Structural Studies of Tryptophan Metabolites by X-ray Diffraction Method. I. The Crystal and Molecular Structure of 5-Hydroxy-DL-Tryptophan

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5-Hydroxy-DL-tryptophan was crystallized from a methanol solution in the monoclinic space group C2/c, with cell-dimensions of $a=16.765$, $b=5.892$, $c=20.887$ Å, and $\beta=92.06°$. The molecular structure and stereoconfiguration have been elucidated by the direct method for non-primitive space group. A Fourier map, calculated with the largest 198 normalized structure factors as Fourier coefficients, revealed the whole structure which was refined by the least-squares method. The molecule is a zwitterion as in the crystal structure of amino acids, each amino nitrogen atom having an extra proton. The indole ring plane forms a dihedral angle of 40° with that formed by an acid group. With respect to the conformation about the C(α)–C(β) bond, the orientation of C(β)–C(γ) bond is *trans* with respect to the C(α)–COO^-. The molecules are arranged in double layers parallel to the *ab*-plane. The layer by polar groups is held together by a series of hydrogen bonds in a three-dimensional network, and by non-polar groups in the other layer, indole rings being stacked by van der Waals forces. The D- and L-forms of 5-hydroxytryptophan are hydrogen-bonded into two types of dimer related by the center of symmetry, one through N–H···O, and the other through O–H···O hydrogen bonding.

5-Hydroxytryptophan (5-HTP) was found as a precursor of 5-hydroxytryptamine (serotonin) in a metabolic pathway of tryptophan.[1-3] In animal tissues 5-HTP is decarboxylated to serotonin,[4] a similar reaction being observed between tryptophan and tryptamine.[5] Bell and Fellows have isolated 5-HTP as a free plant amino acid from seeds of *Griffonia simplicifolia*.[6] X-ray structure determination of tryptophan has been made by several authors because of its biochemical importance. With the exception of tryptophan hydrochloride,[7] their attempts did not succeed due to the difficulty of obtaining a good single crystal.[8-10] The pharmacological action of 5-HTP is also of interest, because of the fact that 5-HTP has excellent radiation protective ability.[11-13] Sano recently showed that 5-HTP is most effective for medical treatment of endogenous depression.[14] As a part of a programme of studies on the crystal and molecular structures of tryptophan metabolites, we performed the structure analysis on 5-hydroxy-DL-tryptophan. A preliminary result has been reported.[15] Refinement based on the three-dimensional photographic data has now been completed.

Experimental

5-Hydroxy-DL-tryptophan (Sigma Chemical Co.) was dissolved in methanol at room temperature and kept at 5 °C. Crystals were very thin colourless laths elongated parallel to the b-axis. Recrystallization of the commercial sample was extremely difficult. The crystal used for the determination of unit-cell parameters and for the collection of intensity data had dimensions of the order $0.03\times0.06\times0.75$ mm. Approximate lattice parameters were determined from oscillation and Weissenberg photographs taken around the b-axis, and were later refined by the precise measurement of the 2θ angles for 8 reflections on a Rigaku Denki manual four circle diffractometer. The systematic extinctions showed that the space group was either C2/c or Cc. From the distribution of the normalized structure magnitudes, a centro-

TABLE 1. CRYSTAL DATA OF 5-HYDROXY-DL-TRYPTOPHAN

$C_{11}H_{12}N_2O_3$, M.W. 220.23
colorless and transparent needles, Monoclinic
$a=16.765(9)$, $b=5.892(4)$, $c=20.887(9)$ Å
$\beta=92.06(4)°$
$V=2074.2$ Å^3, $Z=8$, $F(000)=928$
μ(for CuKα) $=10.0$ cm^{-1}
$D_m=1.405$ g/cm^3, $D_x=1.408$ g/cm^3
Absent spectra; (kkl) : $h+k=2n+1$
$(h0l)$: $l=2n+1$
Space group; C2/c

TABLE 2. STATISTICAL AVERAGES

	Experimental	Centrosymmetric	Noncentrosymmetric
$\langle\|E\|\rangle$	0.733	0.798	0.886
$\langle\|E^2-1\|\rangle$	0.962	0.968	0.736
$\langle\|E\|^2\rangle$	1.000	1.000	1.000

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symmetric space group C2/c was chosen as the correct space group. The crystal and physical data are given in Table 1. Intensity data were recorded on equi-inclination Weissenberg films of *h0l* to *h4l* zones, for a crystal rotating about the b-axis, using Cu$K\alpha$ radiation. Intensities were estimated visually by comparison with a calibrated film strip. These were corrected for spot size, Lorentz and polarization factors. Intensity data of 1084 non-zero reflections were then adjusted to the absolute scale and normalized structure factor E, and Σ_2 lists were computed. The statistical averages in Table 2 confirm that the crystal is centro-symmetric.

Determination and Refinement of the Structure

Phases for 5-hydroxy-DL-tryptophan were determined by means of the symbolic addition procedure by Hauptman and Karle. To specify the origin for non-primitive space group C2/c, two structure factors of large magnitude having linearly independent vectors were assigned as having positive signs.[16] Three other reflections whose signs were specified by symbols a, b, and c were chosen among reflections with many Σ_2 interactions. This starting set is shown in Table 3. By hand calculation, the phases of additional 193 reflections were determined in terms of the starting signs and letters. The three dimensional E-map, computed with the assignments a=b=c=−, revealed high peaks corresponding to each atom in the molecule.

TABLE 3. STARTING SET FOR SYMBOLIC ADDITION PROCEDURE

h	k	l	Phase	$\|E\|$
3	3	17	+	2.88
8	2	−17	+	2.84
1	3	16	a	4.23
8	2	−14	b	3.61
7	1	−18	c	2.93

The map has no spurious peaks of density greater than that of the 16 non-hydrogen atoms. None of the phases was subsequently found to be incorrect when compared with the phase corresponding to the fully refined structure. The positional coordinates of the sixteen atoms as selected from the E-map were subjected to the structure factor calculation and the three-dimensional Fourier synthesis. At this stage, the discrepancy factor $R=\Sigma||F_o|-|F_c||/\Sigma|F_o|$ was 0.32. The structure was refined by successive Fourier syntheses and least-squares method based on only the observed non-zero reflections; using the isotropic thermal parameters for all the nonhydrogen atoms, the R index converged to 0.20 after 5 cycles. The difference synthesis was then computed to obtain the hydrogen atoms. The peaks of the twelve hydrogen atoms clearly appeared on this map, where their heights are within the range 0.3—0.8 e.Å^{-3}. It was confirmed that the molecule of 5-hydroxy-DL-tryptophan exists as a zwitterionic form in crystalline state. The block-diagonal approximation was used for the least-squares refinement. This refinement proceeded including these hydrogen atoms and applying the anisotropic temperature factors for nonhydrogen atoms. Since the shifts in the positional parameters in the final cycle were less than one tenth of the estimated standard deviations, the refinement was terminated at this stage. It was thought that the unfavorable shape of the crystal resulted in a rather high R factor of 0.119. Observed and calculated structure factors from the last cycle are given in Table 4, and the atomic coordinates and thermal parameters with their estimated standard deviations in Table 5. Overall isotropic temperature factor for hydrogen atoms was also refined, the final value being 2.2 Å^2. A difference Fourier map synthesized with the phases by only heavy atom contributions and the final electron density map for the heavy atoms are illustrated in Fig. 1.

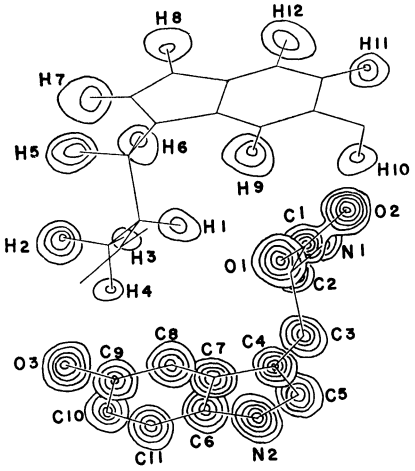

Fig. 1. Superimposed three-dimensional electron-density distribution for the heavy atoms (the lower half) and the hydrogen atoms (the upper half), viewed along the b-axis; contours at intervals of 2 e.Å^{-3} for the heavy atoms, and 0.2 e.Å^{-3} for the hydrogen atoms.

All the numerical calculations were carried out on an NEAC 2200-500 computer of this University, a HITAC 5020 E in the computing center, the University of Tokyo, and a FACOM 230-60 in the data processing center, Kyoto University, using the programs written by Dr. Tamaichi Ashida and by the authors.

Description and Discussion of the Structure

Bond Lengths and Angles. The bond distances and valency angles in the molecule are shown in Fig. 2; the average standard deviations are about 0.012 Å for bonds and 0.8° for angles. The average of six C–C bond lengths in the six-membered ring is 1.382 Å, while that of C–N bonds in the five-membered ring is 1.384 Å. The C(10)—C(11) bond (1.352 Å) is significantly shorter than the mean value taken from other indole derivatives, such a short distance being found only in 5-methoxy-(*N*,*N*)-dimethyltryptamine hydrochloride (1.360 Å).[17] As expected, the molecule is a zwitterion, with an amino nitrogen atom accepting a proton from an acid group and assuming the tetrahedral configuration C–NH_3^+. The value

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TABLE 4. OBSERVED AND CALCULATED STRUCTURE AMPLITUDES FOR 5-HYDROXY-DL-TRYPTOPHAN

The columns in each group headed by the values of h and k give l, $10|F_o|$, and $10|F_c|$.

L	FO	FC	L	FO	FC	L	FO	FC	L	FO	FC	L	FO	FC	L	FO	FC	L	FO	FC	L	FO	FC	L	FO	FC
H,K=	0	0	8	49	-49	0	95	-86	6	11	9	5	35	-33	2	4	-4	16	93	-96	12	41	-56	-3	4	-4	-2	28	-22
4	41	-34	10	18	-22	1	8	7	8	8	7	6	54	45	3	32	-25	17	45	-42	15	36	-32	-4	25	-27	-3	19	-19
6	283	320	18	45	-33	2	6	-7	12	28	26	7	21	27	4	44	48	18	14	18	18	13	-8	-5	9	-10	-4	12	17
8	88	82	-2	7	6	3	23	-25	14	13	11	8	65	64	6	18	-17	19	30	25	21	7	-8	-13	3	-2	-5	30	-33
10	48	41	-4	30	26	4	41	-44	15	30	27	9	67	-60	7	35	-42	21	10	13	-1	13	-12	H,K=	19	3	-6	28	-22
12	59	-52	-6	26	-23	5	62	-69	16	14	10	10	64	-59	8	13	-16	22	66	-71	-2	26	25	0	6	-7	-8	35	-27
16	33	27	-12	36	-25	7	22	-22	21	23	23	11	33	-30	10	14	-18	23	15	-20	-3	9	-12	1	11	-12	-10	45	45
18	61	-56	-14	43	37	8	30	-29	-1	13	-10	12	71	60	11	18	19	-1	11	5	-4	21	-17	2	6	-8	-11	22	-18
20	39	30	-18	37	-29	9	35	-37	-2	30	-25	13	33	34	13	16	-18	-2	6	-5	-5	26	26	3	6	-6	-12	24	-17
22	43	40	H,K=	14	0	10	29	-28	-3	35	-29	14	52	45	14	37	-31	-3	67	59	-6	62	55	4	11	12	-15	14	12
24	15	-15	0	40	-42	11	49	-54	-4	21	-19	15	37	-33	15	35	25	-4	79	-76	-7	27	-28	5	11	-11	-16	12	10
26	13	18	2	32	29	12	15	18	-5	21	-19	16	57	-57	16	59	-52	-6	66	-52	-8	49	-59	-1	9	-7	-18	33	-28
H,K=	2	0	4	58	68	13	33	-26	-7	23	20	18	21	-21	17	24	19	-7	38	29	-9	13	-17	-5	7	-9	-20	2	2
0	78	-92	6	61	-59	19	20	-17	-8	17	15	19	24	22	19	20	-17	4	43	-30	-10	34	-31	H,K=	0	4	H,K=	8	4
2	98	107	10	37	36	20	20	19	-10	41	-35	24	37	-40	20	10	-6	-9	58	50	-11	31	28	2	20	22	0	25	-22
4	87	99	12	43	-40	23	22	30	-13	39	34	-1	17	-14	21	27	25	-10	28	-19	-12	15	12	4	8	10	1	19	-19
6	30	-20	14	34	-35	-1	21	-15	-14	19	16	-2	38	-31	22	16	-15	-11	15	11	-13	10	-11	5	9	4	2	6	8
8	65	63	-2	29	28	-2	43	-44	-15	24	24	-3	48	-45	23	13	12	-12	46	-35	-14	62	-63	6	19	-14	3	15	-9
10	21	13	-8	68	-70	-3	6	-7	-18	23	22	-4	131	-135	-1	14	16	-13	24	16	-16	36	-33	7	37	-35	4	27	26
12	70	61	-10	64	-65	-4	46	42	-20	21	-24	-5	74	-66	-2	68	73	-14	52	-42	-17	11	15	8	21	21	5	12	14
14	55	43	-12	40	30	-5	7	8	-23	12	-14	-6	92	-86	-3	32	-25	-18	23	-16	-18	13	-16	9	19	-20	6	28	-28
18	39	37	-14	64	-59	-7	8	-9	H,K=	13	1	-7	9	10	-4	17	-19	-23	19	-26	-19	12	-7	10	28	25	7	10	13
20	18	18	-16	64	-71	-8	24	-14	0	47	51	-8	57	51	-6	68	-64	-24	23	-23	-21	22	24	11	29	23	8	21	21
24	29	29	H,K=	16	0	-9	34	-29	1	32	-25	-10	54	-40	-7	15	15	H,K=	3	3	H,K=	9	3	12	41	-40	12	10	-3
-2	104	111	0	38	28	-10	56	-62	2	43	-40	-11	42	-43	-8	36	-35	0	44	-44	0	15	12	13	8	6	16	25	-16
-4	51	-46	2	39	35	-11	28	-19	3	18	15	-12	41	-39	-9	11	-10	1	10	-10	1	8	5	14	14	13	17	23	-22
-6	97	-89	4	38	-39	-12	35	32	4	37	-29	-13	9	11	-10	14	-14	2	29	26	3	28	28	15	31	-26	18	3	5
-8	24	21	8	18	22	-13	16	-14	5	39	-31	-14	28	24	-11	52	55	3	17	12	4	44	-50	18	18	-14	-1	15	18
-10	48	-39	-2	37	-34	-14	16	17	7	33	-30	-15	22	21	-12	28	-24	4	15	-11	7	14	17	19	32	16	-2	48	56
-12	74	-61	-12	16	-15	-15	24	-26	9	14	17	-16	35	38	-14	91	-101	5	10	-13	9	26	21	20	33	40	-3	29	-28
-14	82	-83	H,K=	18	0	-16	63	-60	10	19	-19	-17	11	12	-15	36	-33	6	22	21	10	28	-28	21	6	-6	-4	17	-17
-18	35	36	2	21	17	-17	28	-24	12	45	-53	-18	33	38	-16	21	-22	7	10	-12	11	13	-16	H,K=	2	4	-5	57	-61
-20	49	-54	-4	29	22	-20	37	-30	13	25	-24	-23	20	17	-17	58	61	8	19	15	16	24	-22	0	12	5	-6	21	-20
-24	33	31	-6	31	23	-26	41	-42	14	17	19	-24	19	18	-19	16	15	9	32	28	17	20	-17	1	19	12	-8	43	43
H,K=	4	0	-8	42	33	H,K=	7	1	18	23	-25	-25	21	19	-20	34	-33	10	17	16	18	13	-13	2	38	45	-9	11	-10
0	209	-235	-10	14	14	0	42	36	-1	55	-56	H,K=	4	2	-21	29	-32	11	41	35	-1	10	-14	3	33	-40	-11	32	-32
2	206	-219	-14	22	20	1	65	71	-2	12	-13	0	8	7	-23	13	17	12	47	41	-2	32	-24	5	38	-43	-12	29	21
4	87	-102	H,K=	20	0	2	11	9	-4	26	-25	1	45	41	H,K=	10	2	13	31	-26	-3	12	-14	6	14	-14	-13	14	-12
6	123	-149	0	13	10	3	46	-46	-6	35	32	2	37	32	0	28	-19	14	30	20	-4	60	-64	7	28	24	-17	17	19
8	116	-130	-6	38	37	4	39	-35	-7	35	-28	3	3	2	1	25	19	15	41	35	-5	35	-39	8	2	1	-18	31	37
10	88	-97	H,K=	1	1	6	72	-82	-8	19	-20	4	43	41	3	19	-17	16	13	14	-6	35	-30	9	9	-9	-19	8	-7
12	51	-49	1	59	-67	8	40	39	-9	19	-20	6	42	51	4	16	-16	17	57	53	-8	26	22	10	3	-2	-20	16	14
20	9	6	2	61	65	9	51	-56	-15	24	-21	8	42	47	5	9	-10	19	37	-36	-9	36	-36	11	11	-11	H,K=	10	4
-4	76	-60	3	231	216	10	14	17	-18	32	-39	9	36	-35	6	30	-37	23	29	28	-10	59	-62	13	25	21	0	13	-16
-6	51	-38	4	198	208	12	49	-54	-21	27	-30	10	28	26	8	15	-17	24	5	-8	-11	65	-73	14	28	-20	1	17	21
-8	61	44	5	49	50	14	13	-13	H,K=	15	1	11	42	-36	18	25	-22	-1	56	-60	-12	55	-60	15	28	22	2	16	10
-16	25	19	6	187	-193	15	31	-30	1	24	20	12	19	18	-2	34	-28	-2	85	-99	-16	16	-20	17	24	21	3	12	11
-18	40	-33	7	62	-51	18	28	28	3	19	-24	14	37	32	-4	15	-12	-3	8	9	-17	37	-36	19	16	-19	4	37	36
-20	54	-54	8	13	-15	22	32	-37	6	19	14	15	35	-26	-5	37	36	-4	6	-2	-18	14	-15	20	32	-37	5	23	-20
-24	32	-30	9	75	70	24	32	32	7	30	34	16	57	53	-6	17	20	-5	34	-26	-22	10	9	21	8	7	6	8	6
-26	23	-24	10	129	109	-1	40	30	8	20	20	17	45	-34	-7	36	39	-6	27	-17	H,K=	11	3	22	26	34	10	32	38
H,K=	6	0	12	56	-56	-2	43	-42	9	13	-18	20	26	-22	-9	31	24	-7	31	-25	0	31	-30	-1	28	-29	11	8	-5
2	109	-122	13	31	-23	-3	10	9	10	23	-26	22	33	34	-10	37	-33	-8	33	-23	1	26	-26	-2	13	6	12	40	32
4	64	-67	14	22	-17	-4	37	-30	13	21	17	23	25	-34	-11	22	21	-9	2	-1	4	32	-31	-3	25	-23	13	13	-17
8	41	-31	15	31	-26	-5	134	120	15	15	-14	24	27	27	-13	41	44	-10	5	8	5	21	24	-4	16	12	15	26	-19
10	50	-50	16	12	-18	-6	40	34	16	23	-25	-1	42	39	-16	29	-26	-11	12	16	6	30	-35	-5	30	26	16	20	12
12	73	-85	17	23	-16	-7	47	45	17	16	-20	-2	3	2	-22	19	-21	-13	24	20	7	26	-33	-6	27	20	-1	45	-47
16	21	13	20	20	16	-8	9	-8	-1	14	-11	-3	51	45	H,K=	12	2	-14	52	49	9	16	-20	-7	37	32	-3	15	15
18	64	-47	21	27	-38	-10	19	18	-2	58	59	-4	29	25	0	30	-34	-16	59	63	10	26	-25	-8	41	31	-4	8	6
20	22	-16	25	23	27	-11	54	56	-3	24	-32	-5	54	45	1	10	10	-17	11	-12	11	14	18	-9	20	15	-5	29	23
-2	81	79	-1	38	-33	-12	33	-24	-5	19	-19	-6	44	38	7	27	27	-18	11	11	12	8	-8	-10	6	2	-6	12	-14
-4	85	82	-2	30	24	-13	19	18	-6	58	-60	-8	7	8	8	43	-45	-20	34	29	13	30	-21	-11	15	15	-7	48	-48
-6	78	-70	-3	161	147	-14	31	28	-7	19	-20	-9	31	27	9	22	23	-22	29	36	14	11	-13	31	19	-8	8	-9	
-8	75	65	-4	54	-49	-15	6	-7	-8	36	32	-10	23	21	15	35	28	-23	7	-5	15	12	-15	-15	24	25	-10	16	14
-10	84	92	-5	49	-42	-16	23	24	-11	27	-24	-12	46	43	16	15	15	H,K=	5	3	-2	20	-15	-16	14	14	-14	11	-9
-12	27	-24	-6	138	139	-18	71	-71	-12	27	-27	-13	22	-24	17	14	-16	1	45	-47	-3	14	20	-17	14	11	-15	18	-17
-14	26	20	-7	85	-87	-20	42	49	-13	18	-18	-14	34	35	18	9	11	2	54	53	-4	15	18	-18	22	20	-16	13	17
-16	49	-40	-8	58	-58	-21	18	19	H,K=	17	1	-15	7	6	-3	15	-17	3	33	-32	-6	10	13	-20	13	-11	-17	17	-23
-18	28	-21	-9	14	12	-22	36	38	10	16	18	-16	64	66	-4	81	95	4	33	34	-7	46	-43	-22	11	-12	-18	23	28
-22	67	-72	-10	33	-31	-23	21	-28	12	20	15	-18	21	25	-9	14	-13	5	13	12	-8	37	39	H,K=	4	4	-19	26	28
-24	28	29	-11	9	10	-24	27	-37	-14	13	-15	-19	17	-21	-10	57	58	6	11	10	-13	39	-39	0	9	8	H,K=	12	4
H,K=	8	0	-12	63	71	H,K=	9	1	-15	15	18	-22	42	46	-11	12	-10	7	9	11	-14	34	32	1	23	-24	1	4	1
0	19	14	-13	34	-27	0	44	41	H,K=	19	1	-25	16	-16	-12	15	14	8	11	11	H,K=	13	3	2	32	-37	3	9	-12
2	53	44	-14	47	-44	1	35	-33	1	11	12	H,K=	6	2	-14	26	21	10	24	28	0	19	19	4	23	-25	4	23	-24
4	4	4	-15	33	-27	2	39	40	2	14	-14	0	99	99	-17	19	-18	13	49	36	1	32	29	5	28	32	5	25	26
6	68	70	-17	37	30	3	28	27	3	11	13	1	43	38	-19	22	-18	14	55	-43	2	25	-28	6	26	27	-1	45	47
8	68	66	-18	34	31	5	28	29	4	3	-2	2	34	-30	H,K=	14	2	15	22	19	3	11	12	7	31	-35	-2	45	-46
12	82	89	-20	32	27	6	22	14	5	15	15	3	43	36	1	37	-47	16	53	47	4	17	18	9	19	18	-3	11	12
14	19	16	-21	19	-22	7	14	-13	8	11	-14	4	36	32	15	28	-24	17	28	-23	6	16	20	10	44	-56	-8	33	-31
16	24	-22	-25	13	15	8	24	18	-1	16	22	5	20	-19	-1	24	-23	18	30	26	8	12	-18	11	53	48	-10	23	-23
18	44	41	-26	26	31	9	16	17	-3	11	11	6	78	103	-2	26	23	19	28	24	-1	25	27	12	17	13	-12	9	5
-2	38	-30	H,K=	3	1	10	38	40	-5	16	13	7	16	15	-3	16	18	20	24	-24	-2	39	38	13	33	-25	-13	25	-32
-6	21	16	0	19	-17	11	27	30	-7	15	17	8	12	-8	-5	45	-56	21	15	15	-4	32	30	14	37	33	-14	12	14
-8	76	-70	1	34	26	12	13	14	-10	18	19	9	22	23	-6	33	37	22	17	17	-5	34	30	15	11	10	-15	7	3
-10	21	15	2	50	48	13	13	16	H,K=	21	1	17	42	34	-7	41	-45	-1	17	15	-6	11	14	16	14	-16	-16	20	-25
-12	81	78	3	51	48	14	24	-20	-4	16	21	18	21	-16	-9	24	23	-2	26	21	-7	45	43	17	29	25	-17	14	12
-14	50	-39	4	12	12	15	19	18	H,K=	0	2	20	33	33	-11	20	-18	-3	32	-26	-8	18	17	-3	9	1	H,K=	14	4
-18	62	50	5	34	29	16	24	18	2	90	-98	21	34	-32	-12	39	46	-4	91	91	-10	47	52	-4	31	-25	1	13	13
-20	60	55	7	38	35	17	20	13	3	101	93	23	20	23	-13	19	-17	-5	41	-38	-11	8	6	-5	32	25	10	26	-14
-24	36	-39	8	38	-39	19	23	18	4	88	-80	-1	23	-19	-18	15	-18	-6	40	30	-12	15	-13	-6	27	27	11	8	-5
H,K=	10	0	10	9	7	20	17	-16	5	31	25	-2	75	75	H,K=	16	2	-7	11	10	-13	33	31	-9	6	4	12	20	-12
0	61	-57	11	13	-11	22	16	21	6	76	-63	-3	45	40	13	19	-17	-8	23	14	-16	26	30	-10	34	-31	-1	19	18
4	58	51	12	42	35	-1	42	34	7	33	-29	-4	61	53	-2	33	-37	-9	10	-6	-18	36	-40	-11	52	49	-3	16	15
6	13	12	16	8	7	-3	58	58	8	56	-51	-5	13	-12	-4	16	-17	-10	23	14	H,K=	15	3	-12	8	11	-4	9	10
10	46	46	17	18	-15	-4	30	-28	9	139	136	-6	22	-24	-5	21	17	-11	16	18	0	16	14	-13	13	15	-5	14	14
12	50	54	20	20	-19	-7	43	41	10	53	49	-7	34	-27	H,K=	18	2	-12	48	51	1	32	33	-17	23	15	-7	14	15
14	28	25	26	22	-23	-8	44	43	11	39	34	-8	12	-13	0	15	-14	-13	32	34	6	24	20	-20	32	-41	-8	22	-20
18	17	12	-1	17	15	-9	58	59	12	75	-74	-9	25	22	2	17	-15	0	74	81	-12	18	17	4	35	-35	7	16	-14
20	31	24	-2	71	-77	-10	11	7	13	46	-43	-10	45	39	1	18	19	-14	53	51	7	22	21	-21	6	-8	-12	8	6
-2	36	-29	-3	31	30	-11	17	14	14	54	-54	-11	49	-46	-1	11	14	-17	16	20	8	24	22	-22	16	-13	-13	11	11
-4	34	-23	-4	29	24	-15	31	21	15	61	54	-12	28	-28	-2	21	-24	-18	18	19	-5	22	19	H,K=	6	4	-14	18	-20
-6	29	-23	-5	60	-60	-16	37	32	16	7	7	-13	52	-51	-5	21	20	-19	40	41	-6	11	-9	1	15	14	-15	9	-15
-8	9	-11	-6	77	77	-17	30	25	18	31	-25	-15	16	16	H,K=	1	3	-24	11	10	-9	14	16	2	49	-54	H,K=	16	4
-10	45	34	-7	57	-46	-18	42	35	19	34	-28	-16	31	-23	1	33	-37	H,K=	7	3	-10	3	3	17	16	0	10	15	
-12	29	25	-8	11	10	-19	39	-34	20	16	-21	-17	37	-35	2	17	-15	0	74	81	-12	18	17	4	35	-35	7	16	-14
-14	21	20	-9	43	-36	-20	13	-11	21	11	13	-18	8	-7	3	18	12	1	30	23	-13	12	-15	5	16	-18	-2	15	17
-16	72	81	-10	45	-37	-23	29	36	22	36	-34	-19	33	-26	4	55	48	2	20	17	-14	15	-18	6	11	16	-12	11	-8
-18	53	54	-11	82	-87	-24	15	16	25	7	-7	-21	22	22	5	19	-18	4	40	43	H,K=	17	3	7	27	35	H,K=	18	4
-22	35	42	-13	35	-36	H,K=	11	-1	H,K=	2	7	-22	20	-21	6	11	-13	5	23	24	0	9	-7	8	38	-43	1	18	-19
-24	9	14	-14	36	33	0	18	-15	0	51	-46	-23	9	-12	7	7	-9	6	5	-10	1	22	-21	9	35	45	-2	10	-10
H,K=	12	0	-15	24	-22	1	40	-35	1	36	-32	-24	26	26	9	26	-23	7	12	10	2	9	-10	10	12	-12	-5	11	-10
2	33	-33	-17	46	-45	2	15	18	2	5	-3	H,K=	8	2	10	8	6	8	23	23	3	11	-10	13	11	9			
4	24	22	-22	19	-24	3	32	-26	3	53	-57	0	37	-29	11	45	-40	9	13	-12	7	17	-17	14	16	-14			
6	46	43	H,K=	5	1	5	11	-7	4	47	-47	1	42	-45	12	46	42	10	31	37	9	7	-9	15	11	12			
															13	45	42	11	26	30	-2	22	-19	20	10	13			

of 1.491 Å for the C(2)—N(1) bond length is in good agreement with the average value, C–N$^+$=1.487 Å, for α-amino acids.[18] In the ionized carboxyl group, the two C–O distances differ significantly, and C(1)–O(2) bond length (1.283 Å) is somewhat longer than that usually observed in many COO$^-$ groups. This might be explained by the fact that the O(2) atom is an acceptor of two short hydrogen bondings. The angle C(α)–C(β)–C(γ) is significantly larger than the tetrahedral value, the value 114.9° being very close to a mean angle of 114° of the examined 27 compounds.[19]

Planarity of the Molecule. As far as tryptophan derivatives are concerned, the conformation of a molecule as a whole can be well described in the two

18) R. E. Marsh and J. Donohue, *Advan. Protein Chem.*, **22**, 235 (1967).

19) G. N. Ramachandran and A. V. Lakshminarayanan, *Biopolymers*, **4**, 495 (1966).

Table 5. Fractional coordinates and thermal parameters with standard deviations ($\times 10^4$)
The anisotropic temperature factors are in the form of $\exp[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)]$.

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C (1)	0.3793 (4)	0.7124 (15)	0.0032 (3)	0.0014 (3)	0.0079 (33)	0.0005 (1)	−0.0025 (14)	0.0004 (3)	0.0016 (10)
C (2)	0.3568 (5)	0.4858 (15)	0.0339 (3)	0.0021 (3)	0.0074 (33)	0.0004 (1)	−0.0002 (15)	0.0012 (3)	−0.0016 (10)
C (3)	0.3744 (4)	0.4831 (14)	0.1049 (3)	0.0018 (3)	0.0068 (32)	0.0001 (1)	−0.0007 (15)	0.0006 (3)	−0.0011 (9)
C (4)	0.3348 (5)	0.3021 (14)	0.1396 (3)	0.0024 (3)	0.0050 (33)	0.0001 (1)	0.0035 (15)	0.0005 (3)	−0.0015 (9)
C (5)	0.3683 (5)	0.1148 (15)	0.1690 (3)	0.0021 (3)	0.0091 (35)	0.0007 (2)	0.0007 (16)	0.0011 (4)	−0.0012 (11)
C (6)	0.2372 (5)	0.0880 (15)	0.1843 (3)	0.0028 (3)	0.0059 (33)	0.0001 (1)	−0.0006 (15)	0.0008 (3)	0.0015 (9)
C (7)	0.2500 (4)	0.2876 (14)	0.1484 (3)	0.0020 (3)	0.0042 (31)	0.0000 (1)	0.0020 (14)	0.0003 (3)	0.0011 (9)
C (8)	0.1874 (4)	0.4281 (15)	0.1321 (3)	0.0014 (3)	0.0112 (34)	0.0001 (1)	0.0012 (14)	0.0001 (3)	0.0001 (9)
C (9)	0.1116 (5)	0.3623 (16)	0.1472 (3)	0.0016 (3)	0.0153 (36)	0.0004 (1)	0.0008 (15)	0.0005 (3)	0.0025 (11)
C (10)	0.1007 (5)	0.1628 (16)	0.1823 (3)	0.0019 (3)	0.0143 (38)	0.0006 (2)	−0.0033 (16)	0.0004 (3)	0.0037 (11)
C (11)	0.1615 (5)	0.0241 (17)	0.2008 (3)	0.0029 (4)	0.0196 (40)	0.0004 (1)	−0.0072 (19)	0.0011 (4)	−0.0004 (11)
N (1)	0.4011 (4)	0.2985 (13)	0.0030 (3)	0.0036 (3)	0.0097 (29)	0.0003 (1)	−0.0009 (15)	0.0012 (3)	0.0024 (9)
N (2)	0.3100 (4)	−0.0154 (14)	0.1968 (3)	0.0032 (3)	0.0135 (31)	0.0006 (1)	0.0047 (15)	0.0018 (3)	0.0017 (10)
O (1)	0.3426 (4)	0.8794 (12)	0.0217 (3)	0.0039 (3)	0.0157 (28)	0.0015 (2)	−0.0008 (14)	0.0020 (3)	0.0008 (10)
O (2)	0.4358 (3)	0.7093 (10)	−0.0366 (3)	0.0022 (2)	0.0103 (24)	0.0013 (1)	0.0019 (11)	0.0027 (3)	0.0047 (9)
O (3)	0.0447 (3)	0.4804 (14)	0.1291 (3)	0.0015 (2)	0.0460 (35)	0.0015 (2)	0.0043 (14)	0.0017 (3)	0.0123 (12)
H (1)	0.290	0.460	0.022						
H (2)	0.464	0.290	0.019						
H (3)	0.379	0.159	0.019						
H (4)	0.412	0.432	−0.026						
H (5)	0.441	0.460	0.111						
H (6)	0.357	0.639	0.122	Final thermal parameter for hydrogen atoms: overall isotropic; 2.2 Å^2					
H (7)	0.429	0.076	0.172						
H (8)	0.319	−0.161	0.224						
H (9)	0.199	0.580	0.104						
H (10)	0.050	0.600	0.096						
H (11)	0.041	0.124	0.193						
H (12)	0.152	−0.133	0.228						

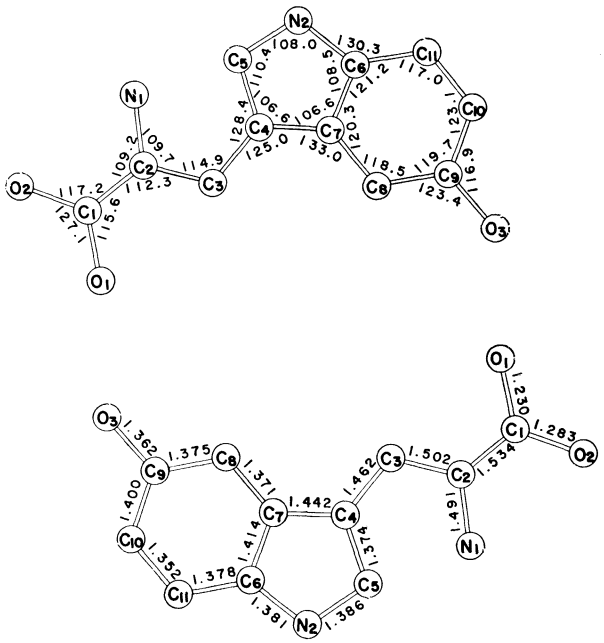

Fig. 2. Bond distances and angles of 5-hydroxy-DL-tryptophan. The standard deviation for the bond lengths ranges between 0.011 and 0.013Å. The standard error for the angles is approximately 0.8°.

planes which consist of the indole ring and the acid group. The equations of the least-squares planes are: for the indole ring, $0.0846X+0.5114Y+0.8552Z=3.8776$ and for the carboxyl group with α-carbon, $0.6536X+0.1469Y+0.7425Z=4.8350$ in rectangular Ångstrom space. These two planes form a dihedral angle of 40.1°, which is considerably differing from 70.6° in L-tryptophan hydrochloride.[7] This is attributed to the difference in conformation of the ionized carboxyl group. The deviations of the individual atoms from the best planes are given in Table 6. It is concluded that nine atoms of indole ring and C(β) atom are almost in a plane within the limit of experimental error.

Table 6. Deviations (Å) of atoms from the best plane

Indole group		Acid group	
Atom	Distance	Atom	Distance
C (4)	0.009	O (1)	−0.005
C (5)	0.003	O (2)	−0.005
N (2)	−0.017	C (1)	0.013
C (6)	−0.001	C (2)	−0.003
C (7)	0.017		
C (8)	−0.028	*N (1)	0.137
C (9)	0.009	*C (3)	−1.260
C (10)	0.003		
C (11)	0.005		
*O (3)	0.070		
*C (3)	0.025		
*C (2)	1.305		
*H (10)	0.290		

* Excluded from the least-squares calculations. The mean deviation from the indole ring is 0.010 Å and that from the acid group 0.007 Å.

However, the O(3) atom of the hydroxyl group is 0.07 Å out of the plane as found in serotonin picrate monohydrate.[20] The amino nitrogen atom is 0.137 Å, being displaced from the acid plane as in α-amino acid, the N(1)–C(2) bond forming an angle of 5.4° with this plane.

Molecular Conformation. As shown in Fig. 3, in the present molecule, the C(β)–C(γ) bond lies at *trans* position to the C(α)–COO^- bond and *gauche* to the C(α)–NH_3^+ bond. Similar conformations have been observed in glycyl-L-tryptophan dihydrate[21] and DL-tryptophan formate.[22] On the other hand, L-tryptophan hydrochloride occurs in a different conformation, and the orientation of C(β)–C(γ) bond moves to *gauche* position with respect to both the C(α)–COOH and C(α)–NH_3^+. In the case of tryptophan, Ramachandran and Lakshminarayanan pointed out that C(γ) atom should take I or III position in Fig. 3.[19] Some torsion angles are given in Table 7.

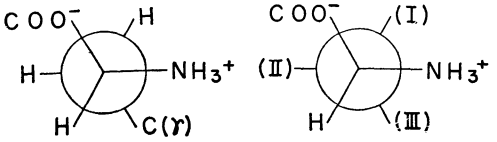

Fig. 3. Newman projections about C(α)–C(β) bond.

Table 7. Torsion angles

C(5)–C(4)–C(3)–C(2)	±110.7°
C(4)–C(3)–C(2)–C(1)	±163.6°
C(4)–C(3)–C(2)–N(1)	± 74.8°
C(10)–C(9)–O(3)–H(10)	±165.9°

Two Modes of Dimers. An interesting aspect of this crystal structure is the hydrogen-bonding scheme. The D- and L-forms of 5-hydroxytryptophan are hydrogen-bonded into two types of dimers related by center of symmetry. Molecule (A) is an original molecule whose coordinates are given in Table 5. Two molecules (A) and (B) or (A) and (C) form DL-dimer in solid state. The A-B type of dimer is a typical cyclic dimer[23] joined through O(3)–H(10)···O(2) hydrogen bonding (2.688 Å). Another type (A-C dimer) is a nonplanar dimer[23] linked together by an N(1)–H(2)···O(2) hydrogen bridge (2.798 Å). This hydrogen-bonded dimer has been found in the crystal structure of DL-valine.[24] Judging from the distances of the hydrogen bonds and the molecular packing in crystals, we suppose that A-B dimers are originally formed in solution and then the crystallization is performed by A-C dimerization.

20) U. Thewalt and C. E. Bugg, *Acta Crystallogr.*, **B28**, 82 (1972).
21) R. A. Pasternak, *ibid.*, **9**, 341 (1956).
22) E. Bye, A. Mostad, and C. Römming, to be published in *Acta Chem. Scand.* (1973).
23) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," ed. by L. Pauling, W. H. Freeman and Company, San Francisco and London (1960), p. 100.
24) M. Mallikarjunan and S. T. Rao, *Acta Crystallogr.*, **B25**, 296 (1969).

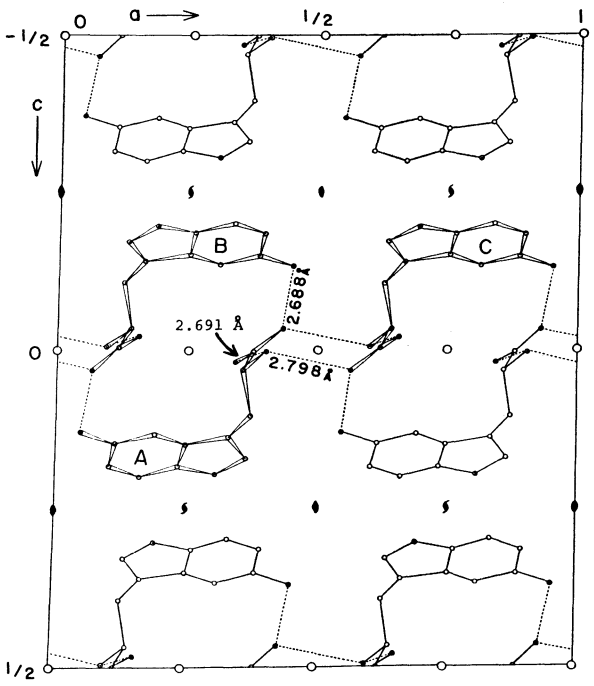

Fig. 4. Molecular packing of 5-hydroxy-DL-tryptophan as seen along the b-axis. The dotted lines show hydrogen bonds.

Packing of the Molecules. The packing in the structure is illustrated in Fig. 4. The molecules are arranged in double layers parallel to (001), and connected through hydrogen bondings described above. The third hydrogen bond of 2.691 Å is observed between the N(1) atom and the O(1) atom (Table 8). By this linkage along b-axis, dimers are connected into an infinite three-dimensional network. It is of considerable interest that the nitrogen atom of the indole ring is not involved in any hydrogen bonds, and nonpolar indole planes are stacked by van der Waals forces. All the intermolecular contacts of less than 3.5 Å between pairs of non-hydrogen atoms are summarized in Table 8. All the atoms other than C(2), C(3), C(4), C(6), and C(7) have one or more intermolecular neighbors within 3.5 Å. Unusually close contact (3.201 Å) is found between C(5) and O(3) of the adjacent molecule. The distance of H(7)···O(3) is 2.24 Å and the C(5)–H(7)–O(3) angle is 153±6°. This might suggest that this short contact arises from hydrogen bonding of the C–H···O type described by Sutor.[25] This work was partly supported by a research grant from the Ministry of Education.

TABLE 8. INTERMOLECULAR DISTANCES LESS THAN 3.5 Å

(a) Hydrogen bonds

Donor	Acceptor	Distance	Angle formed by carbon atom-Donor-Acceptor
O(3)–H(10)	O(2) on (B)	2.688 Å	115.3°
N(1)–H(2)	O(2) on (C)	2.798	113.7°
N(1)–H(3)	O(1) on (D)	2.691	115.2°

(b) Other distances

Atom cn (A)	Atom	Distance
O(1)	C(8) (B)	3.425 Å
O(2)	C(9) (B)	3.494
N(1)	C(1) (D)	3.473
C(5)	O(1) (D)	3.390
N(1)	C(8) (E)	3.412
N(1)	C(9) (E)	3.277
O(3)	C(5) (F)	3.201
C(11)	N(2) (G)	3.477
C(10)	N(2) (G)	3.456

Symmetry code;				
	(A)	x	y	z
	(B)	$1/2-x$	$3/2-y$	$-z$
	(C)	$1-x$	$1-y$	$-z$
	(D)	x	$-1+y$	z
	(E)	$1/2-x$	$1/2-y$	$-z$
	(F)	$-1/2+x$	$1/2+y$	z
	(G)	$1/2-x$	$1/2+y$	$1/2-z$

25) D. J. Sutor, *J. Chem. Soc.*, **1963**, 1105.