

Table 1. Atomic coordinates ($\times 10^4$) with e.s.d.'s in parentheses

	x	y	z
C(1)	3537 (4)	4045 (4)	4065 (10)
C(2)	2704 (5)	3299 (4)	3019 (10)
C(3)	1539 (5)	3338 (4)	4003 (12)
C(4)	1218 (5)	4049 (4)	5881 (11)
C(5)	2065 (5)	4789 (4)	6939 (9)
C(6)	3226 (5)	4766 (4)	5975 (10)
C(7)	3025 (5)	2556 (4)	962 (11)
C(8)	1703 (5)	5520 (4)	8983 (11)
C(9)	4769 (7)	4308 (9)	3556 (17)
C(10)	5705 (8)	4650 (6)	3515 (18)

angles, with molecular symmetry mmm (D_{2h}) assumed, are shown in Fig. 2.

Discussion. The precision of the present analysis of (III) is limited by disorder. Nevertheless, the following structural features are worthy of note. (1) The molecule is planar within experimental error. (2) As far as molecular packing is concerned, the central ethylenic and acetylenic bridges are equivalent since they have virtually the same span between the benzene rings. Presumably the difference in length of the double and triple bonds is compensated by the different arching of the $-C=C-$ and $-C\equiv C-$ bridges. (3) The central eight-membered ring has an average span of 3.863 (7) Å which is significantly longer than the corresponding distance of 3.834 (3) Å in compound (I) (Destro, Pilati & Simonetta, 1975, 1977), and the difference gives a measure of the greater span of the ethylenic bridge.

We are grateful to Mr Masao Chiku of Jasco/Syntex Co. Ltd, Tokyo, for his intermediation in having the intensity data collected on a Syntex $P2_1$ diffractometer.

Acta Cryst. (1979). B35, 219–222

Structure of β -6-Deoxyoxytetracycline Hydrochloride

BY J. BORDNER

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27650, USA

(Received 8 June 1978; accepted 26 September 1978)

Abstract. $C_{22}H_{24}N_2O_8 \cdot HCl$, orthorhombic, $P2_12_12_1$, $a = 11.638$ (4), $b = 12.177$ (3), $c = 15.840$ (4) Å. The unit cell contains four molecules; $D_m = 1.42$, $D_x = 1.426$ Mg m $^{-3}$. Full-matrix least-squares refinement of the structure resulted in an R index of 0.066. The absolute configuration has been determined.

0567-7408/79/010219-04\$01.00

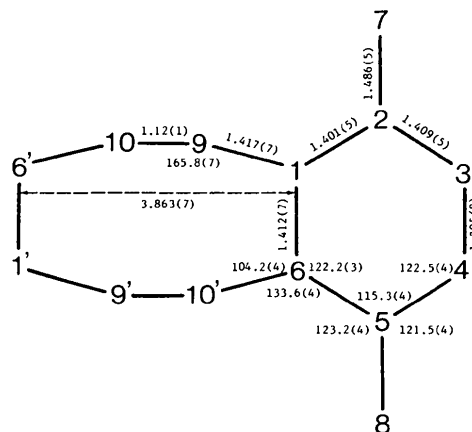
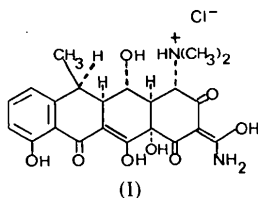


Fig. 2. Molecular dimensions of idealized model of (III) having symmetry mmm . Primed and unprimed atoms are related by the centre of symmetry at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$.

References

- AU, M.-K., SIU, T.-W., MAK, T. C. W. & CHAN, T.-L. (1978). *Tetrahedron Lett.* In the press.
- BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1962). *ORFLS*. Report ORNL-TM-305. Oak Ridge National Laboratory, Tennessee.
- DESTRO, R., PILATI, T. & SIMONETTA, M. (1975). *J. Am. Chem. Soc.* **97**, 658–659.
- DESTRO, R., PILATI, T. & SIMONETTA, M. (1977). *Acta Cryst.* B33, 447–456.
- GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A27, 368–376.
- International Tables for X-ray Crystallography* (1974). Vol. IV. Birmingham: Kynoch Press.
- WONG, H. N. C., GARRETT, P. J. & SONDEIMER, F. (1974). *J. Am. Chem. Soc.* **96**, 5604–5605.

chlorotetracycline hydrochloride or Aureomycin (Donohue, Dunitz, Trueblood & Webster, 1963), oxytetracycline, or Terramycin, hydrochloride (Cid-Dresdner, 1965), 5,12a-diacetyloxytetracycline (Von Dreele & Hughes, 1971), oxytetracycline (various forms, Stezowski, 1976; Prewo & Stezowski, 1977), tetracycline hexahydrate (Caira, Nassimbeni & Russell, 1977) and α -6-deoxyoxytetracycline hydrochloride or doxycycline hyclate (Stezowski, 1977). I now report the crystalline structure of the 6-epimer of the last-mentioned compound, namely β -6-deoxyoxytetracycline hydrochloride (I). The α -epimer (doxycycline hyclate) is sold by Pfizer, Inc., under the registered trademark of Vibramycin.



Crystals of the title compound were obtained from Pfizer, Inc. These crystals were surveyed and a 1 Å intensity data set (maximum $\sin \theta/\lambda = 0.5 \text{ \AA}^{-1}$) was collected on a Syntex P1 diffractometer equipped with a graphite incident-beam monochromator. All diffraction measurements were made with Cu radiation ($\lambda = 1.5418 \text{ \AA}$) at room temperature. Unit-cell dimensions were obtained by a least-squares fit of 15 high-angle reflections. Data were collected using a $\theta/2\theta$ scan, a scan speed of 2° min^{-1} in 2θ and a scan width of 1.2° below $K\alpha_1$ and 1.2° above $K\alpha_2$. Of the 1361 reflections collected, 1193 were considered non-zero. All intensities with a value less than 3σ were set equal to zero with zero weight.

Atomic scattering factors for C, N, O and Cl^- were taken from *International Tables for X-ray Crystallography* (1962) and for H from Stewart, Davidson & Simpson (1965). The scattering factor for the chloride was corrected for both anomalous-scattering components. The diffractometer output and all subsequent crystallographic calculations were processed using subprograms of the CRYM crystallographic computer system (Duchamp, 1964). The data processing included corrections for background, Lorentz and polarization effects. Polarization due to the monochromator was corrected for by a method suggested by Azaroff (1955). Processing also included the calculation of F^2 and its standard deviation for each of the reflections. The standard deviations were assigned on the basis of $\sigma^2(I) = S + \alpha^2(B_1 + B_2) + (dS)^2$, where S is the number of counts collected during the scan, B_1 and B_2 are the background counts, d is an empirical constant set at 0.02, and α is the scan time to total background time ratio.

β -6-Deoxyoxytetracycline hydrochloride was isomorphous with oxytetracycline hydrochloride. Appropriate published coordinates of oxytetracycline hydrochloride (Cid-Dresdner, 1965) provided a trial structure for the title compound.

Refinement of the title compound proceeded in a routine manner. The quantity minimized by the full-matrix least-squares refinement was $\sum w(F_o^2 - F_c^2)^2$. The weights used throughout the refinement of the structure were set equal to $1/\sigma^2(F_o^2)$. H positions were calculated wherever possible, and the remaining H atoms were located by difference Fourier techniques. During the latter stages of refinement H positions were refined. Three matrices were used in the final refinement: non-hydrogen coordinates, H coordinates, and non-hydrogen anisotropic temperature factors, scale factor and secondary-extinction coefficient. H temperature factors were not refined. The shifts calculated in the final cycle of least-squares refinement were in every case less than one-third the corresponding standard deviations. A final difference Fourier map revealed no missing or misplaced electron density. Final refinement parameters are summarized in Table 1.

The absolute configuration of the molecule was determined by the method of Ibers & Hamilton (1964). The absolute configuration of β -6-deoxyoxytetra-

Table 1. *Final refinement parameters*

Scale factor	0.799 (5)
Secondary extinction coefficient, $g \times 10^6$ { $F_{\text{corr}}^2 = (F_{\text{cal}})^2/[1 + g\beta(F_{\text{cal}})^2]$ }	1.4 (7)
R index ($R = \sum F_o - F_c / \sum F_o$), correct enantiomer	0.066
incorrect enantiomer	0.071
wR index ($wR = \sum w(F_o^2 - F_c^2)^2 / \sum wF_o^4 ^{1/2}$), correct enantiomer	0.0148
incorrect enantiomer	0.0168
GOF ($\{ \sum w(F_o^2 - F_c^2)^2 / (N - P) ^{1/2}\}$), correct enantiomer	2.76
incorrect enantiomer	2.84

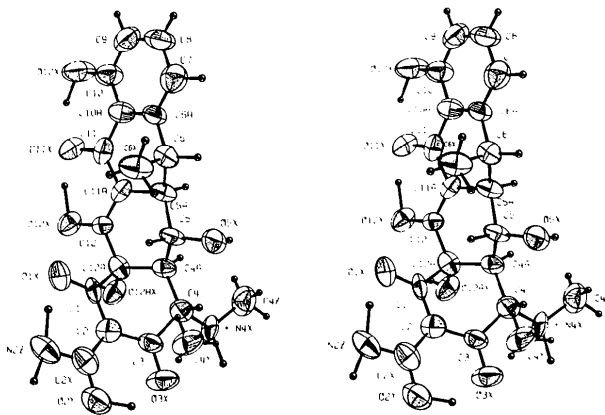
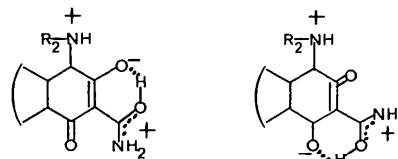


Fig. 1. Stereoview of β -6-deoxyoxytetracycline hydrochloride.

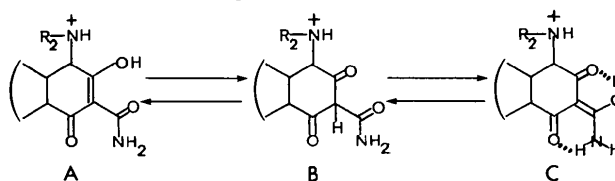
cycline hydrochloride was established as correct at the 0.5% level of significance (*i.e.* with 99.5% confidence) (Hamilton, 1965). The absolute configurations of this compound and that reported by Stezowski (1977) were consistent except for the epimerization at C(6). The refined structure of β -6-deoxyoxytetracycline hydrochloride was plotted using the *ORTEP* computer program of Johnson (1965) (Fig. 1). Positional parameters for the molecule appear in Tables 2 and 3.*

Discussion. The main controversy in previous papers concerned the conformation of ring *A*. Ring *A* is chemically very interesting. It is a 1,3-diketone with amide functionality at the acidic 2 position. The amide group plays a major role in controlling the conformation of the ring. The amide is in a position to form two strong hydrogen bonds with the 1,3-diketone system. One of the ambivalences in the literature

concerns the source of the H on the O of the amide needed for the second hydrogen bond. A major reference work (*Molecular Structures and Dimensions*, 1972) indicates that this H comes from the hydrochloride. This is obviously not the case. The hydrochloride proton is associated with the tertiary amine and has been located at this position in our structure using difference Fourier techniques. This question, along with an insight into the conformation of ring *A*, can be answered if tautomeric forms are considered. Stezowski proposed the following tautomeric forms for the two molecules in the asymmetric unit for the α epimer.



He then states that these tautomeric forms are confirmed by his observed bond distances. I have summarized results pertinent to his observations in Table 4. As can be seen, there is no dispute on the bond distances. However, I propose that the following tautomeric forms explain the data better.



* Lists of structure factors, anisotropic thermal parameters, and Tables 5–8 have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33925 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Non-hydrogen atom positional parameters ($\times 10^4$) and their standard deviations*

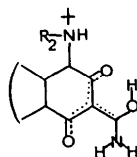
	<i>x</i>	<i>y</i>	<i>z</i>
C(1)	338 (9)	3478 (7)	1690 (6)
C(2)	−510 (9)	3184 (8)	1084 (6)
C(3)	−1381 (8)	3953 (7)	843 (6)
C(4)	−1206 (9)	5144 (7)	1018 (5)
C(4a)	−239 (8)	5446 (7)	1612 (6)
C(5)	866 (8)	5818 (8)	1110 (6)
C(5a)	1717 (8)	6348 (7)	1718 (5)
C(6)	2872 (8)	6648 (8)	1315 (6)
C(6a)	3682 (8)	7090 (8)	1963 (6)
C(7)	4481 (10)	7858 (10)	1719 (7)
C(8)	5292 (9)	8220 (9)	2337 (8)
C(9)	5355 (10)	7750 (10)	3113 (8)
C(10)	4561 (10)	6991 (9)	3359 (7)
C(10a)	3747 (9)	6637 (8)	2777 (6)
C(11)	2886 (8)	5826 (8)	3012 (5)
C(11a)	1897 (8)	5619 (8)	2492 (5)
C(12)	1129 (8)	4825 (7)	2728 (6)
C(12a)	96 (9)	4556 (8)	2212 (6)
O(1 <i>X</i>)	1172 (7)	2907 (5)	1847 (4)
O(2 <i>X</i>)	−556 (10)	2158 (9)	671 (6)
O(2 <i>Y</i>)	−1397 (7)	1822 (5)	220 (4)
N(2 <i>Z</i>)	316 (8)	1424 (6)	792 (5)
O(3 <i>X</i>)	−2240 (5)	3664 (5)	434 (4)
N(4 <i>X</i>)	−2346 (7)	5708 (6)	1168 (5)
C(4 <i>Y</i>)	−3008 (8)	5256 (10)	1916 (7)
C(4 <i>Z</i>)	−2240 (11)	6904 (9)	1211 (8)
O(5 <i>X</i>)	589 (6)	6495 (5)	410 (4)
C(6 <i>X</i>)	3414 (9)	5629 (9)	858 (6)
O(10 <i>X</i>)	4685 (6)	6559 (7)	4128 (5)
O(11 <i>X</i>)	3011 (5)	5304 (5)	3711 (4)
O(12 <i>X</i>)	1232 (5)	4258 (5)	3434 (3)
O(12a <i>X</i>)	−887 (5)	4304 (5)	2706 (4)
Cl(−13)	1175 (2)	8964 (2)	381 (1)

Table 3. *Hydrogen atom coordinates ($\times 10^3$)*

The temperature factors were fixed at 3.2 \AA^2 .

	<i>x</i>	<i>y</i>	<i>z</i>
H(C4)	−98 (5)	539 (5)	48 (4)
H(C7)	445 (5)	827 (5)	110 (4)
H(C8)	580 (5)	873 (5)	214 (4)
H(C9)	591 (5)	795 (5)	350 (4)
H(C4a)	−48 (5)	608 (5)	191 (4)
H(C5)	130 (6)	507 (5)	84 (4)
H(C5a)	134 (6)	704 (5)	192 (4)
H(C6)	275 (5)	717 (6)	77 (4)
H(O2 <i>Y</i>)	−193 (6)	248 (6)	−3 (4)
H(N2 <i>Z</i>)1	107 (5)	202 (5)	105 (3)
H(N2 <i>Z</i>)2	1 (5)	71 (5)	41 (4)
H(N4 <i>X</i>)	−297 (5)	536 (5)	50 (4)
H(C4 <i>Y</i>)1	−252 (6)	551 (5)	241 (4)
H(C4 <i>Y</i>)2	−317 (5)	477 (5)	177 (4)
H(C4 <i>Y</i>)3	−361 (5)	599 (5)	197 (4)
H(C4 <i>Z</i>)1	−184 (6)	716 (6)	68 (4)
H(C4 <i>Z</i>)2	−202 (5)	722 (5)	189 (4)
H(C4 <i>Z</i>)3	−298 (6)	725 (5)	108 (4)
H(O5 <i>X</i>)	9 (5)	701 (6)	77 (4)
H(C6 <i>X</i>)1	409 (5)	602 (5)	60 (4)
H(C6 <i>X</i>)2	286 (6)	555 (5)	31 (4)
H(C6 <i>X</i>)3	334 (5)	508 (5)	130 (4)
H(O10 <i>X</i>)	399 (5)	591 (5)	424 (3)
H(O12 <i>X</i>)	214 (6)	470 (5)	372 (4)
H(O12a <i>X</i>)	−72 (5)	410 (5)	319 (4)

Form *A* is the one usually written for this class of compound. Bond distances clearly rule out this tautomer. Form *B* is the usually presented 1,3-diketo form. This form suffers from the lack of a H on the amide O. This H is required for the second hydrogen bond. Form *C* best fits the data. The exocyclic C—C double bond requires that C(2) have sp^2 hybridization. This explains the observed planarity of the system. Because this bond is in conjugation with both the carbonyls, the best representation of this moiety would be the following resonance hybrid.



This hybrid would explain the equivalences of the three C—C bonds. Stezowski's tautomer cannot adequately explain the shortening of C(2)—C(2*X*). Form *C* is also superior because it explains all the bond lengths and does not require a separation of charge. In the case of the α epimers, our studies confirm the presence of two molecules which are geometrical isomers, about the C(2)—C(2*X*) double bond. When the above equilibrium of tautomeric forms is considered, the interconversion of these isomers can be easily justified. The isomers observed in the crystalline state apparently depend on the conditions of crystallization. While this paper was being prepared, Caira, Nassimbeni & Russell (1977) proposed an almost identical tautomeric form for the free base, tetracycline hexahydrate. Their results indicated that the 'free base' form was a zwitterion which attests to the fact that the H at C(2) is very acidic indeed. The only difference between the two structures as far as the tautomeric forms are concerned

Table 4. Comparison of bond distances (\AA) in ring *A*

	6 β .HCl	DOXY.- HCl (1) ^(a)	DOXY.- HCl (2) ^(a)
C(1)—O(1 <i>X</i>)	1.22 (1)	1.266 (3)	1.233 (4)
C(1)—C(2)	1.42 (1)	1.417 (3)	1.435 (4)
C(2)—C(2 <i>X</i>)	1.41 (1)	1.440 (3)	1.455 (4)
C(2)—C(3)	1.43 (1)	1.442 (4)	1.406 (4)
C(3)—O(3 <i>X</i>)	1.24 (1)	1.230 (3)	1.268 (3)
C(2 <i>X</i>)—O(2 <i>Y</i>)	1.28 (1)	1.314 (3)	1.305 (4)
C(2 <i>X</i>)—N(2 <i>Z</i>)	1.37 (1)	1.311 (3)	1.312 (5)

(a) These are the values reported by Stezowski for the α -epimer salt.

is the presence of an extra H (from the HCl). This extra H allows for the formation of a second hydrogen bond between O(1) and the 'amide' O.

Complete bond distances and angles for β -6-deoxyoxytetracycline hydrochloride appear in Table 5.* Torsion angles for the four rings are given in Table 6.* Because β -6-deoxyoxytetracycline hydrochloride is isomorphous with Terramycin hydrochloride and simply lacks the O at C(6), it is not surprising to find that intramolecular hydrogen bonding was as previously described by Cid-Dresdner (1965). These values for β -6-deoxyoxytetracycline hydrochloride are summarized in Table 7.* The crystal structure of this epimer is held together by a network of hydrogen bonds to the chloride ion. Again, with the exception of O(6), these intermolecular hydrogen bonds are as described by Cid-Dresdner (1965). Four atoms [N(4*X*), O(5*X*), O(12*aX*) and N(2*Z*)] are all within 3.3 \AA of a chloride ion. Data pertinent to the intermolecular hydrogen bonding are summarized in Table 8.*

* Tables 5–8 have been deposited. See previous footnote.

References

- AZAROFF, L. V. (1955). *Acta Cryst.* **8**, 701–704.
 CAIRA, M. R., NASSIMBENI, L. R. & RUSSELL, J. C. (1977). *Acta Cryst.* **B33**, 1171–1176.
 CID-DRESDNER, H. (1965). *Z. Kristallogr.* **121**, 170–189.
 DONOHUE, J., DUNITZ, J. D., TRUEBLOOD, K. N. & WEBSTER, M. S. (1963). *J. Am. Chem. Soc.* **85**, 851–856.
 DUCHAMP, D. J. (1964). Am. Crystallogr. Assoc. Meeting, Bozeman, Montana. Paper B-14, p. 29.
 HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502–510.
 IBERS, J. & HAMILTON, W. C. (1964). *Acta Cryst.* **17**, 781–782.
International Tables for X-ray Crystallography (1962). Vol. III, pp. 202, 214. Birmingham: Kynoch Press.
 JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee.
Molecular Structures and Dimensions (1972). Vol. A1, p. 305. Utrecht: Oosthoek.
 PREWO, R. & STEZOWSKI, J. J. (1977). *J. Am. Chem. Soc.* **99**, 1117–1121.
 STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.
 STEZOWSKI, J. J. (1976). *J. Am. Chem. Soc.* **98**, 6012–6018.
 STEZOWSKI, J. J. (1977). *J. Am. Chem. Soc.* **99**, 1122–1129.
 VON DREELE, R. B. & HUGHES, R. E. (1971). *J. Am. Chem. Soc.* **93**, 7290–7296.