X-RAY CRYSTAL STRUCTURE OF RACEMIC 1,1',3,3'-TETRAMETHYLLEUCOISOINDIGO AND ROTATIONAL ISOMER *

Tetsuo Suyama, [a] Takeshi Kato, [a] Yutaka Morita, [a]
and Hiroshi Miyamae [b]

Faculty of Pharmaceutical Sciences, [a] and Faculty of Science ,[b]
Josai University,Keyakidai 1-1, Sakado,Saitama 350-02,Japan

Abstract--- The crystal structure of racemic 1,1',3,3'-tetramethylleucoisoindigo was determined by X-ray analysis. The conformation in solid state *thus obtained was +sc taking 3- and 3'-methyl groups as fiducial groups.*

In the previous paper, [1] we have reported that the conformation of racemic (*threo*) -1,1',3,3'-tetramethylleucoisoindigo (**1**) in solution ($CDCl_3$) might be -*sc* (**1a**) [2] taking 3- and 3'- methyls as fiducial groups from the result of the comparative chemical shift study in the proton nuclear magnetic resonance (^{1}H-nmr) on **1** (Figure 1) and *meso* (*erythro*) isomer (**2**) of which the structure was unambiguously determined by the X-ray analysis.

Since the conformation of **2** has been shown not as *ap* in which the dipole moments may fall but as ±*sc* both in solid state and in solution ($CDCl_3$), we are interested in the conformation of **1** in solid state whether it is same as in solution like in the case of **2**.

The present paper describes the crystal structure determination of **1** by X-ray analysis and a comparative study on molecular structure of **1** and **2** in relation to the conformation in solution ($CDCl_3$).

Dimer **1** was synthesized according to the method given in the literature,[3] and gave correct

---

* The paper is dedicated to Prof. Alan R. Katritzky on the occasion of his 65th anniversary.

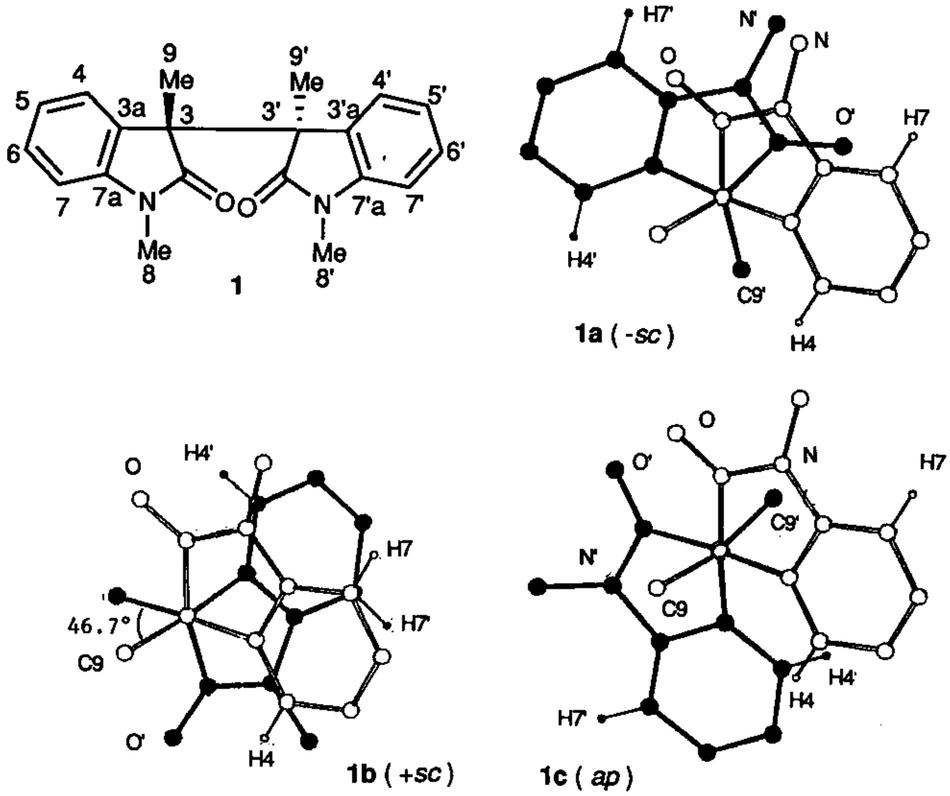

Figure 1 Conformations of Racemic (*threo*) Dimer (**1**).
(Rotamers from one enantiomer are depicted.)
Distances between two atoms in **1b** (+*sc*);
H4-O' 2.76Å, H4-C2' 2.70Å,
H4'-O 2.70Å, H4'-C2 2.73Å.

analytical data.

Crystallographic Measurement ----- A computer - controlled Rikagaku Denki AFC - 5 four circle auto-diffractometer was used for all measurements. A single crystal of **1**, crystal size of 0.3 x 0.3 x0.2 mm^3 was selected for the investigation. 2904 reflections with $2° < 2\theta < 120°$ obtained by the used of graphite-monochromated Cu-K_α radiation, 1841 independent reflections of $|F_o| > 3\sigma(F_o)$ were used in the calculation. No absorption correction was made.

Crystal data ----- $C_{20}H_{20}N_2O_2$, mp 176 °C ($CHCl_3$), M_r = 320.38. Monoclinic, a= 17.333 (2), b=9.193 (1), c=12.369 (3) Å , β=118.62 (1) ° , V=1730.1 (5) $Å^3$, D_c=1.23 gcm^{-3}, Z=4, μ(Cu-Kα)=0.65 cm^{-1}. Space group $P2_1/a$.

Table I. Atomic Positional Parameters ($X10^4$) of **1**(**1b**) and Equivalent Isotropic Thermal Parameters with e.s.d.'s in Parentheses

Atom	*X*	*Y*	*Z*	B_{eqv}
O	2690 (1)	3361 (3)	6710 (2)	4.52 (0.11)
O'	5022 (2)	-850 (3)	8125 (2)	4.20 (0.11)
N	3955 (2)	4707 (3)	7591 (3)	3.34 (0.12)
N'	5434 (2)	524 (3)	6939 (3)	3.32 (0.12)
C2	3486 (2)	3442 (4)	7319 (3)	3.22 (0.14)
C3	4134 (2)	2159 (4)	7902 (3)	2.87 (0.13)
C3a	4997 (2)	2961 (4)	8556 (3)	3.05 (0.13)
C4	5844 (2)	2475 (4)	9306 (4)	4.34 (0.16)
C5	6534 (3)	3462 (5)	9790 (4)	5.68 (0.18)
C6	6370 (3)	4929 (5)	9536 (4)	5.74 (0.19)
C7	5521 (3)	5449 (4)	8790 (4)	4.56 (0.17)
C7a	4853 (2)	4447 (4)	8327 (3)	3.28 (0.14)
C8	3558 (3)	6136 (4)	7205 (4)	4.90 (0.19)
C9	3897 (3)	1347 (4)	8792 (4)	4.52 (0.17)
C2'	4886 (2)	136 (4)	7387 (3)	3.05 (0.13)
C3'	4084 (2)	1152 (4)	6834 (3)	2.64 (0.12)
C3'a	4251 (2)	2009 (4)	5923 (3)	2.75 (0.13)
C4'	3736 (2)	2998 (4)	5028 (3)	3.67 (0.15)
C5'	4054 (3)	3616 (4)	4293 (4)	4.60 (0.17)
C6'	4870 (3)	3227 (4)	4455 (4)	4.92 (0.19)
C7'	5392 (2)	2223 (4)	5332 (4)	4.26 (0.17)
C7'a	5061 (2)	1619 (4)	6044 (3)	3.01 (0.13)
C8'	6293 (2)	-127 (5)	7330 (4)	5.34 (0.19)
C9'	3243 (2)	237 (4)	6222 (3)	3.63 (0.14)

e.s.d., estimated standard deviation.

Structure Analysis and Refinement ----- The structure was solved by the direct method using MULTAN 78 [4] and refined by the block-diagonal least-squares procedure in the UNICS III system [5] with the assumption of positional and isotropic thermal parameters for all non-hydrogen atoms. All the hydrogen atoms were located on the difference Fourier maps and were included in

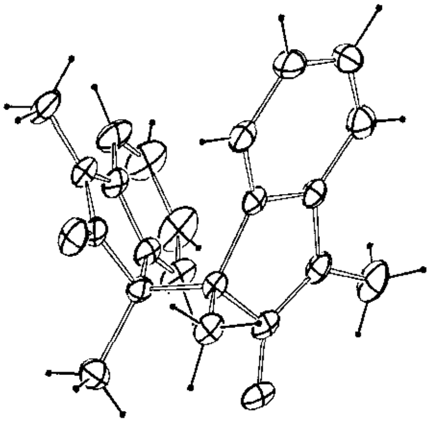

Figure 2 ORTEP Projection of **1**.

Table II. Bond Lengths in **1**(**1b**)(Å)

C3- C3'	1.580 (5)		
O - C2	1.217 (4)	O' - C2'	1.227 (4)
N - C2	1.366 (5)	N' - C2'	1.356 (6)
N - C7a	1.397 (4)	N' - C7'a	1.404 (4)
N - C8	1.454 (5)	N' - C8'	1.456 (5)
C2 - C3	1.549 (5)	C2' - C3'	1.537 (5)
C3 - C3a	1.510 (5)	C3' - C3'a	1.512 (6)
C3 - C9	1.540 (7)	C3' - C9'	1.533 (5)
C3a - C4	1.381 (5)	C3'a - C4'	1.379 (5)
C3a - C7a	1.393 (5)	C3'a - C7'a	1.387 (6)
C4 - C5	1.387 (6)	C4' - C5'	1.389 (7)
C5 - C6	1.384 (6)	C5' - C6'	1.377 (7)
C6 - C7	1.394 (5)	C6' - C7'	1.381 (5)
C7 - C7a	1.372 (5)	C7' - C7'a	1.377 (7)

(e.s.d. $x10^3$)

the subsequent refinement with isotropic thermal parameters. Final refinement utilitized anisotropic thermal parameters for all non-hydrogen atoms and converged to R=0.066. The atomic parameters and bond lengths are given in Tables I and II, respectively, and an ORTEP [6] drawing of the molecule, one of the racemic counterparts, is given in Figure 2.

The ORTEP drawing of **1** showed clearly that **1** has the *threo* structure and exists as +*sc* form (**1b**) in the crystal. As reported in the previous paper[1],**1** gave the proton sequence of H-7 (δ 6.44), H-5 (6.81), H-6 (7.01),and H-4 (7.05 ppm) like that in **3** (Figure 3).

The higher field shift of H-4 in **2** was explained by the ±*sc* conformation in which H-4 was located on benzene plane of the other half near to C3'a and C7'a, *vide infra*, with distances of 2.77 and 2.92Å, respectively. [7] On the other hand, the chemical shift of H-4 in **1** was somewhat (*ca*.0.2ppm) higher than that of 1,3-dimethyl-2-indolinone(**3**), but it was still lower than that of H-7 (Figure 3).[1]

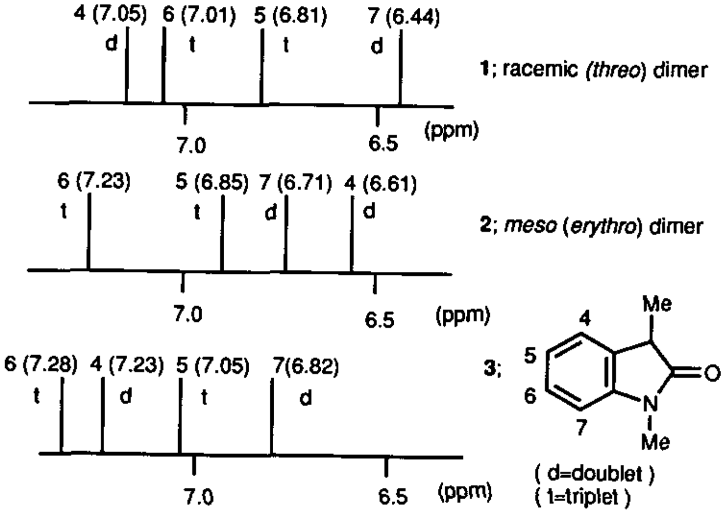

Figure 3 ^{1}H-nmr (aromatics, 270 MHz,δ) of **1**,**2**, and **3**.

As shown in Figure 1, distances between H-4 and non-benzenic atoms of indolinone moieties in the crystal of **1b** suggest that there might be expected a considerable higher field shift of H-4 due to the overlapping of those with the π-orbital of carbonyl group. The shift range might nearly be same as in the case of **2**, because distances between H-4 and carbonyl atoms in **1b** are 2.70-2.76Å, comparable to distances of H-4 with C3'a and C7'a in **2**, *vide supra*. Actually this was not the case in the solution of **1,** denying the possibility in existing as +*sc* (**1b**). If *ap* (**1c**) exists as the predominant species in solution, there might also be expected a considerable higher field shift of H-4 because of the overlapping of H-4 protons and benzene rings.

This was also not the case. The NOE experiment on H-4 in **1** ($CDCl_3$) by irradiating at 3- or 3'-methyl protons showed about 7% inhancement of the signal intensity contrasting to 3% inhancement of the H-4 signal in **3**.[8] As the result, the conformation of **1** in solution ($CDCl_3$) was confirmed to be as -*sc* (**1a**) by the aid of the present X-ray analysis of **1**.

Bond lengths and bond angles in **1** (**1b**) are shown in Table II and Table III , respectively. The torsion angle between two methyl groups along the axis C3-C3' is 46.7° in **1** (**1b**).

Table III. Bond Angles in **1**(**1b**) (°)

C2	-N-	C7a	111.1 (3)	C2'	-N'-	C7'a	111.3 (3)
C2	-N-	C8	123.8 (3)	C2'	-N'-	C8'	124.1 (3)
C7a	-N-	C8	125.0 (3)	C7'a	-N'-	C8'	124.6 (4)
O	-C2-	N	124.7 (3)	O'	-C2'-	N'	125.2 (3)
O	-C2-	C3	126.6 (3)	O'	-C2'-	C3'	126.2 (4)
N	-C2-	C3	108.7 (3)	N'	-C2'-	C3'	108.6 (3)
C2	-C3-	C3a	100.9 (3)	C2'	-C3'-	C3'a	101.1 (3)
C2	-C3-	C9	108.6 (4)	C2'	-C3'-	C9'	109.3 (3)
C2	-C3-	C3'	108.7 (3)	C2'	-C3'-	C3	108.0 (2)
C3a	-C3-	C9	112.9 (3)	C3'a	-C3'-	C9'	113.2 (3)
C3a	-C3-	C3'	112.2 (3)	C3'a	-C3'-	C3	111.4 (3)
C9	-C3-	C3'	112.8 (3)	C9'	-C3'-	C3	113.1 (3)
C3	-C3a-	C4	131.6 (3)	C3'	-C3'a-	C4'	131.4 (4)
C3	-C3a-	C7a	109.6 (3)	C3'	-C3'a-	C7'a	109.3 (3)
C4	-C3a-	C7a	118.9 (3)	C4'	-C3'a-	C7'a	119.3 (4)
C3a	-C4-	C5	119.8 (4)	C3'a	-C4'-	C5'	119.3 (4)
C4	-C5-	C6	119.9 (3)	C4'	-C5'-	C6'	119.9 (4)
C5	-C6-	C7	121.5 (4)	C5'	-C6'-	C7'	121.9 (5)
C6	-C7-	C7a	117.2 (4)	C6'	-C7'-	C7'a	117.1 (4)
N	-C7a-	C3a	109.6 (3)	N'	-C7'a-	C3'a	109.3 (4)
N	-C7a-	C7	127.6 (3)	N'	-C7'a-	C7'	128.2 (4)
C3a	-C7a-	C7	122.7 (3)	C3'a	-C7'a-	C7'	122.5 (3)

(e.s.d. x 10)

The dihedral angle between the plane consisting of C3, C3a, and C7a and that of C3', C3'a, and C7'a in **1**(**1b**) is 56.9°.

EXPERIMENTAL

Melting points were recorded on Yanagimoto MP micro melting points apparatus and are uncorrected. ^{1}H-Nmr spectra were measured as $CDCl_3$ solution on a JEOL GX-270 instrument, and chemical shifts are reported on the δ-scale from internal TMS. Mass spectrum were measured with a JEOL DX-300 spectrometer.

1: mp 174 °C (CH_2Cl_2). Ms *m/z* (%) : 320 (M^+, 6), 160 (100), 130 (10). ^{1}H-Nmr : 1.61 (6H, s, C(3)-Me), 3.08 (6H, s, N-Me), 6.44 (2H, d, *J*=7.6 Hz, H(7)), 6.81 (2H, t, *J*=7.6 Hz, H(5)), 7.01 (2H, t, *J*=7.6 Hz, H(6)), 7.05 (2H, d, *J*=7.3 Hz, H(4)). *Anal.* Calcd for $C_{20}H_{20}N_2O_2$: C,74.98; H, 6.29; N, 8.74. Found: C, 75.00; H, 6.41; N, 8.73.

2: mp 218 °C (CH_2Cl_2). Ms *m/z* (%) : 320 (M^+, 6),160 (100), 130 (14). ^{1}H-Nmr : 1.67 (6H, s, C(3)-Me), 2.97 (6H ,s, N-Me), 6.61 (2H, d, *J*=7.7 Hz, H(4)), 6.71 (2H, d,*J*=7.7 Hz, H(7)),6.85 (2H, t, *J*=7.7 Hz, H(5)), 7.23 (2H, d, *J*=7.7 Hz, H(6)). *Anal.* Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C,74.72: H,6.23: N, 8.63.

3: mp 140 °C (CH_2Cl_2). Ms *m/z* (%) : 161 (M^+, 100),146 (54),132 (18),118(51). ^{1}H-Nmr : 1.48 (3H, d, *J*=7.3 Hz, C(3)-Me), 3.20 (3H, s, N-Me), 3.43 (1H, q, *J*=7.7,7.3Hz, H(3)), 6.82 (1H, d, *J*=7.7 Hz, H(7)), 7.05 (1H, t, *J*=7.3 Hz,H(5)), 7.23 (1H, d, *J*=7.7 Hz, H(4)), 7.28 (1H, t, *J*=7.3 Hz, H(6)). *Anal.* Calcd for $C_{10}H_{11}NO$ 1/6 H_2O: C, 73.14; H, 6.95; N,8.52. Found: C, 73.08; H, 6.81; N, 8.36.

REFERENCES AND NOTES

1. T. Kato, A. Inada, Y. Morita, and H. Miyamae, *Chem. Pharm. Bull.,* 1985, **33**, 5270.
2. R. S. Cahn, Sir C. Ingold, and V. Prelog, *Angew. Chem.,Internat. Edit. Engl.*, 1966, **5**, 385.
3. J. Harley-Mason and R. F. J. Ingleby, *J. Chem. Soc.*, 4782, **1958.**
4. P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M Woolfson, 1978, MULTAN78. A system of computer programs for the automatic solution of crystal structures for X-ray diffraction data, Univs. of York, England, and Louvain, Belgium.
5. T. Sakurai and K. Kobayashi, *Rikagaku Kenkyusho Houkoku* (*Rep.Inst. Phys. Chem. Res.,* in Japanese), 1978, **55**, 69.
6. C. K. Johnson, ORTEP II, Report ORNL-3794 revised, 1971, Oak Ridge National Laboratory, Tennessee.
7. As reported, [1] **2**, mp 223-225 °C, was obtained according to the method reported in the literature 3 and the structure has been determined by the X-ray analysis with the final R-value 0.045.
8. T.Suyama, T.Kato, and Y. Morita, *Yakugaku Zasshi* , **113**, No.12, in press 1993.

Received, 5th October, 1993