

Table 2. Ring B torsion angles ($^{\circ}$) for the α - and β -isomers

τ	α	β
C(5)–C(6)–C(7)–C(8)	–9.9 (5)	5.1
C(6)–C(7)–C(8)–C(9)	36.0 (4)	–37.9
C(7)–C(8)–C(9)–C(10)	–59.6 (4)	65.7
C(8)–C(9)–C(10)–C(5)	55.3 (4)	–55.3
C(9)–C(10)–C(5)–C(6)	–29.2 (4)	21.1
C(10)–C(5)–C(6)–C(7)	6.6 (5)	3.1
$\sum \tau_i $	196.6	188.2

substituted cyclopropyl ring, C(5)–C(6)–C(20). The ring B torsion angles for the α - and β -isomers shown in Table 2 clearly indicate opposite configurations. An almost 'normal' chair conformation is adopted by the C ring (torsion angle summation of 342°), but deviation is caused by the fusion of a five-membered and six-membered ring system.

The geometry of the D ring is of special interest due to C(17) sp^2 hybridization. The distances C(13)–C(17) and C(16)–C(17), 1.516 (4) and 1.525 (3) Å, are

intermediate between 1.505 Å, predicted for sp^2 – sp^3 bonds, and 1.533 Å, predicted for sp^3 – sp^3 bonds (Bartell & Bonham, 1960). The overall configuration of the D ring with a maximum torsion angle of 42.6° , is a slightly distorted 14 α -envelope.

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Structures of 7-Chloro-5-phenyl-1-[(S)-1-phenylethyl]-1,3-dihydro-2H-1,4-benzodiazepin-2-one and its 3-Methyl Derivative

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Abstract. C₂₃H₁₉ClN₂O (I), $M_r = 374.86$, orthorhombic, space group $P2_12_12_1$, $a = 17.500$ (3), $b = 12.036$ (2), $c = 9.212$ (2) Å, $Z = 4$, $U = 1940.32$ Å³, $D_x = 1.283$ Mg m⁻³, $\mu(\text{Mo } K\alpha) = 0.216$ mm⁻¹; C₂₄H₂₁ClN₂O (II), $M_r = 388.91$, orthorhombic, space group $P2_12_12_1$, $a = 15.912$ (7), $b = 14.403$ (7), $c = 8.835$ (4) Å, $Z = 4$, $U = 2024.81$ Å³, $D_x = 1.275$ Mg m⁻³, $\mu(\text{Mo } K\alpha) = 0.209$ mm⁻¹. Final $R = 0.047$ for 1778 observed reflexions [$I > 2\sigma(I)$] (compound I) and $R = 0.029$ for 1482 observed reflexions [$I > 3\sigma(I)$] (compound II). The interatomic distances and angles are in agreement with the given atom type, hybridization and conjugation. The benzodiazepine ring exhibits a boat form with a *P* absolute conformation in both compounds. The absolute configuration at C(1) is

S (compounds I and II) whereas at the induced chiral centre C(3) (compound II) it is *R*.

Introduction. Over 2000 benzodiazepines have been synthesized and more than 100 have been tested for pharmacological activities. In man and mammals, the effects are sedation, hypnosis, decreased anxiety, muscle relaxation, and anticonvulsant activity (Goodman, Gilman, Goodman & Gilman, 1980).

Moreover, chiral 1,4-benzodiazepin-2-ones can be used for enantioselective synthesis of α -amino acids (Decorte, Toso, Sega, Šunjić, Ružić-Toroš, Kojić-Prodić, Bresciani-Pahor, Nardin & Randaccio, 1981). In the course of that work it was crucial to determine the absolute conformation of the seven-membered ring

and to find the absolute configuration at the induced chiral centre C(3). This paper deals with the structures of two nonactive benzodiazepines used as a starting compound (I) and the product (II) of C(3)-alkylation.

Weissenberg photographs recorded with Cu *K* α radiation determined uniquely the space group *P*2₁2₁2₁ for both crystals.

The intensities were collected with crystals of dimensions 0.046 × 0.069 × 0.052 mm (compound I) and 0.40 × 0.30 × 1.0 mm (compound II) on a Siemens diffractometer in the $\theta/2\theta$ scan mode. 1778 independent observed reflexions [$I > 2\sigma(I)$] in the range $3 < \theta < 48^\circ$ (compound I) and 1482 reflexions [$I > 3\sigma(I)$] in the range $3 < \theta < 27^\circ$ (compound II) were recorded and used in calculations. The data were not corrected for absorption.

The structure of (I) was solved by the Patterson method. *MULTAN* 80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) failed for structure (II). The Patterson method located the Cl atom. Among the reflexions phased on the basis of the Cl-atom coordinates, 12 were selected, and used as known phases in the *MULTAN* input. In this way, the solution of structure (II) was obtained. The structures were refined by full-matrix least squares, minimizing $\sum W(|F_o| - |F_c|)^2$. Weights were assigned (compound I) as $W = W_1 \cdot W_2$ where $W_1 = 1$ for $|F_o| \leq 25$ and $25/|F_o|$ for $|F_o| > 25$; $W_2 = 1$ for $\sin \theta \geq 0.35$ and $\sin \theta/0.35$ for $\sin \theta < 0.35$. For (II) unit weights were used. A scale factor, atomic coordinates, and anisotropic thermal parameters (244 variables) were refined for compound (I). The H atoms were included in structure-factor calculations only. For (II) a scale factor, atomic coordinates of all atoms, anisotropic parameters of non-H atoms and isotropic of the H atoms (337 variables) were refined. Anisotropic thermal parameters are in the usual range; the maximum values are U_{33} for C(13) [0.190 (9) Å², compound I] and Cl [0.138 (1) Å², compound II]. The final $R = 0.047$, $R_w = 0.064$ for 1778 reflexions with $I > 2\sigma(I)$ (compound I) and $R = 0.029$ for 1482 reflexions with $I > 3\sigma(I)$ (compound II).

The scattering factors given by Cromer & Mann (1968) were used. An anomalous-dispersion correction was included for Cl (Cromer & Liberman, 1970).

Calculations were carried out on a Univac 1110 computer at the University Computing Centre in Zagreb with the XRAY system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976). Atomic coordinates and equivalent isotropic thermal parameters are listed in Table 1.*

* Lists of structure factors, anisotropic thermal parameters, displacements from planes, H-atom coordinates and bond lengths and angles involving H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36992 (45 pp.). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final atomic coordinates* ($\times 10^4$) and *equivalent isotropic thermal parameters* ($\times 10^2$) for non-H atoms

	x	y	z	U_{eq}^\dagger (Å ²)
Compound (I)				
Cl	707 (1)	1804 (1)	12978 (1)	7.0 (1)
O	300 (2)	4339 (3)	5010 (4)	7.8 (3)
N(1)	910 (2)	3956 (3)	7157 (4)	4.9 (3)
C(2)	334 (3)	3793 (4)	6133 (5)	5.4 (3)
C(3)	-201 (2)	2843 (4)	6456 (5)	5.2 (3)
N(4)	239 (2)	1806 (3)	6300 (3)	4.7 (3)
C(5)	718 (2)	1561 (3)	7313 (3)	4.1 (3)
C(6)	748 (2)	1763 (3)	10032 (4)	4.3 (3)
C(7)	786 (2)	2422 (4)	11268 (4)	4.9 (3)
C(8)	865 (3)	3558 (4)	11179 (5)	6.0 (4)
C(9)	911 (3)	4052 (4)	9800 (5)	5.8 (3)
C(10)	888 (2)	3423 (3)	8546 (4)	4.1 (3)
C(11)	805 (2)	2264 (3)	8648 (3)	3.8 (3)
C(12)	1592 (3)	4608 (4)	6691 (6)	6.5 (4)
C(13)	1608 (5)	5788 (5)	7300 (12)	11.4 (6)
C(14)	2311 (2)	3924 (3)	6889 (5)	5.1 (4)
C(15)	2390 (3)	2954 (4)	6067 (6)	6.6 (4)
C(16)	3041 (3)	2304 (5)	6176 (7)	7.4 (5)
C(17)	3630 (3)	2620 (5)	7089 (7)	7.5 (5)
C(18)	3563 (3)	3586 (6)	7902 (7)	8.0 (5)
C(19)	2904 (3)	4215 (5)	7801 (6)	6.8 (4)
C(20)	1212 (2)	568 (3)	7108 (4)	4.4 (3)
C(21)	1854 (2)	396 (4)	7997 (6)	5.9 (3)
C(22)	2345 (3)	-508 (5)	7756 (7)	7.2 (5)
C(23)	2195 (3)	-1237 (4)	6626 (8)	7.3 (4)
C(24)	1558 (3)	-1075 (4)	5736 (6)	6.7 (4)
C(25)	1062 (3)	-170 (4)	5975 (5)	5.5 (4)
Compound (II)				
Cl	2381 (1)	4720 (1)	5052 (1)	8.2 (2)
O	-1421 (1)	8250 (1)	6296 (2)	5.6 (3)
N(1)	-383 (1)	7242 (1)	6919 (3)	4.0 (4)
C(2)	-775 (1)	7845 (2)	5937 (3)	4.1 (4)
C(3)	-328 (1)	8009 (2)	4458 (3)	4.2 (4)
N(4)	466 (1)	8492 (1)	4793 (3)	4.2 (4)
C(5)	1069 (1)	8017 (1)	5350 (3)	3.7 (4)
C(6)	1665 (1)	6410 (2)	5334 (3)	4.1 (4)
C(7)	1600 (1)	5482 (2)	5654 (4)	4.8 (5)
C(8)	915 (2)	5127 (2)	6439 (4)	5.8 (5)
C(9)	266 (2)	5715 (2)	6834 (4)	5.3 (5)
C(10)	297 (1)	6662 (1)	6469 (3)	3.8 (4)
C(11)	1009 (1)	7016 (1)	5745 (3)	3.5 (4)
C(12)	-716 (1)	7206 (2)	8506 (4)	4.7 (4)
C(13)	-1435 (2)	6501 (2)	8718 (4)	6.5 (6)
C(14)	13 (1)	7141 (2)	9608 (3)	4.2 (4)
C(15)	566 (2)	7883 (2)	9672 (4)	5.4 (4)
C(16)	1251 (2)	7871 (2)	10633 (4)	6.2 (6)
C(17)	1394 (2)	7118 (2)	11557 (4)	5.9 (5)
C(18)	841 (2)	6385 (2)	11524 (4)	5.8 (5)
C(19)	156 (2)	6393 (2)	10542 (4)	5.0 (5)
C(20)	1895 (1)	8501 (1)	5564 (3)	3.9 (4)
C(21)	2117 (2)	9214 (2)	4576 (4)	5.0 (4)
C(22)	2886 (2)	9672 (2)	4720 (4)	6.1 (5)
C(23)	3422 (2)	9423 (2)	5866 (5)	6.2 (6)
C(24)	3214 (2)	8730 (3)	6858 (5)	5.8 (6)
C(25)	2449 (2)	8265 (2)	6709 (4)	4.8 (5)
C(26)	-844 (2)	8610 (3)	3373 (5)	6.2 (5)

$^\dagger U_{eq}$ is derived from the anisotropic parameters by $U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$.

Discussion. The structural formula with the atom numbering for compound (II) is given in Fig. 1. Molecular packing is illustrated in Figs. 2 (compound I) and 3 (compound II). Interatomic distances and angles for both compounds are listed in Table 2. The conformation of benzodiazepine rings is defined with torsional angles (Table 3) and displacements from the best least-squares planes.*

Bond distances and angles of both compounds are similar ($<3\sigma$) (Table 2) and in good agreement with those in 5-phenyl-1,4-benzodiazepin-2-ones, e.g. 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (diazepam) (Camerman & Camerman, 1972), 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one (lorazepam) (Ban-

* See previous footnote.

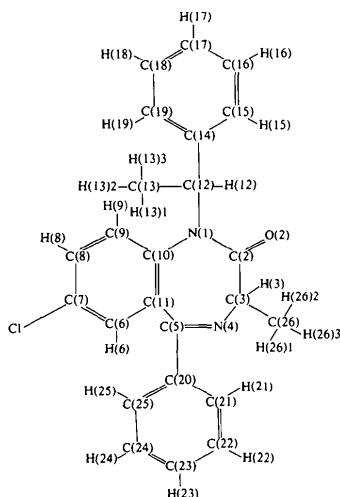


Fig. 1. Structural formula and atom numbering of compound (II); the same numbering is valid for compound (I) but C(3) substituents are H(3)I and H(3)2.

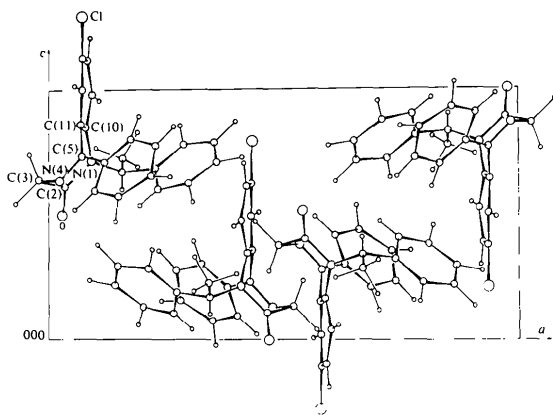


Fig. 2. A view of the crystal structure (I) along *b* showing the packing and a boat conformation of the seven-membered ring.

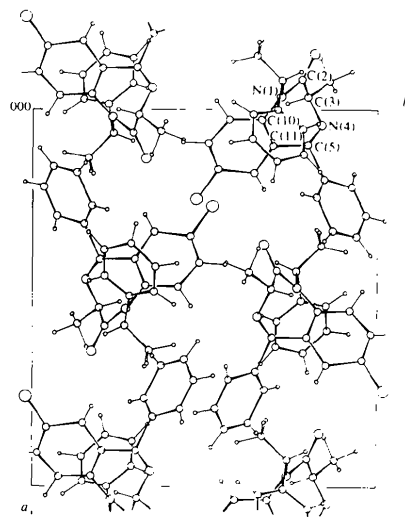


Fig. 3. A view of the crystal structure (II) along *c* showing the packing and a boat conformation of the ring with a fold at C(3) and C(10), C(11).

doli & Clemente, 1976), and 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (oxazepam) (Gilli, Bertolasi, Sacerdoti & Borea, 1978). All values are in accordance with the given atom type and hybridization. However, the shortening of the C(10)–N(1) from the trigonal-carbon and trigonal-nitrogen single-bond length of 1.47 Å (Camerman, 1970) suggests that there is an electron delocalization between the chlorophenyl ring and the adjacent amide group. This effect was also observed in all cited benzodiazepines.

The benzodiazepine rings in both structures exhibit a boat conformation (Table 3, Figs. 2 and 3) with a *P* absolute conformation of the seven-membered ring (Konowa, Snatzke, Alebić-Kolbah, Kajfež, Rendić & Šunjić, 1979). The absolute configuration of the incorporated α -phenylethyl moiety (determined as *S* in I and II) establishes the absolute conformation of the seven-membered ring which determines the absolute configuration at the induced chiral centre C(3) (in II). In accordance with a *P* absolute conformation of the ring, the absolute configuration at C(3) is found to be *R* (in II). ¹H NMR spectroscopy and the polarimetric determination of the temperature-dependent ring inversion (*P* \rightleftharpoons *M*) rates revealed that the *P* conformer remains as the more stable in solution (Decorte *et al.*, 1981).

Intermolecular contacts less than 3.5 Å are Cl...N(4), 3.168 (4) (I) and Cl...C(18), 3.498 (4) and C(8)...O, 3.458 (4) Å (II) indicating only weak van der Waals interactions. Therefore, both molecules (I, II) should maintain the same conformations in crystals and solutions.

The phenyl rings in both molecules are planar within the limits of experimental errors; atom displacements

Table 2. *Interatomic distances (Å) and angles (°)*

	Compound (I)	Compound (II)
N(1)–C(2)	1.393 (6)	1.377 (4)
N(1)–C(10)	1.432 (6)	1.424 (4)
N(1)–C(12)	1.492 (7)	1.500 (4)
C(2)–O	1.227 (6)	1.224 (4)
C(2)–C(3)	1.510 (7)	1.507 (5)
C(3)–N(4)	1.475 (6)	1.472 (4)
C(3)–C(26)	–	1.531 (6)
N(4)–C(5)	1.288 (5)	1.277 (3)
C(5)–C(11)	1.500 (5)	1.487 (4)
C(5)–C(20)	1.487 (6)	1.501 (4)
C(6)–C(7)	1.389 (6)	1.371 (4)
C(6)–C(11)	1.414 (5)	1.408 (4)
C(7)–Cl	1.748 (4)	1.740 (3)
C(7)–C(8)	1.377 (7)	1.391 (5)
C(8)–C(9)	1.404 (7)	1.380 (5)
C(9)–C(10)	1.382 (7)	1.403 (4)
C(10)–C(11)	1.404 (6)	1.397 (4)
C(12)–C(13)	1.527 (9)	1.540 (5)
C(12)–C(14)	1.516 (7)	1.518 (4)
C(14)–C(15)	1.398 (8)	1.387 (4)
C(14)–C(19)	1.380 (8)	1.375 (5)
C(15)–C(16)	1.386 (8)	1.382 (5)
C(16)–C(17)	1.383 (9)	1.376 (6)
C(17)–C(18)	1.388 (10)	1.375 (5)
C(18)–C(19)	1.382 (9)	1.393 (5)
C(20)–C(21)	1.407 (7)	1.393 (4)
C(20)–C(25)	1.396 (7)	1.383 (5)
C(21)–C(22)	1.405 (8)	1.396 (5)
C(22)–C(23)	1.386 (9)	1.371 (6)
C(23)–C(24)	1.397 (9)	1.368 (6)
C(24)–C(25)	1.410 (8)	1.395 (5)
C(2)–N(1)–C(10)	121.5 (4)	122.6 (3)
C(2)–N(1)–C(12)	117.2 (4)	116.7 (2)
C(10)–N(1)–C(12)	120.9 (4)	120.6 (2)
O–C(2)–N(1)	122.1 (5)	121.2 (3)
O–C(2)–C(3)	122.7 (5)	123.2 (3)
N(1)–C(2)–C(3)	115.0 (4)	115.5 (2)
C(2)–C(3)–N(4)	107.3 (4)	107.8 (2)
C(2)–C(3)–C(26)	–	112.2 (3)
N(4)–C(3)–C(26)	–	108.6 (3)
C(3)–N(4)–C(5)	117.6 (4)	118.0 (2)
N(4)–C(5)–C(11)	122.0 (4)	124.2 (2)
N(4)–C(5)–C(20)	118.0 (4)	117.3 (2)
C(11)–C(5)–C(20)	119.9 (3)	118.5 (2)
C(7)–C(6)–C(11)	119.5 (4)	119.7 (3)
Cl–C(7)–C(6)	119.5 (4)	119.9 (2)
Cl–C(7)–C(8)	118.9 (3)	118.8 (2)
C(6)–C(7)–C(8)	121.5 (4)	121.3 (3)
C(7)–C(8)–C(9)	118.6 (4)	119.2 (3)
C(8)–C(9)–C(10)	121.5 (5)	120.8 (3)
N(1)–C(10)–C(9)	120.0 (4)	118.6 (3)
N(1)–C(10)–C(11)	120.5 (3)	122.0 (2)
C(9)–C(10)–C(11)	119.4 (4)	119.3 (3)
C(5)–C(11)–C(6)	119.4 (4)	119.6 (2)
C(5)–C(11)–C(10)	121.1 (3)	120.9 (2)
C(6)–C(11)–C(10)	119.4 (3)	119.5 (2)
N(1)–C(12)–C(13)	113.5 (5)	113.5 (3)
N(1)–C(12)–C(14)	110.1 (4)	109.3 (2)
C(13)–C(12)–C(14)	116.4 (5)	116.7 (3)
C(12)–C(14)–C(15)	118.1 (5)	117.6 (3)
C(12)–C(14)–C(19)	124.0 (5)	124.0 (3)
C(15)–C(14)–C(19)	117.9 (5)	118.3 (3)
C(14)–C(15)–C(16)	120.9 (5)	121.1 (3)
C(15)–C(16)–C(17)	120.1 (6)	120.3 (3)
C(16)–C(17)–C(18)	119.7 (6)	119.1 (3)

Table 2 (cont.)

	Compound (I)	Compound (II)
C(17)–C(18)–C(19)	119.5 (6)	120.5 (3)
C(14)–C(19)–C(18)	121.9 (6)	120.6 (3)
C(5)–C(20)–C(21)	120.6 (4)	119.0 (3)
C(5)–C(20)–C(25)	119.9 (4)	122.4 (3)
C(21)–C(20)–C(25)	119.5 (4)	118.6 (3)
C(20)–C(21)–C(22)	120.7 (5)	120.9 (3)
C(21)–C(22)–C(23)	119.6 (6)	119.3 (3)
C(22)–C(23)–C(24)	120.2 (5)	120.8 (3)
C(23)–C(24)–C(25)	120.5 (5)	120.0 (4)
C(20)–C(25)–C(24)	119.5 (5)	120.4 (3)

Table 3. *Torsion angles (°)*

	Compound (I)	Compound (II)
C(10)–N(1)–C(2)–C(3)	–12.9 (6)	–12.7 (4)
N(1)–C(2)–C(3)–N(4)	–68.4 (5)	–66.0 (3)
C(2)–C(3)–N(4)–C(5)	74.6 (5)	75.8 (3)
C(3)–N(4)–C(5)–C(11)	2.9 (6)	–2.8 (4)
N(4)–C(5)–C(11)–C(10)	–48.4 (6)	–42.2 (5)
C(5)–C(11)–C(10)–N(1)	–1.5 (6)	–2.7 (5)
C(11)–C(10)–N(1)–C(2)	53.7 (6)	52.3 (4)
C(9)–C(10)–N(1)–C(12)	63.8 (6)	48.0 (4)
C(10)–N(1)–C(12)–C(13)	–81.6 (6)	–90.7 (3)
C(10)–N(1)–C(12)–C(14)	51.0 (6)	41.5 (3)
N(1)–C(12)–C(14)–C(15)	63.8 (6)	63.9 (4)
N(4)–C(5)–C(20)–C(21)	165.7 (4)	–30.6 (4)
N(1)–C(2)–C(3)–C(26)	–	174.4 (3)

from the best least-squares planes through the rings are in the range: C(7)–C(11), 0.002–0.007 (5); C(14)–C(19), 0.001–0.002 (1); C(20)–C(25), 0.001–0.005 (5) Å (I) and 0.007–0.0024 (15); 0.001–0.005 (4); 0.0001–0.008 (5) Å (II). The relative orientation of the phenyl rings is given by the dihedral angle between them in the sequence given above: 61.4 (5), 69.8 (4), 10.8 (5)° (I) and 62.8 (4), 62.8 (4), 16.8 (3)° (II).

The conformation of active and nonactive benzodiazepines has not revealed any significant difference; it has also been proved that no correlation exists between molecular geometry and activity (Bandoli & Clemente, 1976; Gilli, Bertolasi, Sacerdoti & Borea, 1977, 1978; Chananont, Hamor & Martin, 1980; Chananont & Hamor, 1981).

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Benzocantharidin*

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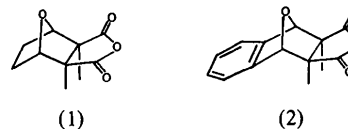
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Abstract. C₁₄H₁₂O₄, monoclinic, *P*2₁, *a* = 7.511 (1), *b* = 7.297 (3), *c* = 11.084 (1) Å, β = 104.78 (2)°, *Z* = 2, *D*_x = 1.381 Mg m⁻³, *T* = 295 K, Mo *K*α (λ = 0.7107 Å). The structure was solved by direct methods and refined by full-matrix least-squares techniques to a conventional *R* of 0.034 for 1025 reflections with intensities above 2σ. The structure consists of discrete molecules with only van der Waals forces between them. The structure is nearly identical to the parent cantharidin molecule with some distortions due to the added fused aromatic ring. In particular the internal angles in the saturated six-membered rings, at the fusion with the aromatic ring, increase because of the shortening of the common C–C bond. Whereas the parent compound has crystallographic mirror symmetry, the present compound has only approximate mirror symmetry because of the crystallographic environment. Bond distances and angles are normal.

Introduction. Benzocantharidin (2) is a relative of the well known, physiologically active, natural product cantharidin (1, Windholz, 1976) whose structure has been reported (Zehnder & Thewalt, 1977). A straightforward synthesis from isobenzofuran and dimethyl-

maleic anhydride (McCormick & Shinmyozu, 1982) has recently been developed.



Experimental. Benzocantharidin was prepared as described (McCormick & Shinmyozu, 1982). Crystals for the diffraction study were obtained by crystallization from diethyl ether. A crystal of approximate dimensions 0.2 × 0.3 × 0.4 mm was chosen for the X-ray study. The crystal system, cell dimensions, and space group were determined using an Enraf–Nonius CAD-4 automated diffractometer.

All computations were performed on a PDP 11/34 computer using the Enraf–Nonius SDP software. A total of 1284 reflections were measured to a maximum 2θ of 50° using the θ–2θ step-scan technique with a variable speed to give 2% counting statistics to a maximum scan time of 120 s. Three standard reflections, measured after every 8000 s of X-ray exposure, showed no significant variation. The orientation was checked with three standard reflections after every 200 reflections; recentering of 25 reflections and calculation of a new orientation matrix were performed if

* Cantharidin is hexahydro-3α,7α-dimethyl-4β,7β-epoxyisobenzofuran-1,3-dione.