be formed without serious change to the tetrahedral arrangement of the hydrogen bond around the nitrogen atom. In this model there are no unreasonable intermolecular contacts. Thus this may be a plausible model of the molecular structure in benzene solution, consistent with dimer formation, infrared spectra and, qualitatively, with the dipole moment in solution.

The author wishes to express his thanks to Professor Masao Haisa for his guidance and valuable discussion.

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The Crystal Structure of Strophanthidin, a Cardioactive Steroid, $C_{23}H_{32}O_6 \cdot \frac{1}{2}H_2O$

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Strophanthidin, $C_{23}H_{32}O_6 \cdot \frac{1}{2}H_2O$, is the aglycone of the strophanthus group of active cardiac glycosides which have a digitalis-like action on the heart. A partial structure was obtained using the symbolic addition procedure for non-centrosymmetric crystals and the complete structure was then developed using the tangent formula. The space group is $P2_1$ with $a = 13{\cdot}608$ (8), $b = 12{\cdot}068$ (8), $c = 13{\cdot}693$ (8) Å, $\beta = 109{\cdot}4$ (2)° and $Z = 4$. The X-ray analysis confirmed the expected configuration. As in other cardioactive steroids, the A/B and C/D ring junctions are *cis*. The two molecules in the asymmetric unit differ in the vicinity of the lactone rings, in such a way as to indicate a disorder in one of the molecules.

Introduction

Symptoms of congestive heart failure can be relieved with proper dosages of specific cardiotonic agents. These drugs allow the heart to empty more completely with each beat with no increase in oxygen consumption. The heart becomes a better mechanical pump, more able to meet the needs of the circulatory system. The drugs usually contain a mixture of compounds called cardiac glycosides. Removal of the glycoside by hydrolytic cleavage leaves the aglycone or genin which also exhibits cardiac activity but usually to a lesser degree. The best known and most widely used drug of this type is digitalis. Strophanthidin, the aglycone of the strophanthus group of active cardiac glycosides, is a naturally occurring steroid which is obtained from the seeds of the *Strophanthus kombe* (dogbane) tree found in Africa and Asia. The determination of its structure is part of a series of studies on steroids exhibiting cardiac activity. Prior structures which relate to this study are digitoxigenin (DTG, Karle & Karle, 1969*b*); Δ-8,14-anhydrodigitoxigenin (ADTG, Gilardi & Karle, 1970) and batrachotoxinin A (Karle & Karle, 1969*a*). The first two are illustrated in Fig. 1, along with the two molecules of strophanthidin found in the asymmetric unit.

Experimental

Single crystals were selected from a commercial sample of strophanthidin (Sandoz Ltd., Basle, Switzerland).

This sample was kindly provided by Dr A. Hybl of the University of Maryland Medical School. The 3700 independent reflections used in the refinement were collected on an automatic diffractometer using Cu $K\alpha$ radiation ($\lambda = 1{\cdot}54178$) and the θ–2θ scan mode (maximum $\sin\theta/\lambda = 0{\cdot}521$). The absorption coefficient is $7{\cdot}60\ cm^{-1}$; no absorption corrections were applied. A preliminary set of data, covering an identical region of reciprocal space, was used to solve the structure. However, high thermal factors and dubious structural features in molecule *B* led to a suspicion of systematic error in this data set, most likely due to radiation damage. The first data set was collected in shells of increasing 2θ, which would maximize the effects of radiation damage on the thermal parameters. The second data set, which was used for refinement, was collected from a different crystal along rows in reciprocal space, with minimum radiation exposure. This data set was collected using a new crystal which was selected from the same commercial sample. The structural results were very similar, which seems to indicate that the unusual bond distances and angles calculated for the lactone ring of molecule *B* are indeed an intrinsic feature of the crystal.

The solution of the structure was initiated by using the symbolic addition procedure for phase determination in non-centrosymmetric crystals (Karle & Karle, 1966) which led to a partial structure. The fragments (5 atoms from one molecule and 7 atoms from the second molecule) were developed into the full structure using the tangent formula (Karle, 1968) and finally a difference map. Coordinates and thermal factors were refined on *F* values using full-matrix least-squares methods. All parameters could not be varied simultaneously on our computer; therefore, the refinement was carried out on large blocks of parameters (243 parameters per cycle). Data having $|F_o| < 4{\cdot}0$ were given zero weights and omitted from the refinement, primarily to conserve computing time. The function minimized was $\sum W(|F_o| - |F_c|)^2$. The weights, $W = 1/\sigma_F^2$, were derived from an assumed variance in a diffractometer count using the form: $\sigma_n^2 = N + 0{\cdot}01N^2$. 44 of 68 possible hydrogen atoms were located in a difference map and were used to calculate final structure factors but were not included during any refinement cycles. The final *R* index for data used in the refinement (2697 reflections) was 10·7%. For the full set of 3700 reflections the *R* index was 13·0% ($R = \sum||F_o| - |F_c||/\sum|F_o|$).

Coordinates and thermal parameters for the carbon and oxygen atoms are listed in Table 1. Based solely on least-squares calculations, the indicated standard deviations are on the order of 0·0011 for coordinates and 0·7 Å^2 for thermal factors; however, the disorder in molecule *B* makes these values unreliable. The observed and calculated structure factors are compared in Table 2.

Discussion

The conformations of the independent strophanthidin molecules are illustrated in Fig. 1. The A/B and C/D ring junctions of strophanthidin are *cis*, the same configuration as in DTG, giving folded steroid nuclei, in contrast to the semi-planar nuclei of most steroids. The batrachotoxinin A molecule (not illustrated) also has A/B and C/D *cis* ring junctions but has a severely folded steroid nucleus held in position by bridging atoms not found in strophanthidin.

The averaged bond distances, angles and torsions, calculated for molecules *A* and *B* of strophanthidin are shown in Figs. 2 and 3. In molecule *A*, and in the steroid nucleus of *B*, no single distance or angle differs

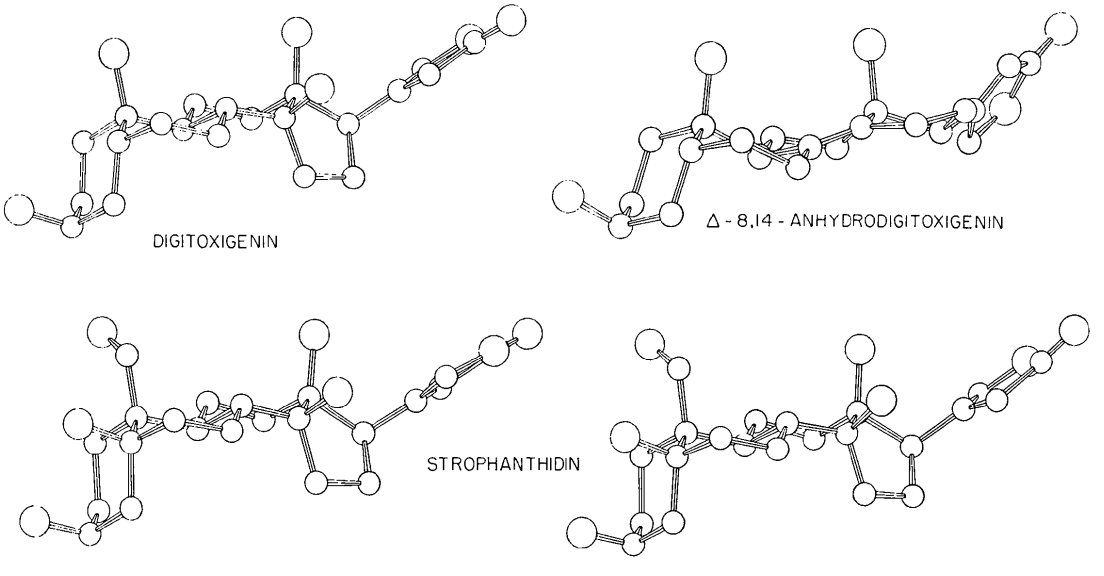


Fig. 1. A comparison of the conformations of strophanthidin, digitoxigenin, and Δ-8,14-anhydrodigitoxigenin.

significantly from values reported for DTG and ADTG. However, in molecule *B*, almost every distance and angle in ring E, the lactone ring, is significantly distorted. The crystal is probably disordered, in which case these parameters correspond to an averaged view of two or more chemically sensible structural fragments. However, extensive study of difference maps (discussed below) failed to indicate the nature of the disorder.

The distances and angles observed for the lactone ring of molecule *A* are quite similar to those reported for DTG, and the apparent thermal vibration param-

Table 1. *Fractional coordinates and thermal parameters with standard deviations*

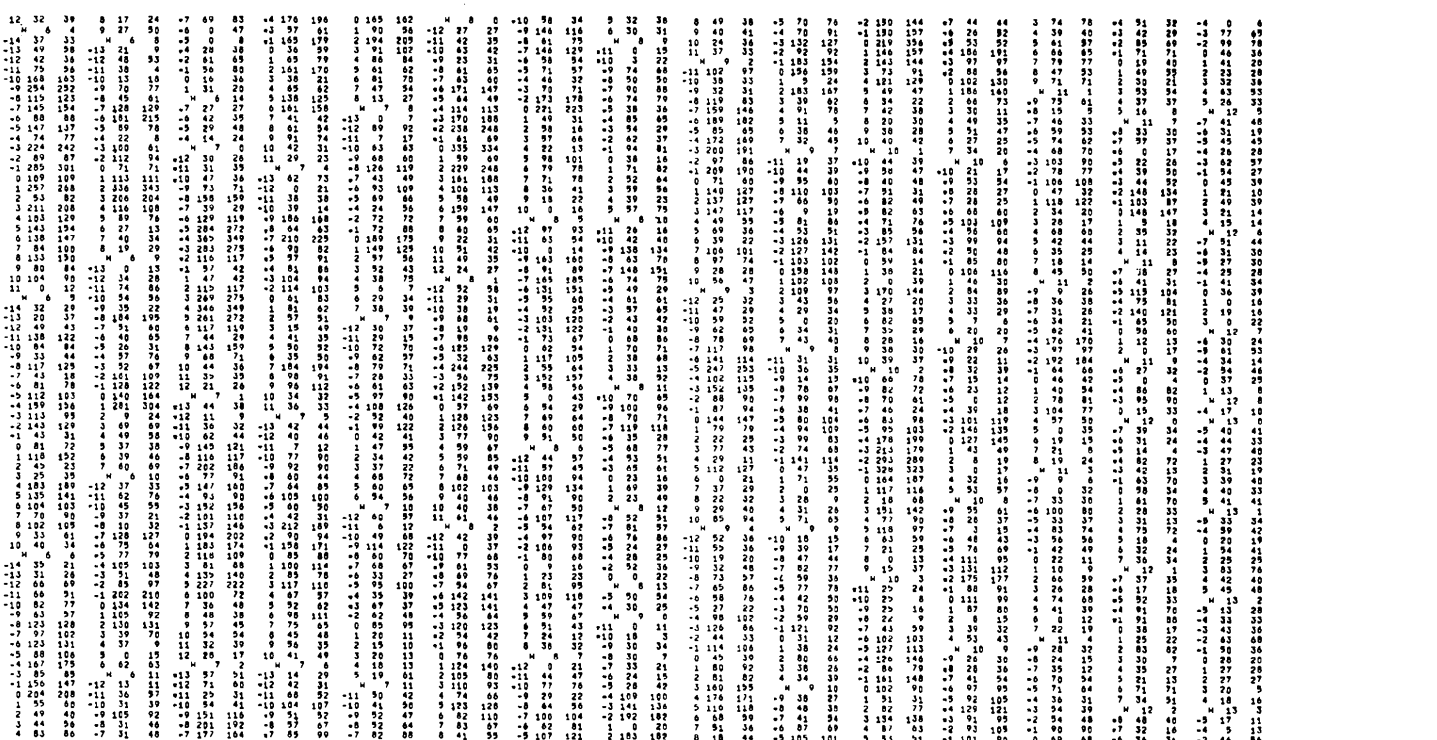
The temperature factor is of the form $T=\exp[-\frac{1}{4}(B_{11}h^2a^{*2}+B_{22}k^2b^{*2}+B_{33}l^2c^{*2}+2B_{12}hka^*b^*+2B_{13}hla^*c^*+2B_{23}klb^*c^*)]$.

	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1*A*)	0·3274	0·9033	0·8693	5·95	3·69	4·00	−0·28	2·18	0·58
C(2*A*)	0·2372	0·9347	0·9077	4·55	3·44	5·09	1·18	0·43	−0·01
C(3*A*)	0·2747	0·9355	1·0300	4·20	3·03	4·74	1·32	1·58	0·33
C(4*A*)	0·3211	0·8244	1·0692	3·88	3·39	3·32	−0·15	1·70	−0·06
C(5*A*)	0·4097	0·7832	1·0281	3·04	3·01	4·41	−0·81	1·52	−0·29
C(6*A*)	0·4509	0·6706	1·0724	4·02	3·51	2·45	0·68	0·17	0·60
C(7*A*)	0·3686	0·5777	1·0307	4·76	2·79	2·73	−0·41	0·32	0·11
C(8*A*)	0·3321	0·5753	0·9082	3·04	2·76	3·66	1·01	1·00	1·20
C(9*A*)	0·2905	0·6912	0·8641	4·14	3·40	3·96	−0·44	1·21	0·46
C(10*A*)	0·3738	0·7874	0·9086	3·70	3·82	2·70	−0·41	1·42	0·37
C(11*A*)	0·2565	0·6858	0·7431	4·63	3·94	3·56	−1·03	−0·01	0·26
C(12*A*)	0·1685	0·6010	0·7044	5·99	4·86	4·06	−0·37	0·61	0·23
C(13*A*)	0·2074	0·4815	0·7450	3·90	5·08	3·95	−0·11	0·99	0·31
C(14*A*)	0·2531	0·4835	0·8674	2·90	3·24	4·17	0·47	1·43	0·57
C(15*A*)	0·1563	0·4909	0·9013	3·35	5·08	3·93	−0·00	1·33	−0·36
C(16*A*)	0·0727	0·4120	0·8231	3·65	5·81	6·07	−0·74	2·13	−1·24
C(17*A*)	0·1030	0·4109	0·7205	4·22	3·70	4·94	−1·04	−0·13	0·25
C(18*A*)	0·2838	0·4363	0·6934	5·53	5·03	4·87	−0·62	2·35	−1·25
C(19*A*)	0·4696	0·7649	0·8763	4·98	4·66	5·50	−1·58	2·71	−0·42
C(20*A*)	0·1045	0·2947	0·6814	4·47	4·55	3·48	−1·17	0·91	−0·41
C(21*A*)	0·1646	0·2011	0·7449	8·66	3·68	4·76	−0·15	0·90	−0·60
C(22*A*)	0·0523	0·2621	0·5869	5·13	7·04	6·45	−1·30	2·60	−0·74
C(23*A*)	0·0769	0·1404	0·5827	4·65	5·06	7·51	−1·62	2·89	−1·27
O(1*A*)	0·3538	1·0213	1·0680	5·50	3·47	4·17	0·44	1·35	−0·34
O(2*A*)	0·2976	0·3787	0·9016	3·42	2·73	3·37	0·28	0·87	0·66
O(3*A*)	0·1398	0·1065	0·6786	6·81	4·82	6·37	−0·99	2·21	−0·76
O(4*A*)	0·0449	0·0747	0·5112	7·18	9·43	7·52	−0·72	0·97	−4·73
O(5*A*)	0·4957	0·8623	1·0671	2·70	3·83	4·24	−0·32	0·52	−0·37
O(6*A*)	0·4821	0·8169	0·8051	7·12	11·73	8·65	0·02	4·97	2·27
C(1*B*)	0·4394	0·0742	0·5462	6·15	8·26	5·56	1·24	1·03	2·35
C(2*B*)	0·3616	0·0478	0·6077	7·59	8·09	4·86	1·25	1·70	1·47
C(3*B*)	0·3039	−0·0536	0·5663	8·18	6·77	6·45	2·81	3·50	2·89
C(4*B*)	0·2449	−0·0504	0·4534	6·20	6·62	4·69	1·63	2·97	1·44
C(5*B*)	0·3109	−0·0202	0·3909	6·24	6·67	5·35	2·94	2·67	2·52
C(6*B*)	0·2448	−0·0126	0·2716	7·79	5·46	5·23	3·42	1·95	2·16
C(7*B*)	0·1773	0·0928	0·2493	6·05	4·21	5·38	−0·01	2·21	1·15
C(8*B*)	0·2431	0·1966	0·2874	3·48	4·38	2·86	1·01	0·84	0·84
C(9*B*)	0·3057	0·1887	0·4039	4·63	3·96	4·39	0·83	1·79	0·30
C(10*B*)	0·3781	0·0816	0·4272	4·97	5·48	4·99	1·33	2·25	2·06
C(11*B*)	0·3650	0·2977	0·4402	4·15	5·15	3·72	−0·10	−0·19	0·88
C(12*B*)	0·2882	0·3957	0·4169	5·24	6·97	2·92	−0·45	0·04	0·01
C(13*B*)	0·2305	0·4102	0·3026	2·38	3·34	3·32	0·29	0·45	−0·11
C(14*B*)	0·1746	0·3011	0·2568	2·49	3·74	2·86	−0·21	0·62	0·12
C(15*B*)	0·0788	0·2980	0·2932	2·91	5·02	5·92	0·11	1·65	0·25
C(16*B*)	0·0449	0·4200	0·2911	6·99	4·05	9·15	−0·23	5·05	1·29
C(17*B*)	0·1394	0·4944	0·2944	4·63	5·05	3·48	−0·11	0·89	−0·51
C(18*B*)	0·3035	0·4495	0·2438	2·36	5·64	5·87	−0·41	1·69	0·24
C(19*B*)	0·4534	0·0905	0·3687	2·65	10·19	10·65	2·51	2·65	0·75
C(20*B*)	0·1075	0·5699	0·1978	3·58	2·84	12·72	1·13	5·16	1·37
C(21*B*)	0·1595	0·6868	0·2438	16·72	6·72	12·61	0·97	7·48	4·71
C(22*B*)	0·0377	0·5517	0·0958	14·13	18·38	5·24	11·47	4·63	5·71
C(23*B*)	0·0537	0·6701	0·0520	11·24	15·47	3·85	10·62	5·17	6·76
O(1*B*)	0·3675	−0·1480	0·5878	12·82	7·97	8·76	4·39	5·29	4·77
O(2*B*)	0·1379	0·3117	0·1456	3·71	3·82	1·85	−0·13	0·56	0·65
O(3*B*)	0·1195	0·7425	0·1447	11·31	15·58	12·87	3·44	8·01	2·31
O(4*B*)	0·0408	0·7192	−0·0112	10·26	33·31	5·67	12·76	2·67	8·15
O(5*B*)	0·3798	−0·1161	0·3909	8·53	6·07	7·99	3·94	3·94	2·75
O(6*B*)	0·5395	0·1030	0·4105	10·64	11·05	16·69	1·70	8·70	4·04
H_2O	0·2488	0·2157	0·0220	6·06	3·72	6·36	0·92	2·92	0·72

Table 2. *Observed and calculated structure factors for strophanthidin*

The columns are the index h, $10|F_o|$, and $10|F_c|$.

Table 2 (*cont.*)



eters, although large, are again of similar magnitude in the two molecules. However, the conformation of the lactone ring relative to the steroid nucleus is different. The torsion angle, w[C(13)–C(17)–C(20)–C(22)], is $-110{\cdot}9°$ in strophanthidin A, and is $76{\cdot}2°$ in DTG. The conformations are related by a rotation of nearly 180° about the C(17)–C(20) bond. It is likely that both conformations exist in equilibrium in solutions of these drugs. This immediately suggests an attempt to explain the unusual electron density in the lactone region of strophanthidin B as a superposition of the two conformations. Attempts to force such a solution, with either rigid lactone rings or flexible ones, always led to the conclusions that the density was fit best by a distorted lactone ring in the DTG conformation. Adding a minor population of the strophanthidin A conformation to strophanthidin B did not improve the R index, the thermal parameters, or the bond distances and angles (if these were allowed to vary).

The possibilities of multifold disorder, or a disorder involving a very similar steroidal impurity, were not fully explored, due to the magnitude of the computations involved in refining this pair of molecules. The resultant positional and thermal parameters obtained from an unconstrained refinement of the lactone ring are included in Table 1 only to indicate the nature and magnitude of the distortions, but they must otherwise be considered almost meaningless. The rotation of the lactone ring corresponds quite closely to the DTG lactone conformation.

Strophanthidin packs in a complicated network which contains eight distinct O–H···O hydrogen bonds (see Table 3 for a list of hydrogen bond lengths). The water molecule, unexpectedly found in the asymmetric unit, is fully utilized in the hydrogen bonding net, being a donor in two hydrogen bonds and the acceptor in one. Despite the overall resemblance between the conformations of DTG and strophanthidin, their

is no resemblance in the packing. In DTG, chains of head-to-tail molecules were linked by hydrogen bonds between the terminal hydroxyl and the carbonyl of the lactone ring. In strophanthidin, the carbonyl from the lactone ring of molecule *B* participates in a hydrogen bond to a different hydroxyl, O(2), while the lactone carbonyl in molecule *A* does not participate in any hydrogen bonding at all.

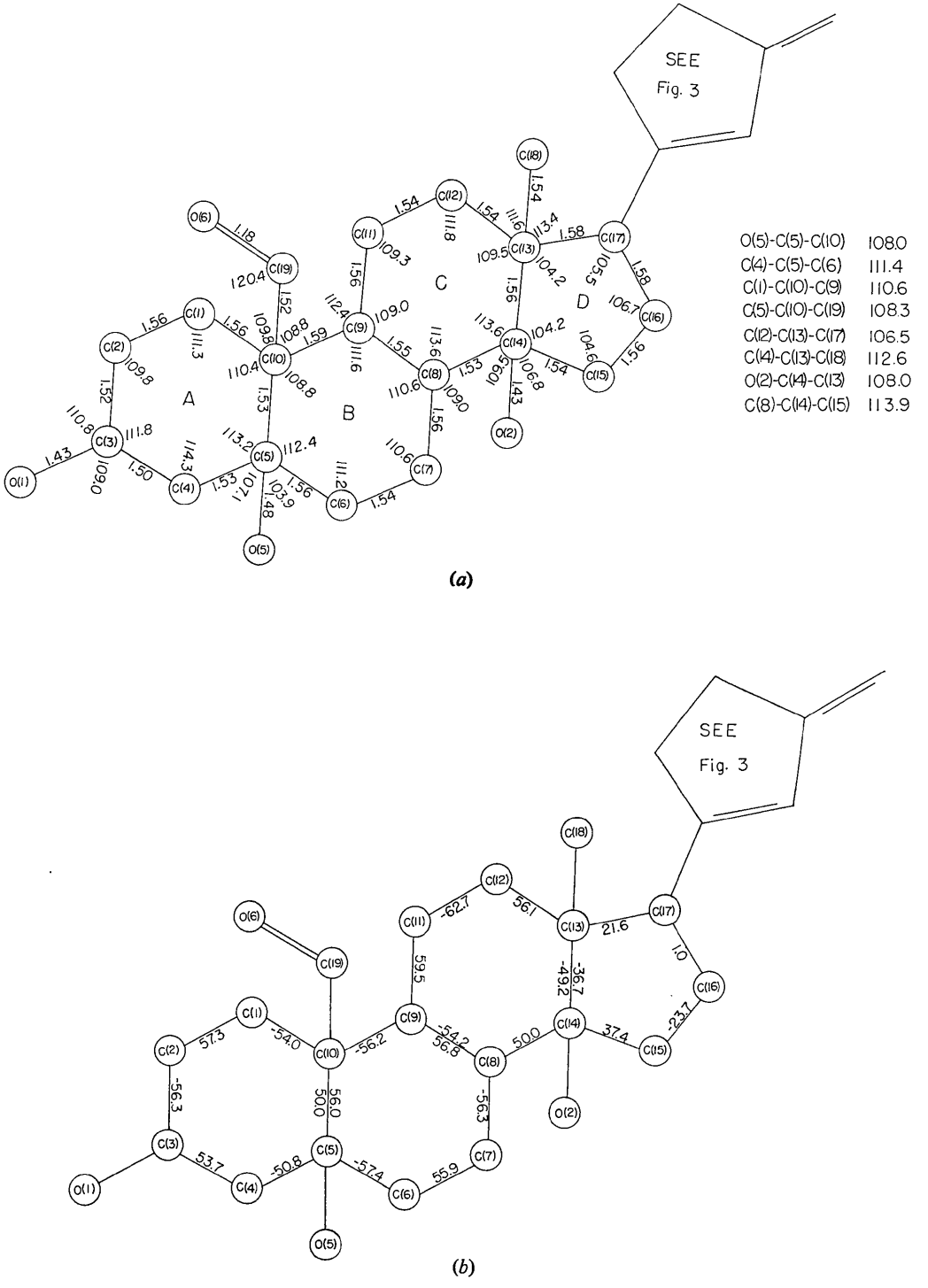
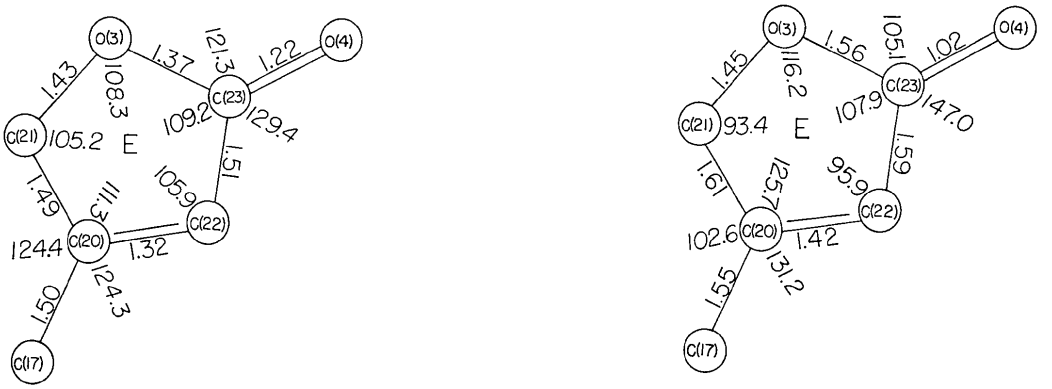
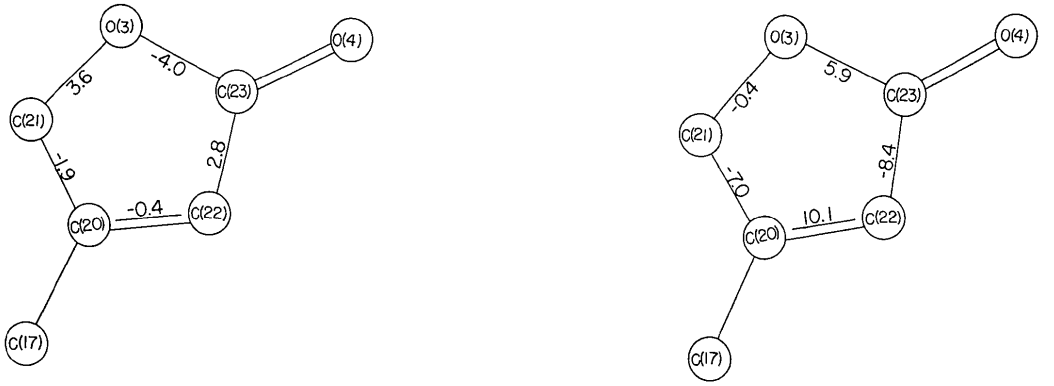


Fig. 2. (*a*) Averaged bond distances and angles for the two independent molecules of strophanthidin; rings *A–D*. (*b*) Averaged torsion angles; rings *A–D*.



(*a*)



(*b*)

Fig. 3. (*a*) Bond distances and angles for ring E of the two independent molecules of strophanthidin. (*b*) Torsion angles for ring E.

Table 3. *Hydrogen bonds*

Donor	Acceptor	Distance (Å)	Symmetry operation on acceptor	
H_2O	O(1*A*)	2·71	x $y-1$ $z-1$	
O(5*A*)	O(2*A*)	2·71	$1-x$ $\frac{1}{2}+y$ $2-z$	
O(2*B*)	O(4*B*)	2·75	$\bar{x}$ $-\frac{1}{2}+y$ $\bar{z}$	
O(2*A*)	H_2O	2·79	x y $1+z$	
H_2O	O(2*B*)	2·86	x y z	
O(1*B*)	O(6*A*)	2·90	x $1+y$ z	
O(1*A*)	O(5*A*)	2·72	$x\ y\ z$	intramolecular
O(5*B*)	O(1*B*)	2·79	$x\ y\ z$	intramolecular

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