion has structure (IX), from which all the major



(IX) *a*; *m/e* 145, 143, 129
b; *m/e* 159, 158
c; *m/e* 186, 185, 184

ions between *m/e* 100 and 200 can arise by the cleavages indicated. In the acid-catalysed conversion of compactin into the tetralin (V) the ring which becomes aromatic is not that from which 2-methylbutyric acid is eliminated. The subsequent hydrogen shifts are illustrated in the Scheme, but need not occur in the order shown.

Biosynthetic studies have not yet been carried out on compactin, but the compound is apparently polyketide-derived. Both the manner in which the nonaketide chain is folded and the low oxidation level are unusual in



SCHEME

cyclic polyketides. The ester side chain is not located at an ' expected ' position, and the oxygen at C-8′ may have been introduced by autoxidation at an intermediate stage in the biosynthesis.

EXPERIMENTAL

Spectroscopic measurements were made on solutions in ethanol (u.v.), KBr discs (i.r.), and solutions in $CDCl_3$ (n.m.r.) unless otherwise stated.

Isolation of Compactin (I).—Compactin,[2] obtained by extraction of a culture filtrate of a strain of *Penicillium brevicompactum*, had m.p. 152° (from aqueous ethanol) (Found: C, 70.85; H, 8.7%; M^+, 390.2403. $C_{23}H_{34}O_5$ requires C, 70.75; H, 8.8%; M, 390.2406), $[\alpha]_D^{22}$ +283° (*c* 0.84 in Me_2CO), $\lambda_{max.}$ 230, 237, and 246 nm (log ε 4.28, 4.30, and 4.11), $\nu_{max.}$ ($CHCl_3$) 3 510 and 1 724 cm^{-1} (lactone and ester CO), $\nu_{max.}$ (KBr) 3 520, 1 750 (lactone CO), and 1 710 cm^{-1} (ester CO), δ 5.95 (1 H, d, *J* 10 Hz, H-4), 5.71 (1 H, dd, *J* 10 and 5 Hz, H-3′), 5.44br (1 H, s, H-5′), 5.33br (1 H, s, H-8′), 4.62 (1 H, m, H-3), 4.35 (1 H, m, H-5), 3.28br (1 H, s, OH), 2.64 (2 H, d, *J* 4 Hz, H-6), 2.37 (2 H, m, H-2′ and H-2″), 2.2—1.3 (14 H, m, CH_2, and CH), 1.13 (3 H, d, *J* 7 Hz, 2″-Me), 0.90 (3 H, d, *J* 7 Hz, 2′-Me), and 0.88 (3 H, t, *J* 7.5 Hz, CH_3·CH_2); *m/e* 390 (4%), 372 (3), 288 (4), 273 (6), 270 (12), 210 (14), 186 (12), 185 (42), 184 (57), 183 (24), 169 (11), 159 (34), 158 (56), 155 (30), 145 (100), 144 (40), 143 (81), 129 (28), 91 (15), and 57 (31); *benzoate*, m.p. 88—89° (from aqueous ethanol) (Found: M^+, 494.2667. $C_{30}H_{38}O_6$ requires M, 494.2668).

Anhydrocompactin.—(*a*) Compactin (200 mg) was heated under reflux with potassium hydrogen sulphate (150 mg) in dimethylformamide (2 ml) for 6 h. After filtration the solution was concentrated *in vacuo* to give a brown oil which was chromatographed on silica gel in benzene–acetone (9 : 1). The least polar component crystallised from ethanol to give *anhydrocompactin* (II) {7-[1,2,6,7,8,8a-*hexahydro*-2-*methyl*-8-(2-*methylbutyryloxy*)*naphthyl*]*hept*-2-*en*-5-*olide*} as needles, m.p. 118—122° (60%) (Found: C, 73.5; H, 8.7%; M^+, 372.2303. $C_{23}H_{32}O_4$ requires C, 74.2; H, 8.7%; M, 372.2300), $\nu_{max.}$ 1 730 cm^{-1}; for δ see formula (II), otherwise the same as compactin.

(*b*) Compactin (100 mg) in pyridine (1 ml) was treated with *p*-bromobenzenesulphonyl chloride (66 mg) at room temperature and left for several days. The red solution was poured into ice–water and extracted with chloroform; the extract was washed, dried ($MgSO_4$), and concentrated *in vacuo* to a syrup. This crystallised from ethanol to give the anhydro-compound, m.p. 120—124° (73%), identical (i.r. and n.m.r.) with that obtained in (*a*).

7-(2-*Methyl*-1-*naphthyl*)*hept*-2-*en*-5-*olide* (VI).—Compactin (100 mg) was heated under reflux in toluene (3 ml) containing toluene-*p*-sulphonic acid (5 mg). The solution was then extracted with aqueous sodium hydrogen carbonate, dried, transferred to a silica gel column, and eluted with benzene–acetone (9 : 1). The tetralin (V), the least polar product, was isolated as a pale yellow, viscous liquid (60 mg) which crystallised from ethanol, m.p. 92—94° (Found: M^+, 270.1620. $C_{18}H_{22}O_2$ requires M, 270.1619), $\lambda_{max.}$ 228, 276, 285, and 293 nm (log ε 4.94, 3.70, 3.74, and 3.60), $\nu_{max.}$ ($CHCl_3$ or KBr) 1 700 cm^{-1}, δ 7.0—6.7 (3 H, m, ArH and =CH·CO), 6.02 (1 H, dt, *J* 10 and 2 Hz, CH_2·C*H*=), 4.50 (1 H, m, CH·O), 2.72 (6 H, m, $ArCH_2$), 2.36 (2 H, m, CH_2·CH=), 2.29 (3 H, s, CH_3), and 1.90 (6 H, m, $ArCH_2$·CH_2); in $CDCl_3$–C_6D_6 (50 : 50) the aromatic proton signals were clearly seen as a narrow quartet (*J* 8 Hz). The alkaline extract was acidified and extracted with ether; the organic layer was dried and evaporated leaving a sharp smelling liquid, identified (i.r., n.m.r.) as 2-methylbutyric acid by comparison with an authentic sample.

The tetralin (V) (140 mg) was heated under reflux in dry benzene (5 ml) with DDQ (236 mg) for 24 h. After cooling and filtration, the least polar product was isolated by chromatography on silica gel in benzene–acetone (9 : 1). It crystallised from ethanol to give the *naphthalene derivative* (VI) as needles, m.p. 109—110° (32%) (Found: C, 80.8; H, 6.8%; M^+, 266.1306. $C_{18}H_{18}O_2$ requires C, 81.2; H, 6.8%; M, 266.1306), $\lambda_{max.}$ 228, 276, 285, 293, 308, and 323 nm (log ε 4.94, 3.70, 3.74, 3.60, 2.90, and 2.70), $\nu_{max.}$ (KBr) 1 705 cm^{-1}, δ 8.1—7.3 (6 H, m, ArH), 6.84 (1 H, ddd, *J* 10, 5, and 4 Hz, CH_2·C*H*=), 6.02 (1 H, dt, *J* 10 and 2 Hz, =CH·CO), 4.52 (1 H, m, CH·O), 3.30 (2 H, m, $ArCH_2$), 2.50 (3 H, s, CH_3), 2.34 (2 H, m, CH_2·CH=), and 2.00 (2 H, m, $ArCH_2$·CH_2), *m/e* 266 (52%), 171 (23), 180 (24), 179 (14), 155 (100), 154 (68), and 141 (10).

The lactone (VI) was hydrogenated in ethyl acetate over palladised charcoal (10%) at room temperature until 1 mol. equiv. of hydrogen had been absorbed. After filtration and evaporation the residue was chromatographed on silica gel plates in chloroform to give the *dihydro-derivative* as a gum (Found: M^+, 268.1462. $C_{18}H_{20}O_2$ requires M, 268.1463), $\nu_{max.}$ 1 735 cm^{-1}, δ 8.1—7.3 (6 H, m, ArH), 4.42 (1 H, m, CH·O), 3.24 (2 H, m, $ArCH_2$), 2.51 (3 H, s, CH_3), 2.47 (2 H, m, CH_2·CO), and 2.16—1.42 (6 H, m, CH_2).

7-(8-*Methyl*-1-*naphthyl*)-5-*oxohept*-6-*enoic Acid*.—To 8-methyl-1-naphthaldehyde[5] (1.02 g) and 4-acetylbutyric acid (0.98 g) in ethanol (15 ml) was added 2N-sodium hydroxide (4.2 ml). The mixture was heated under reflux for 1 h, cooled, diluted with water, acidified, and extracted with ether. The extract was shaken with 2N-sodium carbonate; the aqueous layer was acidified and the precipitate transferred to ether; this solution was dried ($MgSO_4$) and evaporated. The residue crystallised from methanol to give the *acid* as light yellow plates, m.p. 131—132° (33%) (Found: C, 76.4; H, 6.7. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%), $\nu_{max.}$ 3 400br, 1 731, 1 670, and 1 603 cm^{-1}, δ 8.55 and 6.48 (each 1 H, d, *J* 16 Hz, CH=CH), 7.7br and 7.4br (each 3 H, m, ArH), 2.82 (3 H, s, $ArCH_3$), 2.80 (2 H, t, *J* 7 Hz, =CH·CO·CH_2), 2.48 (2 H, t, *J* 7 Hz, CH_2·CO_2H), and 2.05 (2 H, m, CH_2·CH_2·CH_2). Hydrogenation as for (VI) gave

[5] L. P. Zalukaev and V. V. Moiseev, *Zhur. org. Khim.*, **1966**, **2**, 282.

the lactone (VII) as a gum, δ 7.8—7.2 (6 H, m, ArH), 4.45 (1 H, m, CH·O), 3.40 (2 H, m, $ArCH_2$), 2.92 (3 H, s, CH_3), 2.51 (2 H, m, CH_2·CO), and 2.20—1.47 (6 H, m, CH_2).

7-(6-*Methyl-2-naphthyl*)-5-*oxohept-6-enoic Acid*.—This *acid*, prepared as above from 6-methyl-2-naphthaldehyde,[6] formed light yellow leaflets, m.p. 195—196° (from ethanol) (65%) (Found: C, 76.4; H, 6.7. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%), $\nu_{max.}$ 3 400br, 1 700, 1 675sh, and 1 620 cm^{-1}, δ($CDCl_3$ + 1 drop CF_3·CO_2D) 7.92 and 6.94 (each 1 H, d, *J* 16 Hz, CH=CH), 7.82—7.23 (6 H, m, ArH), 2.98 (2 H, t, *J* 7 Hz, =CH·CO·CH_2), 2.60 (2 H, t, *J* 7 Hz, CH_2·CO_2H), 2.54 (3 H, s, CH_3), and 2.10 (2 H, m, CH_2·CH_2·CH_2). Hydrogenation as for (VI) gave the 2,6-isomer of the lactone (VII) as a gum, δ 7.8—7.2 (6 H, m, Ar), 4.24 (1 H, m, CH·O), 2.93 (2 H, m, $ArCH_2$), 2.49 (5 H, m, CH_3 + CH_2·CO), and 2.20—1.38 (6 H, m, CH_2).

Crystal Structure Determination.—A fragment was cut from a large crystal of compactin of indeterminate shape. The cell dimensions and symmetry were determined by oscillation and Weisenberg photographs (Cu-K_α radiation) and refined and confirmed on a Hilger–Watt four-circle diffractometer.

Crystal data. $C_{23}H_{34}O_5$, $M = 390$. Orthorhombic, $a = 9.728$ (1), $b = 24.030$ (2), $c = 9.185$ (1) Å, $U = 2\,147$ Å^3, $D_m = 1.20$, $D_c = 1.207$ g cm^{-3}, $Z = 4$, $F(000) = 848$. Space group $P2_12_12_1$ (from systematic absences); μ(Mo-K_α) = 0.90 cm^{-1}.

Intensity measurements were made by 2θ—ω scans out to θ = 30° (monochromatic Mo-K_α radiation) and 2 179 reflections with a net count $>3\sigma$ were deemed observed. The structure was solved by using the direct methods program MULTAN[7] and the best *E* map revealed the position of all but one non-hydrogen atom. The position of the missing atom was found from a difference map following two cycles of isotropic block-diagonal least-squares refinement. Further refinement proceeded smoothly; all the hydrogen atoms were located from difference maps and their parameters were allowed to refine isotropically for four cycles with the other atoms varying anisotropically. A weighting scheme of the form $w = 1$ for $F_o < 22.0$ and $w = (22.0/F_o)^2$ for the stronger reflections was then employed for final

TABLE 1

Fractional co-ordinates of atoms (× 10^4) with standard deviations in parentheses. Hydrogen atoms are numbered with reference to the atom to which they are attached

Atom	*x*/*a*	*y*/*b*	*z*/*c*	Atom	*x*/*a*	*y*/*b*	*z*/*c*
C(1)	139(3)	2 849(1)	7 499(3)	C(13)	1 242(3)	4 621(1)	4 603(3)
C(2)	195(3)	2 452(1)	6 171(3)	C(14)	2 293(4)	5 087(1)	4 519(4)
C(3)	−575(3)	1 922(1)	6 491(4)	C(15)	3 708(4)	4 833(1)	4 379(4)
C(4)	−796(3)	1 737(1)	7 832(4)	C(16)	4 024(3)	4 394(1)	5 492(4)
C(4a)	−329(3)	2 017(1)	9 138(4)	C(1B)	−720(3)	3 689(1)	10 949(4)
C(5)	−616(3)	1 825(1)	10 473(4)	C(2B)	−2 152(4)	3 901(1)	11 204(5)
C(6)	−157(3)	2 095(1)	11 861(4)	C(3B)	−2 260(5)	4 131(2)	12 775(6)
C(7)	944(3)	2 540(1)	11 607(3)	C(4B)	−2 509(5)	4 364(2)	10 109(7)
C(8)	636(3)	2 893(1)	10 268(3)	C(5B)	−2 378(7)	4 180(2)	8 548(7)
C(8a)	562(3)	2 536(1)	8 898(3)	O(1)	−709(2)	3 162(1)	10 470(2)
C(9)	1 658(3)	2 311(1)	5 653(4)	O(2)	305(2)	3 956(1)	11 157(3)
C(10)	1 014(3)	3 372(1)	7 292(3)	O(3)	2 966(2)	4 088(1)	6 017(3)
C(11)	704(3)	3 710(1)	5 917(3)	O(4)	5 150(3)	4 278(1)	5 879(4)
C(12)	1 524(3)	4 252(1)	5 903(3)	O(5)	2 191(3)	5 404(1)	5 836(3)
H(C1)	−925(56)	2 959(21)	7 577(60)	H′(C13)	1 307(63)	4 345(24)	3 611(69)
H(C2)	−349(61)	2 673(23)	5 315(70)	H(C14)	1 994(68)	5 350(25)	3 593(74)
H(C3)	−1 012(58)	1 717(22)	5 742(63)	H(C15)	4 619(40)	5 118(16)	4 359(45)
H(C4)	−1 419(48)	1 417(19)	7 965(53)	H′(C15)	3 785(72)	4 647(28)	3 351(77)
H(C5)	−1 373(57)	1 470(22)	10 558(66)	H(C9)	2 167(45)	2 720(19)	5 278(52)
H(C6)	260(57)	1 784(22)	12 560(60)	H′(C9)	2 274(56)	2 129(21)	6 494(58)
H′(C6)	−1 171(67)	2 245(26)	12 331(77)	H″(C9)	1 659(57)	2 021(21)	4 758(60)
H(C7)	1 089(59)	2 808(23)	12 509(67)	H(C2B)	−2 795(50)	3 569(18)	11 199(53)
H′(C7)	2 090(55)	2 361(21)	11 516(58)	H(C3B)	−3 261(102)	4 308(38)	12 907(111)
H(C8)	1 617(49)	3 175(19)	10 203(52)	H′(C3B)	−2 097(85)	3 804(35)	13 547(10)
H(C8a)	1 567(41)	2 385(16)	8 662(45)	H″(C3B)	−1 424(79)	4 435(30)	12 787(88)
H(C10)	964(43)	3 607(16)	8 066(45)	H(C4B)	−3 667(68)	4 435(26)	10 276(77)
H′(C10)	2 094(48)	3 238(18)	7 365(50)	H′(C4B)	−1 865(77)	4 695(30)	10 114(87)
H(C11)	1 037(45)	3 494(17)	5 017(47)	H(C5B)	−2 924(101)	3 767(37)	8 523(109)
H′(C11)	−290(53)	3 846(21)	5 960(59)	H′(C5B)	−2 851(92)	4 444(33)	7 850(95)
H(C12)	1 113(48)	4 471(18)	6 875(51)	H″(C5B)	−1 251(84)	4 141(32)	8 237(92)
H(C13)	154(44)	4 793(17)	4 730(46)	H(O5)	3 176(80)	5 580(29)	6 101(87)

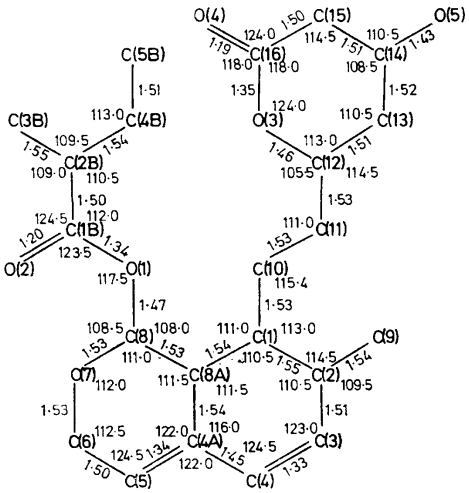


FIGURE 1 Compactin: interatomic distances, bond angles, and crystallographic numbering

[6] L. Syper, *Tetrahedron Letters*, 1967, 4193.

[7] G. Germain, P. Main, and M. M. Wolfson, *Acta Cryst.*, 1971, **A27**, 368.

refinement by full matrix methods with the hydrogen atoms fixed and reflections (30) with $w\Delta F > 2.0$ not contributing to the shifts. At convergence, R was 5.2%.

TABLE 2

Interatomic distances and angles

(*a*) Bond lengths in Å, with standard deviations in parentheses; an asterisk designates an atom in another molecule

C(1)–C(2)	1.549(4)	C(8)–O(1)	1.471(3)	C(15)–C(16)	1.501(5)
C(1)–C(8a)	1.544(4)	C(8)–H(C8)	1.17(5)	C(15)–H(C15)	1.12(4)
C(1)–C(10)	1.531(4)	C(8a)–H(C8a)	1.07(4)	C(15)–H′(C15)	1.05(7)
C(1)–H(C1)	1.07(5)	C(9)–H(C9)	1.15(5)	C(16)–O(4)	1.186(4)
C(2)–C(3)	1.507(4)	C(9)–H′(C9)	1.07(5)	C(16)–O(3)	1.354(4)
C(2)–C(9)	1.538(4)	C(9)–H″(C9)	1.08(5)	O(1)–C(1B)	1.341(3)
C(2)–H(C2)	1.09(6)	C(10)–C(11)	1.531(4)	C(1B)–O(2)	1.201(4)
C(3)–C(4)	1.327(5)	C(10)–H(C10)	0.91(4)	C(1B)–C(2B)	1.501(5)
C(3)–H(C3)	0.95(6)	C(10)–H′(C10)	1.10(5)	C(2B)–C(3B)	1.549(7)
C(4)–C(4a)	1.448(5)	C(11)–C(12)	1.528(4)	C(2B)–C(4B)	1.540(6)
C(4)–H(C4)	0.99(5)	C(11)–H(C11)	1.03(4)	C(2B)–H(C2B)	1.01(5)
C(4a)–C(5)	1.339(5)	C(11)–H′(C11)	1.02(5)	C(4B)–C(5B)	1.506(8)
C(4a)–C(8a)	1.535(4)	C(12)–C(13)	1.513(4)	C(HB)–H(CHB)	1.15(7)
C(5)–C(6)	1.499(5)	C(12)–O(3)	1.461(4)	C(HB)–H′(CHB)	1.01(7)
C(5)–H(C5)	1.13(5)	C(12)–H(C12)	1.11(5)	C(3B)–H(CBB)	1.07(10)
C(6)–C(7)	1.531(5)	C(13)–C(14)	1.518(4)	C(3B)–H′(C3B)	1.07(9)
C(6)–H(C6)	1.07(5)	C(13)–H(C13)	1.14(4)	C(3B)–H″C(3B)	1.09(8)
C(6)–H′(C6)	1.14(7)	C(13)–H′(C13)	1.13(6)	C(5B)–H(C5B)	1.13(9)
C(7)–C(8)	1.523(4)	C(14)–C(15)	1.511(5)	C(5B)–H′(C5B)	1.01(8)
C(7)–H(C7)	1.06(6)	C(14)–O(5)	1.432(4)	C(5B)–H″(C5B)	1.14(8)
C(7)–H′(C7)	1.20(5)	C(14)–H(C14)	1.10(7)	H(O5)–O(2) *	1.85(8)
C(8)–C(8a)	1.525(4)	O(5)–H(O5)	1.08(8)	O(5)–O(2) *	2.896(4)

(*b*) Bond angles in degrees, with standard deviations in parentheses; an asterisk designates an atom in another molecule

C(2)–C(1)–(C8a)	110.3(2)	C(12)–C(11)–H(C11)	105(2)
C(2)–C(1)–C(10)	112.8(2)	C(12)–C(11)–H′(C11)	103(3)
C(8a)–C(1)–C(10)	110.8(2)	H(C11)–C(11)–H′(C11)	119(4)
C(2)–C(1)–H(C1)	104(3)	C(11)–C(12)–C(13)	114.3(3)
C(10)–C(1)–H(C1)	110(3)	C(11)–C(12)–O(3)	105.7(2)
C(1)–C(2)–C(3)	110.4(3)	C(13)–C(12)–O(3)	112.9(2)
C(9)–C(2)–C(3)	109.5(3)	C(11)–C(12)–H(C12)	102(2)
C(9)–C(2)–C(1)	114.3(3)	O(5)–C(12)–H(C12)	115(2)
C(1)–C(2)–H(C2)	105(3)	C(13)–C(12)–H(C12)	107(2)
C(3)–C(2)–H(C2)	108(3)	C(12)–C(13)–C(14)	110.5(3)
C(9)–C(2)–H(C2)	110(3)	C(12)–C(13)–H(C13)	107(2)
C(2)–C(3)–C(4)	123.0(3)	C(12)–C(13)–H′(C13)	106(3)
C(2)–C(3)–H(C3)	121(3)	C(14)–C(13)–H(C13)	111(2)
C(4)–C(3)–H(C3)	115(3)	C(14)–C(13)–H′(C13)	111(3)
C(3)–C(4)–C(4a)	124.3(3)	H(C13)–C(13)–H′(C13)	110(4)
C(3)–C(4)–H(C4)	118(3)	C(13)–C(14)–C(15)	108.7(2)
C(4a)–C(4)–H(C4)	117(3)	C(13)–C(14)–O(5)	107.6(3)
C(4)–C(4a)–C(5)	122.2(3)	C(15)–C(14)–O(5)	110.5(3)
C(4)–C(4a)–C(8a)	115.8(3)	C(13)–C(14)–H(C14)	107(3)
C(5)–C(4a)–C(8a)	122.0(3)	C(15)–C(14)–H(C14)	114(3)
C(4a)–C(5)–C(6)	124.5(3)	O(5)–C(14)–H(C14)	109(3)
C(4a)–C(5)–H(C5)	117(3)	C(14)–C(15)–C(16)	114.4(3)
C(6)–C(5)–H(C5)	118(3)	C(14)–C(15)–H(C15)	118(2)
C(5)–C(6)–C(7)	112.4(3)	C(14)–C(15)–H′(C15)	108(4)
C(5)–C(6)–H(C6)	109(3)	C(16)–C(15)–H(C15)	106(2)
C(5)–C(6)–H′(C6)	102(3)	C(16)–C(15)–H′(C15)	107(4)
C(7)–C(6)–H(C6)	108(3)	H(C15)–C(15)–H′(C15)	101(4)
C(7)–C(6)–H′(C6)	116(3)	C(15)–C(16)–O(3)	118.0(3)
H(C6)–C(6)–H′(C6)	109(5)	C(15)–C(16)–O(4)	124.0(3)
C(6)–C(7)–C(8)	112.0(3)	O(3)–C(16)–O(4)	117.9(3)
C(6)–C(7)–H(C7)	113(3)	C(16)–O(3)–C(12)	123.9(2)
C(6)–C(7)–H′(C7)	114(2)	C(14)–O(5)–H(05)	110(4)
C(8)–C(7)–H(C7)	109(3)	C(8)–O(1)–C(1B)	117.6(2)
C(8)–C(7)–H′(C7)	109(3)	O(1)–C(1B)–C(2B)	112.3(2)
H(C7)–C(7)–H′(C7)	99(4)	O(1)–C(1B)–O(2)	123.4(3)
C(7)–C(8)–C(8a)	111.2(2)	C(2B)–C(1B)–O(2)	124.4(3)
C(7)–C(8)–O(1)	108.5(2)	C(1B)–C(2B)–C(3B)	109.3(3)
C(8a)–C(8)–O(1)	108.0(2)	C(1B)–C(2B)–C(4B)	110.6(3)
C(7)–C(8)–H(C8)	102(2)	C(3B)–C(2B)–C(4B)	109.6(3)
C(8a)–C(8)–H(C8)	109(2)	C(1B)–C(2B)–H(C2B)	108(3)
O(1)–C(8)–H(C8)	118(3)	C(3B)–C(2B)–H(C2B)	104(3)
C(8)–C(8a)–C(1)	115.2(2)	C(4B)–C(2B)–H(C2B)	115(3)
C(8)–C(8a)–C(4a)	111.4(2)	C(2B)–C(3B)–H(C3B)	108(5)
C(1)–C(8a)–C(4a)	111.4(2)	C(2B)–C(3B)–H′(C3B)	110(5)
C(8)–C(8a)–H(C8a)	108(2)	C(2B)–C(3B)–H″(C3B)	101(4)
C(4a)–C(8a)–H(C8a	106(2)	H(C3B)–C(3B)–H′(C3B)	111(7)
C(1)–C(8a)–H(C8a)	104(2)	H(C3B)–C(3B)–H″(C3B)	114(6)
C(2)–C(9)–H(C9)	108(2)	H′(C3B)–C(3B)–H″(C3B)	112(6)
C(2)–C(9)–H′(C9)	113(3)	C(2B)–C(4B)–C(5B)	113.0(4)
C(2)–C(9)–H″(C9)	112(3)	C(2B)–C(4B)–H(C4B)	104(3)
H(C9)–C(9)–H′(C9)	109(4)	C(2B)–C(4B)–H′(C4B)	115(4)
H(C9)–C(9)–H″(C9)	109(4)	C(5B)–C(4B)–H(C4B)	105(4)
H′(C9)–C(9)–H″(C9)	107(4)	C(5B)–C(4B)–H′(C4B)	100(5)
C(1)–C(10)–C(11)	115.4(3)	H(C4B)–C(4B)–H′(C4B)	119(5)
C(1)–C(10)–H(C10)	113(3)	C(4B)–C(5B)–H(C5B)	104(5)
C(11)–C(10)–H(C10)	108(3)	C(4B)–C(5B)–H′(C5B)	112(5)
C(1)–C(10)–H′(C10)	106(2)	C(4B)–C(5B)–H″(CB5)	110(4)
C(11)–C(10)–H′(C10)	113(2)	H(C5B)–C(5B)–H′(C5B)	109(7)
H(C10)–C(10)–H′(C10)	101(4)	H(C5B)–C(5B)–H″(C5B)	112(6)
C(10)–C(11)–C(12)	110.9(2)	H′(C5B)–C(5B)–H″(C5B)	109(6)
C(10)–C(11)–H(C11)	110(2)	O(5)–H(05)–O(2) *	163(6)
C(10)–C(11)–H′(C11)	109(3)	C(1B)–O(2)–H(02) *	168(2)

Figure 1 shows the structure and the crystallographic numbering with bond lengths to three significant figures and angles to the nearest half degree. The atoms of the butyrate chain are less well defined than the others and have higher temperature factors. The estimated standard deviations of bond lengths were *ca.* 0.004 Å, and of angles 0.25°, except for the butyrate carbon atoms which have errors approximately twice these values. All dimensions involving hydrogen are within 3 σ of expected values. Full details of all atomic co-ordinates, bond lengths and angles, and thermal parameters are given in Tables 1—3. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 21719 (13 pp., 1 microfiche).*

TABLE 3

Thermal parameters

(*a*) Anisotropic, in the form $\exp[-2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + 2U_{12}a^*b^*hk + 2U_{13}a^*c^*hl + 2U_{23}b^*c^*kl)]$, multiplied by 10^4, with standard deviations in parentheses

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	378(14)	294(12)	429(14)	−49(11)	−51(12)	−3(12)
C(2)	462(15)	381(13)	440(16)	−29(13)	−44(14)	−8(14)
C(3)	531(18)	375(14)	580(19)	−102(13)	−51(17)	−72(14)
C(4)	446(17)	360(14)	656(20)	−73(13)	3(16)	−31(15)
C(4a)	337(13)	317(12)	556(18)	17(11)	74(14)	29(13)
C(5)	406(15)	386(14)	584(18)	−12(12)	54(15)	116(14)
C(6)	484(17)	500(17)	532(18)	−31(15)	36(16)	127(15)
C(7)	429(15)	535(17)	475(17)	−79(15)	−48(14)	86(16)
C(8)	299(13)	368(13)	464(16)	−17(11)	−10(13)	32(12)
C(8a)	325(12)	316(11)	410(14)	−14(11)	7(12)	22(12)
C(9)	496(17)	596(18)	464(18)	−12(15)	65(16)	−13(16)
C(10)	488(16)	351(13)	412(15)	−120(13)	−87(14)	62(12)
C(11)	534(17)	343(13)	420(15)	−86(13)	−107(15)	43(12)
C(12)	453(15)	343(12)	400(15)	−48(12)	−24(14)	42(12)
C(13)	548(18)	411(14)	417(16)	−79(14)	−74(15)	70(14)
C(14)	578(19)	397(15)	425(16)	−73(14)	8(16)	49(13)
C(15)	583(20)	465(16)	469(17)	−86(16)	96(16)	23(15)
C(16)	507(17)	436(15)	559(19)	−82(16)	3(17)	−51(15)
C(1B)	419(15)	339(12)	550(18)	−35(12)	4(15)	3(14)
C(2B)	500(18)	361(14)	926(27)	−22(14)	62(20)	−103(18)
C(3B)	846(32)	913(30)	1 142(39)	−32(27)	329(32)	−364(31)
C(4B)	769(30)	630(23)	1 331(43)	181(22)	119(30)	90(28)
C(5B)	1 297(49)	1 129(39)	1 106(42)	324(38)	−484(40)	98(35)
O(1)	342(10)	331(9)	556(12)	−21(8)	1(10)	−30(9)
O(2)	500(13)	444(11)	934(19)	−118(10)	5(14)	−113(14)
O(3)	456(11)	419(10)	580(13)	−31(9)	−35(11)	99(11)
O(4)	442(18)	880(18)	1 071(23)	−75(13)	−122(16)	227(19)
O(5)	669(14)	390(10)	576(13)	−82(11)	99(13)	−68(11)

(*b*) Isotropic, multiplied by 10^3

Atom	U	Atom	U	Atom	U
H(C1)	31(16)	H(C9)	17(13)	H(C15)	14(10)
H(C2)	49(20)	H′(C9)	28(17)	H′(C15)	86(26)
H(C3)	44(18)	H″(C9)	35(17)	H(C2B)	27(14)
H(C4)	21(14)	H(C10)	29(11)	H(C3B)	83(44)
H(C5)	48(19)	H′(C10)	16(13)	H′(C3B)	141(39)
H(C6)	67(24)	H(C11)	29(12)	H″(C3B)	90(30)
H′(C6)	33(16)	H′(C11)	30(16)	H(C4B)	92(24)
H(C7)	49(19)	H(C12)	25(13)	H′(C4B)	137(30)
H′(C7)	38(17)	H(C13)	13(11)	H(C5B)	147(42)
H(C8)	15(14)	H′(C13)	30(16)	H′(C5B)	116(36)
H(C8a)	24(11)	H(C14)	58(23)	H″(C5B)	117(33)
				H(O5)	86(28)

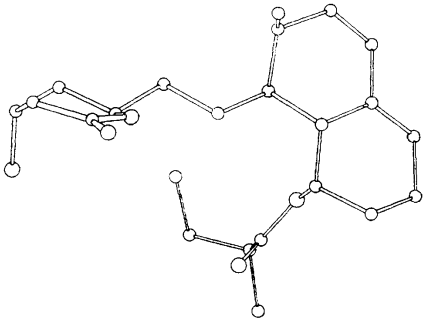


FIGURE 2 Compactin: relative configuration

The hydrogen of the hydroxy-group of the lactone ring is *ca.* 1.85 Å from the carbonyl oxygen atom of the butyrate group of the adjacent molecule, suggesting that there is hydrogen bonding in the crystal between these two oxygen atoms. No other intermolecular distances are significantly short.

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

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