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THE CRYSTAL AND MOLECULAR STRUCTURE OF THE EPOXYBROMO DERIVATIVE OF ATRACTYLIGENIN.

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Abstract—The complete configuration of atractyligenin has been obtained by a three-dimensional single-crystal X-ray diffraction study. Previous structural work has been confirmed, in particular the configuration of the epoxy group.

The space group is *C*2, with four molecules in the cell, $a = 19{\cdot}005$, $b = 7{\cdot}165$, $c = 14{\cdot}450$ Å, $\beta = 108°\ 31'$, and the final *R* is 0·125 for 1320 observed reflections.

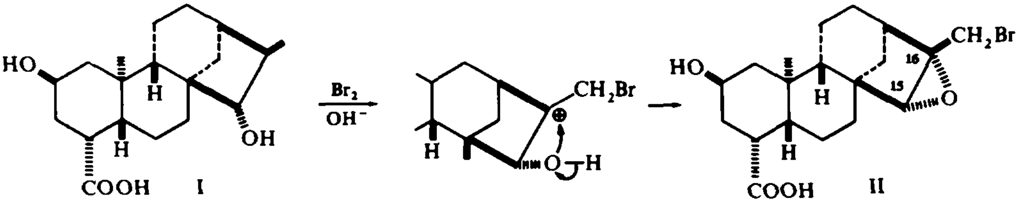
The stress in the molecule (as indicated by the torsional angles) and the molecular packing are discussed.

INTRODUCTION

Previous work has been published[1–4] on atractyligenin $C_{19}H_{28}O_4$ (I), the aglycone of atractyloside $C_{30}H_{44}O_{16}S_2K_2$:[5] this toxic glucoside has been found of considerable interest to biochemists in the last decade.

During the structural work on atractyligenin, a $C_{19}H_{27}O_4Br$ was obtained[1] and assigned the structure (II)[3,4] of 2β-hydroxy-17-bromo-15α,16α-epoxy-19-carboxy-18-nor-*ent*-kaurane[6] (epoxybromoatractyligenin).

A plausible mechanism of formation of (II) by bromine treatment of (I) in alkaline solution is reported here: it should afford a 15α,16α-epoxybridge, but this configuration was inferred and not demonstrated.



Epoxybromoatractyligenin was selected for an X-ray study aiming to elucidate the complete configuration of atractyligenin. However, the configurations of atractyligenin and hence of epoxybromoatractyligenin were confirmed in the meantime by chemical methods[7] as (I) and (II) respectively, apart from the configuration of the epoxybridge in (II).

The present work confirms by X-ray analysis the proposed structure (II) for epoxybromoatractyligenin, having the 15α,16α-epoxybridge.

EXPERIMENTAL

Epoxybromoatractyligenin, $C_{19}H_{27}O_4Br$, M.W. 399·1, m.p. 199–200°. The crystals were prepared[4] and recrystallized from EtOH. Monoclinic, tabular, pinacoidal {100}; $a = 19{\cdot}005 \pm 0{\cdot}008$, $b = 7{\cdot}165 \pm 0{\cdot}005$, $c = 14{\cdot}150 \pm 0{\cdot}014$ Å, $\beta = 108°\ 31' \pm 7'$, $V = 1873$ Å^3, $D_{calc} = 1{\cdot}34$ g.cm^{-3}, $Z = 4$, Cu-*K* radiation. Cell

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dimensions calculated from the $\alpha_1\alpha_2$-separation on *hk0* and *h0l* Weissenberg photographs.[8,9] Space group *C*2, from absences, and the optical activity of this and related compounds.

Intensity data were collected from an approximately cylindrical crystal, rotating about the *b* axis (layers 0–6). Spots from multiple-film packs were measured by a Nonius Mark 1 densitometer, corrected for splitting[9] and deformation,[10] and scaled later against calculated structure factors.

The "X-ray 63" system[11] was used for all calculations, but the least-squares population analysis was run in Cambridge (UK) with a program written by A. Larson for the IBM 360/44 (GENLES).

STRUCTURE DETERMINATION

A brief account of the difficulties encountered in the initial steps, subsequent to the positioning of the Br, has been published elsewhere.[12] The pseudosymmetry caused by the Br was overcome by a trial-and-error method, which produced most of the molecule in three cycles of structure factor–Fourier calculation, with an agreement factor of 0·28.

Although rings B, C and D were clearly defined, the carboxy group and adjacent atoms were not resolved in the Fourier maps. Pseudosymmetry was in fact still present at this stage, and it was realized later that the poor resolution for ring A and its substituents was caused by the fact that the flat C–COOH group intersects the false mirror plane at an angle of 90°.

A least-squares refinement of the population factor of four sites, believed to be C5, C6, C7 and C10, and of seven more sites, non chemically bonded, was carried out for three cycles; then ring A appeared in the electron-density maps and two out of four peaks, previously considered as good, faded out. For example, a peak, believed to be C7, was fortuitously closing ring B in a reasonable way, but the population refinement revealed that the false-symmetry related position, $\frac{1}{2}-x$, $\frac{1}{2}-y$, $-z$, was in fact the "true" one.

The possibility of solvent being present in the crystal cell was also considered. After the whole molecule was found, six more peaks were assigned a population factor of 1, but this dropped to zero or a negative value for all peaks in the first least-squares cycle.

Table 1 Atomic parameters

Atom	x	y	z	B or β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br	0·1075	0·0024	0·0694	0·0017	0·0127	0·0069	−0·0042	0·0007	−0·0041
C1	0·5410	0·3239	0·3566	2·16					
C2	0·6268	0·3109	0·4084	1·81					
C3	0·6739	0·2576	0·3449	2·12					
C4	0·6438	0·0791	0·2878	1·45					
C5	0·5584	0·0919	0·2390	1·22					
C6	0·5275	−0·0606	0·1655	1·95					
C7	0·4501	−0·0130	0·0939	2·09					
C8	0·3947	0·0396	0·1519	1·26					
C9	0·4301	0·1829	0·2370	1·63					
C10	0·5108	0·1403	0·3008	1·91					
C11	0·3713	0·2126	0·2916	2·23					
C12	0·3216	0·0458	0·3008	1·99					
C13	0·2937	−0·0729	0·2066	2·60					
C14	0·3672	−0·1354	0·1881	1·74					
C15	0·3252	0·1306	0·0910	2·32					
C16	0·2633	0·0604	0·1212	1·53					
C17	0·1953	0·1612	0·1107	1·82					
C19	0·6658	−0·0895	0·3583	2·05					
C20	0·5115	−0·0158	0·3775	0·0020	0·0025	0·0033	0·0015	−0·0002	−0·0046
O·21	0·6475	0·4937	0·4514	0·0030	0·0012	0·0041	0·0001	−0·0021	0·0003
O·22	0·7082	−0·0814	0·4395	0·0027	0·0036	0·0054	0·0002	−0·0041	0·0052
O·23	0·6386	−0·2550	0·3201	0·0028	0·0011	0·0037	0·0002	−0·0016	0·0004
O·24	0·2711	−0·0102	0·0322	2·14					

Six further cycles of full-matrix least-squares refinement brought the R factor down to 0·125. During the third, Br was assigned an anisotropic temperature factor, and during the fifth C20, O21, O22 and O23 were also refined anisotropically, as they had higher values of B (more than 3 Å^2 against a homogeneous average of 1·9 Å^2). It is worth noticing that these atoms are the ones external to the nucleus of the diterpenoid.

The final coordinates (Table 1) were used to calculate a difference Fourier; no clear indication for hydrogen positions was found, so the analysis was stopped. Distances and angles are reported in Fig 1 and torsional angles in the rings in Fig 2.*

DISCUSSION

To the authors' knowledge no structural work on similar substances has been published and, unfortunately, data on (+)-cedrol are not available.[13]

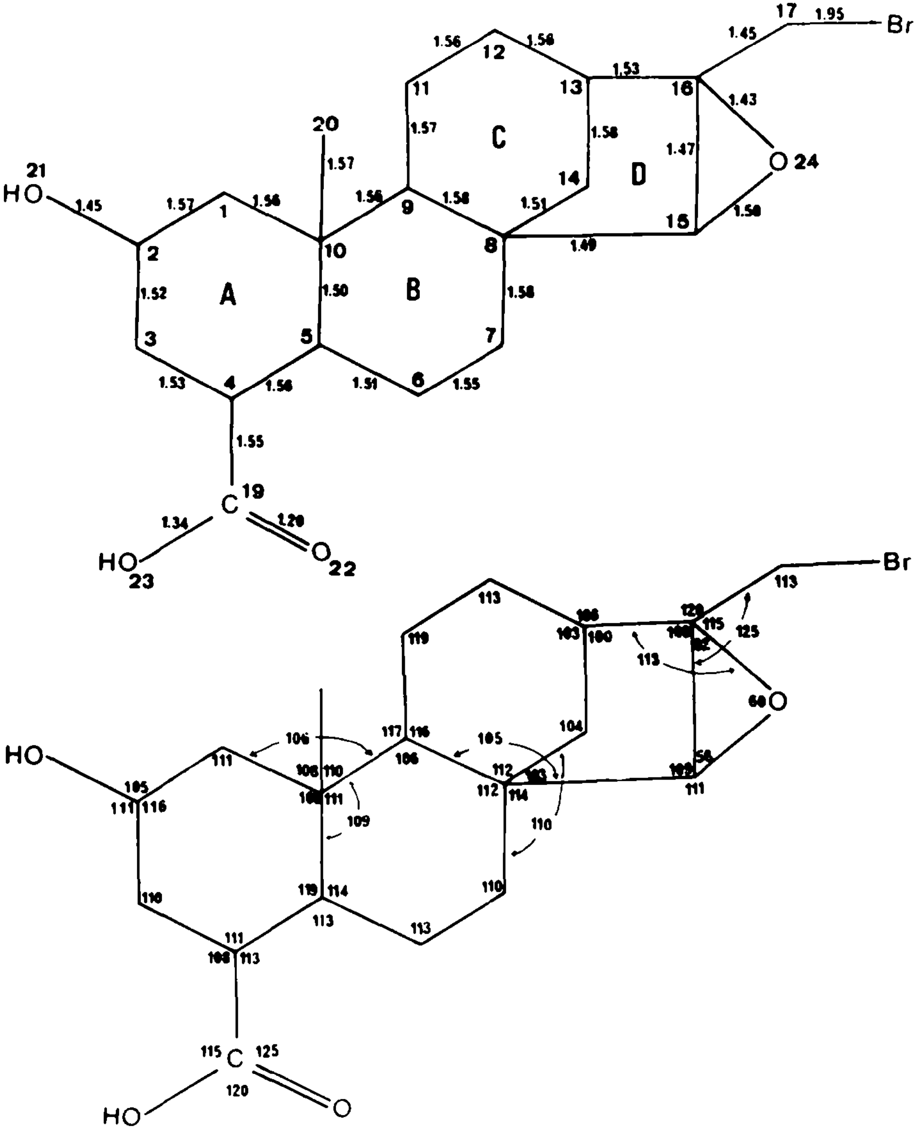

Fig 1. Bond distances and angles[6] with ring identification.

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* A list of observed and calculated structure factors is available from the second author on request.

Distances and angles are regular within the standard deviations, which were evaluated as $\langle\sigma_{\text{bond}}\rangle$ = 0·035 Å with a maximum of 0·044 Å for the C2—C3 bond, and $\langle\sigma_{\text{angle}}\rangle$ = 2·1° with a maximum of 2·5° for the C13–C16–C17 angle.

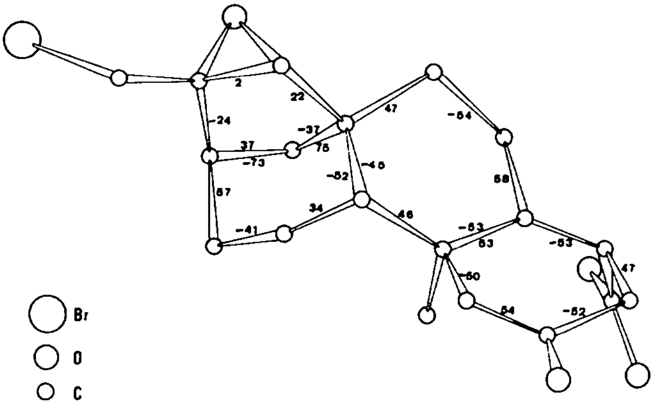

Fig 2. A perspective view of the molecule along the b axis; the torsional angles in the rings are added, a proof of a considerable degree of strain.

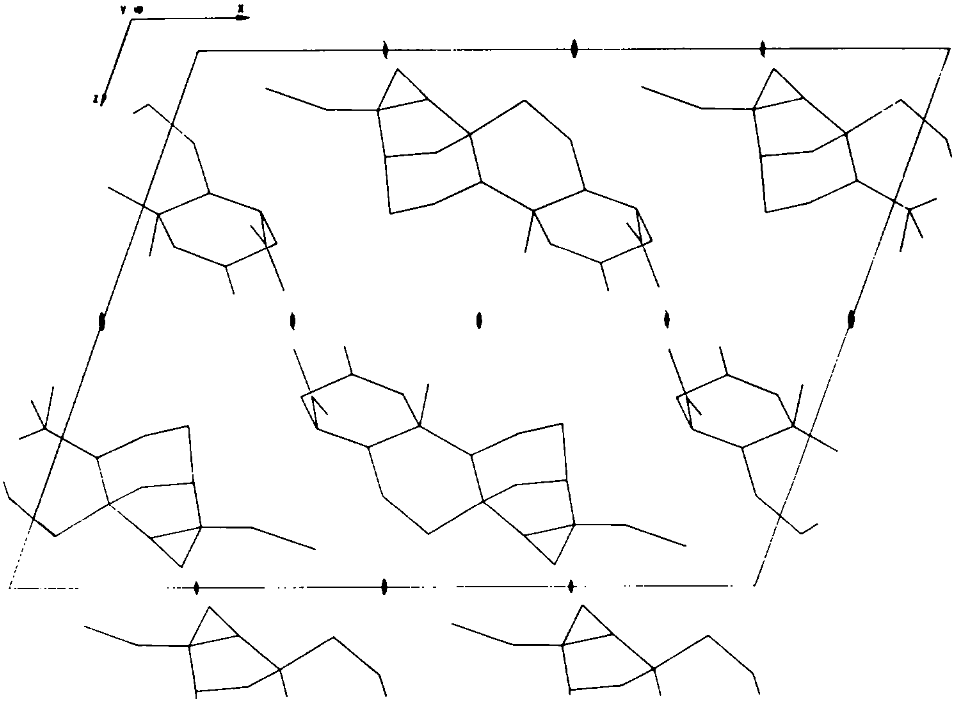

Fig. 3. The packing diagram of the molecules along the *b* axis.

TABLE 2. INTERMOLECULAR DISTANCES

Bond	Length (Å)	Symmetry operation on second atom		
C2 –O22	3·31	$\frac{3}{2} - x$	$\frac{1}{2} + x$	$1 + z$
C3 –O22	2·76	$\frac{3}{2} - x$	$\frac{1}{2} + y$	$1 + z$
O21–O22	3·43	$\frac{3}{2} - x$	$\frac{1}{2} + y$	$1 + z$
C2 –O23	3·40	x	$1 + y$	z
O21–C19	3·34	x	$1 + y$	z
O21–O23	2·59	x	$1 + y$	z
O21–O22	3·28	x	$1 + y$	z
C15–O24	3·34	$\frac{1}{2} - x$	$\frac{1}{2} + y$	$-z$
C17–O24	3·33	$\frac{1}{2} - x$	$\frac{1}{2} + y$	$-z$

All cyclohexane rings are in the chair form. A considerable strain results in rings C and D. This is probably due to steric hindrance in that part of the molecule, connected with the presence of the epoxy group. This strain is more evident in Fig 2, where the torsional angles are reported. Some intermolecular bonds shorter than 3·5 Å are listed in Table 2. Both translation and C-face centering work together to produce strong hydrogen bonds between the hydroxy and carboxy groups of ring A. Different molecules have further short head-to-head contacts: superposition of the C3-C2-O21 group on C4–COOH along the *y* direction is parallelled by that of C24 on C17 and C15. The molecular packing is shown in Fig 3.

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