to Dr F. R. Ahmed for programming assistance. This investigation was supported by Public Health Service Research Grant No. CA-15171-01 from the National Cancer Institute.

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The Crystal Structure of the Triterpene Gymnemagenin, $C_{30}H_{50}O_6$

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Gymnemagenin, $C_{30}H_{50}O_6$, is the deacylated aglycone of 'gymnemic acid', the antisweet principle of *Gymnema sylvestre*. The compound crystallizes in the orthorhombic space group $P2_12_12_1$ with 4 molecules in a unit cell of dimensions $a = 12{\cdot}714$ (3), $b = 30{\cdot}99$ (1) and $c = 6{\cdot}954$ (1) Å. The crystal structure has been determined by direct methods, and refined to $R = 0{\cdot}036$ for 2630 observed reflections. The results confirm that the structure of gymnemagenin is 3β,16β,21β,22α,23,28-hexahydroxyolean-12-ene. Four intermolecular and two intramolecular hydrogen bonds per molecule employ all six hydrogens available for hydrogen bonding. Attempts to solve the structure by rigid-body Patterson search techniques led to ambiguous results; these were ultimately found to have arisen from a large, unanticipated distortion of the molecular skeleton from the assumed model.

Introduction

Gymnemagenin (Stöcklin, Weiss & Reichstein, 1967), is the hydrolysis product of gymnemic acid A, a glycoside present in the leaves of *Gymnema sylvestre* R. Br. (*Asclepiadaceae*). Acid A has been shown (Stöcklin *et al.*, 1967; Sinsheimer, Rao, McIlhenny, Smith, Maassab & Cochran, 1968) to be the chief contributor to the long-known strange property of this tropical plant, that of temporarily depressing the ability to taste sweet substances. Chemical and spectral evidence

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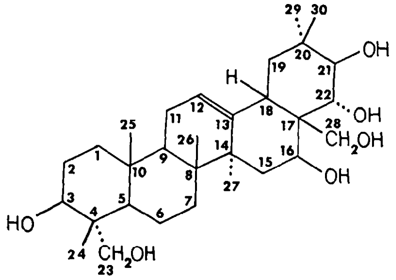
enabled Rao & Sinsheimer (1968), and, independently, Stöcklin (1969*a*) to deduce the structure of gymnemagenin to be 3β,16β,21β,22α,23,28-hexahydroxyolean-12-ene (I).



(I)

This work was undertaken to confirm their conclusions and to provide a model for the eventual elucidation of the structure of the parent compound and antisweet principle, gymnemic acid A, by Patterson search techniques.

Experimental

A small sample of crystalline gymnemagenin was kindly provided by Professor J. E. Sinsheimer. On account of the small amount of available material no density determination was made. The crystal used in this investigation was colorless, and pinacoidal in shape, with approximate dimensions 0·2 × 0·2 × 0·4 mm. X-ray data were collected on a computer-controlled Syntex $P\bar{1}$ diffractometer using Cu $K\alpha$ radiation and a graphite monochromator.

Crystal data

$C_{30}H_{50}O_6$, M.W. 506·7. Orthorhombic, space group $P2_12_12_1$; $a=12{\cdot}714$ (3), $b=30{\cdot}99$ (1), $c=6{\cdot}954$ (1) Å; $V=2739{\cdot}9$ Å^3, $Z=4$; $D_x=1{\cdot}230$ g cm^{-3}; $F(000)=1112$; μ for Cu $K\alpha$ ($\lambda=1{\cdot}5418$ Å) $=7{\cdot}8$ cm^{-1}.

Reflections were recorded by $\theta/2\theta$ scans from 0·9° below α_1 to 1·0° above α_2, with a scanning speed varying between 1° min^{-1} and 24° min^{-1} depending on the intensity of the peak. The intensities of the reflections 193 and 5,20,1 were monitored every 40 reflections; their intensity showed no significant change with time. All 2998 reflections with 2θ less than 140° were recorded in this manner. The intensities and their standard deviations were corrected for Lorentz and polarization factors and the polarization of the monochromator, but not for absorption.

Phase determination

Normalized structure factors, $|E|$, were calculated with an overall isotropic temperature factor of 3·07 Å^2 and overall scale determined by Wilson's method.

The phases of four reflections were assigned to specify the origin and enantiomorph:

h	k	l	$\|E\|$	φ
0	22	3	4·89	0
1	14	0	4·03	90
4	27	0	2·55	0
0	21	4	2·55	90

The application of the phase-determining formula $\varphi_{\mathbf{h}} \simeq \varphi_{\mathbf{k}} + \varphi_{\mathbf{h}-\mathbf{k}}$ and the introduction of symbols for phases of 0,35,2 ($|E|=3{\cdot}63$) and 073 ($|E|=2{\cdot}48$) allowed assignment of phases with a high degree of probability (low variance) to 19 reflections. Iterative application of the tangent formula (Karle & Hauptman, 1956) in the *TANGEN* program of the X-RAY system (Stewart, Kundell & Baldwin, 1970) was carried out for each of the four possible sets of phases. In the attempted phasing of 180 $|E|$ values greater than 1·8, one of the four possible solutions was better than the others on the basis of an 'R value' calculated from $|E|_{\text{calc}}$ values obtained as described by Karle & Karle (1966). The four R values were 0·27, 0·25, 0·30 and 0·21. Tangent iteration was then used to extend the $R=0{\cdot}21$ solution to 282 E values greater than 1·6, giving a final 'R value' of 0·21 for the 282 E values. The 282 reflections were used to calculate an E map which clearly showed the positions of all non-hydrogen atoms.

Refinement

Three-dimensional refinement was commenced with the least-squares program *CLS* (Schilling, 1970*a*). The quantity minimized was $\sum w[F_o-(1/K)F_c]^2$ where $w=1/\sigma^2(F_o)$, as derived from counter statistics. Reflections for which I was less than $3\sigma(I)$ were considered 'unobserved' and assigned zero weight. Atomic scattering factors for carbon and oxygen were obtained from *International Tables for X-ray Crystallography* (1962). The hydrogen scattering factors were those of Stewart, Davidson & Simpson (1965).

The block-diagonal algorithm was used throughout the refinement. The scale factor was placed in a 2 × 2 block with a dummy overall thermal parameter, whose indicated shifts were never applied (Cruickshank, Pilling, Bujosa, Lovell & Truter, 1961).

Refinement of positional and isotropic thermal parameters for carbons and oxygens resulted in an R value of 0·16. Introduction of anisotropic thermal parameters with further refinement reduced the R value to 0·106. A difference map was then calculated, from which the positional parameters for all hydrogens attached to carbons were obtained. Subsequent positional and isotropic thermal parameter refinement for the hydrogens was followed by another difference map which now readily indicated the positions of the remaining hydrogens (attached to oxygens). The final cycles of refinement were carried out (anisotropic thermal parameters for carbons and oxygens, isotropic thermal parameters for hydrogens), resulting in a final R value of 0·036 (weighted R value 0·039) for 2630 nonzero weight reflections. Reflections 011, 101, 110, 200,

Table 1. *Atomic parameters for carbon and oxygen atoms*

Thermal parameters are of the form exp $[-2\pi^2(U_{11}h^2a^{*2}+2U_{12}hka^*b^*+\ldots)]$. Estimated standard deviations of the last figure are given in parentheses.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	−0·0526 (3)	0·30751 (7)	0·1259 (4)	0·054 (2)	0·019 (1)	0·037 (1)	0·003 (1)	−0·015 (2)	0·000 (1)
C(2)	−0·0570 (3)	0·35687 (7)	0·1090 (4)	0·062 (2)	0·022 (1)	0·033 (1)	0·006 (1)	−0·010 (2)	0·002 (1)
C(3)	−0·0458 (2)	0·37782 (7)	0·3041 (4)	0·046 (2)	0·016 (1)	0·035 (1)	0·001 (1)	0·003 (1)	0·000 (1)
C(4)	0·0564 (2)	0·36606 (7)	0·4100 (4)	0·038 (1)	0·015 (1)	0·028 (1)	−0·001 (1)	0·003 (1)	−0·001 (1)
C(5)	0·0617 (2)	0·31579 (7)	0·4207 (3)	0·035 (1)	0·018 (1)	0·023 (1)	−0·001 (1)	0·001 (1)	−0·001 (1)
C(6)	0·1551 (2)	0·29780 (7)	0·5316 (4)	0·040 (2)	0·019 (1)	0·033 (1)	−0·001 (1)	−0·006 (1)	−0·004 (1)
C(7)	0·1364 (2)	0·25030 (7)	0·5856 (4)	0·042 (2)	0·019 (1)	0·028 (1)	0·000 (1)	−0·008 (1)	−0·001 (1)
C(8)	0·1141 (2)	0·22075 (7)	0·4113 (4)	0·033 (1)	0·017 (1)	0·024 (1)	0·001 (1)	−0·001 (1)	−0·000 (1)
C(9)	0·0320 (2)	0·24235 (7)	0·2777 (4)	0·041 (2)	0·017 (1)	0·026 (1)	0·000 (1)	−0·006 (1)	0·000 (1)
C(10)	0·0492 (2)	0·29142 (7)	0·2254 (3)	0·041 (2)	0·017 (1)	0·023 (1)	−0·001 (1)	−0·000 (1)	0·000 (1)
C(11)	0·0095 (3)	0·21395 (8)	0·1002 (4)	0·079 (2)	0·018 (1)	0·029 (1)	−0·001 (1)	−0·015 (2)	−0·002 (1)
C(12)	0·0167 (2)	0·16626 (7)	0·1387 (4)	0·055 (2)	0·018 (1)	0·025 (1)	−0·002 (1)	−0·006 (1)	−0·003 (1)
C(13)	0·0429 (2)	0·14785 (7)	0·3058 (3)	0·031 (1)	0·017 (1)	0·025 (1)	0·001 (1)	−0·002 (1)	−0·003 (1)
C(14)	0·0655 (2)	0·17602 (6)	0·4810 (3)	0·032 (1)	0·016 (1)	0·022 (1)	0·002 (1)	−0·003 (1)	−0·001 (1)
C(15)	0·1408 (2)	0·15342 (7)	0·6236 (4)	0·035 (1)	0·018 (1)	0·026 (1)	0·004 (1)	−0·007 (1)	−0·001 (1)
C(16)	0·1246 (2)	0·10461 (7)	0·6451 (3)	0·037 (1)	0·021 (1)	0·022 (1)	0·006 (1)	−0·007 (1)	−0·002 (1)
C(17)	0·1298 (2)	0·08079 (7)	0·4485 (4)	0·030 (1)	0·018 (1)	0·025 (1)	0·004 (1)	−0·001 (1)	0·000 (1)
C(18)	0·0397 (2)	0·09909 (6)	0·3222 (3)	0·028 (1)	0·016 (1)	0·025 (1)	0·001 (1)	−0·002 (1)	−0·002 (1)
C(19)	−0·0700 (2)	0·08296 (7)	0·3871 (4)	0·030 (1)	0·018 (1)	0·045 (2)	−0·002 (1)	0·002 (1)	−0·001 (1)
C(20)	−0·0788 (2)	0·03330 (7)	0·3857 (4)	0·034 (1)	0·019 (1)	0·045 (2)	−0·002 (1)	0·006 (1)	−0·001 (1)
C(21)	0·0066 (2)	0·01628 (7)	0·5242 (4)	0·053 (2)	0·013 (1)	0·033 (1)	−0·001 (1)	0·006 (1)	0·001 (1)
C(22)	0·1168 (2)	0·03106 (7)	0·4690 (4)	0·038 (1)	0·020 (1)	0·032 (1)	0·006 (1)	−0·005 (1)	0·000 (1)
C(23)	0·0469 (3)	0·38251 (8)	0·6201 (4)	0·068 (2)	0·021 (1)	0·030 (1)	0·005 (1)	0·000 (2)	−0·006 (1)
C(24)	0·1535 (2)	0·38756 (8)	0·3203 (5)	0·043 (2)	0·022 (1)	0·051 (2)	−0·008 (1)	0·006 (2)	−0·003 (1)
C(25)	0·1422 (3)	0·29870 (8)	0·0868 (4)	0·063 (2)	0·025 (1)	0·033 (1)	−0·000 (1)	0·017 (2)	0·001 (1)
C(26)	0·2200 (2)	0·21310 (8)	0·3059 (4)	0·036 (1)	0·028 (1)	0·047 (2)	0·001 (1)	0·009 (1)	−0·001 (1)
C(27)	−0·0419 (2)	0·18255 (7)	0·5868 (4)	0·036 (1)	0·025 (1)	0·031 (1)	0·004 (1)	0·006 (1)	−0·003 (1)
C(28)	0·2360 (2)	0·08896 (8)	0·3480 (4)	0·034 (1)	0·029 (1)	0·033 (1)	0·002 (1)	0·001 (1)	−0·005 (1)
C(29)	−0·1873 (3)	0·02063 (9)	0·4601 (6)	0·045 (2)	0·029 (1)	0·088 (3)	−0·009 (1)	0·019 (2)	0·000 (2)
C(30)	−0·0671 (2)	0·01621 (8)	0·1787 (4)	0·047 (2)	0·023 (1)	0·048 (2)	−0·001 (1)	−0·009 (2)	−0·008 (1)
O(3)	−0·0567 (2)	0·42366 (5)	0·2758 (3)	0·053 (1)	0·018 (1)	0·044 (1)	0·006 (1)	0·001 (1)	0·002 (1)
O(16)	0·2034 (2)	0·09103 (5)	0·7802 (3)	0·057 (1)	0·031 (1)	0·030 (1)	0·013 (1)	−0·016 (1)	−0·001 (1)
O(21)	0·0041 (2)	−0·02985 (5)	0·5428 (3)	0·073 (1)	0·016 (1)	0·037 (1)	−0·001 (1)	0·008 (1)	0·006 (1)
O(22)	0·1919 (2)	0·01694 (6)	0·6098 (3)	0·069 (1)	0·022 (1)	0·058 (1)	0·010 (1)	−0·028 (1)	0·001 (1)
O(23)	0·0259 (2)	0·42789 (6)	0·6173 (3)	0·107 (2)	0·024 (1)	0·039 (1)	0·013 (1)	0·004 (1)	−0·008 (1)
O(28)	0·2445 (2)	0·06716 (5)	0·1668 (3)	0·052 (1)	0·029 (1)	0·032 (1)	0·012 (1)	0·007 (1)	−0·001 (1)

201, and 210 were excluded in the later stages of the refinement, since they show large effects of extinction (F_o consistently much less than F_c).* The positional and thermal parameters for the final structure are given in Tables 1 and 2 respectively.

Table 2. *Atomic parameters for hydrogen atoms*

Estimated standard deviations for the least significant figure are given in parentheses.

	x	y	z	B (Å^2)
H′(1)	−0·116 (3)	0·294 (1)	0·192 (5)	4·9 (8)
H″(1)	−0·066 (3)	0·293 (1)	−0·009 (5)	6·0 (9)
H′(2)	−0·126 (3)	0·366 (1)	0·048 (5)	5·2 (8)
H″(2)	0·009 (3)	0·366 (1)	0·023 (5)	5·9 (10)
H(C3)	−0·110 (2)	0·365 (1)	0·390 (4)	1·9 (5)
H(5)	−0·005 (2)	0·306 (1)	0·491 (4)	2·2 (5)
H′(6)	0·220 (2)	0·297 (1)	0·460 (5)	4·8 (8)
H″(6)	0·177 (3)	0·314 (1)	0·656 (5)	5·7 (9)
H′(7)	0·203 (2)	0·236 (1)	0·663 (5)	4·6 (8)
H″(7)	0·074 (2)	0·251 (1)	0·673 (5)	4·1 (7)
H(9)	−0·306 (2)	0·244 (1)	0·351 (4)	3·0 (6)
H′(11)	−0·073 (3)	0·219 (1)	0·050 (5)	5·7 (9)
H″(11)	0·064 (3)	0·221 (1)	−0·007 (5)	6·4 (9)
H(12)	−0·002 (2)	0·149 (1)	0·024 (4)	3·1 (6)
H′(15)	0·129 (2)	0·165 (1)	0·759 (4)	3·7 (7)
H″(15)	0·219 (2)	0·160 (1)	0·588 (4)	3·7 (7)
H(C16)	0·053 (2)	0·097 (1)	0·711 (4)	4·1 (7)
H(18)	0·051 (2)	0·089 (1)	0·195 (4)	1·8 (5)
H′(19)	−0·093 (2)	0·095 (1)	0·527 (4)	3·1 (7)
H″(19)	−0·129 (2)	0·097 (1)	0·300 (5)	4·4 (7)
H(C21)	−0·012 (2)	0·028 (1)	0·671 (5)	4·5 (8)
H(C22)	0·134 (2)	0·018 (1)	0·322 (4)	3·5 (7)
H′(C23)	−0·025 (2)	0·366 (1)	0·682 (4)	2·9 (6)
H″(C23)	0·119 (2)	0·380 (1)	0·680 (4)	3·2 (6)
H(24)	0·228 (3)	0·373 (1)	0·365 (6)	7·2 (10)
H″(24)	0·158 (2)	0·416 (1)	0·350 (5)	4·5 (8)
H‴(24)	0·170 (3)	0·385 (1)	0·173 (6)	6·4 (9)
H′(25)	0·219 (2)	0·302 (1)	0·159 (5)	4·9 (8)
H″(25)	0·154 (3)	0·276 (1)	0·003 (6)	6·3 (10)
H‴(25)	0·144 (3)	0·324 (1)	0·015 (6)	6·6 (10)
H′(26)	0·253 (2)	0·241 (1)	0·270 (5)	4·7 (8)
H″(26)	0·271 (3)	0·197 (1)	0·390 (5)	6·7 (9)
H‴(26)	0·214 (2)	0·196 (1)	0·189 (5)	5·0 (8)
H′(27)	−0·103 (2)	0·191 (1)	0·496 (5)	4·4 (7)
H″(27)	−0·042 (2)	0·205 (1)	0·683 (5)	4·8 (8)
H‴(27)	−0·068 (2)	0·156 (1)	0·664 (5)	4·5 (8)
H′(C28)	0·251 (2)	0·121 (1)	0·325 (4)	3·2 (6)
H″(C28)	0·298 (2)	0·078 (1)	0·429 (4)	4·1 (7)
H′(29)	−0·197 (2)	−0·008 (1)	0·475 (5)	5·3 (8)
H″(29)	−0·201 (3)	0·035 (1)	0·597 (5)	6·2 (9)
H‴(29)	−0·244 (3)	0·033 (1)	0·377 (6)	8·1 (10)
H′(30)	−0·114 (2)	0·035 (1)	0·089 (5)	5·2 (8)
H″(30)	0·002 (2)	0·021 (1)	0·120 (4)	4·1 (7)
H‴(30)	−0·088 (2)	−0·014 (1)	0·169 (4)	4·0 (7)
H(O3)	−0·045 (3)	0·436 (1)	0·381 (6)	7·6 (10)
H(O16)	0·216 (3)	0·066 (1)	0·762 (6)	7·4 (11)
H(O21)	0·016 (3)	−0·038 (1)	0·451 (6)	7·2 (10)
H(O22)	0·183 (3)	−0·010 (1)	0·624 (5)	7·4 (10)
H(O23)	0·014 (3)	0·439 (1)	0·727 (6)	8·5 (11)
H(O28)	0·220 (3)	0·083 (1)	0·092 (6)	7·3 (10)

Discussion

The results confirm the predicted molecular structure (I). An *ORTEP* drawing (Johnson, 1965) is shown in Fig. 1. Intramolecular distances and angles involving non-hydrogen atoms are given in Fig. 2, superimposed

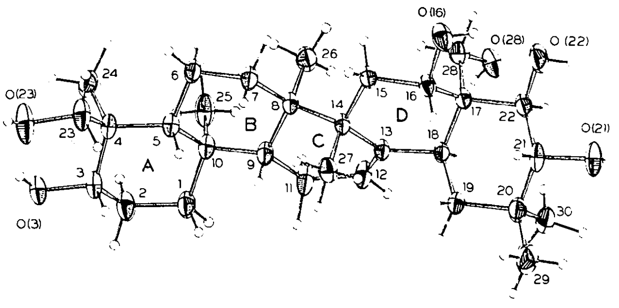


Fig. 1. *ORTEP* drawing of the gymnemagenin molecule, with carbon and oxygen atoms shown as 50% probability thermal ellipsoids.

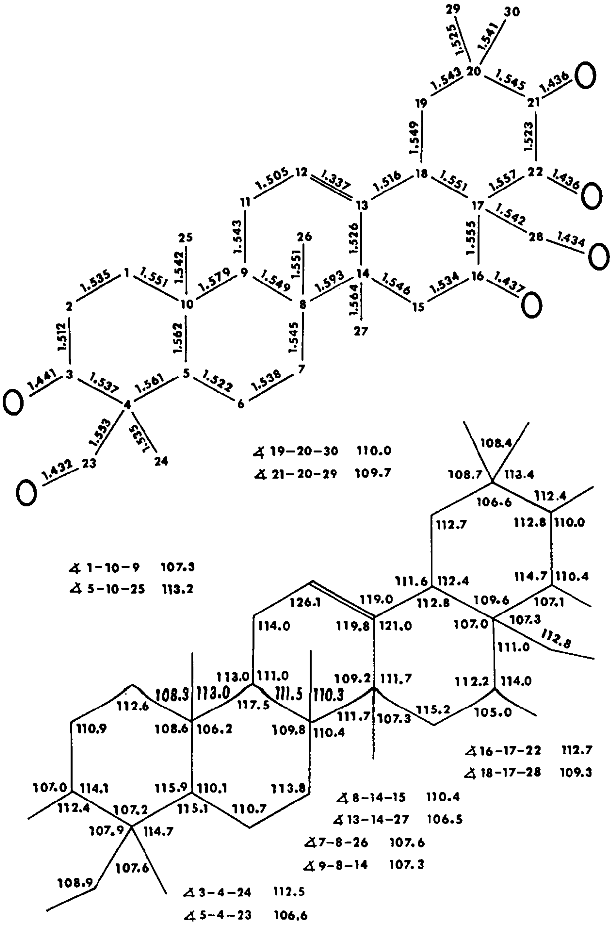


Fig. 2. Intramolecular distances and angles involving non-hydrogen atoms. E.s.d.s' from block-diagonal refinement are: C–C, 0·003–0·004 Å; C–O, 0·003 Å; C–C–C and C–C–O, 0·2°.

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* A table of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30387 (18 pp., 1 microfiche). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Hydrogen bonding: distances and angles*

	O···O	C–O···O	O–H	H···O	C–O–H	H–O···O
C(23)–O(23)–H···O(21^{i})	2·729 Å	119·0°	0·85 Å	1·89 Å	114°	5°
C(21)–O(21)–H···O(3^{ii})	2·726	116·6	0·71	2·04	106	11
C(22)–O(22)–H···O(28^{iii})	2·757	125·5	0·85	2·02	107	25
C(28)–O(28)–H···O(16^{iv})	2·837	134·1	0·78	2·19	106	30
C(3)—O(3)—H···O(23)	2·600	83·4	0·84	1·89	108	27
C(16)–O(16)–H···O(22)	2·588	85·5	0·79	1·89	108	23
e.s.d.	0·003	0·2	0·04	0·04	3	3

on schematic diagrams of the gymnemagenin molecule. The C–C single bonds, excluding those adjacent to the C(12)–C(13) double bond, range from 1·512 to 1·593 Å in length, with a mean value of 1·546 Å. There are significant deviations from this mean, possibly associated with the large distortions caused by the axial methyl groups (see below and Fig. 3). The single bonds involving C(12) and C(13) are, as expected (Bartell & Bonham, 1960), significantly shorter than the above means. The C–O bond lengths range from 1·432 to 1·441 Å with a mean value of 1·436 Å. There is no significant deviation from this value. C–H bond lengths vary from 0·91 to 1·12 with a mean value of 1·03 Å, while O–H bond lengths vary from 0·71 to 0·85 with a mean value of 0·80 Å. There are no significant deviations of individual lengths from these values.

Fig. 3 shows the distortions in the actual molecule compared to a model generated assuming that the C(11)–C(12)=C(13)–C(14) grouping is planar with a C=C distance of 1·34 Å, and assuming that angles not including C(12) and C(13) are tetrahedral with a C–C distance of 1·54 Å and a C–O distance of 1·44 Å. The actual molecule was rotated and translated so that the best fit occurred between it and the generated model for the 18 atoms in rings *A*, *B*, *C*, and *D*. The differences occur as a twist about the long direction of the molecule and a bend along that direction so that axial atoms 24, 25, and 26 are further removed from each other.

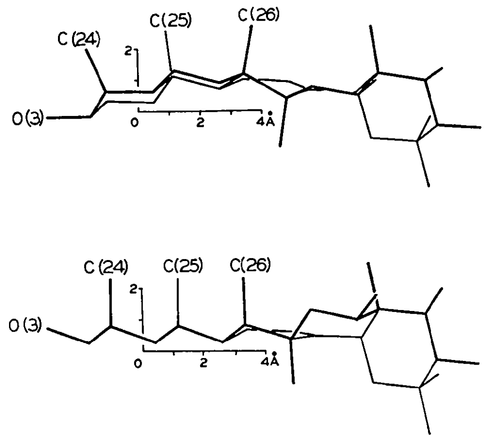

Fig. 3. Comparative views of a mathematically generated, undistorted model of gymnemagenin (bottom) and 'best fit' for atoms in rings *A*, *B*, *C*, and *D* in the true, distorted molecule.

Table 3 (*cont.*)

Superscript	Coordinates		
None	x	y	z
i	$-x$	$y+0·5$	$-z+1·5$
ii	$-x$	$y-0·5$	$-z+0·5$
iii	$-x+0·5$	$-y$	$z+0·5$
iv	x	y	$z-1·0$

Fig. 4 shows the packing in the unit cell. The molecules are arranged in such a way that all the oxygens cluster about the screw axis in the z direction. A system of hydrogen bonds exists which involves four distinct intermolecular hydrogen bonds, shown by dashed lines in Fig. 4, joining molecules in a three-dimensional network. A molecule of gymnemagenin contains six hydrogens theoretically capable of forming hydrogen bonds between the six oxygens in the molecule. The remaining two hydrogens are directed toward neighbouring oxygens in the same molecule, indicating the existence of possible intramolecular hydrogen bonding. The parameters associated with these hydrogen bonds are summarized in Table 3.

Vector search

The determination of the structure of gymnemagenin was first attempted unsuccessfully with vector search methods using various search groups consisting of different groups of atoms from the theoretical model of Fig. 3. It was only after the structure was solved that the full extent of the distortion of the actual structure was realized. When one of the search groups (consisting of the *A*, *B*, *C*, and *D* rings) is fitted, by the method of least squares, to the final coordinates, the 'best' fit is one for which the average deviation of equivalent atoms is 0·41 Å, with the maximum deviation in the position of one atom being 0·83 Å. Since these deviations exceed the 0·33 Å estimated half-width of a single vector peak in the sharpened Patterson function used in the searches, it is clear why vector search proved to be unsuccessful in this case.

Small errors in a search model can be compensated by the application of a damping factor to the Patterson coefficients, and by use of an image-seeking function such as the minimum average function (Schilling, 1970*b*). The errors in the model of the gymnemagenin

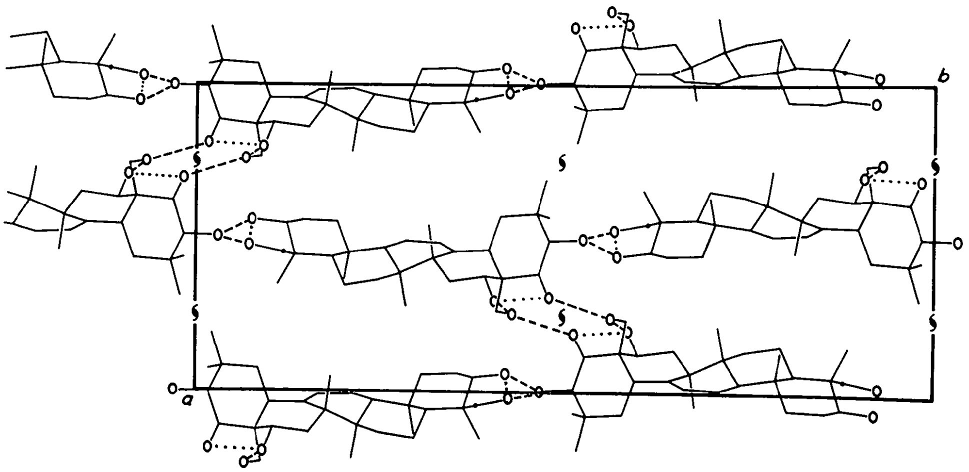

Fig. 4. Projection of the gymnemagenin structure along [001]. Intermolecular and intramolecular hydrogen bonds are indicated; the former with dashed, the latter with dotted lines.

skeleton used in these searches were, however, too great.

Test searches with the true conformation of the gymnemagenin skeleton, using coordinates at the $R=0{\cdot}12$ stage of refinement, showed both the rotational and translational solutions clearly and unambiguously.

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