

C(2)–C(3)–C(10)–C(11), which was found to be  $102^\circ$  ( $90^\circ$ ). This means that the plane defined by C(3)–C(10)–C(11) is nearly perpendicular to the plane of the indole nucleus. The torsion angle  $\tau_2 = \text{C}(3)\text{--C}(10)\text{--C}(11)\text{--N}(12)$  is  $176^\circ$  ( $188^\circ$ ), and the amino nitrogen atom is thus as far as possible from the centre of the pyrrole ring (Fig. 2).

#### Description of the crystal structure

The crystal structure viewed along the *b* axis is shown in Fig. 3. The *A*-molecules are linked together by N(1)–H(1)···N(12) hydrogen bonds which run in a helical fashion around a screw axis. The *B*-molecules are connected by the same type of hydrogen bond in a nearly identical manner and the two hydrogen bonds thus give rise to N–N distances of 2.92 Å and 2.89 Å respectively. In both cases the hydrogen atoms involved lie almost on the straight line between the nitrogen atoms (see Table 6). In both hydrogen bonding systems, the hydrogen bonds form nearly tetrahedral angles with the carbon atoms around the acceptor amino nitrogen atom (Table 6). There are no connexions between the *A*- and *B*-molecules other than ordinary van der Waals contacts, the shortest intermolecular distance being 3.5 Å for non-hydrogen atoms.

I wish to express my gratitude to Professor Diego Carlström for his support and patient guidance. My thanks to 'Docent' Rolf Bergin for computer programming and practical help with the IBM 360/75 computer.

I thank Professor Bo Holmstedt of the Toxicology Department at Karolinska Institutet for providing crystals of (*N,N*)-dimethyltryptamine and Doctor Jan

Lundström of the Institute of Pharmacognosy for his considerable help with the crystallization.

My thanks go also to Mrs Ingrid Hacksell for her excellent typing of the manuscript and for preparing the drawings.

This work has been supported by the Swedish Medical Research Council (Project No 13X-144).

#### References

- BERGIN, R. (1971). *Crystallographic Programs for the IBM 360/75*. Internal Report I/71, Karolinska Institutet, Stockholm.
- BERGIN, R., CARLSTRÖM, D., FALKENBERG, G. & RINGERTZ, H. (1968). *Acta Cryst.* B24, 882.
- BERGMAN, J., ABRAHAMSSON, S. & DAHLÉN, B. (1971). *Tetrahedron*, 27, 6143.
- FALKENBERG, G. & CARLSTRÖM, D. (1971). *Acta Cryst.* B27, 411.
- FISH, M. S., JOHNSON, N. M. & HORNING, E. C. (1955). *J. Amer. Chem. Soc.* 77, 5892.
- HAHN, T. (1957). *Z. Kristallogr.* 109, 438.
- International Tables for X-ray Crystallography* (1962). Vol. III. Birmingham: Kynoch Press.
- JOHNSON, C. K. (1970). *ORTEP*. Report ORNL-3794 (2nd rev.), Oak Ridge National Laboratory, Oak Ridge, Tennessee.
- KARLE, I. L. & KARLE, J. (1963). *Acta Cryst.* 16, 969.
- KARLE, J. & KARLE, I. L. (1966). *Acta Cryst.* 21, 849.
- MCDOWELL, J. J. H. (1969). *Acta Cryst.* B25, 2175.
- QUARLES, W. G. (1971). Dissertation 71-9896. Univ. of California, Berkeley.
- SAYRE, D. (1952). *Acta Cryst.* 5, 60.
- SZARA, S. (1956). *Experientia*, 12, 441.
- Tables of Interatomic Distances and Configuration in Molecules and Ions* (1965). Supplement. London: The Chemical Society.

*Acta Cryst.* (1972). B28, 3083

## The Crystal and Molecular Structure of an Addition Compound of Cholic Acid and Ethanol

BY PAUL L. JOHNSON AND JOHN P. SCHAEFER

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721, U.S.A.

(Received 21 July 1971)

A 1:1 addition compound of cholic acid and ethanol,  $\text{C}_{26}\text{H}_{46}\text{O}_6$ , crystallizes in the orthorhombic space group  $P2_12_12_1$  with four molecules in the unit cell. The cell constants are  $a = 14.661$ ,  $b = 11.759$ , and  $c = 15.066$  Å. The structure was solved using acentric direct methods. Refinement of the parameters of all nonhydrogen atoms by a full-matrix least-squares procedure reduced the conventional *R* index to 0.113. The carbon atoms in the rings were assigned isotropic temperature factors; all carbon and oxygen atoms not in the rings were assigned anisotropic temperature factors. A hydrogen bonding scheme has been formulated which involves three molecules of cholic acid around one ethanol with five hydrogen bonds being formed.

#### Introduction

The bile acids are physiologically important steroids. We have carried out a single-crystal structural analysis

of an addition compound of cholic acid and ethanol,  $\text{C}_{26}\text{H}_{46}\text{O}_6$ , which takes the form of a one to one complex. The purpose of this study was to elucidate any unusual structural features of the molecule which

might be related to biological activity. Furthermore, the details of hydrogen bonding should provide information on the nature of complex formation.

A recent X-ray study of desoxycholic acid *p*-bromoanilide (Schaefer & Reed, 1972) has revealed a molecular association which is dimeric in nature. Additional information on the nature of hydrogen bonding in this class of compounds may help explain the role of bile acids in biological systems. The chemistry of these compounds has been explained in detail (Fieser & Fieser, 1959).

### Experimental

Cholic acid was obtained from Mann Research Laboratories and was used without further purification. Colorless prisms of the 1:1 complex formed upon crystallization from absolute ethanol.

#### Crystal data

$C_{24}H_{40}O_5 \cdot C_2H_6O$ , M.W. 454.6. Orthorhombic,  $a = 14.661$  (2),  $b = 11.759$  (1),  $c = 15.066$  (3) Å,  $V = 2590$  Å<sup>3</sup>.  $D_m = 1.16$  (floatation in a  $CCl_4$  and EtOAc mixture),  $Z = 4$ ,  $D_c = 1.162$  g.cm<sup>-3</sup>,  $F(000) = 1000$ . Absent spectra:  $h00$  when  $h = 2n + 1$ ;  $0k0$ , when  $k = 2n + 1$ , and  $00l$ , when  $l = 2n + 1$ . Space group,  $P2_12_12_1$ .  $\mu(Cu K\alpha) = 3.2$  cm<sup>-1</sup>.

The cell parameters were determined by least-squares fit to the settings for the four angles of seven reflections on a Picker FACS-I diffractometer (Cu  $K\alpha$ ,  $\lambda = 1.54178$  Å). The crystal was mounted about the [112] zone. The length of the crystal along the mounting axis was 0.60 mm while the thick and thin directions perpendicular to this were 0.35 and 0.63 mm. The maximum and minimum transmission factors were estimated as 0.89 and 0.82.

Data were collected using a Picker FACS-I system with monochromatic radiation and a  $\theta$ - $2\theta$  scan technique. When the count rate exceeded 10,000 counts per sec, attenuators were inserted. The diffracted intensities were measured with a scintillation counter equipped with a pulse height analyzer. The scan rate was 1.0° per min with 10 sec backgrounds measured at the two extremes of each scan. The scan range had a base width of 1.8°, with a dispersion factor allowing for  $\alpha_1$ - $\alpha_2$  splitting being applied at large  $2\theta$  values. One complete set of data was measured, which consisted of 2375 reflections of which 2110 were considered to be observed using the criterion that a reflection be greater than three times its standard deviation. Three standard reflections were monitored every 100 measurements to check the crystal alignment and stability; no decrease in the intensities of the standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

#### Structure determination

The structure was determined by direct methods from the observed intensities in the manner described by Karle & Karle (1966). The computer program of

Germain, Main & Woolfson (1970) was used to carry out the calculations. The origin and enantiomorph were selected, known information in the form of  $\sum_1$  relationships was included and three unknown reflections were tried in each allowed quadrant. The starting set of phases is listed in Table 1. A tangent formula calculation was carried out 32 times to allow the unknown reflections to be permuted through all combinations of sign. One solution was clearly the best according to the criterion of Germain *et al.* (1966) and the  $E$  map calculated from this phase set revealed 26 of 32 nonhydrogen atoms in the complex. At this stage at which 26 atoms were known, a difference map was computed to locate the remaining atoms.

Table 1. Starting set of phases

	<i>h</i>	<i>k</i>	<i>l</i>	Phase
Origin	0	3	8	0
	5	5	0	90
	6	0	9	0
Enantiomorph $\sum_1$ 's	12	1	0	90
	2	2	0	0
	0	12	12	180
	0	6	4	180
	4	0	0	180
	10	0	0	0
	4	6	0	180
Unknowns	5	6	6	$\pm 45, \pm 135$
	6	4	1	$\pm 45, \pm 135$
	0	1	3	$\pm 90$

Table 2. Final atomic parameters in fractions of the unit-cell edge ( $\times 10^4$ ) with estimated standard deviations in parentheses

	<i>x</i>	<i>y</i>	<i>z</i>
O(3)	5756 (6)	3216 (6)	3852 (5)
O(7)	5248 (4)	2068 (5)	680 (5)
O(12)	4290 (4)	5977 (5)	546 (4)
O(24a)	1158 (5)	5793 (7)	-3258 (6)
O(24b)	1388 (5)	7508 (7)	-3845 (7)
O(26)	4606 (8)	4787 (7)	4535 (7)
C(25)	3379 (11)	4076 (15)	5379 (10)
C(26)	4301 (14)	4485 (11)	5410 (13)
C(18)	5805 (6)	5554 (8)	-1483 (6)
C(19)	7827 (6)	4609 (9)	790 (7)
C(20)	3818 (7)	6162 (8)	-1910 (7)
C(21)	3817 (8)	7324 (8)	-1405 (8)
C(22)	2836 (7)	5897 (9)	-2311 (7)
C(23)	2600 (7)	6736 (10)	-2997 (8)
C(24)	1638 (7)	6617 (9)	-3364 (8)
C(1)	7025 (7)	5053 (8)	2220 (6)
C(2)	6293 (7)	4707 (8)	2937 (6)
C(3)	6443 (7)	3502 (9)	3166 (7)
C(4)	6307 (7)	2726 (9)	2381 (7)
C(5)	7021 (6)	3035 (8)	1641 (6)
C(6)	6905 (6)	2224 (8)	836 (6)
C(7)	6078 (6)	2465 (8)	260 (6)
C(8)	5997 (6)	3723 (7)	-4 (6)
C(9)	6054 (6)	4495 (7)	858 (5)
C(10)	6955 (6)	4299 (7)	1349 (6)
C(11)	5956 (6)	5766 (7)	570 (6)
C(12)	5090 (6)	6016 (7)	-3 (6)
C(13)	5025 (5)	5239 (7)	-804 (5)
C(14)	5098 (6)	3993 (7)	-480 (6)
C(15)	4857 (6)	3273 (8)	-1296 (6)
C(16)	4143 (6)	4025 (8)	-1803 (6)
C(17)	4091 (6)	5186 (7)	-1274 (6)

Table 3. *Thermal parameters*

The temperature factor is of the form  $\exp [-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl) + 10^4]$ .

Estimated standard deviations are given in parentheses.

	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
O(3)	112 (6)	66 (6)	65 (4)	3 (5)	36 (5)	9 (5)
O(7)	44 (3)	62 (5)	66 (4)	1 (4)	14 (3)	1 (4)
O(12)	47 (3)	58 (5)	49 (3)	9 (4)	8 (3)	-9 (4)
O(24a)	72 (5)	87 (7)	109 (6)	-7 (5)	-42 (5)	7 (6)
O(24b)	71 (5)	103 (7)	138 (8)	-3 (5)	-34 (5)	30 (7)
O(26)	172 (10)	63 (7)	120 (7)	26 (7)	64 (7)	15 (6)
C(25)	86 (10)	214 (21)	95 (11)	-32 (13)	17 (9)	-17 (13)
C(26)	153 (15)	83 (12)	128 (13)	6 (12)	-7 (13)	13 (11)
C(18)	36 (5)	72 (8)	46 (5)	-11 (5)	6 (4)	3 (6)
C(19)	33 (5)	88 (9)	79 (7)	2 (6)	11 (5)	21 (7)
C(20)	48 (5)	61 (8)	57 (6)	-1 (5)	-20 (5)	11 (6)
C(21)	87 (8)	54 (8)	74 (7)	20 (7)	-40 (7)	-4 (7)
C(22)	46 (6)	99 (10)	60 (6)	11 (6)	-26 (5)	1 (7)
C(23)	52 (6)	119 (11)	65 (7)	-8 (7)	-18 (6)	1 (8)
C(24)	56 (6)	60 (8)	71 (7)	2 (6)	-18 (6)	5 (7)

	$B^*$	$B^*$	$B^*$	$B^*$			
C(1)	4.4 (2)	C(6)	4.0 (2)	C(10)	3.3 (2)	C(14)	3.1 (2)
C(2)	4.1 (2)	C(7)	3.5 (2)	C(11)	3.3 (2)	C(15)	3.8 (2)
C(3)	4.8 (2)	C(8)	3.1 (2)	C(12)	3.2 (2)	C(16)	3.8 (2)
C(4)	4.7 (2)	C(9)	2.9 (2)	C(13)	2.6 (2)	C(17)	3.0 (2)
C(5)	3.6 (2)						

\* Isotropic thermal parameter ( $\text{\AA}^2$ ).

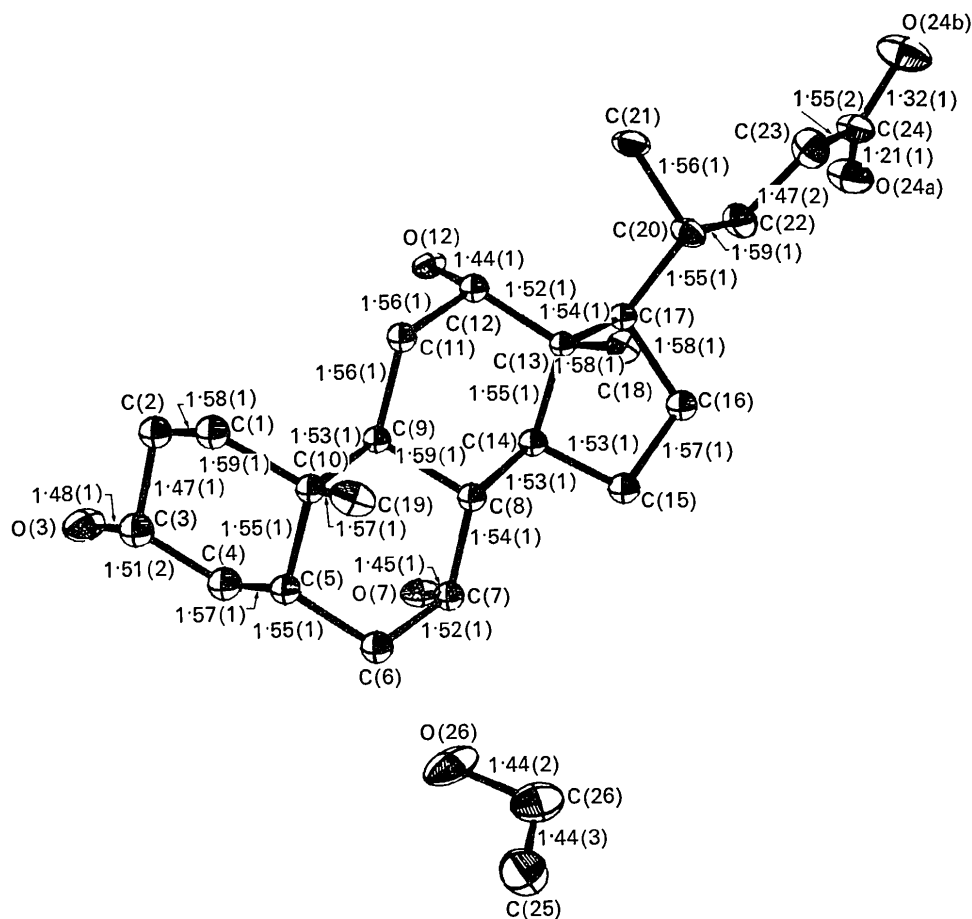


Fig. 1. Bond lengths and numbering system for cholic acid and ethanol.

Full-matrix least-squares refinement, in which positional and isotropic thermal parameters were varied, reduced  $R$  to 0.146. The weighting scheme was based on counter statistics as defined by Corfield, Doedens & Ibers (1966); the value of  $p$  was 0.01. Refinement was based on  $F_o$ , the quantity minimized being  $\sum \omega(F_o - F_c)^2$ . Subsequent refinement was made by varying the thermal parameters of the atoms outside the ring system anisotropically and the remaining thermal parameters isotropically. The atoms in the rings are the ones numbered C(1) through C(17). The  $R$  index ( $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ ) from this refinement was 0.113. Scattering factors used were those of Hanson, Herman, Lea & Skillman (1964).

Final positional parameters are shown in Table 2 and thermal parameters in Table 3. In our judgment, the  $R$  factor is high owing to incomplete refinement.

### Results and discussion

The geometry of the rings was as expected with the  $A:B$  ring juncture *cis* while the  $B:C$  and  $C:D$  ring junctures are *trans*. The torsional angles are listed in Table 4; they show that rings  $A$ ,  $B$ , and  $C$  can all be given the conventional 'chair' description. The only unusual feature found in these rings is the large torsional angle of  $68.1^\circ$  found for C(2)–C(3)–C(4)–C(5).

Table 4. *Torsional angles in the ring*

The torsional angle  $w-x-y-z$  is the projected angle between  $wx$  and  $yz$ . When viewed along the  $x-y$  bond, the clockwise rotation of bond  $yz$  with reference to bond  $wx$  is considered positive.  $\varphi$  is the torsional angle about the bond shown, in which the other two atoms required to define the angle are those attached to either end of the bond and are in the ring in question.

	Bond	$\varphi$
A Ring	C(1)–C(2)	59.4
	C(2)–C(3)	–62.5
	C(3)–C(4)	68.1
	C(4)–C(5)	–57.2
	C(5)–C(10)	55.3
	C(10)–C(1)	–54.7
B Ring	C(10)–C(5)	55.3
	C(5)–C(6)	–50.2
	C(6)–C(7)	49.4
	C(7)–C(8)	–52.0
	C(8)–C(9)	58.9
	C(9)–C(10)	–60.8
C Ring	C(9)–C(8)	–56.0
	C(8)–C(14)	62.3
	C(14)–C(13)	–60.5
	C(13)–C(12)	53.1
	C(12)–C(11)	–53.4
	C(11)–C(9)	53.5
D Ring	C(13)–C(14)	48.1
	C(14)–C(15)	–32.6
	C(15)–C(16)	4.8
	C(16)–C(17)	24.5
	C(17)–C(13)	–43.4

The bond lengths are in Fig. 1 and the bond angles are in Table 5. The average of 28  $C(sp^3)–C(sp^3)$

distances in the molecule is 1.54 Å. The C(25)–C(26) bond length (1.44 Å) is anomalously short; this can be attributed to inaccurate location of the ethanol due to the high thermal motion in this part of the structure. The average isotropic temperature factor for ethanol is approximately  $7 \text{ \AA}^2$  while the atoms in the ring average approximately  $3 \text{ \AA}^2$ . No correction to bond lengths has been made to allow for thermal motion.

Table 5. *Bond angles with estimated standard deviations in parentheses*

O(3)—C(3)—C(2)	106.3 (7)°
O(3)—C(3)—C(4)	108.6 (7)
O(7)—C(7)—C(6)	111.1 (6)
O(7)—C(7)—C(8)	110.0 (6)
O(12)—C(12)—C(11)	109.7 (6)
O(12)—C(12)—C(13)	112.8 (6)
O(24a)—C(24)—O(24b)	123.0 (7)
O(24a)—C(24)—C(23)	124.5 (8)
O(24b)—C(24)—C(23)	112.5 (7)
O(26)—C(26)—C(25)	110.2 (13)
C(18)—C(13)—C(12)	109.2 (6)
C(18)—C(13)—C(14)	112.1 (6)
C(18)—C(13)—C(17)	110.8 (6)
C(19)—C(10)—C(1)	105.1 (6)
C(19)—C(10)—C(5)	108.8 (6)
C(19)—C(10)—C(9)	114.1 (6)
C(21)—C(20)—C(22)	110.8 (7)
C(20)—C(22)—C(23)	110.4 (7)
C(21)—C(20)—C(17)	110.3 (7)
C(22)—C(20)—C(17)	108.9 (7)
C(20)—C(17)—C(13)	118.9 (6)
C(20)—C(17)—C(16)	109.8 (6)
C(22)—C(23)—C(24)	114.3 (8)
C(1)—C(2)—C(3)	107.9 (7)
C(2)—C(1)—C(10)	112.2 (7)
C(1)—C(10)—C(5)	107.2 (7)
C(1)—C(10)—C(9)	111.8 (7)
C(2)—C(3)—C(4)	112.2 (7)
C(3)—C(4)—C(5)	109.2 (7)
C(4)—C(5)—C(6)	109.8 (7)
C(4)—C(5)—C(10)	112.4 (7)
C(5)—C(6)—C(7)	114.9 (7)
C(6)—C(5)—C(10)	110.0 (7)
C(5)—C(10)—C(9)	109.6 (6)°
C(6)—C(7)—C(8)	112.9 (7)
C(7)—C(8)—C(9)	109.6 (6)
C(7)—C(8)—C(14)	112.8 (6)
C(8)—C(9)—C(10)	110.8 (6)
C(8)—C(9)—C(11)	108.4 (6)
C(9)—C(8)—C(14)	108.0 (6)
C(8)—C(14)—C(13)	113.8 (6)
C(8)—C(14)—C(15)	117.2 (6)
C(10)—C(9)—C(11)	110.9 (6)
C(9)—C(11)—C(12)	114.1 (6)
C(11)—C(12)—C(13)	112.2 (6)
C(12)—C(13)—C(14)	108.4 (6)
C(12)—C(13)—C(17)	116.5 (6)
C(13)—C(14)—C(15)	104.7 (6)
C(14)—C(13)—C(17)	99.6 (6)
C(13)—C(17)—C(16)	103.0 (6)
C(14)—C(15)—C(16)	103.4 (6)
C(15)—C(16)—C(17)	105.8 (6)

The bond angles in Table 5 have the usual values found in steroids. The estimated standard deviation of bond angles is 0.6 to 0.8° for all angles in the cholic acid

moiety of the compound. The bond angle in ethanol ( $110.2^\circ$ ) has an e.s.d. of  $1.3^\circ$ . Again, this is attributed to the thermal motion.

The *D* ring of cholic acid is best characterized as a  $\beta$ -envelope although this is not exact (Brutcher & Leopold, 1966; Brutcher & Bauer, 1962). It is actually between a half chair and a  $\beta$ -envelope but closer to the

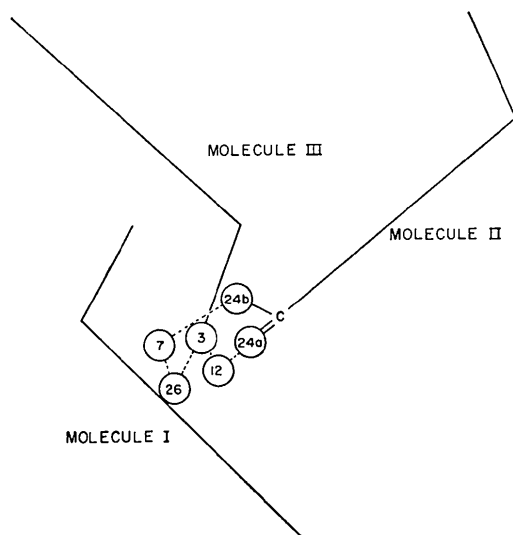


Fig. 2. Schematic drawing of hydrogen bonding. Atoms O(7), O(12), and O(26) belong to molecule I.

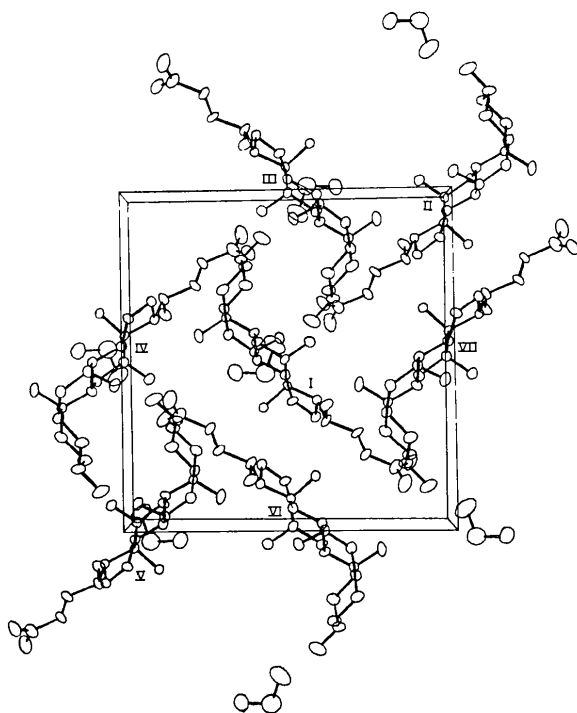


Fig. 3. Packing diagram of cholic acid and ethanol.

$\beta$ -envelope. The conformation of the *D* ring can also be evaluated using the parameters proposed by Altona, Geise & Romers (1968). They use the maximum possible torsion angle,  $\varphi_m$ , and the phase angle,  $\Delta$ . The values of  $\varphi_m$  and  $\Delta$  for cholic acid are  $49.2$  and  $23.3^\circ$  respectively.

Intermolecular contacts less than  $3.8 \text{ \AA}$  are listed in Table 6. The first five contacts are hydrogen bonds. There is an intricate hydrogen bonding scheme involving three molecules of cholic acid and one molecule of ethanol linked by five hydrogen bonds. This is shown schematically in Fig. 2. The packing diagram is given in Fig. 3.

Table 6. Intermolecular contacts ( $< 3.8 \text{ \AA}$ ) in cholic acid and ethanol complex

O(3)—O(12 <sup>iii</sup> )	2.79 Å
O(24a)—O(12 <sup>i</sup> )	2.83
O(24b)—O(7 <sup>i</sup> )	2.55
O(7)—O(26 <sup>iii</sup> )	2.71
O(3)—O(26)	2.71
O(24a)—O(7 <sup>i</sup> )	3.62
O(24a)—C(9 <sup>i</sup> )	3.52
O(24b)—C(14 <sup>i</sup> )	3.73
C(24)—O(7 <sup>i</sup> )	3.48
C(24)—O(12 <sup>i</sup> )	3.72
O(24b)—C(2 <sup>ii</sup> )	3.55
O(3)—C(12 <sup>iii</sup> )	3.35
O(7)—C(26 <sup>iii</sup> )	3.52
C(3)—O(12 <sup>iii</sup> )	3.71
C(6)—O(26 <sup>iii</sup> )	3.66
C(7)—O(26 <sup>iii</sup> )	3.32
C(7)—C(26 <sup>iii</sup> )	3.69

The Roman numerals as superscripts refer to the equivalent positions relative to the reference molecule at  $x, y, z$ .

i	$\frac{1}{2}-x,$	$1-y,$	$-\frac{1}{2}+z$
ii	$-\frac{1}{2}+x,$	$1\frac{1}{2}-y,$	$-z$
iii	$1-x,$	$-\frac{1}{2}+y,$	$\frac{1}{2}-z$

Observed and calculated structure factors are listed in Table 7.

The authors wish to thank the University of Arizona Computer Center for financial assistance and Dr Larry L. Reed for helpful discussions.

Programs used in this study included Zalkin's *FORDAP*, Busing and Levy's *ORFFE* and *ORFLS*, and Johnson's *ORTEP*.

## References

- ALTONA, C., GEISE, H. J. & ROMERS, C. (1968). *Tetrahedron*, **24**, 13.  
 BRUTCHER, F. V. JR & BAUER, W. (1962). *J. Amer. Chem. Soc.* **84**, 2233.  
 BRUTCHER, F. V. JR & LEOPOLD, E. J. (1966). *J. Amer. Chem. Soc.* **88**, 3156.  
 CORFIELD, P. W. R., DOEDENS, R. J. & IBERS, J. A. (1966). *Inorg. Chem.* **5**, 1877.

