Crystal Structure of Mycophenolic Acid

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Crystals of the title compound, are triclinic, a = 9·555(2), b = 11·639(3), c = 7·341(3) Å, α = 90·75(10), β = 90·77(5), γ = 102·70(2)°, Z = 2, space group $P\bar{1}$. The structure was determined from diffractometer data by direct methods, and was refined by full-matrix least-squares techniques to R 0·076 for 1548 observed reflexions. The molecule contains two approximately planar sections, the ring system and the extended side-chain, at an angle of 79°. The configuration of the C=C double bond in the side chain is *trans*, and bond lengths and angles are normal. The molecules are joined by one normal O–H · · · O hydrogen bond between carboxy-groups, and by one bifurcated hydrogen bond, which is partly intra- and partly inter-molecular.

MYCOPHENOLIC acid is a potential anti-cancer compound and has been shown to be active against mice fibroblasts.[1] Its structure was suggested by Raistrick,[2] and this was confirmed by the synthesis of a degradation product,[3] and later by a total synthesis[4] of the acid which revealed the *trans* nature of the double bond in the side chain. The biosynthesis of the compound has been studied by several workers,[5,6] and the present study was carried out to provide further information about its structure.

EXPERIMENTAL

Crystals of mycophenolic acid are plates, elongated along c. The unit-cell dimensions and space group were determined initially from precession photographs, and the final unit-cell parameters by a least-squares treatment of 16 $\sin^2\theta$ values measured on a General Electric XRD 6 diffractometer.

Crystal Data.—$C_{17}H_{20}O_6$, M = 320·35. Triclinic, a = 9·555(2), b = 11·639(3), c = 7·341(3) Å, α = 90·75(10), β = 90·77(5), γ = 102·70(2)°, U = 796·19 Å^3, D_m = 1·33 Z = 2, D_c = 1·34. Space group $P\bar{1}(C_i^1)$. Cu-K_α radiation, λ = 1·5418 Å; μ(Cu-K_α) = 8·6 cm^{-1}.

The intensity data were collected on a Datex-automated General Electric XRD 6 diffractometer using a θ—2θ scan of 2° min^{-1} in 2θ. Of the 2347 independent reflexions with $\theta \leqslant 60°$, 799 were classified as unobserved, having intensities $<3\sigma(I)$ above background, where $\sigma^2(I) = S + B + (0·05S)^2$, S = scan count and B = background count. A check reflexion was monitored every 40 reflexions and the largest fluctuation in its count was 5%. The data were corrected for Lorentz and polarization factors but not for absorption.

Structure Determination and Refinement.—The structure solved by the symbolic addition procedure, using the SAP programmes of Ahmed and Hall. Full-matrix refinement of the non-hydrogen atom parameters with the scattering factors of ref. 7, first with isotropic and then anisotropic thermal parameters, resulted in R 0·092. A difference-Fourier synthesis indicated the positions of the hydrogen atoms other than those belonging to methyl groups. A number of peaks also appeared in the vicinity of the methyl carbon atoms but these could not be interpreted systematically. In the further refinement, the positional and isotropic temperature factors of the eleven located hydrogen atoms were also allowed to vary. A weighting scheme of the form $\sqrt{w}$ = 1·0 when $|F_o| \leqslant 7·5$; $\sqrt{w} = 7·5/|F_o|$ when $|F_o| >$ 7·5 was used in the final stages, and its usefulness was confirmed by an analysis of $w(|F_o| - |F_c|)^2$ over ranges of $|F_o|$. The unobserved reflexions were given zero weight. For the 1548 observed reflexions the final R was 0·076. The final positional and thermal parameters are given in Table 1. The observed and calculated structure factors are listed in Supplementary Publication No. SUP 20419 (22 pp., 1 microfiche).*

TABLE 1

Final positional parameters (fractional) and thermal parameters, with standard deviations in parentheses

Atom:	x	y	z	B/Å^2
O(1)	0·8457(3)	−0·3057(3)	0·6503(5)	
O(2)	0·7695(3)	−0·5028(3)	0·6374(4)	
O(3)	0·1921(2)	−0·4909(2)	0·9072(3)	
O(4)	0·6039(4)	−0·1956(2)	0·7740(4)	
O(5)	0·0115(4)	−0·1461(3)	0·0881(5)	
O(6)	0·1028(4)	0·0360(3)	0·1821(5)	
C(1)	0·7517(5)	−0·3913(5)	0·6699(5)	
C(2)	0·6409(5)	−0·5881(4)	0·6732(6)	
C(3)	0·5342(4)	−0·5162(3)	0·7322(4)	
C(4)	0·3940(3)	−0·5528(3)	0·7863(4)	
C(5)	0·3275(3)	−0·4603(3)	0·8344(4)	
C(6)	0·3930(3)	−0·3411(3)	0·8292(4)	
C(7)	0·5363(4)	−0·3112(3)	0·7759(4)	
C(8)	0·6043(3)	−0·3995(3)	0·7282(4)	
C(9)	0·3125(5)	−0·2470(4)	0·8775(5)	
C(10)	0·2552(4)	−0·1953(3)	0·7123(5)	
C(11)	0·2839(5)	−0·0852(4)	0·6628(6)	
C(12)	0·2235(7)	−0·0386(5)	0·4968(8)	
C(13)	0·1350(6)	−0·1234(4)	0·3702(8)	
C(14)	0·0831(5)	−0·0686(4)	0·2053(6)	
C(15)	0·3213(5)	−0·6813(3)	0·7963(6)	
C(16)	0·0734(4)	−0·5188(5)	0·7793(6)	
C(17)	0·3854(7)	0·0134(4)	0·7700(9)	
H(1)	0·704(7)	−0·183(5)	0·773(8)	8·1
H(2)	−0·026(7)	−0·119(5)	−0·022(9)	13·0
H(3)	0·670(5)	−0·634(4)	0·781(7)	6·5
H(4)	0·607(5)	−0·638(4)	0·567(7)	5·6
H(5)	0·223(4)	−0·286(3)	0·960(5)	4·6
H(6)	0·371(4)	−0·189(4)	0·936(6)	4·5
H(7)	0·191(5)	−0·252(4)	0·637(6)	6·0
H(8)	0·296(7)	0·012(6)	0·395(9)	13·6
H(9)	0·181(5)	0·029(4)	0·542(7)	7·4
H(10)	0·172(6)	−0·181(5)	0·328(8)	8·9
H(11)	0·057(7)	−0·167(5)	0·454(8)	10·5

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[*] For details see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue, No. 20.

[1] S. B. Carter, T. J. Franklin, D. F. Jones, B. J. Leonard, S. D. Mills, R. W. Turner, and W. B. Turner, *Nature*, 1969, **223**, 848.

[2] J. H. Birkinshaw, H. Raistrick, and D. Ross, *Biochem. J.*, 1952, **50**, 630.

[3] W. R. Logan and G. T. Newbold, *J. Chem. Soc.*, 1957, 1946.

[4] A. J. Birch and J. J. Wright, *Austral. J. Chem.*, 1969, **22**, 2635.

[5] L. Canonica, W. Kroszczynski, B. M. Ranzi, B. Rindone, and C. Scholastico, *Chem. Comm.*, 1970,1357.

[6] C. T. Bedford, J. C. Fairlie, P. Knittel, T. Money, and G. T. Phillips, *Chem. Comm.*, 1971, 323.

[7] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962.

TABLE 1 (*Continued*)

U_{ij} are components of the vibration tensors, in Å × 10^2

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}	Mean σ (U)
O(1)	4·47	12·70	8·59	−0·48	0·59	1·62	0·21
O(2)	5·08	11·44	5·40	3·80	−0·09	−0·11	0·18
O(3)	3·65	8·16	4·60	1·02	0·18	0·49	0·14
O(4)	6·80	5·10	7·79	−0·31	−1·12	1·34	0·17
O(5)	11·00	7·43	9·14	0·21	−4·71	2·04	0·23
O(6)	11·51	6·80	9·94	0·65	−5·63	2·02	0·23
C(1)	4·35	10·41	4·23	1·49	−0·49	0·90	0·25
C(2)	6·62	8·55	4·32	4·35	−0·69	−0·70	0·25
C(3)	4·83	6·06	3·14	2·50	−0·88	−0·21	0·19
C(4)	4·19	4·48	3·67	0·88	−0·84	0·05	0·18
C(5)	3·67	5·52	3·08	1·02	−0·41	0·54	0·18
C(6)	4·44	4·76	3·68	1·67	−0·68	0·48	0·18
C(7)	4·99	4·58	3·99	0·60	−0·86	1·03	0·19
C(8)	4·08	6·29	3·39	1·42	−0·48	0·57	0·19
C(9)	6·64	5·63	4·61	2·78	−0·90	0·07	0·24
C(10)	6·46	4·96	5·76	2·41	−1·34	−0·19	0·22
C(11)	8·96	5·69	6·17	3·67	−1·67	0·06	0·25
C(12)	11·22	7·07	7·73	4·23	−2·91	0·73	0·33
C(13)	8·80	6·12	8·26	2·35	−3·02	1·05	0·30
C(14)	6·80	5·58	7·44	0·88	−2·03	1·41	0·26
C(15)	8·06	4·52	6·78	0·54	−1·72	0·18	0·24
C(16)	3·49	12·63	6·61	0·43	−0·88	0·20	0·27
C(17)	15·10	5·39	13·02	1·86	−6·66	−0·89	0·40

TABLE 2

(*a*) Equations of some weighted least-squares planes in the form $AX + BY + CZ + D = 0$ where X, Y, and Z are co-ordinates in Å with respect to orthogonal axes *a*, *b′*, *c**. Deviations (Å) of relevant atoms from the planes are given in square brackets

	A	B	C	D
Plane (1): O(1)—(4), C(1)—(9), C(15)	−0·3207	0·0503	−0·9458	7·4563
[O(1) −0·058, O(2) −0·010, O(3) −0·090, O(4) −0·019, C(1) −0·025, C(2) 0·018, C(3) 0·037, C(4) 0·041, C(5) 0·041, C(6) 0·042, C(7) 0·014, C(8) 0·012, C(9) 0·086, C(15) 0·016]				
Plane (2): C(3)—(8)	−0·3115	0·0572	−0·9485	7·4243
[O(1) −0·046, O(2) −0·015, O(3) −0·151, O(4) −0·025, C(1) −0·027, C(2) −0·004, C(3) 0·008, C(4) −0·003, C(5) −0·005, C(6) 0·009, C(7) −0·005, C(8) −0·004, C(9) 0·049, C(15) −0·042]				
Plane (3): O(2), C(1)—(3), C(8)	−0·3014	0·0643	−0·9513	7·4098
[O(1) −0·011, O(2) 0·003, O(3) −0·194, O(4) −0·010, C(1) −0·005, C(2) −0·004, C(3) 0·001, C(4) −0·027, C(5) −0·032, C(6) −0·005, C(7) −0·002, C(8) 0·001, C(9) 0·031, C(15) −0·081]				
Plane (4): O(5), O(6), C(9)—(14), C(17), H(2), H(7)	0·8673	−0·0762	−0·4920	−0·1442
[O(5) 0·077, O(6) −0·075, C(9) −0·028, C(10) −0·053, C(11) 0·028, C(12) −0·005, C(13) −0·010 ,C(14) −0·001, C(17) 0·169, H(2) 0·088, H(7) −0·132]				
Plane (5): C(9)—(12), C(17), H(7)	0·8325	−0·1526	−0·5326	0·0458
[O(5) 0·352, O(6) 0·001, C(9) −0·001, C(10) 0·001, C(11) 0·000, C(12) −0·001, C(13) 0·126, C(14) 0·156, C(17) 0·000, H(2) 0·385, H(7) 0·009]				
Plane (6): O(5), O(6), C(13), C(14), H(2)	0·8845	−0·0145	−0·4663	−0·1437
[O(5) −0·001, O(6) −0·001, C(9) 0·019, C(10) −0·011, C(11) 0·138, C(12) 0·096, C(13) −0·002, C(14) 0·005, C(17) 0·380, H(2) 0·003, H(7) −0·152]				
Plane (7): O(1), O(4) O(6″), H(1)	−0·1493	0·3616	−0·9203	6·9897
[O(1) 0·000, O(4) 0·000, O(6″) 0·000, H(1) −0·077]				

TABLE 2 (*Continued*)

(*b*) Angles (deg.) between planes

(1)—(2)	0·7	(4)—(5)	5·4
(1)—(3)	1·4	(4)—(6)	4·0
(2)—(3)	0·7	(5)—(6)	9·3
(1)—(4)	79·4	(1)—(7)	20·5

O(6″) refers to the atom at 1 − *x*, −*y*, 1 − *z*

TABLE 3

Bond distances (Å) and angles (deg.), with standard deviations in parentheses

(*a*) Distances

C(1)–O(1)	1·197(5)	C(4)–C(5)	1·409(5)
C(1)–O(2)	1·363(5)	C(5)–C(6)	1·391(5)
C(2)–O(2)	1·430(6)	C(6)–C(7)	1·399(5)
C(5)–O(3)	1·381(4)	C(7)–C(8)	1·375(5)
C(16)–O(3)	1·441(5)	C(6)–C(9)	1·512(5)
C(7)–O(4)	1·359(4)	C(9)–C(10)	1·509(5)
C(14)–O(5)	1·309(5)	C(10)–C(11)	1·308(5)
C(14)–O(6)	1·205(5)	C(11)–C(12)	1·500(6)
C(1)–C(8)	1·461(6)	C(12)–C(13)	1·463(7)
C(2)–C(3)	1·518(5)	C(13)–C(14)	1·504(6)
C(3)–C(4)	1·379(5)	C(4)–C(15)	1·507(5)
C(3)–C(8)	1·377(5)	C(11)–C(17)	1·531(7)
O(4)–H(1)	0·93(6)	C(10)–H(7)	0·96(4)
O(5)–H(2)	0·96(7)	C(12)–H(8)	1·11(7)
C(2)–H(3)	1·03(5)	C(12)–H(9)	1·02(5)
C(2)–H(4)	0·98(5)	C(13)–H(10)	0·88(6)
C(9)–H(5)	1·07(4)	C(13)–H(11)	1·02(6)
C(9)–H(6)	0·88(4)		

(*b*) Angles

C(1)–O(2)–C(2)	111·1(3)	C(4)–C(3)–C(8)	123·0(3)
C(5)–O(3)–C(16)	116·6(3)	C(3)–C(4)–C(5)	114·2(3)
O(1)–C(1)–O(2)	122·8(4)	C(3)–C(4)–C(15)	122·1(3)
O(1)–C(1)–C(8)	129·2(5)	C(5)–C(4)–C(15)	123·7(3)
O(2)–C(1)–C(8)	108·0(4)	C(4)–C(5)–C(6)	124·8(3)
O(2)–C(2)–C(3)	104·7(3)	C(5)–C(6)–C(7)	117·5(3)
O(3)–C(5)–C(4)	117·2(3)	C(5)–C(6)–C(9)	121·5(3)
O(3)–C(5)–C(6)	117·8(3)	C(7)–C(6)–C(9)	120·9(3)
O(4)–C(7)–C(6)	118·8(3)	C(6)–C(7)–C(8)	119·1(3)
O(4)–C(7)–C(8)	122·1(3)	C(3)–C(8)–C(7)	121·3(3)
O(5)–C(14)–O(6)	122·6(4)	C(6)–C(9)–C(10)	112·9(3)
O(5)–C(14)–C(13)	113·3(4)	C(9)–C(10)–C(11)	127·6(4)
O(6)–C(14)–C(13)	124·2(4)	C(10)–C(11)–C(12)	125·3(4)
C(2)–C(3)–C(4)	129·9(4)	C(10)–C(11)–C(17)	123·4(4)
C(2)–C(3)–C(8)	107·0(3)	C(12)–C(11)–C(17)	111·2(4)
C(1)–C(8)–C(3)	109·2(3)	C(11)–C(12)–C(13)	118·0(4)
C(1)–C(8)–C(7)	129·5(4)	C(12)–C(13)–C(14)	114·1(4)
C(7)–O(4)–H(1)	114(4)	C(9)–C(10)–H(7)	114(3)
C(14)–O(5)–H(2)	119(4)	C(11)–C(10)–H(7)	118(3)
O(2)–C(2)–H(3)	103(3)	C(11)–C(12)–H(8)	121(4)
O(2)–C(2)–H(4)	112(3)	C(11)–C(12)–H(9)	106(3)
C(3)–C(2)–H(3)	111(3)	C(13)–C(12)–H(8)	97(3)
C(3)–C(2)–H(4)	112(3)	C(13)–C(12)–H(9)	117(3)
H(3)–C(2)–H(4)	114(4)	H(8)–C(12)–H(9)	97(4)
C(6)–C(9)–H(5)	108(2)	C(12)–C(13)–H(10)	118(4)
C(6)–C(9)–H(6)	109(3)	C(12)–C(13)–H(11)	102(3)
C(10)–C(9)–H(5)	108(2)	C(14)–C(13)–H(10)	106(4)
C(10)–C(9)–H(6)	107(3)	C(14)–C(13)–H(11)	116(3)
H(5)–C(9)–H(6)	111(3)	H(10)–C(13)–H(11)	102(5)

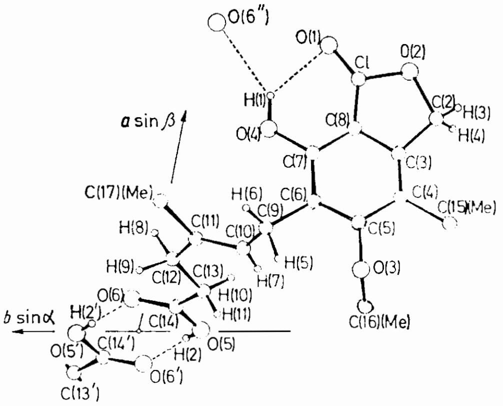
(*c*) Hydrogen bonds

	O · · · O	H · · · O	O–H · · · O
O(5)–H(2) · · · O(6′)	2·719(4)	1·78(7)	164(6)
O(4)–H(1) · · · O(1)	3·022(5)	2·36(7)	128(5)
O(4)–H(1) · · · O(6″)	3·013(5)	2·24(6)	140(5)
[C(14″)–O(6″) · · · H(1)	132·0(1·7)]		

DISCUSSION

The structure of the mycophenolic acid molecule (Figure) can be described in terms of two planes, that of the ring system and that of the side chain. The ring system and its substituent atoms are coplanar with *ca.*

0·1 Å [plane (1), Table 2], with the rings themselves being accurately planar [planes (2) and (3)]. The whole side-chain is planar within *ca.* 0·2 Å [plane (4)], with the double-bond and substituents [plane (5)], and the carboxy-group [plane (6)] each being accurately planar.



Structure of mycophenolic acid viewed along *c*

The angle between the ring system and side-chain mean plane is 79°. The configuration of the C(10)=C(11) double-bond is found to be *trans*, in agreement with the chemical studies.[4] The only slightly unusual feature is the conformation about the C(11)–C(12) single-bond, where C(10) and C(13) are eclipsed; a gauche position for C(13) with H(8) or H(9) eclipsing C(10) or C(17) might have been expected.

The bond distances and valency angles are listed in Table **3**. The bond lengths should all probably be increased slightly to allow for thermal libration errors but it is difficult to make accurate estimates of the corrections. The thermal parameters (Table 1) indicate that the ring system is fairly rigid, with the substituent atoms exhibiting larger vibrations, particularly outer atoms such as C(16) and C(17). With allowance for possible small librational increases, all the bond distances, and valency angles, are close to normal values.[8]

The molecules are joined in the crystal by two independent hydrogen bonds (Table **3** and Figure). One is a normal O–H · · · O bond (2·72 Å) between carboxy-groups, forming centrosymmetric dimers; this bond is nearly linear (O–H · · · O angle, 164°). The other bond is part of a bifurcated system, involving hydrogen H(1) of O(4) in an intramolecular bond to O(1) and in an intermolecular bond to O(6''); the relevant distances and angles are in Table **3** (see also Figure). H(1) lies on the O(4), O(1), O(6'') plane [plane (7) of Table 2].

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