

The Crystal Structure of Strychnine Hydrogen Bromide

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The structure of strychnine hydrobromide, $C_{21}H_{22}N_2O_2 \cdot HBr \cdot 2H_2O$, has been fully determined. The crystals are orthorhombic with space group $P2_12_12_1$, and cell dimensions $a=7.64$, $b=7.70$, $c=33.20$ Å. The positions of the bromine atoms were found from Patterson projections. The general intensities were determined and a three-dimensional Fourier synthesis was calculated in which the F values were given the phases of the bromine atoms alone. Also the vector convergence diagram, using the bromine positions, was obtained from the three-dimensional Patterson summation, and this was also employed to deduce the parameters of the complete structure. The structure possesses sheets of bromine atoms approximately at levels $z=\frac{1}{2}$ and $\frac{3}{4}$ which are linked together by water molecules. Each bromine atom is bonded to a strychnine molecule through the basic nitrogen atom of each molecule. The strychnine molecule found has a configuration identical with that found by Bokhoven, Schoone & Bijvoet, and has the same structure as that now favoured by the organic chemists.

Introduction

Interest in the structure of crystalline strychnine began in this laboratory as early as 1944 when intensity data relating to the free base were collected. It was realized, however, that the complexity of the problem without a heavy atom in the structure was extremely great and in 1947 the crystal structures of several strychnine and other salts were surveyed, with a view to finding the most suitable for another attempt at full analysis. For this purpose the hydrobromide of strychnine was chosen. It is not isomorphous with either the hydrochloride or hydroiodide, but the presence of the bromine atom was considered very advantageous compared with the strychnine itself.

It was discovered about one year after the commencement of work that strychnine salts were also the subject of study by Bokhoven, Schoone & Bijvoet (1947, 1948, 1949). In this case it was the sulphate and selenate that were being examined in detail, the method used being that of isomorphous replacement of a heavy atom at a symmetry centre. The results of these workers became available at the time that our first Fourier projections of the strychnine hydrobromide structure were being calculated. Our results were communicated briefly to *Nature* (Robertson & Beevers, 1950). The present paper is presented with the main emphasis laid upon the fresh ground it breaks in the interpretation of the three-dimensional Patterson synthesis, the potentialities of which we think have not yet been fully appreciated in crystal-structure determination.

Physical and X-ray data

Strychnine hydrobromide crystallizes from water in long slender needles or laths, parallel to the a axis, of

composition $C_{21}H_{22}N_2O_2 \cdot HBr \cdot 2H_2O$. The crystals are fairly hard and brittle, with irregular fracture if crushed, but have also a tendency to split, sometimes spontaneously, parallel to the (100) plane. The crystals are orthorhombic, with space group $P2_12_12_1$, and with unit-cell dimensions:

$$a=7.64, \quad b=7.70, \quad c=33.20 \text{ Å.}$$

These dimensions were obtained by an extrapolation method following Bradley & Jay (1932). There are four molecules in the unit cell; the observed density is 1.520 g.cm.^{-3} and that calculated from the X-ray data is 1.537 g.cm.^{-3} ; the volume of the cell is 1953 Å^3 . Optically, the crystals are biaxial negative, with refractive indices 1.688, 1.653 and 1.621. The crystals would seem to be the same as those described by Poe & Sellers (1932) for which were reported indices 1.73, 1.65 and 1.646, and one molecule of water of crystallization.

All reflexion intensity data were obtained from Weissenberg photographs, using $Cu K\alpha$ radiation. These were taken about the a axis, b axis and $a:b$ diagonal, using exposures varying from 20 to 600 min. to cover the desired range of intensities. A single spherically cut specimen was used throughout the general intensity work. Intensities were measured visually by comparison with a graded scale of standard reflexions, and the ($h0l$) and ($0kl$) intensities were carefully corrected for Lorentz and polarization factors. In order to bring the general intensities on to the same scale the Lorentz and polarization corrections, the Cox-Shaw factor and all other corrections which could be regarded as continuous functions of $\sin \theta$ were taken into account simultaneously by an empirical method, devised to cope with the large numbers of reflexions involved. For this, the ratios of the corrected and uncorrected intensities

occurring in a series such as $(10l)$ ($l=0-20$) common to the $(h0l)$ and $(1kl)$ photographs were plotted against their respective values of $\sin \theta$. Separate treatment of the two halves of the Weissenberg photographs made it possible also to take into account the shortening and lengthening of spots at low values of θ in high-layer-line photographs. General intensities were left on a relative scale, once having been made consistent as a whole. The measured F values in the $(h0l)$ and $(0kl)$ zone were placed on the absolute scale, first by means of the method of Wilson (1942), but subsequently, when the approximate structure had been determined, by comparison with the calculated F 's as described below. Throughout, the James & Brindley atomic scattering curves were used, uncorrected for thermal vibration.

Determination of the structure

(a) *The approximate structure by three-dimensional methods*

The first step, taken at the outset of the analysis, was the location of the bromine ion by calculation of the three Patterson projections on (100) , (010) and (001) . Quite rough calculations gave projections which showed self-consistent peaks with a bromine position: $x=\frac{1}{6}$, $y=\frac{2}{6}$, $z=\frac{1}{6}$ (expressed as fractions of the respective cell edges). Next Fourier projections on (100) and (010) were calculated with the signs of the contributions of the bromine atom at this position. These, however, were not easy to interpret; and it was thought necessary to proceed to the use of the general intensities in a study of the three-dimensional Fourier and Patterson functions.

For the three-dimensional calculations, considerable simplifications were necessary to make the project feasible. First, the data employed were confined to relatively low-order reflexions: h and k up to 5, and l up to 20 only. This included well over 700 reflexions, but represented only about one-third of the total number (about 2300) of unique $F_{(hkl)}$ values obtainable with copper radiation. Secondly, the subdivision of the unit cell was made extremely rough: a and b were divided into 15ths only, and c into 60ths. Computation extended over the quarter volume of the cell bounded by a and b axes and one-quarter of the c axis—i.e. over 3400 points, in a volume nearly cubic in shape. Preliminary to the Fourier calculation, the contributions of the bromine atom were calculated for all the structure factors concerned; then the observed values of $|F_{(hkl)}|^2$ were split into components A and B such as that $A^2 + B^2 = |F_{(hkl)}|^2$, and such that the ratio A/B was the same as that for the bromine atom contribution. This was equivalent to using the observed intensities but with the phases of the bromine contributions alone. Finally, the scale of all the terms employed was reduced, so that the calculations could be done quickly by hand, using the Beever's-Lipson strips. The three-dimensional Patterson function was calculated directly from the corrected F^2 values.

A careful comparison of the three-dimensional Fourier and Patterson synthesis was then made. It was realized that the Fourier synthesis, owing to the assumptions upon which it was based, was undoubtedly erroneous in much, if not most, of its detail. On the other hand, the Patterson synthesis, while considerably more difficult to interpret, was much more reliable. Atoms were placed on several of the largest peaks in the Fourier synthesis, the vectors between them and the bromine atom were calculated, and the Patterson synthesis was studied to see whether high ground did in fact occur at the predicted positions. The procedure, however, was slow, and did not lead to much progress.

It was at this stage that systematic interpretation of the Patterson synthesis was begun, using the vector convergence method (Beever's & Robertson, 1950). Without recapitulating the details of the process, it will suffice to say that, by use of the known positions of the four equivalent bromine atoms, a three-dimensional function, similar to the Fourier synthesis, was derived. This function, the 'vector convergence density', possessed peaks where, from the evidence of vectors to bromine in the Patterson synthesis, atoms could be expected to lie. Direct comparison of the three-dimensional Fourier synthesis with the vector convergence function was possible; they were drawn to scale together on a system of glass plates, using differently coloured inks to give the effect of the two co-extensive functions.

A considerable measure of agreement was at once apparent. The correlation was sufficiently good, particularly in certain regions, to indicate at once the orientation of ring structures in space. This was especially so for the shell-shaped cavity formed by the reduced pyrrol, pyridine and cyclohexane rings of the strychnine molecule. Once having fixed the position of these atoms, it was possible, with the aid of the available information as to the chemical structure of the molecule, to find the approximate location of all the remaining atoms quite quickly, by careful study of the glass-plate model. There was one exception: the chain of atoms forming the seven-membered ring and containing the ether oxygen was not clear; the atoms were placed provisionally in what were thought to be the most likely positions, and subsequent refinement of the structure made the necessary adjustments. The parameters of this approximate structure were in 60ths of the unit-cell edges.

(b) *Improvement of parameters by two-dimensional Fourier methods*

The succeeding stages of the analysis were quite usual and consisted of the standard process of Fourier approximation. Two-dimensional calculations were used for this, because of the vastly reduced labour relative to three-dimensional computations, and also because of the existence of a centre of symmetry in the

projections, which allowed precise determination of phase angles as either 0 or π .

The a -axis and b -axis projections were worked on concurrently (there was little value in the c -axis projection since in it four molecules were superimposed).

was shifted in such a way as to alter its z parameter, the evidence of both the $h0l$ and $0kl$ projections was considered. After this point it was felt justifiable to substitute for the Wilson method for absolute intensities a procedure based on the comparison of summed groups

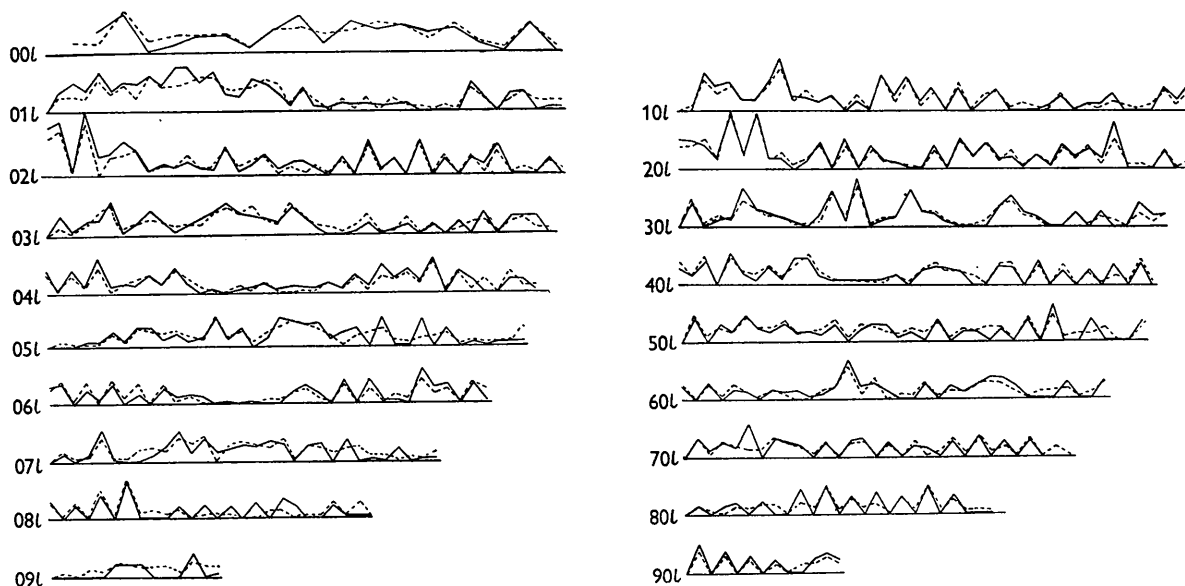


Fig. 1. Comparison of observed (full line) and calculated (broken line) F values for $(0kl)$ and $(h0l)$ planes. l begins with the value 0 at the left-hand end of each line.

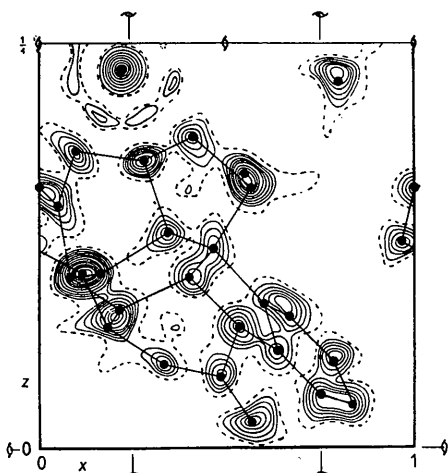


Fig. 2. Final Fourier projection down the y axis, showing the quarter of the unit cell from $z=0$ to $z=\frac{1}{4}$, together with a plot of the atomic centres chosen.

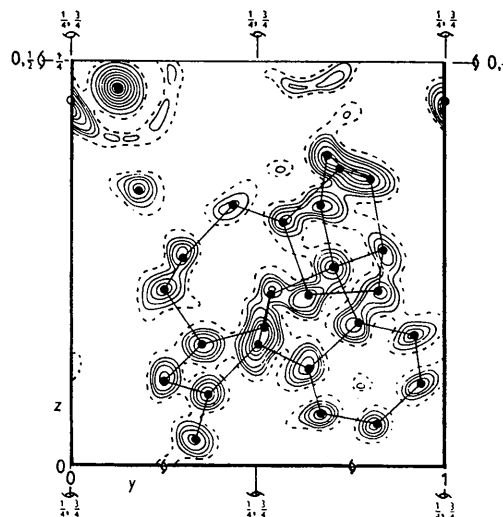


Fig. 3. Final Fourier projection down the x axis. The bromine atom near $z=\frac{1}{4}$ shows a diffraction ring. The bromine contours in Figs. 2 and 3 are at five times the interval between the rest of the contours.

Two stages were carried out while still using a limited range of relative F values (up to the 20th order of l), but these did not improve the F agreement greatly. All measurable reflexion intensities were then taken into account, viz. h and k up to 9, and l up to the 40th order. This meant that about 340 terms were involved for each projection. The Wilson method (Wilson, 1942) was used to place the structure amplitudes on the absolute scale and a further three stages of approximation were carried out in the two projections. Whenever an atom

of calculated and observed F values at about the same value of $\sin \theta$. Thirty-five to forty reflexions were used in each grouping, and the ratios of calculated to observed structure amplitudes were then corrected by the curve with respect to $\sin \theta$ so obtained. A graphical comparison of the observed and calculated structure amplitudes is given in Fig. 1. One more stage of Fourier approximation gave the parameters recorded in Table 1. The final Fourier projections are shown in Figs. 2 and 3.

Table 1. Atomic parameters of strychnine hydrogen bromide

(Parameters are expressed in 360ths of the respective cell edges.)

	<i>x</i>	<i>y</i>	<i>z</i>
C ₁	228 ± 3	228 ± 3	22 ± ½
C ₂	270	240	12
C ₃	300	294	10
C ₄	282	336	19
C ₅	240	330	29
C ₆	216	276	32
C ₇	168	252	44
C ₈	144	192	38
C ₉	126	300	48
C ₁₀	150	246	69
C ₁₁	204	240	58
C ₁₂	60	294	39
C ₁₃	30	228	38
C ₁₄	78	186	31
C ₁₅	36	258	66
C ₁₆	18	204	54
C ₁₇	0	156	58
C ₁₈	348	108	46
C ₁₉	66	126	27
C ₂₀	120	90	19
C ₂₁	174	132	16
N ₁	192	180	27
N ₂	104	288	64
O ₁	204	120	6
O ₂	42	90	39
O ₃ (water)	198	66	61
O ₄ (water)	288	0	81
Br	81 ± 0.5	46 ± 0.5	84 ± 0.2

The value of $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ found for the (0*kl*) intensities given by this structure was below 0.30. Actually, the precise figure obtained depended very much on the extent to which very weak intensities or reflexions of very high order were included in the calculation. When *R* was worked out for groups of thirty-five reflexions and plotted as a function of sin θ , its gradual increase with increase of sin θ was seen to change to a sharp rise beyond sin $\theta = 0.9$ (see Fig. 4). This was attributed to the much less reliable measurement of absolute reflexion intensity possible at these high angles owing to the rapid falling off of measurable intensity in this region (at room temperature, at least). Omitting all reflexions beyond sin $\theta = 0.87$, the average value of *R* is 0.27. It is worth noting that the same result, 0.27, is obtained from all the reflexions up to sin $\theta = 1.0$ if a temperature correction, $\exp[-B \sin \theta]$, is applied with $B = 2.30$.

For final confirmation of the structure and also to provide an additional estimate of its accuracy, a number of general structure amplitudes were calculated, and compared with the observed values, the latter having been placed on the absolute scale by the graphical method referred to above. Table 2 lists these observed and calculated *F* values. The broken curve in Fig. 4 refers to the value of *R* calculated from them.

Discussion of the structure

The structure of strychnine hydrogen bromide is based on an orthorhombic lattice with two small and almost

equal axes $a = 7.64$ and $b = 7.70$ Å. The third lattice constant *c* is 33.20 Å. and is thus more than four times the length of *a* or *b*. The space group is $P2_12_12_1$, with equivalent positions

$$(x, y, z), (\frac{1}{2} - x, -y, \frac{1}{2} + z), (\frac{1}{2} + x, \frac{1}{2} - y, -z)$$

and $(-x, \frac{1}{2} + y, \frac{1}{2} - z)$.

The symmetry elements present are thus only screw axes, and these occupy the following positions:

$$\begin{matrix} (x, \frac{1}{4}, 0) & (x, \frac{3}{4}, 0) & (x, \frac{1}{4}, \frac{1}{2}) & (x, \frac{3}{4}, \frac{1}{2}) \\ (0, y, \frac{1}{4}) & (\frac{1}{2}, y, \frac{1}{4}) & (0, y, \frac{3}{4}) & (\frac{1}{2}, y, \frac{3}{4}) \\ (\frac{1}{4}, 0, z) & (\frac{3}{4}, 0, z) & (\frac{1}{4}, \frac{1}{2}, z) & (\frac{3}{4}, \frac{1}{2}, z) \end{matrix}$$

Table 2. Observed and calculated values of $F_{(hkl)}$

(The series 11*l*, 21*l*, 22*l* and 42*l*, where *l* = 0–20, are arranged in order of increasing sin θ .)

(Relative scale)					
<i>hkl</i>	<i>F_o</i>	<i>F_c</i> = √(<i>A</i> ² + <i>B</i> ²)	<i>hkl</i>	<i>F_o</i>	<i>F_c</i> = √(<i>A</i> ² + <i>B</i> ²)
110	6	4	2.1.14	32	36
111	37	38	1.1.16	12	11
112	51	51	2.2.12	32	27
113	29	30	2.1.15	25	20
114	49	41	2.2.13	9	6
115	105	114	1.1.17	28	27
116	39	38	2.1.16	40	39
117	44	50	2.2.14	6	6
210	11	22	1.1.18	9	19
211	23	22	2.1.17	33	30
118	51	51	2.2.15	31	29
212	53	41	420	22	10
213	27	25	421	30	36
214	33	24	422	13	20
119	29	38	423	35	32
215	8	3	1.1.19	9	8
216	30	32	424	11	7
1.1.10	30	27	425	32	38
217	46	38	2.1.18	30	32
220	16	16	2.2.16	32	31
221	32	36	426	33	25
1.1.11	27	34	427	37	27
218	35	30	428	16	20
222	17	18	1.1.20	24	21
223	49	64	2.1.19	19	23
219	45	36	2.2.17	16	18
224	18	15	429	33	36
1.1.12	20	17	4.2.10	37	42
225	71	70	2.1.20	27	26
2.1.10	34	45	2.2.18	7	9
226	4	8	4.2.11	24	28
1.1.13	7	8	4.2.12	19	12
2.1.11	35	30	2.2.19	25	16
227	25	34	2.2.20	10	11
228	19	10	4.2.13	10	8
1.1.14	14	14	4.2.14	7	16
2.1.12	48	49	4.2.15	22	15
229	51	56	4.2.16	14	13
1.1.15	20	21	4.2.17	0	5
2.1.13	49	46	4.2.18	29	31
2.2.10	20	18	4.2.19	0	5
2.2.11	22	34	4.2.20	25	25

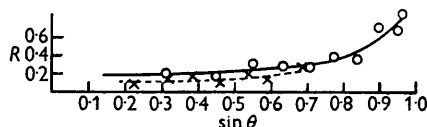
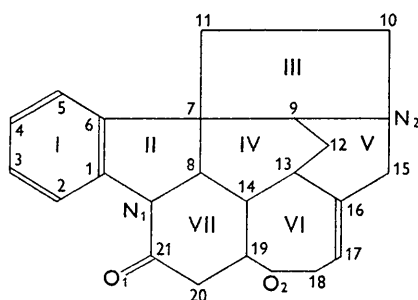


Fig. 4. Value of *R* plotted against sin θ for the (0*kl*) reflexions (full line and circles) and for some general planes (broken line and crosses).

C_9 , C_{13} , C_{16} and N_2 , which lie almost in a plane. The last ring III is plane except for C_7 , which lies inside the plane of the other atoms of the ring, C_9 , N_2 , C_{10} and C_{11} .



Thus the rings II to VII form a compact three-dimensional structure with the plane benzene ring I projecting outwards.

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The Fourier Synthesis of the Crystal Structure of Strychnine Sulphate Pentahydrate

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Strychnine sulphate pentahydrate is monoclinic with space group $C2$ and cell edges $a = 35.85 \pm 0.05$, $b = 7.56 \pm 0.01$, $c = 7.84 \pm 0.01$ Å.; $\beta = 107^\circ 20'$. There are four molecules of strychnine in the unit cell. As the heavy atom lies on the symmetry centre of the [010] projection, the application of the Fourier method for this projection follows the well-known lines developed for the phthalocyanine structure. For the non-centro-symmetrical [001] projection the phase angles, except for their signs, were derived from the intensity comparison of the isomorphous structures of the sulphate and the selenate. A symmetrical Fourier synthesis was made, and from this and the [010] projection the atomic positions were found. The strychnine structure thus derived proved to be concordant with that one of the competing structure formulas which just then was unequivocally accepted by the organic chemists. After suitable refinement, averaged errors amount to 0.08 Å. for both projections.

Introduction

The purpose of this structure investigation was to solve the strychnine structure, which at the beginning of our research had not yet been established beyond doubt by organic chemistry. Especially there was no definite evidence as to the confirmation of the *E* and *F* ring in the polycyclic system. It is very satisfactory that in the last few years the brilliant work of organic chemists (Robinson & Stephen, 1948; Woodward & Brehm, 1948) on one side, and independently the X-ray methods on the other (Bokhoven, Schoone & Bijvoet, 1948, 1949; Robertson & Beevers, 1950), gave concordant results.

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Our structure determination has been carried out by the method of isomorphous derivatives with the sulphate and selenate pentahydrate.

Experimental

Strychnine sulphate and selenate are prepared by adding 4*N*-sulphuric or selenic acid to an alcoholic solution of strychnine. Single crystals of the pentahydrate are obtained by crystallization from a 70% alcoholic solution in the form of long needles or laths, elongated in the *b*-axis direction. Always the (*h*00) faces are prominently developed. Previous crystallographic studies are recorded by Groth (1906–19, vol. 5, p. 993), who described the crystals as monoclinic sphenoidal with $a:b:c = 4.7390:1:1.0363$. Weissenberg photographs,