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Structure of Enprofylline: 3,7-Dihydro-3-propyl-1*H*-purine-2,6-dione

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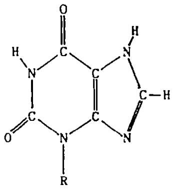
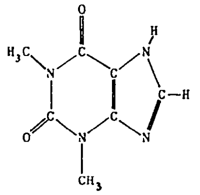
Abstract. $C_8H_{10}N_4O_2$, $M_r = 194{\cdot}19$, monoclinic, $P2_1/c$, $a = 15{\cdot}11$ (1), $b = 13{\cdot}606$ (3), $c = 19{\cdot}877$ (6) Å, $\beta = 111{\cdot}92$ (3)°, $V = 3791$ (3) Å^3, $Z = 16$, $D_m = 1{\cdot}38$, $D_x = 1{\cdot}36$ g cm^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}5418$ Å, $\mu = 8{\cdot}65$ cm^{-1}, $F(000) = 1632$, $T = 295$ K. $R = 0{\cdot}079$ for 1671 observed reflections. The four independent molecules show no significant differences. The molecules are planar except for the $-CH_2CH_3$ part of the propyl groups. The molecules are stacked in layers, two adjacent enprofylline layers being separated by a layer with disordered $-CH_2CH_3$ groups. Molecules within a layer are connected by hydrogen bonds.

Introduction. Xanthin derivatives with formula (I) have been tested for the treatment of chronic obstructive airway diseases or cardiac diseases (Persson & Kjellin, 1981). The compounds have a relaxing effect on the bronchial smooth muscle and they are less likely to produce toxic side effects than the currently used theophylline (II) preparates. The present structural investigation deals with the compound (I) with R = n-propyl, which is called enprofylline.



(I)



(II)

Experimental. Crystal of dimensions $0{\cdot}35 \times 0{\cdot}25 \times 0{\cdot}20$ mm used for intensity data collection. Crystals obtained by crystallization from an aqueous solution of the enprofylline compound synthesized according to Persson & Kjellin (1981) at AB Draco in Lund, Sweden. D_m measured by flotation. Unit-cell dimensions derived from least-squares analysis of setting angles for 15 reflections. No correction for absorption. Intensities measured on a Nicolet $P3m$ four-circle diffractometer, graphite-monochromatized Cu $K\alpha$ radiation, interval $4 < 2\theta < 116°$, ω–2θ scans of width $2{\cdot}4° + \alpha_1,\alpha_2$-splitting, scan rates 1–30° min^{-1}. Of 4445 reflections, collected in one quadrant of reciprocal space, 3685 remained after rejection of systematically absent reflections. Two reflections used to check the performance of the instrument.

An attempt to solve the structure by direct methods with *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), showed that the molecules were packed in layers perpendicular to the c^* axis, which was also obvious from the very strong 002, 004 and 006 reflections. In spite of many attempts no solution was found which could be refined.

The orientation of one enprofylline molecule was determined with *DIRDIF* (Beurskens *et al.*, 1984) using the orientation search program *ORIENT,* which is a fully automated version of the procedures of Nordman & Schilling (1970). A search fragment, $C_5N_4O_2$ [formula (I), with R = H], was retrieved from the literature (Mercer & Trotter, 1978). The subsequent *TRADIR* (Doesburg & Beurskens, 1983) and *DIRDIF* runs failed to give the solution; instead *DIRDIF* Fourier maps gave a multiple image of the structure, in which many well defined molecular fragments could be recognized. From these, the following possibilities became apparent:

(i) equally oriented symmetry-independent molecules in different layers,

(ii) molecules which differ by a rotation of 60° relative to one another within a layer,

(iii) the existence of additional (local) symmetry elements,

(iv) a positional ambiguity of the origin which could be in or between the layers, and

(v) unequal distribution of molecules over six layers within the unit cell.

A way of finding the relative positions of independent fragments and the positions of the symmetry elements was achieved by $|E|$-correlation methods similar to those described by Tollin & Cochran (1964) and Tollin (1966) [see also Beurskens (1981)]. A new program, which was developed for problem structures consisting

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of planar molecules packed in layers (Bruins Slot & Beurskens, 1985) was used to find the positions of two equally oriented enprofylline molecules relative to the *c*-glide plane. In this case a three-dimensional search was applied: the first molecule was kept fixed in one of the layers; two parameters were used to define the position of the second molecule in an adjacent layer; the third parameter was used to define the position of these molecules relative to the *c*-glide plane. Thus four molecules contributed to the calculation of the partial structure factors used in the translation search.

The best results were used in subsequent *DIRDIF* runs, and the fourth trial revealed the two remaining independent molecules. (In the case of failure we would have tried to position the second molecule in one of the other layers!) It was found that four of the six layers were filled with molecules and that two layers contained the terminal $-CH_3$ of the propyl groups.

From least-squares refinement and difference Fourier maps with *SHELX*76 (Sheldrick, 1976) disorder for the *n*-propyl chains was found; a number of different configurations with acceptable geometries were taken into account. Some high-order, weak reflections appeared to be poorly measured and only 1671 reflections with $I > \sigma(I)$ and $\sin\theta < 0.313$ were used (h −13→12, k 0→11, l 0→17). The anisotropic refinement, with all H atoms at calculated positions, riding with fixed isotropic temperature factors of their parent atoms, and C(*i*7) and C(*i*8) atoms (*i* = 1,2,3,4) isotropically refined, gave $R = 0.11$. It was found that the sites of the C(*i*8) atoms were not fully occupied, and the site-occupancy factors of these atoms were refined. Subsequent difference Fourier maps showed other possible C(*i*8) sites at geometrically reasonable positions from the C(*i*7) atoms. Site-occupancy factors for the various C(*i*8) positions were refined keeping all other parameters fixed. Finally the site-occupancy factors of the disordered C(*i*8) atoms were kept fixed, and the C(*i*7) atoms and the C(*i*8) atoms with the highest site-occupancy factors were refined anisotropically. Anisotropic refinement on F converged to $R = 0.079$; $wR = 0.091$, $w = 1/[\sigma^2(F) + 0.0025|F|^2]$, $\sigma(F)$ from counting statistics; 577 independent parameters. Maximum shift/error in final cycle = 1·5. The largest values are for parameters involving the disordered *n*-propyl chains. Final difference map density < 0.36 e Å^{-3}. No correction for secondary extinction. Atomic scattering factors from *SHELX*76.

Discussion. Atomic coordinates are given in Table 1.* Because of the poor quality of the data, the strong anisotropy of atoms in the purine fragment, and the unusual packing, *i.e.* with layers of disordered atoms, a number of anisotropic temperature factors became non-positive definite during the refinement. Geometry data are collected in Table 2. The aliphatic C—C distances are not given, because they have limited

Table 1. *Fractional coordinates* (×10⁴) *and isotropic thermal parameters with e.s.d.'s in parentheses*

$$U_{eq} = \tfrac{1}{3}\textstyle\sum_i\sum_j U_{ij}a^*_i a^*_j \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	S.o.f.	U_{eq}/U_{iso}(Å^2)
C(11)	−2742 (7)	−1282 (8)	1508 (4)	1	0·049 (6)†
C(12)	−1043 (9)	−1493 (7)	1412 (5)	1	0·057 (6)†
C(13)	−1980 (7)	−2950 (8)	1522 (5)	1	0·041 (5)†
C(14)	−2710 (6)	−2349 (8)	1531 (4)	1	0·042 (5)†
C(15)	−3011 (7)	−3908 (7)	1676 (5)	1	0·051 (5)
N(11)	−1869 (6)	−1010 (5)	1455 (4)	1	0·080 (4)
N(12)	−1209 (5)	−2534 (7)	1441 (4)	1	0·078 (4)
N(13)	−2161 (5)	−3901 (6)	1600 (4)	1	0·078 (4)
N(14)	−3365 (5)	−2981 (7)	1635 (4)	1	0·082 (4)
O(11)	−3316 (4)	−705 (5)	1549 (3)	1	0·031 (3)†
O(12)	−370 (5)	−1132 (5)	1370 (4)	1	0·046 (4)†
C(16)	−457 (6)	−3171 (8)	1353 (6)	1	0·068 (5)
C(17)	−758 (9)	−3362 (13)	483 (8)	1	0·156 (10)
C(18)	−72 (19)	−3779 (23)	254 (14)	0·52 (2)	0·123 (16)
C(18′)	−714	−2927	139	0·16 (2)	0·116
C(18″)	−254	−4411	82	0·09 (2)	0·116
C(18‴)	−1320	−3765	222	0·15 (2)	0·116
C(21)	4322 (7)	−2324 (8)	1757 (4)	1	0·041 (5)†
C(22)	2562 (8)	−2077 (7)	1725 (4)	1	0·047 (5)†
C(23)	3533 (7)	−660 (7)	1679 (4)	1	0·039 (5)†
C(24)	4282 (7)	−1244 (9)	1720 (4)	1	0·045 (5)†
C(25)	4650 (6)	311 (7)	1687 (5)	1	0·045 (4)†
N(21)	3419 (6)	−2608 (5)	1753 (3)	1	0·073 (3)
N(22)	2688 (5)	−1044 (6)	1665 (3)	1	0·065 (4)
N(23)	3735 (5)	328 (6)	1656 (4)	1	0·080 (4)
N(24)	5004 (5)	−615 (6)	1725 (3)	1	0·073 (3)
O(21)	4936 (4)	−2873 (4)	1789 (4)	1	0·035 (3)†
O(22)	1876 (5)	−2451 (5)	1741 (3)	1	0·033 (3)†
C(26)	1857 (6)	−430 (6)	1547 (5)	1	0·038 (4)
C(27)	1350 (9)	−203 (10)	766 (8)	1	0·098 (7)
C(28)	1164 (14)	−855 (20)	251 (11)	0·56 (2)	0·100 (12)
C(28′)	2100	−640	213	0·09 (2)	0·083
C(28″)	1122	−620	−239	0·06 (2)	0·083
C(28‴)	1753	131	276	0·27 (2)	0·083
C(31)	2321 (7)	2663 (7)	1665 (4)	1	0·054 (5)†
C(32)	3968 (7)	2931 (8)	1508 (4)	1	0·055 (5)†
C(33)	3051 (7)	4353 (8)	1660 (4)	1	0·043 (5)†
C(34)	2363 (6)	3746 (9)	1690 (4)	1	0·047 (5)†
C(35)	2025 (6)	5274 (8)	1837 (4)	1	0·044 (5)†
N(31)	3167 (5)	2409 (4)	1569 (3)	1	0·072 (3)
N(32)	3813 (5)	3966 (6)	1557 (3)	1	0·066 (4)
N(33)	2869 (5)	5319 (5)	1739 (3)	1	0·072 (4)
N(34)	1690 (4)	4344 (6)	1799 (3)	1	0·075 (3)
O(31)	1736 (4)	2098 (5)	1706 (4)	1	0·039 (3)†
O(32)	4625 (5)	2556 (5)	1430 (4)	1	0·042 (3)†
C(36)	4546 (8)	4583 (10)	1468 (5)	1	0·052 (5)
C(37)	4363 (9)	4786 (10)	651 (6)	1	0·104 (7)
C(38)	3501 (11)	5174 (14)	224 (8)	0·73 (2)	0·113 (9)
C(38′)	3963	4143	195	0·16 (2)	0·091
C(38″)	3333	4965	29	0·04 (2)	0·091
C(38‴)	4259	5159	619	0·04 (2)	0·091
C(41)	−703 (7)	3711 (7)	1761 (4)	1	0·045 (5)†
C(42)	−2501 (7)	3462 (7)	1597 (4)	1	0·043 (5)†
C(43)	−1488 (7)	2093 (7)	1619 (4)	1	0·037 (5)
C(44)	−729 (6)	2659 (8)	1716 (4)	1	0·043 (5)†
C(45)	−376 (7)	1060 (7)	1728 (5)	1	0·052 (5)
N(41)	−1653 (5)	3989 (4)	1681 (3)	1	0·065 (3)
N(42)	−2366 (5)	2440 (5)	1546 (3)	1	0·067 (4)
N(43)	−1306 (5)	1090 (5)	1631 (4)	1	0·077 (4)
N(44)	3 (4)	1956 (6)	1781 (4)	1	0·079 (3)
O(41)	−83 (4)	4264 (5)	1836 (4)	1	0·039 (3)†
O(42)	−3213 (4)	3855 (4)	1567 (3)	1	0·031 (3)†
C(46)	−3226 (7)	1833 (7)	1395 (5)	1	0·053 (5)
C(47)	−3741 (8)	1738 (12)	521 (8)	1	0·141 (9)
C(48)	−4631 (19)	1321 (25)	188 (15)	0·47 (2)	0·129 (17)
C(48′)	−4237	2285	163	0·16 (2)	0·114
C(48″)	−3373	1349	261	0·20 (2)	0·114
C(48‴)	−3359	2449	149	0·07 (2)	0·114

† Non-positive definite temperature factors.

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* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42297 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

physical significance. Because of the disorder, various C(*i*6)—C(*i*7)—C(*i*8) chains are possible; C(*i*6) atoms are at reliable positions, various C(*i*8) positions are found and the corresponding C(*i*7) atoms are close together and indistinguishable in the Fourier map.

The crystallographic numbering scheme is given in Fig. 1. Within the molecular layers the molecules are connected by hydrogen bonds, which are shown in Fig. 2 and of which relevant distances are given in Table 3. The adjacent enprofylline layers are held together by van der Waals and electrostatic interactions. Selected intermolecular distances are given in Table 4. The double layers are connected only by van der Waals contacts through the disordered *n*-propyl chains. The packing of the molecular layers is shown in Fig. 3.

Table 2. *Averaged bond lengths* (Å) *and bond angles* (°)

The e.s.d. for the average bond length is 0·007 Å, the e.s.d. for the average bond angle is 0·5°.

C(*i*1)–C(*i*4)	1·458	C(*i*1)–N(*i*1)	1·416
C(*i*1)–O(*i*1)	1·183	C(*i*2)–N(*i*1)	1·444
C(*i*2)–N(*i*2)	1·431	C(*i*2)–O(*i*2)	1·171
C(*i*3)–C(*i*4)	1·355	C(*i*3)–N(*i*2)	1·360
C(*i*3)–N(*i*3)	1·370	C(*i*4)–N(*i*4)	1·395
C(*i*5)–N(*i*3)	1·354	C(*i*5)–N(*i*4)	1·352
N(*i*2)–C(*i*6)	1·467		
C(*i*4)–C(*i*1)–N(*i*1)	104·0	C(*i*4)–C(*i*1)–O(*i*1)	131·3
N(*i*1)–C(*i*1)–O(*i*1)	124·7	N(*i*1)–C(*i*2)–N(*i*2)	108·9
N(*i*1)–C(*i*2)–O(*i*2)	125·0	N(*i*2)–C(*i*2)–O(*i*2)	126·2
C(*i*4)–C(*i*3)–N(*i*2)	120·9	C(*i*4)–C(*i*3)–N(*i*3)	112·9
N(*i*2)–C(*i*3)–N(*i*3)	126·1	C(*i*1)–C(*i*4)–C(*i*3)	127·6
C(*i*1)–C(*i*4)–N(*i*4)	127·6	C(*i*3)–C(*i*4)–N(*i*4)	104·8
N(*i*3)–C(*i*5)–N(*i*4)	112·2	C(*i*1)–N(*i*1)–C(*i*2)	135·8
C(*i*2)–N(*i*2)–C(*i*3)	122·8	C(*i*2)–N(*i*2)–C(*i*6)	115·0
C(*i*3)–N(*i*2)–C(*i*6)	122·1	C(*i*3)–N(*i*3)–C(*i*5)	103·2
C(*i*4)–N(*i*4)–C(*i*5)	106·9		

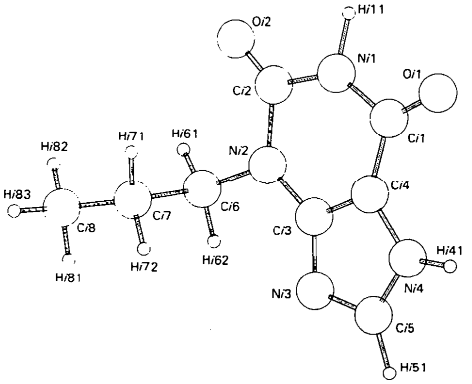

Fig. 1. Atomic numbering, with $i = 1,2,3,4$ for four independent molecules.

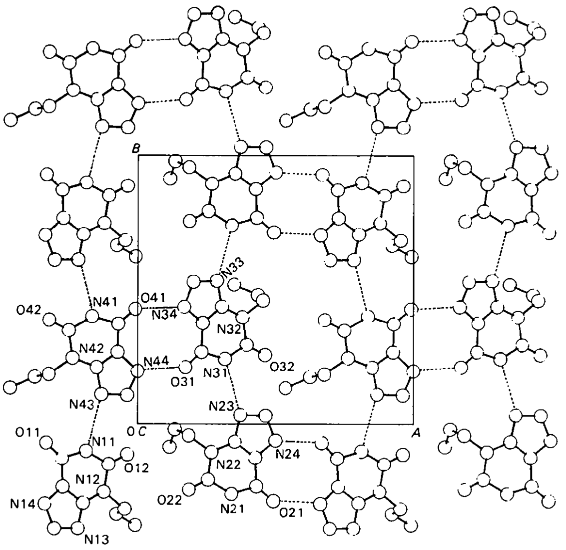

Fig. 2. One molecular layer parallel to the *ab* plane showing the hydrogen-bonding pattern.

Table 3. *Interatomic distances* <3·0 Å *within the molecular layers*

N(11)···N(43)	2·964 (10)	N(33)···N(21^{ii})	2·938 (10)
N(23)···N(31)	2·945 (10)	N(34)···O(41)	2·710 (8)
N(24)···O(11^{i})	2·690 (9)	O(31)···N(44)	2·685 (9)
O(21)···N(14^{i})	2·700 (10)	N(41)···N(13^{ii})	2·961 (10)

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

Table 4. *Interatomic distances* <3·5 Å *between two adjacent molecular layers*

C(11)···C(34^{i})	3·410 (12)	O(12)···C(41^{i})	3·461 (12)
C(11)···N(34^{i})	3·253 (11)	O(12)···O(41^{i})	3·414 (12)
C(12)···O(41^{i})	3·415 (14)	C(21)···C(32^{ii})	3·469 (13)
C(13)···O(31^{i})	3·402 (13)	C(21)···O(32^{ii})	3·356 (12)
C(14)···C(31^{i})	3·410 (12)	C(22)···C(42^{i})	3·450 (13)
C(14)···O(31^{i})	3·341 (12)	C(22)···O(42^{i})	3·407 (11)
C(15)···O(31^{i})	3·362 (13)	N(22)···O(42^{i})	3·304 (9)
N(11)···N(34^{i})	3·413 (11)	N(24)···C(33^{ii})	3·450 (12)
N(12)···N(44^{i})	3·389 (11)	N(24)···N(32^{ii})	3·259 (9)
N(13)···O(31^{i})	3·462 (12)	N(24)···C(36^{ii})	3·408 (13)
N(14)···C(31^{i})	3·270 (12)	O(21)···C(32^{ii})	3·348 (12)
N(14)···O(31^{i})	3·299 (11)	O(21)···N(31^{ii})	3·469 (10)
O(11)···C(33^{i})	3·431 (11)	O(21)···O(32^{ii})	3·400 (12)
O(11)···C(34^{i})	3·335 (11)	O(22)···C(42^{i})	3·320 (11)
O(11)···C(35^{i})	3·347 (11)	O(22)···N(42^{i})	3·206 (9)
O(11)···N(34^{i})	3·287 (9)		

Symmetry code: (i) $-x, -\frac{1}{2}+y, \frac{1}{2}-z$; (ii) $1-x, -\frac{1}{2}+y, \frac{1}{2}-z$.

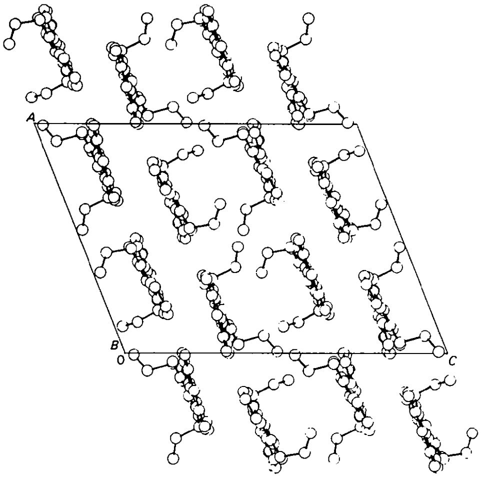

Fig. 3. Packing of the molecular layers, projected on the *ac* plane. The disorder of the *n*-propyl chains is not shown.

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References

Beurskens, P. T. (1981). *Acta Cryst.* A**37**, 426–430.

Beurskens, P. T., Bosman, W. P., Doesburg, H. M., Gould, R. O., Van den Hark, Th. E. M., Prick, P. A. J., Noordik, J. H., Beurskens, G., Parthasarathi, V., Bruins Slot, H. J. & Haltiwanger, R. C. (1984). *DIRDIF*. Tech. Rep. 1984/1. Crystallography Laboratory, Univ. of Nijmegen, The Netherlands.

Bruins Slot, H. J. & Beurskens, P. T. (1985). *Acta Cryst.* A**41**. In the press.

Doesburg, H. M. & Beurskens, P. T. (1983). *Acta Cryst.* A**39**, 368–376.

Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain-la-Neuve, Belgium.

Mercer, A. & Trotter, J. (1978). *Acta Cryst.* B**34**, 450–453.

Nordman, C. E. & Schilling, J. W. (1970). *Crystallographic Computing*, edited by F. R. Ahmed, pp. 110–114. Copenhagen: Munksgaard.

Persson, C. G. A. & Kjellin, P. G. (1981). *Acta Pharmacol. Toxicol.* **49**, 313–316.

Sheldrick, G. M. (1976). *SHELX76*. A program for crystal structure determination. Univ. of Cambridge, England.

Tollin, P. (1966). *Acta Cryst.* **21**, 613–614.

Tollin, P. & Cochran, W. (1964). *Acta Cryst.* **17**, 1322–1324.

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Structure of *cis*-9-[(Benzyloxy)methoxy]-4a,9,9a,10-tetrahydro-9,10-*o*-benzenoanthracene-1,4-dione, a Sterically Congested 2-Ene-1,4-dione

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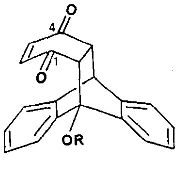
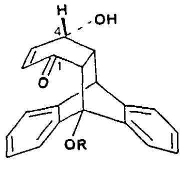
Abstract. $C_{28}H_{22}O_4$, $M_r = 422{\cdot}48$, orthorhombic, $P2_12_12_1$, $a = 13{\cdot}898\,(1)$, $b = 7{\cdot}285\,(1)$, $c = 20{\cdot}704\,(2)$ Å, $V = 2096{\cdot}2\,(6)$ Å^3, $Z = 4$, $D_m = 1{\cdot}32\,(1)$, $D_x = 1{\cdot}339$ Mg m^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) = 1{\cdot}5418$ Å, $\mu = 0{\cdot}54$ mm^{-1}, $F(000) = 888$, $T = 298\,(1)$ K, $R = 0{\cdot}052$ for 1285 observed reflections. The structure contains discrete molecules in which the 2-ene-1,4-dione rings are shallow boats with both carbonyl groups pointed away from an underlying benzene ring. One carbonyl O atom and the (benzyloxy)methoxy O atom are in close contact [2·810 (6) Å]. Several distances and angles in the vicinity of this contact show substantial deviations from expected values, indicating that the molecule is strained.

Introduction. As part of our work on aminocyclitol synthesis (Knapp, Ornaf & Rodriques, 1983), we became interested in site-selective reduction reactions of the 2-ene-1,4-dione (1). Specifically, reaction conditions were sought under which the C(4) carbonyl group could be reduced without reaction at C(1) as in (1)→(2) below. Although reagents can approach (1) from the *exo* face of the enedione ring without any apparent steric hindrance, borohydride reduction of (1) gave (2) in 99% yield without detectable reduction at C(1), implying that the (benzyloxy)methoxy group of (1) somehow slows reaction at C(1) relative to C(4) even though this group is behind the C(1) carbonyl. To help understand this difference in reactivity, the present structural analysis was undertaken.



(1), R CH_2OCH_2Ph



(2)

Experimental. Title compound prepared by Diels–Alder reaction of 9-[(benzyloxy)methoxy]anthracene with *p*-benzoquinone (Knapp *et al.*, 1983). Suitable crystals

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