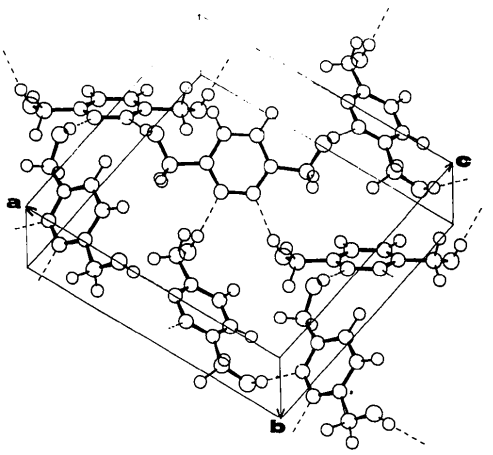

Fig. 2. L'empilement cristallin et les liaisons H.

puis par le groupement ($-CH_2-OH$) se traduit par un renforcement des liaisons C—N [1,341 (2), 1,334 (9) et 1,328 (7) Å respectivement] au détriment de la liaison N—N [1,330 (1), 1,339 (8) et 1,343 (4) Å respectivement].

La dissymétrie observée au niveau des groupements méthoxyles entraîne une dissymétrie des interactions stériques de ces groupements avec le cycle: l'ouverture de l'angle C(5)—C(6)—C(7) [124,1 (9)°] au détriment de l'angle N(1)—C(6)—C(7) [113,9 (6)°] est plus importante que celle de l'angle C(4)—C(3)—C(8) [122,9 (7)°] au détriment de l'angle N(2)—C(3)—C(8) [115,3 (6)°]. Un tel effet stérique entre atome d'hydrogène du substituant du cycle pyridazine et atome d'hydrogène du cycle avait été relevé dans le cas du dérivé diacide, la dicarbohydroxy-3,6 pyridazine (Sueur, Lagrenee, Abraham & Brémard, 1987).

La cohésion cristalline est assurée par un schéma tridimensionnel de liaisons hydrogène. Chaque molécule est reliée à quatre autres molécules par quatre liaisons N···H—O (Fig. 2): (*a*) O(9)—HO(9)···$N(2^{iii})_{\bar{1}10}$ [et $N(2)\cdots HO(9^{iii})_{010}-O(9^{iii})_{010}$] dont les caractéristiques sont: O—H = 0,76 (5), O···N = 2,851 (4), H···N = 2,09 (5) Å; et (*b*) O(10)—HO(10)···$N(1^{ii})_{11\bar{1}}$ [et $N(1)\cdots HO(10^{ii})_{110}-O(10^{ii})_{110}$] dont les caractéristiques sont: O—H = 0,76 (6), O···N = 2,793 (5), N···H = 2,04 (6) Å [code de symétrie: (ii) = $\bar{x}$, $\bar{y}$, $\frac{1}{2}+z$; (iii) = $\frac{1}{2}+x$, $\bar{y}$, z].

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Structure of a Modified Cytosine: an Antiviral Nucleoside Analog, Homo-Ara-C

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Abstract. Homo-Ara-C [5′-(hydroxymethyl)-5′-deoxy-1-β-D-arabinofuranosyl-3*H*-cytosine], $C_{10}H_{16}N_3O_5$, M_r = 258·25, $P2_12_12$, a = 8·261 (2), b = 19·644 (4), c = 6·993 (6) Å, V = 1134·8 Å^3, Z = 4, D_x = 1·511 g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ = 10·5 cm^{-1}, $F(000)$ = 548, T = 288 K, final R = 0·053 for 1189 observed reflections. Conformational features of the nucleoside include a glycosidic bond conformation in the *anti* range, a ribose moiety in the ^2E [C(2′)-*endo*] form like 5′-N3-Ara-C, 5-NO_2-Ara-U and Ara-C and a C(5′)—C(6′) bond that is *gauche* to C(4′)—O(4′) but *trans* to C(4′)—C(3′).

Introduction. The crystal and molecular structure of the title compound was undertaken as part of a series of structure determinations of nucleic acid components and their analogs of antiviral, antitumour or anticancer activities. We report here the molecular conformation of homo-Ara-C which is available only as a synthetic nucleoside. The mechanism of the inhibition of DNA

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synthesis involves inhibition of DNA polymerase by the triphosphorylated derivative of these analogs. Pharmacological and enzymatic studies have indicated that Ara-C is deaminated to Ara-U, an inactive metabolite, reducing its chemotherapeutic value. The recognition of the importance of this system in biochemical studies has made it necessary to make similar analogs for effective drugs with less-toxic effects.

It is interesting that a minor modification changes the activity of these analogs; homo-Ara-C is inactive against *Herpes simplex* virus, and did not inhibit the growth of several cell lines, including human lymphocytes in concentrations up to 500 μg ml^{-1}, while Ara-C inhibits the growth of tumour cells and multiplication of DNA viruses in cell culture.

Our objective is to determine the crystal structures of these analogs to obtain details of the molecular conformation and hydrogen bonding for comparison with the naturally occurring substrate 2′-deoxycytidine.

Experimental. Crystals of the title compound (received through the courtesy of T. Kulikowski of Warszawa, Poland) were obtained by slow evaporation from EtOH/water (less than 10% water) in the form of transparent needles at room temperature, dimensions 0·31 × 0·24 × 0·14 mm. Lattice parameters from 15 intermediate $\sin\theta$ axial reflections in the range $17 < 2\theta < 38°$. 3 standard reflections, no significant intensity variation. 1245 [1189 with $I \geq 3\sigma(I)$] unique reflections collected on a CAD-4 diffractometer. Ni-filtered Cu $K\alpha$ radiation, θ–ω step-scan mode, $2\theta \leq 110°$. Range of h, k and l 0 to 10, 0 to 24 and 0 to 8. Data corrected for Lorentz–polarization factors but not for absorption. Structure solved by *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) and refined by full-matrix least squares on F. All the H atoms were located from ΔF syntheses and refined isotropically. Final $R = 0.05$ and $wR = 0.07$; $w = 1/\sigma^2(F_o)$; $\Delta\rho$ peaks are 0·3 to −0·2 e $Å^{-3}$, $(\Delta/\sigma)_{max} = 0.65$. Atomic scattering factors were from *International Tables for X-ray Crystallography* (1974). Programs used from *XRAY ARC* (*World List of Crystallographic Computer Programs,* 1973), modified for the B6700 Computer.

Discussion. Final atomic parameters are given in Table 1.* The bond lengths, bond angles and some dihedral angles of the molecule are in Table 2. Fig. 1 shows a view of the molecular configuration with minimum overlap and Fig. 2 is a stereo packing diagram of the molecule. The correct enantiomorph was selected in conformity with known analogs.

The bond distances and angles (Table 2) of homo-Ara-C are similar to those of other arabinoside nucleosides. The pyrimidine base is almost planar, with maximum deviation of the ring from the mean plane of −0·022 (4) Å. The attached atoms N(4) and O(2) deviate −0·011 (4) and −0·075 (3) Å from the mean plane.

Table 1. *Final atomic coordinates with e.s.d.'s in parentheses and equivalent isotropic values of the anisotropic thermal parameters for non-*H *atoms*

$B_{eq} = \frac{4}{3}\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}(Å²)
C(2)	−0·3127 (5)	−0·4656 (2)	−0·2056 (6)	2·283
C(4)	−0·3504 (5)	−0·4364 (2)	−0·5261 (6)	2·276
O(2)	−0·3304 (4)	−0·4555 (1)	−0·0327 (4)	3·088
C(1′)	−0·1525 (5)	−0·5665 (2)	−0·1191 (6)	2·246
C(6)	−0·1901 (5)	−0·5326 (2)	−0·4553 (6)	2·480
O(2′)	−0·3609 (4)	−0·6517 (1)	−0·1857 (4)	2·589
O(6′)	0·1604 (5)	−0·7888 (2)	−0·4544 (5)	3·519
O(4′)	−0·0251 (4)	−0·6039 (1)	−0·2039 (4)	2·853
N(3)	−0·3801 (4)	−0·4250 (2)	−0·3419 (5)	2·245
C(3′)	−0·1470 (5)	−0·6709 (2)	0·0425 (6)	2·435
C(5)	−0·2513 (6)	−0·4914 (2)	−0·5872 (5)	2·789
C(4′)	−0·0016 (5)	−0·6657 (2)	−0·0957 (6)	2·272
O(3′)	−0·0964 (5)	−0·6528 (2)	0·2308 (4)	3·490
C(2′)	−0·2689 (5)	−0·6194 (2)	−0·0391 (5)	1·986
N(4)	−0·4130 (5)	−0·3945 (2)	−0·6563 (5)	3·097
N(1)	−0·2201 (4)	−0·5214 (1)	−0·2663 (4)	2·073
C(5′)	0·0096 (5)	−0·7265 (2)	−0·2279 (6)	2·639
C(6′)	0·1385 (6)	−0·7217 (2)	−0·3831 (6)	2·924

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

C(2)–O(2)	1·234 (5)	C(2)–N(3)	1·362 (5)
C(2)–N(1)	1·403 (5)	C(4)–N(3)	1·330 (5)
C(4)–C(5)	1·422 (6)	C(4)–N(4)	1·331 (5)
C(1′)–O(4′)	1·414 (5)	C(1′)–C(2′)	1·523 (5)
C(1′)–N(1)	1·467 (5)	C(6)–C(5)	1·326 (6)
C(6)–N(1)	1·362 (5)	O(2′)–C(2′)	1·426 (5)
O(6′)–C(6′)	1·420 (5)	O(4′)–C(4′)	1·443 (5)
C(3′)–C(4′)	1·544 (6)	C(3′)–O(3′)	1·427 (5)
C(3′)–C(2′)	1·537 (5)	C(4′)–C(5′)	1·514 (5)
C(5′)–C(6′)	1·523 (6)		

O(2)–C(2)–N(3)	122·9 (4)	O(2)–C(2)–N(1)	119·1 (4)
N(3)–C(2)–N(1)	117·9 (3)	N(3)–C(4)–C(5)	121·7 (4)
N(3)–C(4)–N(4)	119·1 (4)	C(5)–C(4)–N(4)	119·2 (4)
O(4′)–C(1′)–C(2′)	105·6 (3)	O(4′)–C(1′)–N(1)	107·6 (3)
C(2′)–C(1′)–N(1)	115·4 (3)	C(5)–C(6)–N(1)	120·5 (4)
C(1′)–O(4′)–C(4′)	108·5 (3)	C(2)–N(3)–C(4)	120·2 (3)
C(4′)–C(3′)–O(3′)	109·4 (3)	C(4′)–C(3′)–C(2′)	103·4 (3)
O(3′)–C(3′)–C(2′)	111·6 (3)	C(4)–C(5)–C(6)	118·3 (4)
O(4′)–C(4′)–C(3′)	106·2 (3)	O(4′)–C(4′)–C(5′)	110·6 (3)
C(3′)–C(4′)–C(5′)	112·1 (3)	C(1′)–C(2′)–O(2′)	112·1 (3)
C(1′)–C(2′)–C(3′)	99·9 (3)	O(2′)–C(2′)–C(3′)	108·8 (3)
C(2)–N(1)–C(1′)	117·8 (3)	C(2)–N(1)–C(6)	121·2 (3)
C(1′)–N(1)–C(6)	120·9 (3)	C(4′)–C(5′)–C(6′)	115·4 (3)
O(6′)–C(6′)–C(5′)	106·4 (3)		

C(2′)–C(3′)–C(4′)–O(4′)	15·09 (4)	N(1)–C(1′)–C(2′)–O(2′)	44·18 (4)
C(1′)–C(2′)–C(3′)–C(4′)	−32·63 (4)	O(2′)–C(2′)–C(3′)–O(3′)	−157·40 (3)
O(4′)–C(1′)–C(2′)–C(3′)	40·58 (4)	O(3′)–C(3′)–C(4′)–C(5′)	135·02 (4)
C(6′)–C(5′)–C(4′)–C(3′)	173·60 (4)	C(6′)–C(5′)–C(4′)–O(4′)	55·20 (5)
C(1′)–O(4′)–C(4′)–C(5′)	132·60 (3)	C(4′)–C(5′)–C(6′)–O(6′)	164·15 (3)
C(1′)–O(4′)–C(4′)–C(3′)	10·68 (4)	N(4)–C(4)–C(5)–C(6)	−179·99 (4)
N(4)–C(4)–N(3)–C(2)	−177·55 (4)	O(4′)–C(4′)–C(3′)–O(3′)	−104·05 (4)
C(4)–N(3)–C(2)–O(2)	176·74 (4)	O(4′)–C(1′)–C(2′)–O(2′)	−74·54 (4)
O(2)–C(2)–N(1)–C(1′)	1·75 (5)	C(6)–N(1)–C(1′)–C(2′)	−100·46 (4)
O(4′)–C(1′)–N(1)–C(6)	17·12 (5)		

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, least-squares planes and intermolecular short contacts have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44863 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The most common conformation around the C(4′)–C(5′) bond in nucleosides is *gauche–gauche* (Sundaralingam, 1965). However, in homo-Ara-C the C(5′)–C(6′) bond is *gauche* to C(4′)–O(4′) and *trans* to C(4′)–C(3′) [corresponding torsion angles C(6′)–C(5′)–C(4′)–O(4′) 55·2° and C(6′)–C(5′)–C(4′)–C(3′) 173·6°]; this is reversed in the case of 5′-N3-Ara-C (Biswas, Banerjee & Saenger, 1987) where the conformation is *trans–gauche* even though the sugar ring is in the same ^2E conformation.

The furanose ring has C(2′) and C(3′) deviating from the plane of the other three atoms in the sugar moiety by 0·79 (4) and 0·27 (4) Å, respectively. The O(2′) atom is displaced 1·65 (3) Å from the mean plane of the furanose ring but O(3′) is displaced by −1·52 (3) Å on the opposite side of C(5′). The sugar pucker is C(2′)-*endo* (^2E), similar to those in the related 5-NO_2-Ara-U (Biswas, Banerjee, Shugar & Duax, 1988), 5′-N3-Ara-C (Biswas, Banerjee & Saenger, 1987), Ara-U (Tollin, Wilson & Young, 1973), Ara-C (Tougard & Soubeyran, 1974), Ara-C–HCl (Sherfinski & Marsh, 1973), 3′-*O*-MeAra-C (Birnbaum, Darżynkiewicz & Shugar, 1975), 5-fluoro-Ara-C (Ferguson, Scrimgeour, Low & Tollin, 1986) but differs from those observed in Ara-CMP trihydrate (Sherfinski, Marsh, Chwang & Sundaralingam, 1979), 2′-fluoro-5-iodoarabinosylcytosine (Birnbaum, Cygler, Watanabe & Fox, 1982) and 1-β-D-arabinofuranosyl-4-thiouracil (Saenger, 1972) where the sugar puckerings are C(3′)-*endo* (^3E) or C(3′)-*endo*, C(2′)-*exo* ($^3T_2$).

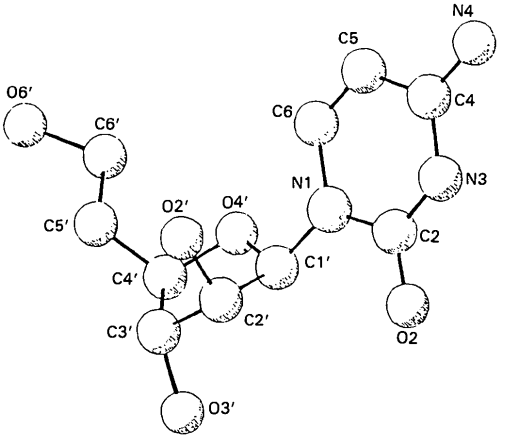

Fig. 1. A *PLUTO* drawing of the molecule, showing the atomic numbering with minimum overlap.

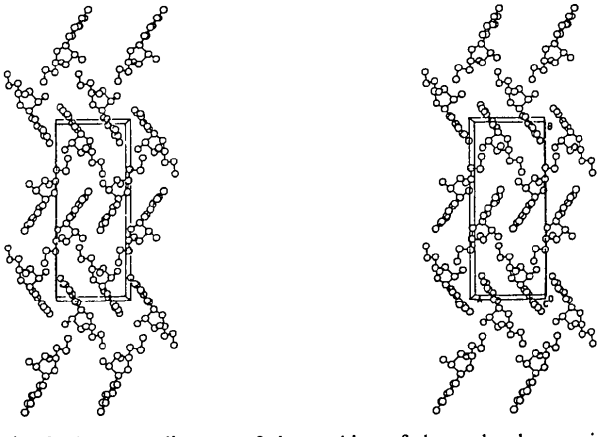

Fig. 2. A stereo diagram of the packing of the molecule. *a* axis horizontal, *b* axis vertical.

The molecular conformation of the base moiety is in the *anti* range with torsion angle O(4′)–C(1′)–N(1)–C(6) 17·12° which is characteristic of β-arabinonucleosides. But in arabinosyladenine (Bunick & Voet, 1974), the glycosyl torsion angle of 57·8° is substantially different from those in other compounds. It has also been pointed out that in β-arabinosides the distance between O(2′) and N(1) is shorter than the van der Waals contact of 2·9 Å; in the case of homo-Ara-C this distance is 2·86 Å. An intramolecular hydrogen bond exists in homo-Ara-C, O(2′)–H···O(6′) = 2·78 Å, and O(2′)–H···O(5′) = 2·64 Å in Ara-C (Chwang & Sundaralingam, 1973). This type of hydrogen bonding is stereochemically not feasible in ribonucleosides. Probably this hydrogen bond constrains the arabinose to the ^2E conformation, though Ara-C hydrochloride shows no intramolecular hydrogen bond even with the sugar ring in the ^2E conformation.

The major stereochemical difference between Ara-C and the ribonucleosides is the inversion of the asymmetric centre at C(2′). This brings about large changes in the torsion angles involving O(2′). The torsion angles O(2′)–C(2′)–C(3′)–O(3′) and N(1)–C(1′)–C(2′)–O(2′) are −156, 35° in Ara-C, −157·4, 44·2° in homo-Ara-C, −155, 35° in 5-NO_2-Ara-U and −164, 38° in 5′-N_3-Ara-C, *i.e.* in the ranges 155–165° and 35–45° compared with the values of 35–50° and 75–85° respectively in ribonucleosides with ^3E or $^3T_2$ puckering.

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A Novel Bridged-*A*-Ring Steroid

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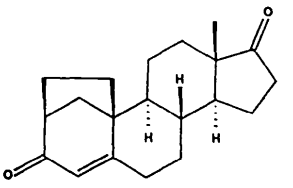
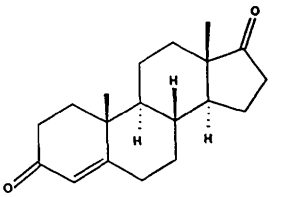
Abstract. 2,10-Ethano-10-norandrost-4-ene-3,17-dione, $C_{20}H_{26}O_2$, $M_r = 298{\cdot}43$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}566$ (3), $b = 11{\cdot}478$ (7), $c = 18{\cdot}681$ (7) Å, $V = 1622{\cdot}5$ (13) Å^3, $Z = 4$, D_m (flotation in aqueous $ZnCl_2$) $= 1{\cdot}21$ (2), $D_x = 1{\cdot}222$ Mg m^{-3}, λ(Mo $K\bar{\alpha}$) $= 0{\cdot}71073$ Å, $\mu = 0{\cdot}0716$ mm^{-1}, $F(000) = 648$, $T = 293$ K, $R = 0{\cdot}038$, $wR = 0{\cdot}052$ for 1629 observations. The title molecule was prepared as part of synthetic efforts in the design of inhibitors for steroid 5α-reductase. Based upon a desire to lift the *A* ring in the β direction, relative to the parent androst-4-ene-3,17-dione, this novel steroid contains an ethano bridge between atoms C(2) and C(10). The *A* ring displays a highly distorted 1α-sofa conformation with C(1) disposed 0·844 (2) Å below the plane defined by atoms C(2), C(3), C(4), C(5) and C(10). Mirror symmetry is dominant in the *A* ring with $\Delta C_s^1 = 9{\cdot}0$. The remainder of the steroid nucleus displays a normal conformation including a flattened 14α-envelope for the *D* ring. Relative to androst-4-ene-3,17-dione the position of atom O(3) is lifted 0·151 Å toward the β face. The observed structure is consistent with molecular modeling predictions.

Introduction. The enzyme steroid 5α-reductase converts the substrate testosterone into dihydrotestosterone (Brooks, Berman, Hichens, Primka, Reynolds & Rasmussen, 1982). Inhibition of this enzyme is of considerable interest (Rasmussen, Reynolds, Utne, Jobson, Primka, Berman & Brooks, 1984) since elevated levels of dihydrotestosterone have been linked to such undesirable androgenic activities in man as acne, male-pattern baldness and benign prostatic hypertrophy (Peterson, Imperato-McGinley, Gautier & Sturla, 1977; Price, 1975). In connection with an interest in inhibition of steroid 5α-reductase, the report of Rasmussen *et al.* (1984) regarding the inhibitory activity of a 19-nor analog in a series of 4-aza steroids was intriguing. In the testosterone series, the solid-state structure of the 19-nor analog shows the steroidal *A* ring arched towards the β face relative to the parent testosterone molecule (Duax & Norton, 1975). Our *MM*2 (Burkert & Allinger, 1982) calculations supported the anticipation that incorporation of a bridge between atoms C(2) and C(10) also would promote β arching of the *A* ring, relative to the parent, while simultaneously reducing the known flexibility of 19-nor steroids (Duax, Weeks & Rohrer, 1976). Since androst-4-ene-3,17-dione also is a substrate for steroid 5α-reductase, compound (1) was prepared to test these structural hypotheses and their biological effects. We report here the solid-state structure of (1), as determined by X-ray diffraction, and compare this structure to relevant analogs, such as (2) (Bussetta, Comberton, Courseille & Hospital, 1972).



(1)



(2)

Experimental. The synthetic pathway leading to (1) has been reported previously (Lan-Hargest, Elliott, Eggleston, Holt, Levy & Metcalf, 1987). Colorless prism, approximately 0·30 × 0·30 × 0·35 mm on edge,

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