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## Structure of a Low-Temperature Polymorph of Chenodeoxycholic Acid, $C_{24}H_{40}O_4$ , Determined with Synchrotron Radiation

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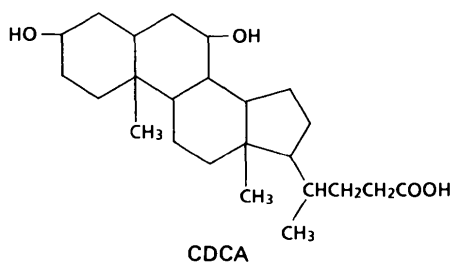
### Abstract

The low-temperature polymorph of chenodeoxycholic acid ( $3\alpha,7\alpha$ -dihydroxy- $5\beta$ -cholanic acid) forms very fine needle-shaped crystals (30–60  $\mu\text{m}$  cross-section), containing a variable solvent content. The crystal and molecular structure has been solved using synchrotron radiation in conjunction with an area detector.  $M_r = 392.6$  (excluding solvent), hexagonal, space group  $P6_5$ ,  $a = 22.250$  (5),  $c = 10.255$  (2)  $\text{\AA}$ ,  $Z = 6$ ,  $V = 4396.7$   $\text{\AA}^3$ ,  $F(000) = 1296$ ,  $D_m = 1.12$  (6)  $\text{g cm}^{-3}$  (floatation in bromobenzene/toluene),  $D_x = 0.89$   $\text{g cm}^{-3}$  for  $C_{24}H_{40}O_4$  without solvent of crystallization,  $D_x$  (max.) = 1.17  $\text{g cm}^{-3}$  for  $C_{24}H_{40}O_4 \cdot C_6H_5Br$ ,  $\lambda = 1.5418$   $\text{\AA}$  for unit-cell determination,  $\lambda = 0.895$   $\text{\AA}$  for intensity measurements,  $\mu = 1.09$   $\text{cm}^{-1}$ , m.p. = 388–390 K,  $T = 291$  (1) K. The structure refined to  $R = 0.11$  for 578 reflections with  $|F_o| > 2\sigma(F)$ . The molecular conformation is similar to that of the high-melting-point (438–439 K) form, but the molecular packing is far more open. All the oxygen atoms are involved in intermolecular hydrogen bonding. The crystal structure contains wide cylindrical channels, parallel to  $c$ , sufficient to accommodate molecules with van der Waals diameters up to 8.0  $\text{\AA}$ .

### Introduction

Chenodeoxycholic acid,  $3\alpha,7\alpha$ -dihydroxy- $5\beta$ -cholanic acid (CDCA),  $C_{24}H_{40}O_4$ , is a bile acid which is an efficacious agent for inducing dissolution of cholesterol gallstones (see, for example, Hofmann & Paumgartner, 1975). The cholanic bile acids form a number of mixed crystals which may be sub-divided into two categories, choleic acids and 'canal' complexes. The choleic acids contain highly stable complexes of host (bile acid) and guest (second organic molecule) which may, indeed, be stable outside the crystalline state. The crystal structures of the canal complexes contain channels or 'canals' which contain the guest molecules. The host–guest interactions in these complexes are usually less specific than for the choleic acids and can have non-integral coordination numbers. The canals can be either hydrophilic whereby they readily accommodate guest molecules with polar substituents, or hydrophobic where the guest molecules tend to be apolar. Although several canal complexes involving deoxycholic acid, DCA, have been reported, very few where the host molecule is another bile acid have been characterized. Polymorphism of CDCA has been reported (Guisepetti & Paciotti, 1978), and the high-temperature

polymorph has a crystal structure (Lindley, Mahmoud, Watson & Jones, 1980) containing pleated bilayers held together by a complex hydrogen-bonding network. In contrast, the low-temperature polymorph of CDCA is known to retain solvent very tenaciously, but can be transformed into the high-melting-point form by heating in water at 333–353 K for several hours (Forst, Garden, James & Arthur, 1974; Bonaldi, 1979). In order to determine the relationship of this polymorph to the high-temperature form and that of the canal complexes of DCA we undertook the crystal structure analysis reported herein.



### Experimental

Chenodeoxycholic acid (3.92 g, 10 mmol) was dissolved in 30 ml chloroform (Bonaldi & Mulinori, 1979; Pavan & Bulidon, 1978) by heating in a water bath and the solution allowed to stand at room temperature for 1 h without stirring. An additional 90 ml chloroform was added and the mixture heated under reflux for several minutes to dissolve the crystals. On slow cooling of this solution to room temperature over a period of up to 5 h, fine hexagonal needle crystals were obtained (2.7 g), which were filtered off and air dried; some of the crystals appeared 'twisted' about the needle axis, and the majority showed varying degrees of opacity. All attempts to prepare larger or better crystals than these were unsuccessful. Chemical analysis gave: m.p. 388–390 K; found, C 73.05 H 9.94 O 15.51 Cl 0.72%, water (Karl Fischer) 1.21%, chloroform (gas chromatography) 0.8%; expected, C 73.54, H 10.28, O 16.30%; the presence of chloroform in the crystal samples was confirmed by IR spectroscopy (KBr/Nujol disks, Perkin-Elmer 983 spectrometer). <sup>1</sup>H NMR (400 MHz, DMSO, CDCl<sub>3</sub>/TMS internal standard) gave a spectrum consistent with chenodeoxycholic acid with typical shifts,  $\delta$  = 0.69 (s, 3H, 18-CH<sub>3</sub>), 0.88 (s, 3H, 19-CH<sub>3</sub>), 0.94 (Cl, 3H, 21-CH<sub>3</sub>), 3.38 (1H, multiplet, 3 $\beta$ ) and 3.78 (1H, multiplet, 7 $\beta$ ).

Unit-cell dimensions were determined using a Hilger & Watts Y290 four-circle diffractometer and Cu K $\alpha$  radiation,  $\lambda$  = 1.54178 Å, 19 reflections with  $6.3 < \theta < 14.5^\circ$ . An intensity data set, set 1, was also

collected on this device to 1.54 Å resolution, 4322 measurements in the range  $1 < \theta < 30^\circ$ ,  $h, k \pm 13$ ,  $l \pm 8$ , moving-window technique (60 out of 90 0.01° steps) (Tickle, 1975). Reduction of these data including Lorentz and polarization corrections and an empirical absorption correction using the (006) reflection (North, Phillips & Mathews, 1968) gave 473 unique reflections with  $R_{\text{merge}} = 0.044$ . However, these data were rather weak, some 25% had  $I < 3\sigma(I)$  for  $20^\circ < \theta < 30^\circ$  and all attempts at a structure solution were unsuccessful.

Synchrotron radiation data collection on work-station 9.6 at the SERC Daresbury Laboratory and using an Enraf-Nonius FAST TV detector system followed procedures described by Rizkallah, Maginn & Harding (1990). A crystal of dimensions  $60 \times 40 \times 500 \mu\text{m}$  was mounted with its needle  $c$  axis parallel to the spindle. The diffraction pattern for  $102^\circ$  of rotation about this axis was recorded in  $0.5^\circ$  steps. The crystal-to-detector distance was 43.5 mm with the detector normal tilted  $26^\circ$  from the direct-beam direction, giving data to a resolution of 0.94. A collimator of 0.2 mm diameter was used and the SRS source was operated in single bunch mode (2 GeV and 18 mA) with the wiggler magnet at 5 T; the total data-collection time was about 2 h. Processing of this data with *MADNES* software (Messerschmidt & Pflugrath, 1987) gave a unit cell in agreement with the Cu K $\alpha$  measurements and 4500 individual reflection intensities; merging of this data set, set 2, yielded 592 unique reflections designated 'good' (*i.e.* *MADNES* flag = 0), with an  $R_{\text{merge}}$  of 0.044. The average mosaic spread for all reflections was  $5.8^\circ$ . Comparison of this data set with that collected using Cu K $\alpha$  radiation gave an  $R_{\text{merge}}$  of 22%; the largest discrepancies were at the extremes of the resolution range, *i.e.* the low-angle data susceptible to solvent effects and the weak intensity data near 1.5 Å.

On station 9.6 it is difficult to assess the quality of the data at recording time and this can only be usefully achieved when the processing is complete. The crystals used, like many other small crystals, were of variable and indifferent quality. To ensure that some usable data were obtained, a further data set, set 3, from another long crystal with cross-section  $60 \times 30 \mu\text{m}$ , was recorded in the same session. Processing of this data set yielded 1008 unique reflections designated 'good', with a lower mosaic spread,  $3.6^\circ$ , but with a higher merging  $R$  of 0.077. All reflections have  $|h| \leq 18$ ,  $|k| \leq 23$ ,  $|l| \leq 7$ .

Data set 3 was used for the structure solution in conjunction with the programs *PATSEE* (Egert & Sheldrick, 1985) and *SHELXS86* (Sheldrick, 1986). *SHELX76* (Sheldrick, 1976) was used for the refinement. The carbon-atom positions found in the high-temperature polymorph of CDCA (Lindley, Mahmoud, Watson & Jones, 1980), but excluding

the  $17\beta$  side chain, were used as the search molecule in *PATSEE*. A solution was found in space group  $P6_5$  for both the rotation and translation functions which could be refined and extended; in the enantiomorphic space group  $P6_1$  no solution for the translation search could be found. Separate refinements were carried out with each of the synchrotron data sets 2 and 3 using full-matrix least squares, all atoms isotropic, hydrogen atoms included at the stereochemically expected positions, and weights  $w = 1/[\sigma^2(F) + 0.0005|F|^2]$ . These converged to  $R = 0.13$  and  $0.15$  for sets 2 and 3, respectively, and it was clear that the largest discrepancies between  $|F_o|$  and  $|F_c|$  were in the very-low-angle reflections. A difference map computed from set 2 data showed a region of electron density within the wide channel through the structure, see Fig. 2. This density could not be interpreted in terms of ordered solvent structure. It was therefore approximated as four carbon atoms, each with a site occupancy of 0.25 and inclusion of these atoms in the structure-factor calculations gave  $R = 0.114$  and  $wR = 0.114$ ; the agreement between  $F_o$  and  $|F_c|$  was much improved. A difference synthesis computed from data set 3 showed electron density in the same region, but with different peaks.

### Results and discussion

The atom parameters for data set 2 are given in Table 1; they do not differ significantly (apart from the solvent structure) from those of set 3. Bond lengths and angles are given in Table 2. Figs. 1 and 2 illustrate the molecular and crystal structures respectively.\*

The molecular conformation in the low-temperature polymorph of CDCA is essentially that found in the high-temperature form. Thus, the *A*, *B* and *C* rings adopt chair conformations with rings *A* and *B* and *B* and *C* *cis* and *trans* fused, respectively. In the five-membered *D* ring, which is *trans* to ring *C*, the half-chair conformation is dominant with a pseudo-rotational phase parameter,  $\Delta = 10^\circ$  (Altona, Geise & Romers, 1968). In the  $17\beta$  side chain of a number of cholanic acids, the carboxyl moiety shows a preference for adopting an antiperiplanar conformation with respect to C20; in the low-temperature polymorph the torsion angle C20—C22—C23—C24 is  $65(3)^\circ$  indicating a synclinal conformation as observed in one of the two molecules in the asymmetric unit of the high-temperature form (Lindley,

\* Lists of structure amplitudes and hydrogen-atom parameters for dataset 2 have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52409 (4 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Fractional coordinates ( $\times 10^4$ ) and isotropic thermal parameters ( $\text{\AA}^2 \times 10^3$ ) for the low-temperature polymorph of chenodeoxycholic acid

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{iso}$
C1	3311 (11)	-1873 (10)	178*	40 (7)
C2	3490 (11)	-1128 (10)	-99 (43)	42 (7)
C3	4248 (12)	-642 (11)	151 (45)	42 (7)
C4	4429 (12)	-726 (11)	1550 (47)	42 (7)
C5	4243 (11)	-1468 (11)	1859 (45)	36 (6)
C6	4451 (11)	-1548 (12)	3197 (51)	46 (7)
C7	3965 (10)	-1540 (11)	4289 (45)	36 (6)
C8	3207 (10)	-2041 (11)	4026 (47)	38 (7)
C9	3014 (10)	-1934 (11)	2632 (49)	38 (6)
C10	3487 (11)	-1994 (10)	1515 (43)	30 (6)
C11	2236 (10)	-2378 (12)	2333 (43)	39 (6)
C12	1758 (11)	-2363 (11)	3434 (50)	45 (7)
C13	1925 (11)	-2540 (11)	4714 (47)	47 (8)
C14	2727 (11)	-2000 (12)	4937 (44)	43 (7)
C15	2819 (12)	-2094 (12)	6465 (45)	43 (7)
C16	2153 (11)	-2207 (13)	7126 (48)	52 (7)
C17	1633 (10)	-2321 (12)	5996 (51)	43 (6)
C18	1746 (12)	-3270 (11)	4877 (50)	47 (8)
C19	3380 (12)	-2726 (11)	1543 (44)	50 (9)
C20	867 (12)	-2818 (14)	6310 (50)	58 (9)
C21	371 (16)	-3031 (16)	5246 (59)	91 (12)
C22	684 (14)	-2453 (14)	7467 (52)	68 (9)
C23	-16 (14)	-2890 (14)	8060 (57)	70 (9)
C24	-106 (12)	-3530 (12)	8768 (48)	44 (7)
O3	4400 (8)	52 (8)	-103 (38)	51 (5)
O7	4141 (7)	-827 (7)	4479 (37)	39 (5)
O241	-392 (9)	-4122 (9)	8477 (42)	80 (7)
O242	258 (9)	-3348 (9)	9980 (45)	72 (6)
S1	780 (50)	2030 (50)	9670 (150)	100†
S2	920 (50)	2450 (50)	8010 (150)	100†
S3	750 (50)	2520 (50)	5990 (150)	100†
S4	830 (50)	1780 (50)	6370 (150)	100†

\* This parameter was held constant during the refinement.

† These 'solvent' molecules were treated as C atoms with an occupancy of 0.25.

Mahmoud, Watson & Jones, 1980), and presumably arising from the nature of the molecular packing, *vide infra*.

The presence of the fused-ring steroid nucleus and steric hindrance between the  $\beta$ -methyl substituents at C10 and C13 give rigidity to the cholanic acid structure. In addition, the molecules possess amphipathic character in that the  $\beta$ -side is hydrophobic whereas the  $\alpha$ -side on which the hydroxyl groups lie, C3 and C7 in the case of CDCA, can be considered hydrophilic. These properties appear to confer two main types of molecular packing on mixed crystals of the cholanic acids and on the acids themselves, *viz.* structures composed of pleated double sheets of molecules and structures containing helical arrays (Ealick & Bugg, 1988). In both cases the hydrophobic regions pack close to one another. The high-temperature polymorph is an example of a double-sheet structure with the molecules held together by a comprehensive hydrogen-bonding network. The low-temperature polymorph, as crystallized from chloroform, falls into the latter category to give a canal complex.

In the crystal structure of the low-temperature polymorph of CDCA all the oxygen atoms lie within  $3.5 \text{\AA}$  of a crystallographic twofold screw axis. Hydrogen bonds  $O3 \cdots O7$ ,  $2.85(5) \text{\AA}$ , link successive

Table 2. *Interatomic bond lengths (Å) and angles (°) for the non-hydrogen atoms in the low-temperature polymorph of chenodeoxycholic acid*

Estimated standard deviations including cell-parameter errors are given in parentheses.

C1—C2	1.53 (4)	C1—C10	1.48 (4)
C2—C3	1.50 (3)	C3—C4	1.53 (6)
C3—O3	1.43 (4)	C4—C5	1.52 (4)
C5—C6	1.49 (7)	C5—C10	1.54 (3)
C6—C7	1.56 (6)	C7—C8	1.51 (3)
C7—O7	1.45 (3)	C8—C9	1.55 (7)
C8—C14	1.46 (5)	C9—C10	1.61 (5)
C9—C11	1.54 (3)	C10—C19	1.52 (4)
C11—C12	1.56 (5)	C12—C13	1.47 (7)
C13—C14	1.59 (3)	C13—C17	1.65 (6)
C13—C18	1.48 (4)	C14—C15	1.61 (6)
C15—C16	1.53 (4)	C16—C17	1.57 (6)
C17—C20	1.53 (3)	C20—C21	1.45 (7)
C20—C22	1.60 (6)	C22—C23	1.49 (5)
C23—C24	1.52 (5)	C24—O241	1.18 (4)
C24—O242	1.43 (6)		
C2—C1—C10	114 (2)	C1—C2—C3	110 (2)
C2—C3—C4	110 (3)	C2—C3—O3	109 (2)
C4—C3—O3	112 (3)	C3—C4—C5	113 (3)
C4—C5—C6	113 (3)	C4—C5—C10	112 (2)
C6—C5—C10	114 (3)	C5—C6—C7	114 (3)
C6—C7—C8	113 (3)	C6—C7—O7	108 (3)
C8—C7—O7	115 (2)	C7—C8—C9	110 (3)
C7—C8—C14	115 (3)	C9—C8—C14	108 (3)
C8—C9—C10	114 (2)	C8—C9—C11	113 (3)
C10—C9—C11	112 (3)	C1—C10—C5	111 (3)
C1—C10—C9	114 (2)	C1—C10—C19	107 (3)
C5—C10—C9	107 (3)	C5—C10—C19	110 (2)
C9—C10—C19	109 (3)	C9—C11—C12	114 (3)
C11—C12—C13	112 (3)	C12—C13—C14	105 (3)
C12—C13—C17	116 (3)	C12—C13—C18	116 (4)
C14—C13—C17	97 (3)	C14—C13—C18	114 (2)
C17—C13—C18	108 (3)	C8—C14—C13	116 (3)
C8—C14—C15	118 (3)	C13—C14—C15	102 (3)
C14—C15—C16	106 (3)	C15—C16—C17	106 (3)
C13—C17—C16	106 (2)	C13—C17—C20	115 (3)
C16—C17—C20	115 (4)	C17—C20—C21	118 (4)
C17—C20—C22	105 (3)	C21—C20—C22	112 (3)
C20—C22—C23	115 (3)	C22—C23—C24	114 (3)
C23—C24—O241	132 (4)	C23—C24—O242	111 (3)
O241—C24—O242	117 (3)		

molecules related by a twofold screw axis. Each molecule is also linked to the carboxyl group of two others by O7...O241 (at  $x-y, x, z-\frac{1}{6}$ ), 2.89 (5) Å, and O242...O3 (at  $y, y-x, z+\frac{7}{6}$ ), 2.60 (5) Å. In the resulting open structure, Fig. 2, the molecules form helices around the sixfold screw axes in a very similar manner to the hexagonal phase of the DCA-ethanol-water canal complex (De Sanctis, Coiro, Giglio, Pagliuca, Pavel & Quagliata, 1978). The structure contains channels which are sufficiently wide to accommodate guest molecules with van der Waals diameters up to 8.0 Å. In the case of the DCA complex, the internal surfaces of the helices are hydrophilic and the guest molecules participate in hydrogen bonding with the DCA. In contrast, in the low-temperature polymorph of CDCA the internal surfaces of the helices are hydrophobic, which may well account for the apparent disordered structure of the polar solvent molecules and the variable amount of solvent components found in different crystals.

In the solvent model derived from data set 2, the four peaks, S1–S4, lie in a roughly planar region less than 4 Å across. There are no contacts less than

3.8 Å between successive S1–S4 groups along the sixfold axis and nearly all the contacts between the group and the host molecules are greater than 3.2 Å; the closest approach, S3—H231 = 2.75 Å. The model as described above would give a calculated density rather lower than that observed. The chemical analysis on fresh crystals indicates the presence of only small amounts of solvent (water/chloroform), in agreement with this model. One possible explanation for the discrepancy is that during the density measurement molecules of bromobenzene and/or toluene diffused into the crystals *via* the channels.

The hexagonal canal-type structure of the low-temperature polymorph enables some insight to be gained into possible mechanisms involved in the transformation of this polymorph into the high-temperature form by heating in water at 333–353 K for several hours (Bonaldi, 1979; Forst, Garden, James & Arthur, 1974). During the transformation, an increase in volume of the CDCA is observed and this is presumably caused by an initial intake of

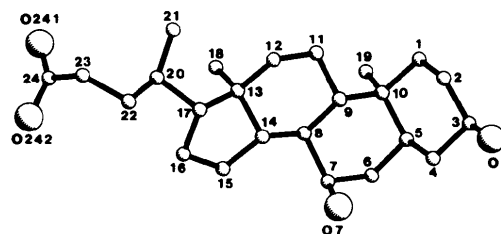


Fig. 1. A molecule of the low-temperature polymorph of chenodeoxycholic acid showing the atom labelling; hydrogen atoms are not included.

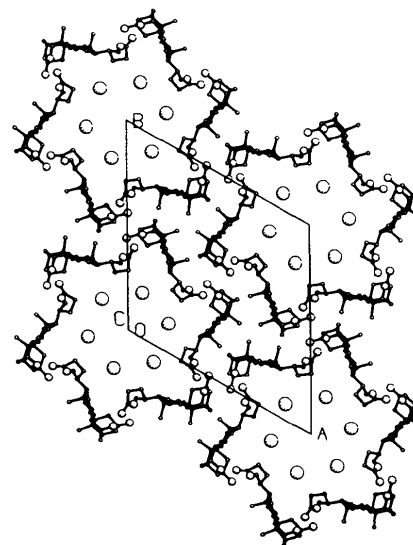


Fig. 2. The molecular packing viewed along the unit-cell *c* axis; the isolated large circles indicate the solvent region. Hydrogen atoms are not included.

water molecules into the channels of the crystals, before complete loss of solvent on the formation of the high-temperature phase.

Fig. 3 shows a Laue diffraction photograph of another crystal of hexagonal CDCA. The streaking, which is particularly marked in the  $hk0$  plane of the reciprocal lattice, indicates large mosaic spread or rotational disorder about the  $c$  axis, *i.e.* the sixfold screw axis parallel to the needle morphology of the crystals. The reflections with low  $h, k$  but high  $l$  indices are much less streaked, consistent with a greater degree of ordering in the  $c$  direction; that is in the direction in which the molecules are linked by chains of hydrogen bonds close to the twofold screw axis.

The synchrotron radiation source and the FAST diffractometer have thus allowed useful data to be collected for these crystals leading to the establishment of a structure where a conventional source and diffractometer did not succeed. The difficulty in data collection is due not only to the low intensity of the diffraction pattern (proportional to the sample volume) but also to the extended diffraction spots which result from poor crystal quality, *i.e.* large mosaic spread (Andrews *et al.*, 1988). The poor crystal quality may be sufficient to explain the failure of the structure to refine to an  $R$  factor of 0.07 or less. In this case the variable composition and dis-

ordered nature of the solvent in the channels also make good simulation of the solvent structure difficult; the very large disagreements in observed and calculated structure factors found for low-order reflections,  $\sin\theta < 0.1$ , in data set 2 are associated with this problem. The small number of reflection data, 592 observations for data set 2, means that anisotropic refinement of non-hydrogen atoms was not practicable. However, despite these limitations the data have given an unambiguous determination of the crystal structure, which in turn has assisted our understanding of the polymorphism of CDCA and the transformation between polymorphs.

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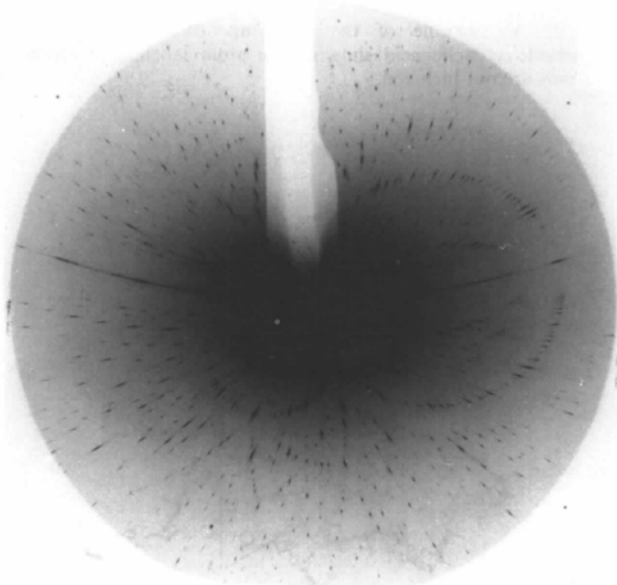


Fig. 3. Laue diffraction pattern of a chenodeoxycholic acid crystal, recorded on beamline 9.7. The  $c$  axis is approximately vertical.