potential acceptor explains the fact that the OH group is not involved in a hydrogen bond.

References

BELLEAU, B., GULINI, V., CAMICHIOLI, R., GOUR-SALIN, B. J. & SAUVÉ, G. (1986). *Can. J. Chem.* **64**, 110–116.

BIJVOET, J. M., PEERDEMAN, A. F. & VAN BOMMEL, A. J. (1951). *Nature (London)*, **168**, 271.

COTTON, R., GILES, M. G., MILLER, L., SHAW, J. S. & TIMMS, D. (1984). *Eur. J. Pharmacol.* **97**, 331–332.

DIMAIO, J., BAYLY, C. I., VILLENEUVE, G. & MICHEL, A. G. (1986). *J. Med. Chem.* **29**, 1658–1663.

GABE, E. J., LEE, F. L. & LE PAGE, Y. (1985). *The NRCVAX Crystal Structure System.* In *Crystallographic Computing* 3: *Data Collection, Structure Determination, Proteins and Databases*, edited by G. M. SHELDRICK, C. KRÜGER & R. GODDARD, pp. 167–174. Oxford: Clarendon Press.

HAHN, E. F., STZHAK, Y., HISHIMURA, S., JOHNSON, M. & PASTERNAK, G. W. (1985) *J. Pharmacol. Exp. Ther.* **235**, 846–850.

LEMAIRE, S., BELLEAU, B. & JOLICOEUR, F. (1989). *Adv. Biosci.* **75**, 105–108.

MICHEL, A. G., EVRARD, G., NORBERG, B. & MILCHERT, E. (1988). *Can. J. Chem.* **66**, 1763–1769.

MICHEL, A. G. & MICHEL-DEWEZ, N. (1990). *Acta Cryst.* B**46**, 405–409.

MICHEL, A. G., PROULX, M., EVRARD, G., NORBERG, B. & MILCHERT, E. (1988). *Can. J. Chem.* **66**, 2498–2505.

MOTHERWELL, W. D. S. & CLEGG, W. (1978). *PLUTO*. Program for plotting molecular and crystal structures. Univ. of Cambridge, England.

PORTOGHESE, P. S., LIPKOWSKI, A. W. & TAKEMORI, A. E. (1987). *Life Sci.* **40**, 1287–1292.

RICE, K., JACOBSON, A. E., BURKE, T. R., BAJWA, B. S., STREATZ, R. A. & KLEE, W. A. (1983). *Science*, **220**, 314–316.

ROGERS, D. (1981). *Acta Cryst.* A**37**, 734.

Acta Cryst. (1990). C**46**, 2416–2419

Structure of an Aspirin Derivative: 2-(2-Methoxybenzyloxy)-2-methyl-4*H*-1,3-benzodioxin-4-one

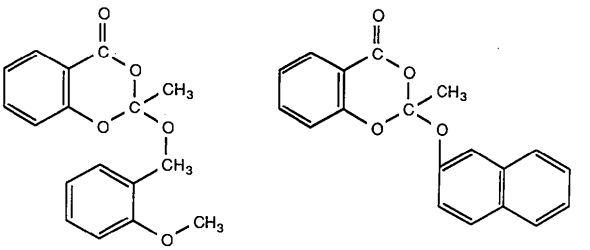
BY KNUD BJARNE JENSEN

Aarhus University, Department of Chemistry, Langelandsgade 140, *DK*-8000 *Aarhus C, Denmark*

(*Received* 13 *February* 1990; *accepted* 13 *March* 1990)

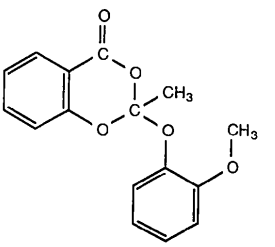
Abstract. $C_{17}H_{16}O_5$, $M_r = 300{\cdot}31$, monoclinic, $P2_1/n$, $a = 14{\cdot}196\ (2)$, $b = 10{\cdot}131\ (1)$, $c = 10{\cdot}601\ (1)$ Å, $\beta = 104{\cdot}658\ (7)°$, $V = 1475{\cdot}0\ (3)$ Å^3, $Z = 4$, $D_x = 1{\cdot}352$ g cm^{-3}, λ(Mo $K\alpha$) $= 0{\cdot}71073$ Å, $\mu = 0{\cdot}9075$ cm^{-1}, $F(000) = 632$, $T = 295$ K, $R = 0{\cdot}056$, $wR = 0{\cdot}071$ for 1052 unique reflections ($I > 3\sigma$) and 200 variables. The title compound (I) is a cyclic ortho ester derivative of aspirin. The dioxane ring of the aspirin moiety is in a half-boat conformation, the 2-methoxybenzyloxy group is axial to this ring. The structure of (I) shows similarities to those of two other cyclic ortho ester aspirin derivatives, 2-methyl-2-(2-naphthyloxy)-(II) and 2-(2-methoxyphenoxy)-2-methyl-4*H*-1,3-benzodioxin-4-one (III).

Introduction. Aspirin (IV) is in common clinical use, but unfortunately it has several bad qualities such as a relatively narrow therapeutic margin, it irritates the gastric mucosa, and it hydrolyses relatively quickly to salicylic acid (V). Therefore, various attempts have been made to design prodrugs for aspirin which do not have the mentioned undesirable effects (Hansen & Senning, 1983). (The term *prodrug* refers to a compound which will act as a precursor of a particular drug when administered to an organism.) The chemical structure of the title compound (I) and two other cyclic ortho ester aspirin derivatives whose crystal structures are known by X-ray analysis, (II) (Jørgensen & Hansen, 1982) and (III) (Destro &



(I)

(II)

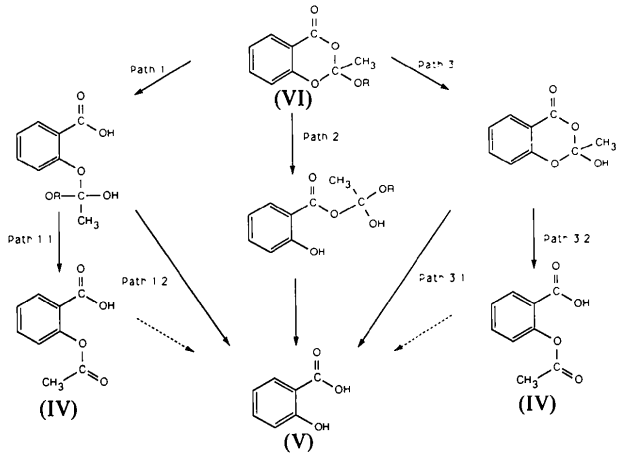


(III)

Saccarello, 1983), can be generalized as (VI). This type of ortho ester will undergo hydrolysis according to the scheme below, which shows model pathways

0108-2701/90/122416-04$03.00

for hydrolytic breakdown of (VI) to (IV) and (V) (Hansen & Senning, 1983), where only following path 1, path 1.1 and path 3, path 3.2 will yield aspirin (IV). Depending upon the substituent *R*, compounds (VI) can undergo hydrolysis either solely to aspirin (IV) or solely to salicylic acid (V) or to a mixture of both (Ankersen & Senning, 1989).



The question of the reaction mechanism is still open, but it has been suggested that the strength (length) of the bonds from C(8) (Fig. 1) to the adjacent oxygens will control the path of hydrolysis so that the weakest (longest) bond will be hydrolysed in the first step in the reaction (Ankersen, Nielsen & Senning, 1989).

This makes it essential to know the binding geometry around C(8) in Fig. 1, to be able to predict which paths the hydrolysis of the ortho ester will follow according to the proposed hypothesis.

Experimental. Compound (I) was synthesized by Ankersen & Senning (1989). A crystal grown from chloroform solution was chosen. Its size was 0·5 × 0·25 × 0·50 mm. Preliminary cell dimensions and the space group were determined from 0*kl*, 1*kl*, *hk*0 and *hk*1 precession pictures and *h*0*l* and *h*1*l* Weissenberg pictures. The crystal was mounted on a Huber four-circle diffractometer. The cell dimensions were determined from the setting angles of 115 reflections with $18° \le 2\theta \le 29°$.

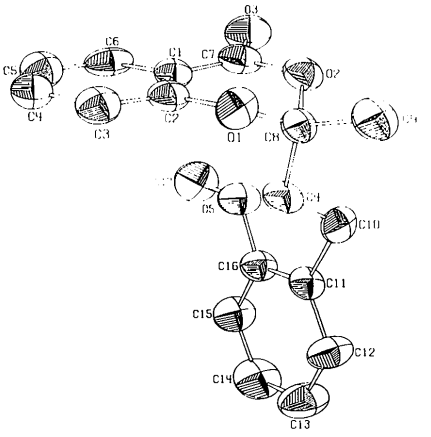


Fig. 1. *ORTEP* drawing of (I) showing the atom-numbering scheme. The thermal ellipsoids are set at the 50% level. H atoms not shown.

Intensities were measured out to $2\theta_{max} = 50°$ using an ω–2θ scan with Nb-filtered Mo $K\alpha$ radiation, scan width $(2{\cdot}0 + 0{\cdot}692\tan\theta)°$ divided into 50 steps, the counting time was 4 s step^{-1}. Reflections with $0 \le h \le 16$, $-12 \le k \le 0$, $-12 \le l \le 12$ were measured giving 2619 independent reflections of which 1052 had $I > 3\sigma(I)$. Reflections 600 and 404 were monitored every 50 reflections, the overall fall-off in intensity was 43%, so the data were rescaled to correct for this. Reflections were integrated using the Nelmes (1975) method. No absorption correction was made.

The positions of all the non-H atoms were determined from *MULTAN*80 (Main *et al.*, 1980). The H atoms were identified on a $\Delta\rho$ map, and ideal positions were calculated assuming C—H = 0·95 Å and were not refined. All non-H atoms were refined anisotropically, a common isotropic thermal parameter was refined for the H atoms. The final $R(F) = 0{\cdot}056$, $wR(F) = 0{\cdot}071$, $w = 1/\sigma(F)$, where $\sigma(F) = [\sigma_c(F^2) + 1{\cdot}05F^2]^{1/2} - |F|$, where $\sigma_c(F^2)$ is the standard deviation of F^2 from counting statistics, $S = 1{\cdot}6613$, $(\Delta/\sigma)_{max} = 0{\cdot}005$, $-0{\cdot}3 \le \Delta\rho \le 0{\cdot}3$ e Å^{-3}.

Fractional coordinates are listed in Table 1,* bond distances and angles are listed in Table 2, and equations of least-squares planes of the molecule and the deviation of the atoms from these planes are listed in Table 3. Computations were carried out on a VAX6210 computer with the following programs: *INTEG* based on the Nelmes (1975) algorithm for integration; *DATAP* and *DSORTH* (State University of New York, Buffalo) for rescaling and sorting; modified *ORFLS* (Busing, Martin & Levy, 1962) for least-squares refinement; *ORFFE* (Busing, Martin & Levy, 1964) for geometry and errors; *ORTEP* (Johnson, 1965) for drawings. Atomic scattering factors: Cromer & Mann (1968) for C and O; Stewart, Davidson & Simpson (1965) for H.

Discussion. The crystal packing is shown in Fig. 2. No intermolecular distances in the crystal are shorter than would be expected from van der Waals radii; it can be assumed that the molecular geometry

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53133 (11 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional atomic coordinates and equivalent isotropic temperature factors*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}(Å^2)
O(1)	1·1057 (3)	0·0024 (3)	0·3670 (3)	0·047 (2)
O(2)	1·0089 (3)	0·0727 (3)	0·1645 (3)	0·047 (2)
O(3)	1·0622 (3)	0·2183 (4)	0·0430 (4)	0·061 (3)
O(4)	0·9816 (2)	0·1390 (3)	0·3610 (3)	0·039 (2)
O(5)	0·9703 (3)	0·4028 (3)	0·2402 (3)	0·053 (2)
C(1)	1·1611 (4)	0·1791 (5)	0·2557 (5)	0·038 (3)
C(2)	1·1754 (4)	0·0955 (5)	0·3613 (6)	0·038 (4)
C(3)	1·2588 (4)	0·0980 (5)	0·4603 (5)	0·047 (4)
C(4)	1·3301 (4)	0·1881 (6)	0·4530 (6)	0·055 (4)
C(5)	1·3175 (4)	0·2756 (6)	0·3498 (7)	0·052 (4)
C(6)	1·2342 (5)	0·2714 (5)	0·2515 (5)	0·047 (4)
C(7)	1·0760 (4)	0·1645 (5)	0·1484 (6)	0·044 (4)
C(8)	1·0110 (4)	0·0331 (5)	0·2954 (5)	0·043 (4)
C(9)	0·9496 (4)	−0·0894 (5)	0·2859 (6)	0·061 (4)
C(10)	0·8822 (4)	0·1804 (5)	0·3092 (5)	0·046 (4)
C(11)	0·8696 (4)	0·3158 (5)	0·3622 (5)	0·039 (3)
C(12)	0·8106 (4)	0·3321 (5)	0·4466 (6)	0·059 (4)
C(13)	0·7948 (5)	0·4566 (7)	0·4930 (7)	0·073 (5)
C(14)	0·8397 (5)	0·5625 (6)	0·4567 (6)	0·066 (4)
C(15)	0·8982 (4)	0·5499 (5)	0·3728 (6)	0·056 (4)
C(16)	0·9135 (4)	0·4262 (5)	0·3251 (5)	0·042 (4)
C(17)	1·0141 (5)	0·5131 (6)	0·1927 (6)	0·072 (5)

Table 2. *Bond distances* (Å), *bond angles* (°) *and selected torsion angles* (°)

C(2)—O(1)	1·379 (6)	C(3)—C(2)	1·370 (10)
C(8)—O(1)	1·401 (8)	C(4)—C(3)	1·379 (7)
C(7)—O(2)	1·373 (6)	C(5)—C(4)	1·384 (8)
C(8)—O(2)	1·438 (6)	C(6)—C(5)	1·365 (10)
C(7)—O(3)	1·214 (6)	C(9)—C(8)	1·505 (7)
C(8)—O(4)	1·399 (6)	C(11)—C(10)	1·510 (7)
C(10)—O(4)	1·441 (7)	C(12)—C(11)	1·380 (8)
C(16)—O(5)	1·372 (7)	C(16)—C(11)	1·386 (7)
C(17)—O(5)	1·431 (6)	C(13)—C(12)	1·392 (8)
C(2)—C(1)	1·377 (7)	C(14)—C(13)	1·353 (8)
C(6)—C(1)	1·405 (7)	C(15)—C(14)	1·368 (9)
C(7)—C(1)	1·442 (10)	C(16)—C(15)	1·388 (7)

C(2)—O(1)—C(8)	115·2 (4)	O(1)—C(8)—O(2)	111·5 (5)
C(7)—O(2)—C(8)	117·6 (5)	O(1)—C(8)—O(4)	105·5 (5)
C(8)—O(4)—C(10)	114·8 (4)	O(1)—C(8)—C(9)	108·3 (4)
C(16)—O(5)—C(17)	118·4 (4)	O(2)—C(8)—O(4)	109·3 (4)
C(2)—C(1)—C(6)	118·5 (6)	O(2)—C(8)—C(9)	107·1 (5)
C(2)—C(1)—C(7)	120·0 (5)	O(4)—C(8)—C(9)	115·2 (4)
C(6)—C(1)—C(7)	121·4 (5)	O(4)—C(10)—C(11)	108·6 (4)
O(1)—C(2)—C(1)	119·8 (6)	C(10)—C(11)—C(12)	119·9 (5)
O(1)—C(2)—C(3)	118·0 (5)	C(10)—C(11)—C(16)	121·5 (5)
C(1)—C(2)—C(3)	122·1 (5)	C(12)—C(11)—C(16)	118·5 (5)
C(2)—C(3)—C(4)	118·3 (5)	C(11)—C(12)—C(13)	121·1 (5)
C(3)—C(4)—C(5)	121·2 (6)	C(12)—C(13)—C(14)	119·2 (5)
C(4)—C(5)—C(6)	119·9 (5)	C(13)—C(14)—C(15)	121·2 (5)
C(1)—C(6)—C(5)	120·0 (5)	C(14)—C(15)—C(16)	119·8 (5)
O(2)—C(7)—O(3)	117·6 (6)	O(5)—C(16)—C(11)	115·3 (4)
O(2)—C(7)—C(1)	116·2 (5)	O(5)—C(16)—C(15)	124·5 (5)
O(3)—C(7)—C(1)	126·0 (6)	C(11)—C(16)—C(15)	120·1 (5)

O(2)—C(8)—O(4)—C(10)	64·6 (6)	O(4)—C(10)—C(11)—C(16)	68·8 (6)
C(8)—O(4)—C(10)—C(11)	−163·9 (4)		

observed in the crystal structure is similar to the molecular geometry of (I) in solution. The aspirin moiety of (I) [O(1), O(2), O(3), C(1), C(2), C(3), C(4), C(5), C(6), C(7) and C(8)] is in a half-boat conformation with the 2-methoxybenzyloxy group in the axial position (Fig. 1). As seen from Table 3 all

Table 3. *Least-squares planes of the aspirin moiety and the 2-methoxybenzyloxy moiety of* (I)

Equation for the least-squares plane of the aspirin moiety of (I) ($ax + by + cz - d = 0$):

$a = 7·89$ (8), $b = 7·26$ (7), $c = -5·82$ (6), $d = 6·45$ (6)

Distance from the plane (Å)

O(1)	0·121 (3)
O(2)	0·025 (3)
O(3)	0·097 (4)
C(1)	−0·076 (5)
C(2)	0·028 (4)
C(3)	0·091 (5)
C(4)	0·043 (5)
C(5)	−0·091 (5)
C(6)	−0·147 (5)
C(7)	−0·017 (5)
C(8)	−0·433 (5)

Equation for the least-squares plane of the 2-methoxybenzyloxy moiety of (I):

$a = 8·8$ (8), $b = -1·4$ (1), $c = 6·3$ (5), $d = 9·4$ (8)

Distance from the plane (Å)

O(5)	0·016 (4)
C(10)	−0·020 (6)
C(11)	0·012 (5)
C(12)	−0·002 (6)
C(13)	−0·024 (7)
C(14)	−0·002 (7)
C(15)	0·006 (6)
C(16)	0·014 (5)
C(17)	−0·049 (7)

Angle between the two planes 83·3°

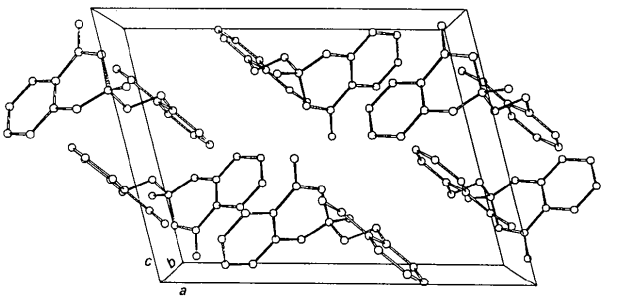


Fig. 2. *ORTEP* view of unit cell along the *b* axis, atom spheres are on an arbitrary scale.

atoms of the aspirin moiety of (I) except C(8) are lying in a plane – the largest deviation from the plane, 0·147 (5) Å, is found for C(6) in the benzene ring. This agrees with the bond distances and angles of a conjugated π-electron system for all the aspirin moiety atoms except C(8), which is also observed for (II) (Jørgensen & Hansen, 1982) and (III) (Destro & Saccarello, 1983).

With the exception of O(4), the atoms of the 2-methoxybenzyloxy group [O(4), O(5), C(10), C(11), C(12), C(13), C(14), C(15), C(16) and C(17)] also lie in a plane. This plane is almost perpendicular to the first (see Table 3, Figs. 1 and 2). The largest deviation from the common plane is 0·049 (7) Å for C(17). This value as well as the bond angles and distances indicate a conjugated π-electron system for the atoms O(5), C(11), C(12), C(13), C(14), C(15) and C(16).

Although the 2-methoxybenzyloxy group is rather flexibly linked to the aspirin moiety of (I) through O(4) and C(10) – in particular much more flexibly than for the β-naphthyl group of (II) and the 2-

methoxyphenoxy group of (III) – it should be noted that there are contacts shorter than van der Waals radii between the two parts in (I). These contacts, which are not strictly determined either by cyclic structure or by two atoms being bonded to the same atom, are O(2)···C(10) 2·86 Å, C(9)···C(10) 2·93 Å and O(5)···C(7) 3·13 Å. These short non-bonding contacts must be due to favourable packing of the crystal with this conformation of the molecule, as no favourable intramolecular contacts are seen here such as the contact O(5)···C(7) observed for (III) (Destro & Saccarello, 1983).

To some extent the bonding geometry around C(8) in (I) must be caused by short non-bonding intramolecular contacts and the crystal-packing forces. For that reason, care has to be taken when trying to predict the behaviour of (I) in solution, but keeping this in mind one would predict that the O(2)—C(8) bond, which is somewhat longer than the two other O—C bonds around C(8), should be the most susceptible to hydrolysis according to the hypothesis proposed by Ankersen, Nielsen & Senning (1989). This assumption is supported by the fact that (I) yields 51·1% aspirin (IV) and 48·9% salicylic acid (V) upon hydrolysis at pH = 7·4 and a temperature of 310 K (Ankersen & Senning, 1989), indicating that the hydrolysis follows either path 1 or 3 of the reaction scheme.

The conformation of the half boat of the aspirin moiety of (I) is closer to ideality (see Table 2) than the equivalent part of (III) (Destro & Saccarello, 1983), probably because of the more flexible linkage between the two parts of the molecule causing fewer unfavourable short non-bonding intramolecular contacts.

I would like to thank Dr A. C. Hazell and Dr R. G. Hazell for their advice, help and stimulating interest.

References

ANKERSEN, M., NIELSEN, K. K. & SENNING, A. (1989). *Acta Chem. Scand.* **43**, 213–221.
ANKERSEN, M. & SENNING, A. (1989). *Acta Chem. Scand.* **43**, 793–798.
BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1962). *ORFLS.* Report ORNL-TM-305. Oak Ridge National Laboratory, Tennessee, USA.
BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1964). *ORFFE.* Report ORNL-TM-305. Oak Ridge National Laboratory, Tennessee, USA.
CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A**24**, 321–324.
DESTRO, R. & SACCARELLO, M. L. (1983). *Tetrahedron*, **39**, 3151–3157.
HANSEN, A. B. & SENNING, A. (1983). *Acta Chem. Scand.* B**37**, 351–359.
JOHNSON, C. K. (1965). *ORTEP.* Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.
JØRGENSEN, J. E. & HANSEN, A. B. (1982). *Acta Cryst.* B**38**, 991–993.
MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN*80. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.
NELMES, R. J. (1975). *Acta Cryst.* A**31**, 273–279.
STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

Acta Cryst. (1990). C**46**, 2419–2421

Structure of Tetraphenylphosphonium Decahydro-8-hydroxy-9-methyl-6-carba-*nido*-decaborate(1 −) Ethanol Solvate

BY V. ŠUBRTOVÁ AND V. PETŘÍČEK

Institute of Physics, Czechoslovak Academy of Sciences, Na Slovance 2, 180 40 *Praha* 8, *Czechoslovakia*

(*Received* 30 *November* 1989; *accepted* 7 *March* 1990)

Abstract. $C_{24}H_{20}P^+.C_2H_{14}B_9O^-.C_2H_5OH$, M_r = 536·89, triclinic, $P\bar{1}$, a = 10·253 (3), b = 10·971 (2), c = 14·326 (5) Å, α = 89·96 (2), β = 81·22 (3), γ = 88·74 (2)°, V = 1592·2 (8) Å^3, Z = 2, D_m (flotation) = 1·122, D_x = 1·120 g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, μ = 1·06 cm^{-1}, $F(000)$ = 568, T = 293 K, R = 0·058 for 3982 observed independent reflections. The novel monocarbadecaborane anions have OH ligands attached to the B8 atoms. The oxygen of the OH group is involved in O—H···O hydrogen bonding with the ethanol solvent. Two anions and two alcohols form a centrosymmetric 'dimer'. Mean O1···O2 = 2·763 (4) Å, mean O—H···O = 174 (5)°.

Introduction. Crystals of the title compound were prepared in the Institute of Inorganic Chemistry of the Czechoslovak Academy of Sciences by the specific stepwise degradation reaction of a reactive isomer (r-$C_2B_{10}H_{13}$) (Plešek, Jelínek, Štíbr & Heřmánek, 1989). The removal of one B and one C atom from

0108-2701/90/122419-03$03.00