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Benzocantharidin*

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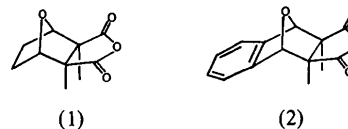
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Abstract. C₁₄H₁₂O₄, monoclinic, $P2_1$, $a = 7.511$ (1), $b = 7.297$ (3), $c = 11.084$ (1) Å, $\beta = 104.78$ (2)°, $Z = 2$, $D_x = 1.381$ Mg m⁻³, $T = 295$ K, Mo $K\alpha$ ($\lambda = 0.7107$ Å). The structure was solved by direct methods and refined 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-3 α ,7 α -dimethyl-4 β ,7 β -epoxyisobenzofuran-1,3-dione.

required. The data were integrated and corrected for Lp to yield 1122 independent reflections of which the 1025 having $F_o^2 > 1.50\sigma(F_o^2)$ were used to solve and refine the structure. Several ψ scans indicated that no absorption correction was required (range of transmission factors less than 2%, $\mu = 1.10 \text{ cm}^{-1}$).

The structure was solved using *MULTAN* (Germain, Main & Woolfson, 1971) and difference Fourier methods (for H atoms). Full-matrix least-squares refinement included anisotropic thermal parameters for C and O atoms as well as isotropic thermal parameters for H atoms (total of 210 variables) and minimized the function $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(F_o)$, $\sigma^2(F_o) = \sigma^2(F_o^2)/4F_o^2$, and $\sigma^2(F_o^2) = \sigma_{\text{counting}}^2 + (0.05F_o^2)^2$. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The final agreement factors were $R = \sum ||F_o| - |F_c|| / \sum F_o = 0.034$ and $wR = [\sum w(|F_o| - |F_c|)^2 / \sum wF_o^2]^{1/2} = 0.043$. The error of an observation of unit weight was 1.38. The largest shift of any parameter on the last cycle was 0.08 times its e.s.d. A final difference Fourier synthesis revealed no density greater than $0.4 \text{ e } \text{Å}^{-3}$.

The final positional parameters and equivalent isotropic B values are given in Table 1 and selected

Table 1. Positional and thermal parameters with their e.s.d.'s in parentheses

	x	y	z	$B_{\text{eq}}^*/B_{\text{iso}}$ (Å^2)
O(1)	0.7774 (2)	0.2500	0.6541 (1)	3.49 (6)
O(2)	1.0692 (2)	0.2653 (4)	0.9642 (2)	5.57 (8)
O(3)	1.0496 (2)	0.0167 (3)	0.8465 (2)	4.12 (6)
O(4)	0.9517 (3)	-0.2336 (3)	0.7330 (2)	5.81 (8)
C(1)	0.3014 (3)	0.1196 (4)	0.5551 (2)	3.47 (6)
C(2)	0.1538 (3)	0.2252 (4)	0.5728 (2)	4.00 (7)
C(3)	0.1837 (3)	0.3708 (4)	0.6541 (2)	4.03 (7)
C(4)	0.3622 (3)	0.4172 (4)	0.7213 (2)	3.73 (6)
C(5)	0.5057 (3)	0.3164 (3)	0.7025 (2)	3.10 (6)
C(6)	0.4743 (3)	0.1683 (3)	0.6203 (2)	2.93 (5)
C(7)	0.6649 (3)	0.0887 (4)	0.6311 (2)	3.12 (6)
C(8)	0.7255 (3)	-0.0099 (3)	0.7617 (2)	3.06 (6)
C(9)	0.7660 (3)	0.1573 (4)	0.8507 (2)	3.13 (6)
C(10)	0.7120 (3)	0.3192 (3)	0.7561 (2)	3.21 (6)
C(11)	0.9729 (3)	0.1593 (4)	0.8961 (2)	3.75 (6)
C(12)	0.9116 (4)	-0.0935 (4)	0.7746 (2)	3.85 (7)
C(13)	0.6773 (4)	0.1646 (5)	0.9605 (2)	4.69 (8)
C(14)	0.5887 (4)	-0.1550 (4)	0.7801 (2)	4.33 (7)
H(C1)	0.296 (3)	0.023 (4)	0.490 (2)	3.6 (5)
H(C2)	0.025 (3)	0.199 (3)	0.525 (2)	3.7 (6)
H(C3)	0.093 (3)	0.440 (3)	0.670 (2)	2.8 (5)
H(C4)	0.384 (3)	0.527 (6)	0.780 (2)	5.6 (7)
H(C7)	0.689 (3)	0.019 (4)	0.563 (2)	2.8 (5)
H(C10)	0.786 (3)	0.440 (4)	0.788 (2)	3.6 (6)
H1(C13)	0.573 (3)	0.162 (4)	0.931 (2)	3.6 (5)
H2(C13)	0.707 (4)	0.043 (5)	1.018 (3)	5.4 (7)
H3(C13)	0.715 (4)	0.290 (6)	1.012 (3)	6.3 (7)
H1(C14)	0.613 (4)	-0.228 (6)	0.860 (3)	7.0 (8)
H2(C14)	0.471 (4)	-0.094 (4)	0.779 (2)	4.2 (6)
H3(C14)	0.544 (4)	-0.238 (7)	0.708 (3)	8.1 (9)

$$* B_{\text{eq}} = \frac{1}{3} \sum_{i,j} B_{ij} a_i^* a_j^* a_i \cdot a_j$$

Table 2. Selected bond angles ($^\circ$) in benzocantharidin

C(6)–C(1)–C(2)	117.5 (2)	C(12)–C(8)–C(14)	110.4 (2)
C(1)–C(2)–C(3)	120.9 (2)	C(8)–C(9)–C(10)	101.1 (2)
C(2)–C(3)–C(4)	120.7 (2)	C(8)–C(9)–C(11)	103.8 (2)
C(3)–C(4)–C(5)	118.3 (2)	C(8)–C(9)–C(13)	118.6 (2)
C(4)–C(5)–C(6)	120.7 (2)	C(10)–C(9)–C(11)	106.6 (2)
C(4)–C(5)–C(10)	134.7 (2)	C(10)–C(9)–C(13)	114.6 (2)
C(6)–C(5)–C(10)	104.7 (2)	C(11)–C(9)–C(13)	110.8 (2)
C(5)–C(6)–C(7)	104.2 (2)	C(5)–C(10)–C(9)	108.6 (2)
C(1)–C(6)–C(5)	121.9 (2)	C(5)–C(10)–O(1)	102.0 (2)
C(1)–C(6)–C(7)	133.9 (2)	C(9)–C(10)–O(1)	100.4 (2)
C(6)–C(7)–O(1)	101.6 (2)	C(9)–C(11)–O(2)	128.9 (3)
C(6)–C(7)–C(8)	107.1 (2)	C(9)–C(11)–O(3)	111.2 (2)
C(8)–C(7)–O(1)	101.1 (2)	O(2)–C(11)–O(3)	119.9 (2)
C(7)–C(8)–C(9)	100.9 (2)	C(8)–C(10)–O(3)	111.1 (2)
C(7)–C(8)–C(12)	108.6 (2)	C(8)–C(12)–O(4)	129.3 (3)
C(7)–C(8)–C(14)	113.2 (2)	O(3)–C(12)–O(4)	119.6 (3)
C(9)–C(8)–C(12)	103.5 (2)	C(7)–O(1)–C(10)	97.1 (2)
C(9)–C(8)–C(14)	119.4 (2)	C(11)–O(3)–C(12)	109.9 (2)

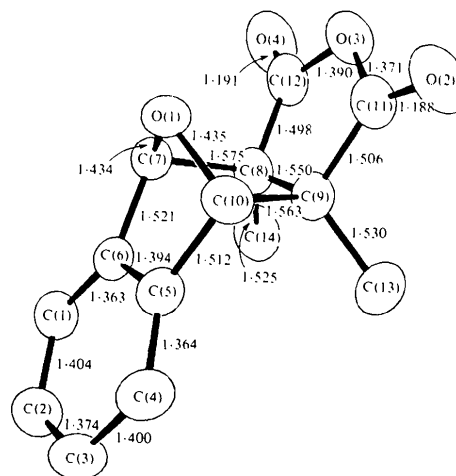


Fig. 1. Perspective view of benzocantharidin showing the atom labelling, thermal ellipsoids, and bond distances (Å). Standard deviations are ± 0.003 – 0.004 Å.

bond angles are in Table 2.* Fig. 1 shows the molecular geometry and bond distances.

Discussion. The primary goals of this study were to confirm the *endo* stereochemistry of the C(13) and C(14) methyl groups and to compare the molecular parameters with the parent cantharidin molecule (1) (Zehnder & Thewalt, 1977). Whereas that compound has crystallographic mirror symmetry, the present compound has only approximate mirror symmetry. The bond distances and some of the angles are compared in Table 3. The major differences

* Lists of structure factors, anisotropic thermal parameters and least-squares-planes' data have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36999 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. Comparison of molecular parameters of benzocantharidin(BC) and cantharidin(C)

	BC(av.)*	C
C(5)–C(6)	1.394 (3) Å	1.528 (3) Å
C(6)–C(7)	1.516 (4)	1.548 (3)
C(7)–O(1)	1.435 (3)	1.447 (3)
C(7)–C(8)	1.569 (6)	1.558 (3)
C(8)–C(9)	1.550 (3)	1.560 (3)
C(8)–C(12)	1.502 (4)	1.522 (3)
O(3)–C(11)	1.380 (9)	1.389 (3)
O(2)–C(11)	1.190 (3)	1.176 (3)
C(8)–C(14)	1.527 (3)	1.525 (3)
O(4)–C(12)–C(8)	129.1 (2)°	130.3 (3)°
O(4)–C(12)–O(3)	119.8 (2)	118.5 (3)
C(5)–C(6)–C(7)	104.3 (3)	102.3 (3)
C(6)–C(7)–C(8)	107.8 (8)	110.0 (3)
C(6)–C(7)–O(1)	101.8 (3)	101.2 (3)
O(1) C(7)–C(8)	100.8 (3)	101.1 (3)
C(7)–C(8)–C(9)	101.0 (2)	101.6 (3)
C(7)–C(8)–C(12)	107.6 (10)	106.7 (3)
C(7)–C(8)–C(14)	113.9 (7)	115.6 (3)
C(9)–C(8)–C(14)	119.0 (4)	118.4 (3)
C(9)–C(8)–C(12)	103.6 (2)	103.7 (3)
C(12)–C(8)–C(12)	110.6 (2)	109.5 (3)
O(3)–C(12)–C(8)	111.1 (2)	111.2 (3)

* Assumes mirror symmetry (average deviation or individual standard deviation whichever is larger).

are a result of the introduction of the aromatic fused ring at C(5) and C(6) which changes that bond from a single bond in the parent compound to an aromatic bond in the present compound. As a result there is also a decrease in the length of the adjacent saturated C–C bonds by about 0.03 Å and some readjustment of the angles about those two C atoms (Table 3). The reason for differences in the anhydride portion are not obvious. Because of the constraints of the bicyclic system and the fusion with the aromatic ring, the angles around C(5) and C(6) deviate dramatically from the 'ideal' 120° values for aromatic C atoms. In particular, the large external angles of 133.9 (2) and 134.7 (2)° compensate for the small internal angles to the saturated ring [104.7 (2) and 104.2 (4)°]. In the aromatic ring the angles at C(1) and C(4) are contracted to 117.5 (2) and 118.3 (2)°, and the distances C(1)–C(6) and C(4)–C(5) are significantly shorter than the others. The C–H distances are normal with an average value of 0.99 (6) Å (average deviation given; standard deviation of a single measurement was 0.03–0.05 Å).

It is possible to describe the molecule as consisting of two nearly parallel planar portions [C(1) to C(7) and C(10) = plane 1 and C(8), C(9), C(11), C(12), O(2), O(3) and O(4) = plane 2] separated by a perpendicular distance of ~1.5 Å. Only O(1), C(13) and C(14) are significantly displaced from both of these planes (see least-squares planes and dihedral angles*). However, careful examination reveals a slight (*ca* 2.5°) bend in the carbocyclic π system if C(1)C(4)C(5)C(6) and C(5)C(6)C(7)C(8) are analyzed separately. Such distortion of the planarity of the π -bond of the bicyclo[2.2.1] system away from the one-atom bridge would be in agreement with somewhat larger distortions which have been observed (Watson, Galloy, Bartlett & Roof, 1981; Hagenbuch, Vogel, Pinkerton & Schwarzenbach, 1981) and theoretically calculated (Wipff & Morokuma, 1980) in norbornene systems, leading to an increase in π -electron density on the *exo* side. Since this uneven π -electron distribution may play a role in the preferential reactivity of the norbornene double bond at the *exo* face, the possibility of π -bond non-planarity and the resulting effects on the reactivity of the carbocyclic π -system of benzocantharidin should be considered when examining its chemistry.

There are no unusually short intermolecular contacts. The shortest contacts are O(1)–C(3) [3.176 (3) Å], O(1)–C(2) [3.184 (3) Å] and O(4)–C(2) [3.292 (3) Å].

* See previous footnote.

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