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Bile Pigment Structures. II. The Crystal Structure of Mesobilirubin IXα–Bis(chloroform)

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Mesobilirubin IXα (mesobilirubin) crystallizes with two molecules of chloroform in space group $P\bar{1}$ with a = 12·146 (14), b = 15·093 (14), c = 11·815 (14) Å, α = 103·56 (10), β = 105·58 (11), γ = 78·10 (9)°, Z = 2. The structure was refined to R = 0·112 for 2790 reflexions. The chromophore takes up a 'ridge-tile' conformation with an angle of 104·0° between local planar *syn-Z* configurated pyrromethenone units. This conformation is stabilized by two sets of three intramolecular hydrogen bonds involving the carboxylic acid function, the two pyrrole-imino H atoms and the terminal lactam system. The diffraction data allow an unequivocal assignment of the lactam formulation. The bond-length distribution suggests that there is relatively limited delocalization over the local pyrromethenone systems. The molecules are stacked with their pyrromethenone systems parallel to one another, thereby giving rise to channels in the crystal lattice in which the two chloroform molecules occur.

Introduction

The orange-yellow bile pigment bilirubin IXα (hereafter bilirubin) is the first isolable product of the oxidative breakdown of haem in mammals. It is excreted as its conjugated water-soluble diglucuronide salt with the bile into the duodenum, but hydrolysis in the intestinal tract regenerates free bilirubin, which is reduced by intestinal bacteria to yield urobilinoid chromogens as the final products. A complex mixture of bile pigments is excreted in the faeces of healthy mammals (Fig. 1). The most common source of bilirubin is ox gallstones, in which it occurs as the pure Ca salt. The yellow skin pigmentation observed under pathological conditions (jaundice) is the result of an increased concentration of bilirubin in the gall; it is then retained, in particular, in the elastin-rich tissues and also excreted in the urine.

Although the constitution of bilirubin is well established (Fischer, Plieninger & Weissbarth, 1941), stereochemical ambiguities have remained. The significant possible structural variables for the bilirubin molecule may be summarized as:

(1) *Z* or *E* configuration at the methine bridges.

(2) Conformational preference at the methine bridges (*i.e. syn* or *anti* forms, degree of twisting of the interplanar angles between pyrrole rings).

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(3) Tautomerism in the *A* and *D* rings between lactam and lactim forms.

(4) Total conformation of the chromophore: linear, 'ridge-tile' or helical.

(5) Possible stabilization of the molecular conformation through intramolecular hydrogen bonds involving the carboxylic acid functions, *e.g.* N—H···O(=C) and (C=)O···H—O bonds.

(6) Possible stabilization of the molecular conformation through N—H···O(=C) intermolecular hydrogen bonds between pyrrolone rings.

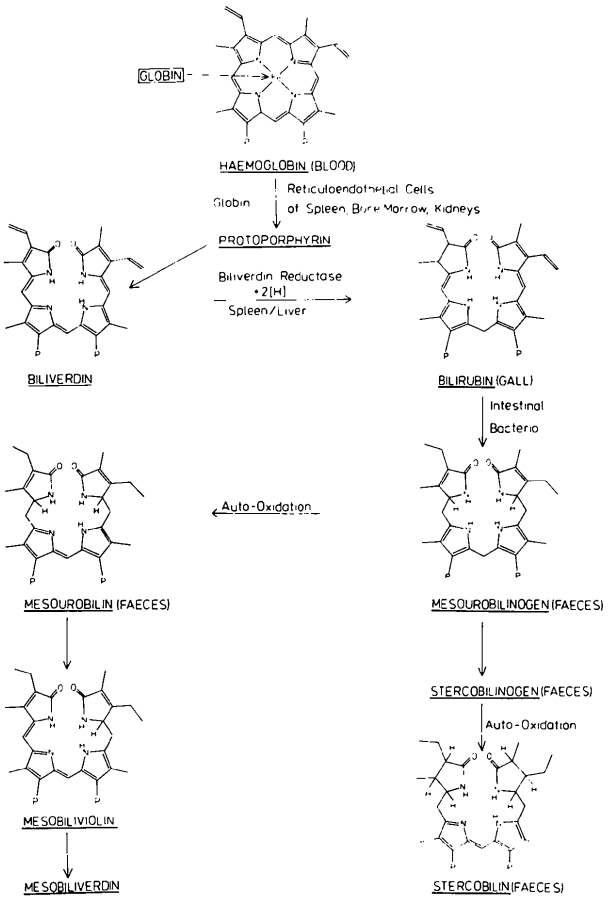

Fig. 1. Oxidative breakdown of haem in mammals.

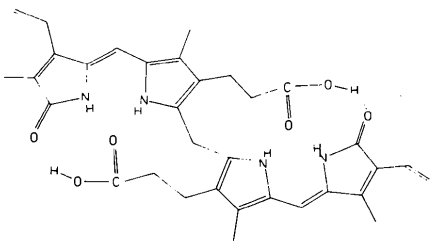

Fig. 2. Intramolecular hydrogen bonding in bilirubin.

(7) Bonding pattern within the tetrapyrrole skeleton (degree of bond delocalization).

The recently reported X-ray analysis of bilirubin (Bonnett, Davies & Hursthouse, 1976) has shown it to have a 'ridge-tile' conformation, which is stabilized (Fig. 2) by six intramolecular hydrogen bonds (two sets, each involving a carboxylic acid group, a pyrrole-imino H atom, and presumably a terminal lactam system). This type of structure was first proposed for bilirubin by Kuenzle, Weibel, Pelloni & Hemmerich (1973). The bond lengths suggested that delocalization over the local 5(1*H*)-pyrromethenone systems (*i.e.* rings *A* + *B* and *C* + *D*), which have planar *syn-Z* configurations, is rather limited, thereby lending support to the view that bilirubin is best regarded as a 2,2′-dipyrromethane (rings *B* and *C*) with conjugating π substituents. Thus C(4)—C(5) and C(15)—C(16) appear to be essentially double bonds (average 1·30 Å), whereas C(5)—C(6) and C(14)—C(15) resemble single bonds (average 1·48 Å). These results contrast with the observation of a considerable degree of delocalization over the conjugated system of the model compound 3′,5′-dimethyl-3,4,4′-triethyl-5(1*H*)-2,2′-pyrromethenone for which methine bridge bonds of 1·41 (1) and 1·35 (1) Å were determined (Cullen, Black, Meyer, Lightner, Quistad & Pak, 1977). A lesser degree of conjugation [methine bridge bonds 1·466 (5) and 1·321 (6) Å] was found for 5′-ethoxycarbonyl-3,4-dihydro-3′,4′-dimethyl-5(1*H*)-2,2′-pyrromethenone (Sheldrick, Borkenstein, Blacha-Puller & Gossauer, 1977). However, the structure of bilirubin could not be accurately determined, on account of the limited data set (1323 observed reflexions for two independent molecules in the asymmetric unit), and it was necessary to adopt a constrained bond-length model (e.s.d.'s 0·02–0·05 Å). An unequivocal assignment of either the lactam or lactim formulations for the *A* and *D* rings could not, therefore, be made.

Mesobilirubin IXα (hereafter mesobilirubin), in which the vinyl substituents of bilirubin have been reduced to ethyl groups, crystallizes well, and is more soluble in organic solvents than bilirubin itself. It is, in particular, readily soluble in chloroform, from which it crystallizes as yellow rhombic plates (Siedel, 1937) which contain solvent chloroform (Fischer, Plieninger & Weissbarth, 1941). We have, therefore, carried out a structural analysis of mesobilirubin crystallized from chloroform in the belief that, on account of the better crystals, it should enable an unequivocal assignment of the lactam or lactim formulation to bilirubin derivatives in the solid state and provide more detailed information about the degree of conjugation within the local pyrromethenone units. A short conference report of the structure of bilirubin crystallized with one molecule of chloroform has recently appeared in which the authors state that there are strong indications in favour of the lactam configuration for the outer rings (Le Bas,

Allegret & de Rango, 1977). The present paper is part of a systematic study of bile pigment structures. The first paper of the series reported the structure of biliverdin dimethyl ester (Sheldrick, 1976).

Preparation

Mesobilirubin was prepared by the method of Fischer, Plieninger & Weissbarth (1941). NH_3 gas was passed through a suspension of 1 g of bilirubin (Merck, Darmstadt) in 250 ml methanol until total solution was obtained. The solution was then hydrogenated over 10% Pd/charcoal. Mesobilirubin was extracted by filtration, dried at 35 °C on a rotary evaporator, and dissolved in chloroform. After washing twice with distilled water, the product was redried and allowed to crystallize from a chloroform solution in the dark to yield large rhombic yellow plates suitable for X-ray analysis.

Experimental

Crystal and refinement data for mesobilirubin are summarized in Table 1. Cell parameters were determined by a least-squares fit to the settings for 15 reflexions ($\pm hkl$) on a Syntex $P2_1$ diffractometer. Intensities were collected with graphite-monochromated radiation. Measurements were carried out in the θ–2θ mode at scan speeds varying linearly between 2·93° min^{-1} (150 c.p.s. and below) and 29·30° min^{-1} (1500 c.p.s. and above). On account of the broadness of the reflexions the angular 2θ range traversed was from 1·4° below the $K\alpha_1$ to 1·4° above the $K\alpha_2$ reflexion. The net intensity of each reflexion (scaled to counts per minute) was assigned a standard deviation, based on the counting statistics, of $\sigma(I) = t(N_s + N_b)^{1/2}$, where t is the scan rate, N_s the gross count and N_b the total background count. Lorentz and polarization corrections (but no absorption correction) were applied. Only those reflexions with $F \geq 4{\cdot}0\sigma(F)$ were retained in the refinement.

Table 1. *Crystal and refinement data for mesobilirubin*

Stoichiometry	$C_{33}H_{40}N_4O_6 \cdot 2CHCl_3$
Space group	$P\bar{1}$
a	12·146 (14) Å
b	15·093 (14)
c	11·815 (14)
α	103·56 (10)°
β	105·58 (11)
γ	78·10 (9)
V	2004·3 (30) Å^3
Z	2
M_r	827·5
D_c	1·27 g cm^{-3}
Radiation	Cu $K\alpha$
μ	41·5 cm^{-1}
2θ range	3·5–125·0°
F rejection criterion	$<4{\cdot}0\sigma(F)$
Number of reflexions	2790
R	0·112
$R_w = \Sigma w^{1/2}\Delta/\Sigma w^{1/2}F_o$	0·115
$R_g = (\Sigma w\Delta^2/\Sigma wF_o^2)^{1/2}$	0·127
k	3·8099
g	0·001237
Largest shift/e.s.d.	−0·37
Highest electron density peak	0·55 e Å^{-3}

Structure solution and refinement

All reflexions were included in the direct-methods solution, those with $I < 1{\cdot}0\sigma(I)$ being assigned a value of $0{\cdot}25\sigma(I)$. After the *SHELX*-76 (G. M. Sheldrick) automatic multisolution technique had failed to yield the solution, the structure was eventually solved by multisolution tangent refinement (E_{min} = 1·5, 455 reflexions) using seven reflexions with high estimated α values. The solution and subsequent refinement were carried out with *SHELX*-76.

The structure was refined by blocked full-matrix least squares, $\Sigma w\Delta^2$ being minimized; anisotropic temperature factors were introduced for all nonhydrogen atoms. Difference syntheses revealed the presence of two independent chloroform molecules in the unit cell. 28 of the methylene and methyl H atoms [*i.e.* all with the exception of the outer methyl H atoms on C(32) and C(182)] were included in the refinement under geometrical constraints and with group isotropic temperature factors. The methylene H atoms were allowed to ride on their respective C atoms, whereas the methyl groups were refined as rigid groups. The respective group isotropic temperature factors refined to 0·125 (16) and 0·168 (21) Å^2. A difference synthesis then clearly revealed the positions of the methine bridge H atoms at C(5) and C(15) and of four N–H protons, which were then allowed to refine freely with bond-length constraints for the C–H bond of 1·08 ± 0·02 and for the N–H bond of 1·01 ± 0·02 Å. Their group isotropic temperature factors refined to 0·060 (23) and 0·049 (15) Å^2 respectively. This successful refinement of four N–H protons, with the bond-length distribution in the pyrrolone *A* and *D* rings and the two characteristic C=O distances of 1·25 (2) and 1·22 (2) Å for C(1)–O(1) and C(19)–O(191), provides unequivocal proof for the lactam formulation of mesobilirubin. The C(83)–O and C(123)–O distances also allow a unique assignment of the carboxyl single and double bonds. However, the carboxyl O–H protons on O(84) and O(124) could not be located in difference syntheses and were not, therefore, included in the refinement. The presence of three large residual electron density peaks at 1·71–1·90 Å from C(20′) (*e.g.* 0·55 e Å^{-3} at 1·71

Table 2. *Positional parameters* ($\times 10^4$) *of the non-hydrogen atoms*

	x	y	z		x	y	z
N(24)	630 (7)	4565 (6)	3464 (6)	C(6)	2064 (8)	121 (6)	2739 (9)
C(19)	1095 (10)	5146 (6)	3010 (8)	C(81)	3835 (7)	1663 (6)	5150 (8)
C(18)	100 (11)	5760 (6)	2491 (8)	C(82)	4186 (8)	2358 (7)	4554 (9)
C(17)	9121 (9)	5556 (7)	2636 (8)	C(83)	3334 (9)	3187 (7)	4336 (9)
C(16)	9456 (9)	4770 (6)	3250 (7)	O(84)	3601 (6)	3685 (5)	3720 (6)
O(191)	2123 (6)	5097 (4)	3071 (6)	O(83)	2435 (5)	3386 (4)	4704 (5)
C(181)	214 (10)	6518 (7)	1863 (10)	C(71)	4202 (9)	165 (7)	2841 (10)
C(182)	346 (19)	6157 (12)	625 (13)	C(5)	1780 (9)	9466 (7)	1586 (10)
C(171)	7888 (10)	5987 (7)	2218 (10)	N(21)	9809 (7)	9279 (5)	1439 (7)
C(15)	8753 (8)	4340 (6)	3569 (8)	C(4)	811 (9)	9130 (6)	1053 (9)
N(23)	101 (6)	3026 (5)	4396 (6)	C(3)	534 (10)	8556 (7)	9837 (10)
C(14)	9010 (8)	3521 (6)	4086 (8)	C(2)	9472 (10)	8388 (6)	9599 (8)
C(13)	8238 (8)	3091 (6)	4373 (8)	C(1)	8962 (10)	8873 (7)	649 (10)
C(12)	8897 (8)	2300 (6)	4833 (7)	C(31)	1373 (12)	8306 (9)	8940 (13)
C(11)	44 (7)	2277 (6)	4863 (7)	C(32)	2115 (16)	7468 (14)	9209 (15)
C(131)	6949 (8)	3407 (6)	4231 (10)	C(21)	8760 (10)	7809 (8)	8479 (9)
C(121)	8440 (9)	1635 (6)	5324 (8)	O(1)	7955 (6)	8899 (5)	754 (6)
C(122)	7530 (8)	1112 (6)	4453 (9)	Cl(1)	6450 (3)	2855 (2)	7524 (3)
C(123)	8042 (9)	395 (6)	3454 (9)	Cl(2)	4984 (3)	4490 (2)	6852 (5)
O(123)	9056 (5)	203 (4)	3545 (5)	Cl(3)	6124 (7)	4458 (3)	9296 (4)
O(124)	7244 (6)	57 (5)	2590 (6)	C(20)	6229 (9)	4070 (7)	7808 (9)
C(10)	1138 (7)	1697 (6)	5321 (7)	C(20′)	4242 (11)	1960 (9)	107 (10)
N(22)	1293 (6)	551 (5)	3459 (7)	Cl(1′)	4429 (4)	2109 (3)	8816 (3)
C(9)	1821 (8)	1157 (5)	4385 (7)	Cl(2′)	5419 (4)	1217 (4)	724 (5)
C(8)	2928 (7)	1127 (6)	4317 (8)	Cl(3′)	4164 (6)	3014 (4)	1075 (5)
C(7)	3073 (8)	444 (6)	3265 (8)				

Table 3. *Hydrogen-atom positional parameters* ($\times 10^3$)

The methylene H atoms were allowed to ride on their respective C atoms, whereas the methyl H atoms were refined as part of rigid methyl groups. The standard deviations of these H atoms are, therefore, those of their parent C atoms.

	x	y	z		x	y	z
H(4)	130 (4)	414 (4)	383 (5)	H(102)	94 (1)	120 (1)	573 (1)
H(181)	97 (1)	683 (1)	236 (1)	H(2)	46 (2)	47 (4)	322 (5)
H(182)	945 (1)	703 (1)	185 (1)	H(81)	351 (1)	204 (1)	592 (1)
H(171)	740 (1)	599 (1)	286 (1)	H(82)	460 (1)	118 (1)	543 (1)
H(172)	759 (1)	552 (1)	140 (1)	H(83)	438 (1)	200 (1)	371 (1)
H(173)	777 (1)	667 (1)	204 (1)	H(84)	496 (1)	259 (1)	515 (1)
H(15)	784 (2)	450 (4)	324 (5)	H(71)	501 (1)	25 (1)	350 (1)
H(3)	93 (2)	306 (4)	441 (5)	H(72)	410 (1)	57 (1)	217 (1)
H(131)	680 (1)	412 (1)	413 (1)	H(73)	421 (1)	945 (1)	242 (1)
H(132)	684 (1)	338 (1)	510 (1)	H(5)	254 (3)	937 (4)	126 (5)
H(133)	634 (1)	303 (1)	354 (1)	H(1)	964 (5)	968 (4)	219 (3)
H(121)	809 (1)	201 (1)	608 (1)	H(31)	188 (1)	885 (1)	910 (1)
H(122)	917 (1)	113 (1)	561 (1)	H(32)	89 (1)	820 (1)	802 (1)
H(123)	717 (1)	75 (1)	493 (1)	H(21)	790 (1)	820 (1)	842 (1)
H(124)	686 (1)	161 (1)	405 (1)	H(22)	875 (1)	711 (1)	852 (1)
H(101)	168 (1)	214 (1)	599 (1)	H(23)	905 (1)	782 (1)	770 (1)

Å) and the very high anisotropic temperature factor components for Cl(1′), Cl(2′) and Cl(3′) indicate that this solvent chloroform molecule is disordered. Attempts to include a model for this disorder in the refinement were, however, unsuccessful. The relatively high R factor of 0·112 is in accordance with the presence of this disorder and with the poor quality of the mesobilirubin crystals. Taken together with values of R = 0·125 (1323 reflexions) and 0·090 (2357 reflexions) which were obtained for bilirubin and biliverdin dimethyl ester, this indicates that poor quality diffraction data will probably be a general feature of X-ray diffraction studies on bile pigments and that it will not be possible to obtain such detailed information about bond lengths and angles for this class of compounds as is now abundantly available for the porphyrins. The weights were given by $w = k/[\sigma^2(F_o) + g(F_o)^2]$. Complex neutral-atom scattering factors

Table 4. *Bond lengths* (Å)

C(19)–N(24)	1·400 (17)	C(16)–N(24)	1·362 (14)
C(18)–C(19)	1·449 (15)	O(191)–C(19)	1·219 (16)
C(17)–C(18)	1·350 (20)	C(181)–C(18)	1·549 (19)
C(16)–C(17)	1·465 (15)	C(171)–C(17)	1·503 (15)
C(15)–C(16)	1·344 (17)	C(182)–C(181)	1·476 (21)
C(14)–C(15)	1·446 (15)	C(14)–N(23)	1·381 (12)
C(11)–N(23)	1·391 (14)	C(13)–C(14)	1·393 (17)
C(12)–C(13)	1·428 (14)	C(131)–C(13)	1·515 (14)
C(11)–C(12)	1·377 (15)	C(121)–C(12)	1·526 (17)
C(10)–C(11)	1·476 (11)	C(122)–C(121)	1·507 (14)
C(123)–C(122)	1·572 (14)	O(123)–C(123)	1·186 (13)
O(124)–C(123)	1·292 (12)	C(9)–C(10)	1·539 (13)
C(9)–N(22)	1·358 (11)	C(6)–N(22)	1·392 (13)
C(8)–C(9)	1·359 (15)	C(7)–C(8)	1·443 (13)
C(81)–C(8)	1·499 (12)	C(6)–C(7)	1·350 (14)
C(71)–C(7)	1·529 (16)	C(5)–C(6)	1·486 (14)
C(82)–C(81)	1·573 (17)	C(83)–C(82)	1·477 (14)
O(84)–C(83)	1·298 (16)	O(83)–C(83)	1·236 (14)
C(4)–C(5)	1·318 (15)	C(4)–N(21)	1·370 (16)
C(1)–N(21)	1·335 (13)	C(3)–C(4)	1·485 (14)
C(2)–C(3)	1·308 (18)	C(31)–C(3)	1·593 (21)
C(1)–C(2)	1·503 (17)	C(21)–C(2)	1·555 (14)
O(1)–C(1)	1·253 (16)	C(32)–C(31)	1·442 (24)
C(20)–Cl(1)	1·763 (12)	C(20)–Cl(2)	1·728 (11)
C(20)–Cl(3)	1·749 (12)	Cl(1′)–C(20′)	1·673 (16)
Cl(2′)–C(20′)	1·731 (13)	Cl(3′)–C(20′)	1·729 (13)

(Cromer & Waber, 1965; Cromer & Liberman, 1970) were employed for the nonhydrogen atoms. The final heavy-atom coordinates are listed in Table 2 and the H positional parameters in Table 3. The proposed

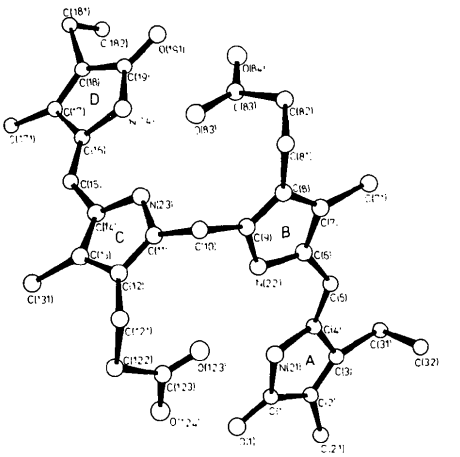

Fig. 3. Perspective drawing of mesobilirubin with ring and atom labelling.

Table 5. *Bond angles* (°)

C(16)–N(24)–C(19)	111·4 (8)	C(18)–C(19)–N(24)	104·5 (11)
O(191)–C(19)–N(24)	124·3 (9)	O(191)–C(19)–C(18)	131·1 (12)
C(17)–C(18)–C(19)	110·2 (11)	C(181)–C(18)–C(19)	122·2 (12)
C(181)–C(18)–C(17)	127·6 (10)	C(16)–C(17)–C(18)	107·1 (9)
C(171)–C(17)–C(18)	129·1 (11)	C(171)–C(17)–C(16)	123·6 (12)
C(17)–C(16)–N(24)	106·7 (10)	C(15)–C(16)–N(24)	126·1 (9)
C(15)–C(16)–C(17)	127·2 (10)	C(182)–C(181)–C(18)	112·9 (11)
C(14)–C(15)–C(16)	130·1 (9)	C(11)–N(23)–C(14)	110·2 (9)
N(23)–C(14)–C(15)	124·8 (10)	C(13)–C(14)–C(15)	127·7 (9)
C(13)–C(14)–N(23)	107·5 (9)	C(12)–C(13)–C(14)	106·8 (9)
C(131)–C(13)–C(14)	126·6 (9)	C(131)–C(13)–C(12)	126·6 (11)
C(11)–C(12)–C(13)	108·7 (10)	C(121)–C(12)–C(13)	126·2 (9)
C(121)–C(12)–C(11)	124·9 (8)	C(12)–C(11)–N(23)	106·8 (8)
C(10)–C(11)–N(23)	118·2 (9)	C(10)–C(11)–C(12)	134·9 (10)
C(122)–C(121)–C(12)	116·1 (9)	C(123)–C(122)–C(121)	111·5 (9)
O(123)–C(123)–C(122)	121·0 (8)	O(124)–C(123)–C(122)	112·2 (9)
O(124)–C(123)–O(123)	126·8 (10)	C(9)–C(10)–C(11)	116·0 (7)
C(6)–N(22)–C(9)	108·9 (8)	N(22)–C(9)–C(10)	118·1 (9)
C(8)–C(9)–C(10)	132·0 (8)	C(8)–C(9)–N(22)	109·9 (8)
C(7)–C(8)–C(9)	105·3 (8)	C(81)–C(8)–C(9)	128·6 (8)
C(81)–C(8)–C(7)	126·1 (9)	C(6)–C(7)–C(8)	108·9 (9)
C(71)–C(7)–C(8)	123·9 (8)	C(71)–C(7)–C(6)	127·3 (8)
C(7)–C(6)–N(22)	107·0 (8)	C(5)–C(6)–N(22)	125·2 (9)
C(5)–C(6)–C(7)	127·8 (10)	C(82)–C(81)–C(8)	113·0 (8)
C(83)–C(82)–C(81)	116·6 (10)	O(84)–C(83)–C(82)	114·5 (10)
O(83)–C(83)–C(82)	122·7 (12)	O(83)–C(83)–O(84)	122·8 (9)
C(4)–C(5)–C(6)	129·4 (11)	C(1)–N(21)–C(4)	113·5 (9)
N(21)–C(4)–C(5)	128·7 (10)	C(3)–C(4)–C(5)	126·9 (12)
C(3)–C(4)–N(21)	104·2 (9)	C(2)–C(3)–C(4)	109·2 (11)
C(31)–C(3)–C(4)	123·5 (11)	C(31)–C(3)–C(2)	126·9 (10)
C(1)–C(2)–C(3)	108·0 (9)	C(21)–C(2)–C(3)	130·6 (11)
C(21)–C(2)–C(1)	121·3 (11)	C(2)–C(1)–N(21)	105·0 (10)
O(1)–C(1)–N(21)	127·5 (10)	O(1)–C(1)–C(2)	127·5 (9)
C(32)–C(31)–C(3)	105·3 (14)	Cl(2)–C(20)–Cl(1)	110·6 (6)
Cl(3)–C(20)–Cl(1)	108·0 (7)	Cl(3)–C(20)–Cl(2)	110·4 (7)
Cl(2′)–C(20′)–Cl(1′)	108·6 (8)	Cl(3′)–C(20′)–Cl(1′)	108·9 (9)
Cl(3′)–C(20′)–Cl(2′)	109·2 (7)		

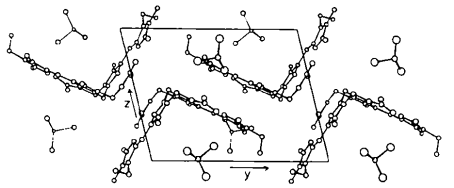

Fig. 4. Unit-cell contents in projection perpendicular to [100].

systematic numbering scheme for the bile pigments (Bonnett, 1977) has been used throughout (Fig. 3). The bond lengths and angles for the nonhydrogen atoms are presented in Tables 4 and 5. Fig. 4, which shows a projection of the cell contents, was drawn by *MIRAGE* (W. S. Sheldrick and D. N. Lincoln).*

Discussion

The chromophore of mesobilirubin takes up a 'ridge-tile' conformation with an angle of 104·0° between local planar *syn-Z* configurated pyrromethenone units. This is similar to those of 98, 107 and 99·6° between the methylene bridged systems in bilirubin, a biladiene-a,c dihydrobromide derivative (Struckmeier, Thewalt & Engel, 1976) and a model 2,2′-dipyrromethane (Sheldrick, Becker & Engel, 1977). In mesobilirubin this conformation is stabilized by six intramolecular hydrogen bonds (two sets, each involving a carboxylic acid group, a pyrrole-imino H atom and a terminal lactam system). The following distances are observed for the N—H···O(C) bridges: N(21)···O(123) 2·84, H(1)···O(123) 1·87, N(22)···O(123) 2·90, H(2)···O(123) 1·98, N(23)···O(83) 2·91, H(3)···O(83) 1·91, N(24)···O(83) 2·83, H(4)···O(83) 1·85 Å. The N—H···O hydrogen bonds to the inner *B* and *C* rings are therefore significantly stronger than those to the outer *A* and *D* rings. Although it proved impossible to locate the protons on O(84) and O(124), it may be assumed from the O(84)···O(191) and O(124)···O(1) distances of 2·61 and 2·67 Å that these are involved in strong O—H···O hydrogen bonds. The weighted least-squares planes for the individual rings and for the pyrromethenone units are presented in Table 6. Interplanar angles of −9·6 and −5·8° are observed between the *A* and *B*, and *C* and *D* rings respectively, which are presumably necessary to optimize the hydrogen bonding.

The diffraction data allow an unequivocal assignment of the lactam formulation to the *A* and *D* rings. For instance, C=N and C—O(Et) distances of 1·282 (3) and 1·326 (3) Å were observed for the lactim (ether) bonds in 5-ethoxy-5′-ethoxycarbonyl-3,4-dihydro-3′,4′-dimethyl-2,2′-pyrromethene (Sheldrick, Borkenstein, Blacha-Puller & Gossauer, 1977). In contrast, the C—N lengths of 1·335 (15) and 1·400 (17) Å, and the C—O lengths of 1·253 (16) and 1·219 (16) Å in the *A* and *D* rings of mesobilirubin are in accordance with the lactam formulation, which is also necessitated by the successful location and refinement of four N—H protons. It has been demonstrated by photometric p*K* measurements that the lactam is preferred by at least four to more than ten orders of magnitude over the lactim form for bile pigments in solution (Falk, Gergely, Grubmayr & Hofer, 1977). This characterization of the lactam form for mesobilirubin by X-ray analysis is also in agreement with their X-ray photoelectron spectroscopic studies on crystalline bilirubin derivatives.

The limited π delocalization over the local 5(1*H*)-pyrromethenone systems suggests that mesobilirubin is best regarded as a 2,2′-dipyrromethane with conjugating π substituents. The symmetrical bond-length distribution in the *B* and *C* rings resembles that of pyrrole itself (Nygaard, Nielsen, Kirchheiner, Maltesen, Rastrup-Andersen & Sørensen, 1969). The methine bridge bonds of 1·318 (15) and 1·486 (14) Å between the *A* and *B* rings appear to be essentially double and single bonds. Although, as a result of the limited quality of the data, the differences between the methine bridge bonds at C(15) and C(5) are not significant, they do indicate that there is a greater degree of delocalization over the *C* and *D* rings than over the *B* and *A* rings. This interpretation is corroborated by a comparison of the bond-length distribution in the *A* and *D* rings. Thus the C(17)—C(18) length of 1·350 (20) in the *D* ring is longer than the corresponding 1·308 (18) Å in the *A* ring, and the C(16)—C(17) and C(18)—C(19) lengths

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33208 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 6. *Distances of atoms* (Å) *from weighted least-squares planes*

The weights are equal to the atomic numbers.

(1) C(1) 0·001, C(2) −0·006, C(3) 0·009, C(4) −0·008, N(21) 0·004

(2) C(6) −0·017, C(7) 0·011, C(8) −0·000, C(9) −0·010, N(22) 0·014

(3) C(11) 0·005, C(12) −0·015, C(13) 0·019, C(14) −0·016, N(23) 0·006

(4) C(16) −0·008, C(17) 0·010, C(18) −0·008, C(19) 0·003, N(24) 0·003

(5) O(1) 0·014, C(1) 0·022, C(2) −0·096, C(3) −0·106, C(4) 0·040, N(21) 0·090, C(5) 0·055, C(6) 0·059, C(7) 0·070, C(8) −0·054, C(9) −0·108, N(22) −0·005

(6) C(11) −0·049, C(12) −0·047, C(13) 0·040, C(14) 0·014, N(23) −0·008, C(15) 0·068, C(16) 0·015, C(17) −0·057, C(18) −0·079, C(19) 0·015, N(24) 0·068, O(191) 0·007

of 1·465 (15) and 1·449 (15) Å are shorter than the corresponding distances of 1·485 (14) and 1·503 (17) Å in the *A* ring. The breakdown in the local C_2 symmetry between the two pyrromethenone units is also evidenced by the difference of 0·05 Å between the O···H–O hydrogen bonds and of 3·8° between the interplanar angles.

Fig. 4 shows that the mesobilirubin molecules are stacked with their pyrromethenone systems parallel to one another (at the van der Waals distance), thereby giving rise to channels in the crystal lattice in which the two chloroform molecules occur. The stacking pattern is very similar to that of bilirubin crystallized with one chloroform molecule. Short intermolecular contacts are observed between C(20) and O(191) (3·07 Å), C(20′) and O(1) (3·03 Å), Cl(2′) and O(124) (3·23 Å) and Cl(3′) and O(84) (3·26 Å).

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Structure Cristalline et Moléculaire d'un Diurétique Dérivé de l'Alkyl-1 [(Phénylamino-4 pyridyl-3)sulfonyl]-3 Urée: la Torasémide ($C_{15}H_{20}N_4SO_3$)

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The crystal structure of torasemide has been determined from 5667 independent intensities collected on a four-circle automatic diffractometer. Crystals are monoclinic, space group $P2_1/c$, with $Z = 8$, $a = 13{\cdot}308$, $b = 8{\cdot}223$, $c = 31{\cdot}970$ Å, $\beta = 107{\cdot}01°$. The structure was solved by the direct method, and refined by least squares to a final R value of 0·074. The two independent molecules of the asymmetric unit have very different conformations. In one, the proton of the N from the SO_2N group is transferred to the pyridyl ring. This H^+ is involved in a very short N···N bond (2·778 Å) which links the two molecules.

Introduction

Afin de mieux comprendre le rôle de la conformation comme facteur de potentialité diurétique, nous avons entrepris la détermination des structures de plusieurs composés diurétiques semblant agir d'une façon analogue. Le présent travail concerne la torasémide qui est un dérivé de l'alkyl-1 [(phénylamino-4 pyridyl-3)-sulfonyl]-3 urée (Fig. 1). Une étude pharmacologique et toxicologique d'une série de telles substances a montré que ces produits sont actifs à des concentrations plus faibles que les diurétiques connus antérieurement et que