The Molecular and Crystal Structure of Allokainic Acid*

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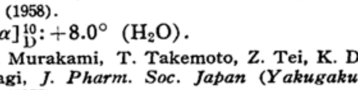
As parts of our studies1) on the structures of kainic acid and its isomer, we reported in the previous papers the X-ray investigations on zinc kainate2) and kainic acid3), which determined the three-dimensional structure of kainic acid $C_{10}H_{15}O_4N$, the most active component of *Digenea simplex* Agardh. *Digenea simplex* Agardh contains also an isomer of kainic acid, allokainic acid4), in a very small proportion. Allokainic acid $C_{10}H_{15}O_4N$ is an acidic and optically active** compound of m. p. 237°(decomp.), and is said to have a very weak anthelmintic effect if any. It is of interest to elucidate the relationship between the structures of the two isomers of which the physiological nature (anthelmintic effect) of one is very different from that of the other.

According to the reports5) based on organic chemistry, the chemical behavior of one of the two isomers is similar to that of the other, and the structural formula of allokainic acid is concluded to be the same as that of kainic acid, 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine.



To confirm this conclusion and to determine moreover the stereochemical configuration of the molecule, the structure of allokainic acid has been investigated by means of X-ray crystal analysis. The electron-density projections along the two principal crystal axes were derived by the trial method, and the three-dimensional structure of the molecule was determined quantitatively.

In this paper is described the structure determination of allokainic acid in detail.

Experimental

Allokainic acid crystallizes with no molecules of water from its aqueous solution. Crystalline allokainic acid is of a colorless prism elongated along a principal crystal axis chosen as the *b* axis, having a plane of cleavage perpendicular to another principal axis (*a* axis).

Oscillation and Weissenberg photographs were taken about two principal crystal axes (*b* and *c* axes), using filtered Cu K_α radiation. The specimens used had the following cross-sections at right angles to the axis of rotation; 0.15×0.2 mm. for the *b* axis rotation and 0.2×0.4 mm. for the *c* axis***.

The intensity data of (h 0 l) and (h k 0) used in the two-dimensional analyses were prepared from the integrated Weissenberg photographs. 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, and the effects of absorption were neglected, the linear absorption coefficient for Cu K_α radiation being $\mu=10.1/\text{cm}$****.

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

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* Part of this paper was presented at the autumnal joint meeting of chemical societies of 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).

3) H. Watase, Y. Tomiie and I. Nitta, This Bulletin, **31**, 714 (1958).

** $[\alpha]^{10}_{D}$: +8.0° (H_2O).

4) S. Murakami, T. Takemoto, Z. Tei, K. Daigo and S. Takagi, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **75**, 766 (1955).

5) H. Morimoto, ibid., **75**, 937 (1955); S. Murakami, K. Daigo, S. Takagi, T. Takemoto and Z. Tei, ibid., **75**, 1252 (1955).

*** The specimen used for the *c* axis rotation was prepared by cutting the crystal at right angle to the elongated *b* axis.

**** This value comes from the unit cell containing four molecules (see next section).

Results and Discussion

Unit Cell and Space Group.—From the X-ray examinations, the crystal is found to belong to the orthorhombic system, and the dimensions of the unit cell are as follows;

$$a=26.08\pm0.07\ \text{Å}$$
$$b=5.83\pm0.02\ \text{Å}$$
$$c=6.95\pm0.03\ \text{Å}$$

Systematic absence of reflections being recognized only in (h 0 0), (0 k 0) and (0 0 l) when h, k and l are odd respectively, the space group is uniquely determined to be D_2^4-$P2_12_12_1$. The unit cell with this crystal symmetry has four-fold general positions[6]. Judging from the cell size, in the present case, four formula units of $C_{10}H_{15}O_4N$ are expected to be contained in the unit cell, an asymmetric unit being unimolecular.

The axial periods of the b and c axes seemed to be short enough to permit a good resolution of many of the atoms, while the a axis is very long, and the projections along the b and c axes were tried to obtain the atomic parameters.

Determination of the Structure. — As already given, the space group involved is D_2^4–$P2_12_12_1$, and each two-dimensional projection was treated separately with the origin lying on the two-fold screw axis so that the origin is a center of symmetry in the projection, as in the analysis of zinc kainate dihydrate[2] with the same space group. However, the atomic parameters (Table I), the final electron-density projections (Figs. 2 and 3) and the projections of the crystal structure (Figs. 6 and 7) are described returning to the customary space group origin.

The structure-factor maps (see Fig. 1 given below) for all the possible reflections of (h 0 l) and (h k 0) were prepared in order to locate all the atoms by the trial method in the projections along the b and c axes. By assuming the structure of allokainic acid to be 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine, the b axis projection was investigated in the first place.

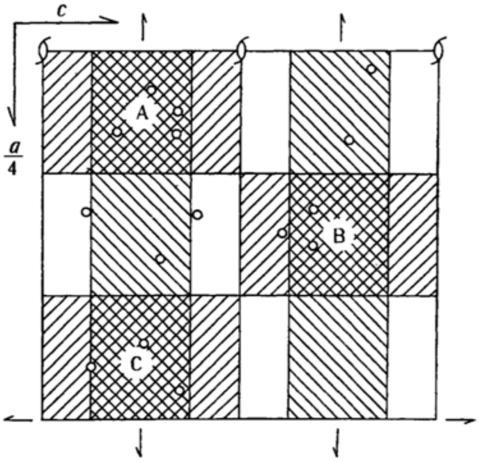

Fig. 1. Superposed structure-factor maps for (6 0 1) with negative sign and (0 0 2) with negative sign, the positive areas being shaded. The F values of these reflections being large, the regions **A**, **B** and **C** are strongly positive. Circles show the final atomic positions. Origin is on the projection of a two-fold screw.

The sign of (6 0 1) with a large F value was defined to be negative. Considering the various structures compatible with the structure factors for the lower order reflections, the absolute values of the structure factors were roughly known, and the sign of (0 0 2) with the largest F value was determined to be negative. Fig. 1 shows the structure-factor map by superposing those for (6 0 1) and (0 0 2), in which the positive areas are shaded. The regions around **A**, **B** and **C** of Fig. 1 being strongly positive, it seems probable that most of the atoms will be found in these regions, and it might be considered at this stage that each of the three side-chains of allokainic acid has its location in each of these regions; the carboxyl group in the region **A** or **C**, the carboxyl group of the carboxymethyl group in the region **B** and the isopropenyl group in the region **A** or **C**.

There was an ambiguous point about the probable positions of the carboxyl and the isopropenyl group. Since packing consideration of the isopropenyl group was found helpful for the further analysis, the trial was carried out, using the structure-factor maps only for the reflections with h even because the $|F|$ values of these reflections are estimated independently of the above ambiguity. All the atoms were then roughly located, leaving the ambiguity about the choice of the origin of the projection out of the

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[6] "Internationale Tabellen zur Bestimmung von Kristallstrukturen", Bornträger, Berlin (1935); "International Tables for X-ray Crystallography", Kynoch Press, Birmingham (1952).

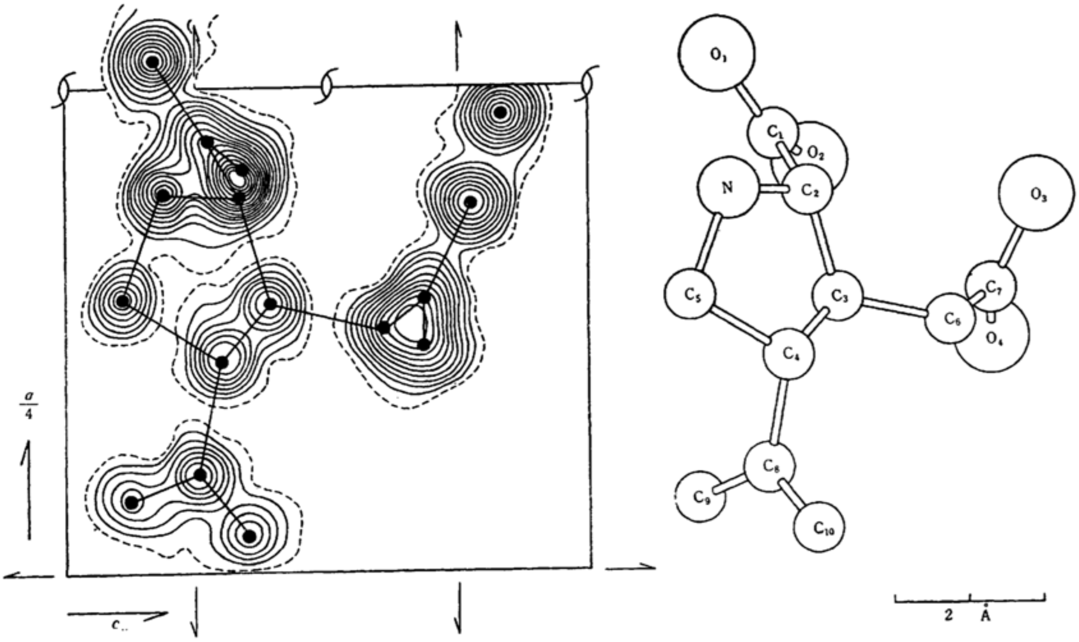

Fig. 2. Electron-density projection along the *b* axis. Contour lines at unit electron intervals, the lowest line, broken line, being 2 electron per Å^2. Black circles show the atomic positions. The interpretation of the density map is given on the right side.

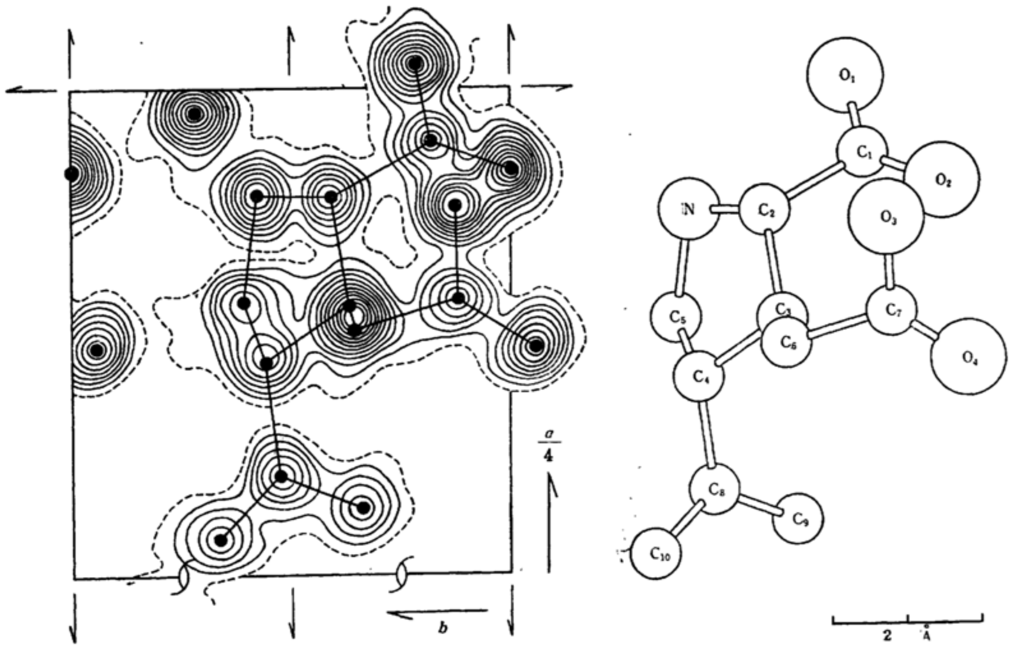

Fig. 3. Electron-density projection along the *c* axis. Contours and symbols are the same as those of Fig. 2. The interpretation of the density map is given on the right side.

question, and in order to be compatible with the F values of (5 0 2) and (7 0 2) it was determined that the carboxyl group is in the region **A** and the isopropenyl group in the region **C**. In this trial (12 0 0) could be used powerfully. The observed structure factors were reduced from the relative values nearly to those in the absolute scale.

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. In this way the electron-density projection along the b axis was derived.

On the basis of the x parameters obtained from the b axis projection, the electron-density projection along the c axis was derived in the same way. Figs. 2 and 3 show the final electron-density projections along the b and c axes respectively. In these maps, each peak has a reasonable height, the peaks of oxygen or nitrogen being higher than those of carbon. The final atomic parameters referred to the customary space group origin are listed in Table I.

TABLE I

ATOMIC PARAMETERS

Atom	x/a	y/b	z/c
C_1	0.222_9	0.183	0.273
C_2	0.194_2	0.402	0.339
C_3	0.138_8	0.363	0.393
C_4	0.109_2	0.558	0.298
C_5	0.140_8	0.608	0.115
C_6	0.126_6	0.353	0.607
C_7	0.142_2	0.117	0.683
C_8	0.051_7	0.525	0.260
C_9	0.035_8	0.337	0.123
C_{10}	0.020_0	0.663	0.350
N	0.195_1	0.578	0.184
O_1	0.237_1	0.718	0.828
O_2	0.208_3	0.998	0.340
O_3	0.190_0	0.127	0.773
O_4	0.117_5	0.942	0.683

At this stage, the discrepancy indices ($R=\sum||F_o|-|F_c||/\sum|F_o|$) are 0.178 for ($h$ 0 l) and 0.192 for (h k 0), employing the data up to $\sin\theta/\lambda=0.640$ for (h 0 l) and 0.642 for (h k 0), 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 value of $B=4.0$ Å^2 was used for each zone as the temperature factor common to all the atoms. The atomic scattering factors were taken from McWeeny's paper⁷⁾; for oxygen $\bar{f}_o=1/3(f^{\parallel}+2f^{\perp})$ and for carbon the values for 'valence states'.

The observed and the calculated structure factors for (h 0 l) and (h k 0) are listed in Tables II and III respectively, in which the signs of the calculated structure factors are given as those for the coordinates used in the analysis for each projection.

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 ±0.03 Å and the bond angles to ±3°. As a result, it is confirmed that allokainic acid is a stereoisomer of kainic acid, its structure being 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine. Namely, the five-membered ring (N, C_2, C_3, C_4, C_5) is of pyrrolidine, and the side-chains C_2–(C_1–O_1, O_2), C_3–(C_6–C_7–O_3, O_4) and C_4–(C_8–C_9, C_{10}) are the carboxyl, the carboxymethyl and the isopropenyl group respectively. In the isopropenyl group, the C_8–C_{10} bond of the length 1.31 Å is its double bond.

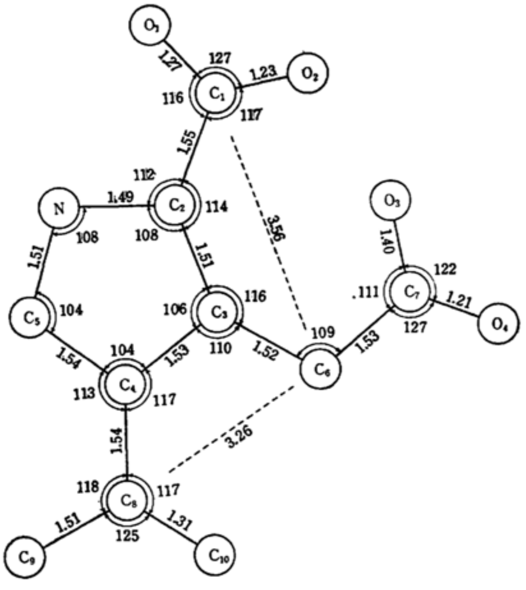

Fig. 4. Bond lengths (Å) and bond angles (°).

The observed bond lengths except for the C_7–O_3 distance are in agreement within ±0.03 Å with those of the corresponding

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

TABLE II

OBSERVED AND CALCULATED STRUCTURE FACTORS $F(h\ 0\ l)$
THE VALUES FOR $(h\ 0\ 0)$ ARE LISTED IN TABLE III

$h\ k\ l$	$1/4F_o$	$1/4F_c$
1 0 1	6.6	−8.1
2 0 1	10.2	−7.7
3 0 1	7.6	7.0
4 0 1	0.7	0.5
5 0 1	8.6	9.4
6 0 1	21.4	−21.7
7 0 1	4.4	−4.3
8 0 1	0.8	0.0
9 0 1	—	−0.3
10 0 1	4.4	−2.8
11 0 1	7.9	7.5
12 0 1	1.5	1.7
13 0 1	3.2	4.2
14 0 1	3.6	1.6
15 0 1	1.3	1.0
16 0 1	4.3	5.0
17 0 1	0.8	−1.4
18 0 1	6.5	7.2
19 0 1	1.7	2.3
20 0 1	2.3	2.6
21 0 1	0.7	−1.1
22 0 1	—	−0.3
23 0 1	0.7	−0.5
24 0 1	1.4	1.7
25 0 1	1.0	−1.1
26 0 1	0.8	0.9
27 0 1	—	−0.2
28 0 1	0.7	−0.6
29 0 1	—	−0.1
30 0 1	—	−0.2
31 0 1	0.7	−0.5
32 0 1	1.3	0.7
33 0 1	—	0.4
0 0 2	37.1	−34.8
1 0 2	2.6	−3.0
2 0 2	13.4	−12.3
3 0 2	1.1	−0.2
4 0 2	2.6	−3.7
5 0 2	14.4	14.4
6 0 2	—	−1.4
7 0 2	12.4	12.6
8 0 2	4.6	4.4
9 0 2	5.7	5.2
10 0 2	7.7	6.9
11 0 2	2.2	−3.1
12 0 2	6.5	6.9
13 0 2	2.6	4.2
14 0 2	2.5	−2.7
15 0 2	2.3	1.7
16 0 2	2.7	−3.2
17 0 2	0.9	−0.1
18 0 2	—	0.5
19 0 2	0.7	−0.7
20 0 2	1.9	−1.6
21 0 2	—	0.6
22 0 2	—	−0.4
23 0 2	2.0	2.0
24 0 2	3.1	1.9
25 0 2	0.7	−1.0
26 0 2	2.2	1.8
27 0 2	1.4	1.4
28 0 2	1.0	1.0
29 0 2	—	0.1
30 0 2	0.7	−0.7
31 0 2	1.1	0.8
32 0 2	0.7	0.3
1 0 3	6.4	5.6
2 0 3	4.4	−3.9
3 0 3	10.5	−8.8
4 0 3	5.3	−5.0
5 0 3	8.7	−6.9
6 0 3	2.2	1.0
7 0 3	4.1	3.3
8 0 3	6.4	5.5
9 0 3	1.3	0.9
10 0 3	—	0.2
11 0 3	7.8	−8.5
12 0 3	0.8	1.5
13 0 3	5.3	−4.2
14 0 3	—	−0.1
15 0 3	2.0	−2.0
16 0 3	4.1	4.0
17 0 3	—	−0.7
18 0 3	—	0.0
19 0 3	1.7	−2.8
20 0 3	3.3	−3.3
21 0 3	1.7	1.7
22 0 3	1.0	−0.9
23 0 3	0.7	0.9
24 0 3	0.7	−0.6
25 0 3	1.0	0.9
26 0 3	1.6	1.3
27 0 3	1.0	0.8
28 0 3	—	−0.5
29 0 3	0.9	0.8
30 0 3	1.2	−1.0
31 0 3	0.7	0.6
0 0 4	6.7	−6.7
1 0 4	1.2	−1.3
2 0 4	—	0.5
3 0 4	1.1	−0.2
4 0 4	2.0	1.7
5 0 4	4.3	−6.2
6 0 4	2.7	2.6
7 0 4	5.7	−6.0
8 0 4	6.5	−5.8
9 0 4	3.4	−2.9
10 0 4	2.0	−2.0
11 0 4	—	−0.2
12 0 4	1.6	2.6
13 0 4	—	−0.6
14 0 4	1.8	2.0
15 0 4	1.4	−2.0
16 0 4	0.7	0.8
17 0 4	2.0	−0.6
18 0 4	4.6	−3.9
19 0 4	—	−0.2
20 0 4	0.7	0.7
21 0 4	—	−0.2
22 0 4	—	−0.5
23 0 4	0.7	−0.6
24 0 4	1.0	−0.8
25 0 4	—	0.1
26 0 4	1.4	−0.8
27 0 4	0.6	−0.6
28 0 4	0.6	−0.5
29 0 4	—	0.0
1 0 5	0.9	−0.2
2 0 5	1.3	1.2
3 0 5	2.6	4.0
4 0 5	3.6	3.6
5 0 5	—	0.2
6 0 5	2.4	4.3
7 0 5	1.5	−1.4
8 0 5	1.2	−0.9
9 0 5	1.2	−1.9
10 0 5	1.5	−1.2
11 0 5	0.7	1.4
12 0 5	5.1	−4.8
13 0 5	0.7	0.8
14 0 5	1.7	−1.5
15 0 5	0.7	0.9
16 0 5	4.2	−4.0
17 0 5	3.1	2.9
18 0 5	1.0	−1.2
19 0 5	—	0.7
20 0 5	—	0.4
21 0 5	1.6	−0.5
22 0 5	—	0.2
23 0 5	—	−0.3
24 0 5	1.1	0.8
25 0 5	0.6	0.4
26 0 5	0.5	−0.3
27 0 5	0.7	−0.7
0 0 6	2.4	3.0
1 0 6	0.7	1.1
2 0 6	2.2	2.2
3 0 6	—	0.0
4 0 6	1.6	1.5
5 0 6	—	−0.1
6 0 6	—	0.2
7 0 6	1.4	0.9
8 0 6	0.7	0.7
9 0 6	—	0.0
10 0 6	2.2	−2.4
11 0 6	—	0.8
12 0 6	—	−0.2
13 0 6	0.7	−0.6
14 0 6	1.0	0.5
15 0 6	1.2	1.3
16 0 6	—	0.0
17 0 6	1.6	0.9
18 0 6	1.4	0.8
19 0 6	—	0.1
20 0 6	1.0	0.4
21 0 6	—	0.2
22 0 6	1.6	1.7
23 0 6	0.8	−0.4
24 0 6	—	−0.1
1 0 7	0.7	−0.4
2 0 7	1.0	1.0
3 0 7	1.0	−1.2
4 0 7	1.4	−1.6
5 0 7	0.7	0.6
6 0 7	1.7	−1.6
7 0 7	1.9	2.0
8 0 7	1.9	−1.7
9 0 7	1.8	1.8
10 0 7	1.9	1.9
11 0 7	1.0	1.0
12 0 7	5.6	3.2
13 0 7	—	−0.2
14 0 7	1.8	1.1
15 0 7	—	0.4
16 0 7	0.6	0.8
17 0 7	1.7	−1.5
18 0 7	—	0.0
19 0 7	0.7	−0.4
20 0 7	0.9	0.9
0 0 8	—	−0.1
1 0 8	—	0.1
2 0 8	1.0	−1.3
3 0 8	—	−0.3
4 0 8	—	0.4
5 0 8	0.8	0.9
6 0 8	—	−0.5
7 0 8	—	0.0
8 0 8	—	−0.3
9 0 8	—	0.4
10 0 8	1.8	1.2
11 0 8	—	0.1
12 0 8	0.7	−0.4
13 0 8	—	0.0
14 0 8	0.9	−0.3

TABLE III

OBSERVED AND CALCULATED STRUCTURE FACTORS $F(h\ k\ 0)$

$h\ k\ l$	$1/4F_o$	$1/4F_c$
0 0 0		114
2 0 0	20.1	−21.0
4 0 0	5.5	−5.7
6 0 0	7.6	7.1
8 0 0	8.4	6.9
10 0 0	5.2	5.4
12 0 0	22.2	−21.3
14 0 0	0.3	−0.3
16 0 0	6.3	5.7
18 0 0	5.8	−5.6
20 0 0	1.5	1.7
22 0 0	1.3	0.4
24 0 0	3.3	−2.5
26 0 0	1.5	1.6
28 0 0	1.2	−0.7
30 0 0	—	0.0
32 0 0	1.6	−1.0
1 1 0	3.6	−4.1
2 1 0	10.6	−8.2
3 1 0	9.5	10.4
4 1 0	9.5	−10.1
5 1 0	1.8	−3.9
6 1 0	0.2	−1.3
7 1 0	0.5	−0.6
8 1 0	9.3	−10.3
9 1 0	5.4	5.1
10 1 0	1.4	−0.2
11 1 0	1.8	1.8
12 1 0	0.6	−0.4
13 1 0	2.5	4.1
14 1 0	1.9	0.6
15 1 0	4.9	−4.7
16 1 0	—	0.4
17 1 0	2.5	3.3
18 1 0	0.4	−0.4
19 1 0	0.6	0.8
20 1 0	2.8	3.1
21 1 0	0.6	−0.7
22 1 0	2.6	−2.9
23 1 0	3.4	−3.0
24 1 0	0.5	−0.1
25 1 0	0.8	0.8
26 1 0	0.6	−0.4
27 1 0	1.7	−1.7
28 1 0	0.7	0.6
29 1 0	0.3	0.4
30 1 0	0.3	0.3
31 1 0	2.0	−1.5
32 1 0	1.2	−0.9
33 1 0	0.4	0.1
0 2 0	7.3	−8.5
1 2 0	9.2	−9.8
2 2 0	1.3	0.1
3 2 0	7.8	8.6
4 2 0	9.7	10.4
5 2 0	1.1	−2.3
6 2 0	2.4	−2.3
7 2 0	3.5	−5.3
8 2 0	8.3	6.6
9 2 0	3.5	3.6
10 2 0	8.7	−8.3
11 2 0	0.8	0.9
12 2 0	7.4	8.0
13 2 0	2.0	−1.8
14 2 0	0.5	−1.0
15 2 0	1.1	−2.8
16 2 0	1·8	−2.3
17 2 0	0.6	−1.4
18 2 0	1.1	−1.6
19 2 0	0.4	1.4
20 2 0	3.8	−3.3
21 2 0	1.7	−1.9
22 2 0	2.3	2.1
23 2 0	3.8	−3.7
24 2 0	0.5	−0.9
25 2 0	2.2	1.7
26 2 0	0.3	0.2
27 2 0	0.4	0.4
28 2 0	0.4	−0.2
29 2 0	0.9	−0.4
30 2 0	0.9	0.8
31 2 0	—	0.0
32 2 0	0.4	0.5
1 3 0	2.2	−2.9
2 3 0	4.4	−4.4
3 3 0	1.4	−1.3
4 3 0	0.5	−0.2
5 3 0	5.6	5.3
6 3 0	1.6	1.1
7 3 0	0.5	−0.9
8 3 0	—	−1.3
9 3 0	2.2	−2.5
10 3 0	7.1	−7.5
11 3 0	—	−0.3
12 3 0	1.3	−0.6
13 3 0	2.5	3.1
14 3 0	0.5	−0.4
15 3 0	0.4	0.2
16 3 0	2.5	−2.7
17 3 0	1.1	−0.6
18 3 0	0.4	−0.8
19 3 0	3.2	−3.1
20 3 0	—	0.1
21 3 0	2.4	2.3
22 3 0	1.2	1.7
23 3 0	—	−0.1
24 3 0	1.1	1.1
25 3 0	0.3	0.1
26 3 0	1.3	−1.1
27 3 0	0.5	−0.5
28 3 0	2.1	1.6
29 3 0	0.6	0.4
30 3 0	1.1	−0.8
0 4 0	4.3	−5.5
1 4 0	0.7	−1.3
2 4 0	—	−0.2
3 4 0	4.0	3.9
4 4 0	5.7	5.0
5 4 0	2.3	−2.0
6 4 0	7.3	−6.2
7 4 0	2.3	2.6
8 4 0	0.4	−0.8
9 4 0	0.6	−0.5
10 4 0	0.4	0.2
11 4 0	0.4	−0.2
12 4 0	0.7	1.5
13 4 0	1.0	−1.5
14 4 0	0.6	−0.7
15 4 0	0.8	−0.9
16 4 0	2.0	−1.6
17 4 0	0.5	−0.1
18 4 0	5.1	4.2
19 4 0	1.9	−2.5
20 4 0	0.4	0.4
21 4 0	0.5	0.2
22 4 0	1.9	−1.6
23 4 0	—	0.2
24 4 0	1.8	1.7
25 4 0	0.4	0.2
26 4 0	0.3	−0.5
27 4 0	0.7	−0.6
28 4 0	0.2	−0.2
1 5 0	4.5	4.2
2 5 0	1.9	0.8
3 5 0	4.9	−4.3
4 5 0	3.0	−3.0
5 5 0	0.6	−0.9
6 5 0	1.2	0.7
7 5 0	—	−0.4
8 5 0	2.5	−2.0
9 5 0	1.7	1.7
10 5 0	0.6	0.3
11 5 0	2.0	−2.2
12 5 0	0.9	0.3
13 5 0	2.2	−2.4
14 5 0	1.2	−1.1
15 5 0	0.6	0.5
16 5 0	2.2	2.1
17 5 0	0.9	1.3
18 5 0	1.1	−1.2
19 5 0	0.7	−0.4
20 5 0	0.6	0.7
21 5 0	1.1	0.9
22 5 0	0.3	−0.3
23 5 0	0.5	−0.1
24 5 0	—	0.1
0 6 0	0.4	−0.7
1 6 0	1.0	−0.6
2 6 0	0.5	−1.2
3 6 0	0.6	0.4
4 6 0	1.2	−1.8
5 6 0	1.8	−1.7
6 6 0	0.5	0.0
7 6 0	0.8	0.8
8 6 0	0.5	0.0
9 6 0	0.6	−0.3
10 6 0	0.8	0.8
11 6 0	0.3	0.3
12 6 0	0.7	0.9
13 6 0	0.3	0.1
14 6 0	1.4	−0.7
15 6 0	0.3	0.5
16 6 0	1.8	1.2
17 6 0	0.4	0.7
18 6 0	1.0	−0.4
19 6 0	0.3	−0.3
20 6 0	1.2	0.8
1 7 0	0.8	−0.7
2 7 0	0.5	0.1
3 7 0	0.4	0.3
4 7 0	2.2	1.7
5 7 0	—	0.1
6 7 0	2.6	−1.4
7 7 0	—	−0.2
8 7 0	2.0	1.4
9 7 0	0.6	0.2
10 7 0	0.6	0.8
11 7 0	1.1	−0.7

bonds in kainic acid[3], the differences being not definitely significant, while some of the bond angles are fairly different from the corresponding ones of kainic acid.

The C–O distances of the carboxymethyl group of C_3 are found to be 1.40 Å for C_7–O_3 and 1.21 Å for C_7–O_4, the oxygen O_3 being of the hydroxyl group (OH) and forming a hydrogen bond as will be described in the next section (Figs. 6 and 7). The corresponding distances of kainic acid are found to be 1.34 and 1.23 Å, both the oxygens being linked to others by hydrogen bonds.

The C–O distances of the carboxyl group of C_2 are 1.27 Å for C_1–O_1 and 1.23 Å for C_1–O_2, both forming hydrogen bonds. These values are in good agreement with those of the carboxyl group in kainic acid (1.24 and 1.27 Å), similarly hydrogen bonded.

Judging from the dimensions of the carboxyl group of C_2 and the consideration about the observed hydrogen bonds, as in the case of kainic acid, the allokainic 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.

As for the stereochemical relations of the atoms in allokainic acid molecule, the carboxyl group of C_2 and the carboxymethyl group of C_3 take the *trans*-configuration relative to the ring. This relation is the same as that in kainic acid. The carboxymethyl group of C_3 and the isopropenyl group of C_4 are in the *trans*-configuration, while in kainic acid it was the *cis*-configuration. This fact supports the reasoning based on chemical evidences[8]. The relationship between the structure of kainic acid and allokainic acid is shown in Fig. 5. It is of interest that the anthelmintic effects of the two isomers are very different from each other due only to the configurations of their isopropenyl groups.

The five-membered pyrrolidine ring being fairly flexible, as found in the case of kainic acid, this ring is in the present case also considerably distorted from the planar form owing presumably to the influences of its side-chains and of the interactions between molecules. Deviations from the ordinary values of the bond angles of the pyrrolidine ring (108°, 108°, 106°, 104°, 104°) are found to be of the same order as those of hydroxyproline[9] (109°, 105°, 108°, 104°, 105°), the deviations being, however, smaller than those of kainic acid (108°, 104°, 103°, 102°, 105°) or zinc kainate[2] (105°, 110°, 102°, 105°, 102°).

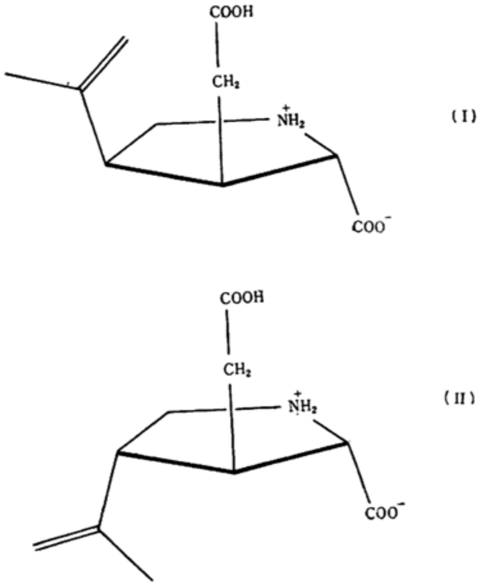

Fig. 5. Stereochemical configuration, (I) kainic acid, (II) allokainic acid.

Crystal Structure.—The projections of the crystal structure along the *b* and *c* axes are illustrated in Figs. 6 and 7 respectively, giving the intermolecular distances. The unit cell contains four zwitter ion molecules of allokainic acid. As a whole, the crystal structure resembles that of kainic acid[3].

From the short intermolecular N...O or O...O distances, three kinds of hydrogen bond are considered to be formed among the molecules. The two hydrogens of N^+H_2 form the intermolecular hydrogen bonds between the nitrogen of one molecule and the carboxyl groups $(COO)^-$ of other two molecules. These hydrogen bond distances are 2.82 Å for $N—H...O_1$ and 2.70 Å for $N—H...O_2$. The hydrogen of the oxygen O_3 of the carboxymethyl group also forms an intermolecular hydrogen bond between this group and the carboxyl group, its $O_3—H...O_1$ distance being 2.71 Å. The hydrogen bond angles are as follows:

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[8] 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).

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

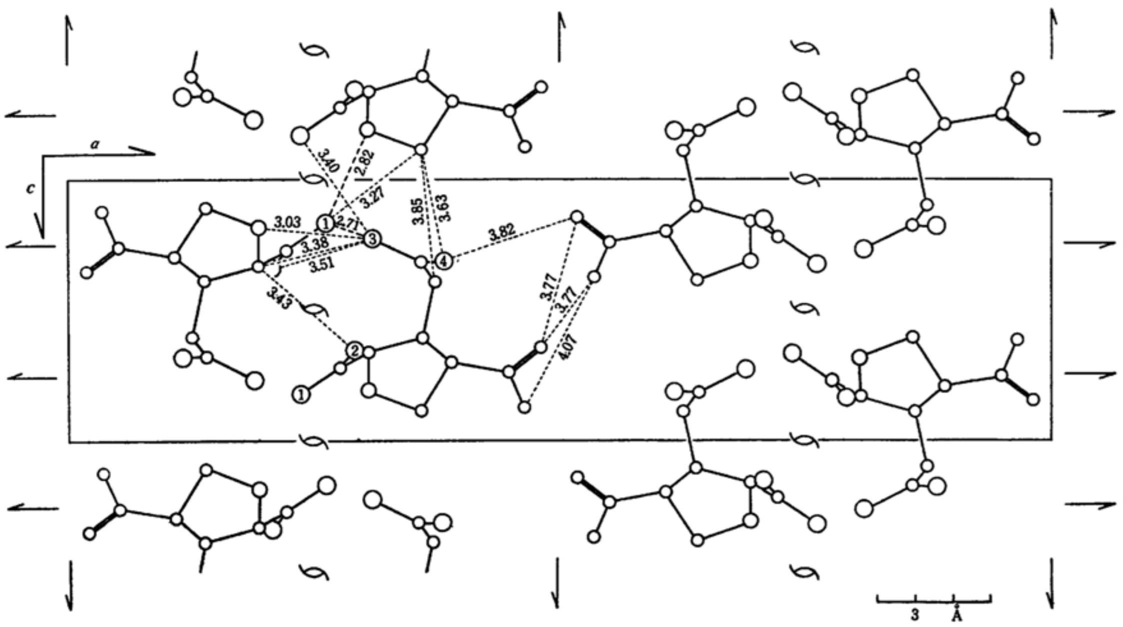

Fig. 6. View of the crystal structure along the *b* axis. The intermolecular distances are shown in Å. Large circles represent oxygens, intermediate nitrogens and small carbons.

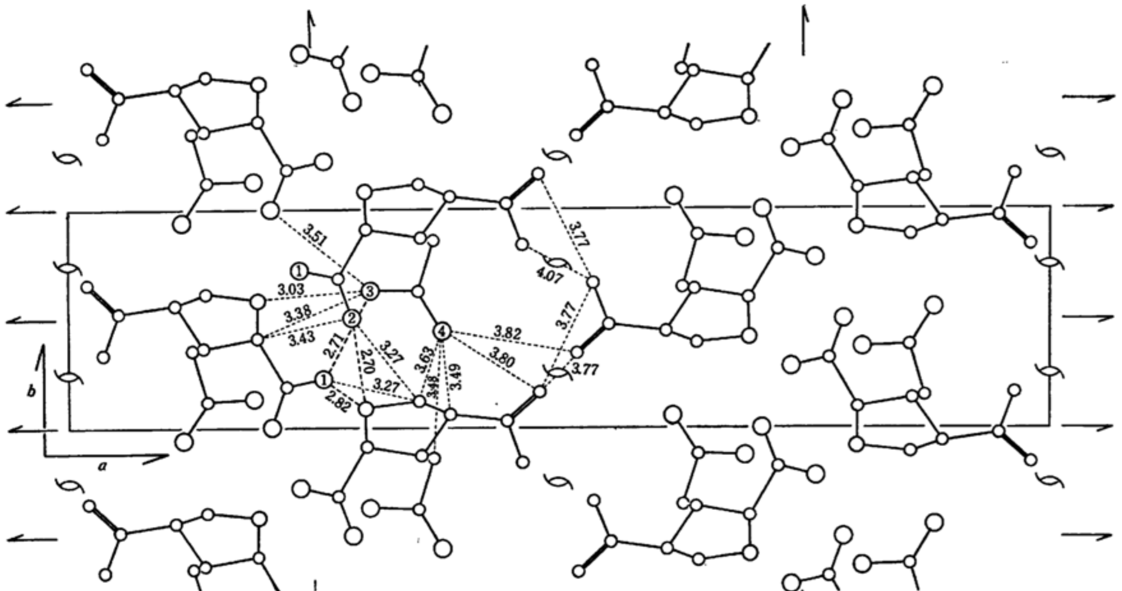

Fig. 7. View of the crystal structure along the *c* axis. The intermolecular distances are shown in Å. Symbols are the same as those of Fig. 6.

$C_2—N...O_1 = 144°$
$C_5—N...O_1 = 93°$
$O_1...N...O_2 = 93°$
$C_1—O_1...N = 139°$
$C_1—O_2...N = 132°$
$C_2—N...O_2 = 110°$
$C_5—N...O_2 = 98°$
$C_1—O_1...O_3 = 116°$
$O_3...O_1...N = 102°$
$C_7—O_3...O_1 = 114°$

By these hydrogen bonds, the molecules are linked to each other infinitely, forming a layered structure perpendicular to the *a* axis. Between the layers, the isopropenyl groups are in contact with each other, the distances of the closest approach being 3.77 Å for $C_9...C'_{10}$, 3.77 Å for $C_9...C''_{10}$, 3.77 Å for $C_{10}...C'_{10}$ and 4.07 Å for $C_9...C'_9$. It is compatible with the existence of the cleavage along the (1 0 0) plane.

The configuration of the isopropenyl group in allokainic acid being different from that of kainic acid as shown in Fig. 5, crystalline allokainic acid has no sufficient space to contain water of crystallization among molecules, while kainic acid crystallizes with one water molecule which is packed in the space and links the kainic acid molecules by forming the hydrogen bonds in addition to the other hydrogen-bridges such as described above. Corresponding to this difference between the crystal structures, allokainic acid is found to be much more soluble in water than kainic acid. In connection with this fact, it is of interest to note that, although zinc kainate easily crystallizes with two waters, the zinc salt of allokainic acid is too soluble in water to obtain crystals. The crystal structure of zinc kainate[2)] being, in a sense, similar to that of kainic acid[3)], it seems that in the case of zinc allokainate, water molecules may not be packed so as to link the molecules to form the crystal because of the configuration of the molecule.

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