– Coordinence 5 de type bipyramidal à base triangulaire pour le titane ou le vanadium dans In_2VO_5 (ou In_2TiO_5) et La_2TiO_5.

Différences

– La base triangulaire des bipyramides est perpendiculaire au petit axe (c=3,93 Å) dans le cas de La_2TiO_5, parallèle (b=3,468 Å) dans le cas de In_2VO_5.

– Les rubans $(La_2O_4)_n^{2n-}$ se connectent par l'intermédiaire de sommets communs dans le plan médian, alors que les rubans $(In_2O_4)_n^{2n-}$ s'associent au niveau de l'octaèdre les bordant.

Les Figs. 5(a) et 5(b) montrent les détails des connections entre octaèdres InO_6 et LaO_6 et bipyramides VO_5 ou TiO_5 dans les deux structures In_2VO_5 et La_2TiO_5. Le sommet de la bipyramide TiO_5 est lié à deux atomes de lanthane, cet oxygène complétant ainsi la coordinence de ce cation à 7.

La réorientation de l'axe de la bipyramide, lorsqu'on passe d'une structure à l'autre semble directement liée au glissement des rubans $(M_2O_4)_n^{2n-}$ (M=La,In) les uns par rapport aux autres. Ces bipyramides sont schématisées aux Figs. 5(c) et 5(d).

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The Molecular Structures and Absolute Configurations of Eupalmerin Acetate and Eupalmerin Acetate Dibromide at Low Temperature

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The crystal structures of eupalmerin acetate dibromide, $C_{22}H_{32}O_5Br_2$, and eupalmerin acetate, $C_{22}H_{32}O_5$, have been determined and refined by three-dimensional least-squares techniques. Eupalmerin acetate dibromide crystallizes in space group $P2_12_12_1$, $Z=4$, with a=12·967 (2), b=16·392 (2) and c=10·5605 (8) Å at T= –110°C. The final R value for 2184 reflections, collected at –110°C, is 0·023. The absolute configuration was determined from the anomalous contribution of the bromine atoms. Eupalmerin acetate also crystallizes in space group $P2_12_12_1$, $Z=4$, with a=10·693 (6), b=18·842 (7) and c=10·321 (4) Å at T= –110°C. The final R value for 2433 reflections, collected at –110°C, is 0·033. The absolute configuration of eupalmerin acetate was determined from the anomalous contribution of the five oxygen atoms and was in agreement with the absolute configuration of its heavy-atom derivative. The bromine addition reaction involves transannular participation of the epoxide function and does not reveal the absolute configuration of the epoxide except by inference. The absolute configuration of atoms C(3) and C(4) is the opposite of that in other similar compounds determined in this laboratory, while the lactone fusion is the same.

Introduction

Eupalmerin acetate (EPA) is a diterpene lactone isolated from the gorgonian *Eunicea palmeri* Bayer (Rehm, 1971).

The gorgonians are a prominent group of marine invertebrates (coelenterates) in the Caribbean region and have been the subject of considerable study in these laboratories. A number of terpenoids and other organic compounds isolated from gorgonians have shown various levels of biological activity (*e.g.* Ciereszko, Sifford & Weinheimer, 1960; Ciereszko,

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1962; Weinheimer & Spraggins, 1970; Schmitz & Lorance, 1971; Rehm, 1971). The general structure for one group of these compounds, the cembranolides, is shown in Fig. 1. The structures have the following features in common: (1) a 14-membered carbocyclic ring, (2) a γ-lactone or δ-lactone fused at C(1) and C(2) or C(1) and C(13) respectively, (3) methyl substitution at C(4), C(8) and C(12) typical of a regular isoprenoid diterpene structure, (4) an isolated endocyclic double bond, C(8)–C(9), and (5) various types of oxygenation at atoms C(3), C(12) and C(13). The molecules differ primarily in the type of oxygenation and the stereochemistry at atoms C(3), C(4), C(12) and C(13). Fig. 2 shows the structures of five of these compounds. Of these structures, four have been determined crystallographically. They are EPA, eunicin (Hossain, Nicholas & van der Helm, 1968), jeunicin (Enwall, van der Helm, Karns & Weinheimer, to be published) and crassin acetate (Hossain & van der Helm, 1969). In addition the structure of ceunicin acetate, as shown, has been proposed from n.m.r. analysis and chemical transformations (Gross, 1974). The original structural investigation of EPA was carried out on the bromine addition product, eupalmerin acetate dibromide (EPA-Br_2), and a preliminary report has been published (van der Helm, Ealick & Weinheimer, 1974). The numbering scheme used in the present publication for both EPA and EPA-Br_2 is the common numbering scheme. In the preliminary report of the structure of EPA-Br_2 (van der Helm *et al.*, 1974) the IUPAC nomenclature and numbering was required. The relationship of the common numbering scheme and the IUPAC numbering scheme is given in Table 1. Because the epoxide ring was involved in the addition reaction the stereochemistry of atoms C(12) and C(13) in EPA could not be determined. For this reason the structural investigation of the natural product, EPA itself, was undertaken.

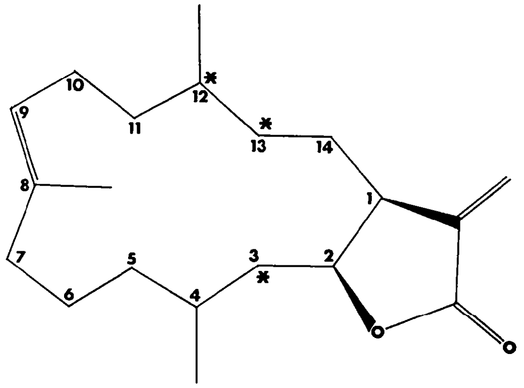
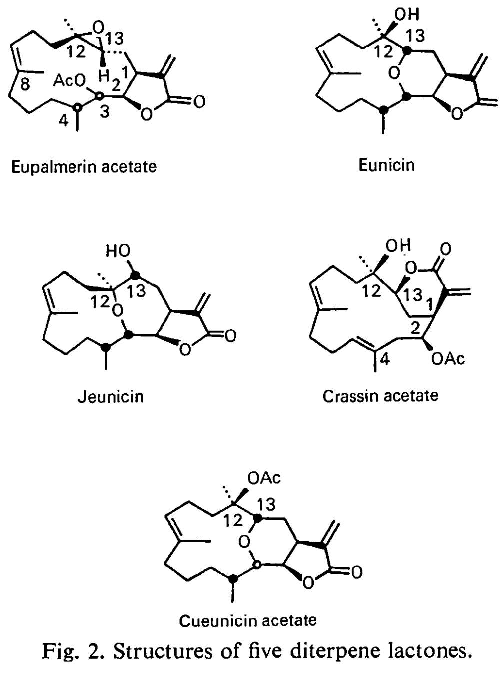


Fig. 1. General structure for a group of diterpene lactones isolated from gorgonians. Asterisks indicate possible sites for oxidation.



Eupalmerin acetate

Eunicin

Jeunicin

Crassin acetate

Cueunicin acetate

Fig. 2. Structures of five diterpene lactones.

Table 1. *Relationship of the two numbering schemes for* EPA-Br_2

This publication	IUPAC	This publication	IUPAC
Br(1)	Br(2)	C(14)	C(4)
Br(2)	Br(1)	C(15)	C(21)
C(1)	C(3a)	C(16)	C(20)
C(2)	C(15a)	C(17)	C(22)
C(3)	C(15)	C(18)	C(17)
C(4)	C(14)	C(19)	C(15)
C(5)	C(13)	C(20)	C(16)
C(6)	C(12)	C(21)	C(18)
C(7)	C(11)	C(22)	C(19)
C(8)	C(10)	O(1)	O(1)
C(9)	C(9)	O(2)	O(24)
C(10)	C(8)	O(3)	O(23)
C(11)	C(7)	O(4)	O(22)
C(12)	C(6)	O(5)	O(25)
C(13)	C(5)		

Experimental

The bromine addition product of EPA was prepared by treating EPA with one molar equivalent of bromine in CCl_4 solution at 0°, followed by chromatographic purification (Florisil, benzene). It was recrystallized from benzene/hexane, m.p. 184–185·5°, and was shown to possess the molecular formula expected for the adduct, $C_{22}H_{32}O_5Br_2$, by elemental analysis and mass spectrometry. After the solution of the structure it was discovered that formation of the addition product had involved transannular participation of the epoxide function and not simply addition to the isolated double bond.

Purified EPA-Br_2 was dissolved in benzene and slowly cooled. Large colorless crystals of suitable quality for a diffraction experiment were obtained. During preliminary investigation of the crystals it was found that the crystals decomposed rapidly in an X-ray beam. For this reason data were collected at low temperature where no significant decomposition was observed. Crystallographic data (Table 2) and integrated X-ray intensity data were collected at $-110\,^{\circ}\mathrm{C}$ using a Nonius CAD-4 automatic diffractometer and a Nonius low-temperature apparatus.

Table 2. *Crystallographic data for* EPA-$\mathrm{Br_2}$

Formula $\mathrm{C_{22}H_{32}O_5Br_2}$	F.W. 536·30
Systematic absences $h00$, $h=2n+1$	
$0k0$, $k=2n+1$	
$00l$, $l=2n+1$	
Space group $P2_12_12_1$	$Z=4$
$T=25\,^{\circ}\mathrm{C}$	$T=-110\,^{\circ}\mathrm{C}$
$a=13{\cdot}0971$ (7) Å	$a=12{\cdot}967$ (2) Å
$b=16{\cdot}603$ (1)	$b=16{\cdot}392$ (2)
$c=10{\cdot}6758$ (3)	$c=10{\cdot}5605$ (8)

(determined by least-squares fit to the $+2\theta$ and -2θ values of 32 reflections)

$V=2321{\cdot}5$ Å^3	$V=2244{\cdot}7$ Å^3
$D_c=1{\cdot}534$ g cm^{-3}	$D_c=1{\cdot}587$ g cm^{-3}
$D_o=1{\cdot}537$ g cm^{-3}	

(measured by flotation in $\mathrm{CCl_4/C_6H_{14}}$)

$F(000)=1096$

The 2184 data, comprising all unique reflections with $2\theta<144^{\circ}$, were measured using Cu $K\alpha$ radiation ($\lambda=1{\cdot}5418$ Å) and θ–2θ scans. The θ scan width was calculated as $1{\cdot}0+0{\cdot}1\tan\theta$. The maximum scan time was 90 s with $\frac{2}{3}$ of the time used in scanning the peak and $\frac{1}{6}$ of the time used in scanning each the high and low-θ backgrounds. Four different crystals were used in the collection of data because of difficulties with adhesives and formation of ice. Through our experience we have found that any epoxy glue serves as an adequate low-temperature adhesive. There were 19 reflections which could not be distinguished from the background on the basis that the net count was less than $1{\cdot}4\sigma(I)$. These reflections were assigned intensities equal to the square root of the total count for the purpose of least-squares refinement. The observed intensities were corrected for Lorentz and polarization factors and for absorption ($\mu=53{\cdot}4$ cm^{-1}). For the absorption corrections the program uses the numerical integration method of Gauss and in this case eight sampling points were used along each axis (Coppens, Leiserowitz & Rabinovich, 1965).

For the crystallization of EPA a purified sample was dissolved in benzene and a few drops of hexane were added to aid crystallization. Block-like, colorless crystals were obtained which were suitable for data collection. Preliminary photographs indicated high thermal motion and for this reason data were collected at low temperature. Crystallographic data (Table 3) and integrated X-ray intensities were collected at $-110\,^{\circ}\mathrm{C}$. The 2433 reflections, comprising all unique data with $2\theta<150^{\circ}$ were measured using Cu $K\alpha$ radiation ($\lambda=1{\cdot}5418$ Å) and θ–2θ scans. The scan widths and scan times were calculated in the same way as for EPA-$\mathrm{Br_2}$. In total, 128 reflections were measured with a net intensity less than $1{\cdot}4\sigma(I)$ and were assigned intensities equal to the square root of the total count. The observed intensities were corrected for Lorentz and polarization effects and absorption ($\mu=6{\cdot}86$ cm^{-1}).

Table 3. *Crystallographic data for* EPA

Formula $\mathrm{C_{22}H_{32}O_5}$	F.W. 376·48
Systematic absences	$h00$, $h=2n+1$
	$0k0$, $k=2n+1$
	$00l$, $l=2n+1$
Space group $P2_12_12_1$	$Z=4$
$T=25\,^{\circ}\mathrm{C}$	$T=-110\,^{\circ}\mathrm{C}$
$a=10{\cdot}834$ (2) Å	$a=10{\cdot}694$ (6) Å
$b=19{\cdot}041$ (2)	$b=18{\cdot}842$ (7)
$c=10{\cdot}4237$ (8)	$c=10{\cdot}321$ (4)

(determined by least-squares fit to the $+2\theta$ and -2θ values of 52 and 44 reflections, respectively)

$V=2150{\cdot}3$ Å^3	$V=2079{\cdot}6$ Å^3
$D_c=1{\cdot}163$ g cm^{-3}	$D_c=1{\cdot}202$ g cm^{-3}
$D_o=1{\cdot}166$ g cm^{-3}	

(measured by flotation in $\mathrm{CCl_4/C_6H_{14}}$)

$F(000)=816$

Structure determination and refinement

The positions of the two bromine atoms of EPA-$\mathrm{Br_2}$ were located from the three Harker sections of a sharpened Patterson map. The bromine atoms were given anisotropic temperature factors and after several cycles of least-squares refinement the R $(\sum||kF_o|-|F_c||/\sum|kF_o|)$ was 0·27. A difference Fourier map was calculated from which the positions of all 27 carbon and oxygen atoms were located. The five oxygen atoms were identified as the five largest peaks in the difference Fourier. After several more cycles of refinement a difference Fourier map was calculated which indicated that anisotropic effects for carbon and oxygen atoms were not significant. In addition all but three hydrogen atom positions were clearly defined. The absolute configuration was determined using the method of Bijvoet, Peerdeman & van Bommel (1951). The observed values of I_{hkl} and $I_{\bar{h}\bar{k}\bar{l}}$ were compared with calculated values of F^2_{hkl} and $F^2_{\bar{h}\bar{k}\bar{l}}$ for 24 pairs of enantiomorph-sensitive reflections. All 24 pairs indicated the absolute configuration reported. At this point the observed structure factors were corrected for anomalous dispersion of bromine (Patterson, 1963). A subsequent difference Fourier calculation revealed the positions of the remaining three hydrogen atoms. Least-squares refinement of the bromine atoms using anisotropic temperature factors, and carbon, oxygen and hydrogen atoms using isotropic temperature factors, was terminated when all shifts for non-hydrogen atoms were less than $\frac{2}{5}$ the corresponding standard deviation. A difference Fourier map based on the final parameters showed a large amount of detail. Several peaks between 0·2 and 0·3 e Å^{-3} which seemed to be associated with the areas of bonding electrons were observed. Two peaks of about 0·5 e Å^{-3} associated with each bromine atom were the most significant features. The peaks were located at a distance of about 1·0 Å from the bromine atoms. The unweighted R value based on the final parameters (van der Helm *et al.*, 1974) is 0·023 for all data.

The structure of EPA was solved by direct methods using the program *MULTAN* (Germain, Main & Wolfson, 1971). The phases for 284 normalized structure factors greater than 1·5 were used in generating and *E* map. Reflections in the starting set were 1,14,0, 081, 870, 051, 1,20,0, 508 and 521. The first three reflections were used to define the origin with the fourth reflection being used as the enantiomorph-defining reflection. The *E* map calculated from one of four sets of phases showing high figures of merit (1·18–1·19) and similar residuals (27·7–27·8) revealed the position of all 27 carbon and oxygen atoms. The other three *E* maps were not investigated. The five highest peaks in the *E* map were consistent with the expected locations of the five oxygen atoms. The initial structure-factor calculation resulted in an *R* of 0·34. After several cycles of least-squares refinement all carbon and oxygen atoms were given anisotropic temperature factors. After several more cycles the *R* was 0·10 and had appeared to converge. A difference Fourier map was then calculated from which the position of all hydrogen atoms were located. Least-squares refinement of the non-hydrogen atoms using anisotropic temperature factors, and hydrogen atoms using isotropic temperature factors, was terminated when all shifts for the non-hydrogen atoms were less than $\frac{3}{5}$ of the corresponding standard deviation. A final difference Fourier map was calculated in which all electron densities were between −0·20 and 0·20 e Å^{-3}. The unweighted *R* based on final parameters (Tables 4, 5 and 6) is 0·033 for all data.

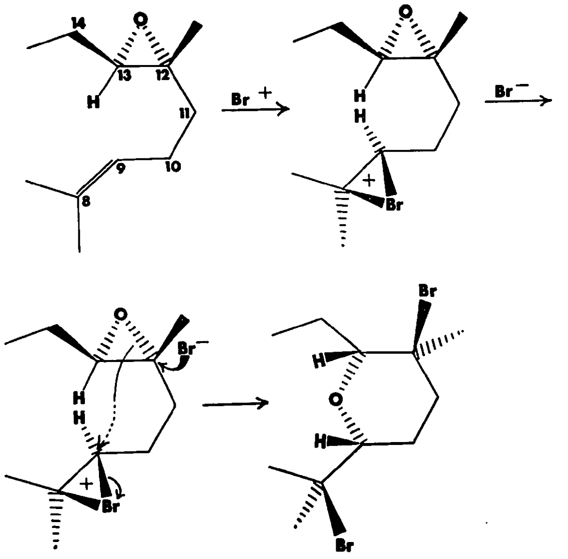


Fig. 3. Proposed reaction mechanism for the conversion of EPA to EPA-Br$_2$.

All least-squares refinements for both EPA and EPA-Br$_2$ were carried out using the block-diagonal least-squares program of Ahmed (1966). The atomic scattering factors for Br, O and C atoms and the anomalous scattering factors for Br atoms were taken from *International Tables for X-ray Crystallography* (1962). The scattering factors for hydrogen atoms were those of Stewart, Davidson & Simpson (1965). A weighting scheme was used for each compound which assigns an experimental weight, W_F, to each structure factor as defined below:

$$W_F=\frac{1}{\sigma_F^2},$$

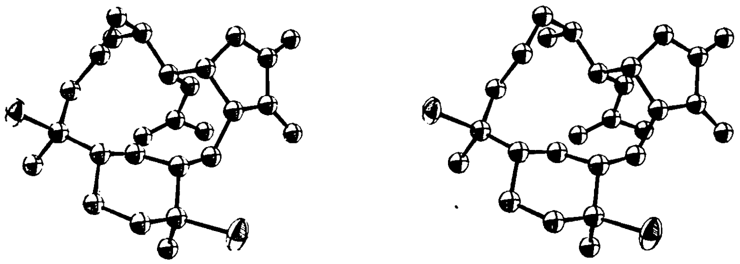


Fig. 4. Stereo view of a single molecule of EPA-Br$_2$ (Johnson, 1965).

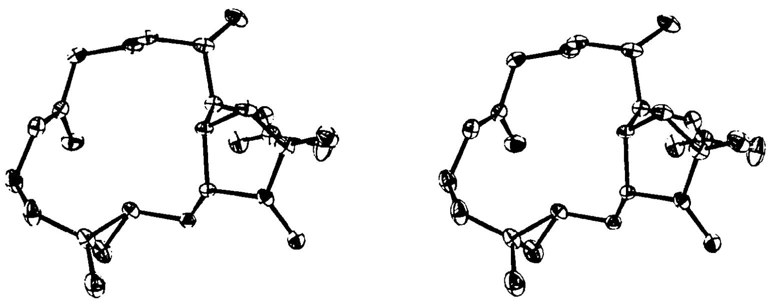


Fig. 5. Stereo view of a single molecule of EPA (Johnson, 1965).

Table 4. *Positional parameters of carbon and oxygen atoms for* EPA

Calculated standard deviations for the last digit are listed in parentheses.

	x	y	z
C(1)	0·5483 (2)	0·47367 (8)	0·3730 (2)
C(2)	0·5603 (2)	0·39728 (8)	0·4265 (2)
C(3)	0·5496 (2)	0·33697 (8)	0·3286 (2)
C(4)	0·5764 (2)	0·26438 (9)	0·3922 (2)
C(5)	0·7191 (2)	0·25226 (9)	0·3885 (2)
C(6)	0·7700 (2)	0·22879 (8)	0·2566 (2)
C(7)	0·9122 (2)	0·24153 (9)	0·2436 (2)
C(8)	0·9446 (2)	0·31687 (9)	0·2060 (2)
C(9)	0·9836 (2)	0·36500 (10)	0·2919 (2)
C(10)	1·0280 (2)	0·43900 (10)	0·2648 (2)
C(11)	0·9620 (2)	0·49976 (10)	0·3379 (2)
C(12)	0·8371 (2)	0·52496 (9)	0·2859 (2)
C(13)	0·7433 (2)	0·47445 (8)	0·2381 (2)
C(14)	0·6040 (2)	0·48796 (8)	0·2391 (2)
C(15)	0·4107 (2)	0·48751 (8)	0·3885 (2)
C(16)	0·3653 (2)	0·43772 (9)	0·4900 (2)
C(17)	0·3369 (2)	0·53341 (9)	0·3283 (2)
C(18)	0·5035 (2)	0·20309 (10)	0·3311 (2)
C(19)	0·9305 (2)	0·33180 (10)	0·0636 (2)
C(20)	0·8004 (2)	0·59731 (11)	0·3354 (3)
C(21)	0·4137 (2)	0·33774 (9)	0·1445 (2)
C(22)	0·2797 (2)	0·34542 (14)	0·1043 (2)
O(1)	0·4576 (1)	0·39090 (6)	0·5190 (1)
O(2)	0·4242 (1)	0·34068 (6)	0·2752 (1)
O(3)	0·8171 (1)	0·51500 (8)	0·1474 (1)
O(4)	0·2653 (1)	0·43643 (7)	0·5436 (2)
O(5)	0·5004 (1)	0·33169 (8)	0·0722 (1)

Table 5. *Anisotropic temperature factors for carbon and oxygen atoms*

Temperature factors are of the form $\exp[-(b_{11}h^2+b_{22}k^2+b_{33}l^2+b_{12}hk+b_{13}hl+b_{23}kl)]$. The parameters and standard deviations are multiplied by 10^4.

	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	31 (1)	8·1 (4)	26 (1)	0 (1)	0 (2)	3 (1)
C(2)	36 (1)	8·3 (4)	28 (1)	0 (1)	7 (2)	4 (1)
C(3)	38 (1)	9·3 (4)	28 (1)	0 (1)	3 (2)	−3 (1)
C(4)	57 (2)	8·0 (4)	33 (2)	−1 (1)	22 (3)	1 (1)
C(5)	59 (2)	8·5 (4)	34 (2)	8 (1)	1 (3)	3 (1)
C(6)	50 (2)	8·3 (4)	40 (2)	2 (1)	7 (3)	−5 (1)
C(7)	45 (1)	10·7 (4)	42 (2)	11 (1)	−7 (3)	3 (1)
C(8)	33 (1)	12·2 (4)	38 (2)	6 (1)	−8 (2)	−2 (1)
C(9)	34 (1)	15·2 (5)	45 (2)	3 (1)	−8 (3)	−10 (2)
C(10)	36 (1)	14·4 (5)	74 (2)	−5 (1)	14 (3)	−26 (2)
C(11)	34 (1)	16·4 (5)	75 (2)	−4 (1)	1 (3)	−34 (2)
C(12)	36 (1)	12·8 (4)	44 (2)	−12 (1)	21 (3)	−13 (1)
C(13)	35 (1)	10·6 (4)	34 (1)	−6 (1)	9 (2)	−2 (1)
C(14)	34 (1)	8·9 (4)	29 (1)	−3 (1)	−4 (2)	6 (1)
C(15)	33 (1)	8·4 (4)	35 (1)	−6 (1)	8 (2)	−9 (1)
C(16)	46 (1)	10·5 (4)	36 (2)	−4 (1)	16 (3)	−10 (1)
C(17)	34 (1)	11·9 (4)	60 (2)	−3 (1)	−4 (3)	1 (2)
C(18)	68 (2)	9·6 (5)	59 (2)	−12 (2)	40 (3)	−8 (2)
C(19)	72 (2)	13·9 (5)	41 (2)	−6 (2)	−15 (3)	2 (2)
C(20)	44 (2)	13·9 (5)	114 (3)	−5 (2)	5 (4)	−35 (2)
C(21)	48 (1)	13·1 (4)	40 (2)	−2 (1)	−5 (3)	−15 (1)
C(22)	50 (2)	32·8 (8)	63 (2)	14 (2)	−21 (3)	−32 (2)
O(1)	54 (1)	9·4 (3)	29 (1)	−1 (1)	25 (2)	1 (1)
O(2)	37 (1)	12·9 (3)	36 (1)	−2 (1)	8 (2)	−11 (1)
O(3)	47 (1)	20·5 (4)	42 (1)	−14 (1)	34 (2)	2 (1)
O(4)	54 (1)	16·1 (4)	64 (1)	−4 (1)	56 (2)	−3 (1)
O(5)	52 (1)	21·0 (4)	37 (1)	−8 (1)	10 (2)	−13 (1)

Table 6. *Positional parameters and isotropic temperature factors for the hydrogen atoms*

Standard deviations in the last digits are given in parentheses

	x	y	z	B (Å^2)
H(C1)	0·591(2)	0·504 (1)	0·437 (2)	1·3 (4)
H(C2)	0·635 (2)	0·389 (1)	0·473 (2)	0·9 (3)
H(C3)	0·608 (2)	0·344 (1)	0·254 (2)	0·9 (3)
H(C4)	0·544 (2)	0·268 (1)	0·493 (2)	2·1 (4)
H(C5)*A*	0·743 (2)	0·216 (1)	0·455 (2)	2·6 (5)
H(C5)*B*	0·763 (2)	0·295 (1)	0·412 (2)	2·2 (4)
H(C6)*A*	0·725 (2)	0·254 (1)	0·186 (2)	1·8 (4)
H(C6)*B*	0·754 (2)	0·176 (1)	0·248 (2)	2·6 (5)
H(C7)*A*	0·945 (2)	0·208 (1)	0·173 (2)	2·5 (5)
H(C7)*B*	0·956 (2)	0·230 (1)	0·331 (2)	2·6 (5)
H(C9)	0·994 (2)	0·350 (1)	0·388 (2)	2·4 (5)
H(C10)*A*	1·118 (2)	0·443 (1)	0·286 (3)	3·1 (5)
H(C10)*B*	1·025 (2)	0·449 (1)	0·172 (2)	2·0 (4)
H(C11)*A*	0·948 (3)	0·488 (2)	0·429 (3)	4·8 (7)
H(C11)*B*	1·020 (2)	0·543 (1)	0·334 (3)	3·5 (6)
H(C13)	0·764 (2)	0·422 (1)	0·240 (2)	3·0 (5)
H(C14)*A*	0·590 (2)	0·537 (1)	0·214 (2)	1·3 (4)
H(C14)*B*	0·564 (2)	0·459 (1)	0·170 (2)	2·0 (4)
H(C17)*A*	0·249 (2)	0·534 (1)	0·354 (2)	1·8 (4)
H(C17)*B*	0·366 (2)	0·566 (1)	0·259 (2)	2·3 (5)
H(C18)*A*	0·931 (3)	0·383 (1)	0·044 (3)	4·8 (7)
H(C18)*B*	0·847 (3)	0·313 (2)	0·033 (3)	4·4 (6)
H(C18)*C*	0·997 (3)	0·307 (2)	0·020 (3)	4·7 (7)
H(C19)*A*	0·520 (2)	0·199 (1)	0·237 (2)	2·4 (5)
H(C19)*B*	0·530 (2)	0·158 (1)	0·374 (2)	2·9 (5)
H(C19)*C*	0·410 (2)	0·209 (1)	0·345 (2)	3·2 (5)
H(C20)*A*	0·806 (3)	0·596 (1)	0·434 (3)	4·4 (6)
H(C20)*B*	0·715 (2)	0·615 (1)	0·306 (3)	3·5 (6)
H(C20)*C*	0·859 (3)	0·633 (2)	0·309 (3)	4·8 (7)
H(C22)*A*	0·227 (2)	0·321 (1)	0·159 (3)	3·7 (6)
H(C22)*B*	0·256 (3)	0·397 (2)	0·104 (3)	5·0 (7)
H(C22)*C*	0·270 (3)	0·325 (1)	0·010 (3)	4·3 (6)

where

$$\sigma_F=\tfrac{1}{2}\left[\frac{\sigma^2+(CP)^2}{(P)\,(\mathrm{Lp})}\right]^{1/2},$$

in which $\sigma=\mathrm{T}^{1/2}v$, v=scan speed, $T=Pk+2(R+L)$, $P=[Pk-2(R+L)]v$, R=right background, L=left background, Lp=Lorentz and polarization corrections, C=0·05 for EPA and 0·02 for EPA-Br$_2$.

In the structure-factor analysis for both EPA and EPA-Br$_2$ the average values of $W_F\Delta F^2$ did not show a significant variation with either F_o or $\sin\theta/\lambda$, indicating that the weighting scheme used was reasonable.*

Determination of the absolute configuration of EPA

Because of the close agreement of observed and calculated structure factors in EPA, it was thought that it might be reasonable to attempt to determine the absolute configuration using the anomalous contribution of the oxygen atoms. In addition the results should

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* Lists of structure factors for EPA and EPA-Br$_2$ have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30905 (26 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

be consistent with the absolute configuration of EPA-Br_2, thus providing a test of our procedure. Already there are a number of examples in the literature in which absolute configurations of light-atom structures have been determined (*e.g.* Hope & De la Camp, 1969; Thiessen & Hope, 1970; Wetherington, Ament & Moncrief, 1974). In addition Engel (1972) has published an analysis of the determination of the absolute configuration of seven light-atom compounds in which he concluded that the 'Bijvoet method' was more effective than the '*R* method'. The Bijvoet method involves measurement of Bijvoet differences while the *R* method is a variation of the Hamilton (1965) *R* test in which the *R* comparisons are restricted to a set of enantiomer-sensitive reflections.

With this as background we chose to use the Bijvoet method with 15 pairs of reflections. Our goal then was to select the 15 reflections most sensitive to the choice of enantiomer. We chose to do this by selecting the reflections for which the absolute value of difference in the calculated values of F^2_+ and F^2_- was largest compared to the corresponding value $\sigma(F^2)$. That is we chose reflections for which the sensitivity factor $[SF=|F^2_+-F^2_-|/(F^2_o)]$ was the largest. The values of F^2_+ and F^2_- are calculated according to the method of James (1948) and $\sigma(F^2_o)$ may be derived from the value of σ_F mentioned previously in which $\sigma(F^2_o)=2F_o\sigma_F$. Using this method we have chosen the reflections in which the difference to be observed is most likely to be significant compared with the standard deviation of the values to be measured. After the 15 enantiomorph-sensitive reflections were chosen the values of I_{hkl} and $I_{\bar{h}\bar{k}\bar{l}}$ were measured ten times each. The results are summarized in Table 7. Of the 15 pairs of reflections chosen, 11 indicated the absolute configuration derived from EPA-Br_2, one indicated the opposite configuration, and three pairs showed no difference in intensity. It may be important to point out that intuitively the value of ΔI compared with $\sigma(I)$ might appear to be of questionable significance. However, this is not the statistically important feature, which is the consistency of the measurements. Although each individual measurement is associated with a relatively low probability, the fact that 11 measurements indicate one absolute configuration, while only one measurement indicates the opposite configuration, allows one to accept one configuration and reject the other at a high probability. It might also be noted that the reflection which indicated the opposite configuration (634) has the smallest value of F^2_c of all the reflections measured. It is apparent that the use of the anomalous contribution of oxygen atoms in determining absolute configuration is limited by the inherent errors of the model from which F^2_+ and F^2_- are derived. We believe that our method of selection of enantiomer-sensitive reflections is reasonable and has the advantage of requiring very little computer time. The anomalous scattering factors used for the oxygen atoms were those of Cromer & Liberman (1970).

Table 7. *Comparison of observed and calculated Bijvoet differences*

The values are $\Delta I_o=I_{hkl}-I_{\bar{h}\bar{k}\bar{l}}$, $\Delta F^2_c=F^2_{hkl}-F^2_{\bar{h}\bar{k}\bar{l}}$, $\sigma(I_o)$ = internal estimation of the standard deviation of I_o and $\sigma(F^2_c)$ = external estimation of the standard deviation of F^2_c. The consistent agreement of observed and calculated differences indicates the configuration reported.

h	k	l	F^2_c	ΔI_o	$\sigma(I_o)$	$\frac{\Delta I_o}{I_o}$	ΔF^2_c	$\sigma(F^2_c)$	$\frac{\Delta F^2_c}{F^2_c}$
1	2	4	290	13·0	4·0	5 %	11·8	8·5	4 %
1	11	10	210	0·0	4·8	0	−7·8	7·3	−4
2	8	4	355	4·1	3·9	2	11·4	11·2	3
2	10	3	135	−0·2	2·7	−0	6·7	6·0	5
2	15	2	140	−1·3	2·3	−2	−5·8	5·7	−4
2	15	4	300	4·5	2·7	4	13·3	10·5	4
3	8	5	110	−1·7	2·5	−3	−7·1	4·6	−6
4	8	3	250	−1·2	3·9	−1	−8·3	8·4	−3
4	9	9	70	−0·1	2·7	−0	−3·5	3·4	−5
5	4	4	100	−1·4	2·7	−2	−4·0	4·1	−4
5	20	1	40	0·9	2·3	4	2·3	2·2	5
6	3	4	20	0·9	2·4	7	−2·8	2·5	−13
7	9	1	95	2·6	2·8	7	4·3	3·9	5
7	12	3	265	−2·3	3·3	−2	−10·0	8·7	−4
8	9	2	65	−2·5	1·7	−9	−5·5	3·8	−8

Description and discussion of the structures

As mentioned above, the conversion of EPA to EPA-Br_2 proceeded with participation of the epoxide oxygen in the addition to the double bond. The proposed reaction mechanism is shown in Fig. 3. The first step involves the formation of a bromonium ion intermediate. The stereochemistry of this intermediate is determined by the fold of the molecule with the configuration shown being favored. The second step involves the concerted attack by the epoxide oxygen on the bromonium ion, forming the ether bridge [C(9)–C(13)], and attack by the bromide ion at the epoxide function [C(12)]. This mechanism was proposed prior to the solution of the structure of EPA and is consistent with the observed stereochemistry of both reactant and product molecules.

Considering the relative positions of the epoxide and isolated double-bond functions, it is not surprising that the epoxide participated in the addition reaction. Such participation is not unprecedented, and reaction of the sensitive epoxide function with the proximate electrophilic bromonium ion intermediate in the addition reaction can be considered normal. Of interest is the fact that the participation reaction showed complete stereospecificity in both the intramolecular attack by oxygen at the bromonium ion, and attack by external bromide at the epoxide function. The configurations at C(8) and C(9), and C(12) and C(13) in the dibromide all reflect the occurrence of the mechanistically normal *trans* addition and ring opening at these sites. A slightly unusual feature of the reaction at the double bond is the attack by the nucleophilic oxygen at the secondary carbon atom [C(9)]. In additions to isolated double bonds, nucleophilic opening of the bromonium ion normally occurs by attack at the tertiary center. In this case, steric factors favor the formation of the sixmembered oxygen-containing ring rather than the seven-membered possibility.

A stereo view of a single molecule of EPA-Br_2 is shown in Fig. 4 and a stereo view of EPA in Fig. 5. The natural product, EPA, consists of a 14-membered, cembrane-type ring (Drew, Templeton & Zalkin, 1969). A γ-lactone is fused at carbons C(1) and C(2). The molecule contains an epoxide function [C(12)–C(13)] and an acetoxy group [C(3)]. The only double bond in the ring is C(8)–C(9) and its geometry with respect to the ring is *trans*. The conversion to EPA-Br_2 results in bromination at C(8) and C(13) and the loss of the double bond. The epoxide function is converted to an ether bridge [C(9)–C(13)]. All other chemical features of the molecules are identical. The most noticeable feature of both molecules is the relative flatness of the cembrane (saturated cembrene) rings.

The bond distances for EPA are shown in Fig. 6 and bond angles in Fig. 7. The bond distances and angles for EPA-Br_2 have been published in a preliminary publication (van der Helm *et al.*, 1974). For the purpose of comparison, bond distances for EPA and EPA-Br_2 have been listed in Table 8. There are several differences in bond distances which appear to be significant. Three of these distances are for carbon–carbon single bonds [C(3)–C(4), C(4)–C(5), C(6)–C(7)] in which case there is no chemical explanation for the differences (about four standard deviations based on EPA-Br_2) and may tend to indicate some underestimation of the standard deviations. A second group of distances where differences occur is as expected because they involve carbons C(8) and C(9) which are converted from sp^2 hybridized atoms in EPA to sp^3 hybridized atoms in EPA-Br_2. The final group of bond distances with differences are those associated with the epoxide

Table 8. *Comparison of bond distances for* EPA *and* EPA-Br_2

Standard deviations in the last digits are given in parentheses.

	EPA	EPA-Br_2
C(1)—C(2)	1·547 (2)	1·547 (6)
C(1)—C(14)	1·529 (2)	1·530 (6)
C(1)—C(15)	1·503 (2)	1·513 (5)
C(2)—O(1)	1·460 (2)	1·460 (4)
C(2)—C(3)	1·525 (2)	1·534 (5)
C(3)—O(2)	1·451 (2)	1·456 (4)
C(3)—C(4)	1·544 (3)	1·524 (5)
C(4)—C(5)	1·544 (3)	1·567 (5)
C(4)—C(18)	1·529 (3)	1·536 (5)
C(5)—C(6)	1·532 (3)	1·535 (5)
C(6)—C(7)	1·545 (3)	1·524 (5)
C(7)—C(8)	1·512 (3)	1·529 (5)
C(8)—C(9)	1·335 (3)	1·542 (5)
C(8)—C(19)	1·504 (3)	1·519 (6)
C(9)—C(10)	1·499 (3)	1·528 (6)
C(10)–C(11)	1·542 (3)	1·529 (6)
C(11)–C(12)	1·515 (3)	1·537 (5)
C(12)–C(13)	1·469 (2)	1·542 (6)
C(12)–C(20)	1·508 (3)	1·519 (6)
C(13)–O(3)	1·443 (2)	1·449 (4)
C(13)–C(14)	1·511 (2)	1·543 (5)
C(15)–C(16)	1·488 (2)	1·490 (6)
C(15)–C(17)	1·325 (3)	1·328 (5)
C(21)–O(2)	1·354 (2)	1·367 (5)
C(21)–O(5)	1·196 (2)	1·206 (5)
C(21)–C(22)	1·498 (3)	1·491 (5)

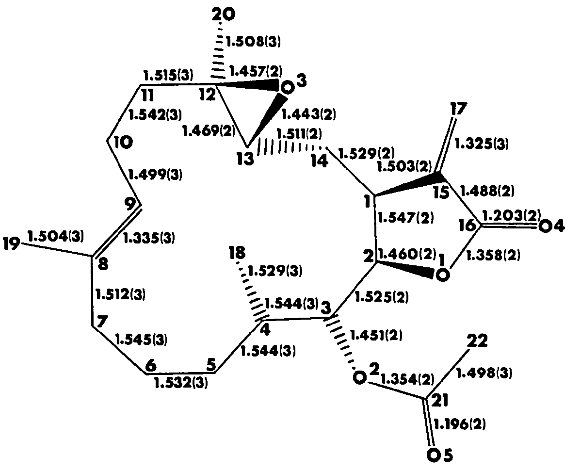

Fig. 6. Bond distances in EPA (Å).

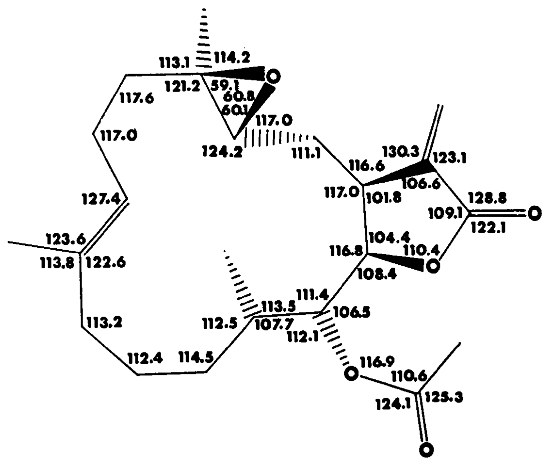

Fig. 7. Bond angles in EPA (°).

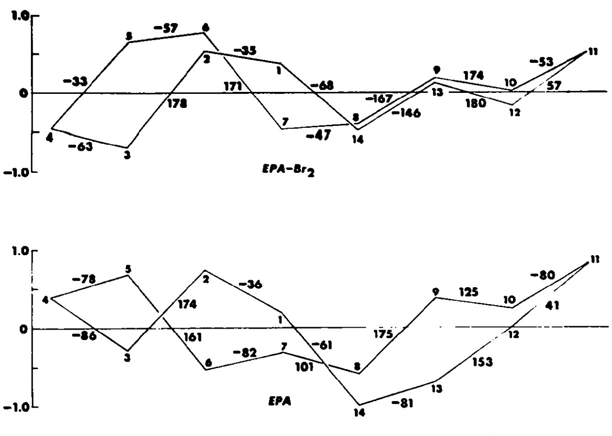

Fig. 8. Least-squares planes and torsion angles for 14-membered ring of EPA and EPA-Br_2.

function in EPA. The C(12)–C(13) bond in the epoxide ring is seen to be extremely short compared with the expected value for a bond between two sp^3 hybridized carbon atoms. In addition, bonds C(11)–C(12) and C(13)–C(14) show shortening as a result of being adjacent to the epoxide function. In EPA-Br_2 all three of these bond distances are observed as not being significantly different from the value expected for a carbon–carbon single bond.

The differences in bond angles of the two structures may serve as an approximation to the relative degree of ring strain. If the potential-energy function for deformation of a bond angle is assumed to be proportional to the difference in the observed angle and an equilibrium value for that angle, squared [*i.e.* $V(\theta)=k\Delta\theta^2$], then the sum of $\Delta\theta^2$ for the interior angles of the cembrane ring may be taken as an indication of ring strain. The equilibrium values for bond angles are taken to be 109·5° and 120° for angles subtended at an sp^3 and sp^2 carbon atom respectively. The values of $\sum\Delta\theta^2$ calculated for EPA and EPA-Br_2 are 50·2 deg^2 and 28·4 deg^2 respectively. This is expected, as the inclusion of a double bond and epoxide group in EPA will provide large contributions to ring strain.

Torsion angles in the cembrane rings along with the least-squares planes through the ring, are given in Fig. 8 for EPA and EPA-Br_2. The flatness of the cembrane ring for each molecule is easily seen as the maximum deviation of a ring atom for either molecule from the least-squares plane is less than 1·0 Å. The torsion angles serve as a further indication of the ring strain. An investigation of the angles shows a larger deviation from the minimum energy conformations (60, 180, 300°) in the case of EPA. Again the epoxide function is responsible for a large amount of the strain while the ether bridge C(9)–O(3)–C(13) plus atoms C(10), C(11) and C(12) in EPA-Br_2 form a relatively low-energy chair conformation.

At least some mention should be made of the intermolecular contacts in these structures. Neither EPA nor EPA-Br_2 contains active hydrogens (*i.e.* –O–H or –NH_2 groups) and no hydrogen bonding is anticipated. There are, however, several intermolecular contacts which are less than the sum of the van der Waals radii of the atoms involved. In EPA the distances H(C1)–O(3) and H(C4)–H(C7)*A* are 2·41 and 2·05 Å. In both cases the C–H bonds are directed generally towards the center of the contact such that systematic errors in the C–H bond length tends to increase the error in the intermolecular distance. In EPA-Br_2 intermolecular distances of 3·03 and 3·06 Å were observed for Br(2)–H(C19)*B* and Br(1)–H(C3) respectively. Although these intermolecular interactions observed in both EPA and EPA-Br_2 apparently provide little in stabilization energy it is interesting to note that the atoms involved in three of these are the epoxide oxygen, O(3), in EPA and the two bromine atoms of EPA-Br_2.

It is of interest to discuss the possible biogenetic relationship of the diterpene lactones isolated from gorgonians. There have been four such compounds isolated for which X-ray crystallographic analyses have been completed. They are EPA, eunicin (Hossain *et al.*, 1968), jeunicin (Enwall *et al.*, to be published) and crassin acetate (Hossain & van der Helm, 1969). Of these EPA, eunicin and jeunicin have the same general structural features (Fig. 2) while crassin acetate has a δ-lactone. In addition the stereochemistry of the lactone is identical for all three compounds containing γ-lactones.

Based upon the gross structure of EPA deduced by chemical methods (Rehm, 1971), and without the knowledge of stereochemical detail provided by this work, it was attractive to consider EPA as the direct biogenetic precursor of eunicin and jeunicin. The configuration of the oxygenated centers C(12) and C(13) in these two oxa-bridged compounds is compatible with their formation from a single *trans* epoxide function, such as is present in EPA. Attack at the epoxide at either C(12) or C(13) by the oxygen function at C(3) would establish the oxa-bridge from C(3) to C(13) (eunicin) or to C(12) (jeunicin). Stereospecific ring opening of the epoxide in each of these attacks, occurring with the mechanistically preferred inversion at the epoxide sites, would generate precisely the configurations which exist in eunicin and jeunicin. However, EPA cannot be the precursor of the other two cembranolides because it possesses the opposite configurations at both C(3) and C(4).

Nevertheless, this speculation appears reasonable, and suggests that there remains to be found in the *Eunicea* gorgonians an 'iso' EPA which will indeed possess configurations at C(3) and C(4) corresponding to those in eunicin and jeunicin. It further suggests that an 'iso' eunicin and an 'iso' jeunicin remain to be found, in which the configurations at C(3) and C(4) are common with those present in EPA.

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Hydroxyguanidinium Sulphate Monohydrate

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$2[CH_6N_3O]^+[SO_4]^{2-}.H_2O$, $M=266{\cdot}24$, monoclinic, $P2_1/c$, $a=6{\cdot}284$ (2), $b=12{\cdot}042$ (2), $c=14{\cdot}94$ (2) Å, $\beta=110{\cdot}38$ (4)°, $Z=4$, D_m(flotation) $=1{\cdot}66$, $D_x=1{\cdot}67$ g cm^{-3}. The dimensions of the two crystallographically non-equivalent hydroxyguanidium ions are almost identical. The ions are not quite planar and are linked to the sulphate ions and the water molecules by a network of hydrogen bonds.

X-ray intensities were collected on a Nonius three-circle automatic diffractometer by the moving-crystal stationary-detector technique, with graphite-monochromatized Mo $K\alpha$ radiation ($\lambda=0{\cdot}71069$ Å), scan range 1·2°, and scan speed 1·2° min^{-1} in the θ range 2·5–25°. Single crystals of hydroxyguanidium sulphate monohydrate (Eastman) were obtained by recrystallization from aqueous ethanol. The crystal chosen for data collection (0·2 × 0·3 × 0·4 mm) was mounted in a glass capillary and oriented with **c** parallel to the φ axis of the goniostat. 1873 independent reflexions were measured; 1530 with $I>2{\cdot}5\sigma(I)$ were used in the analysis. μ(Mo $K\alpha$) is 3·5 cm^{-1} and no absorption correction was applied.

The structure was solved by the heavy-atom method. Full-matrix least-squares refinement of the parameters of the non-hydrogen atoms resulted in $R=0{\cdot}057$, and a subsequent difference map revealed the 14 H atoms. Further least-squares refinement of positional parameters for all atoms and anisotropic temperature parameters for the non-hydrogen atoms led to a final R of 0·035. The quantity minimized was $\sum w(|F_o|-|F_c|)^2$ with the weighting scheme $w=1{\cdot}0/\{1+[(F_o-B)/A]^2\}$, where $A=13{\cdot}0$ and $B=15{\cdot}0$. Scattering factors were taken from *International Tables for X-ray Crystallography* (1962). The final values of atomic positions and temperature parameters are listed in Table 1.* The programs used in the refinement were the X-RAY System (Stewart, Kundell & Baldwin, 1972) and the figures were drawn with *ORTEP* (Johnson, 1965).

Discussion

Hydroxyguanidine, $H_2NC{:}NHNHOH$, was found to be an inhibitor of DNA synthesis (HeLa cells) of the same inhibitory potency as that of hydroxyurea and some other hydroxamic acid derivatives (Young, Schochetman, Hodas & Balis, 1967). Hill & Gordon (1968) pointed out the possible importance of the pK_a values for the inhibitory action of such compounds. Recently hydroxyguanidine was reported to be an antitumour drug because of antiviral as well as cytotoxic effects (Adamson, 1972). A structure determination of the compound, as the sulphate monohydrate, was undertaken as part of a series of structure determinations of this type of inhibitor (Larsen, 1974). It is the

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30894 (30 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.