The Structure of Kainic Acid, the Most Active Component of Digenea Simplex Ag. II. The Molecular and Crystal Structure of Kainic Acid Monohydrate*

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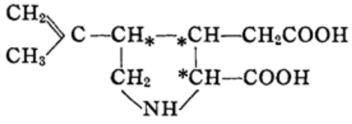
As reported in the general survey⁽¹⁾ of our studies on the structures of kainic acid and its isomer, investigations based on X-ray crystal analysis were carried out. In the preceding paper⁽²⁾ of this series, we already concluded that the structure of kainic acid, $C_{10}H_{15}O_4N$, was 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine, and also determined the stereochemical configuration of the molecule from the structure of the kainate anion in the zinc salt.



However, it will be of still greater interest to determine the molecular structure of kainic acid in its own crystal, and thus to know how the molecular structures in the crystals of the salt and the free acid are related to each other.

The structure of the kainic acid crystal has been examined by two-dimensional

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* Part of this paper was presented at the Autumnal Joint Meeting of Chemical Societies in Japan, Tokyo, 1956.

(1) I. Nitta, H. Watase and Y. Tomiie, *Nature*, **181**, 761 (1958).

(2) H. Watase and I. Nitta, This Bulletin, **30**, 889 (1957).

X-ray procedure. The electron-density projections along the three principal crystal axes were derived by the trial method, and the structure was determined. In this account, moreover, some general remarks on X-ray crystal analysis are added.

Experimental

Kainic acid crystallizes with one water molecule from its aqueous solution. Crystalline kainic acid monohydrate ($C_{10}H_{15}O_4N \cdot H_2O$) is composed of colorless thin needles elongated along a principal crystal axis (monoclinic b axis).

Oscillation-, Sauter- and Weissenberg-photographs, were taken about the three principal crystal axes, using Cu K_α radiation. The specimens used had the following cross-sections at right angles to the axis of rotation; 0.08×0.30 mm. for the b axis rotation, 0.15×0.6 mm. for the c axis and 0.4×0.5 mm. for the a axis**.

The intensity data for ($h0l$), ($hk0$) and ($0kl$) used in the two-dimensional analyses were taken from the integrated Weissenberg photographs for each zone. By comparing them with a calibrated scale, the intensities of the reflections were estimated visually, multiple-film technique being used for accurate measurements of strong reflections. The corrections for polarization and Lorentz factors were made in the usual way. The corrections for absorption and the form of the specimen were made only for ($hk0$) in an approximate way, the linear absorption coefficient for Cu K_α radiation being $\mu = 10.4/\text{cm}$***.

Relative structure factors were then deduced from these intensity data by the ordinary process.

Results and Discussion

Unit Cell and Space Group.—It was found from the X-ray examinations that the crystal belongs to the monoclinic system, and the dimensions of the unit cell are as follows;

$$a = 12.07 \pm 0.03\ \text{Å}$$
$$b = 5.86 \pm 0.02\ \text{Å}$$
$$c = 8.19 \pm 0.03\ \text{Å}$$
$$\beta = 94.7^\circ \pm 0.2^\circ.$$

Systematic absence of reflections being only ($0k0$) with k odd, the space group may be either $C_2^2 - P2_1$ or $C_{2h}^2 - P2_1/m$. However, since kainic acid is of an optically active compound, the space group is uniquely determined to be $C_2^2 - P2_1$ with no centers of symmetry. Judging from the cell size and the symmetry element of the crystal, it is clear that the unit cell contains two formula units of $C_{10}H_{15}O_4N \cdot H_2O$.

The axial period of b is short enough for a projection to provide useful information about the structure. Moreover, the two-fold screw axis lying parallel to this axis, the b axis projection is effectively centro-symmetrical. Therefore the determination of the structure was approached from the b axis projection.

Determination of the Structure. — As will be described in the last section of this paper, neither did the inequality method bring success in the present case, nor did the Patterson method give any information about the structure. On the other hand, we analyzed the zinc salt[2] and gave kainic acid the structure as mentioned previously (2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine). Adopting this structure, the trial method making use of the structure-factor maps for all the possible reflections of ($h0l$) was applied to locate all the atoms in the projection along the b axis.

Considering the packing, the probable position of the isopropenyl group could be roughly determined. Considering the various possible structures conceivable in connection with the position of the isopropenyl group, the signs of the structure factors of the lowest order except for those of small F values could be determined, and it was known that the absolute structure-factor values are close to those which are obtained from Wilson's method[3]. Then, determining the signs of the structure factors, the quantitative trial was carried on step by step from the lower to the higher orders so as to obtain a good agreement between the calculated and the observed F values, until all the atoms were located satisfactorily to permit the Fourier refinements. The final electron-density projection of Fig. 1 was thus derived, and the atomic positions were further refined from this map. The x and z atomic parameters were thus obtained.

In order to estimate the unknown y parameters, the projection along the c axis was investigated, using the structure-factor data of ($hk0$). Since this projection has no center of symmetry, differing from the case of the centro-symmetrical b axis projection, each structure factor consists of real and imaginary parts. By the trial use of the structure-factor maps for the

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** To take the photographs about the a and c axes, the specimens were prepared by cutting the crystals at right angles to the needle axis (b axis).

*** This value comes from the unit cell containing two formula units. (see next section).

[3] A. J. C. Wilson, *Acta Cryst.*, **2**, 318 (1949).

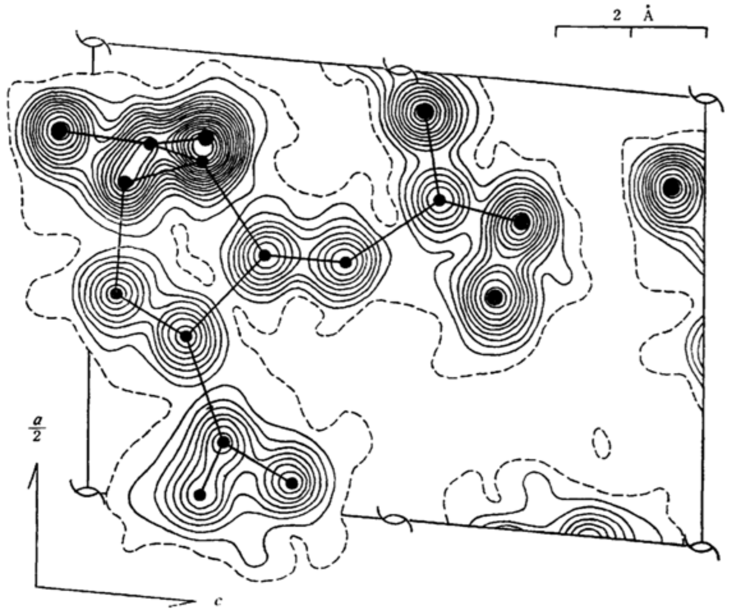

Fig. 1. The final electron-density projection along the *b* axis. Contour lines are at unit electron intervals, the lowest line, broken line, being 1 electron per Å². Black circles show the final atomic positions, there being large, intermediate and small circles for oxygen, nitrogen and carbon respectively.

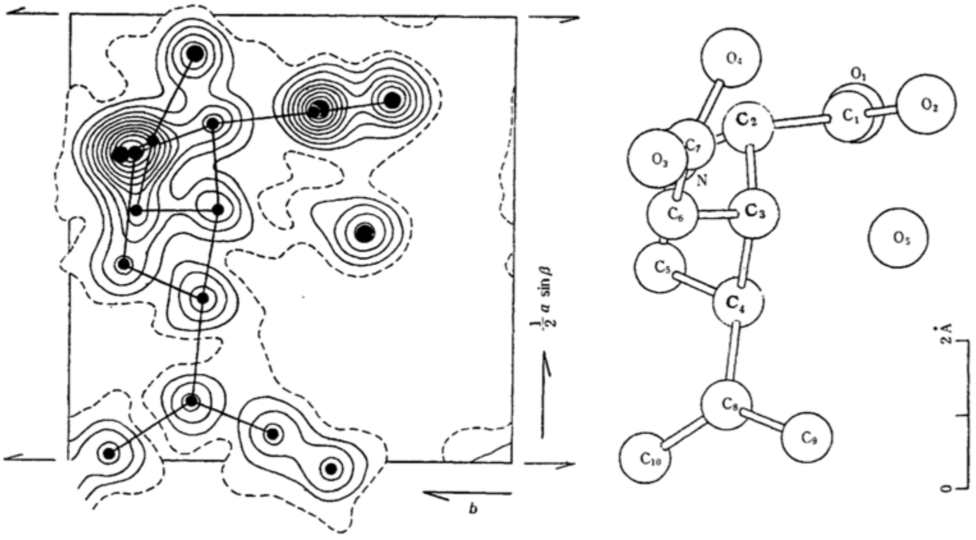

Fig. 2. The final electron-density projection along the *c* axis. Contour lines are at two electrons intervals, the lowest line, broken line, being 2 electrons per Å². Black circles show the atomic positions, there being large, intermediate and small circles for oxygen, nitrogen and carbon respectively. The interpretation of the density map is given on the right side.

lower order reflections only, the *y* parameters of all the atoms were easily obtained, and these parameters were further refined by the Fourier refinements. In this trial, since for a weak reflection, both the real and the imaginary part of the structure factor should be small, the structure-factor maps of the weak reflections were most useful. The final electron-density projection along the *c* axis was thus derived as shown in Fig. 2. The final *x*, *y* and *z* atomic parameters are listed in Table I.

The phases of the structure factors for

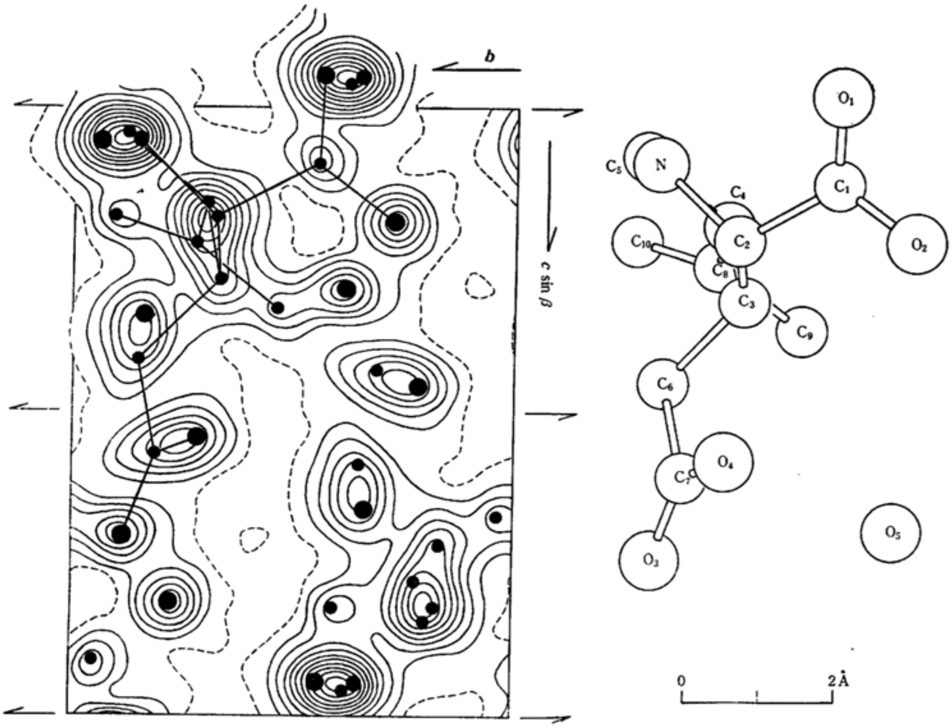

Fig. 3. The final electron-density projection along the *a* axis. Contours and symbols are the same as those of Fig. 2. The interpretation of the density map is given on the right side.

(0*kl*) were calculated from the *y* and *z* atomic parameters, and the electron-density projection along the *a* axis was obtained as shown in Fig. 3.

TABLE I

ATOMIC PARAMETERS

Atom	*x*/*a*	*y*/*b*	*z*/*c*
C_1	0.393	0.451	0.094
C_2	0.379	0.679	0.178
C_3	0.282	0.667	0.282
C_4	0.183	0.698	0.158
C_5	0.222	0.878	0.042
C_6	0.281	0.850	0.415
C_7	0.360	0.815	0.567
C_8	0.069	0.722	0.220
C_9	0.030	0.540	0.332
C_{10}	0.008	0.908	0.182
N	0.347	0.855	0.053
O_1	0.397	0.438	0.943
O_2	0.405	0.277	0.185
O_3	0.344	0.887	0.704
O_4	0.458	0.719	0.540
O_5 (H_2O)	0.257	0.337	0.658

At this stage, the discrepancy indices ($R=\sum||F_o|-|F_c||/\sum|F_o|$) are 0.175 for (*h*0*l*), 0.159 for (*hk*0) and 0.244 for (0*kl*), employing the data up to $\sin\theta/\lambda=0.625$ for (*h*0*l*) and 0.640 for (*hk*0) and (0*kl*), assuming the values of the unobserved structure factors to be precisely zero and neglecting the contributions from hydrogen atoms. In the structure-factor calculations, the effect of thermal motion was taken into account, the value of $B=3.0$ Å^2 being used for each zone as the temperature factor common to all the atoms. The atomic scattering factors were taken from McWeeny's paper$^{4)}$; for oxygen $\bar{f}_0=1/3(f^{\parallel}+2f^{\perp})$ and for carbon the values for 'valence states'.

The observed and the calculated structure factors for (*h*0*l*) are listed in Table II, and those for (*hk*0) and (0*kl*) in Table III.

Molecular Structure.—The bond lengths and bond angles, calculated from the atomic parameters of Table I, are shown in Fig. 4. It may be said that the bond lengths will be correct to ±0.03Å and the bond angles to ±3°. As a result, it was confirmed that the structure of kainic acid is 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine in agreement with the structure determined from that of the

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4) R. McWeeny, *Acta Cryst.*, **4**, 513 (1951).

TABLE II

OBSERVED AND CALCULATED STRUCTURE FACTORS $F(h0l)$

$h\ k\ l$	$1/2F_o$	$1/2F_c$
0 0 0	—	124
1 0 0	20.0	−23.1
2 0 0	5.2	−5.2
3 0 0	29.8	29.8
4 0 0	3.2	−5.4
5 0 0	15.8	15.6
6 0 0	5.0	−4.6
7 0 0	2.5	−1.9
8 0 0	3.2	5.1
9 0 0	3.5	−3.9
10 0 0	0.8	−0.5
11 0 0	3.3	3.3
12 0 0	—	−0.3
13 0 0	—	−0.2
14 0 0	—	−0.2
15 0 0	1.5	2.3
0 0 1	7.7	7.7
1 0 1	13.2	−12.6
2 0 1	1.0	−2.6
3 0 1	9.6	−8.5
4 0 1	14.3	−14.7
5 0 1	13.1	11.5
6 0 1	6.6	−8.0
7 0 1	3.7	−4.1
8 0 1	5.7	−6.0
9 0 1	2.8	3.1
10 0 1	7.0	7.4
11 0 1	6.6	−8.0
12 0 1	2.2	2.4
13 0 1	1.2	1.8
14 0 1	—	−0.9
0 0 2	4.7	−5.6
1 0 2	34.5	−35.9
2 0 2	9.9	12.0
3 0 2	15.9	−15.0
4 0 2	5.3	3.4
5 0 2	6.2	4.6
6 0 2	7.5	−6.6
7 0 2	1.6	−0.5
8 0 2	5.4	5.1
9 0 2	0.8	0.5
10 0 2	0.8	0.6
11 0 2	1.9	2.0
12 0 2	1.8	−2.4
13 0 2	—	0.1
14 0 2	—	0.0
0 0 3	1.5	0.4
1 0 3	1.3	0.9
2 0 3	17.0	−15.4
3 0 3	17.8	17.0
4 0 3	1.9	2.1
5 0 3	1.4	0.0
6 0 3	1.6	−1.5
7 0 3	2.9	−3.3
8 0 3	3.6	4.8
9 0 3	1.9	1.1
10 0 3	5.2	−5.6
11 0 3	1.8	−1.2
12 0 3	—	−0.4
13 0 3	2.5	−2.7
14 0 3	1.3	0.8
0 0 4	0.9	−0.3
1 0 4	2.8	4.4
2 0 4	—	−1.0
3 0 4	2.7	2.7
4 0 4	2.1	−2.0
5 0 4	4.4	−4.3
6 0 4	2.4	3.2
7 0 4	6.8	−7.4
8 0 4	2.7	2.8
9 0 4	1.9	−0.7
10 0 4	2.9	−2.9
11 0 4	—	−0.7
12 0 4	1.9	−1.2
13 0 4	2.3	2.8
0 0 5	—	0.5
1 0 5	—	1.0
2 0 5	1.9	−2.3
3 0 5	8.5	9.4
4 0 5	6.1	−5.9
5 0 5	—	0.3
6 0 5	1.8	0.7
7 0 5	2.3	2.7
8 0 5	2.3	1.8
9 0 5	1.3	−0.8
10 0 5	1.2	1.3
11 0 5	2.5	2.8
12 0 5	—	0.3
0 0 6	1.2	2.6
1 0 6	0.8	−0.5
2 0 6	4.7	4.2
3 0 6	5.4	−4.6
4 0 6	2.3	2.3
5 0 6	3.3	4.0
6 0 6	—	−1.0
7 0 6	1.3	−1.4
8 0 6	5.7	5.4
9 0 6	—	−0.8
10 0 6	—	−0.9
11 0 6	1.2	1.5
0 0 7	—	−0.7
1 0 7	—	−0.9
2 0 7	4.8	−4.1
3 0 7	1.0	−0.4
4 0 7	1.0	0.6
5 0 7	1.0	−0.7
6 0 7	—	−0.5
7 0 7	1.2	−0.3
8 0 7	1.1	−1.2
9 0 7	—	0.3
10 0 7	1.1	−2.0
0 0 8	9.7	−7.8
1 0 8	1.3	0.1
2 0 8	—	−0.5
3 0 8	—	0.3
4 0 8	4.3	3.6
5 0 8	4.2	−4.5
6 0 8	2.2	1.7
7 0 8	—	0.6
8 0 8	1.2	−1.6
0 0 9	2.0	−1.6
1 0 9	2.0	2.1
2 0 9	—	0.5
3 0 9	—	0.3
4 0 9	1.0	1.0
5 0 9	—	0.4
6 0 9	2.3	−1.9
0 0 10	1.0	−1.1
1 0 10	—	1.0
2 0 10	1.3	−1.0
1 0 $\bar{1}$	11.2	10.1
2 0 $\bar{1}$	2.6	4.2
3 0 $\bar{1}$	13.3	13.5
4 0 $\bar{1}$	16.0	−15.8
5 0 $\bar{1}$	24.1	22.4
6 0 $\bar{1}$	3.7	3.9
7 0 $\bar{1}$	4.4	−3.8
8 0 $\bar{1}$	11.1	10.2
9 0 $\bar{1}$	5.3	−6.3
10 0 $\bar{1}$	3.2	4.2
11 0 $\bar{1}$	—	0.2
12 0 $\bar{1}$	1.9	1.1
13 0 $\bar{1}$	1.2	1.4
14 0 $\bar{1}$	—	0.1
15 0 $\bar{1}$	1.3	1.6
1 0 $\bar{2}$	5.4	5.7
2 0 $\bar{2}$	14.1	−13.5
3 0 $\bar{2}$	0.7	−1.9
4 0 $\bar{2}$	12.2	−9.4
5 0 $\bar{2}$	1.8	−2.5
6 0 $\bar{2}$	9.5	6.9
7 0 $\bar{2}$	4.3	−4.0
8 0 $\bar{2}$	3.7	−4.9
9 0 $\bar{2}$	5.6	5.6
10 0 $\bar{2}$	2.3	−2.6
11 0 $\bar{2}$	1.9	−2.7
12 0 $\bar{2}$	2.3	−2.1
13 0 $\bar{2}$	2.1	2.4
14 0 $\bar{2}$	—	−0.8
15 0 $\bar{2}$	1.6	−1.3
1 0 $\bar{3}$	3.7	3.9
2 0 $\bar{3}$	14.2	−14.3
3 0 $\bar{3}$	1.7	−2.2
4 0 $\bar{3}$	10.6	10.0
5 0 $\bar{3}$	13.6	−13.6
6 0 $\bar{3}$	1.5	1.0
7 0 $\bar{3}$	1.6	−0.2
8 0 $\bar{3}$	0.8	−0.1
9 0 $\bar{3}$	1.8	1.9
10 0 $\bar{3}$	1.9	−1.4
11 0 $\bar{3}$	2.7	−2.5
12 0 $\bar{3}$	—	1.5
13 0 $\bar{3}$	2.0	−2.8
14 0 $\bar{3}$	—	0.2
1 0 $\bar{4}$	9.8	−8.5
2 0 $\bar{4}$	6.5	6.9
3 0 $\bar{4}$	3.3	−3.1
4 0 $\bar{4}$	—	−0.6
5 0 $\bar{4}$	2.2	−2.8
6 0 $\bar{4}$	3.0	−2.0
7 0 $\bar{4}$	3.0	3.6
8 0 $\bar{4}$	6.3	−8.5
9 0 $\bar{4}$	6.5	6.4
10 0 $\bar{4}$	—	0.5
11 0 $\bar{4}$	—	0.2
12 0 $\bar{4}$	1.2	0.6
13 0 $\bar{4}$	—	0.6
14 0 $\bar{4}$	2.1	2.9
1 0 $\bar{5}$	2.6	4.6
2 0 $\bar{5}$	7.2	6.7
3 0 $\bar{5}$	12.1	−12.6
4 0 $\bar{5}$	5.6	6.9
5 0 $\bar{5}$	3.4	4.8
6 0 $\bar{5}$	4.7	−4.8
7 0 $\bar{5}$	1.8	−2.0
8 0 $\bar{5}$	2.3	−1.9
9 0 $\bar{5}$	—	−1.2
10 0 $\bar{5}$	2.3	2.6
11 0 $\bar{5}$	2.1	−2.6
12 0 $\bar{5}$	—	0.4
13 0 $\bar{5}$	—	0.0
1 0 $\bar{6}$	6.7	6.7
2 0 $\bar{6}$	2.7	−1.7
3 0 $\bar{6}$	2.8	2.9
4 0 $\bar{6}$	4.0	4.2
5 0 $\bar{6}$	1.8	2.6
6 0 $\bar{6}$	3.0	3.1
7 0 $\bar{6}$	3.3	4.4
8 0 $\bar{6}$	5.4	−5.0
9 0 $\bar{6}$	3.2	3.1
10 0 $\bar{6}$	1.2	0.9
11 0 $\bar{6}$	1.9	−1.9
12 0 $\bar{6}$	—	1.4
1 0 $\bar{7}$	1.0	−0.8
2 0 $\bar{7}$	1.0	−1.3
3 0 $\bar{7}$	—	0.4
4 0 $\bar{7}$	1.0	0.0
5 0 $\bar{7}$	3.3	−4.0
6 0 $\bar{7}$	6.6	7.6
7 0 $\bar{7}$	1.9	1.3
8 0 $\bar{7}$	—	−0.6
9 0 $\bar{7}$	—	0.3
10 0 $\bar{7}$	—	1.5
11 0 $\bar{7}$	2.9	2.9
1 0 $\bar{8}$	7.0	5.9
2 0 $\bar{8}$	—	−0.8
3 0 $\bar{8}$	10.2	−8.2
4 0 $\bar{8}$	1.3	0.3
5 0 $\bar{8}$	1.0	−1.5
6 0 $\bar{8}$	3.0	−3.2
7 0 $\bar{8}$	1.7	0.7
8 0 $\bar{8}$	2.2	−2.0
9 0 $\bar{8}$	—	0.2
10 0 $\bar{8}$	0.8	−1.4
1 0 $\bar{9}$	—	0.8
2 0 $\bar{9}$	3.8	3.3
3 0 $\bar{9}$	2.3	−1.9
4 0 $\bar{9}$	1.6	2.3
5 0 $\bar{9}$	3.7	−4.0
6 0 $\bar{9}$	—	0.0
7 0 $\bar{9}$	1.3	1.1
8 0 $\bar{9}$	3.2	−2.7
1 0 $\overline{10}$	—	−0.7
2 0 $\overline{10}$	1.7	2.1
3 0 $\overline{10}$	1.2	1.2
4 0 $\overline{10}$	—	−0.1

TABLE III

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR (*hk*0) AND (0*kl*)

The values for (*h*00) and (00*l*) are listed in Table II.

h k l	1/2F_o	1/2F_c	*h k l*	1/2F_o	1/2F_c	*h k l*	1/2F_o	1/2F_c	*h k l*	1/2F_o	1/2F_c
1 1 0	22.1	23.2	6 3 0	2.8	4.6	1 6 0	1.5	2.2	0 3 2	3.8	5.7
2 1 0	3.2	4.8	7 3 0	1.9	2.3	2 6 0	4.1	4.2	0 3 3	9.3	10.5
3 1 0	9.6	12.1	8 3 0	2.8	2.6	3 6 0	1.1	0.8	0 3 4	5.8	5.9
4 1 0	10.9	11.8	9 3 0	2.0	2.1	4 6 0	2.8	2.7	0 3 5	2.1	2.8
5 1 0	10.6	9.8	10 3 0	3.9	5.2	5 6 0	2.2	2.2	0 3 6	4.4	3.5
6 1 0	1.9	2.5	11 3 0	1.5	0.5	6 6 0	2.1	2.0	0 3 7	4.0	4.1
7 1 0	13.8	13.8	12 3 0	2.2	1.9	7 6 0	1.9	1.4	0 3 8	1.0	2.4
8 1 0	13.2	12.7	13 3 0	1.4	0.8	8 6 0	0.9	1.5	0 3 9	1.3	0.6
9 1 0	4.1	3.8	14 3 0	1.2	0.4	9 6 0	1.3	1.9	0 4 1	3.5	6.0
10 1 0	5.8	4.4	0 4 0	7.3	6.2	1 7 0	3.0	2.2	0 4 2	4.3	0.8
11 1 0	2.3	3.1	1 4 0	2.3	2.0	2 7 0	2.2	1.5	0 4 3	5.3	7.5
12 1 0	3.4	3.9	2 4 0	8.8	9.1	3 7 0	2.0	2.1	0 4 4	0.6	2.2
13 1 0	3.9	4.2	3 4 0	5.3	5.4	4 7 0	1.2	1.0	0 4 5	1.6	1.9
14 1 0	1.0	1.0	4 4 0	2.9	3.3	5 7 0	1.2	0.6	0 4 6	1.0	0.7
15 1 0	2.0	2.5	5 4 0	3.0	3.5	0 1 1	17.3	17.5	0 4 7	1.4	1.2
0 2 0	26.9	28.3	6 4 0	3.1	2.8	0 1 2	9.5	8.9	0 4 8	1.4	1.1
1 2 0	14.3	13.4	7 4 0	2.0	1.2	0 1 3	10.5	10.8	0 5 1	5.1	4.6
2 2 0	8.3	11.0	8 4 0	3.6	3.0	0 1 4	7.3	8.2	0 5 2	1.9	4.9
3 2 0	15.1	15.2	9 4 0	3.0	2.5	0 1 5	5.5	5.4	0 5 3	0.6	2.2
4 2 0	1.9	3.5	10 4 0	2.8	3.0	0 1 6	10.8	9.5	0 5 4	1.5	2.7
5 2 0	5.0	6.2	11 4 0	1.7	1.4	0 1 7	1.1	2.1	0 5 5	0.6	0.5
6 2 0	2.6	3.1	12 4 0	1.8	0.9	0 1 8	3.4	2.1	0 5 6	1.6	2.6
7 2 0	3.4	2.9	13 4 0	1.2	2.5	0 1 9	2.1	1.5	0 5 7	2.3	1.4
8 2 0	7.2	6.4	1 5 0	6.3	7.4	0 1 10	0.4	0.3	0 6 1	1.0	2.1
9 2 0	3.2	3.0	2 5 0	6.7	7.0	0 2 1	6.7	11.0	0 6 2	0.6	0.8
10 2 0	1.7	2.5	3 5 0	1.3	2.0	0 2 2	13.1	9.3	0 6 3	0.7	1.6
11 2 0	2.9	3.2	4 5 0	—	1.0	0 2 3	16.8	15.1	0 6 4	0.6	1.4
12 2 0	2.2	2.6	5 5 0	3.1	4.4	0 2 4	4.3	2.7	0 6 5	1.1	0.1
13 2 0	1.1	1.1	6 5 0	2.9	2.2	0 2 5	6.8	5.4	0 6 6	0.4	1.3
14 2 0	1.9	1.3	7 5 0	4.3	3.3	0 2 6	3.2	2.9	0 7 1	1.9	2.4
1 3 0	0.9	0.9	8 5 0	2.7	1.1	0 2 7	1.2	2.1	0 7 2	1.4	1.2
2 3 0	4.1	4.9	9 5 0	2.3	1.3	0 2 8	3.1	3.6	0 7 3	1.2	1.2
3 3 0	3.7	6.1	10 5 0	1.9	0.9	0 2 9	0.6	0.8			
4 3 0	5.4	7.0	11 5 0	1.7	1.3	0 2 10	1.0	0.6			
5 3 0	5.6	7.0	0 6 0	2.2	3.8	0 3 1	5.8	4.4			

kainate anion in the zinc salt[2] and also with the conclusion deduced from the chemical evidences[5].

The observed lengths of the bonds except for the C—O distances are in agreement within ±0.03 Å with those of the corresponding bonds in the kainate anion, the differences being not definitely significant, if the errors be taken into consideration, while some of the bond angles are fairly different from those of the kainate anion.

The C—O distances of the carboxymethyl group of C_3 are found to be 1.23 Å for C_7—O_3 and 1.34 Å for C_7—O_4, owing presumably to the formations of the hydrogen bonds involved (Fig. 9). The oxygen O_4 is of the hydroxyl group (OH). The C—O distances of the carboxyl group of C_2 are 1.24 Å for C_1—O_1 and 1.27 Å for C_1—O_2, being also due to hydrogen bond formations. The dimensions of this group are in good agreement with those of the CH_2COO^- group in the kainate anion (1.24 and 1.28 Å) or with those of the COO^- groups in similar hydrogen-bonded cases; hydroxyproline (1.25 and 1.27 Å)[6] and hexamethylene-diammonium adipate (1.24 and 1.28 Å)[7].

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[5] M. Miyasaki, *J. Pharm. Soc. Japan* (Yakugaku Zasshi), **75**, 695 (1955); Y. Ueno, H. Nawa, J. Ueyanagi, H. Morimoto, R. Nakamori and T. Matsuoka, ibid., **75**, 840 (1955); S. Murakami, T. Takemoto, Z. Tei and K. Daigo, ibid., **75**, 869 (1955).

[6] J. Zussman, *Acta Cryst.*, **4**, 493 (1951); J. Donohue and K. N. Trueblood, ibid., **5**, 419 (1952).

[7] S. Hirokawa, T. Ohashi and I. Nitta, *Acta Cryst.*, **7**, 87 (1954).

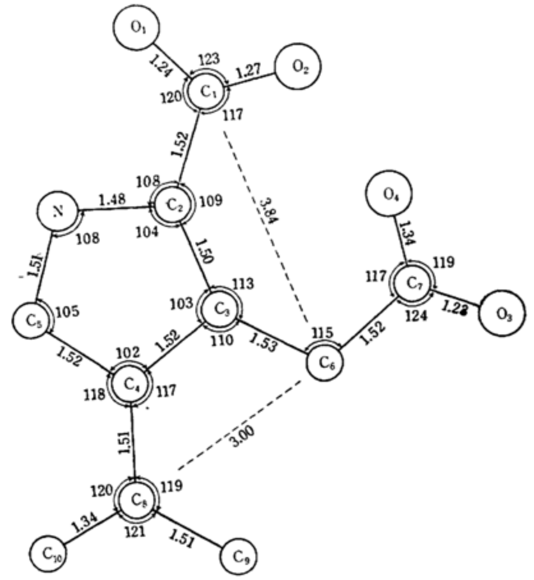

Fig. 4. Bond lengths (Å) and bond angles (°).

Judging from the dimensions of the carboxyl group of C_2 and the consideration about the observed hydrogen bonds (Fig. 9), at least in crystalline state, the kainic acid molecule is considered to be of the 'zwitter ion' structure in which the carboxyl group of C_2 is of COO^- and the nitrogen is of N^+H_2, although the positions of no hydrogen atoms are located in the present work. The infrared spectrum of this crystal also suggests the existence of the ionized carboxyl group, showing the absorption at 6.20 μ[8].

The stereochemical relations of the atoms in kainic acid molecule are in agreement with those of the kainate anion. Namely, the carboxyl group of C_2 and the carboxymethyl group of C_3 take the *trans*-configuration relative to the ring, and the latter group and the isopropenyl group of C_4 are in the *cis*-configuration. This fact supports the reasoning based on chemical evidences[9]. In the isopropenyl group, the double bond C_8—C_{10} is so located as to be more close to the ring than the single bond C_8—C_9 as in the case of the kainate anion. The stereochemical configuration of the molecule is shown in Fig. 5.

Owing mainly to the *cis*-configuration of the two side-chains attached to the neighboring C_3 and C_4, the five-membered pyrrolidine ring (N, C_2, C_3, C_4, C_5) is considerably distorted from the planar form as it is in the case of the kainate anion, their valence angles being remarkably deviated from the ordinary values. The distance between C_6 and C_8 is found to be 3.00 Å, a value similar to 2.96 Å in the kainate anion. As seen clearly in Fig. 3, the four atoms N, C_2, C_4 and C_5 of the pyrrolidine ring are approximately lying on one plane, and the carbon atom C_3 is shifted from the plane of the other four by about 0.6 Å, much greater than about 0.4 Å of the similar displacement in hydroxyproline[6]. The mode of the deformation of the pyrrolidine ring is different in the kainate anion due presumably to the difference of crystalline field, the pyrrolidine ring being thus found to be fairly flexible. In the case of the kainate anion, the carbon atom C_5 is displaced much farther from the mean plane than the other four.

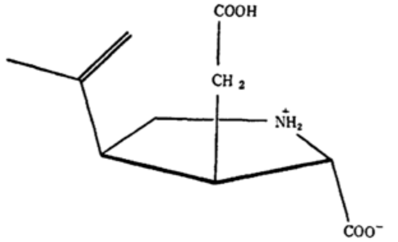

Fig. 5. Stereochemical configuration.

Finally, in Fig. 6, the molecule of kainic acid is indicated by the model which is derived from the atomic parameters of the present X-ray analysis, viewed along the *b* axis.

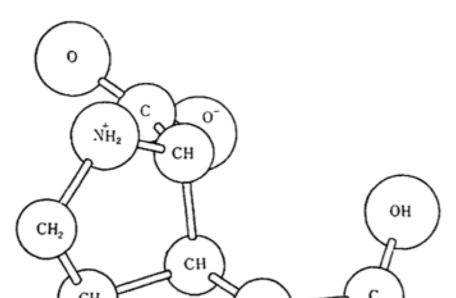

Fig. 6. The arrangement of the atoms in kainic acid, viewed along the *b* axis.

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[8] Y. Ueno, H. Nawa, J. Ueyanagi, H. Morimoto, R. Nakamori and T. Matsuoka, *J. Pharm. Soc. Japan* (Yakugaku Zasshi), **75**, 807 (1955).

[9] H. Morimoto and R. Nakamori, *J. Pharm. Soc. Japan* (Yakugaku Zasshi), **76**, 294 (1956); *Proc. Japan Acad.*, **32**, 41 (1956); T. Takemoto, Z. Tei and K. Daigo, *J. Pharm. Soc. Japan* (Yakugaku Zasshi), **76**, 298 (1956).

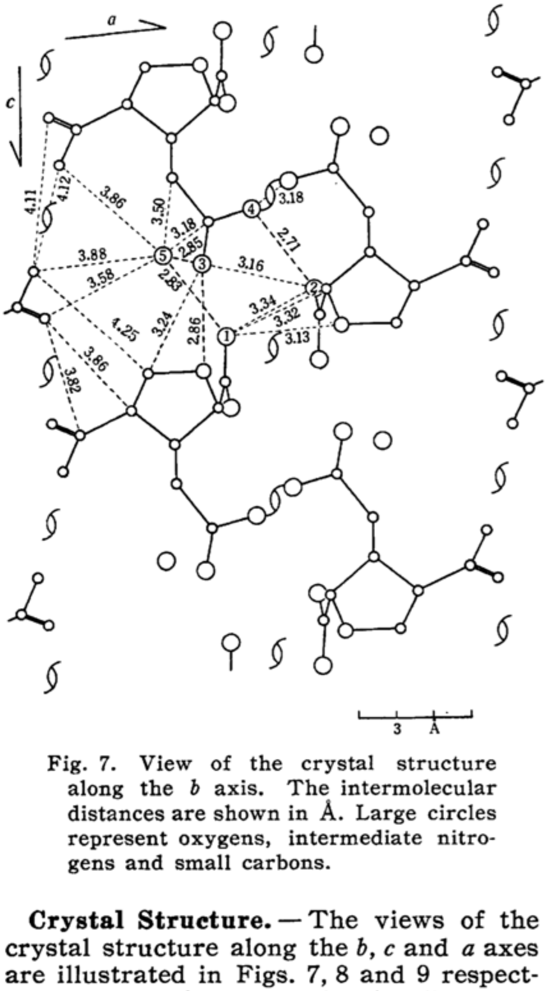

Fig. 7. View of the crystal structure along the *b* axis. The intermolecular distances are shown in Å. Large circles represent oxygens, intermediate nitrogens and small carbons.

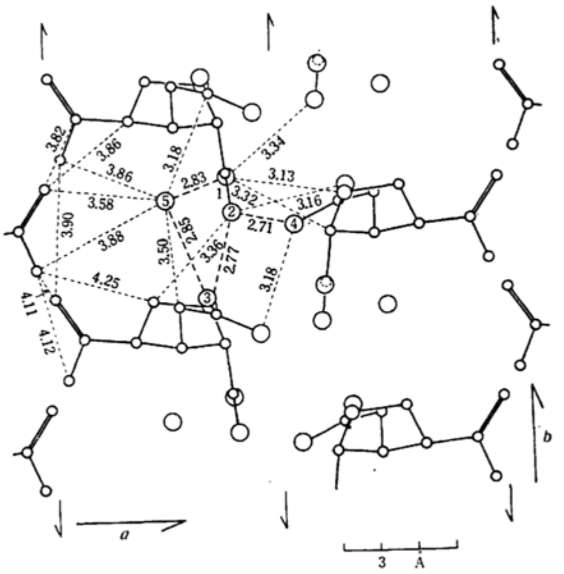

Fig. 8. View of the crystal structure along the *c* axis. The intermolecular distances are shown in Å. Symbols are the same as those of Fig. 7.

Crystal Structure. — The views of the crystal structure along the *b*, *c* and *a* axes are illustrated in Figs. 7, 8 and 9 respectively, giving the intermolecular distances. The space group being $C_2{}^2—P2_1$, the crystal has only two-fold screw axes parallel to the *b* axis as the symmetry element. The unit cell contains two molecules of kainic acid and two waters, the kainic acid molecule being the zwitter ion of which the account is given in the last section. As a whole, the crystal structure is a layered one, like those of the zinc salt[2)] or allokainic acid[10)].

There are five kinds of short intermolecular distance of 2.71~2.86 Å between oxygens or oxygen and nitrogen, and the intermolecular hydrogen bonds are considered to be formed there. The two hydrogens of N^+H_2 form the intermolecular hydrogen bonds between the nitrogen and the oxygen O_2 of the carboxyl group $(COO)^-$ or the oxygen O_3 of the carboxymethyl group. These hydrogen bond distances are 2.77 Å for $N—H\cdots O_2$ and 2.86 Å for $N—H\cdots O_3$. The hydrogen attached to the oxygen O_4 of the carboxymethyl group also forms the hydrogen bond between the molecules, its $O_4—H\cdots O_2$ distance being 2.71 Å. The water which is packed into the crystal to fill the space links one molecule to another by forming two hydrogen-bridges between the water oxygen O_5 and two molecules. They are $O_5—H\cdots O_1$ of 2.83 Å and $O_5—H\cdots O_3$ of 2.85 Å. The hydrogen bond angles are given in Fig. 9.

The projection along the *a* axis (Fig. 9) shows well how one molecule is linked to others by the hydrogen bonds. By these hydrogen bonds, the molecules and the waters are linked to each other infinitely, forming a double layered structure parallel to the (100) plane. In the projections along the *b* and *c* axes (Figs. 7 and 8), it is clearly seen that between the double layers the nonpolar groups or atoms are in contact with each other, the distances of the closest approach being 3.82 Å for $C_8\cdots C_{10}$, 3.86 Å for $C_4\cdots C_{10}$, 4.11 Å for $C_9\cdots C_{10}$ and 4.12 Å for $C_9\cdots C_9$. This is compatible with the observed cleavage parallel to the (100) plane.

Some Remarks on X-ray Crystal Analysis

In order to derive the *b* axis electron-density projection, the analysis based on

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10) H. Watase, to be published.

TABLE IV

SIGN RELATIONS AND CORRECT SIGNS (+OR−)

ξ	(3 0 0) +	(1 0 $\bar{4}$)*−		$-ad\xi$	(3 0 6) −	
η	(8 0 $\bar{1}$) +			acd	(2 0 $\bar{6}$) −	
$\xi\eta$	(5 0 $\bar{1}$) +	(3 0 $\bar{5}$) −		$acd\eta$	(4 0 1)*−	
a	(0 0 8) −	(2 0 $\bar{4}$) +	(8 0 2) +	$acd\xi\eta$	(1 0 1) −	(3 0 5) +
$a\xi$	(3 0 $\bar{8}$) −			ae	(6 0 $\bar{6}$) +	
$a\eta$	(2 0 7) −	(8 0 $\bar{9}$) −		$b\xi$	(5 0 0) +	
$a\xi\eta$	(3 0 3) +	(5 0 $\bar{9}$) −		$c\xi$	(1 0 $\bar{8}$) +	(3 0 $\bar{4}$) −
ab	(8 0 $\bar{8}$) −			$c\eta$	(2 0 3) −	
$ab\xi$	(5 0 8) −			$cd\xi\eta$	(5 0 1) +	(5 0 $\bar{3}$)*−
$ac\xi$	(1 0 0) −			d	(2 0 $\overline{10}$) +	(4 0 $\bar{6}$) +
$ac\eta$	(4 0 $\bar{1}$) −			$d\xi$	(1 0 $\bar{6}$) +	
ad	(2 0 $\bar{2}$) −	(4 0 2) +		$d\eta$	(4 0 5) −	(6 0 $\bar{7}$) +
$ad\xi$	(1 0 2) −	(9 0 $\bar{4}$) +		$e\xi$	(3 0 2) −	
$ad\eta$	(4 0 $\bar{3}$) +	(6 0 1) −		−	(4 0 8) +	
$ad\xi\eta$	(3 0 1) −			+	(8 0 $\bar{6}$) −	

* These were determined by Sayre's method.

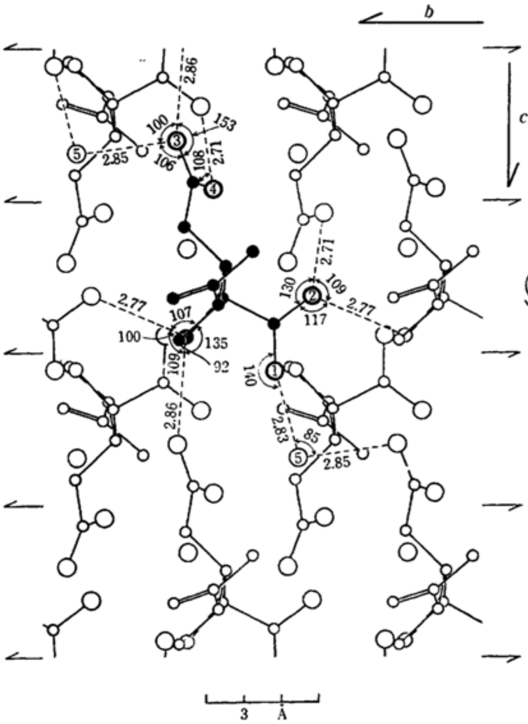

Fig. 9. View of the crystal structure along the a axis. The hydrogen bonds about one molecule are shown by broken lines, their distances (Å) and angles (°) being given. Symbols are the same as those of Fig. 7.

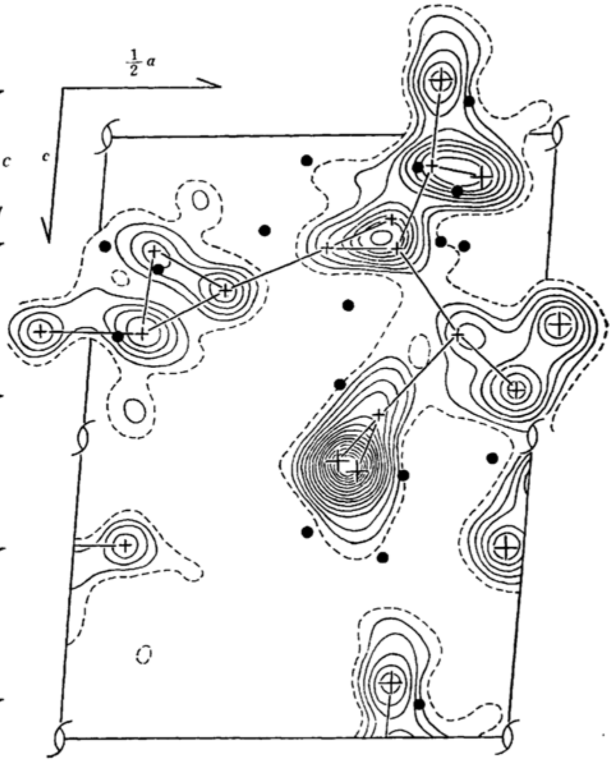

Fig. 10. Projection of incorrect electron-density on (010). Contours are drawn at equal intervals on an arbitrary scale, the lowest contour, broken line, being drawn at zero level of Fourier summations. Cross-symbols indicate the incorrect atomic positions considered from this map, there being large, intermediate and small symbols for oxygen, nitrogen and carbon respectively. The correct atomic positions are shown by black circles. An incorrect structure considered from this map is indicated by interatomic bonds.

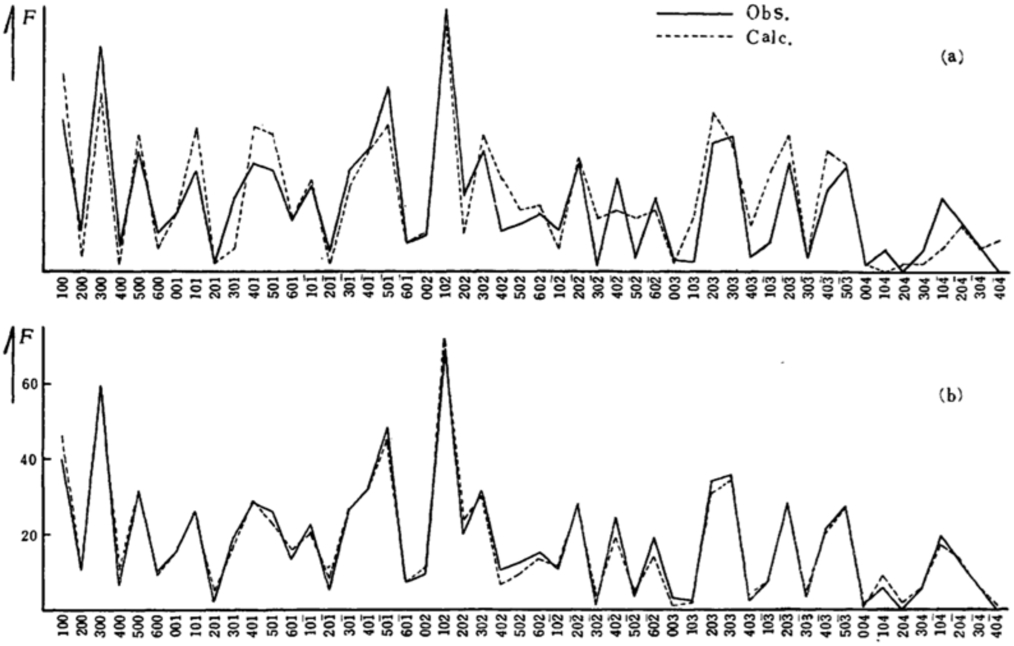

Fig. 11. F-values, (a) for the incorrect structure of Fig. 10, (b) for the correct structure of Fig. 1. The values for only fifty reflections of lower orders ($\sin\theta/\lambda < 0.29$) are shown.

direct methods was first attempted, because the crystal of kainic acid contains no heavy atom, and, furthermore, the chemical structure was entirely unknown when this work began.

The Harker-Kasper inequalities[11] was applied to obtain the sign relations of the structure factors for ($h0l$), using Sakurai's chart[12]. Unitary structure factors $U(h0l)$ were calculated from the relative structure factors $F'(h0l)$, as follows:

$$U(h0l),\ K=|F'(h0l)|\exp B(\sin\theta/\lambda)^2/\sum f_i$$

where f_i is the atomic scattering factor[13] of the i th atom. The scale factor K and the temperature factor B were obtained by Wilson's method[3].

However, since by this procedure sign relations could not be given because of low magnitudes of the unitary structure factors, an attempt was made to determine sign relations of some terms as in the case of the analysis of sodium tropolonate[14]. Namely, the unitary structure factors were multiplied by an artificial constant of about 1.3, and the sign relations of 44 terms were then obtained without contradiction by the Harker-Kasper inequalities. In addition, these relations were also checked by Sayre's method[15]. These sign relations together with the correct signs for the structure of Fig. 1 are listed in Table IV, where ξ and η are arbitrary parameters[16].

By the Fourier method based on these signs and further trial-and-error, an electron-density map was derived as shown in Fig. 10, the sign relations of Table IV being satisfied except for only four reflections with small F value. From this map a structure might be guessed by connecting reasonably with the peaks found as indicated also in Fig. 10. However, the R index calculated on this structure was about 40%, and it seemed impossible to decrease the R value satisfactorily by the further refinement of this map. Moreover, even in the lower order, some of the calculated structure factors showed considerable discrepancy from their observed values as shown in Fig. 11 (a); for example (301), (402), ($10\bar{3}$), ($10\bar{4}$), etc. We gave up this map, Fig. 10, considering that it was wrong, being of a 'false structure'. When

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[11] D. Harker and J. S. Kasper, *Acta Cryst.*, **1**, 70 (1948).

[12] K. Sakurai, ibid., **5**, 546 (1952).

[13] "Internationale Tabellen zur Bestimmung von Kristallstrukturen", Bornträger, Berlin (1935).

[14] Y. Sasada and I. Nitta, *Acta Cryst.*, **9**, 205 (1956).

[15] D. M. Sayre, ibid., **5**, 60 (1952).

[16] Y. Okaya and I. Nitta, ibid., **5**, 564 (1952).

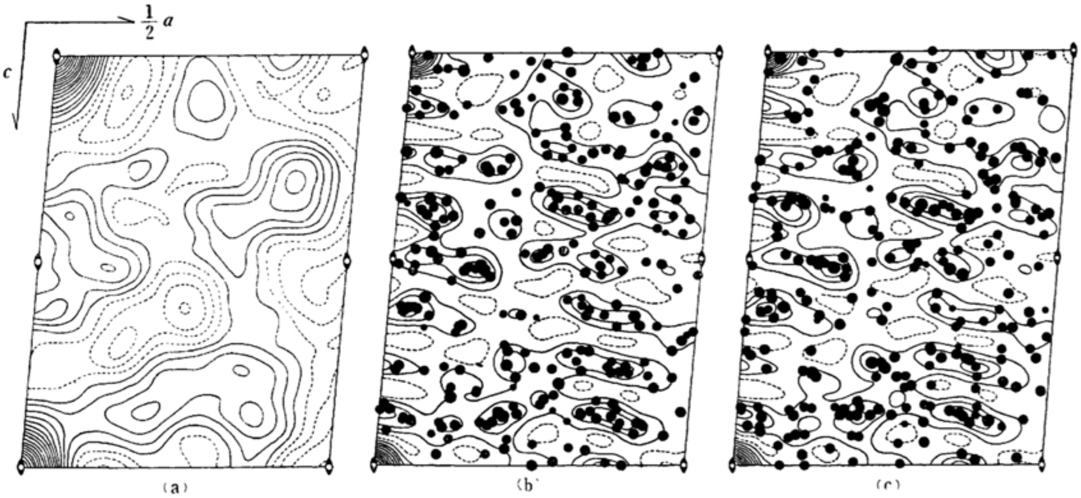

Fig. 12. The Patterson function projected on (010), a) ordinary function, b) and c) modified function to obtain sharp peaks. Contours of each map are drawn at equal intervals on an arbitrary scale, the lowest solid line being drawn at zero level of Fourier summations. Black circles of the maps b) and c) show the positions of the Patterson peaks, b) derived from the correct structure of Fig. 1, c) derived from the incorrect structure of Fig. 10. The area of each black circle is approximately proportional to the weight of the peak.

the correct structure was next determined, it was revealed that the sign relations obtained above were quite random ones, as shown in Table IV, though the above inequalities gave apparently consistent relations.

In the present case, thirty-two atoms are in the unit cell excluding hydrogen atoms, and, generally speaking, this number of atoms per unit cell is too many for the inequality method to be applied. A successful application of the inequality method to tropolone hydrochloride[17] has been reported, the unit cell of which contains forty atoms. However, there are four heavy chlorine atoms which are distinguishable from others, and the signs obtained by this method coincide with those of the contributions from the chlorine atoms except for only one structure factor with a small F value.

Although there is the fortunate case of sodium tropolonate, it must be borne in mind that the sign relations obtained by raising artificially the scale of unitary structure factors may not necessarily correspond to the true structure and even may lead to a false structure as in the present case. It generally seems that the more atoms are contained in a unit cell, the more various false structures will be possible.

As for the application of the Patterson method, the ordinary Patterson function $P(x, z)$ was first calculated, and further to obtain sharp peaks a modified Patterson function $P'(x, z)$ was also calculated as follows:

$$P'(x, z) = k \sum_h \sum_l U(h0l)^2 \cos 2\pi (hx + lz)$$

where k is the scale factor. Both projection maps are shown in Fig. 12. However, no useful information about the structure was provided from these maps. Even in such a case, this function may be applicable as a method to check whether or not a derived structure is correct, as seen from a comparison between the maps b and c of Fig. 12. If a structure derived by any other method is correct, the Patterson map should be quantitatively interpreted as shown in the map b of Fig. 12.

We wish to express our thanks to Professor-Emeritus S. Murakami, Dr. T. Takemoto and their collaborators of this University and Drs. S. Kuwada, S. Tatsuoka, Y. Ueno and their collaborators of the Research Laboratory of Takeda Pharmaceutical Industry, Ltd. for supplying the specimens and kindly discussing problems with us. Thanks are also due to Dr. H. Tani, Mr. Y. Sasada and Mr. T. Shiba of this University for helpful advice and continued interest. Appreciation is

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[17] Y. Sasada, K. Osaki and I. Nitta, ibid., **7**, 113 (1954).

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