Table 8. *Comparison of the present results with those of Felty* (1963)

	Felty	This work
$d_{\text{N-O}}$	1·245 (σ=0·004) Å (*l* odd reflections) 1·250 (σ=0·002) Å (all reflections)	1·241 (σ=0·002) Å (*l*-odd reflections)
R.m.s. amplitude (Å)		
1. along bond	0·156 (σ=0·008)	0·135 (σ=0·004)
2. long axis	0·221 (σ=0·006)	0·226 (σ=0·004)
3. third axis	0·153 (σ=0·006)	0·156 (σ=0·003)
Angle: long axis of thermal ellipsoid *vs* **c**	47° (σ=3°)	48° (σ=2°)

Inkinen found N–O to be 1·222 ± 0·01 Å. More recently Kurki-Suonio (1962) subjected Inkinen's data to a detailed refinement and reported N–O as 1·234 (σ=0·003 Å.)

Felty (1963) measured 266 independent $NaNO_3$ reflections, including 72 'oxygen' reflections, using Mo $K\alpha$ radiation and film methods. Our results are compared with his in Table 8. Agreement between the two sets, particularly with respect to the thermal parameters, is very good. Felty's analysis of the 'oxygen' reflections yielded an N–O bond length of 1·246 Å; our corresponding value is 1·241 Å. When all 266 reflections were included in the calculations he obtained N–O 1·250 Å.

Our results may be compared with corresponding results recently reported for calcite (Chessin, Hamilton & Post, 1965). Although the magnitudes of the thermal motions of the oxygen atoms in calcite are substantially smaller than corresponding values for sodium nitrate, the degree and the type of anisotropy is very similar in both cases. The largest amplitude of thermal motion occurs in the plane normal to the C–O bond in calcite and the N–O bond in sodium nitrate. The longest principal axis of the thermal ellipsoid is inclined 48° to the *c* axis in both calcite and sodium nitrate (full data) at 25°C.

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The Crystal Structure of Diosgenin Iodoacetate

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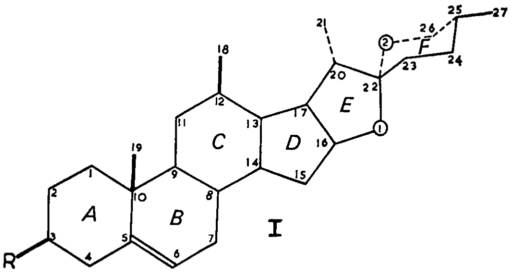
The crystal structure of diosgenin iodoacetate, has been determined by the heavy-atom technique and has been refined by Fourier and least-squares analyses of the three-dimensional data. The stereochemistry of diosgenin iodoacetate has been confirmed; it may be formulated as 25ε-methyl-22β-spirost-5(6)-en-3β-yl iodoacetate, and may be classified as a sterol structure, type *ab*(21)2.

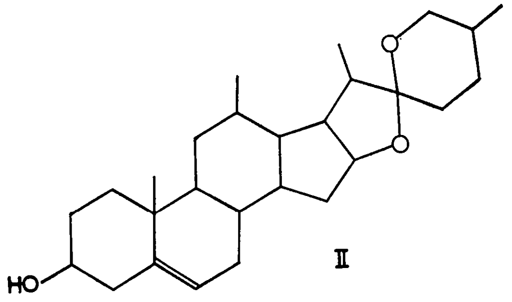
Introduction

The sapogenins are produced by hydrolysis of the plant glycosides and they may be classified as steroid sapogenins or as triterpenoid sapogenins according to the products of their dehydrogenation: the steroid sapogenins yield 3′-methyl-1,2-cyclopentenophenanthrene, and the triterpenoid sapogenins yield derivatives of naphthalene and of picene.

The use of steroid sapogenins as inexpensive precursors of hormones and of their intermediates, for example, cortisone from diosgenin, has prompted their detailed chemical investigation: Simpson & Jacobs (1934*a*,*b*, 1935), Tschesche & Hagedorn (1935), Tukamato, Ueno & Ota, (1936, 1937), Marker & Turner (1941, 1943, 1947). These studies were reviewed by Marker (1947). At this stage, yamogenin, a stereoisomer of diosgenin, was assigned formula (II), whereas in diosgenin itself, the oxygen atom and C(23), both in ring *F*, were interchanged.



I



II

The existence of 'normal' and of 'iso' sapogenins was explained by isomerism at C(22), but the possibility of isomerism at C(25) was neglected. Further studies by Kaufmann & Rosenkranz (1949), Scheer, Kostic & Mosettig (1953), James (1953) and Wall, Eddy & Serota (1954) led to the adoption of formula (I) (R = OH) for diosgenin.

Rosen & Shabica (1954) showed that the absolute configuration of the ring system corresponded to the C(22), C(23) bond having the β orientation, or *cis* to the C(19) methyl group; this configuration required the equatorial (ε) position of the methyl group at C(25).

This crystal structure determination was carried out in order to elucidate the detailed stereochemistry of diosgenin particularly in rings *E* and *F*.

Experimental

Crystals of diosgenin iodoacetate (I, R = ICH_2CO_2) were obtained from Dr C. H. Carlisle of Birkbeck College, London. A preliminary report of this investigation has been published by O'Donnell & Ladd (1963).

Diosgenin iodoacetate, $C_{29}H_{43}O_4I$, exhibited a pinacoidal habit with the order of prominent development $\{001\} > \{100\} > \{010\}$. The material was recrystallized from a 1:1 mixture of ethanol and water. The density was determined by flotation in aqueous sodium bromide solution, with the result $D_m = 1\cdot41 \pm 0\cdot01$ g.cm^{-3}. An optical examination revealed the orientation: $Y \| \mathbf{a}$ (approximately); $X \| \mathbf{b}$; $Z + 2°\mathbf{c}$; birefringence large (+).

The unit-cell dimensions were determined with a calibrated Weissenberg X-ray goniometer. Copper $K\alpha$ radiation was used throughout the experimental work. Values of d_{100}, d_{010}, d_{001} and d_{101} were measured and extrapolated against the function $\cot\theta \cos^2\theta$ (Buerger, 1942). The following results, with limits of error, were obtained: $a = 12\cdot526 \pm 0\cdot005$, $b = 6\cdot161 \pm 0\cdot003$, $c = 35\cdot86 \pm 0\cdot01$ Å; $\beta = 92\cdot00 \pm 0\cdot08°$. The value of β was obtained by solving the triangle $1/d_{100}$, $1/d_{001}$, $1/d_{101}$. There are four molecules in the unit cell and the calculated density (D_c) is 1·399 g.cm^{-3}.

For recording the reflexions, crystals of about 0·2 mm square cross-section and about 1 mm long were prepared. Weissenberg photographs were taken about the *a* and the *b* axes, using the equi-inclination technique, with packs of four films in the camera. The relative intensities were estimated visually and an intensity range of 1 to 2000 was covered. The intensities were corrected for Lorentz and for polarization effects, but not for absorption ($\mu R = 1\cdot46$); a correction for spot shape was applied, (Phillips, 1954, 1956). Altogether, 1146 independent measured reflexions were used for the structure analysis.

The intensities were scaled approximately and an average isotropic temperature factor of 6 Å^2 was deduced, using the method of Wilson (1942). The only condition limiting reflexions was $0k0$: $k = 2n$. The intensity distribution of the $0kl$ reflexions was found to be acentric, by the technique of Howells, Phillips & Rogers (1950), and the space group $P2_1$ was chosen. Thus, the asymmetric unit contained two molecules.

Infrared studies of the sample of diosgenin iodoacetate used in this investigation corresponded to those reported by Jones, Katzenellenbogen & Dobringer (1953) for diosgenin acetate (I, R = CH_3CO_2), although the band at 1086 cm^{-1} was overlapped by spectra due to the iodoacetate group.

Structure determination

The reflexions *hkl* were of noticeably weaker intensity with *l* odd than with *l* even, indicating a subperiod of *c*/2 along the *z* axis; this structural feature was confirmed subsequently.

The Patterson projection on (010) was computed with sharpened coefficients, and is shown in Fig. 1. The peaks *R* and *S* are due to symmetry-related iodine atoms, and the peaks *P* and *Q* are due to iodine atoms not related by the space group symmetry. Patterson sections normal to the *b* axis showed that the maxima of *Q* and of *P*, *R*, *S* were at $V = 0$ and at $V = \frac{1}{2}$ respectively, all to within 0·02. Hence, the iodine atoms not related by symmetry differed in their *y* coordinates by about 0·1 Å, which was insufficient to destroy their pseudo-mirror symmetry. The coordinates of the iodine atoms were deduced with the results as follows:

$$\text{I (i)} \pm (0{\cdot}066, \tfrac{1}{4}, 0{\cdot}308)$$
$$\text{I (ii)} \pm (0{\cdot}033, \tfrac{1}{4}, 0{\cdot}792)\,.$$

The lack of resolution of peak Q was due to the juxtaposition of two such peaks, and to the approximate sub-period of $c/2$ in the unit cell.

The small b dimension indicated probable good resolution in the (010) plane. Phase angles were calculated with the coordinates of the iodine atoms alone. The (010) projection was computed and was refined by Fourier and least-squares methods to an R value of 0·14; the iodine atoms phased most of the $h0l$ reflexions correctly. The final electron density projection is shown in Fig. 2; the molecules are well resolved except in the regions of the iodoacetate groups and of rings F.

Three-dimensional electron density sections, with $|F_o|$ phased on the iodine atoms and weighted by the method due to Sim (1959, 1960), were computed. Subsequent studies involved the selection of two molecules from their mirror images in the asymmetric unit. This process was aided by the well resolved (010) projection. Distances in the range 1·4 to 1·6 Å for C–C bonds together with C–C–C angles in the range 99 to 119° were considered in selecting stereochemically plausible groups of atoms, in the early stages of the structure analysis.

Successive Fourier syntheses refined the structure slowly. Three cycles of least-squares calculations, refining only the atomic coordinates, and a back-shift correction evaluated from an F_c synthesis, led to a final R value of 0·18, calculated from only the observed reflexions.

A composite electron-density map, prepared from the final three-dimensional sections, is shown in Fig. 3. Difference electron density sections calculated at this stage showed fluctuations of less than 1 e.Å^{-3}, except in the region of the iodine atoms; here, strong diffraction effects were observed, and the fluctuations were increased to about 1·3 e.Å^{-3}.

The positions of the oxygen atoms in rings E and F were confirmed by calculating structure factors assuming carbon atoms in these rings and subsequently computing the electron density; the results are summarized in Table 1.

All structure factors* were calculated with the use of atomic scattering factors listed in *International Tables for X-ray Crystallography* (1962), and with an average isotropic temperature factor of 6·0 Å^2. All calculations were carried out with an I.C.T. Sirius computer, using programs written by the authors.

The atomic coordinates, bond lengths and bond angles are recorded in Tables 2, 3 and 4 respectively.

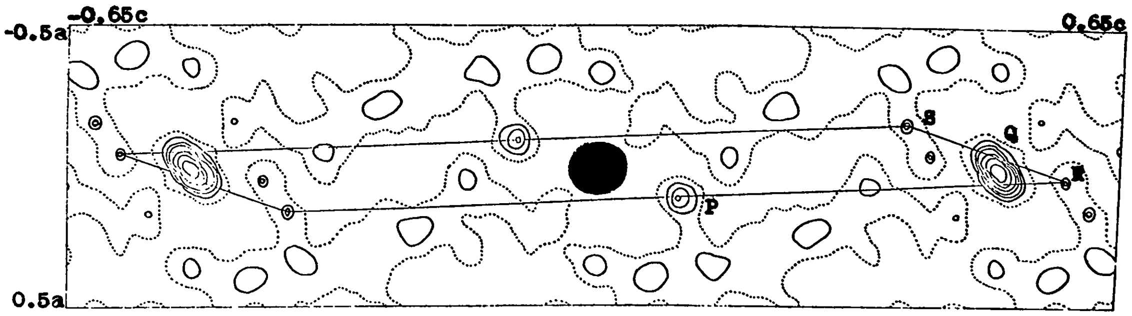


Fig. 1. The Patterson projection on (010).

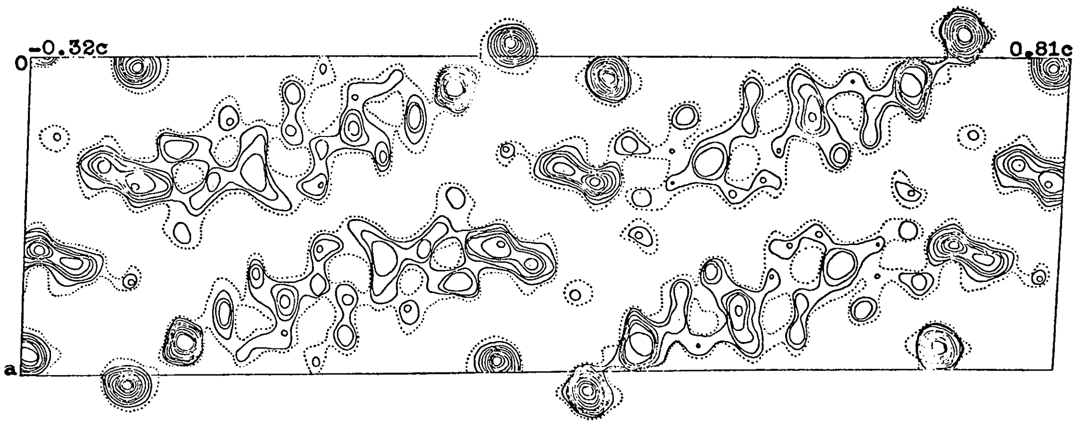


Fig. 2. The electron density projection on (010).

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* The structure factor data can be obtained from M.F.C.L.

Table 1. *Average relative peak heights*

	Molecule (i)					Molecule (ii)				
	O(1)	O(2)	O(3)	O(4)	⟨C⟩	O(1)	O(2)	O(3)	O(4)	⟨C⟩
Carbon atoms in rings *E*, *F*	106	102	113	116	93	106	99	108	111	80
Final synthesis	123	112	118	120	97	118	105	114	116	90

Table 2. *Fractional atomic coordinates for diosgenin iodoacetate*

	Molecule (i)			(Molecule (ii)		
	x	*y*	*z*	*x*	*y*	*z*
I	−0·071	0·760	0·692	−0·029	0·669	0·204
O(1)	0·300	0·765	0·335	0·289	0·950	0·830
O(2)	0·425	0·925	0·295	0·393	0·125	0·803
O(3)	0·133	0·915	0·632	0·122	0·164	0·143
O(4)	0·062	0·313	0·637	0·102	0·514	0·135
C(1)	0·321	0·763	0·563	0·322	0·982	0·066
C(2)	0·275	0·874	0·597	0·268	0·160	0·100
C(3)	0·163	0·871	0·602	0·170	0·163	0·108
C(4)	0·087	0·805	0·577	0·076	0·079	0·075
C(5)	0·128	0·785	0·533	0·117	0·001	0·042
C(6)	0·077	0·993	0·510	0·062	0·950	0·006
C(7)	0·113	0·867	0·473	0·113	0·942	0·972
C(8)	0·218	0·776	0·467	0·230	0·913	0·971
C(9)	0·297	0·766	0·500	0·305	0·011	0·001
C(10)	0·231	0·743	0·538	0·242	0·941	0·033
C(11)	0·396	0·667	0·493	0·400	0·742	0·997
C(12)	0·430	0·812	0·462	0·433	0·958	0·960
C(13)	0·383	0·742	0·427	0·367	0·017	0·925
C(14)	0·281	0·804	0·434	0·264	0·006	0·930
C(15)	0·205	0·830	0·397	0·200	0·921	0·891
C(16)	0·295	0·870	0·379	0·287	0·968	0·866
C(17)	0·400	0·862	0·389	0·395	0·994	0·885
C(18)	0·367	0·500	0·425	0·363	0·758	0·923
C(19)	0·206	0·500	0·535	0·244	0·682	0·038
C(20)	0·465	0·700	0·358	0·451	0·968	0·860
C(21)	0·567	0·807	0·356	0·560	0·014	0·855
C(22)	0·420	0·758	0·321	0·400	0·910	0·826
C(23)	0·392	0·550	0·303	0·419	0·699	0·800
C(24)	0·334	0·583	0·272	0·365	0·750	0·766
C(25)	0·350	0·708	0·247	0·367	0·992	0·738
C(26)	0·362	0·908	0·267	0·367	0·166	0·767
C(27)	0·317	0·742	0·209	0·333	0·050	0·700
C(28)	0·085	0·058	0·645	0·080	0·333	0·153
C(29)	0·030	0·021	0·682	0·021	0·338	0·196

Table 3. *Bond lengths for diosgenin iodoacetate*

	Molecule (i)	Molecule (ii)	Average
C(1)—C(2)	1·51 Å	1·50 Å	1·51 Å
C(2)—C(3)	1·42	1·41	1·42
C(3)—C(4)	1·36	1·69	1·53

Table 3 (*cont.*)

	Molecule (i)	Molecule (ii)	Average
C(3)—O(3)	1·38	1·41	1·40
C(4)—C(5)	1·64	1·40	1·52
C(5)—C(10)	1·32	1·47	1·40
C(5)—C(6)	1·63	1·53	1·58
C(6)—C(7)	1·62	1·39	1·51
C(7)—C(8)	1·46	1·48	1·47
C(8)—C(9)	1·53	1·52	1·53
C(9)—C(10)	1·63	1·53	1·58
C(10)–C(1)	1·42	1·59	1·51
C(10)–C(19)	1·53	1·61	1·57
C(11)–C(9)	1·42	1·54	1·48
C(11)–C(12)	1·50	1·54	1·52
C(12)–C(13)	1·43	1·51	1·47
C(13)–C(18)	1·50	1·60	1·55
C(13)–C(14)	1·36	1·31	1·34
C(14)–C(8)	1·46	1·66	1·56
C(14)–C(15)	1·59	1·66	1·63
C(15)–C(16)	1·59	1·36	1·48
C(16)–C(17)	1·51	1·36	1·44
C(17)–C(13)	1·55	1·53	1·54
C(17)–C(20)	1·70	1·46	1·58
C(20)–C(21)	1·44	1·41	1·43
C(20)–C(22)	1·46	1·41	1·44
C(22)–O(1)	1·69	1·30	1·50
O(1)—C(16)	1·54	1·69	1·62
C(22)–C(23)	1·47	1·61	1·54
C(23)–C(24)	1·33	1·53	1·43
C(24)–C(25)	1·54	1·69	1·62
C(25)–C(27)	1·43	1·48	1·46
C(25)–C(26)	1·43	1·48	1·46
C(26)–O(2)	1·27	1·37	1·32
O(2)—C(22)	1·39	1·55	1·47
C(28)–O(3)	1·18	1·59	1·39
C(28)–O(4)	1·34	1·50	1·42
C(29)–C(28)	1·53	1·68	1·61
C(29)–I	2·08	2·16	2·12

The r.m.s. deviation is 0·08 Å for the bond lengths and is 7° for the bond angles. For the averaged dimensions, these were divided by $\sqrt{2}$, giving 0·06 Å and 5° as reasonable estimates for the standard deviations of the bond lengths and the bond angles respectively.

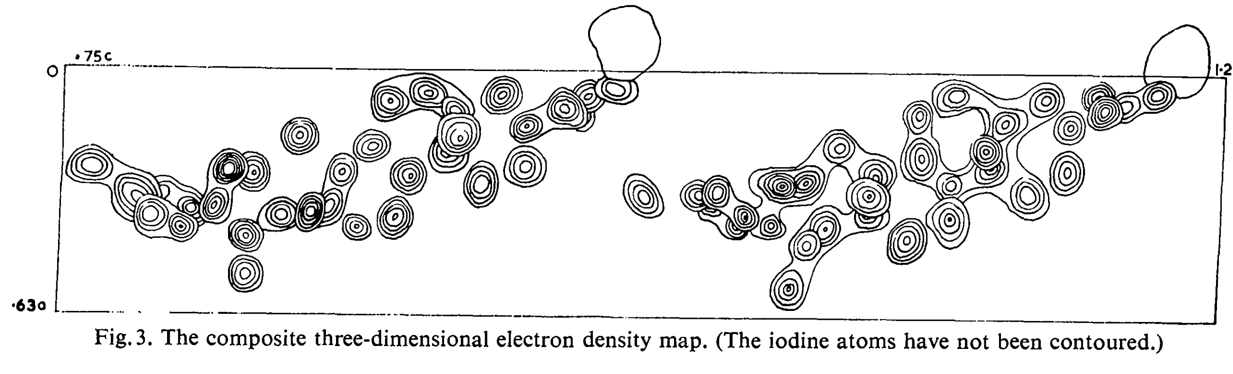
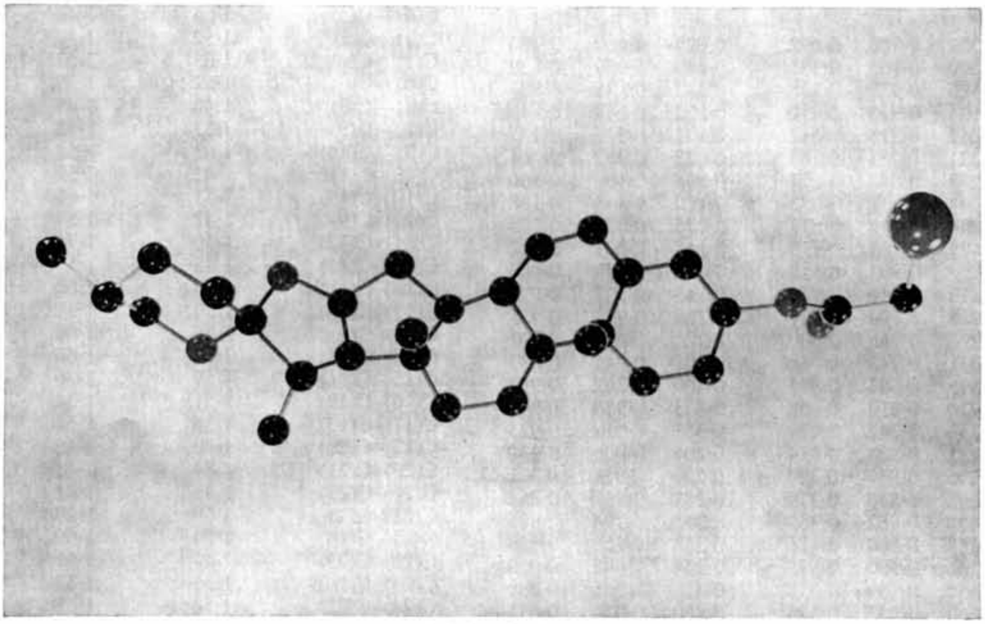


Fig. 3. The composite three-dimensional electron density map. (The iodine atoms have not been contoured.)

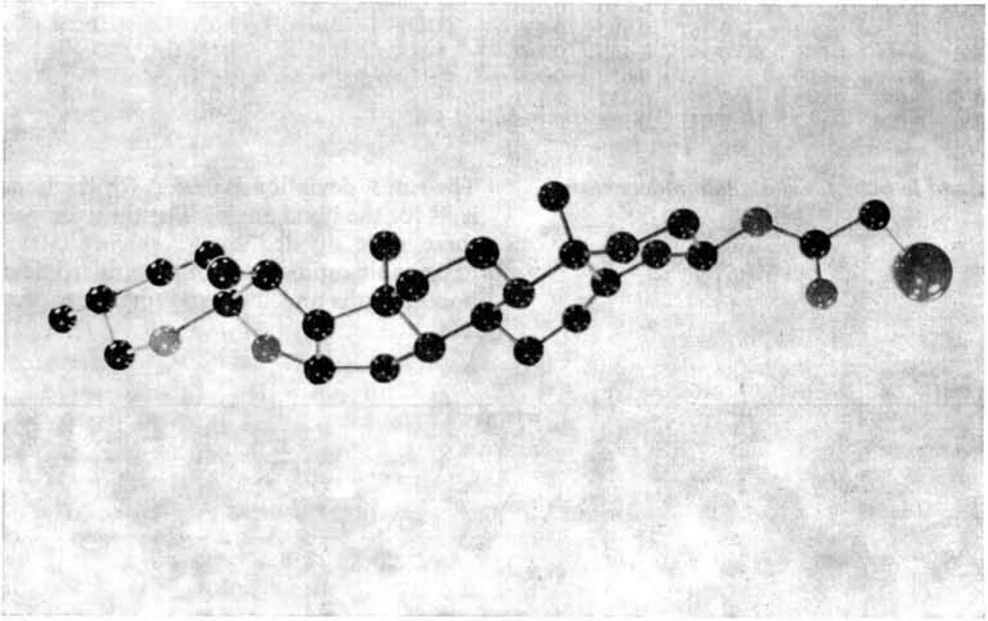
Stereochemistry

Two aspects of a model of diosgenin iodoacetate are shown in Fig. 4. The stereochemistry of diosgenin has been confirmed. The ring systems *B*/*C* and *C*/*D* are *trans* fused and the ring system *D*/*E* is *cis* fused in the β orientation; the C(5), C(6) double bond confers a degree of planarity on the *A*/*B* ring system. The C(22), C(23) single bond has the β orientation, and the methyl group at C(25) is in the equatorial (ε) conformation. These conclusions are compatible with a statement by Kennard (1963) in relation to derivatives of tigogenin and of neotigogenin.

The overall geometry of the two independent molecules of diosgenin iodoacetate is similar, except in the regions of the iodine atoms. Fig. 5 illustrates the configuration of the iodine atoms, in the plane defined approximately by the directions [010] and [1$y\frac{2}{3}$]. In molecule (ii), the I–C(29) bond has rotated with respect to molecule (i), relatively, about the C(28), C(29)



Molecule (i)



Molecule (ii)

Fig. 4. The molecular structure of diosgenin iodoacetate: molecules (i) and (ii).

Table 4. *Bond angles for diosgenin iodoacetate*

	Molecule (i)	Molecule (ii)	Average
I——C(29)-C(28)	124°	106°	115°
C(29)-C(28)-O(4)	119	121	120
C(29)-C(28)-O(3)	103	118	111
O(3)—C(28)-O(4)	138	119	129
C(28)-O(3)—C(3)	136	109	123
O(3)—C(3)—C(2)	120	125	123
O(3)—C(3)—C(4)	113	111	112
C(10)-C(1)—C(2)	103	115	109
C(1)—C(2)—C(3)	120	126	123
C(2)—C(3)—C(4)	127	116	122
C(3)—C(4)—C(5)	115	115	115
C(4)—C(5)—C(10)	103	120	112
C(4)—C(5)—C(6)	105	133	119
C(5)—C(10)-C(1)	135	117	126
C(5)—C(10)-C(19)	107	104	106
C(5)—C(6)—C(7)	105	123	114
C(6)—C(7)—C(8)	130	120	125
C(7)—C(8)—C(9)	117	122	120
C(8)—C(9)—C(10)	109	95	102
C(9)—C(10)-C(5)	114	133	124
C(9)—C(10)-C(19)	96	98	97
C(10)-C(5)—C(6)	129	107	118
C(1)—C(10)-C(19)	107	96	102
C(10)-C(9)—C(11)	126	113	120
C(7)—C(8)—C(14)	127	105	116
C(8)—C(14)-C(13)	131	106	119
C(8)—C(14)-C(15)	111	120	116
C(22)-O(2)—C(26)	115	131	123
C(14)-C(13)-C(12)	97	96	97
C(14)-C(13)-C(18)	99	98	99
C(12)-C(11)-C(9)	99	93	96
C(11)-C(9)—C(8)	115	98	107
C(9)—C(8)—C(14)	107	108	108
C(12)-C(13)-C(18)	113	89	101
C(12)-C(13)-C(17)	123	133	128
C(14)-C(15)-C(16)	99	96	98
C(15)-C(16)-C(17)	106	115	111
C(15)-C(16)-O(1)	104	112	108
C(16)-C(17)-C(13)	106	112	109
C(16)-C(17)-C(20)	108	103	106
C(17)-C(13)-C(14)	108	100	104
C(17)-C(13)-C(18)	117	93	105
C(17)-C(16)-O(1)	97	112	105
C(13)-C(17)-C(20)	113	104	109
C(13)-C(14)-C(15)	115	111	113
C(13)-C(12)-C(11)	110	130	120
C(16)-O(1)—C(22)	126	102	114
O(1)—C(22)-C(20)	95	105	100

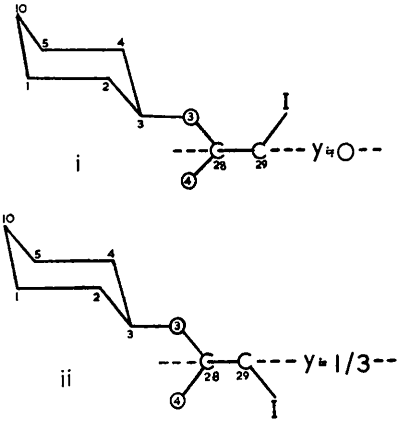


Fig. 5. The environment of the iodine atoms in the unit cell: molecules (i) and (ii).

Table 4 (*cont.*)

	Molecule (i)	Molecule (ii)	Average
C(22)-C(20)-C(21)	99	110	105
C(22)-C(20)-C(17)	106	109	108
C(17)-C(20)-C(21)	102	123	113
C(20)-C(22)-O(2)	136	104	120
O(1)—C(22)-C(23)	99	112	106
C(22)-C(23)-C(24)	110	127	191
C(23)-C(24)-C(25)	129	138	134
C(24)-C(25)-C(27)	139	136	138
C(24)-C(25)-C(26)	101	103	102
C(27)-C(26)-O(2)	118	121	120
C(26)-C(25)-C(27)	112	117	115

bond through an angle of approximately 90°. Figs. 4(i) and 5(i) and Figs. 4(ii) and 5(ii) correspond to the two different environments of the iodine atoms in the molecules.

The closest approach distance of the iodine atoms in diosgenin iodoacetate is 4·6 Å. This is less than is found usually in this type of structure, as is shown in Table 5, but is larger than the van der Waals radius of 4·3 Å which was given by Pauling (1939). If a single configuration had been maintained throughout, the iodine atoms would have approached to about 4 Å, assuming a similar packing of the molecules.

Table 5. *Closest approach distances of iodine atoms*

	I–I
Lanostenyl iodoacetate (Fridrichsons & Mathieson, 1953)	5·6 Å
Epilimonol iodoacetate (Arnott, Davie, Robertson, Sim & Watson, 1961)	6·0
Calciferyl 4-iodo-3-nitrobenzoate (Hodgkin, Rimmer, Dunitz & Trueblood, 1963)	5·2
Euphenyl iodoacetate (Carlisle & Ladd, 1966)	7·3
Diosgenin iodoacetate (this work)	4·6

The crystal data for diosgenin iodoacetate correspond closely to those deduced for α-ergostenol by Bernal, Crowfoot & Fankuchen (1940). Diosgenin iodoacetate may be allocated to the structure type *ab*(21)2; the data are compared in Table 6. The presence of an iodoacetate group does not preclude, necessarily, classification with the sterol structures, as was suggested by Carlisle & Ladd (1966) in the case of euphenyl iodoacetate. In the latter compound, however, a non-extended aliphatic side-chain was an unusual structural feature.

Table 6. *Crystal data for diosgenin iodoacetate and for α-ergostenol*

	Diosgenin iodoacetate	α-ergostenol
a	12·53 Å	12·1 Å
b	6·16	6·1
c	35·86	35·6
β	92·0°	93·0°
Z	4	4
Space group	$P2_1$	$P2_1$
Optics	$X \parallel \mathbf{b}$	$X \parallel \mathbf{b}$
	$Z \perp (001)$, approx.	$Z \perp (001)$, approx.
	$Zc = 2°$	$Zc = 3°$
	+	+

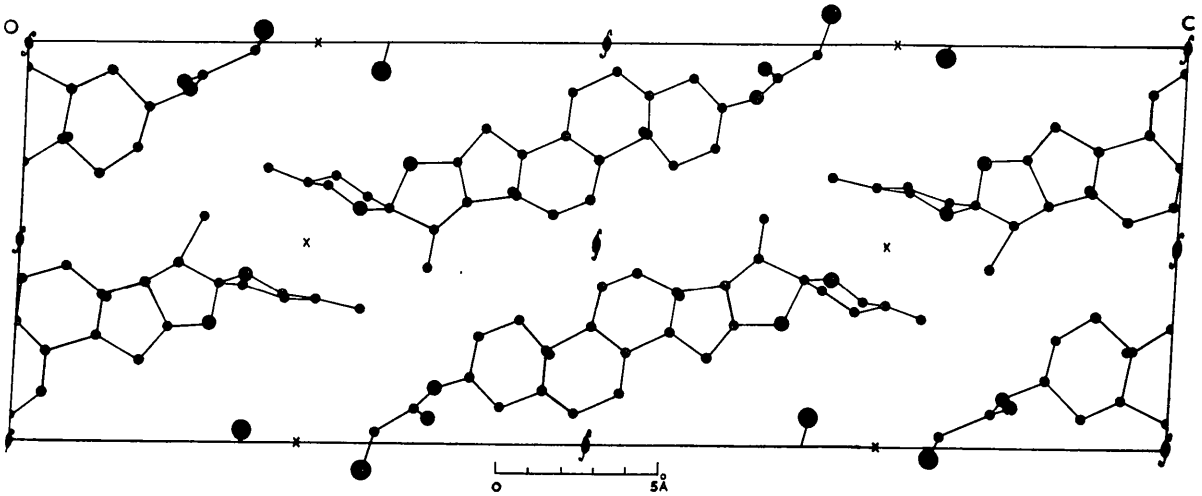


Fig. 6. The packing of the molecules, in projection on (010): the filled circles indicate, in order of increasing size, the atoms of carbon, oxygen and iodine; pseudo-diads are indicated by ×.

The packing of the molecules is shown in projection on (010) in Fig. 6. The sub-period of $c/2$ is clear. Since the two independent molecules have the average coordinates $0{\cdot}3,0{\cdot}0,z$ and $0{\cdot}3,0{\cdot}5,0{\cdot}5+z$, pseudo-diads are introduced; they are indicated by the symbol × in Fig. 6.

The absolute configuration has not been determined in this investigation. However, since diosgenin has been related to cholesterol, the absolute configuration of diosgenin iodoacetate corresponds with the atomic coordinates as listed in Table 2, with respect to right-handed axes.

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