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The Structure of 3,4-Dihydro-4-hydroxy-2*H*-1,3-benzoxazin-2-one, $C_8H_7NO_3$, a Model for the Carbinolamide Moiety in Maytansine

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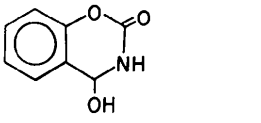
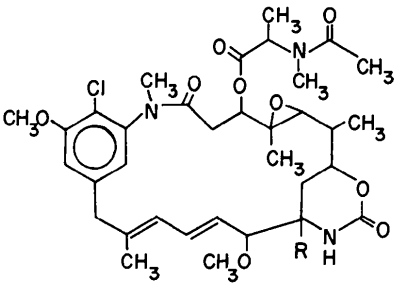
Abstract. $M_r = 165{\cdot}2$, monoclinic, $P2_1/n$, $a = 7{\cdot}998$ (3), $b = 11{\cdot}134$ (4), $c = 9{\cdot}200$ (2), $\beta = 118{\cdot}89$ (3)°, $V = 717{\cdot}3$ (5) Å^3, $D_x = 1{\cdot}53$ Mg m^{-3}, $Z = 4$, $F(000) = 344$; Cu $K\alpha$ ($\lambda = 1{\cdot}5418$ Å); $\mu = 12{\cdot}53$ mm^{-1}; 1176 unique intensities; 1115 I's $\geq 3\sigma$ above background; final $R = 0{\cdot}049$. The –O–C(=O)–NH–C(OH)– region in the molecule presumably is responsible for the bio-alkylation properties of the anti-tumor compound maytansine. Bond lengths and angles are normal and there is no suggestion of chemical lability in any of these values. The molecules form N–H···O(H)–C hydrogen-bonded dimers, while O–H···O=C contacts are formed between the various dimers.

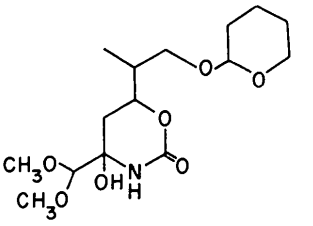
Introduction. The heterocyclic portion of the title compound (I) is believed to be essential for the activity of maytansine (II) (Kupchan, Sneden, Branfman, Howie, Rebhun, McIvor, Wang & Schnaitman, 1978), a complex anticancer agent now in clinical trials. Maytansine was discovered by Kupchan, Komoda, Court, Thomas, Smith, Karim, Gilmore, Haltiwanger & Bryan (1972) and the crystal structure of a derivative (III) has been determined (Bryan, Gilmore & Haltiwanger, 1973). Because of the extreme scarcity of maytansine, a number of groups have reported synthetic studies in this area and, recently, Corey, Weigel, Chamberlin, Cho & Hua (1980) have described the first total synthesis. In an important study bearing on the mechanism of anticancer activity, Lown, Majumdar, Meyers & Hecht (1977) have shown that maytansine and certain synthetic carbinolamide analogs [one of which (V) exhibits antileukemic activity in rodents] rapidly alkylate nucleic acids *in vitro* in a reaction which is promoted by acidic conditions; they interpreted the reaction of maytansine and its analogs as an acid-induced dehydration of the carbinolamide moiety to an azomethine lactone and subsequent attack on this Michael acceptor by nucleophiles on the bases of DNA. A report on the action of maytansine against the growth of murine leukemia cells showed that of the three principal macromolecular processes (DNA, RNA, protein), DNA synthesis was inhibited to the greatest extent (Wolpert-Defilippes, Adamson, Cysyk & Jones, 1975; Wolpert-Defilippes, Bono, Dion & Johns, 1975). Studies of biological activities (Henery-Logan, Badr-Eldin, Hetrick & Voll, 1982; Henery-Logan, Badr-Eldin, White, King, Bledsoe, Christensen, Stern, Leusner, Siu, Northrup, Rodgers, Choe, Hetrick, Voll, Coleman & Stone, 1983) have shown that (I) is cytotoxic to KB (human nasopharynx) cancer cells, demonstrates activity against P388 lymphocytic leukemia in mice and in the MX-1 human mammary tumor xenograft test system in mice, and is non-mutagenic in the Ames assay, a measure of carcinogenicity in animals.



(I)



(II), R = OH
(III), R = $OCH_2CH_2CH_2Br$
(IV), R = $SCH_2CH_2CH_3$



(V)

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Acid-catalyzed alkylation of alcohols and thiols by (II) occurs at the carbinolamide and *not* at the epoxide. For example, the reaction of (II) with 3-bromo-1-propanol and 1-propanethiol gave (III) (Kupchan, Komoda, Branfman, Sneden, Court, Thomas, Hintz, Smith, Karim, Howie, Verma, Nagao, Dailey, Zimmerly & Sumner, 1977) and (IV) (Kupchan *et al.*, 1978), respectively. Similarly, facile acid-catalyzed exchanges of the hydroxyl for alkoxy and thioalkyl groups have been observed in (V) (Meyers & Shaw, 1974) and (I) (Henery-Logan *et al.*, 1982, 1983).

Experimental. (I) was prepared by a procedure in the patent literature (Merck, 1965) which described the treatment of salicylaldehyde with phosgene, followed by reaction of the intermediate chloroformate with ammonia, to afford a crude product of melting point 438–439 K (dec.); a later patent from the same laboratory (Merck, 1966) reported a purified product having a melting point of 435–438 K (resolidified, m.p. 573 K). The product we obtained, after recrystallization by dissolving in tetrahydrofuran–water and reducing the volume *in vacuo*, showed a decomposition point of 486 K and exhibited infrared and proton magnetic resonance spectra and elemental analyses consistent with the assigned structure (Henery-Logan *et al.*, 1982, 1983). Crystals of the title compound suitable for X-ray determination were obtained from an acetone–water solution by slow evaporation at room temperature.

Picker FACS-I diffractometer, graphite-monochromated Cu radiation, crystal 0·45 × 0·30 × 0·10 mm, rhombohedral cross section, 2θ values of 12 reflections manually centered at $\pm 2\theta$ used to obtain accurate cell parameters by least squares (average $|2\theta_o - 2\theta_c| = 0{\cdot}009°$), θ–2θ scan, 2° min^{-1}, 10 s backgrounds, scan width 1·65° + 0·3° tanθ, four standards every 100 reflections, 1176 reflections measured, 2θ maximum of 127°, 1115 unique reflections, 1069 3σ above background; *MULTAN* 80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), full-matrix least squares, anisotropic temperature factors for C, N and O, isotropic for H, $\sum w(F_o - F_c)^2$ minimized, $w = [1/\sigma(F)]^2$, scattering factors for C, N and O from Cromer & Mann (1968), for H from Stewart, Davidson & Simpson (1965), reflections with $I_c < 3\sigma(I)$ not included, $R = 0{\cdot}049$, $R_w = 0{\cdot}055$, UNIVAC 1108 computer, University of Maryland's Computer Science Center, XRAY system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976).

Discussion. Atomic coordinates and temperature factors are listed in Table 1.* An *ORTEP* drawing (Johnson, 1971) of the molecule including bond lengths and angles is given in Fig. 1. The benzene ring is quite planar, the six carbon atoms showing an average deviation of 0·003 (4) Å from their least-squares plane. The O–C(=O)–N–C atoms are close to the aromatic plane with O(1) and C(4) lying 0·003 (5) and 0·063 (6) Å on one side of the plane and C(2), O(2) and N(3) on the other side by 0·102 (5), 0·169 (4) and 0·164 (4) Å, respectively.

Bond lengths and angles have normal values. There is no hint in any of these parameters of unusual chemical lability. A search of the Cambridge Crystallographic Data File (current to May 1982) for the

Table 1. *Fractional coordinates and temperature factors* (Å^2)

An asterisk denotes U_{eq}; $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$. The e.s.d. of the last significant digit is given in parentheses.

	x	*y*	*z*	*U*
O(1)	0·4377 (3)	0·2163 (2)	0·5261 (3)	0·045 (2)*
C(2)	0·3634 (4)	0·1712 (3)	0·6191 (4)	0·050 (4)*
O(2)	0·4065 (4)	0·2202 (2)	0·7517 (3)	0·053 (3)*
N(3)	0·2515 (4)	0·0744 (2)	0·5644 (3)	0·041 (4)*
C(4)	0·1738 (4)	0·0199 (3)	0·4014 (4)	0·038 (5)*
O(4)	−0·0258 (3)	0·0411 (2)	0·3075 (3)	0·044 (1)*
C(4a)	0·2792 (4)	0·0629 (3)	0·3149 (4)	0·040 (3)*
C(5)	0·2518 (5)	0·0128 (3)	0·1679 (4)	0·041 (6)*
C(6)	0·3450 (5)	0·0580 (3)	0·0856 (4)	0·054 (6)*
C(7)	0·4676 (5)	0·1554 (3)	0·1515 (4)	0·065 (6)*
C(8)	0·4972 (5)	0·2062 (3)	0·2995 (4)	0·053 (5)*
C(8a)	0·4024 (4)	0·1607 (3)	0·3775 (4)	0·040 (4)*
H(3)	0·193 (4)	0·041 (3)	0·640 (4)	0·040 (9)
H(4)	0·187 (4)	−0·080 (3)	0·412 (4)	0·031 (8)
H(4′)	−0·042 (6)	0·114 (4)	0·281 (5)	0·08 (1)
H(5)	0·170 (5)	−0·051 (3)	0·126 (4)	0·036 (9)
H(6)	0·336 (5)	0·019 (4)	−0·019 (5)	0·06 (1)
H(7)	0·536 (5)	0·192 (3)	0·089 (4)	0·046 (9)
H(8)	0·577 (6)	0·278 (4)	0·342 (5)	0·07 (1)

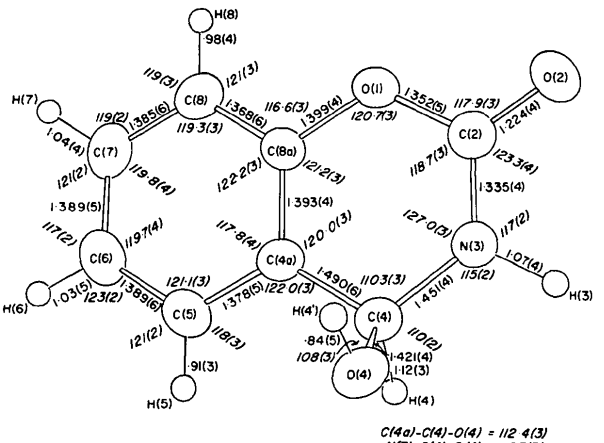
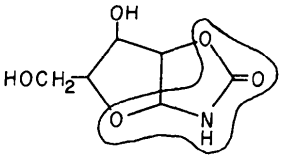


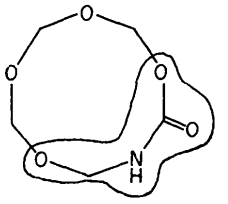
Fig. 1. *ORTEP* drawing of (I) with the C, N and O atoms depicted as 50% probability boundary ellipses. H atoms are shown as 0·1 Å radius circles. (Distances in Å, angles in degrees.)

* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38214 (7 pp.). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

–O–C(=O)–N–C(–O*R*) (*R*=H or C) group in (I) and (II) located two additional structures [(VI) and (VII)] containing this fragment. The low accuracy of



(VI)



(VII)

the (3-bromo-1-propyl)maytansine (III) structure (Bryan, Gilmore & Haltiwanger, 1973) precludes a meaningful comparison with (I), but the common parameters in (I), (VI) (Singh & Hodgson, 1976) and (VII) (Kobelt & Paulus, 1973) are listed in Table 2. The values are surprisingly similar despite the fact that the fragment of interest is part of six-, five- and ten-membered ring structures, respectively, in the three compounds. The largest differences, which are in the endocyclic bond angles at C(2) and N(3), can be attributed to ring size and planarity effects.

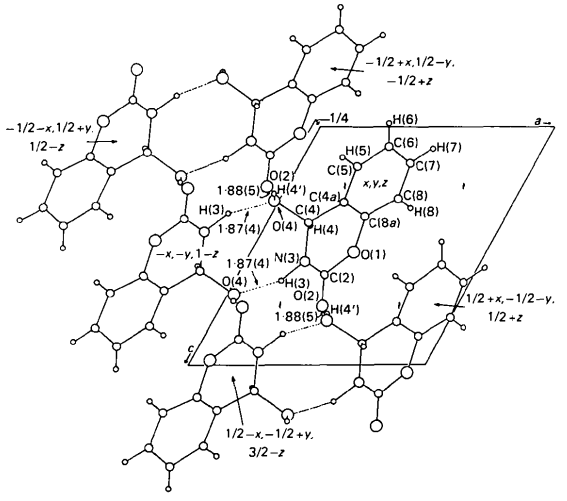
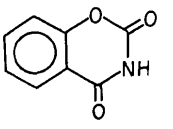


Fig. 2. Packing view down **b**. (Distances in Å.)

Table 2. *Bond lengths* (Å) *and angles* (°) *in the* –O–C(=O)–N–C(–O–)– *fragments of* (I), (IV), *and* (V)

	(I)	(IV)	(V)
O(1)–C(2)	1·352 (5)	1·349 (2)	1·352 (2)
C(2)–O(2)	1·224 (4)	1·219 (3)	1·213 (3)
C(2)–N(3)	1·335 (4)	1·340 (3)	1·342 (4)
N(3)–C(4)	1·451 (4)	1·437 (3)	1·448 (4)
C(4)–O(4)	1·421 (4)	1·421 (2)	1·412 (4)
O(1)–C(2)–N(3)	118·7 (3)	110·4 (2)	111·9 (2)
O(1)–C(2)–O(2)	117·9 (3)	120·6 (2)	123·2 (2)
N(3)–C(2)–O(2)	123·3 (4)	128·9 (2)	124·8 (2)
C(2)–N(3)–C(4)	127·0 (3)	112·9 (2)	123·7 (2)
N(3)–C(4)–O(4)	110·7 (3)	113·2 (2)	113·3 (2)

A packing diagram is given in Fig. 2. The molecule packs in sheets, which are inclined at 39 (1)° to the *b* axis. The principal structural component of the sheets consists of two center-of-symmetry-related molecules which are linked by 1·87 (4) Å N(3)–H(3)···O(4) hydrogen bonds. These hydrogen-bonded dimers are linked to each other *via* 1·88 (5) Å O(4)–H(4')···O(2) contacts. Molecule (VIII) (Kashino, Nakashima & Haisa, 1978) forms a similar sheet-like pattern of hydrogen-bonded dimers, but is limited to this interaction by the presence of only one good hydrogen-bond donor.



(VIII)

We thank Dr Samir M. Badr-Eldin for the preparation and crystallization of (I). This investigation was supported by a grant (CH-148) from the American Cancer Society and through the facilities of the Computer Science Center of the University of Maryland.

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6-Chloro-1-methyl-4-phenyl-1*H*-2,1,3-benzothiadiazine 2,2-Dioxide, $C_{14}H_{11}ClN_2O_2S$

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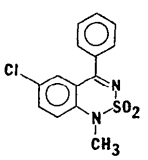
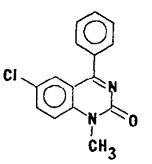
Abstract. $M_r = 306{\cdot}5$, $P2_1/c$, $a = 6{\cdot}098\ (2)$, $b = 14{\cdot}685\ (3)$, $c = 15{\cdot}143\ (2)$ Å, $\beta = 95{\cdot}89\ (2)°$, $V = 1348{\cdot}9\ (6)$ Å^3, $Z = 4$, $D_m = 1{\cdot}49$ Mg m^{-3}, $D_x = 1{\cdot}51$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, μ(Cu $K\alpha$) = 39·9 mm^{-1}, $R = 0{\cdot}066$, $R_w = 0{\cdot}099$ with 1737 independent non-zero reflections. The S atom is tetrahedral and the phenyl ring makes an angle of 55° to the plane of the heterocyclic ring. There is a close intermolecular approach of a Cl atom to an adjacent fused-ring system.

Introduction. The title compound, (1), was obtained as an unexpected by-product in the synthesis of 6-chloro-1-methyl-4-phenylquinazolin-2(1*H*)-one, (2), (Kamal, Rao & Sattur, 1980) and the X-ray investigation was undertaken to confirm the structure of the compound and to ascertain the geometry about the S atom.



(1)



(2)

Experimental. Light-yellow plate, 0·38 × 0·45 × 0·63 mm, D_m by flotation in CCl_4–toluene, data collected on an Enraf–Nonius CAD-4, lattice parameters from 15 high-angle reflections, systematic absences: $h0l$, $l = 2n + 1$; $0k0$, $k = 2n + 1$, maximum sin $\theta/\lambda = 0{\cdot}58$ Å^{-1}, standards (124 and 212) did not vary more than 6%, 2350 reflections measured, 1737 unique non-zero reflections at the 3σ significance level; structure solution with *MULTAN*78 (Main, Woolfson, Lessinger, Germain & Declercq, 1978), least-squares refinement using F's, hydrogens located and refined isotropically, all other atoms refined anisotropically, $R = 0{\cdot}066$, $wR = 0{\cdot}099$, $w = 33{\cdot}57/\{[\sigma(F_o)]^2 + (0{\cdot}045\ F_o)^2\}$ where $\sigma(F_o)$ is the standard deviation based on counting statistics, maximum least-squares shift-to-error in final refinement cycle 0·017, maximum peak height in final difference Fourier synthesis 0·59e Å^{-3}, $F(000) = 632$, scattering factors from *International Tables for X-ray Crystallography* (1974), refinements carried out with *SHELX*76 (Sheldrick, 1976).†

Discussion. The molecular structure of the title compound is confirmed. The atomic coordinates are reported in Table 1. Fig. 1 shows the atom-numbering scheme and the intramolecular bond lengths and angles. All these lengths and angles are normal.

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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 38120 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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