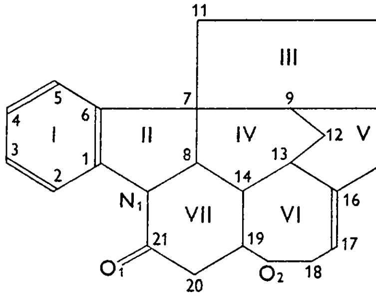
C_9, C_{13}, C_{16} and N_2, which lie almost in a plane. The last ring III is plane except for C_7, which lies inside the plane of the other atoms of the ring, C_9, N_2, C_{10} and C_{11}.



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

By C. Bokhoven†, J. C. Schoone and J. M. Bijvoet

Van 't Hoff Laboratorium, Utrecht, Netherlands

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Strychnine sulphate pentahydrate is monoclinic with space group $C2$ and cell edges $a = 35\cdot85 \pm 0\cdot05$, $b = 7\cdot56 \pm 0\cdot01$, $c = 7\cdot84 \pm 0\cdot01$ A.; $\beta = 107° \, 20'$. 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 A. 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.

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 $4N$-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 $a:b:c = 4\cdot7390:1:1\cdot0363$. Weissenberg photographs,

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† Now at the Central Laboratory of Staatsmijnen, Geleen, Netherlands.

with Cr, Cu and Mo radiation, were made of the zero and first layer lines around [010] and [001]. For the calculation of the absorption of the ($h0l$) reflexions it was a sufficient approximation to consider the crystal as a cylinder. The crystals used for the [001] diagrams were so cut that their dimensions along the a and b axes were not so very different; dimensions of the cross-sections were for the selenate $0{\cdot}50\times0{\cdot}21_5$ mm. and for the sulphate $0{\cdot}58\times0{\cdot}15_5$ mm. In this case the absorption factor was determined by summing over the cross-section. Cell dimensions were obtained from symmetrical oscillation photographs. The results for the sulphate were

$$a=35{\cdot}85\pm0{\cdot}05,\ b=7{\cdot}56\pm0{\cdot}01,\ c=7{\cdot}84\pm0{\cdot}01\text{ A.};$$
$$\beta=107^\circ\ 20'.$$
$$V=2027\text{ A.}^3\quad n=4.\quad d_{\text{obs.}}=1{\cdot}40;\ d_{\text{calc.}}=1{\cdot}41.$$
$$\mu_{\text{lin., Cu}}=14{\cdot}5\text{ cm.}^{-1}.$$

Systematic absences: hkl for $h+k$ odd and $0k0$ for k odd.

Space group: $C2$ or $C2/m$. The compound being optically active, it cannot possess a mirror plane and thus the space group must be $C2$.

The cell dimensions of the selenate were determined somewhat less accurately as

$$a=35{\cdot}9\pm0{\cdot}1,\ b=7{\cdot}58\pm0{\cdot}03,\ c=7{\cdot}90\pm0{\cdot}03\text{ A.};$$
$$\beta=107^\circ\ 40'\pm15'.$$

Structure determination

The comparative shortness of the b and c axes made it probable that projections on (010) and (001) would give valuable information about the structure.

[010] *projection*

For this projection the isomorphous-replacement method is strictly analogous to the case of phthalocyanine. The heavy atom being located on the symmetry centres 0, 0, 0 and $\frac{1}{2}$, $\frac{1}{2}$, 0, the signs of the structure factors $F_{\text{str. sel.}}$ and $F_{\text{str. sulph.}}$ could be easily determined (see Table 1) from the equation

$$F_{\text{str. sel.}}-F_{\text{str. sulph.}}=F_{\text{Se}}-F_{\text{S}}\equiv\Delta F. \tag{1}$$

The structure factors (left-hand side) were deduced from the photometrically measured intensities after correction for the absorption, polarization and Lorentz factors. For the application of equation (1) the structure

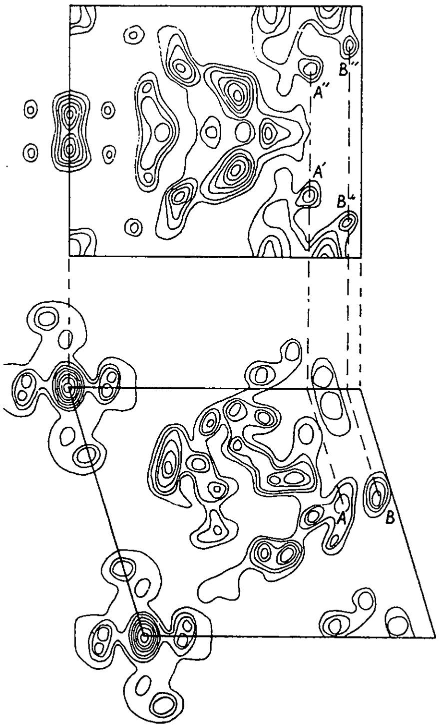


Fig. 1. [010] and double [001] projection Fourier syntheses of strychnine sulphate.

Table 1. *Determination of phase signs and phase angles*

hkl	$\lvert F_{\text{sel.}}\rvert$	$\lvert F_{\text{sulph.}}\rvert$	ΔF	$\cos\alpha_{\text{obs., sulph.}}$†
200	48	16	36	1
400	50	75	36	− 1
600	132	92	33	1
800	< 8	22	32	− 1
10,0,0	63	24	30	1
12,0,0	93	55	29	1
001	16	12	35	− 1
201	174	151	33	1
401	97	79	33	1
601	88	53	32	1
801	70	44	29	1
10,0,1	27	46	28	− 1
$20\bar{1}$	22	64	35	− 1
$40\bar{1}$	152	104	33	1
$60\bar{1}$	110	79	33	1
$80\bar{1}$	102	72	32	1
$10,0,\bar{1}$	62	28	30	1
$12,0,\bar{1}$	55	18	29	1
$14,0,\bar{1}$	42	11	26	1
002	48	12	32	1
202	16	44	29	− 1
402	110	82	29	1
602	< 8	25	28	− 1
$20\bar{2}$	< 8	36	32	− 1
$40\bar{2}$	171	136	32	1
$60\bar{2}$	153	125	30	1
$10,0,\bar{2}$	44	62	29	− 1
$12,0,\bar{2}$	< 8	31	29	− 1
110	116	80	35	(1·0)
310	57	52	35	− 0·17
510	86	103	34	− 0·62
710	137	110	33	0·76
910	36	47	32	− 0·63
11,1,0	55	31	30	0·64
13,1,0	35	4	29	(1·0)
020	107	99	32	0·09
220	64	44	32	0·40
420	139	123	32	0·43
620	113	96	31	0·40
820	24	21	30	− 0·62
10,2,0	49	36	29	0·13

† When the calculated value of cos α is greater than 1·0 it is written as (1·0).

factors must be reduced to absolute scale; this was done by comparison with a crystal of resorcinol.

In order to improve the resolution the structure factors were multiplied by a factor $\exp[3(\sin\theta/\lambda)^2]$; with these 'sharpened' Fourier series the resolution was really improved, while on the other hand the false detail was not serious. The result of this Fourier synthesis is shown in Fig. 1 (lower part).

[001] *projection*

In the non-symmetrical case the replacement method enables the determination of the phase angles α, which are now not restricted to 0 and π. The expression (1) will be used again, but the F's have to be considered as vectors:

$$\mathbf{F}_{\text{str. sel.}}-\mathbf{F}_{\text{str. sulph.}}=\mathbf{F}_{\text{Se}}-\mathbf{F}_{\text{S}}\equiv\Delta\mathbf{F}. \qquad (1')$$

The heavy atom being located at the origin of the cell, the right-hand member of (1) is real,

$$\Delta F=2(f_{\text{Se}}-f_{\text{S}})\exp[-B(\sin\theta/\lambda)^2],$$

having a phase angle zero for every reflexion.

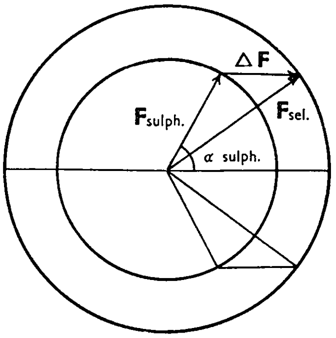


Fig. 2. Phase determination in non-centro-symmetrical case by the isomorphous substitution method.

In Fig. 2 it is shown that the vector equation can be satisfied by two vector sets, one above and one beneath the axis $\alpha=0$. For every reflexion the unknown phase angles, apart from their sign, can be easily constructed or found by calculation (for the sulphate, see Table 1) from

$$\cos\alpha_{\text{obs.},\,hk0}=\frac{F^2_{\text{sel.}}-F^2_{\text{sulph.}}-(\Delta F)^2}{2\,.\,\Delta F\,|F_{\text{sulph.}}|}. \qquad (2)$$

The general formula for a [001] projection,

$$\rho_{xy}=\frac{1}{ab}\sum_{h=-\infty}^{+\infty}\sum_{k=-\infty}^{+\infty}|F_{hk0}|\cos\left[2\pi\left(\frac{hx}{a}+\frac{ky}{b}\right)-\alpha_{hk0}\right],$$

can be re-arranged by use of the equalities

$$\alpha_{\bar{h}\bar{k}0}=\alpha_{h\bar{k}0}=-\alpha_{\bar{h}k0}=-\alpha_{hk0}$$

and $$|F_{hk0}|=|F_{\bar{h}k0}|=|F_{h\bar{k}0}|=|F_{\bar{h}\bar{k}0}|,$$

and gives

$$\rho_{xy}=\frac{4}{ab}\sum_{h=0}^{\infty}\sum_{k=0}^{\infty}|F_{hk0}|\cos2\pi\frac{hx}{a}\cos\left(2\pi\frac{ky}{b}-\alpha_{hk0}\right).$$

The signs of α being unknown, it is impossible to perform a Fourier synthesis according to these expressions. Nevertheless, a symmetrical Fourier synthesis can be carried out by summing every term twice, using the positive value of α as well as the negative one, thus introducing a centre of symmetry in the origin. The latter terms can be denoted by

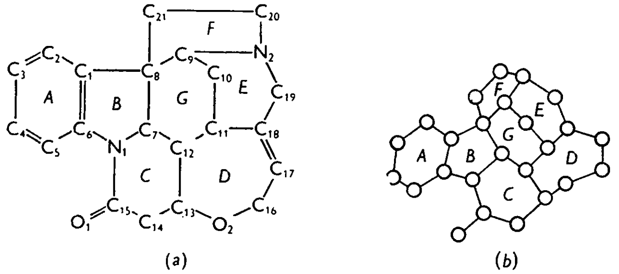
$$\rho^*_{xy}=\frac{4}{ab}\sum_{h=0}^{\infty}\sum_{k=0}^{\infty}|F_{hk0}|\cos2\pi\frac{hx}{a}\cos\left(2\pi\frac{ky}{b}+\alpha_{hk0}\right).$$

The double Fourier

$$\rho_{xy}+\rho^*_{xy}=\frac{8}{ab}\sum_{h=0}^{\infty}\sum_{k=0}^{\infty}|F_{hk0}|\cos\alpha_{hk0}\cos2\pi\frac{hx}{a}\cos2\pi\frac{ky}{b}$$

can be synthesized and the resulting map is given in Fig. 1 (upper part). It gives the strychnine structure, ρ_{xy}, superimposed on its mirror image, ρ^*_{xy}, and shows a plane of symmetry caused by the centre in connexion with the twofold axis already present.

A method which will give nearly the same result is subtracting the Patterson synthesis of the sulphate from that of the selenate. The difference will be a Patterson synthesis, containing the maxima at the corners and those corresponding to the distances between a hypothetical (Se – S) atom and carbon, nitrogen or oxygen atoms, and vice versa. So, apart from the maxima at the corners, a synthesis like the symmetrized Fourier will be obtained with only the maxima broadened.



(a) (b)

Fig. 3. Structure formulae of strychnine: (a) according to chemical custom, (b) according to a model of the molecule.

A three-dimensional Patterson has been used for the strychnine bromide by Robertson & Beevers (1950).

The separation of the two images was accomplished on the basis of the [010] projection and the known interatomic distances and valency angles. In the projection the benzene ring clearly shows and it can be used as a starting point in this procedure which was facilitated by the (non-essential) use of those features which were beyond doubt from the chemical point of view.

It is easy to separate the image and mirror image for the strychnine molecule, so the principal aim of our investigation was reached. Fig. 3 (*a*) gives the ordinary structure formula of strychnine and Fig. 3 (*b*) a projection of the molecule, which might be used as a structure formula.

Although the separation is also easily accomplished for the SO_4 group and each water molecule, the determination of the entire structure requires the simultaneous choice of position for the different groups, and this is rather difficult.

Before making this choice, we found it desirable to refine the co-ordinates. This was done by using an iterative process to minimize

$$\sum_{hl}\left\{\sum_i f_i \cos 2\pi\left(\frac{hx_i}{a}+\frac{lz_i}{c}\right)-F_{\text{obs.}}\right\}^2$$

for the $(h0l)$ reflexions and

$$\sum_{hk}\left(\sum_i f_i \cos 2\pi\frac{hx_i}{a}\cos 2\frac{ky_i}{b}-|F_{\text{obs.}}|\cos\alpha_{\text{obs.},hk0}\right)^2$$

for the $(hk0)$ reflexions; the latter expression is independent of the signs of the y co-ordinates.

In order to obtain a decision concerning the signs of the y co-ordinates for the different groups, the structure factors of about fifty reflexions were calculated for sixteen possible arrangements[†] and the value of

$$D=\Sigma\,(|F_{\text{obs.}}|\sin\alpha_{\text{obs.}}-|F_{\text{calc.}}|\sin\alpha_{\text{calc.}})^2$$

was used to test these various cases. Ten of these possibilities could be excluded at once as the values of D were very high. To test the remaining six configurations all reflexions were taken into account.

From the [010] projection it was not quite clear which position of the third water molecule was to be preferred. Both the origin and the vague maximum between strychnine and sulphuric acid had to be considered as possibilities, the latter if two water molecules were assumed to be spread statistically over four places. The calculation of the sixteen arrangements led in the end to a small preference for the vague maximum as the most probable position of the third water molecule. This gave 2·7 A. for the distances between this water molecule and neighbouring atoms, whereas the very small value of 2·2 A. would follow if the water molecule were placed on top of the sulphuric acid. The first position was therefore adopted.

The best agreement between observed and calculated values is found if a superstructure is supposed with respect to the y location of the water molecules, the signs of the y co-ordinates alternating in cells neighbouring in the b direction. Vague superstructure spots corresponding to this period $2b$ have been observed on [010] diagrams. The diffuse character of these spots, however, points to incomplete order in this sequence. The third water molecule is located in those cells in which enough room is available (see Fig. 4).

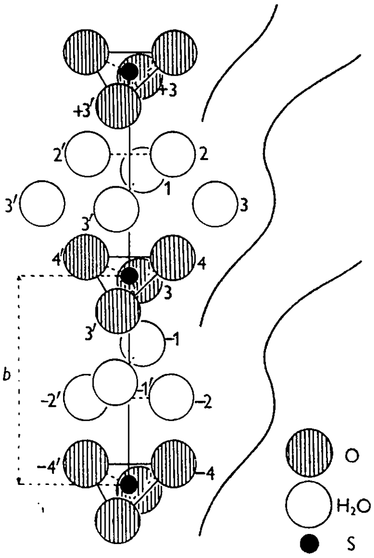


Fig. 4. Grouping of the water molecules in the pentahydrate.

All F values were obtained from integrated intensity measurements because, for the $(hk0)$ reflexions, high accuracy appeared quite essential to give reliable α values. For this reason we had to know also the ΔF values more accurately. In the phase-angle determination of the $(h0l)$ reflexions the ΔF values were calculated from the ordinary scattering factors and the B value, 3·8 A.^{2}, which is commonly used for organic crystals.[‡]

From the signs of $F_{\text{sulph.},h0l}$ and $F_{\text{sel.},h0l}$, now known, we derived more accurate values of ΔF. These were plotted against $\sin^2\theta$, giving a curve from which the ΔF_{hk0} values were taken.

Besides the refinement process already mentioned,

[†] Of the total of twenty-four arrangements, eight could be excluded at the beginning from steric considerations.

[‡] The phase-angle determination in this case (amplitude sign) is scarcely affected by taking another value of B.

Table 2. *Atomic co-ordinates*

Atom	x	y	z
C_1	0·158	0·328	− 0·133
C_2	0·162	0·414	0·033
C_3	0·196	0·483	0·147
C_4	0·225	− 0·450	0·067
C_5	0·222	0·469	− 0·094
C_6	0·189	0·394	− 0·211
N_1	0·175	0·297	− 0·358
C_7	0·149	0·175	− 0·358
C_8	0·128	0·208	− 0·219
C_9	0·118	0·042	− 0·125
C_{10}	0·142	− 0·133	− 0·092
C_{11}	0·144	− 0·167	− 0·286
C_{12}	0·164	− 0·006	− 0·361
C_{13}	0·175	− 0·056	0·478
C_{14}	0·189	0·103	0·400
C_{15}	0·201	0·256	− 0·478
O_1	0·233	0·356	− 0·436
O_2	0·143	− 0·097	0·331
C_{16}	0·118	− 0·242	0·319
C_{17}	0·086	− 0·261	0·411
C_{18}	0·103	− 0·228	− 0·408
N_2	0·075	− 0·017	− 0·233
C_{19}	0·064	− 0·161	− 0·378
C_{20}	0·064	0·142	− 0·306
C_{21}	0·087	0·300	− 0·300
$(H_2O)_1$	0·004	± 0·428	0·308
$(H_2O)_2$	0·042	± 0·411	0·056
O_3	0·014	− 0·097	0·172
O_4	0·033	0·097	− 0·025
S	0	0	0
$\frac{1}{2}(H_2O)_3$	0·083	0·317	0·233

we also used the 'steepest descents' method (Booth, 1948), making Fourier syntheses with amplitudes proportional to $F_{\text{calc.}}-F_{\text{obs.}}$ for the xy and xz projection. We thus had a fair indication of the x corrections to be introduced. The final co-ordinates are shown in Table 2.

In order to avoid the double model the replacement method could be extended as follows: Consider three substances, namely, (I) α-chlorine strychnine sulphate, (II) α-chlorine strychnine selenate and (III) α-bromine strychnine sulphate which are isomorphous. Now comparison between (I) and (II) will give two possibilities for the phase angle of every reflexion of substance (I). Comparison between (I) and (III) also will give two possibilities for the α values of (I). If both ΔF vectors are different—and mostly they are—both pairs of α values must have one in common. So for nearly every reflexion the α value can be determined and one model will result. As the relative positions of chlorine and sulphur will result from Patterson syntheses, there are two possibilities which would give two models, the separate image or mirror image.

Accuracy of analysis

At this stage there was no use in further refining since no three-dimensional work has been done. From $_2R_2=\Sigma(|F_{\text{obs.}}|-|F_{\text{calc.}}|)^2/\Sigma F^2_{\text{obs.}}=0{\cdot}10$ for both projections the r.m.s. value of δx is found to be 0·08 A. The maximum possible error must be expected to amount to about 0·2 A.

Values of $|F|$ were measured accurately within 5 %, except for the weakest reflexions. The reliability of the signs of the $(h0l)$ reflexions will be very good, except for the very weak reflexions. For the $(hk0)$ reflexions, however, it is different. Values of $\cos\alpha$ are calculated using $F_{\text{str. sel.}}$, $F_{\text{str. sulph.}}$ and ΔF, and any error in these quantities will influence the result. For very small

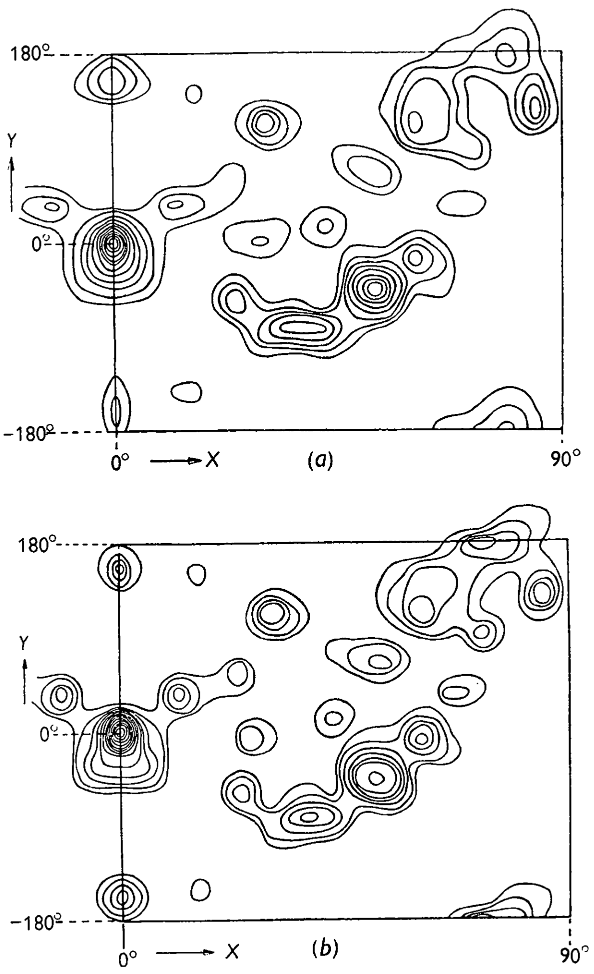


Fig. 5. Comparison of observed (*a*) and calculated (*b*) Fourier syntheses in the [001] projection.

Table 3. *Some observed and calculated values of* $\frac{1}{4}|F|$ *and* $\alpha_{\text{sulph.}}$

hkl	$\frac{1}{4}\|F\|_{\text{calc.}}$	$\frac{1}{4}\|F\|_{\text{obs.}}$	$\|\alpha_{\text{calc.}}\|$	$\|\alpha_{\text{obs.}}\|$
200	4	4	0	0
400	21†	19	180	180
600	27	23	0	0
800	1	5	180	180
10,0,0	2	6	0	0
12,0,0	14	14	0	0
001	3	3	180	180
201	48†	38	0	0
401	22	20	0	0
601	5	13	0	0
801	13	11	0	0
10,0,1	15	12	180	180
$20\bar{1}$	14	16	180	180
$40\bar{1}$	23	26	0	0
$60\bar{1}$	21	20	0	0
$80\bar{1}$	16	18	0	0
$10,0,\bar{1}$	8	7	0	0
$12,0,\bar{1}$	4	4	0	0
$14,0,\bar{1}$	1	3	0	0
002	1	3	180	0
202	11	11	180	180
402	16	20	0	0
602	13	6	180	180
$20\bar{2}$	11	9	180	180
$40\bar{2}$	35	34	0	0
$60\bar{2}$	29	31	0	0
$80\bar{2}$	2	—	180	—
$10,0,\bar{2}$	15	15	180	180
$12,0,\bar{2}$	12	8	180	180
110	24†	20	10	0
310	15	13	70	100
510	24	26	130	130
710	29	28	30	40
910	13	12	140	130
11,1,0	3	8	40	50
13,1,0	2	1	60	0
020	31	25	70	80
220	12	11	70	70
420	28	31	20	60
620	24	24	20	70
820	5	5	50	130
10,2,0	5	9	50	80

† These reflexions are influenced by extinction.

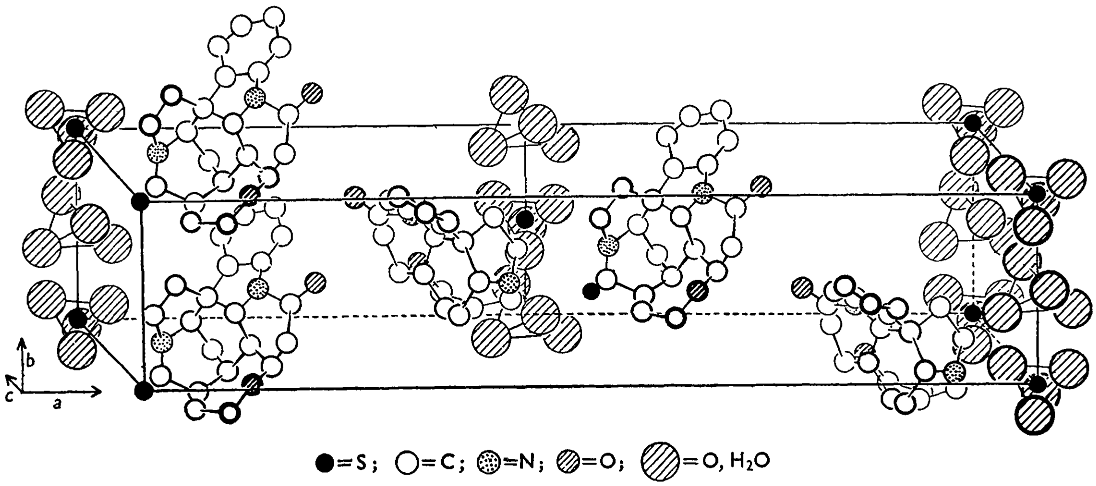


Fig. 6. Crystal structure of strychnine sulphate 5 aq. The complication in the location of the H_2O molecules (see text) is disregarded in the figure.

values of $F_{\text{str. sulph.}}$ or ΔF the phase-angle determination will be inaccurate. When $F_{\text{str. sulph.}}$ has been measured too low, one will find $\cos\alpha$ considerably too high. Actually we got values of $\cos\alpha$ up to 1·4 and in these cases the value 1·0 has been adopted. However, for medium and strong reflexions there was good agreement between $\alpha_{\text{calc.}}$ and $\alpha_{\text{obs.}}$, so the determination of α according to (2) for the non-symmetrical projection proved to be very useful in obtaining a starting point for further analysis. In the course of the refining procedure the use of $\alpha_{\text{obs.}}$ was abandoned at a certain stage in favour of the α values calculated from the model under refinement.

Table 3 gives the calculated and observed F and α values for the lower reflexions. Another test of the correctness of the structure is given by the agreement between the Fourier syntheses calculated with $F_{\text{obs.}}$ and $F_{\text{calc.}}$ respectively (Fig. 5).

Description of the structure

The columns of SO_4 and water molecules have already been shown schematically in Fig. 4. The structure is shown in Fig. 6, where, by the addition of one molecule, the packing of the molecules can be seen. The basic nitrogen atom of the strychnine is directed towards the SO_4 group. As far as the accuracy permits a conclusion, the intra- and inter-molecular distances are all found to have normal values. The resemblance between our [010] projection of the sulphate and the [100] projection of strychnine hydrobromide, as found by Robertson & Beevers (1950), should be noted.

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