Table 3. *Hydrogen-bond distances* (Å) *with their standard deviations in parentheses*

Donor	Acceptor		Donor	Acceptor	
N(1) (I)	O(*W*3)^{i}	2·857 (12)	O(*W*2)	O(*L*)^{i}	2·898 (13)
O(5′) (I)	N(3) (I)^{ii}	2·805 (11)	O(*W*2)*	O(*W*5)^{i}	2·843 (23)
N(1) (A)	O(*W*6)^{i}	2·757 (28)	O(*W*3)	O(6) (I)^{iv}	2·934 (12)
N(6) (A)	N(7) (I)^{iii}	3·017 (10)	O(*W*3)	O(*R*)^{v}	2·737 (13)
N(6) (A)	O(*W*6)^{i}	2·995 (28)	O(*W*4)	O(5′) (I)^{vi}	2·802 (23)
O(3′) (A)	O(*W*5)^{iii}	2·937 (25)	O(*W*5)	O(*W*3)^{vii}	3·039 (23)
O(*W*1)	O(*L*)^{i}	2·794 (15)	O(*W*6)	O(*R*)^{viii}	2·680 (28)
O(*W*1)*	O(*W*2)^{ii}	2·791 (17)	O(*W*6)	O(*W*4)^{viii}	2·849 (34)

Symmetry code: (i) x,y,z; (ii) $x,y,1+z$; (iii) $x,\ 1+y,z$; (iv) $x,y,-1+z$; (v) $1+x,y,-1+z$; (vi) $-1+x,-1+y,z$; (vii) $-1+x,-1+y,\ 1+z$; (viii) $1+x,\ 1-y,z$.

* H atoms were not located; the assignment as donor or acceptor could be reversed.

rings involving the S atom. This stacking is very similar to that of A^spA^s and therefore it may be a common feature in molecular packing of *S*-cyclonucleosides or cyclonucleotides.

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Non-ionized 5a-Epi-6-oxatetracycline* Free Base

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Abstract. $C_{20}H_{20}N_2O_8.C_4H_{10}O$, triclinic, $P\bar{1}$, $a=9{\cdot}864\ (1)$, $b=11{\cdot}129\ (1)$, $c=11{\cdot}713\ (1)$ Å, $\alpha=80{\cdot}967\ (8)$, $\beta=85{\cdot}335\ (9)$, $\gamma=70{\cdot}310\ (7)°$ at 297 (1) K; $Z=2$, $\rho_{calc}=1{\cdot}36$ g cm^{-3}. Racemic 5a-epi-6-oxatetracycline free base cocrystallizes with one molecule of diethyl ether. A total of 3498 reflections ($\sin\theta/\lambda_{max}=0{\cdot}590$ Å^{-1}) contributed to refinement of 436 variables to give standard residues: $R=0{\cdot}040$, $R_w=0{\cdot}053$, $\sigma=1{\cdot}30$ with $w=(\sigma^2|F|+0{\cdot}0125|F_o|+0{\cdot}0001|F_o|^2+0{\cdot}000005|F|^3)^{-1}$. The title compound is a totally synthetic tetracycline analog. The molecular structure in the crystal is that of a non-ionized free base displaying a short intramolecular hydrogen bond, $d(O\cdots H)=1{\cdot}23\ (3)$ Å and $\angle(O\text{–}H\cdots O)=165\ (3)°$, in the *A*-ring chromophore. The conformation is very similar to that of other 5a-epitetracycline derivatives.

Introduction. Numerous tetracycline derivatives are broad spectrum antibiotics that have found extensive application in human and veterinary medicine. The crystal structure of the title compound (I) was undertaken to identify unequivocally the relative configuration of atom C(5a) and to examine further the effects of the introduction of a heteroatom into the ring

* (5a*β*,6a*α*,7*α*,10a*α*)-(±)-7-(Dimethylamino)-5a,6,6a,7,10a-pentahydro-1,8,10a,11-tetrahydroxy-10,12-dioxo-10*H*-benzo[*b*]xanthene-9-carboxamide.

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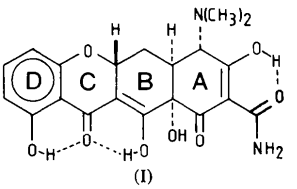
system of the tetracyclines on bonding geometry (Prewo, Stezowski & Kirchlechner, 1980).



(I)

Lattice parameters were refined (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) with 34 automatically centered 2θ values in the angular range: $61{\cdot}3 \le 2\theta \le 96{\cdot}5°$ (monochromatized Cu $K\alpha$ radiation, $\lambda = 1{\cdot}5418$ Å). Intensities were measured to a resolution of $2\theta_{max} = 50°$ (monochromatized Mo $K\alpha$ radiation, $\lambda = 0{\cdot}7107$ Å) with a Syntex $P\bar{1}$ autodiffractometer operating in an ω-scan mode. The scan range was 0·75° and the scan rate varied from 2·0 to 24·0° min^{-1} as a function of maximum peak intensity. Three reference reflections (measured periodically) showed no significant variation in their intensities. Of the 4130 unique reflections measured, 2772 were classified as observed under the criterion $I \ge 3\sigma(I)$. Data were corrected for Lorentz and polarization effects, but not for absorption.

The initial structural model was determined with *MULTAN* (Main, Lessinger, Woolfson, Germain & Declercq, 1977) which provided a correctly oriented, but incorrectly placed fragment. The model was developed in space group $P1$ until the coordinates of the inversion center could be determined. After the appropriate translation was applied, the model was completed by difference Fourier methods and refined in $P\bar{1}$. Refinement was carried out by variable-block–block-diagonal techniques in which blocks consisted of the parameter for one oxatetracycline C, N, or O atom and any H atoms bound to it. Because of obviously high thermal motion, all parameters associated with the ether of crystallization molecules were refined in one block. Anisotropic temperature factors were refined for C, N, and O atoms, isotropic temperature factors for H atoms.*

Fractional atomic coordinates are presented in Table 1. A stereoscopic projection of 5a-epi-6-oxatetracycline free base is presented in Fig. 1. Bond distances for the tetracycline molecule are presented in Fig. 2; bond and dihedral angles have been deposited. Characterization of the bonding geometry of the ether molecule has also been deposited.

* Lists of structure factors, anisotropic temperature factors, additional bond distances, bond angles and dihedral angles have been deposited with the Biritish Library Lending Division as Supplementary Publication No. SUP 36849 (35 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional atomic coordinates and isotropic temperature factors*

The temperature factor has the form of exp(−T) where $T = 8\pi^2 U(\sin\theta/\lambda)^2$ for isotropic atoms. The e.s.d. of the last significant digit is given in parentheses.

	x	y	z	U_{eq}/U(Å^2)
C(1)	0·5352 (2)	−0·2068 (2)	−0·1400 (2)	0·0340
O(1)	0·5531 (2)	−0·1074 (1)	−0·1228 (1)	0·0493
C(2)	0·4324 (2)	−0·2607 (2)	−0·0775 (2)	0·0340
C(2*am*)	0·3555 (2)	−0·2126 (2)	0·0268 (2)	0·0410
N(2*am*)	0·3709 (3)	−0·1132 (2)	0·0640 (2)	0·0615
O(2*am*)	0·2723 (2)	−0·2685 (2)	0·0834 (1)	0·0589
C(3)	0·4046 (2)	−0·3628 (2)	−0·1149 (2)	0·0372
O(3)	0·3171 (2)	−0·4157 (2)	−0·0574 (1)	0·0594
C(4)	0·4727 (2)	−0·4200 (2)	−0·2234 (2)	0·0363
C(4a)	0·5487 (2)	−0·3368 (2)	−0·3028 (2)	0·0342
N(4)	0·3766 (2)	−0·4541 (2)	−0·2907 (2)	0·0567
C(41*M*)	0·3586 (4)	−0·5790 (3)	−0·2487 (4)	0·0936
C(42*M*)	0·2392 (3)	−0·3551 (4)	−0·3145 (4)	0·0838
C(5)	0·6503 (2)	−0·4129 (2)	−0·3921 (2)	0·0392
C(5a)	0·7677 (2)	−0·5260 (2)	−0·3321 (2)	0·0386
O(6)	0·8819 (1)	−0·5710 (1)	−0·4171 (1)	0·0438
C(6a)	1·0005 (2)	−0·6693 (2)	−0·3744 (2)	0·0401
C(7)	1·0857 (2)	−0·7476 (2)	−0·4514 (2)	0·0511
C(8)	1·2070 (3)	−0·8464 (2)	−0·4110 (2)	0·0558
C(9)	1·2450 (3)	−0·8693 (2)	−0·2977 (2)	0·0523
C(10)	1·1635 (2)	−0·7885 (2)	−0·2208 (2)	0·0439
O(10)	1·2089 (2)	−0·8094 (2)	−0·1117 (1)	0·0550
C(10a)	1·0375 (2)	−0·6865 (2)	−0·2581 (2)	0·0367
C(11)	0·9575 (2)	−0·5910 (2)	−0·1846 (2)	0·0372
O(11)	1·0024 (2)	−0·5882 (1)	−0·0883 (1)	0·0496
C(11a)	0·8270 (2)	−0·4948 (2)	−0·2305 (2)	0·0333
C(12)	0·7601 (2)	−0·3873 (2)	−0·1809 (2)	0·0335
O(12)	0·8053 (2)	−0·3619 (2)	−0·0864 (1)	0·0458
C(12a)	0·6316 (2)	−0·2800 (2)	−0·2342 (2)	0·0345
O(12a)	0·6840 (2)	−0·1927 (1)	−0·3113 (1)	0·0473
O(8)	0·1995 (2)	0·9870 (2)	0·2714 (1)	0·0580
C(1*B*)	0·2306 (5)	0·8961 (4)	0·3754 (4)	0·098
C(2*B*)	0·3863 (6)	0·8571 (5)	0·3958 (4)	0·109
C(3*B*)	0·0494 (4)	1·0283 (6)	0·2512 (4)	0·117
C(4*B*)	0·0144 (6)	1·0937 (7)	0·1395 (5)	0·128
H(21)	0·431 (3)	−0·076 (3)	0·025 (2)	0·09 (1)
H(22)	0·315 (3)	−0·083 (2)	0·133 (2)	0·079 (8)
H(3)	0·280 (3)	−0·346 (3)	0·017 (3)	0·10 (1)
H(4)	0·545 (2)	−0·496 (2)	−0·195 (2)	0·035 (5)
H(4a)	0·474 (2)	−0·264 (2)	−0·342 (2)	0·038 (5)
H(41*M*)	0·316 (4)	−0·602 (3)	−0·309 (3)	0·11 (1)
H(42*M*)	0·295 (4)	−0·573 (3)	−0·174 (3)	0·11 (1)
H(43*M*)	0·461 (4)	−0·647 (3)	−0·236 (3)	0·13 (1)
H(44*M*)	0·169 (4)	−0·339 (3)	−0·247 (3)	0·10 (1)
H(45*M*)	0·248 (3)	−0·266 (3)	−0·332 (3)	0·09 (1)
H(46*M*)	0·198 (4)	−0·377 (3)	−0·379 (3)	0·12 (1)
H(51)	0·596 (2)	−0·448 (2)	−0·437 (2)	0·041 (6)
H(52)	0·693 (2)	−0·354 (2)	−0·443 (2)	0·047 (6)
H(5a)	0·733 (2)	−0·601 (2)	−0·307 (2)	0·034 (5)
H(7)	1·053 (2)	−0·730 (2)	−0·532 (2)	0·062 (7)
H(8)	1·263 (2)	−0·901 (2)	−0·467 (2)	0·059 (7)
H(9)	1·329 (3)	−0·935 (2)	−0·269 (2)	0·074 (8)
H(10)	1·152 (3)	−0·743 (3)	−0·073 (2)	0·09 (1)
H(12)	0·880 (3)	−0·438 (3)	−0·061 (2)	0·082 (9)
H(12a)	0·694 (3)	−0·137 (3)	−0·269 (2)	0·081 (9)
H(1*B*1)	0·165 (5)	0·935 (5)	0·436 (4)	0·19 (2)
H(1*B*2)	0·198 (5)	0·836 (4)	0·349 (4)	0·16 (2)
H(2*B*1)	0·441 (6)	0·829 (5)	0·324 (5)	0·23 (3)
H(2*B*2)	0·388 (6)	0·781 (6)	0·458 (5)	0·23 (3)
H(2*B*3)	0·43 (1)	0·910 (8)	0·463 (9)	0·43 (5)
H(3*B*1)	−0·01 (1)	0·96 (1)	0·23 (1)	0·54 (8)
H(3*B*2)	−0·001 (6)	1·095 (5)	0·320 (5)	0·21 (2)
H(4*B*1)	0·055 (5)	1·049 (5)	0·075 (4)	0·16 (2)
H(4*B*2)	−0·079 (5)	1·128 (4)	0·125 (4)	0·15 (2)
H(4*B*3)	0·046 (5)	1·172 (4)	0·131 (4)	0·12 (2)

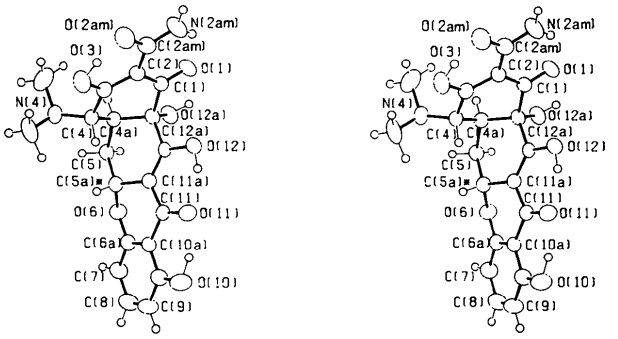


Fig. 1. A stereoscopic projection (Johnson, 1971) for 5a-epi-6-oxatetracycline non-ionized free base. The applicable labeling scheme is depicted.

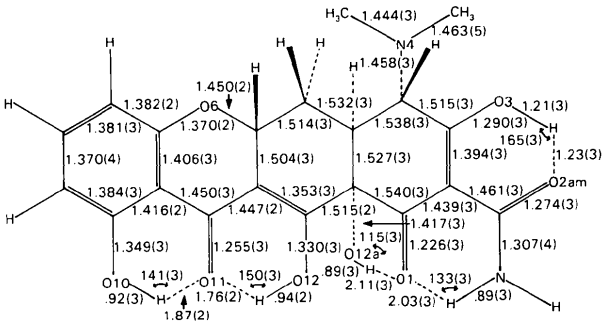


Fig. 2. Selected bond distances (Å) for 5a-epi-6-oxatetracycline non-ionized free base. Bond angles (°) for H atoms involved in intramolecular hydrogen bonds are also indicated.

Discussion. The conformation of 5a-epi-6-oxatetracycline non-ionized free base is very similar to that of the 5a-epi-6-thiatetracycline analog and to that of the cation of 5a-epi-7-chlorotetracycline in the hydrochloride salt (Prewo, Stezowski & Kirchlechner, 1980; Prewo & Stezowski, 1980). For example, the maximum difference in relevant dihedral angles (see Table IV in Prewo & Stezowski, 1980) of the oxa- and thia-derivatives is 12°, the average difference is 4·1°.

The bonding geometry in the *BCD* chromophore, a subunit of the tetracycline structure believed to be necessary for antibacterial activity, remains largely unaffected by the presence of a heteroatom at position 6. The hydrogen bonding between the central carbonyl group of the chromophore and the two β-hydroxyl groups is also typical of that observed earlier. It therefore appears that the introduction of the heteroatom at position C(6) has primarily local effects in the structure of 5a-epitetracyclines. The C(5a)···C(6a) distances in 5a-epi-6-oxatetracycline, 5a-epi-7-chlorotetracycline, and in 5a-epi-6-thiatetracycline are 2·376 (3), 2·524 (4), and 2·681 (4) Å respectively; the bond angles are: C(5a)–O(6)–C(6a) 114·8 (1), C(5a)–C(6)–C(6a) 109·2 (1), and C(5a)–S(6)–C(6a) 99·1 (1)°.

The bonding geometry in the *A*-ring chromophore and the dimethylamino group is generally that observed earlier in non-ionized free bases of tetracyclines. The enolic β-diketone of the chromophore displays a short hydrogen bond: H(3)···O(2*am*) = 1·23 (3), O(3)–H(3) = 1·21 (3) Å, and O(3)–H(3)–O(2*am*) = 165 (3)°. This example presents an apparently more symmetrical hydrogen bond than that found in the 6-thiatetracycline (Prewo, Stezowski & Kirchlechner, 1980) or oxytetracycline (Stezowski, 1976; Prewo & Stezowski, 1977) free bases. The symmetrical appearance is probably an artifact of thermal motion. The other structures, which were determined with data from cooled crystals, can be expected to provide more reliable coordinates for the H atoms.

With the exception of an intermolecular hydrogen bond between an H atom of the amide group and the ether O atom, O(1*B*), N(2*am*)–H(22) = 0·98 (3), H(22)···O(1*B*) = 2·01 (3) Å, N(2*am*)–H(22)–O(1*B*) = 137 (4)°, crystal packing is determined by van der Waals forces. Neither atom N(4) nor O(6), two likely acceptors, is involved in hydrogen bonding.

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