CHEMISTRY LETTERS, pp. 1139-1142, 1972. Published by the Chemical Society of Japan

THE CRYSTAL AND MOLECULAR STRUCTURE OF MELATONIN, N-ACETYL-5-METHOXYTRYPTAMINE

Akio WAKAHARA, Takaji FUJIWARA, and Ken-ichi TOMITA
Faculty of Pharmaceutical Sciences, Osaka University
Toneyama, Toyonaka, Osaka, Japan

The molecular structure and configuration of melatonin, one of tryptophan metabolites, has been determined by X-ray diffraction method and some structural features are compared with those of related compounds. The structure was solved by the symbolic addition procedure and was refined by block-diagonal least-squares method.

Melatonin was first isolated from bovine pineal glands as a factor that lightens skin colour by reversing the darkening effect of the melanocyte stimulating hormone[1] and also found in tryptophan metabolic pathway as a precursor of 6-hydroxymelatonin.[2] As a part of the structural studies of tryptophan metabolites, we have previously reported the crystal and molecular structures of 5-hydroxytryptophan[3] and tryptamine.[4] With this communication, we describe the molecular structure of melatonin and compare the molecular structure with those of other metabolites of tryptophan.

Melatonin (N-acetyl-5-methoxytryptamine), $C_{13}H_{16}N_2O_2$, was recrystallized from benzene solution as yellow plates (m.p. 118-119°), which were shown to be monoclinic with unit cell parameters of a = 7.711, b = 9.282, c = 17.107 Å and β = 96.77°. From systematic extinctions, the space group was determined to be $P2_1/c$. The density value of 1.269 g/cc, measured by the flotation method in calcium chloride aqueous solution, indicated that there are four molecules in a unit cell. Lattice constants and intensities were measured on a Rigaku-Denki automatic four-circle diffractometer with Ni-filtered Cu-Kα radiation.

A total of 1219 independent non-zero intensities were collected within the range less than 0.53 of $\sin\theta/\lambda$ using the ω-2θ scanning technique. A Wilson plot was then made to estimate an approximate scale factor and overall temperature factor (B = 3.43 Å^2). The crystal structure was solved by the symbolic addition method for centrosymmetric crystals proposed by Karle & Karle.[5] The phases of 167 reflections with $|E| > 1.2$ were determined, and three-dimensional E maps were computed for possible eight cases. Of these E maps, one revealed the plausible high peaks corresponding to the atomic sites of melatonin molecule.

The coordinates of the seventeen atoms as selected from the E map were refined by successive Fourier syntheses and the block diagonal least-squares procedure. Five cycles of isotropic least-squares refinement reduced the agreement index (R-factor) to 12.9%.

Next five cycles of refinement with anisotropic temperature factors caused a further reduction of R to 9.6%. A difference synthesis at this stage revealed the location of all the hydrogen atoms, and the contributions of these light atoms reduced the R index to 6.3%. Further refinement of the structure is now in progress. The atomic parameters and temperature factors (B_{ij}) for heavy atoms thus obtained are listed in Table 1. The average standard deviations of the coordinates are about 0.007, 0.006 and 0.005 Å for carbon, nitrogen and oxygen atoms, respectively.

TABLE 1.

				B_{ij} (x10^4)					
Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	1.1750	0.2986	0.8350	247	128	29	-21	-15	13
C(2)	1.0969	0.3563	0.7550	205	86	32	3	52	-8
C(3)	0.9357	0.3088	0.6258	271	101	20	-19	-19	-3
C(4)	0.8703	0.1735	0.5814	215	81	25	-19	-1	-1
C(5)	0.8194	0.2067	0.4943	166	84	28	17	28	1
C(6)	0.8395	0.3324	0.4541	195	95	31	20	17	14
C(7)	0.7145	0.1739	0.3648	172	96	28	33	15	2
C(8)	0.7398	0.1041	0.4383	154	85	25	-5	24	0
C(9)	0.6887	-0.0411	0.4458	165	89	34	-1	22	-10
C(10)	0.6186	-0.1087	0.3775	182	101	40	-1	11	-12
C(11)	0.5943	-0.0400	0.3032	186	131	36	16	9	-18
C(12)	0.6419	0.1030	0.2956	183	138	33	34	12	-1
C(13)	0.5866	-0.3313	0.4485	296	88	55	-26	22	24
N(1)	1.0081	0.2636	0.7059	212	79	25	-12	11	-7
N(2)	0.7730	0.3155	0.3754	215	95	36	8	20	11
O(1)	1.1145	0.4863	0.7368	297	75	33	-55	29	-6
O(2)	0.5659	-0.2539	0.3756	282	108	52	-95	7	-38

Anisotropic temperature factors are in the form:
$T = \exp[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)]$.

Fig. 1 shows a schematic view of the structure as seen along the a-axis with the bond distances and valency angles. The deviations of individual atoms from indole ring plane are also shown in parentheses.
The mean C-C distance in the benzene ring is 1.402 Å, while those of C-C and C-N distances in the pyrrole ring are 1.405 Å and 1.394 Å, respectively.
The indole part of melatonin molecule is planar, the average deviation of the atoms from this plane is 0.011 Å, and the maximum deviation is 0.022 Å for N(2). C(1), C(2) and O(1) of acetyl group and N(1) are almost strictly in a plane. This plane forms a dihedral angle of 12° with that of the indole ring.

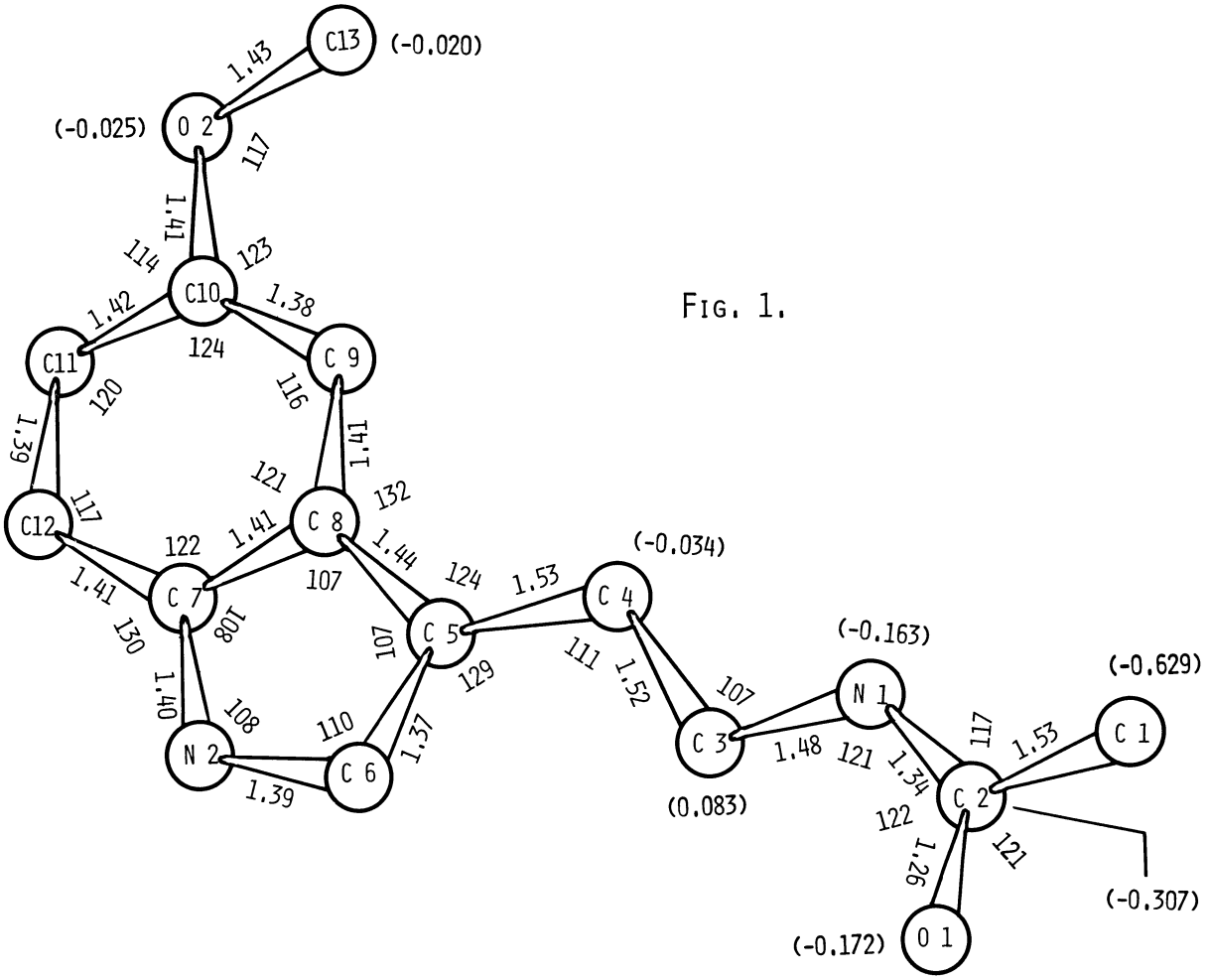
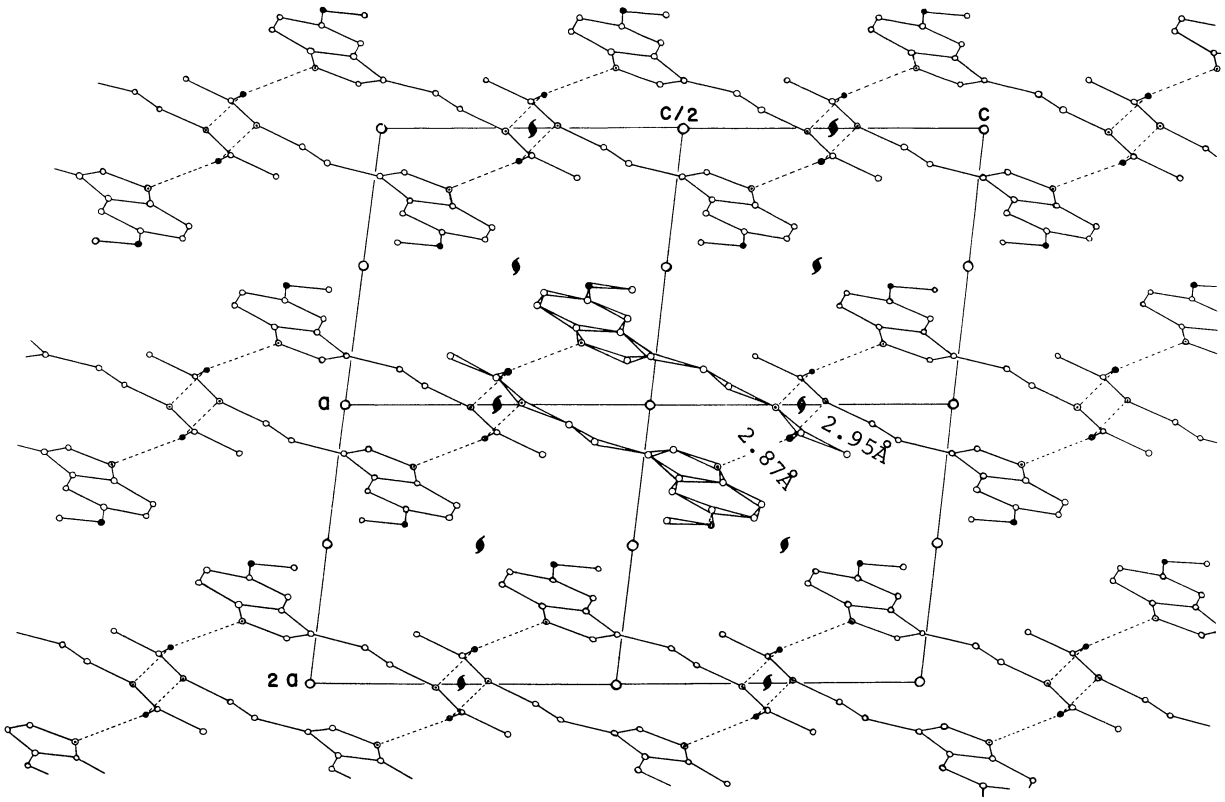


FIG. 1.

The torsion angle as defined by Klyne & Prelog[6] is +0.4° (syn-periplanar) for the atoms C(13)-O(2)-C(10)-C(9), while the equivalent angle in 5-methoxy-(N,N)-dimethyltryptamine hydrochloride is +2.5°.[7]
Three important torsion angles C(2)-N(1)-C(3)-C(4), N(1)-C(3)-C(4)-C(5) and C(3)-C(4)-C(5)-C(6) are +171° (anti-periplanar), -171° (anti-periplanar) and +6° (syn-periplanar), respectively. The extended configuration of the side chain attached to C(5) atom is also found in serotonin-creatinine sulphate complex.[8]

The crystal structure viewed along the b-axis is illustrated in Fig. 2. Two melatonin molecules are hydrogen-bonded through N(2)-H---O(1) (2.87 Å) into dimer related by center of symmetry. These dimers are linked together by N(1)-H---O(1) hydrogen bonds (2.95 Å) in the directions of b and c-axes. The normal van der Waals contacts are found between adjacent indole rings or methoxy groups to stabilize the crystal structure.

FIG. 2.



REFERENCES

1) A.B. Lerner, J.D. Case, Y. Takahashi, T.H. Lee, and W. Mori, J. Am. Chem. Soc., 80, 2587 (1958).
2) I.J. Kopin, C.M.B. Pare, J. Axelrod, and H. Weissbach, Biochim. Biophys. Acta, 40, 377 (1960).
3) A. Wakahara, M. Kido, T. Fujiwara, and K. Tomita, Tetrahedron Lett., 34, 3003 (1970).
4) A. Wakahara, T. Fujiwara, and K. Tomita, Tetrahedron Lett., 57, 4999 (1970).
5) I.L. Karle and J. Karle, Acta Cryst., 16, 969 (1963).
6) W. Klyne and V. Prelog, Experientia, 16, 521 (1960).
7) G. Falkenberg and D. Carlström, Acta Cryst., B27, 411 (1971).
8) I.L. Karle, K.S. Dragonette, and S.A. Brenner, Acta Cryst., 19, 713 (1965).

(Received September 21, 1972)