

The Crystal and Molecular Structure of 3 α ,6 α -Dihydroxy-5 β -cholan-24-oic Acid, C₂₄O₄H₄₀

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The crystal and molecular structure of 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid (C₂₄O₄H₄₀) have been determined by applying the tangent formula to three-dimensional X-ray diffractometer data. The crystals are orthorhombic, *P*2₁2₁2₁, with *a* = 11.574 (2), *b* = 29.921 (4), *c* = 6.443 (2) Å, *Z* = 4. The atomic parameters were refined by block-diagonal least-squares calculations to an *R* value of 0.043. Solution of this structure with two different data sets provided some insight into the tangent iteration process. The structure and hydrogen bonding are compared to other (*A/B*) *cis* C₂₄ steroids.

Introduction

The cholanic acids are a group of (*A/B*) *cis* C₂₄ steroids which have been isolated from the bile acids. They occur as salts of peptide conjugates with glycine or taurine; their general function is to emulsify fats in the lower intestine. 3 α ,6 α -Dihydroxy-5 β -cholan-24-oic acid, which has the structure shown in Fig. 1, was first obtained from the gall bladders of hogs. Its structure has been determined as part of a general program of research aimed at relating structure to function in steroids. The classification of steroid geometry has been formulated by Geise, Altona & Romers (1967) and by Altona, Geise & Romers (1968). The relation between structure and function in steroids has been discussed by Cooper, Norton & Hauptman (1969) and by Weeks, Cooper, Norton, Hauptman & Fisher (1971).

Experimental

Crystal data

Cell dimensions: *a* = 11.574 (2), *b* = 29.921 (4),
c = 6.443 (2) Å.

Space group: *P*2₁2₁2₁ (No. 19), *Z* = 4.

*D*_x = 1.17, *D*_m = 1.17 g cm⁻³.

Radiation used: Cu *K*α with graphite monochromator, μ = 6.2 cm⁻¹.

Intensity data: 2114 unique reflexions measured.

Crystals of 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid have an elongated tabular habit when crystallized by slow evaporation of a solution of methanol and water. A crystal with the dimensions 0.06 × 0.17 × 0.33 mm was selected for data collection. The cell parameters were obtained from a least-squares fit of the diffractometer angles 2θ , φ , and χ of 22 independent reflexions,

assuming a triclinic cell. This gave the cell parameters as above with $\alpha = \beta = \gamma = 90.00$ (1)°.

Diffraction data for this compound were originally measured on a four-circle diffractometer with stationary-counter/stationary-crystal techniques. These data, referred to below as data set 1, were adequate for the solution of the structure but subsequently proved to be of insufficient accuracy to refine the structure below an *R* value ($\sum |\Delta F| / \sum |F_o|$ excluding 'less thans') of 0.19. About two years after the original intensity measurements, a second set of data was collected and the structure was refined to an *R* value of 0.043.

The intensities of the 2114 independent reflexions of data set 2 were measured with a Picker four-circle diffractometer, using graphite-monochromatized Cu *K*α radiation. The 2θ scan rate was 2° min⁻¹ and the scan width was varied according to the angular dispersion (1.4° to 1.8°) out to a 2θ angle of 126°. Background counts were measured each side of the scan for 25 s each. The intensities of three reference reflexions were recorded every 25 measurements in order to monitor crystal and instrumental stability. No significant variation of the reference intensities was observed during the data-collection process.

Generalized absorption corrections were computed on a PDP-8 computer (Gabe & O'Byrne, 1970), by means of Gaussian integration of the crystal shape described above and a μ (Cu *K*α) value of 6.2 cm⁻¹. The measured intensities of 2114 unique reflexions were reduced to structure factors on application of the absorption, Lorentz and polarization factors. Of these reflexions, 342 have *I*(net) values less than 2.58 $\sigma(I_{oi})$ and are coded as 'less thans' with a threshold value of 2.58 $\sigma(I_{oi})$ for subsequent calculations. Secondary extinction was not considered during data reduction, but empirical corrections were made during the refinement.

Structure solution and refinement

The structure was solved by the application of the structure invariant tangent formula (Karle & Hauptman, 1956) to data set 1. Normalized structure factors were calculated and the reflexions with E values greater than 1.4 were used to generate structure-invariant relationships of the type $\varphi_h + \varphi_k + \varphi_{-h-k}$. On the basis of these relationships, four reflexions were selected to fix the cell origin and enantiomorph. These four reflexions enabled four more phases (Table 1) to be estimated from single structure-invariant relationships. To derive further phases with high E values, it was necessary to assign a symbolic phase a to the reflexion 8,13,1. This led directly, through a process of elimination, to the numeric phases of two other reflexions (362 and 962), and to several early indications that the symbol a has the value $3\pi/2$. A numeric phase was assigned to 8,13,1 and to the associated reflexion 13,5,0; this ensured a continuation of the phasing process among reflexions with E values above 1.8. The 12 reflexions shown in Table 1 were used to initiate a tangent-iteration calculation, which was done by means of program *DP5* (Hall, 1968) in which the phases of the 234 reflexions with E values above 1.4 were estimated and refined in successive iterations at five E -threshold values (1.8, 1.7, 1.6, 1.5, and 1.4). The E map, calculated from these phases, indicated clearly the sites of 27 of the 28 non-hydrogen atoms. Despite the apparently unambiguous nature of the solution, refinement of the structural model failed to reduce the R value below 0.19. No conclusive evidence could be found to show whether this was due to the intensity data or to the structural model itself.

At this stage, the data were re-collected and the phasing process was repeated. To initiate the tangent calculation with data set 2, the identical starting reflexions, except for the reflexion 13,5,0 which had an E value less than 1.8, were used. The tangent calculation was performed with the program *TANGEN* in the X-RAY system (Stewart, Kruger, Ammon, Dickenson & Hall, 1972), including constraints identical to

those described above. An E map calculated with the refined phases showed maxima at all 28 non-hydrogen sites located in the first determination. Data set 2 was subsequently used to refine the structure to an R value of 0.043, thus confirming that the intensities of set 1 were imprecisely measured.

A comparison of the application of the tangent formula to these two data sets provides some insight into the dependence of the phasing process on the starting phases. The starting reflexions, listed in Table 1, lead to essentially identical solutions in either data set. Despite this, the phase refined by the tangent-iteration process clearly relates to different cell origins in each case. How did this happen when the starting reflexions used to specify the origin were the same and were fixed in both tangent calculations?

During the tangent calculation involving data set 1, the phases of reflexions 4,21,1 and 8,13,1 changed substantially from their starting values. This was due to their inconsistency with the specified origin. With data set 2, the phases of all starting reflexions except 7,24,1, remained essentially unchanged during the tangent refinement. However, in data set 2, the 'true'

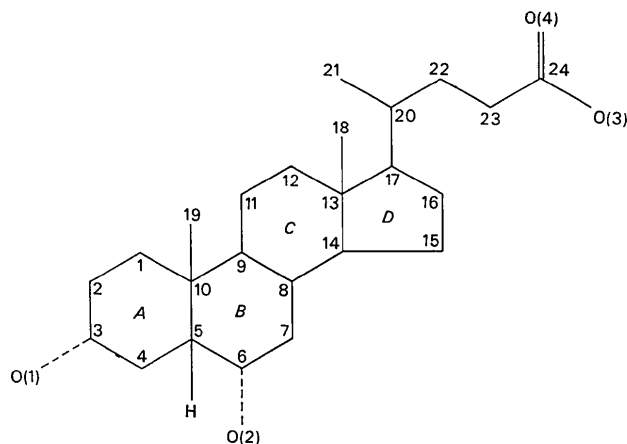


Fig. 1. Conformational diagram of 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid.

Table 1. Reflexions used to initiate tangent-iteration phasing procedures

h	k	l	E	Data set 1			Data set 2		Remarks
				Starting phase	Tangent phase	Final phase	Tangent phase	Final phase	
0	24	3	3.16	0°	0°	0°	0°*	180°	} origin and enantiomorph definition (fixed)
7	0	4	3.06	0	0	0	0	0	
11	3	0	2.55	90	90	90	90	90	
8	13	0	2.16	0	0	0	0	0	
6	0	4	2.29	0	0	0	0	0	
1	13	4	1.95	180	174	171	174	171	
4	21	1	1.92	90	338	331	151	151	
7	24	1	1.86	180	225	240	49	60	
8	13	1	2.17	270	21	46	210	226	} symbol $a = 3\pi/2$
3	6	2	2.08	0	27	25	29	25	
9	6	2	1.86	180	182	222	189	222	
13	5	0	1.82	90	90	90			

* This phase was estimated as 180° in the tangent calculation but was held fixed at 0°.

phase value of the origin-defining reflexion, 0,24,3, is inconsistent with the origin implied by all but one (7,24,1) of the remaining tangent-refined phases. The reason for this is that either one or both starting reflexions, 8,13,1 and 13,5,0, are essential to the rapid extension of the phases among the higher E values. However, the phase value assigned to the former for the tangent calculation is incorrect with respect to the phase of the l -odd, starting reflexion (0,24,3) that had been fixed in order to specify the origin. This means that the influence of 8,13,1 on the tangent calculation is effectively eliminated by the conflicting phase estimates. Therefore, reflexion 13,5,0 dominates in the phase-extension process, and the phases assigned to the l -odd reflexions, 8,13,1 and 4,21,1, are changed, in successive tangent iterations, to values that comply with the specified origin.

In the tangent calculation involving data set 2, the omission of the starting reflexion 13,5,0 changes the equilibrium of the phasing process. Reflexion 8,13,1 is now essential for extension of phase to reflexions with high E values – more important, in fact, than the origin-defining reflexion 0,24,3 with which it is in phase conflict. This results in the phase of 0,24,3, though fixed in value, having no constructive effect on the phasing process, and a shift in origin that satisfies the assigned phase of 8,13,1. The phase of 4,21,1 is now consistent with the new origin, whereas the phase of the other l -odd reflexion, 7,24,1, is not.

The key reason for the difference in the tangent-refined phases between the two data sets is the presence of the 13,5,0 reflexion as a starting phase. Though

this leads to phasing processes that utilize entirely different paths through the structure-invariant relationships, the final tangent-refined phases are, in both cases, internally consistent and correct. It also illustrates another important aspect of the tangent-iteration process that, though several of the early, statistically reliable phase estimates were incorrect (in this instance for reflexions 4,21,1 and 8,13,1), it was still possible for this approach to provide a successful phase refinement and solution.

The structure was refined initially by full-matrix least-squares calculations using the program *CRYLSQ* (Stewart *et al.*, 1972). Unit weights were used throughout the refinement process. The hydrogen atoms were located by means of difference maps. In the structure-factor calculations, the relativistic Hartree-Fock atomic scattering factors of Doyle & Turner (1968) were used for C and O and the curve of Stewart, Davidson & Simpson (1968) for hydrogen. Several rounds of block-diagonal SFLS refinement were done, with anisotropic temperature factors and 9×9 blocks for the 28 non-hydrogen atoms, and isotropic temperature factors with 4×4 blocks for the 38 hydrogen atoms, to reduce the R value to 0.058.

At this stage of the analysis, the calculated structure factors of reflexions with high intensities were consistently higher than the corresponding measured values. An empirical estimate of the secondary extinction coefficient was obtained by plotting the $I(\text{calc.})/I(\text{meas.})$ ratios against $I(\text{calc.})$ values for the reflexions with structure factors above 80 e. The ratio showed a linear increase with $I(\text{calc.})$, which was consistent with

Table 2. Final atomic parameters and standard deviations (in parentheses)

The anisotropic temperature factors are expressed in the form $T = \exp[-2\pi^2(U_{11}a^{*2}h^2 + 2U_{12}a^*b^*hk + \dots) \times 10^{-2}]$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	0.8564 (3)	0.0349 (1)	0.2526 (5)	3.9 (2)	4.2 (2)	5.1 (2)	-0.9 (1)	0.1 (2)	0.6 (2)
C(2)	0.9371 (3)	0.0137 (1)	0.0924 (5)	4.6 (2)	4.1 (2)	4.1 (2)	-0.8 (1)	-0.4 (2)	-0.3 (2)
C(3)	1.0343 (2)	-0.0111 (1)	0.2000 (5)	5.0 (2)	3.7 (2)	4.1 (2)	-0.4 (1)	0.2 (2)	-0.1 (2)
C(4)	1.0988 (2)	0.0185 (1)	0.3519 (5)	4.4 (2)	3.9 (2)	4.0 (2)	0.2 (1)	0.1 (2)	-0.2 (1)
C(5)	1.0181 (3)	0.0414 (1)	0.5097 (4)	4.4 (2)	3.5 (1)	3.7 (2)	-0.1 (1)	0.3 (2)	0.4 (1)
C(6)	1.0866 (2)	0.0718 (1)	0.6559 (5)	4.5 (2)	4.0 (2)	3.2 (2)	0.6 (1)	0.1 (2)	0.5 (1)
C(7)	1.1351 (2)	0.1127 (1)	0.5469 (5)	4.2 (2)	3.7 (2)	3.8 (2)	0.1 (1)	-0.8 (2)	0.1 (1)
C(8)	1.0365 (2)	0.1391 (1)	0.4440 (5)	3.8 (2)	3.4 (1)	3.5 (2)	0.1 (1)	-0.2 (2)	-0.1 (1)
C(9)	0.9684 (2)	0.1092 (1)	0.2914 (5)	3.5 (1)	3.1 (1)	3.3 (2)	-0.1 (1)	0.0 (1)	-0.0 (1)
C(10)	0.9168 (2)	0.0674 (1)	0.4031 (5)	3.5 (1)	3.7 (1)	4.0 (2)	-0.1 (1)	0.2 (1)	0.1 (1)
C(11)	0.8792 (2)	0.1361 (1)	0.1659 (5)	4.1 (2)	3.9 (2)	4.8 (2)	-0.2 (1)	-1.0 (2)	0.2 (2)
C(12)	0.9285 (2)	0.1792 (1)	0.0684 (4)	4.3 (2)	4.0 (2)	3.8 (2)	0.1 (1)	-1.1 (2)	0.4 (1)
C(13)	0.9863 (2)	0.2089 (1)	0.2313 (4)	3.4 (4)	3.5 (1)	3.6 (2)	0.4 (1)	-0.0 (1)	-0.3 (1)
C(14)	1.0816 (2)	0.1800 (1)	0.3322 (5)	3.4 (1)	3.4 (1)	3.4 (2)	0.1 (1)	-0.2 (1)	-0.1 (1)
C(15)	1.1536 (2)	0.2131 (1)	0.4583 (5)	4.9 (2)	4.0 (2)	5.7 (2)	-0.2 (1)	-1.7 (2)	0.2 (2)
C(16)	1.1479 (2)	0.2570 (1)	0.3325 (5)	4.5 (2)	3.8 (2)	5.3 (2)	0.0 (1)	-0.9 (2)	0.1 (2)
C(17)	1.0585 (2)	0.2496 (1)	0.1549 (4)	4.2 (2)	3.0 (1)	4.0 (2)	0.2 (1)	0.1 (2)	-0.1 (1)
C(18)	0.8968 (3)	0.2248 (1)	0.3914 (5)	4.9 (2)	4.7 (2)	5.2 (2)	0.6 (2)	0.9 (2)	-0.3 (2)
C(19)	0.8261 (2)	0.0807 (1)	0.5676 (5)	4.4 (2)	5.8 (2)	4.6 (2)	0.0 (2)	1.0 (2)	0.3 (2)
C(20)	0.9979 (2)	0.2938 (1)	0.0990 (5)	4.6 (2)	3.9 (2)	5.0 (2)	0.6 (2)	-0.6 (2)	0.2 (2)
C(21)	0.9017 (3)	0.2890 (1)	-0.0595 (7)	7.5 (3)	5.8 (2)	8.2 (3)	0.5 (2)	-2.7 (3)	1.4 (2)
C(22)	1.0887 (3)	0.3276 (1)	0.0248 (6)	6.8 (2)	4.0 (2)	8.2 (3)	0.0 (2)	-0.1 (2)	1.4 (2)
C(23)	1.0435 (3)	0.3757 (1)	0.0054 (6)	9.2 (3)	3.8 (2)	7.8 (3)	-0.0 (2)	-2.1 (3)	0.8 (2)
C(24)	1.0094 (3)	0.3909 (1)	-0.2074 (6)	9.0 (3)	5.2 (2)	6.7 (3)	0.4 (2)	0.3 (3)	0.8 (2)
O(1)	1.1141 (2)	-0.0267 (1)	0.0420 (3)	5.7 (1)	5.1 (1)	4.6 (1)	0.6 (1)	-0.1 (1)	-1.6 (1)
O(2)	1.1821 (2)	0.0484 (1)	0.7514 (3)	5.0 (1)	4.5 (1)	4.0 (1)	0.7 (1)	-0.5 (1)	0.6 (1)
O(3)	0.9473 (3)	0.4269 (1)	-0.2032 (4)	15.2 (3)	6.4 (2)	6.9 (2)	3.9 (2)	-1.1 (2)	1.2 (2)
O(4)	1.0341 (4)	0.3724 (1)	-0.3682 (5)	19.5 (4)	10.5 (2)	7.7 (2)	5.8 (3)	2.0 (3)	1.3 (2)

Table 2 (*cont.*)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ($\times 10^3$)
H(11)	0.821 (2)	0.010 (1)	0.338 (5)	4.9 (1.0)
H(12)	0.790 (2)	0.051 (1)	0.178 (5)	4.7 (1.0)
H(21)	0.973 (2)	0.039 (1)	-0.009 (4)	3.2 (8)
H(22)	0.895 (2)	-0.006 (1)	0.008 (5)	5.4 (9)
H(31)	1.000 (2)	-0.038 (1)	0.274 (5)	5.2 (9)
H(41)	1.155 (2)	-0.001 (1)	0.420 (5)	5.4 (1.0)
H(42)	1.153 (2)	0.039 (1)	0.268 (5)	4.4 (9)
H(51)	0.979 (2)	0.017 (1)	0.596 (4)	3.2 (7)
H(61)	1.033 (2)	0.083 (1)	0.778 (4)	4.7 (9)
H(71)	1.198 (2)	0.104 (1)	0.448 (4)	3.4 (8)
H(72)	1.175 (2)	0.131 (1)	0.646 (5)	4.1 (9)
H(81)	0.983 (2)	0.149 (1)	0.566 (5)	4.6 (9)
H(91)	1.028 (2)	0.098 (1)	0.176 (4)	4.5 (8)
H(111)	0.812 (2)	0.143 (1)	0.252 (5)	5.8 (1.0)
H(112)	0.844 (2)	0.116 (1)	0.044 (5)	5.8 (1.0)
H(121)	0.870 (2)	0.195 (1)	-0.015 (5)	4.7 (9)
H(122)	0.994 (3)	0.172 (1)	-0.048 (5)	5.3 (1.0)
H(141)	1.134 (2)	0.172 (1)	0.223 (4)	3.0 (8)
H(151)	1.233 (2)	0.202 (1)	0.481 (5)	4.3 (8)
H(152)	1.117 (3)	0.218 (1)	0.606 (5)	5.2 (1.0)
H(161)	1.116 (2)	0.283 (1)	0.424 (5)	5.3 (1.0)
H(162)	1.223 (2)	0.266 (1)	0.281 (5)	5.5 (1.0)
H(171)	1.101 (2)	0.239 (1)	0.029 (5)	5.3 (9)
H(181)	0.930 (3)	0.247 (1)	0.491 (6)	8.2 (1.0)
H(182)	0.830 (3)	0.242 (1)	0.320 (6)	7.5 (1.0)
H(183)	0.855 (3)	0.201 (1)	0.474 (6)	7.1 (1.0)
H(191)	0.856 (3)	0.106 (1)	0.676 (6)	6.6 (1.0)
H(192)	0.753 (3)	0.093 (1)	0.505 (5)	6.2 (1.0)
H(193)	0.804 (3)	0.054 (1)	0.665 (6)	7.1 (1.0)
H(201)	0.963 (2)	0.308 (1)	0.237 (5)	4.6 (9)
H(211)	0.934 (3)	0.281 (1)	-0.208 (7)	11.3 (1.0)
H(212)	0.839 (3)	0.270 (1)	0.012 (6)	8.0 (1.0)
H(213)	0.857 (3)	0.321 (1)	-0.082 (6)	9.5 (1.0)
H(221)	1.117 (3)	0.315 (1)	-0.120 (6)	7.7 (1.0)
H(222)	1.160 (3)	0.329 (1)	0.135 (6)	7.2 (1.0)
H(231)	1.108 (3)	0.401 (1)	0.059 (7)	12.7 (1.0)
H(232)	0.954 (3)	0.380 (1)	0.106 (6)	6.2 (1.0)
H(10)	1.183 (4)	-0.042 (1)	0.106 (7)	10.8 (2.0)
H(20)	1.152 (4)	0.027 (1)	0.827 (8)	11.8 (2.0)
H(30)	0.929 (5)	0.437 (2)	-0.340 (10)	19.8 (3.0)

For the atoms H(11) to H(232) the digits excluding the last correspond to the number of the carbon to which the hydrogen atom is bonded. H(10), H(20) and H(30) are bonded to O(1), O(2) and O(3) respectively.

a secondary extinction coefficient of 0.7×10^{-5} . Correction of the measured intensities using this coefficient improved the structure-factor agreement and reduced the *R* value to 0.051. Three further rounds of block-diagonal SFLS refinement on all atoms further reduced the *R* value to 0.043, excluding 'less thans'. In the final round, shifts on all parameters had converged to less than one standard deviation, so refinement was considered complete. The final refined atomic positional and thermal parameters are given in Table 2, and the measured and calculated structure factors in Table 3.

Discussion

A diagrammatic representation of the structure, utilizing the thermal ellipsoid probability plot of Johnson (1965), is shown in Fig. 2. The geometry of a steroid may be classified in terms of its bond lengths, bond angles and torsional angles, which are in in-

creasing order of sensitivity to changes in the substituents and in the packing of the structure. The bond lengths and angles in 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid are given in Fig. 3, and the torsional angles are listed in Table 4. These may be compared with corresponding quantities in 5 β -androstane-3 α ,17 β -diol and 3 β -hydroxy-5 α -androstan-17-one (Weeks, Cooper, Norton, Hauptman & Fisher, 1971). The former molecule has the same ring conformation as 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid. It has a hydroxyl substituent at the C(17) position in the *D* ring, but lacks a hydroxyl at C(6). The latter structure has a keto oxygen at C(17) and, in addition, has the opposite configuration at C(5). As a shorthand notation, the present structure is denoted by (I) and the comparison structures by (II) and (III), respectively.

For the *A*, *B* and *C* rings, the largest difference in bond lengths for structures (I) and (II) is in the C(6)–C(7) bond, which is 0.017 Å shorter in the 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid structure. The length of this bond is close to those of C(2)–C(3) and C(3)–C(4), but is shorter than the normal value of 1.533 Å (Bartell, 1959). The foreshortening is clearly due to the hydroxyl substituent, as suggested by Weeks, Cooper, Norton, Hauptman & Fisher (1971).

Excluding the dissimilar C(6)–C(7) bond, the r.m.s. difference between the lengths of corresponding bonds in the *A*, *B* and *C* rings of structures (I) and (II) is 0.006 Å, compared with 0.008 Å expected from the calculated standard deviations. The common assertion that the calculated e.s.d.'s are underestimated is invalid here. The corresponding difference for structures (I) and (III) is 0.010 Å.

The r.m.s. deviation between the bond angles for rings *A*, *B* and *C* in structures (I) and (II), excluding those involving atom C(6), is 0.8°. That for structures (I) and (III) is 1.2°. If the differences between the structures were due to random errors comparable with the standard deviations, the r.m.s. difference would be 0.4°. The r.m.s. deviation between the torsional angles involving the bonds in rings *A*, *B* and *C* for structures (I) and (II) is 1.8°.

The progressive increase in the differences between bond lengths, bond angles and torsional angles is consistent with the relative distortion energies for each type of structural parameter.

In the cyclopentane *D* ring, on the other hand, three of the bond lengths in structures (I) and (II) differ by amounts which are considerably larger than the standard deviations. The C(17)–C(13) and C(16)–C(17) bonds are shorter in structure (II) by 0.025 and 0.014 Å, respectively. This is consistent with the presence of a hydroxyl group at the C(17) position in this structure. The C(14)–C(15) bond is 0.018 Å longer in structure (II). There are corresponding differences in the bond angles.

The torsional angles show larger variations with an r.m.s. deviation of 3.5°, as expected in view of the well-known flexibility of the cyclopentane ring. The ring

Table 3. Observed and calculated structure factors

Structure factors are listed in blocks of *hl* in columns of *k*, (*F_o*) × 10 and (*F_c*) × 10. An asterisk (*) denotes reflexions coded as 'less thans'.

Table with multiple columns containing numerical data for structure factors, organized in blocks of *hl* and columns of *k*. Includes various numerical values and asterisks indicating specific reflexions.

Table 4. Torsional angles ($^{\circ}$) for the rings of 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid

The sign convention is that of Klyne & Prelog (1960).

Ring	Bond	Angle	Ring	Bond	Angle
A	C(1)—C(2)	57.6	C	C(8)—C(9)	-49.2
	C(2)—C(3)	-54.3		C(9)—C(11)	48.4
	C(3)—C(4)	53.3		C(11)—C(12)	-54.2
	C(4)—C(5)	-53.1		C(12)—C(13)	57.8
	C(5)—C(10)	52.4		C(13)—C(14)	-62.4
B	C(10)—C(1)	-55.6	D	C(14)—C(8)	58.7
	C(5)—C(6)	-57.2		C(13)—C(14)	44.5
	C(6)—C(7)	56.8		C(14)—C(15)	-32.7
	C(7)—C(8)	-56.8		C(15)—C(16)	7.9
	C(8)—C(9)	58.4		C(16)—C(17)	19.3
	C(9)—C(10)	-56.5		C(17)—C(13)	-38.5
	C(10)—C(5)	55.3			

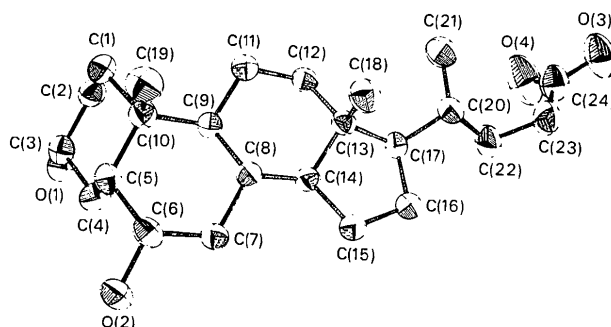
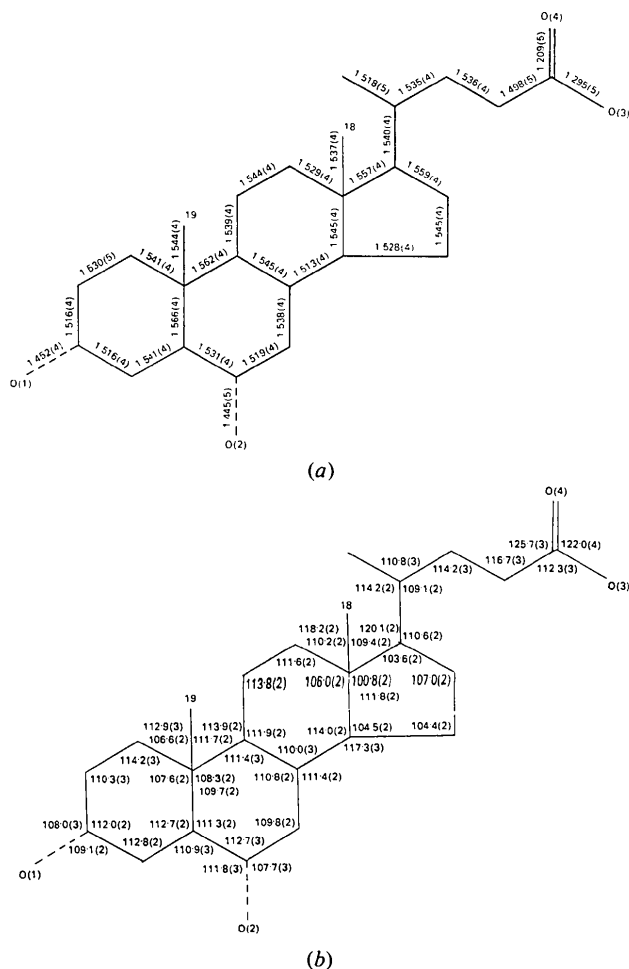
conformation is conveniently characterized in terms of the maximum angle of torsion, φ_m , and the phase angle, Δ , of pseudorotation, as defined by Altona, Geise & Romers (1968). In 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid, φ_m and Δ have values of 44.8 $^{\circ}$ and 14.3 $^{\circ}$, respectively. These are close to the values for 2 α ,3 β -dibromo-5 α -cholestane (Geise & Romers, 1966) and are normal for a steroid structure.

The packing of the 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid structure is illustrated in Fig. 4. The hydrogen-bond network is centred on O(1), which is the donor in an O—H...O bond to atom O(2) at $\frac{1}{2}-x, -y, -\frac{1}{2}+z$, length 2.794 (3) Å and, as an acceptor, in a similar bond from atom O(3) at $2-x, -\frac{1}{2}+y, -\frac{1}{2}-z$, length 2.683 (4) Å. Thus only half the hydrogen-bonding potential of the oxygen atoms is utilized. This permits a slightly higher packing density than in structures (II) and (III), where all the available hydroxyl groups are proton donors and form hydrogen bonds. This is reflected in a small increase in density in 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid.

The most notable difference between the three structures is in the length of the C(3)—O(1) bond, which is 1.452, 1.424 and 1.430 Å in structures (I), (II) and (III), respectively. C—O bond lengths have been found to vary with hydrogen bonding, but the lengths of the two hydrogen bonds to this oxygen in structures (I) and (II) are virtually identical. However, O(3)—H...O(1) is almost co-linear in structure (I), whereas the hydrogen bonds are approximately normal to this bond in structure (II). The change in C—O bond length resulting from hydrogen bonding is clearly orientation-dependent.

The conformation of the side chain in the cholanic acids is related to their biological activity. Assuming that the configuration of the ring skeleton is similar to that determined absolutely for 3 α ,12 α -dihydroxy-5 β -cholan-24-*p*-bromoanilide (Schaefer & Reed, 1972), denoted (IV) below, C(20) has the usual *R* configuration. The dihedral angles for the side chain may be compared with the corresponding angles in (IV), and in 3 α ,12 α -dihydroxy-5 β -cholan-24-oic acid (Candeloro de Sanctis, Giglio, Pavel & Quagliata, 1972) denoted

(V). These are listed in Table 5. Structure (IV) has the normally stressed zigzag chain. In structure (V), where both carboxyl oxygens are involved in hydrogen bonding, the side chain is folded about the C(20)—C(22) bond. In the present structure, where O(4) is not hy-

Fig. 2. Molecule of 3 α ,6 α -dihydroxy-5 β -cholan-24-oic acid showing atoms as thermal ellipsoids plotted at the 50% probability limit by ORTEP (Johnson, 1965).Fig. 3. Interatomic distances (Å) and angles ($^{\circ}$) calculated from the final atomic coordinates in Table 2.

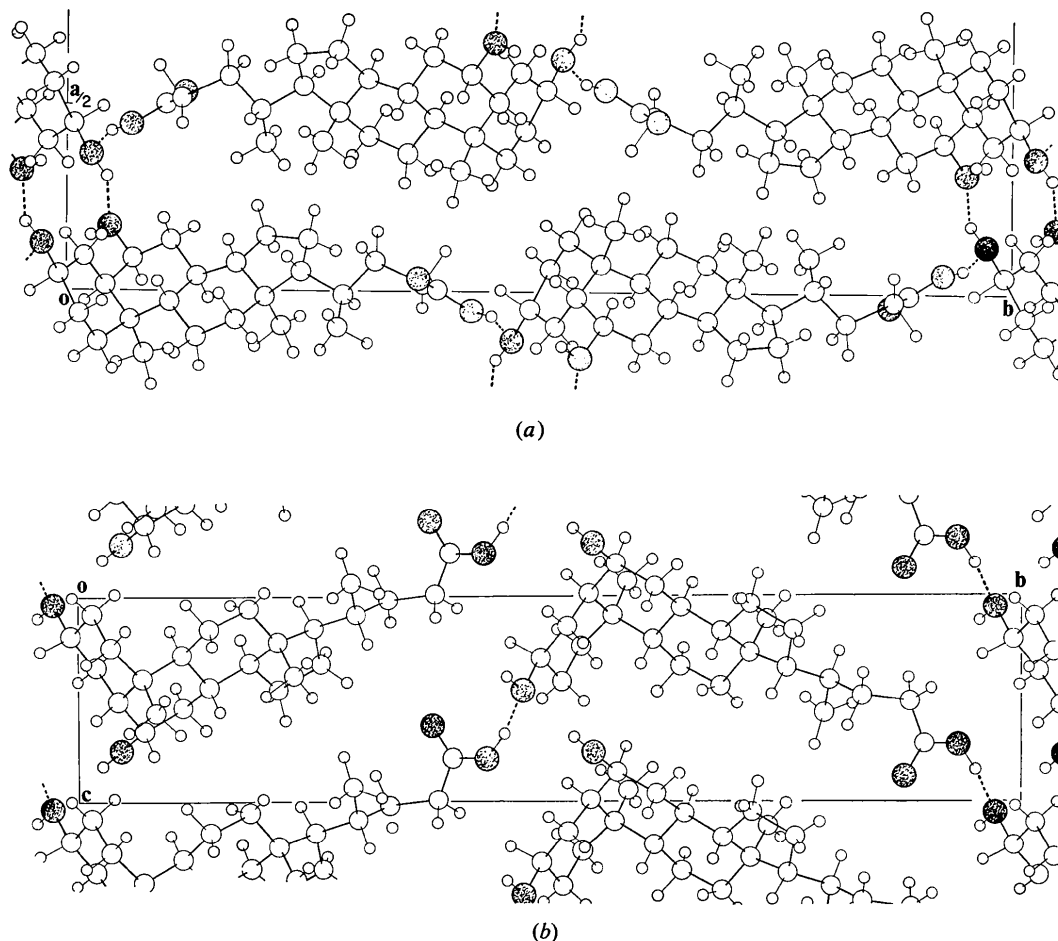


Fig. 4. Diagrammatic representations of the $3\alpha,6\alpha$ -dihydroxy- 5β -cholan-24-oic acid molecules, showing the packing (a) viewed along c, and (b) viewed along a. The oxygen atoms are shown as shaded circles.

drogen-bonded the folding is about C(22)–C(23). This confirms the conformational flexibility of the side chain reported by Candeloro de Sanctis, Giglio, Pavel & Quagliata (1972).

Table 5. Dihedral angles ($^{\circ}$) for the side chains, in $3\alpha,6\alpha$ -dihydroxy- 5β -cholan-24-oic acid (I), $3\alpha,12\alpha$ -dihydroxy- 5β -cholan-24-oic-p-bromoanilide (IV) and $3\alpha,12\alpha$ -dihydroxy- 5β -cholan-24-oic acid (V)

Angle	(I)	(IV)	(V)
C(13)–C(17)–C(20)–C(21)	–54	–63	–59
C(16)–C(17)–C(20)–C(21)	185	177	185
C(13)–C(17)–C(20)–C(22)	181	176	175
C(17)–C(20)–C(22)–C(23)	192	189	62
C(20)–C(22)–C(23)–C(24)	–98	173	179

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