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Structures of Two DNA Minor-Groove Binders, Based on Pyrrolo[2,1-*c*][1,4]-benzodiazepines

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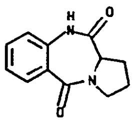
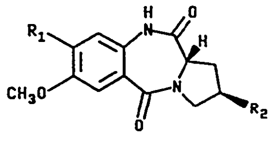
Abstract. (1): (11a*S*)-1,2,3,10,11,11a-Hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione, $C_{12}H_{12}N_2O_2$, $M_r = 216{\cdot}24$, monoclinic, $P2_1$, $a = 8{\cdot}717\,(2)$, $b = 6{\cdot}927\,(1)$, $c = 10{\cdot}950\,(2)$ Å, $\beta = 113{\cdot}01\,(2)^\circ$, $V = 608{\cdot}6$ Å^3, $Z = 2$, $D_x = 1{\cdot}18$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}636$ mm^{-1}, $F(000) = 228$, $T = 293$ K, final $R = 0{\cdot}040$ for 1143 observed reflections. (2): (2*R*,11a*S*)-2,8-Diacetoxy-7-methoxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione, $C_{17}H_{18}N_2O_7$, $M_r = 362{\cdot}14$, orthorhombic, $P2_12_12_1$, $a = 6{\cdot}633\,(1)$, $b = 13{\cdot}435\,(2)$, $c = 19{\cdot}246\,(2)$ Å, $V = 1714{\cdot}9$ Å^3, $Z = 4$, $D_x = 1{\cdot}38$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 9{\cdot}22$ cm^{-1}, $F(000) = 760$, $T = 293$ K, final $R = 0{\cdot}040$ for 1584 observed reflections. The two structures have very similar boat-like conformations for the seven-membered ring of the benzodiazepinedione and the fused five-membered hexahydropyrrole ring. In both cases the secondary amide group is virtually planar. (1) has two water molecules of crystallization.

Experimental. Crystals of both compounds were grown from ethanolic solution as chunky colourless prisms, following synthetic studies (Jones *et al.*, 1990).



(1)



$R_1 = R_2 = OCOCH_3$

(2)

Crystal sizes used in analysis: (1) 0·40 × 0·20 × 0·15 mm; (2) 0·35 × 0·25 × 0·15 mm. In each case, accurate cell dimensions were obtained from least-squares fit of 25 reflections in the range of $15 < \theta < 25^\circ$ measured on an Enraf–Nonius CAD-4 diffractometer with graphite-filtered Cu $K\alpha$ radiation. Intensity data were collected with an ω–2θ scan technique with max scan times per reflection of 120 s for (1) and (2). In each case a unique data set was collected. Reflection ranges for the data collection were $1{\cdot}5 < \theta < 78^\circ$ and $0 \le h \le 11$, $0 \le k \le 8$, $-13 \le l \le 13$ for (1), $1{\cdot}5 < \theta < 75^\circ$ and $0 \le h \le 8$, $0 \le k \le 16$, $0 \le l \le 24$ for (2). Monitoring of standard reflections showed no decay. Data corrected for background, Lorentz and polarization effects. Absorption corrections were not applied. 1468 unique reflections collected for (1), with 1143 having $I \ge 3\sigma(I)$. 2052 unique reflections were measured for (2), with 1584 having $I \ge 3\sigma(I)$. The structures were solved by direct methods using *MULTAN*82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982) and refined by full-matrix least squares based on F with weights $w = 1/[\sigma^2(F) + (0{\cdot}04F)^2]$ using the *SDP* (Frenz, 1980) package and atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV). The positions of H atoms were found in difference Fourier maps. Two water molecules were found in the maps for (1). Non-H atoms were refined anisotropically and H atoms isotropically. For (1), final $R = 0{\cdot}040$ and $wR = 0{\cdot}053$ with a max. shift/e.s.d. of < 0·01 in the final cycle and limits of $\pm 0{\cdot}15$ e Å^{-3} in the final difference map. For (2), final $R = 0{\cdot}040$ and $wR = 0{\cdot}049$ with a max. shift/e.s.d. of < 0·01 in the final cycle and limits of $\pm 0{\cdot}17$ e Å^{-3} in the final difference map. The positional parameters of H atoms were refined in the least-squares runs; their temperature factors were kept fixed at values 0·5 Å^2 higher than the atoms to which they were bonded. Absolute configurations

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Table 1. *Positional parameters and equivalent values of the anisotropic temperature factors, with e.s.d.'s in parentheses*

$$B_{eq} = (8\pi^2/3)\textstyle\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq} (Å^2)
Compound (1)				
O1	0·9712 (3)	−0·1519 (5)	0·3561 (2)	3·95 (6)
O*W*1	0·8687 (4)	0·1970 (6)	0·8026 (3)	5·55 (8)
O2	0·3429 (3)	0·0172 (5)	0·2213 (2)	3·88 (6)
O*W*2	1·0073 (4)	0·1315 (8)	1·0725 (3)	7·5 (1)
N1	0·8162 (3)	0·0886 (5)	0·2303 (3)	3·03 (6)
N2	0·6030 (3)	−0·0379 (5)	0·3674 (2)	2·48 (5)
C1	0·8663 (4)	−0·0264 (6)	0·3377 (3)	2·66 (7)
CP1	0·7416 (5)	0·411	0·1485 (3)	3·83 (9)
C2	0·4922 (4)	0·0635 (6)	0·2678 (3)	2·60 (7)
CP2	0·7043 (4)	0·2446 (6)	0·2029 (3)	2·67 (7)
CP3	0·5516 (4)	0·2358 (6)	0·2191 (3)	2·64 (7)
CP4	0·4442 (5)	0·3942 (7)	0·1778 (3)	3·83 (9)
CP5	0·4827 (6)	0·5556 (6)	0·1256 (4)	4·6 (1)
CP6	0·6324 (6)	0·5649 (6)	0·1107 (4)	4·6 (1)
C51	0·7812 (4)	0·0106 (6)	0·4338 (3)	2·54 (7)
C52	0·8414 (4)	−0·1259 (7)	0·5526 (3)	3·48 (8)
C53	0·7273 (5)	−0·2987 (7)	0·5061 (4)	3·86 (9)
C54	0·5595 (4)	−0·2075 (6)	0·4278 (3)	3·35 (8)
Compound (2)				
O54	0·4187 (4)	0·4418 (2)	4953 (1)	4·27 (6)
O8	−0·5575 (7)	0·2920 (4)	0·9287 (2)	10·0 (1)
O7	−0·6260 (5)	0·2293 (2)	0·8246 (1)	4·27 (6)
O1	0·2559 (5)	0·1788 (2)	0·6377 (2)	5·27 (7)
O56	0·7147 (5)	0·4697 (3)	0·5466 (2)	7·37 (9)
O2	0·0083 (5)	0·5407 (2)	0·7116 (1)	4·07 (6)
O5	−0·6687 (5)	0·4278 (2)	0·8086 (2)	5·42 (7)
N2	0·0956 (5)	0·4143 (2)	0·6410 (1)	2·96 (6)
N1	0·0136 (5)	0·2281 (2)	0·7123 (2)	3·65 (6)
CP6	−0·4700 (6)	0·2832 (3)	0·7946 (2)	3·49 (7)
CP5	−0·4917 (6)	0·3869 (3)	0·7853 (2)	3·64 (8)
CP4	−0·3407 (6)	0·4370 (3)	0·7519 (2)	3·59 (8)
CP3	−0·1706 (6)	0·3888 (2)	0·7254 (2)	2·83 (6)
CP2	−0·1526 (6)	0·2848 (3)	0·7341 (2)	3·10 (7)
C2	−0·0156 (6)	0·4524 (2)	0·6927 (2)	2·91 (7)
C1	0·1173 (6)	0·2351 (3)	0·6525 (2)	3·53 (8)
C51	0·0493 (6)	0·3195 (3)	0·6055 (2)	3·05 (7)
C52	0·1679 (7)	0·3284 (3)	0·5379 (2)	3·87 (8)
C53	0·3450 (6)	0·3938 (3)	0·5573 (2)	3·59 (8)
C54	0·2556 (6)	0·4706 (3)	0·6061 (2)	3·70 (8)
C8	−0·8671 (8)	0·2053 (4)	0·9116 (2)	5·5 (1)
C7	−0·6691 (8)	0·2464 (3)	0·8923 (2)	5·0 (1)
CP1	−0·3054 (7)	0·2353 (3)	0·7703 (2)	3·67 (8)
C57	0·6069 (7)	0·4804 (3)	0·4983 (2)	4·31 (9)
C55	0·6554 (9)	0·5376 (4)	0·4342 (2)	6·1 (1)
C5	−0·6548 (8)	0·5215 (3)	0·8432 (2)	5·1 (1)

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

Compound (1)			
O1—C1	1·220 (5)	CP1—CP6	1·379 (5)
O2—C2	1·240 (4)	C2—CP3	1·480 (6)
N1—C1	1·344 (5)	CP2—CP3	1·411 (5)
N1—CP2	1·408 (5)	CP3—CP4	1·398 (6)
N2—C2	1·339 (4)	CP4—CP5	1·357 (7)
N2—C51	1·473 (4)	CP5—CP6	1·379 (8)
N2—C54	1·469 (5)	C51—C52	1·526 (5)
C1—C51	1·527 (6)	C52—C53	1·512 (6)
CP1—CP2	1·395 (5)	C53—C54	1·515 (5)
C1—N1—CP2	127·1 (3)	CP1—CP2—CP3	118·6 (3)
C2—N2—C51	124·6 (3)	C2—CP3—CP2	124·1 (3)
C2—N2—C54	123·8 (3)	C2—CP3—CP4	117·7 (3)
C51—N2—C54	111·6 (2)	CP2—CP3—CP4	118·1 (4)
O1—C1—N1	122·2 (4)	CP3—CP4—CP5	122·6 (4)
O1—C1—C51	122·8 (3)	CP4—CP5—CP6	119·3 (4)
N1—C1—C51	115·1 (3)	CP1—CP6—CP5	120·2 (4)
CP2—CP1—CP6	121·2 (4)	N2—C51—C1	108·9 (2)
O2—C2—N2	120·4 (4)	N2—C51—C52	103·0 (3)
O2—C2—CP3	121·3 (3)	C1—C51—C52	112·7 (3)
N2—C2—CP3	118·3 (3)	C51—C52—C53	104·4 (3)
N1—CP2—CP1	117·9 (4)	C52—C53—C54	102·9 (3)
N1—CP2—CP3	123·3 (4)	N2—C54—C53	103·1 (3)
Compound (2)			
O54—C53	1·442 (4)	N1—C1	1·343 (5)
O54—C57	1·347 (5)	CP6—CP5	1·413 (5)
O8—C7	1·189 (6)	CP6—CP1	1·351 (6)
O7—CP6	1·389 (5)	CP5—CP4	1·366 (6)
O7—C7	1·353 (5)	CP4—CP3	1·397 (5)
O1—C1	1·224 (5)	CP3—CP2	1·413 (5)
O56—C57	1·181 (6)	CP3—C6	1·477 (5)
O2—C2	1·252 (4)	CP2—CP1	1·399 (5)
O5—CP5	1·372 (5)	C1—C51	1·519 (5)
O5—C5	1·427 (5)	C51—C52	1·525 (5)
N2—C2	1·340 (4)	C52—C53	1·514 (6)
N2—C51	1·478 (4)	C53—C54	1·516 (5)
N2—C54	1·467 (5)	C8—C7	1·472 (7)
N1—CP2	1·404 (5)	C54—C55	1·490 (6)
C53—C54—C57	117·0 (3)	O2—C2—C4	120·8 (3)
CP6—O7—C7	118·0 (3)	N2—C2—C4	118·6 (3)
CP5—O5—C5	116·8 (3)	O1—C1—N1	122·8 (3)
C2—N2—C51	123·9 (3)	O1—C1—C51	123·1 (3)
C2—N2—C54	122·8 (3)	N1—C1—C51	114·2 (3)
C51—N2—C54	112·5 (3)	N2—C51—C1	107·8 (3)
CP2—N1—C1	128·4 (3)	N2—C51—C12	102·6 (3)
O7—CP6—CP5	119·4 (3)	C1—C51—C52	114·5 (3)
O7—CP6—CP5	119·8 (3)	C51—C52—C53	103·7 (3)
CP5—CP6—CP1	120·6 (4)	O54—C53—C52	108·8 (3)
O32—CP5—CP6	116·2 (3)	O54—C53—C54	110·0 (3)
O32—CP5—CP4	125·7 (4)	C52—C53—C54	104·1 (3)
CP6—CP5—CP4	118·1 (4)	N2—C54—C53	102·5 (3)
CP5—CP4—CP3	124·4 (3)	O8—C7—O7	121·5 (4)
CP4—CP3—CP2	118·9 (3)	O8—C7—C8	126·9 (4)
CP4—CP3—C2	116·8 (3)	O24—C7—C8	111·6 (4)
CP2—CP3—C2	124·3 (3)	CP6—CP1—CP2	122·1 (3)
N1—CP2—CP3	124·6 (3)	O54—C54—C56	123·0 (4)
N1—CP2—CP3	117·4 (3)	O54—C47—C55	111·3 (4)
CP3—CP2—CP1	117·9 (3)	O56—C57—C55	125·7 (4)
O2—C2—N2	120·5 (3)		

Table 3. *Selected torsion angles* (°)

	(1)	(2)
CP2—N1—C1—O1	−175·9 (4)	−177·1 (5)
CP2—N1—C1—C51	4·7 (5)	3·6 (5)
C1—C51—N2—C2	−69·9 (4)	−77·9 (5)
C51—C52—C53—C54	−39·6 (4)	−38·8 (6)
C51—N2—C2—CP3	0·6 (5)	11·8 (6)
N1—CP2—CP3—C2	0·7 (5)	−0·7 (5)
NH1—N1—C1—O1	−11·2 (29)	0·3 (50)

were defined by reference to known chemical precedent.

Atomic coordinates are listed in Table 1, bond lengths and valence angles in Table 2 and selected torsion angles in Table 3. The molecular structures are shown in Figs. 1 and 2.*

Related literature. Compounds (1) and (2) with amide groups in the seven-membered ring are related to the naturally occurring pyrrolo[2,1-*c*]-[1,4]benzodiazepine (PBD) family of antitumour antibiotics. However, they have a carbonyl at C11 rather than a hydroxyl or methoxyl group (as found in PBD's such as anthramycin or tomaymycin) or an N1–C1 imine (as found in neothramycin). The crystal structure of anthramycin has been reported (Mostad, Rømming & Storm, 1978; Arora, 1979). The interactions of anthramycin and tomaymycin with DNA involve covalent attachment at C1 and non-covalent binding in the minor groove (Boyd,

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* List 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 54271 (31 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

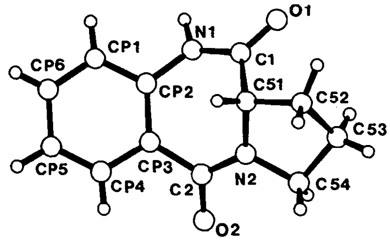

Fig. 1. Structure of (1).

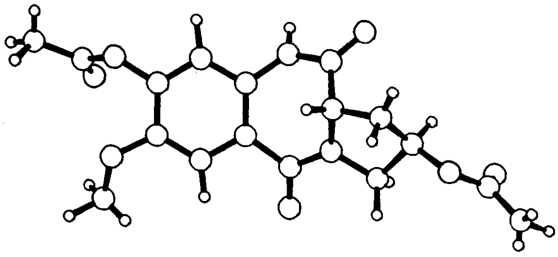

Fig. 2. Structure of (2).

Cheetham, Remers, Hill & Hurley, 1990). The non-covalent binding of (2) to DNA has been studied (Jones *et al.*, 1990).

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Structure of (±)-*exo*-6-Methyl-*endo*-6-nitrobicyclo[2.2.1]heptan-*exo*-2-ol*

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Abstract. $C_8H_{13}NO_3$, $M_r = 171.20$, monoclinic, $C2/c$, $a = 27.89\,(2)$, $b = 6.327\,(2)$, $c = 22.04\,(1)$ Å, $\beta = 114.65\,(4)°$, $V = 3533.53$ Å^3, $Z = 16$, $D_m = 1.29$ (flotation in aqueous CsCl solution), $D_x = 1.29$ Mg m^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, $\mu = 0.106$ mm^{-1}, $F(000) = 1472$, room temperature, final $R = 0.072$ for 2458 unique observed reflections. Two molecules constitute the asymmetric unit, and four molecules are associated as cyclic tetramers by hydrogen bonds involving only the OH groups. The conformations of both nitro groups, given by C(5)—C(6)—N(1)—O(3) and C(5′)—C(6′)—N(1′)—O(3′) torsion angles of −9.5 (6) and −9.2 (6)° respectively, are consistent with orientations in which the C(5)—C(6) bond of the rigid bicyclic skeleton is nearly eclipsed.

Experimental. The title compound and its *exo*-5-methyl-*endo*-5-nitro isomer were obtained by hydroboration and oxidation of *exo*-5-methyl-*endo*-5-nitrobicyclo[2.2.1]hept-2-ene as described previously (Michael, Maqutu & Howard, 1989). Products were separated by chromatography on silica gel. Single crystals of the appropriate isomer were grown by diffusion of hexane vapour into a solution of the compound in benzene. The analysis was performed on a colourless cube of approximate dimensions 0.5 × 0.5 × 0.5 mm. The space group $C2/c$ (No. 15) and preliminary lattice constants were determined from oscillation and Weissenberg photographs. Diffraction data were collected on an Enraf–Nonius CAD-4 automatic diffractometer with graphite-monochromated Mo $K\alpha$ radiation [$\omega/2\theta$ scan technique, $\Delta\omega = (0.6 + 0.35\tan\theta)°$, variable scan speed 1.0–5.5° min^{-1}, $3 < \theta < 30°$, $-39 < h < 39$, $0 < k < 8$, $0 < l < 30$]. Cell dimensions were obtained by least-squares refinement of 25 accurately measured

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* Nitrobicyclo[2.2.1]heptanes. 9. Part 8: Michael, Blom & Glintenkamp (1991).

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