HASLAM, E. & TURNER, M. J. (1971). *J. Chem. Soc.* pp. 1496–1500.

HOFMAN, F. C. (1790). *Crell's Ann.* 2, 314–324.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

IUPAC–IUB (1968). *Eur. J. Biochem.* 5, 1–8.

ROGERS, D. (1981). *Acta Cryst.* A37, 734–741.

SHELDRICK, G. M. (1983). *SHELXTL Users Manual*, revision 4. Nicolet XRD Corporation, Madison, Wisconsin, USA.

WEISS, U. & EDWARDS, J. M. (1980). In *The Biosynthesis of Aromatic Compounds.* New York: John Wiley.

Structure of (−)-3-Dehydroshikimic Acid Monohydrate

BY CHRISTOPHER ABELL, FRANK H. ALLEN,* TIMOTHY D. H. BUGG, MICHAEL J. DOYLE AND PAUL R. RAITHBY

*University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England*

Abstract. (−)-4α,5β-Dihydroxy-3-oxo-1-cyclohexene-carboxylic acid monohydrate, $C_7H_8O_5.H_2O$, $M_r = 190.2$, monoclinic, $P2_1$, $a = 5.723$ (1), $b = 8.554$ (1), $c = 8.693$ (2) Å, $\beta = 107.14$ (1)°, $V = 406.6$ (1) Å^3, $Z = 2$, $D_x = 1.553$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1.54178$ Å, $\mu = 1.157$ mm^{-1}, $F(000) = 200$, $T = 293$ K, $R = 0.032$ for 1106 observed reflections $[I > 3\sigma(I)]$ and 140 parameters. A positive indication of absolute configuration $[\eta = 1.18 (40)]$ is in accord with chemical knowledge. The cyclohexene ring adopts a half-chair conformation, slightly distorted towards the 1,2-diplanar (sofa) form by the 3-oxo substituent. The −COOH group is twisted out of the plane of the endocyclic double bond by 18.7 (3)°. The crystal structure is stabilized by a network of five O−H···O hydrogen bonds with O···O ≤ 2.909 (3) Å. The water molecule is involved in three of these interactions, including a very short COO−H···O(w) bond with O···O = 2.567 (3) Å and O−H···O = 167 (3)°.

Introduction. The shikimate pathway is the biosynthetic route to aromatic amino acids in plants and micro-organisms (Weiss & Edwards, 1980; Conn, 1986). The pathway is of agrochemical interest as a potential target for herbicides, hence we have commenced a series of X-ray studies designed to provide accurate structural data, for molecular modelling purposes, of intermediates on the pathway and of related molecules. The structures of sodium (−)-shikimate dihydrate (Abell, Allen, Bugg, Doyle & Raithby, 1988a) and (−)-quinic acid (Abell, Allen, Bugg, Doyle & Raithby, 1988b) have already been reported. Here we report the structure of (−)-3-dehydroshikimic acid (I) monohydrate. This molecule occupies a key position on the shikimate pathway,

being the immediate precursor of (−)-shikimic acid (II). (I) is the enzyme product of 3-dehydroquinate dehydratase and the substrate for shikimate dehydrogenase. It has been shown to inhibit 3-dehydroquinate dehydratase competitively (Abell & Bugg, 1988).

(−)-3-Dehydroshikimic acid was first isolated by Salamon & Davis (1953) from culture filtrates of a mutant strain of *E. coli*, and has since been isolated from many fungal and plant sources (Weiss & Edwards, 1980). The chemical structure (Salamon & Davis, 1953) was deduced by a variety of analytical and spectroscopic tests, and from its close relationship to shikimic acid whose structure was already known (Fischer & Dangschat, 1934). The conformation of the cyclohexene ring in solution was shown to be a half-chair (Thompson & Haslam, 1974) by ^{1}H NMR spectroscopy.

(I)   (II)
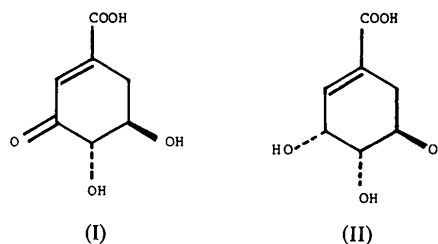
Experimental. 3-Dehydroshikimic acid was prepared by oxidation of shikimic acid (McKittrick & Ganem, 1985) and purified by high-pressure liquid chromatography, using a Bio-Rad Aminex HPX87H Organic Acids column. Colourless prismatic crystals, shown here to be the monohydrate, were obtained by vapour diffusion from ethyl acetate/light (40–60) petroleum. Crystal 0.32 × 0.45 × 0.53 mm; Nicolet $R3m\mu$ diffractometer; graphite-monochromatized Cu $K\alpha$ radiation; cell parameters refined from diffractometer

* Author for correspondence.

setting angles for 25 centred reflections $(50 < 2\theta < 64°)$. Intensity data collected by $\theta-2\theta$ scans for 2326 reflections with $5 < 2\theta < 116°$ $(h-6/6, k-9/9, l-9/9)$; 3 standard reflections measured in every 50 showed no significant decay; absorption neglected. 1106 unique reflections including Friedel pairs $(R_{int} = 0.022)$ with $I > 3\sigma(I)$ were used in the analysis. Structure solved by multisolution direct methods, blocked-cascade least-squares refinement on F, anisotropic thermal parameters for non-H atoms. H atoms from ΔF syntheses: C—H riding on C at 0.96 Å, all O—H positions refined, separate overall U's for different types of H atom. 140 parameters; $R = 0.032$, $wR = 0.044$, $S = 1.575$, $w^{-1} = \sigma^2(F_o) + 0.0006F_o^2$, $\Delta/\sigma = 0.052$ (mean) and 0.385 (max.), $\Delta\rho$ within $+0.28$ and -0.30 e Å^{-3}. The predictive ability of Rogers (1981) η parameter was examined for this molecule of known absolute configuration. Two refinements using the correct enantiomorph and a starting η of (a) 1.0 and (b) -1.0 yielded identical final η values of $+1.18$ (40). Simple enantiomorph inversion yielded values of R, wR identical to those cited above. The value of $(1 + |\eta|)/\sigma(\eta)$ (Rogers, 1981) at 5.5 is comparable to the value of 6.2 obtained for $(-)$-quinic acid (Abell *et al.*, 1988*b*) but lower than the 9.8 obtained for sodium shikimate dihydrate (Abell *et al.*, 1988*a*), despite the fact that Friedel pairs were measured in the present study. Nevertheless the result is statistically acceptable and is consistent with chemical knowledge.

The *SHELXTL* program system (Sheldrick, 1983) was used throughout, with scattering factors and f', f'' corrections from *International Tables for X-ray Crystallography* (1974).

Discussion. Final atomic parameters are given in Table 1* and molecular geometry in Table 2. A perspective view of the molecule is shown in Fig. 1, whilst H-bonding and molecular packing are illustrated in Fig. 2. The crystallographic numbering is based upon IUPAC–IUB (1968) recommendations for cyclitols.

The conformation of the cyclohexene ring is best described as a half-chair (Table 2). By comparison with the conformation of (II) as sodium shikimate dihydrate (Abell *et al.*, 1988*a*) there is some movement towards a 1,2-diplanar (sofa) conformation in (I). Thus the conversion of the 3α-hydroxy group in (II) to the 3-oxo moiety in (I) (see *Experimental*) produces an increased ring asymmetry. The asymmetry parameters (Duax & Norton, 1975) ΔC_2^{1-2} are 2.9 and 5.0° for two independent molecules of (II), but this increases to 11.0° for (I). This process is, of course, reversed in the

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44848 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Atomic coordinates* $(\times 10^4)$ *and equivalent isotropic temperature factors* $(Å^2 \times 10^3)$ *for the non-H atoms*

U_{eq} is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
C(1)	-1350(3)	10240(2)	1212(2)	36(1)
C(2)	406(3)	9215(3)	1229(2)	41(1)
C(3)	2621(3)	9055(2)	2601(2)	38(1)
C(4)	2610(3)	9933	4106(2)	38(1)
C(5)	1421(3)	11534(2)	3651(2)	37(1)
C(6)	-1215(3)	11328(2)	2592(2)	39(1)
C(7)	-3569(3)	10269(2)	-231(2)	37(1)
O(3)	4333(3)	8241(2)	2538(2)	52(1)
O(4)	5025(2)	10044(3)	5117(2)	49(1)
O(5)	1346(2)	12370(2)	5046(2)	46(1)
O(7)	-3560(2)	9707(2)	-1523(2)	49(1)
O(8)	-5460(2)	10931(2)	35(2)	48(1)
O(99)	-9266(3)	10687(3)	-2415(2)	64(1)

Table 2. *Molecular geometry of* $(-)$-*3-dehydroshikimic acid* (I) *monohydrate*

Distances in Å, angles in °, with e.s.d.'s in parentheses.

C(1)—C(2)	1.331(3)	C(5)—C(6)	1.528(2)
C(1)—C(6)	1.502(3)	C(3)—O(3)	1.216(3)
C(1)—C(7)	1.499(2)	C(4)—O(4)	1.405(2)
C(2)—C(3)	1.469(2)	C(5)—O(5)	1.420(3)
C(3)—C(4)	1.511(3)	C(7)—O(7)	1.223(2)
C(4)—C(5)	1.529(2)	C(7)—O(8)	1.301(2)

C(2)—C(1)—C(6)	122.6(1)	C(4)—C(3)—O(3)	122.2(1)
C(2)—C(1)—C(7)	118.1(2)	C(3)—C(4)—O(4)	108.7(1)
C(6)—C(1)—C(7)	119.3(2)	C(5)—C(4)—O(4)	112.5(1)
C(1)—C(2)—C(3)	122.6(2)	C(4)—C(5)—O(5)	110.7(1)
C(2)—C(3)—C(4)	115.7(2)	C(6)—C(5)—O(5)	107.4(2)
C(3)—C(4)—C(5)	109.6(1)	C(1)—C(7)—O(7)	122.0(2)
C(4)—C(5)—C(6)	109.8(1)	C(1)—C(7)—O(8)	113.7(2)
C(5)—C(6)—C(1)	111.2(2)	O(7)—C(7)—O(8)	124.5(1)
C(2)—C(3)—O(3)	122.1(2)		

Selected torsion angles. Values for (I) are compared with values for the two independent molecules of sodium shikimate dihydrate (IIa,b; Abell *et al.*, 1988*a*) and with minimum-energy results of Bucourt & Hainaut (1965) for half-chair and sofa conformations.

	(I)	(IIa)	(IIb)	Half-chair	Sofa
C(6)—C(1)—C(2)—C(3)	0.2(3)	0.1(6)	3.1(5)	0	0
C(1)—C(2)—C(3)—C(4)	9.8(3)	17.3(5)	11.9(4)	15	0
C(2)—C(3)—C(4)—C(5)	-39.9(2)	-49.8(4)	-44.6(4)	-45	-28
C(3)—C(4)—C(5)—C(6)	60.5(2)	65.5(5)	64.6(4)	62	56
C(4)—C(5)—C(6)—C(1)	-50.7(2)	-46.5(5)	-50.0(4)	-45	-54
C(5)—C(6)—C(1)—C(2)	20.9(3)	14.9(5)	16.5(5)	15	27
C(2)—C(1)—C(7)—O(7)	-19.3(3)	-13.1(5)	-19.6(5)		
C(2)—C(1)—C(7)—O(8)	160.3(3)	165.8(3)	160.6(3)		
C(6)—C(1)—C(7)—O(7)	162.2(3)	169.8(3)	160.5(3)		
C(6)—C(1)—C(7)—O(8)	-18.1(3)	-11.2(5)	-19.3(4)		

Hydrogen-bond geometry, H-atom positions normalized to O—H = 0.983 Å

	$d(H \cdots O)$	$d(O \cdots O)$	O—H$\cdots$O
O(4)—H(4O)$\cdots$O(7i)	1.88(4)	2.806(3)	155(2)
O(5)—H(5O)$\cdots$O(3ii)	1.97(4)	2.832(3)	146(3)
O(8)—H(8O)$\cdots$O(99iii)	1.60(4)	2.567(3)	167(2)
O(99)—H(99A)$\cdots$O(7iv)	2.07(4)	2.909(3)	142(5)
O(99)—H(99B)$\cdots$O(5i)	1.80(4)	2.742(3)	159(3)

Symmetry code: (i) $-1 + x, y, -1 + z$; (ii) $1 - x, -0.5 + y, 1 - z$; (iii) x, y, z; (iv) $-1 + x, y, z$.

biosynthetic route by which (II) is produced from (I). A survey of the Cambridge Structural Database (CSD) (Allen *et al.*, 1979) shows that the conformation of (I) is

typical of 1-cyclohexen-3-ones. Of 42 examples un-distorted by fusion or bridging, 39 had conformations similar to (I), with mean absolute intra-annular torsion angles (in the order of Table 2) 4·3 (5), 9·0 (12), 35·4 (14), 52·3 (5), 42·6 (14), 15·8 (15)°; the other three examples all adopt a highly distorted twist-boat conformation.

Two other conformational features are of interest. Firstly the carboxylate group is twisted with respect to the C(1)=C(2) double bond. The mean twist about C(1)—C(7) is 18·7 (3)° in (I) and this feature is preserved in (IIa) [12·4 (4)°] and (IIb) [19·4 (4)°]. In (II) (Abell et al., 1988a), a difference was also noted in the 5β-O—H conformation, O—H being approximately antiperiplanar to C(6)—C(5) in (IIa), and to C(4)—C(5) in (IIb); (I) is directly comparable to (IIa), with C(6)—C(5)—O(5)—H(5O) = −161 (2) and C(4)—C(5)—O(5)—H(5O)=79 (2)°.

For (II) the conformational differences noted above were ascribed to the energetic requirements of an extensive H-bonding scheme. A similar argument may be advanced for (I). There are five discrete O—H···O interactions with O···O in the range 2·567 (3)– 2·909 (3) Å (see Fig. 2, Table 2). Three of these interactions involve the water O(99) atom, including the very short O(8)—H(8O)···O(99) interaction of 2·567 (3) Å. It is notable that in all literature descriptions of the isolation (Salamon & Davis, 1953) or synthesis (Grewe & Jeschke, 1956; McKittrick & Ganem, 1985) of (I) the crystalline samples obtained
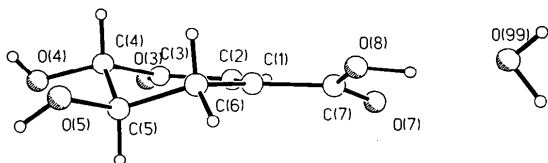
are monohydrates, irrespective of solvent. In our procedures, described above, the hydration must occur during work-up, and is retained during crystallization from anhydrous solvents. Salamon & Davis (1953) report crystal data for the monohydrate as monoclinic, $P2_1$, with $\beta = 111°$ and $a = 5·87$, $b = 8·56$, $c = 8·92$ kX ($a = 5·88$, $b = 8·58$, $c = 8·94$ Å) from which $D_x = 1·500$ Mg m^{-3}. These values are very comparable with those obtained here.

There are no unusual bond lengths and angles in (I). The C(2)—C(3) sp^2—sp^2 single bond of 1·469 (2) Å is close to the mean value for C=C—C=O substructures of 1·464 (1) Å obtained for 211 examples in the CSD (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987). The C(1)—C(7) bond at 1·499 (2) Å is, however, at the high end of the distribution obtained for C=C—COOH substructures [mean = 1·475 (4) Å; Allen et al., 1987], indicative of reduced conjugation implicit in the large torsion angles about C(1)—C(7).

Fig. 1. Perspective view of the structure of (—)-3-dehydroshikimic acid (I) monohydrate.
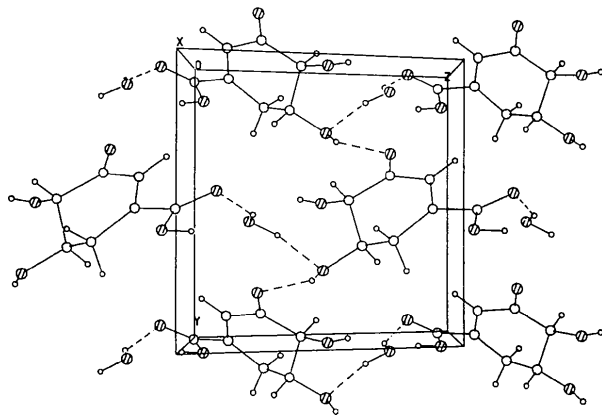
Fig. 2. Packing diagram for (—)-3-dehydroshikimic acid (I) monohydrate. H bonds are shown as broken lines.

References

ABELL, C., ALLEN, F. H., BUGG, T. D. H., DOYLE, M. J. & RAITHBY, P. R. (1988a). Acta Cryst. C44, 1204–1207.
ABELL, C., ALLEN, F. H., BUGG, T. D. H., DOYLE, M. J. & RAITHBY, P. R. (1988b). Acta Cryst. C44, 1287–1290.
ABELL, C. & BUGG, T. D. H. (1988). In preparation.
ALLEN, F. H., BELLARD, S., BRICE, M. D., CARTWRIGHT, B. A., DOUBLEDAY, A., HIGGS, H., HUMMELINK, T., HUMMELINK-PETERS, B. G., KENNARD, O., MOTHERWELL, W. D. S., ROGERS, J. R. & WATSON, D. G. (1979). Acta Cryst. B35, 2331–2339.
ALLEN, F. H., KENNARD, O., WATSON, D. G., BRAMMER, L., ORPEN, A. G. & TAYLOR, R. (1987). J. Chem. Soc. Perkin Trans. 2, pp. S1–S19.
BUCOURT, R. & HAINAUT, D. (1965). Bull. Soc. Chim. Fr. pp. 1366–1378.
CONN, E. E. (1986). Recent Advances in Phytochemistry, Vol. 20: The Shikimic Acid Pathway. New York: Plenum Press.
DUAX, W. L. & NORTON, D. A. (1975). In Atlas of Steroid Structure, Vol. 1. New York: Plenum Press.
FISCHER, H. O. L. & DANGSCHAT, G. (1934). Helv. Chim. Acta, 17, 1200–1207.
GREWE, R. & JESCHKE, J.-P. (1956). Chem. Ber. 89, 2080–2088.
International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)
IUPAC-IUB (1968). Eur. J. Biochem. 5, 1–8.
McKITTRICK, B. & GANEM, B. (1985). J. Org. Chem. 50, 5897–5898.
ROGERS, D. (1981). Acta Cryst. A37, 734–741.
SALAMON, J. J. & DAVIS, B. P. (1953). J. Am. Chem. Soc. 75, 5567–5571.
SHELDRICK, G. M. (1983). SHELXTL Users Manual, revision 4. Nicolet XRD Corporation, Madison, Wisconsin, USA.
THOMPSON, R. S. & HASLAM, E. (1974). The Shikimate Pathway, edited by E. HASLAM, p. 62. London: Butterworths.
WEISS, U. & EDWARDS, J. M. (1980). In The Biosynthesis of Aromatic Compounds. New York: John Wiley.