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The Structure and Absolute Configuration of Viridicatumtoxin: 2′ *S*-(2′α,7′a*β*,11′a*β*,12′*β*)-7′,7′a,8′,11′,11′a,12′-Hexahydro-5′,6′,7′a,10′,11′a,12′-hexahydroxy-3′-methoxy-2,6,6-trimethyl-7′,8′-dioxospiro[2-cyclohexene-1,2′(1′*H*)-cyclopenta[*de*]naphthacene]-9′-carboxamide Methanolate

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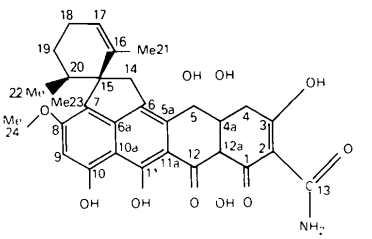
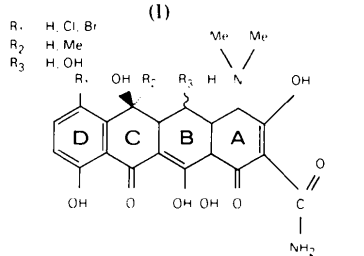
Abstract

$C_{30}H_{31}NO_{10}.2(?)CH_3OH$, M_r = 565·58 + 2(?) × 32·04, habit: prismatic, *I*2 (No. 5), Cu $K\alpha$ (graphite monochromator), λ = 1·5418 Å, a = 12·9784 (12), b = 7·8029 (8), c = 29·3152 (25) Å, β = 99·309 (9)°, V = 2929·63 Å^3, Z = 4, D_x = 1·428 g cm^{-3}, crystal size: 0·25 × 0·15 × 0·15 mm, 3202 ($482 < 1\sigma$) reflections, maximum $\sin\theta/\lambda$: 0·6233 Å^{-1}. The structure was determined by direct methods and has been refined to R = 0·031. The absolute configuration, determined by anomalous scattering, is the same as the tetracyclines at comparable atoms. The bond lengths associated with the carboxamide moiety indicate π-conjugation.



(I)



(II)

Introduction

Details of the isolation and characterization of the title compound (I), which will hereafter be referred to as viridicatumtoxin, are given by Hutchison, Steyn & van Rensburg (1973). The atomic numbering has been chosen to conform to that used in the tetracyclines and does not correspond to the *Chemical Abstracts* name given in the title.

A description of the chemical structure and relative configuration, determined by crystal-structure analysis with very little chemical information, has been given by Kabuto, Silverton, Akiyama, Sankawa, Hutchison, Steyn & Vleggaar (1976). The original X-ray data refined to an R factor of 0·059 which was considered too high for a reliable determination of absolute

Table 1. *Atomic parameters for the heavier atoms* ($\times 10^4$)

The U value given is the geometric mean of the diagonal terms of the vibration tensor except for C(1X) and C(2X) where it is the actual isotropic U value. E.s.d.'s are rounded and actual values of z, denoted as '(1)', are approximately half this value except for solvent and some peripheral atoms.

	x	y	z	U (Å^2)
C(1)	5590 (2)	4361 (3)	4230 (1)	284 (6)
O(1)	5730 (1)	5626 (2)	4482 (1)	408 (5)
C(2)	5759 (2)	2618 (3)	4383 (1)	281 (6)
O(2)	6289 (2)	639 (3)	4987 (1)	484 (6)
N(2)	6398 (2)	3421 (4)	5173 (1)	377 (7)
C(3)	5431 (2)	1257 (3)	4085 (1)	296 (6)
O(3)	5557 (2)	−317 (3)	4211 (1)	414 (5)
C(4)	4897 (2)	1551 (3)	3602 (1)	267 (6)
C(4a)	4406 (1)	3324 (3)	3516 (1)	232 (5)
O(4a)	3539 (1)	3411 (2)	3753 (1)	296 (4)
C(5)	4036 (1)	3497 (3)	2987 (1)	234 (5)
O(5)	3251 (1)	4790 (2)	2899 (1)	288 (4)
C(5a)	4937 (1)	3834 (3)	2728 (1)	229 (5)
C(6)	4832 (1)	3494 (3)	2265 (1)	230 (5)
C(6a)	5658 (2)	3870 (3)	2017 (1)	247 (5)
C(7)	5404 (1)	3493 (3)	1547 (1)	258 (5)
C(8)	6193 (2)	3661 (3)	1282 (1)	304 (7)
O(8)	5985 (1)	3156 (3)	835 (1)	394 (6)
C(9)	7179 (2)	4317 (3)	1482 (1)	342 (5)
C(10)	7393 (2)	4756 (3)	1941 (1)	314 (6)
C(10a)	6630 (2)	4512 (3)	2231 (1)	259 (5)
O(10)	8350 (1)	5408 (3)	2106 (1)	433 (7)
C(11)	6753 (2)	4786 (3)	2715 (1)	264 (5)
C(11a)	5932 (2)	4491 (3)	2960 (1)	243 (7)
O(11)	7695 (1)	5322 (3)	2925 (1)	365 (7)
C(12)	6124 (2)	4773 (3)	3451 (1)	276 (6)
C(12a)	5192 (2)	4699 (3)	3715 (1)	249 (6)
O(12)	6996 (1)	5182 (3)	3667 (1)	400 (6)
O(12a)	4717 (1)	6327 (2)	3657 (1)	330 (5)
C(13)	6174 (2)	2212 (4)	4864 (1)	345 (5)
C(14)	3966 (2)	2668 (3)	1931 (1)	267 (6)
C(15)	4249 (2)	2969 (3)	1431 (1)	235 (5)
C(16)	4092 (2)	1307 (3)	1157 (1)	316 (11)
C(17)	3245 (2)	1029 (4)	843 (1)	379 (6)
C(18)	2377 (2)	2278 (4)	710 (1)	397 (7)
C(19)	2437 (2)	3772 (4)	1046 (1)	340 (7)
C(20)	3558 (2)	4458 (3)	1185 (1)	299 (6)
C(21)	4916 (2)	−40 (4)	1271 (1)	446 (6)
C(22)	3546 (2)	5997 (4)	1507 (1)	435 (8)
C(23)	3960 (2)	5075 (4)	749 (1)	411 (8)
C(24)	6763 (2)	3315 (6)	547 (1)	540 (8)
C(1S)	523 (2)	3479 (4)	2379 (1)	446 (8)
O(1S)	1592 (1)	3228 (3)	2359 (1)	536 (7)
C(1X)	8387 (15)	2900 (29)	4439 (7)	1532 (112)
C(2X)	9116 (16)	3642 (29)	4787 (7)	2090 (135)

Table 2. H-*atom parameters* ($\times 10^3$)

The first column indicates the heavier atom to which the H atom is attached.

	x	y	z	U (Å^2)
N(2)	625 (2)	455 (6)	509 (1)	72 (12)
N(2)′	664 (2)	310 (4)	545 (1)	44 (7)
O(3)	592 (3)	−6 (7)	458 (1)	117 (16)
O(4a)	319 (2)	430 (4)	364 (1)	54 (9)
C(4)	541 (1)	134 (3)	339 (1)	33 (6)
C(4)′	437 (2)	76 (4)	352 (1)	39 (7)
C(5)	367 (1)	234 (2)	288 (1)	32 (5)
O(5)	275 (2)	438 (4)	271 (1)	59 (10)
C(9)	774 (1)	443 (3)	129 (1)	31 (6)
O(10)	834 (2)	566 (4)	239 (1)	55 (8)
O(11)	762 (2)	536 (4)	322 (1)	62 (10)
O(12a)	500 (2)	679 (4)	389 (1)	56 (9)
C(14)	327 (2)	316 (3)	196 (1)	38 (7)
C(14)′	395 (2)	134 (4)	197 (1)	44 (7)
C(17)	324 (2)	−18 (4)	68 (1)	52 (8)
C(18)	169 (2)	169 (3)	71 (1)	38 (7)
C(18)′	239 (2)	279 (4)	37 (1)	53 (8)
C(19)	219 (1)	329 (3)	132 (1)	34 (6)
C(19)′	199 (2)	470 (4)	89 (1)	44 (7)
C(21)	518 (2)	−27 (4)	160 (1)	62 (9)
C(21)′	558 (3)	37 (5)	118 (1)	80 (12)
C(21)″	470 (2)	−118 (5)	108 (1)	78 (11)
C(22)	430 (2)	637 (4)	163 (1)	52 (8)
C(22)′	319 (2)	577 (4)	176 (1)	46 (8)
C(22)″	317 (2)	696 (5)	130 (1)	73 (10)
C(23)	465 (2)	558 (4)	80 (1)	43 (7)
C(23)′	352 (2)	602 (4)	57 (1)	63 (9)
C(23)″	405 (2)	408 (4)	53 (1)	39 (7)
C(24)	746 (3)	273 (6)	66 (1)	103 (14)
C(24)′	642 (2)	306 (5)	24 (1)	67 (10)
C(24)″	682 (3)	474 (6)	49 (1)	87 (12)
O(1S)	164 (3)	210 (7)	225 (1)	110 (15)
C(1S)	983 (3)	267 (6)	740 (1)	110 (15)
C(1S)′	994 (2)	302 (4)	792 (1)	62 (10)
C(1S)″	965 (3)	469 (6)	760 (1)	88 (12)

configuration, especially since the brownish-yellow color of the crystal was subsequently found to be due to decomposition on exposure to light. Crystals, grown in the dark from methanol, were a clear light-yellow. The crystal used in the present work was encapsulated in a sphere of epoxy resin to impede the known loss of solvent and X-ray data were collected in nearly complete darkness. The crystal retained its original color and standard reflections indicated no significant intensity changes. The encapsulation may have had a fortunate side effect, since it was not possible to grind a spherical sample, in that the X-ray absorption of the resin should be similar to that of the crystal and thus absorption errors may have been reduced. The density of the crystals was not measured because loss of solvent of crystallization is fairly rapid.

The previous work used space group $A2$ but a transformation to $I2$ produces more nearly orthogonal axes. Standard methods of least-squares refinement and difference maps (Stewart, Kruger, Ammon, Dickinson & Hall, 1972) revealed all H atoms including some on O atoms and on the molecule of methanol which were indefinite in the earlier work. Anisotropic parameters were used for the heavier atoms and isotropic parameters for the H atoms. The weights used in the least-squares refinement follow Peterson & Levy (1957). The H atom which had been assigned to O(2) earlier appeared between O(2) and O(3) and refinement appeared to indicate that it was most likely attached to O(3). The structure was successfully refined to an R factor of 0·039.

The absolute configuration was determined by the

anomalous scattering of C, N and O since the ratio of R factors was not significant (present model: 0·03921, opposite configuration: 0·03931). The scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The ratios of the F values for both enantiomorphs were calculated and the largest 20 which had good agreement between observed and calculated values, dispersion factors exceeding 1% and F values greater than 20 on an absolute scale were used for the absolute-configuration measurement. Engel's (1972) technique was used together with a version of the Enraf–Nonius (1977) *DATCOL* procedure modified to allow the necessarily long counting times (Silverton, 1981, unpublished program). The program involves a repetitive step scan until a desired theoretical standard deviation is attained or until a maximum number of repetitions has been reached. A statistical error of 0·3% or less on intensity was achieved unless the counting time exceeded 2 h. The measurement of the 20 Friedel pairs and absorption-correcting pairs took nearly as long as the original data collection. Even though the measured difference was very small in three cases and one difference was in the wrong sense, on a basis of Hamilton's (1964) test, the probability of the correctness of the result is 0·9999, using all measurements correct or otherwise. The wrong results can be rationalized in that the absorption correction reflections had setting parameters rather further from optimum than those of the others. The deduced absolute configuration corresponds to that of the related tetracyclines (II) as determined chemically by Dobrynin, Gurevich, Karapetyan, Kolosov & Shemyakin (1962) and is as shown in (I).

A difference map was essentially featureless except for two peaks near a twofold axis where there was an empty region in the crystal. Two C atoms were placed at the peak positions and included in the model with isotropic thermal parameters and population parameters. The final results showed an interatomic distance of 1·40 (3) Å, which is consistent with the presence of a second molecule of methanol. The population parameters are approximately 0·5 and one atom has both a lower temperature factor and a distance from O(12) which, given its large e.s.d., may be short enough to be a hydrogen bond. However, the other atom is close to a symmetry-related atom and the model is not necessarily completely correct. The final R factor was 0·031 and the change from 0·039 indicates that the addition was justified on Hamilton's (1964) R factor ratio test.* Final atomic parameters are given in Tables 1 and 2.

* Lists of structure factors, reflections used for absolute-configuration determination and anisotropic thermal parameters for the heavier atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38035 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

(The structure was refined by dividing the atoms into three groups and refining only one group at a time. The origin was thus effectively defined by the unrefined atoms.)

The identification of the N and O atoms was tested satisfactorily in the original structure determination and is consistent with the finding of two H atoms attached to the N atom and also with the O(2)···O(3) distance which would be unusually short for an O···N hydrogen bond. At the insistence of a referee, the experiment was performed of interchanging the O and N atoms and refining this model. The final R factor was 0·039 which is sufficiently higher to confirm our assignment.

Discussion

The crystal conformation, absolute configuration, atomic nomenclature and bond lengths are shown in Fig. 1. The bond angles and some representative torsion angles are shown in Fig. 2. It is apparent from the torsion angles that there is some distortion of the aromatic rings caused by the fused rings. There is also evidence of strain in the lengths of the C(14)–C(15) and C(15)–C(20) bonds which are 1·584 and 1·570 Å respectively. The five-membered ring is rather flat and is nearly in the half-chair conformation, as indicated by the Altona, Geise & Romers (1968) parameters: P_m = 16·0, Δ = 6·9°. The monoplanar conformation, which Bucourt (1974) states is most likely for cyclohexene, is adopted by the B ring and the spiro ring. The A ring is *cis* fused and O(1), C(1), C(2), C(3), O(3), C(13), N(2) and O(2) are coplanar within 0·06 Å.

The tetracyclines are antibiotics; their structure is based on a highly oxygenated naphthacene skeleton

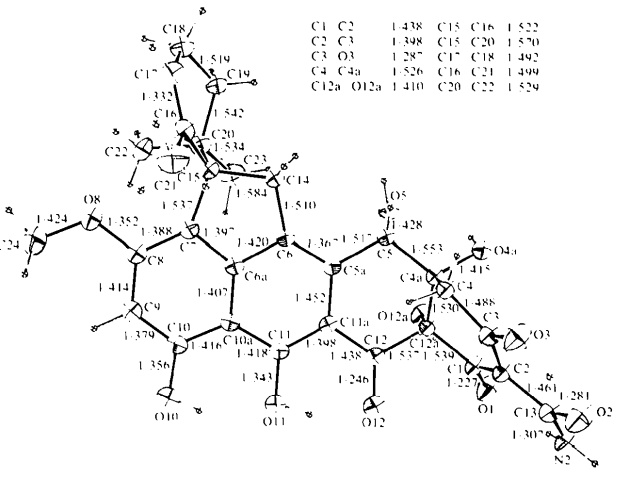


Fig. 1. Crystal conformation, atomic nomenclature and bond lengths (Å). E.s.d.'s are less than 0·004 Å. All figures in this paper were drawn with *ORTEP* (Johnson, 1965).

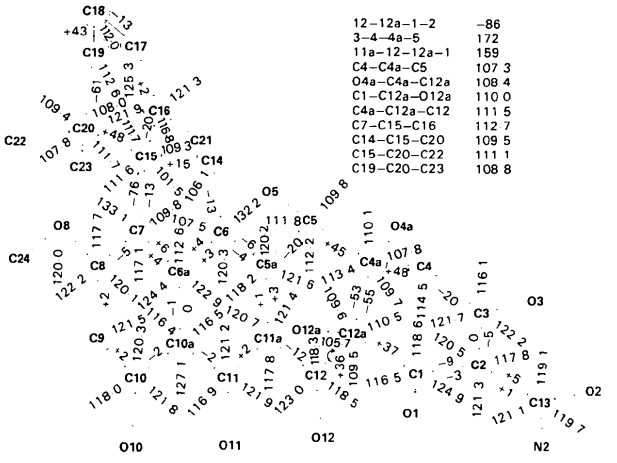


Fig. 2. Torsion angles and bond angles (°). E.s.d.'s of bond angles are 0·2° and those of torsion angles are less than 0·5°.

and there has been considerable crystallographic work on compounds of this type (Table 3).

In all tetracycline structures except for pillaranone bromoacetate (No. 5 in Table 3) the absolute configuration at C(4a) and C(12a), when determined, has been the same as that first reported by Dobrynin *et al.* (1962) using chemical methods. Pillaranone bromoacetate, whose absolute configuration was confirmed by Kamiya *et al.* (1971), is a derivative of pillaromycin (No. 8) but the absolute configuration of the latter compound has not been determined and one cannot eliminate the possibility that the configuration of No. 5 is an artefact of chemical synthesis. Viridicatumtoxin, as stated previously, conforms to the usual absolute configuration. The antibiotics rhodomycin, daunomycin and carminomycin (Nos. 18–20), have an aromatic *B* ring and the question of absolute configuration at C(4a) and C(12a) does not arise.

The molecules listed in Table 3 which possess a carboxamide group on C(2) have an essentially planar set of atoms: O(1), C(1), C(2), C(3), O(3) and the carboxamide group. In the majority of compounds, the O atom of the carboxamide group is *cis* to O(3) and a short O···O hydrogen bond is formed. In the rest, an N···O hydrogen bond is present but, as might be expected, the bond is not as short as the O···O bond. The O···O hydrogen bond is probably symmetric although the reported position of the H atom is not always in the center of the bond. The final refined

Table 3. *Details of structural work on substituted naphthacenes*

In the column designated 'Ionicity', I, Z and N indicate ionic, zwitterionic and neutral molecules, respectively. The carboxamide conformation, where appropriate, is denoted as *cis* or *trans* depending on the orientation of O(2) with respect to O(3).

No.	Name	Ionicity	R_1	R_2	R_3	Carboxamide
(1)	7-Chlorotetracycline.HCl	I	Cl	Me	H	*cis*
(2)	Oxytetracycline.HCl	I	H	Me	OH	*cis*
(3)	7-Chloro-4-hydroxytetracycloxide	N	Cl	–	H	*cis*
(4)	7-Bromo-4-hydroxytetracycloxide	N	Br	–	H	*cis*
(5)	Pillaranone bromoacetate	N	H	des-OH	H	
(6)	5,12a-Diacetyloxytetracycline	N	H	Me	OAc	*cis*
(7)	Tetracycline.HCl	I	H	Me	H	*cis*
(8)	Pillaromycin A	N	H	H, des-OH	H	
(9)	Tetracycline.$6H_2O$	Z	H	Me	H	*trans*
(10)	Dipotassium oxytetracycline	I	H	Me	OH	Unknown
(11)	Oxytetracycline/$HgCl_2$ complex	Z	H	Me	OH	Unknown
(12)	Oxytetracycline.HBr.$2H_2O$	I	H	Me	OH	Disorder
(13)	Oxytetracycline.$2H_2O$	Z	H	Me	OH	*cis*
(14)	Oxytetracycline	N	H	Me	OH	*cis*
(15)	Tetracycline/urea.$4H_2O$	Z	B	Me	H	*trans*
(16)	Anhydrotetracycline.HBr.H_2O	I	H	Me, des-OH	H	*cis*
(17)	7-Chloro-6-demethyltetracycline	I	Cl	H	H	*trans*
(18)	Rhodomycin	N	H	Keto	OH	
(19)	Daunomycin	N	H	Keto	OH	
(20)	Carminomycin I.HCl.H_2O	I	H	Keto	OH	
(21)	Viridicatumtoxin	N	Cyclopentane		OH	*cis*

References and comments: (1) Hirokawa, Okaya, Lovell & Pepinsky (1959*a*,*b*), Takeuchi & Buerger (1960), Cid-Dresner (1965); all references used the same X-ray data. (2) Donohue, Dunitz, Trueblood & Webster (1963), Boggs (1978); second reference is refinement of data of first. (3, 4) van den Hende (1965); O(6) joined to C(4). (5) Kamiya, Asai, Nishikawa, Mizuno, Tomiie & Nitta (1970); derivative of pillaromycin, further ring fusion. (6) von Dreele & Hughes (1971); O(12a) acetylated. (7) Kamiya, Asai, Wada & Nishikawa (1971). (8) Pezzanite, Clardy, Lau, Wood, Walker & Fraser-Reid (1975); O(1) absent, modified sugar on O(6). (9) Stezowski (1976); Caira, Nassimbeni & Russell (1977); independent determinations. (10, 11) Stezowski (1975); no coordinates given. (12) Jugon & Stezowski (1976). (13, 14) Stezowski (1976). (15) Palenik & Mathew (1978). (16, 17) Palenik, Mathew & Restivo (1978). (18) Rohrl & Hoppe (1970); no amide or carboxamide. (19) Angiuli, Foresti, Riva di Sanseverino, Isaacs, Kennard, Motherwell, Wampler & Arcamone (1971); no amide or carboxamide. (20) von Dreele & Einck (1977); no amide or carboxamide. (21) Present structure; no amide.

position of the H atom in viridicatumtoxin is closer to O(3) than O(2), in conformity with the accepted chemical structure of the tetracyclines, but the lengths O(3)···H and O(2)···H are 1·15 (3) and 1·29 (3) Å and the difference may not be significant. A symmetrical hydrogen bond, with two H sites separated by a small energy barrier, is not unlikely for such a short bond [O(3)···O(2) 2·435 Å].

As discussed by Stezowski (1976), Palenik & Mathew (1978) and Palenik, Mathew & Restivo (1978), there have been two conformations reported for the *A* ring of the tetracyclines. The most common conformation occurs in all the ionic and zwitterionic compounds reported in Table 3 which do not have perturbations caused by further ring formation. The two neutral compounds previously reported (Nos. 6 and 14) have a quite different conformation. In both cases, the previously mentioned planar grouping of atoms is present but the orientation of the *A* ring is quite different. The torsion angles are very similar in each class. Viridicatumtoxin, which does not possess a dimethylamide group, should not have an ionic structure and its torsion angles are very similar to those in the two neutral molecules. Compounds 1, 2, 9, 13, 15 and 17 have been used to calculate averages for the zwitterionic/ionic class and Nos. 6, 14 and 21 for the neutral class. No. 16, while clearly a member of the first class, has rather larger deviations from the average values, probably because of the aromatization of the *C* ring. The most characteristic torsion angles appear to be 12–12a–1–2, 3–4–4a–5, 4–4a–12a–1, 11a–12–12a–1, and 12–12a–4a–5, whose average values are −174, 109, 50, 101, and 49° respectively for the ionic/zwitterionic class and −80, 165, −56, 160, and −57° respectively for the neutral class. In both classes the *A* ring is twisted away from the approximately coplanar *B*, *C* and *D* rings and the absolute value of the torsion angle 12a–4a–3–2 is about 30° but the sign of the angle is negative in the ionic/zwitterionic class and positive for the neutral molecules.

As Stezowski (1976) has indicated, there appear to be significant differences in the bond lengths of the planar region of ring *A*. Some caution is needed in making comparisons because Stezowski's data for Nos. 9, 13 and 14 were collected at 123 K whereas the other structure determinations reported in Table 3 were carried out at room temperature. However, if Stezowski's bond lengths are compared with those of other structures in the same classes of ionicity, there do not appear to be very significant differences and it may be useful to have average values in the different classes of ionicity. Averages for the ionic molecules are calculated from Nos. 1, 2, 17 and 16; zwitterionic from Nos. 9, 13 and 15; and neutral from Nos. 6, 14 and 21. The average bond lengths (Å), in the order ionic, zwitterionic, neutral, are as follows: C–O(amide): 1·313, 1·250, 1·276; C–N(amide): 1·299, 1·339, 1·324; C(2)–C(amide): 1·438, 1·469, 1·467; C(1)–C(2): 1·426, 1·426, 1·437; C(2)–C(3): 1·407, 1·433, 1·395; C(3)–C(4): 1·526, 1·542, 1·515; C(3)–O(3): 1·243, 1·232, 1·293. It should be mentioned that the C(3)–C(4) bond in viridicatumtoxin is unusually short.

There are two alternative and not necessarily exclusive explanations for the differences in average lengths: mixtures of keto–enol tautomers or π-conjugation. The present authors favor the latter explanation since maximum directions of apparent thermal parameters appear to be at right angles to the planar system, as may be seen in Fig. 1 for viridicatumtoxin and as appears to be the case in the *ORTEP* drawings published by Stezowski (1976), Palenik & Mathew (1978) and Palenik, Mathew & Restivo (1978). If tautomeric mixtures were present, one might expect the apparent maximal directions of the thermal ellipsoids to be in the plane of the bonds, as was the case in the tautomeric mixture of tropolones reported by Iorio, Brossi & Silverton (1978). The averages corroborate Stezowski's (1976) observation, based on Nos. 9, 13 and 14, that the differences between the bond lengths for C–O(amide) and C(3)–O(3) are more characteristic of ionicity than the bond lengths themselves. The differences are −0·070, −0·018 and +0·017 Å for the ionic, zwitterionic and neutral classes respectively. The predominant canonical form, in the terminology of resonance theory, appears to have C(3)–O(3) as a double bond in the ionic forms, whereas in the zwitterionic and neutral molecules, the forms with double bonds on either of the C–O bonds seem to be of equal importance. In the neutral molecules both bonds seem to have a lower bond order than in the other two classes.

Stezowski (1976) has discussed the relationship between ionicity and biological activity in the tetracyclines, showing that the ionic forms are water soluble and can be readily administered to animals but the action of the drugs may depend on lipid solubility which is characteristic of the neutral molecules. Viridicatumtoxin is typical of a neutral molecule in that its water solubility is low but, injected as a dimethyl sulfoxide solution, the compound is quite toxic [Hutchison *et al.* (1973) report an LD_{50} of 120 mg kg^{-1} in rats].

Table 4 gives a list of short interactions which, apart from C(1*X*)···O(12), involve hydrogen contacts shorter than those derived from the van der Waals radii of Bondi (1964). The ordered solvent molecule appears to have an important role in the crystal packing since its O atom is involved both as a donor and acceptor with the O(5) atoms of different molecules. There are thus linkages along a primitive axis of the cell. There may also be a weak hydrogen bonding, involving O(4a) and N(2), of molecules around a twofold axis. A stereodiagram of the packing is given as Fig. 3. The intramolecular hydrogen bonding is very extensive and

Table 4. *Possible hydrogen bonds (distances in Å and angles in degrees)*

The absence of a symmetry operation indicates that the acceptor coordinates are as in Table 1. Symmetry operations: (i) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z$; (ii) $1-x, y, 1-z$.

Donor	Acceptor	$D\cdots A$	$H\cdots A$	D–H$\cdots A$
N(2)	O(1)	2·962 (3)	1·99 (3)	132 (3)
O(3)	O(2)	2·435 (3)	1·29 (3)	174 (5)
O(4a)	O(5)	2·695 (2)	2·22 (3)	114 (2)
O(5)	O(1*S*)	2·744 (2)	1·90 (3)	171 (3)
O(10)	O(11)	2·675 (2)	1·91 (3)	147 (3)
O(11)	O(12)	2·493 (2)	1·66 (3)	156 (2)
O(12a)	O(1)	2·615 (2)	2·05 (3)	127 (3)
O(1*S*)	O(5^{i})	2·804 (3)	1·87 (5)	174 (3)
N(2)	O(4a^{ii})	3·138 (2)	2·40 (3)	144 (3)
C(1*X*)	O(12)	3·199 (20)	–	–

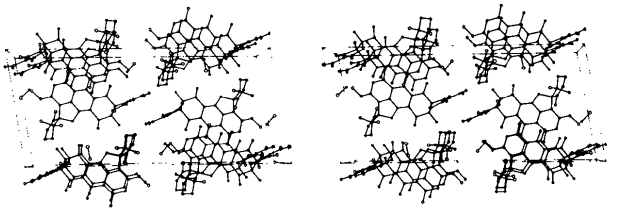


Fig. 3. Packing diagram. The projection is down **a**.

seven hydrogen bonds appear to be likely, in conformity with Stezowski's (1976) observation that neutral tetracyclines tend to form intramolecular rather than intermolecular hydrogen bonds.

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