den unter Annahme dieses Atomformfaktors verfeinerten Angleichungsfaktoren für die Reflexgruppen mit $k \equiv 0 (\mathrm{mod}\ 3)$ und $k \equiv 0 (\mathrm{mod}\ 5)$ steht mit dem experimentell ermittelten Wert im Einklang. Die aus dem obengenannten 'Zellinhalt' errechnete Dichte beträgt 4,53 g cm^{-3} und stimmt mit dem von Takahashi *et al.* (1971) gemessenen Wert (4,45 g cm^{-3}) relativ gut überein. Aus einer alternativen Lösung, 12 La- und 12 S-Lagen leer zu lassen, würde sich eine berechnete Dichte von 4,24 g cm^{-3} ergeben. Eine andere Lösung, mehrere CrS_2-Schichten unmittelbar aufeinander zu stapeln, hält die OD-theoretischen Nachbarschaftsbedingungen nicht ein und würde ausserdem grosse Schwierigkeiten beim lokalen Ladungsausgleich bereiten; denn die Schichten sind offensichtlich elektrisch nicht neutral.

Die mit dem Programm *ORFFE* (Busing, Martin & Levy, 1964) berechneten interatomaren Abstände und Winkel sind in Tabelle 4 aufgeführt. Für die Abstände La—S(2) und S(1)—S(2), die wegen des Fehlens einer kommensurablen Beziehung zwischen verschiedenartigen Schichten nicht sinnvoll definiert werden können, ist jeweils der minimal mögliche Wert angegeben. Die Störung im LaS-Teil wurde nicht berücksichtigt. Alle Werte liegen aber in einem sinnvollen Bereich. Auf die Angabe der geschätzten Standardabweichungen wurde verzichtet.

Zur Beobachtung des Zwillingsgefüges bzw. zur Ermittlung der strukturellen Einzelheiten, die im Rahmen dieser Arbeit nicht geklärt werden konnten, sind die zur Zeit in Aussicht genommenen Untersuchungen mit hochauflösender Elektronenmikroskopie sicher angebracht.

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Crystal and Molecular Structure of Glycyrrhetinic Acid Acetone Monohydrate

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Glycyrrhetinic acid acetone monohydrate (1 : 1 : 1) crystallizes in the orthorhombic space group $P2_12_12$ with $a = 11{\cdot}541$, $b = 36{\cdot}328$, $c = 7{\cdot}406$ Å. The crystal structure was solved by direct methods and refined to $R = 0{\cdot}057$ for 2573 reflexions. All the molecules are linked together by hydrogen bonds; water plays a particularly important role in the crystal packing. Conformational similarities between glycyrrhetinic acid and mineralocorticoids are emphasized.

Introduction

The medicinal properties of licorice (*Glycyrrhiza glabra* L.) have been well known since antiquity, and are still used and studied extensively [*cf.* for instance a recent review by Balthassat-Millet & Ferry (1976)]. Glycyrrhetinic acid (GA), 3β-hydroxy-11-oxo-18β-olean-12-en-30-oic acid, isolated from this plant has,

Table 1. *Conditions of crystallization*

Solvent	Conditions of crystallization	Crystal	Comments
Acetone	Evaporation at room temperature	Plates	Space group $P1$, $Z = 4$, too many atoms in the unit cell
Chloroform	Slow evaporation at room temperature	Plates	Solvate (1 : 1), three chlorine atoms for one molecule GA
Methanol + petroleum spirit	Evaporation at low temperature (~4° C)	Narrow plates (~ needles)	$P2_1$, $Z = 8$, too many atoms in the unit cell
Acetone	Evaporation at low temperature (~4° C)	Plates	$P2_12_12_1$, $Z = 4$, modification retained for structure determination

among other properties, mineralocorticoid and anti-inflammatory properties. Its structure determination thus fits in with our research on mineralocorticoids.

Experimental

GA (Merck) crystallizes in different polymorphic modifications or solvates according to the solvent and the conditions of crystallization. Table 1 gives a brief summary of the different situations encountered and also reasons why we did not study some of the modifications obtained.

The most important crystallographic and physical data are given in Table 2 while Table 3 lists the programs used in the calculations.

The structure was determined by direct methods (program *MULTAN*) which gave 128 sets of phases (four parameters). The real solution corresponds to the 10th COMBINED FOM, 34th ABS FOM, 5th ψ_0 and 11th RESID. An E map computed with these phases revealed 29 atomic positions, with an R index of 0·44. The other atoms were obtained from an $(F_o - F_c)$ synthesis. H positions were then corrected with the help of program *COOR* and remained fixed during refinement.*

Description of the structure

Fig. 1 shows the atomic numbering of GA and the solvent molecules (water and acetone). Atomic coordinates are in Table 4 and the bond lengths, valency angles and torsional angles in Tables 5, 6 and 7.

Most of the bond lengths and valency angles are close to expected values, but, as in steroids, a few are greater.

The rings adopt chair (A, B, D and E) or envelope (C) conformations. All the ring junctions are *trans* except DE which is *cis*. This can easily be seen in the stereoscopic views (Figs. 2 and 3).

Angles between some mean planes are listed in Table 8.

Table 2. *Physical and crystallographic data*

$C_{30}H_{46}O_4.H_2O.CH_3COCH_3$ (1 : 1 : 1)
Space group: $P2_12_12_1$, $Z = 4$
$a = 11{\cdot}541$ Å
$b = 36{\cdot}328$
$c = 7{\cdot}406$
$F(000) = 1200$
$D_x = 1{\cdot}17$ g cm^{-3}
$\lambda(\mathrm{Cu}\ K\alpha) = 1{\cdot}5418$ Å
$V = 3105{\cdot}1$ Å^3
$\mu = 6{\cdot}31$ cm^{-1}
$M_r = 470{\cdot}69\ (+18{\cdot}02 + 58{\cdot}08) = 546{\cdot}79$
Crystal dimensions: 0·5 × 0·5 × 0·1 mm
Number of reflexions measured: 3097
Number of reflexions observed: 2593 [$I > 2\sigma(I)$]
Lorentz and polarization corrections: yes
Absorption correction: no

Table 3. *Programs*

Operation	Name	Origin
Data reduction	*DATRED*	Adapted from Main (1970)
Direct methods	*MULTAN*	Declercq, Germain, Main & Woolfson (1973), Koch (1974)
Fourier transform	*FFT*	
Refinement (block diagonal)	*NRC*-10	Ahmed, Hall, Pippy & Saunderson (1967)
Calculation of positions	*COOR*	Local program (Dupont)
Bond lengths and valency angles	*NRC*-12	Ahmed *et al.* (1967)
Mean planes	*NRC*-22	Ahmed *et al.* (1967)
Torsional angles	*TORS*	Local program (Dupont)
Representations of the molecule and the structure	*ORTEP*-II	Johnson (1971)
Comparison of molecules	*CSCS*	Local program (Campsteyn)
Conformation of rings	*CRPO*	Local program (Campsteyn) from Cremer & Pople (1975)

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* Lists of structure factors, and thermal and H atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32720 (29 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

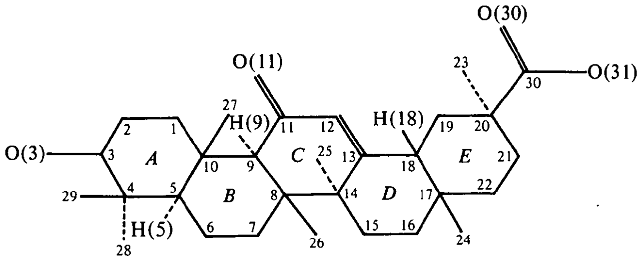

Fig. 1. Numbering of atoms in glycyrrhetinic acid, water [O(50)] and acetone [C(60)–C(61)O(61)–C(62)]. When only one H atom is directly linked to C_i, its number is *i* [except C(12)–H(120)]. When two (or three) atoms are linked to C_i, their numbers are H(*i*1), H(*i*2) [H(*i*3)]. Hydrogen atoms of hydroxyls O(3) and O(31) and of water O(50) are respectively H(300), H(31) and H(501) and H(502).

Table 4. *Fractional atomic coordinates* ($\times 10^4$) *with estimated standard deviations* ($\times 10^4$) *in parentheses*

	x	*y*	*z*
C(1)	1880 (4)	7064 (1)	4511 (5)
C(2)	1858 (4)	6643 (1)	4353 (6)
C(3)	2750 (4)	6473 (1)	5608 (6)
C(4)	2568 (4)	6574 (1)	7583 (6)
C(5)	2533 (3)	7006 (1)	7719 (5)
C(6)	2441 (4)	7153 (1)	9644 (5)
C(7)	2809 (4)	7558 (1)	9684 (5)
C(8)	2093 (3)	7805 (1)	8417 (4)
C(9)	1965 (3)	7622 (1)	6521 (4)
C(10)	1647 (3)	7201 (1)	6452 (5)
C(11)	1205 (3)	7870 (1)	5339 (5)
C(12)	1362 (4)	8270 (1)	5586 (6)
C(13)	2040 (3)	8424 (1)	6843 (5)
C(14)	2742 (3)	8188 (1)	8137 (5)
C(15)	2956 (4)	8383 (1)	9973 (5)
C(16)	3259 (4)	8790 (1)	9760 (5)
C(17)	2311 (4)	9005 (1)	8757 (5)
C(18)	2155 (3)	8845 (1)	6841 (5)
C(19)	3094 (4)	8962 (1)	5473 (6)
C(20)	3348 (4)	9377 (1)	5427 (6)
C(21)	3631 (4)	9504 (1)	7349 (6)
C(22)	2632 (4)	9417 (1)	8633 (6)
C(23)	4390 (5)	9447 (1)	4169 (8)
C(24)	1173 (4)	8974 (1)	9782 (7)
C(25)	3957 (3)	8133 (1)	7256 (6)
C(26)	893 (4)	7870 (1)	9284 (6)
C(27)	367 (3)	7132 (1)	6958 (6)
C(28)	3640 (5)	6437 (1)	8625 (8)
C(29)	1497 (5)	6382 (1)	8368 (7)
C(30)	2322 (4)	9592 (1)	4682 (6)
C(60)	1463 (6)	5383 (1)	−280 (8)
C(61)	2135 (5)	5553 (1)	1197 (7)
C(62)	3377 (6)	5462 (2)	1308 (10)
O(3)	2758 (3)	6076 (1)	5415 (5)
O(11)	514 (3)	7761 (1)	4221 (5)
O(30)	1473 (4)	9461 (1)	3979 (6)
O(31)	2469 (4)	9951 (1)	4829 (6)
O(50)	4012 (3)	5444 (1)	6404 (6)
O(61)	1675 (4)	5763 (1)	2266 (6)

Table 5. *Bond lengths* (Å) ($\sigma \sim 5 \times 10^{-3}$ Å)

C(1)–C(2)	1·534	C(13)–C(14)	1·520
C(1)–C(10)	1·545	C(13)–C(18)	1·536
C(2)–C(3)	1·518	C(14)–C(15)	1·553
C(3)–C(4)	1·522	C(14)–C(25)	1·559
C(3)–O(3)	1·449	C(15)–C(16)	1·528
C(4)–C(5)	1·571	C(16)–C(17)	1·536
C(4)–C(28)	1·541	C(17)–C(18)	1·543
C(4)–C(29)	1·535	C(17)–C(22)	1·544
C(5)–C(6)	1·527	C(17)–C(24)	1·522
C(5)–C(10)	1·558	C(18)–C(19)	1·543
C(6)–C(7)	1·531	C(19)–C(20)	1·536
C(7)–C(8)	1·540	C(20)–C(21)	1·532
C(8)–C(9)	1·560	C(20)–C(23)	1·542
C(8)–C(14)	1·592	C(20)–C(30)	1·522
C(8)–C(26)	1·545	C(21)–C(22)	1·528
C(9)–C(10)	1·576	C(30)–O(30)	1·208
C(9)–C(11)	1·532	C(30)–O(31)	1·320
C(10)–C(27)	1·544	C(60)–C(61)	1·477
C(11)–C(12)	1·475	C(61)–C(62)	1·474
C(11)–O(11)	1·217	C(61)–O(61)	1·221
C(12)–C(13)	1·338		

Table 6. *Valency angles* (°) ($\sigma \sim 0{\cdot}3$ °)

C(2)–C(1)–C(10)	112·9	C(12)–C(13)–C(18)	117·8
C(1)–C(2)–C(3)	110·4	C(14)–C(13)–C(18)	121·1
C(2)–C(3)–C(4)	113·3	C(8)–C(14)–C(13)	108·9
C(2)–C(3)–O(3)	110·4	C(8)–C(14)–C(15)	111·0
C(4)–C(3)–O(3)	109·7	C(8)–C(14)–C(25)	111·4
C(3)–C(4)–C(5)	107·9	C(13)–C(14)–C(15)	112·3
C(3)–C(4)–C(28)	107·0	C(13)–C(14)–C(25)	106·8
C(3)–C(4)–C(29)	111·4	C(15)–C(14)–C(25)	106·4
C(5)–C(4)–C(28)	108·2	C(14)–C(15)–C(16)	112·8
C(5)–C(4)–C(29)	114·1	C(15)–C(16)–C(17)	112·3
C(28)–C(4)–C(29)	108·0	C(16)–C(17)–C(18)	109·7
C(4)–C(5)–C(6)	114·3	C(16)–C(17)–C(22)	110·5
C(4)–C(5)–C(10)	115·6	C(16)–C(17)–C(24)	109·7
C(6)–C(5)–C(10)	110·9	C(18)–C(17)–C(22)	109·7
C(5)–C(6)–C(7)	109·7	C(18)–C(17)–C(24)	109·3
C(6)–C(7)–C(8)	113·5	C(22)–C(17)–C(24)	107·9
C(7)–C(8)–C(9)	110·6	C(13)–C(18)–C(17)	112·6
C(7)–C(8)–C(14)	109·6	C(13)–C(18)–C(19)	109·5
C(7)–C(8)–C(26)	108·5	C(17)–C(18)–C(19)	114·8
C(9)–C(8)–C(14)	107·4	C(18)–C(19)–C(20)	114·7
C(9)–C(8)–C(26)	110·7	C(19)–C(20)–C(21)	108·4
C(14)–C(8)–C(26)	110·1	C(19)–C(20)–C(23)	109·0
C(8)–C(9)–C(10)	117·7	C(19)–C(20)–C(30)	111·4
C(8)–C(9)–C(11)	108·5	C(21)–C(20)–C(23)	110·2
C(10)–C(9)–C(11)	114·8	C(21)–C(20)–C(30)	110·3
C(1)–C(10)–C(5)	107·4	C(23)–C(20)–C(30)	107·6
C(1)–C(10)–C(9)	107·6	C(20)–C(21)–C(22)	110·8
C(1)–C(10)–C(27)	109·9	C(17)–C(22)–C(21)	114·8
C(5)–C(10)–C(9)	105·7	C(20)–C(30)–O(30)	125·8
C(5)–C(10)–C(27)	114·1	C(20)–C(30)–O(31)	112·2
C(9)–C(10)–C(27)	111·8	O(30)–C(30)–O(31)	122·0
C(9)–C(11)–C(12)	116·0		
C(9)–C(11)–O(11)	124·8	C(60)–C(61)–C(62)	117·2
C(12)–C(11)–O(11)	119·2	C(60)–C(61)–O(61)	121·0
C(11)–C(12)–C(13)	124·7	C(62)–C(61)–O(61)	121·8
C(12)–C(13)–C(14)	121·0		

Table 7. *Torsional angles* (°)

A ring			
C(10)–C(1)–C(2)–C(3)	−58·2	C(2)–C(1)–C(10)–C(9)	167·6
C(1)–C(2)–C(3)–C(4)	58·5	C(2)–C(1)–C(10)–C(27)	−70·3
C(2)–C(3)–C(4)–C(5)	−54·6		
C(3)–C(4)–C(5)–C(10)	53·5	C(1)–C(10)–C(5)–C(6)	174·5
C(4)–C(5)–C(10)–C(1)	−53·2	C(1)–C(10)–C(9)–C(8)	−165·6
C(5)–C(10)–C(1)–C(2)	54·3	C(1)–C(10)–C(9)–C(11)	64·7
B ring		C(6)–C(7)–C(8)–C(26)	75·3
C(5)–C(6)–C(7)–C(8)	57·7	C(6)–C(7)–C(8)–C(14)	−164·5
C(6)–C(7)–C(8)–C(9)	−46·3		
C(7)–C(8)–C(9)–C(10)	45·1	C(7)–C(8)–C(14)–C(15)	−59·4
C(8)–C(9)–C(10)–C(5)	−51·1	C(7)–C(8)–C(14)–C(25)	61·0
C(9)–C(10)–C(5)–C(6)	59·8	C(7)–C(8)–C(9)–C(11)	177·6
C(10)–C(5)–C(6)–C(7)	−65·6	C(7)–C(8)–C(14)–C(13)	178·5
C ring		C(10)–C(9)–C(8)–C(14)	164·6
C(14)–C(8)–C(9)–C(11)	−62·8	C(10)–C(9)–C(8)–C(26)	−75·1
C(8)–C(9)–C(11)–C(12)	36·9	C(10)–C(9)–C(11)–O(11)	−10·3
C(9)–C(11)–C(12)–C(13)	−5·4	C(10)–C(9)–C(11)–C(12)	171·0
C(11)–C(12)–C(13)–C(14)	1·1		
C(12)–C(13)–C(14)–C(8)	−28·1	C(9)–C(8)–C(14)–C(15)	−177·6
C(13)–C(14)–C(8)–C(9)	58·3	C(26)–C(8)–C(14)–C(15)	61·8
		C(8)–C(14)–C(15)–C(16)	−163·9
D ring		C(8)–C(14)–C(13)–C(18)	156·5
C(13)–C(14)–C(15)–C(16)	−41·8	C(12)–C(13)–C(14)–C(15)	−151·5
C(14)–C(15)–C(16)–C(17)	58·1	C(25)–C(14)–C(15)–C(16)	74·7
C(15)–C(16)–C(17)–C(18)	−61·0	C(25)–C(14)–C(13)–C(18)	−83·1
C(16)–C(17)–C(18)–C(13)	48·7	C(11)–C(12)–C(13)–C(18)	176·7
C(17)–C(18)–C(13)–C(14)	−37·4		
C(18)–C(13)–C(14)–C(15)	33·1	C(15)–C(16)–C(17)–C(24)	59·1
		C(15)–C(16)–C(17)–C(22)	177·9
E ring		C(16)–C(17)–C(22)–C(21)	70·9
C(18)–C(17)–C(22)–C(21)	−50·2	C(16)–C(17)–C(18)–C(19)	−77·5
C(17)–C(22)–C(21)–C(20)	59·0	C(12)–C(13)–C(18)–C(17)	147·0
C(22)–C(21)–C(20)–C(19)	−57·7	C(12)–C(13)–C(18)–C(19)	−84·0
C(21)–C(20)–C(19)–C(18)	53·7	C(13)–C(18)–C(17)–C(24)	−71·6
C(20)–C(19)–C(18)–C(17)	−48·6	C(13)–C(18)–C(17)–C(22)	170·2
C(19)–C(18)–C(17)–C(22)	44·0	C(13)–C(18)–C(19)–C(20)	−176·3
C(5)–C(4)–C(3)–O(3)	−178·5	C(6)–C(5)–C(10)–C(27)	−63·4
C(1)–C(2)–C(3)–O(3)	−178·0	C(8)–C(9)–C(10)–C(27)	73·6
C(18)–C(19)–C(20)–C(23)	173·7	C(2)–C(3)–C(4)–C(28)	−170·8
C(18)–C(19)–C(20)–C(30)	−67·8	C(10)–C(5)–C(4)–C(28)	168·9
C(19)–C(20)–C(30)–O(30)	−9·6		
C(19)–C(20)–C(30)–O(31)	172·5	C(2)–C(3)–C(4)–C(29)	71·4
C(22)–C(21)–C(20)–C(23)	−176·9	C(10)–C(5)–C(4)–C(29)	−70·9
C(22)–C(21)–C(20)–C(30)	64·5		
C(21)–C(20)–C(30)–O(30)	−130·0	C(11)–C(9)–C(8)–C(26)	57·4
C(21)–C(20)–C(30)–O(31)	52·0	C(13)–C(14)–C(8)–C(26)	62·3
C(3)–C(4)–C(5)–C(6)	−175·8	C(9)–C(8)–C(14)–C(25)	−59·1
C(4)–C(5)–C(6)–C(7)	161·5	C(12)–C(13)–C(14)–C(25)	92·3
C(6)–C(5)–C(4)–C(28)	−60·5		
C(6)–C(5)–C(4)–C(29)	59·8	C(13)–C(12)–C(11)–O(11)	175·7
C(4)–C(5)–C(10)–C(27)	68·8	C(8)–C(9)–C(11)–O(11)	−144·4
C(4)–C(5)–C(10)–C(9)	−167·9		
C(5)–C(10)–C(9)–C(11)	179·3	C(21)–C(22)–C(17)–C(24)	−169·2
		C(19)–C(18)–C(17)–C(24)	162·2

Molecular orientation and packing

The orientation of the molecule in the unit cell may be defined by the direction cosines of elongation [~$\overrightarrow{\mathrm{C(3)–C(18)}}$ direction], −0·0121, 0·9927, 0·1196, and of the normal to the mean plane, C(1)–C(18), 0·9157, 0·0590, −0·3975.

The shortest van der Waals contact (Table 9) is also

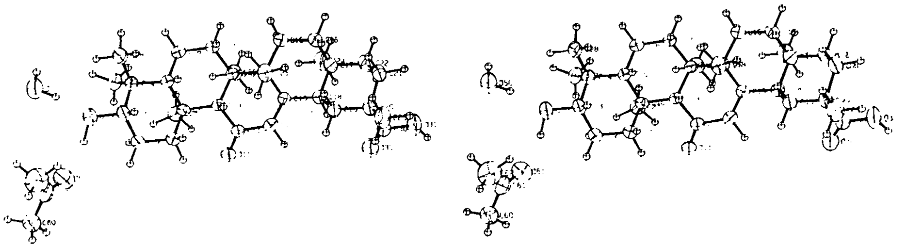

Fig. 2. Stereoscopic view of the molecules.

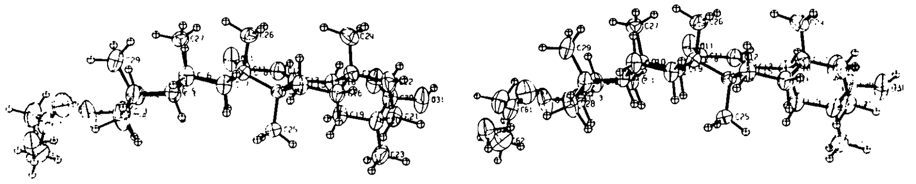

Fig. 3. Stereoscopic view of the molecules.

Table 8. *Angles between mean planes* (°)

Plane I	Plane II	Angle (°)
A	*B*	15·9
B	*C*	13·9
C	*D*	11·4
D	*E*	56·8
ABCD	*E*	52·9

Table 9. *Intermolecular distances* (<3·5 Å)

See Dideberg, Dupont & Campsteyn (1975) for notation.

C(24)–C(28)	3/$\bar{1}$, 1, 2	3·487 (Å)
O(3)–O(50)	1/0, 0, 0	2·812
O(3)–O(61)	1/0, 0, 0	2·879
O(30)–O(50)	3/$\bar{1}$, 1, 1	2·875
O(31)–O(50)	4/0, 0, 1	2·637

by far the most important direct interaction between two molecules of GA [C(24)–C(28), see Table 9]. Acetone is linked to GA by one H bond [O(61)···H(300)–O(3)].

The water molecule is mostly responsible for the cohesion of the crystal: hydrogen bonds around the water molecule are sketched in Fig. 4.

Comparison of the GA conformation with mineralocorticoids and their antagonists

(1) Although the GA chemical formula is quite different from that of steroids, convexities in the region *ABCD* are very similar: in GA the height and angle of the O(3)C(27)C(16) triangle are respectively 2·98 Å and 117·7° which are in the range of experimental values for steroids [O(3)C(19)C(16) triangle – mean values 3·07 Å and 114·9°].

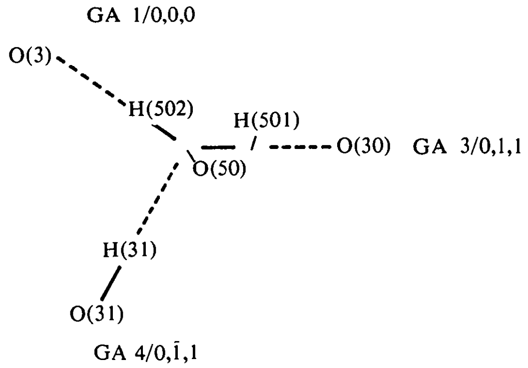

Fig. 4. Hydrogen bonding around the water molecule [O(50)] (for the definition of equivalent positions and translations, see Dideberg *et al.*, 1975).

It is generally accepted that mineralocorticoid activity needs the simultaneous presence of 'interacting' zones at C(3) and C(20)–C(21) for steroids. Geometrical fitting (program *CSCS*) of GA with these compounds (*cf.* Fig. 5) shows that two such functions exist in the acid. O(3) and O(30) positions are, respectively, very close to the conjugated steroid ketone O(3) and hydroxyl O(21). For instance, the fitting of rings *B* and *C* of GA and cortisone acetate gives the following distances:

GA	Cortisone acetate	Distance (Å)
O(3)	O(3)	0·3
O(11)	O(11)	0·3
O(30)	O(21)	0·5

In GA, O(3) lies 12·43 Å from O(30) while in

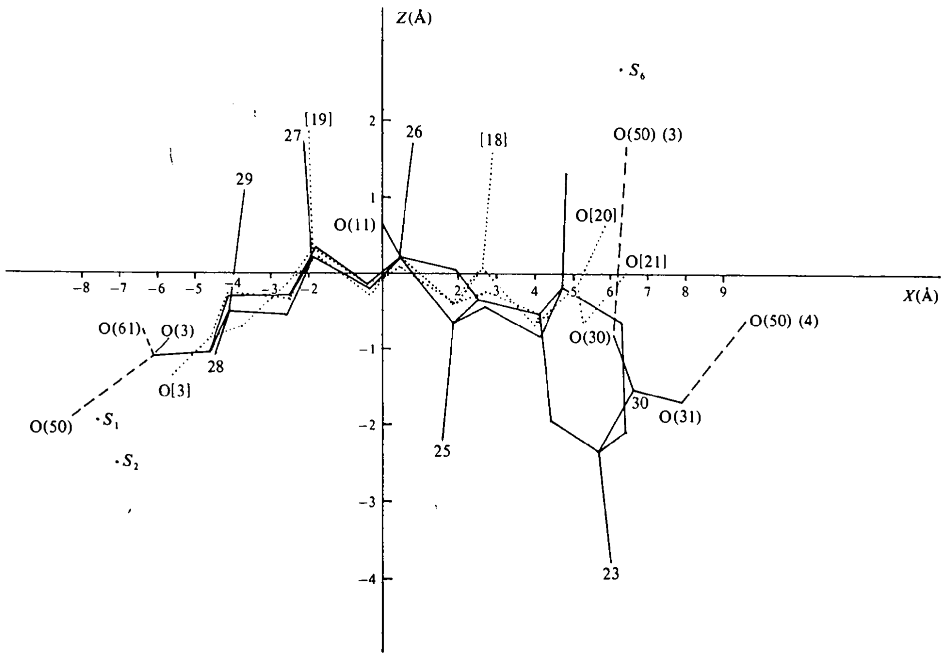

Fig. 5. Projection of GA and mean corticosteroid conformation (Campsteyn *et al.*, to be published; see also Dideberg *et al.*, 1976) with geometrical fitting of rings *B* and *C*. For the definition of sites S_1, S_2 and S_6, see Dideberg *et al.*(1976) (Z scale expansion: 2 × X scale expansion). ·····: mean corticosteroid conformation, ——: GA, – – –: hydrogen bonds.

steroids the distance O(3)–O(21) falls in the range 12·0–12·7 Å.

(2) Interaction sites S_i* around GA: O(3) and O(30) are also similar to the corresponding atoms in steroids. For O(3), O(61) and O(50) are respectively in positions S_1 and S_2; for O(30) [similar to O(21)], O(50) (3) lies in an S_6 position.

Conclusion

The structure determination of GA shows important similarities in shape, position of polar functions and interaction sites with mineralocorticoids and anti-mineralocorticoids. This fits our previous thinking about the necessary conditions of mineralocorticoid activity: a well defined shape of the *ABCD* rings (importance of *β* face of the compound) and two polar functions in the regions C(3) and C(20)–C(21).

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* The sites S_i are the centres of the regions occupied by atoms linked to corticosteroids by hydrogen bonds (Dideberg, Dupont & Campsteyn, 1976).