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X-Ray Analysis of *d*-6-Chloro-5-cyclohexylindan-1-carboxylic Acid (*d*-TAI-284)[1]

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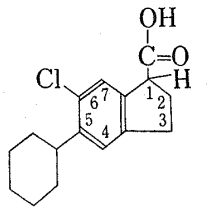
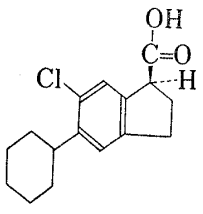
The absolute configuration at C-1 of *d*-6-chloro-5-cyclohexylindan-1-carboxylic acid (*d*-TAI-284) has been assigned to the sinister series by X-ray analysis. The conformation of *d*-TAI-284 was similar to that of indomethacin, which indicates that a hypothetical receptor site contour for indomethacin analogs proposed by Shen is also applicable to *d*-TAI-284. Importance of conformational structure in determining antiinflammatory activities is suggested.

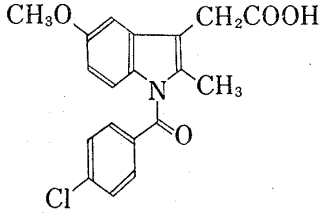
Recently, potent antiinflammatory activities of *p*-alkylphenylacetic acids have received a considerable attention. In the course of the study directed to this field, Noguchi, *et al.*,[3] synthesized various indan-1-carboxylic acid derivatives which are structurally similar to corticosteroids and also to phenylacetic acids clinically used as antiinflammatory agents. Among the compounds prepared, 6-chloro-5-cyclohexylindan-1-carboxylic acid (TAI-284) (Ia) was found to have the most potent antiinflammatory, analgesic and antipyretic activities[4] comparable or even superior to those of indomethacin (II). We have undertaken the X-ray analysis of the dextrorotatory isomer of Ia, the activity of which is 6 or 7 times higher than the levorotatory isomer.[4] Recent studies on X-ray structure analyses of various biologically active compounds have provided valuable informations about the relationships between stereochemical structures and biological activities suggesting that conformation of drug molecules may play an important role in determining their pharmacological properties. The approach based on conformational rather than chemical similarities to existing drugs has thus come to be seen useful for developing new and more effective medicines. In the field of antiinflammatory drugs, however, little informations have been available.



Ia



Ib



II

Experimental

Crystals of *d*-TAI-284 were prepared from *n*-hexane solutions as colorless needles. The axis of this needle was found to be the *b* axis. Crystals used for collecting the three-dimensional data were 0.2×0.1 mm in cross section and those for the comparison between $I_0(hkl)$ and $I_0(\bar{h}\bar{k}\bar{l})$ were cut into 0.3×0.1 mm in cross

1) A part of this work was presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April 1974.
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka 532, Japan.*
3) S. Noguchi, S. Kishimoto, I. Minamida, M. Obayashi, and K. Kawakita, *Chem. Pharm. Bull.* (Tokyo), **19**, 646 (1971); S. Noguchi, S. Kishimoto, I. Minamida, and M. Obayashi, *ibid.*, **22**, 529 (1974).
4) K. Kawai, S. Kuzuna, S. Morimoto, H. Ishii, and N. Matsumoto, *Jap. J. Pharmacol.*, **21**, 621 (1971); S. Kuzuna, N. Matsumoto, T. Kometani, and K. Kawai, *ibid.*,, **24** 695 (1974).

section. The cell parameters were measured both by Weissenberg photography (CuK_α) and with a Hilger & Watts linear diffractometer (MoK_α). Systematic absence of $0k0$ reflections with k odd and the optical activity of the molecule indicate that the space group is $P2_1$. The crystallographic data are summarized in Table I.

The intensities of the reflections were measured on the diffractometer using a scintillation counter and MoK_α radiation with balanced filter operation. The crystal was mounted on the b axis and the intensities of 2386 reflections were collected for the $h0l$ through $h4l$. All the intensities were corrected for background and Lorentz-polarization factors in the usual way. No corrections for absorption or extinction were made. Wilson's statistical method[5] was used to bring the different layers of b axis data to a common scale.

Determination of the Structure

From the preliminary investigations (Table I), 2 molecules were assumed to be contained in an asymmetric unit. Probable co-ordinates of 2 chlorine atoms were therefore selected from vector sets of three-

Table I. Crystal Data

Formula	$C_{16}H_{19}O_2Cl$
Formula weight	278.8
mp	130—135°
$[\alpha]_D^{25}$	+28.1°
Crystal system	monoclinic
Space group	$P2_1$
Cell dimensions	$a = 21.22$ Å
	$b = 5.41$
	$c = 13.00$
	$\beta = 91°\ 15'$
Cell volume	$V = 1492.0$ Å^3
Number of molecules in the unit cell	$z = 4$
Calculated density	1.24 g cm^{-3}
Absorption coefficients	2.1 cm^{-1} (MoKa)
	22.3 cm^{-1} (CuKa)
Wave lengths	1.5418 Å (CuKa)
	0.7107 Å (MoKa)

Table II. Atomic Coordinates and Temperature Factors with Their Standard Deviations in Parentheses

Atom	A				B			
	x/a	y/b	z/c	B	x/a	y/b	z/c	B
Cl	0.6809(02)	0.0054(14)	0.6285(04)	4.89(10)	0.1712(03)	0.6969(16)	0.1478(05)	6.73(14)
O (1)	0.4855(06)	0.6639(30)	0.3711(09)	5.03(30)	0.4166(07)	0.0002(42)	0.2723(11)	7.30(39)
O (2)	0.5271(06)	0.5602(34)	0.2241(10)	5.90(34)	0.4570(07)	0.8854(37)	0.1282(12)	7.76(42)
C (1)	0.5685(09)	0.3497(46)	0.3758(15)	4.79(46)	0.3842(08)	0.2044(46)	0.1250(13)	4.32(40)
C (2)	0.5979(10)	0.1568(51)	0.3047(16)	5.88(52)	0.4139(09)	0.3124(44)	0.0190(14)	4.54(44)
C (3)	0.6660(09)	0.2358(45)	0.2884(14)	4.81(45)	0.3552(10)	0.4026(49)	0.9527(16)	5.72(53)
C (4)	0.7330(08)	0.5378(47)	0.4089(14)	4.26(41)	0.2458(09)	0.1613(47)	0.9395(14)	4.52(43)
C (5)	0.7386(07)	0.6904(42)	0.4890(12)	3.29(36)	0.2019(08)	0.0010(50)	0.9868(14)	5.06(44)
C (6)	0.6792(07)	0.7803(35)	0.5325(12)	2.72(33)	0.2222(09)	0.9032(45)	0.0850(15)	4.74(47)
C (7)	0.6224(08)	0.6758(45)	0.5005(13)	4.01(39)	0.2759(08)	0.9613(44)	0.1352(14)	4.33(41)
C (8)	0.6206(08)	0.4953(45)	0.4240(13)	4.09(38)	0.3185(08)	0.1204(40)	0.0837(14)	4.09(43)
C (9)	0.6767(08)	0.4276(38)	0.3741(13)	3.44(38)	0.3034(08)	0.2272(44)	0.9889(13)	4.15(40)
C (10)	0.5235(09)	0.5273(53)	0.3234(15)	5.07(46)	0.4211(08)	0.0336(47)	0.1791(14)	4.16(41)
C (11)	0.7998(09)	0.8137(44)	0.5316(14)	4.86(44)	0.1371(09)	0.9436(47)	0.9382(15)	5.36(49)
C (12)	0.8485(12)	0.8486(64)	0.4425(20)	8.46(71)	0.1449(10)	0.8931(50)	0.8174(16)	6.05(54)
C (13)	0.9140(12)	0.9360(58)	0.4960(19)	7.90(68)	0.0773(11)	0.8419(56)	0.7721(18)	7.38(62)
C (14)	0.9369(11)	0.7410(55)	0.5707(17)	7.00(58)	0.0392(11)	0.0861(54)	0.7844(18)	6.81(62)
C (15)	0.8873(13)	0.7459(67)	0.6584(21)	8.81(77)	0.0294(11)	0.1439(56)	0.8954(18)	7.53(64)
C (16)	0.8241(11)	0.6262(53)	0.6096(18)	6.77(61)	0.0949(09)	0.1782(53)	0.9502(15)	6.38(51)

5) A.J.C. Wilson, *Nature*, **150**, 152 (1942).

Table III. Bond Distances

	A	B		A	B
C1 — C (6)	1.74Å	1.77Å	C (5) — C (11)	1.55Å	1.53Å
O (1) — C (10)	1.27	1.23	C (6) — C (7)	1.39	1.34
O (2) — C (10)	1.31	1.30	C (7) — C (8)	1.39	1.43
C (1) — C (2)	1.56	1.64	C (8) — C (9)	1.42	1.39
C (1) — C (8)	1.53	1.55	C (11) — C (12)	1.58	1.61
C (1) — C (10)	1.47	1.39	C (12) — C (13)	1.61	1.56
C (2) — C (3)	1.53	1.58	C (13) — C (14)	1.51	1.56
C (3) — C (9)	1.54	1.53	C (14) — C (15)	1.57	1.50
C (4) — C (5)	1.33	1.43	C (15) — C (16)	1.61	1.56
C (4) — C (9)	1.40	1.41	C (16) — C (11)	1.52	1.56
C (5) — C (6)	1.48	1.44			

Table IV. Bond Angles

	A	B		A	B
C (2) — C (1) — C (8)	104	100	C (7) — C (8) — C (9)	120	122
C (2) — C (1) — C (10)	116	116	C (3) — C (9) — C (4)	129	129
C (8) — C (1) — C (10)	108	118	C (3) — C (9) — C (8)	113	112
C (1) — C (2) — C (3)	109	105	C (4) — C (9) — C (8)	117	119
C (2) — C (3) — C (9)	102	102	O (1) — C (10) — O (2)	117	118
C (5) — C (4) — C (9)	125	121	O (1) — C (10) — C (1)	123	123
C (4) — C (5) — C (6)	116	115	O (2) — C (10) — C (1)	120	119
C (4) — C (5) — C (11)	127	122	C (5) — C (11) — C (12)	110	109
C (6) — C (5) — C (11)	116	123	C (5) — C (11) — C (16)	103	108
C1 — C (6) — C (5)	120	118	C (12) — C (11) — C (16)	111	108
C1 — C (6) — C (7)	120	117	C (11) — C (12) — C (13)	107	107
C (5) — C (6) — C (7)	120	126	C (12) — C (13) — C (14)	110	107
C (6) — C (7) — C (8)	121	117	C (13) — C (14) — C (15)	104	111
C (1) — C (8) — C (7)	131	126	C (14) — C (15) — C (16)	106	109
C (1) — C (8) — C (9)	109	112	C (15) — C (16) — C (11)	105	111

Table V. The Observed and Calculated Intensity Ratios of the Reflections (hkl) to $(h\bar{k}l)$

h	k	l	$\frac{Fc(hkl)^2}{Fc(h\bar{k}l)^2}$	$\frac{Io(hkl)}{Io(h\bar{k}l)}$	h	k	l	$\frac{Fc(hkl)^2}{Fc(h\bar{k}l)^2}$	$\frac{Io(hkl)}{Io(h\bar{k}l)}$
−2	1	0	0.80	<1	11	1	2	1.17	>1
−8	1	0	1.19	>1	7	2	2	1.37	>1
−13	1	0	0.81	<1	13	2	2	1.36	>1
−18	1	0	0.78	<1	2	3	2	0.80	>1[a]
−3	2	0	1.42	>1	−9	1	3	0.72	<1
−8	2	0	0.82	<1	1	1	3	0.70	<1
−10	2	0	1.21	>1	5	1	3	0.71	<1
−2	3	0	1.37	<1[a]	8	1	3	0.82	>1[a]
−8	1	1	0.80	<1	13	1	3	0.63	<1
−15	1	1	1.37	>1	15	1	3	1.31	>1
−19	1	1	0.69	<1	8	2	3	1.69	>1
4	1	1	0.84	<1	9	2	3	1.27	>1
18	1	1	0.36	>1[a]	12	2	3	1.56	>1
−16	2	1	1.47	>1	3	3	3	1.24	>1
6	2	1	0.79	<1	5	3	3	0.80	<1
8	2	1	0.84	<1	−8	1	4	1.50	>1
5	4	1	1.26	>1	−9	1	4	0.80	<1
−6	1	2	0.71	<1	1	1	4	1.26	>1
−7	1	2	1.38	>1	2	1	4	1.19	>1
−16	1	2	0.63	<1	3	1	4	1.17	>1
2	1	2	1.27	>1	5	1	4	0.83	<1
6	1	2	1.16	>1	15	1	4	0.64	<1

a) The observations marked with an asterisk are not in accord with the results of the calculation.

dimensional sharpened Patterson function. Starting with these co-ordinates, the co-ordinates of remaining non-hydrogen atoms were determined by the usual procedures. The atomic co-ordinates and temperature factors were refined by the block-diagonal least-squares method to an R-value of 0.135 (non-zero reflections). The final atomic parameters are listed in Table II. Bond distances and angles are listed in Tables III and IV, respectively.

The absolute configuration was determined by the use of anomalous dispersion method.[6] The correction terms used for the scattering factor of the chlorine atom were $\Delta f'=0.3$ and $\Delta f''=0.7$.[7] Out of 44 Friedel pairs of reflections which showed significant differences in the c axis Weissenberg photographs (CuK_α), 40 pairs indicated that the atomic co-ordinates of Table II considered in relation to a right-handed set of axes in space group $P2_1$ gave rise to intensity differences in the same sense as those observed (Table V).

Result and Discussion

Molecular and Crystal Structure

From the present analysis, *d*-TAI-284 was determined to be 6-chloro-5-cyclohexylindan-1*S*-carboxylic acid (Ib). The perspective view of molecules in the unit cell is given in Fig. 1. Conformations of the 2 molecules contained in an asymmetric unit of the crystal (tentatively named as molecules A and B) can be compared in Fig. 2 which is drawn by projecting the molecules on the least-squares plane[8] of the indan group. As a whole, the molecular shapes are similar to each other. In both molecules, the five-membered ring of the indan group is puckered with C(2) out of plane and cyclohexane ring attached to C(5) is in a chair form, the C(5)—C(11) bond being equatorial. Slight conformational differences between molecules A and B are:

1. The angle between the normals to the indan group and to the "best plane" of the cyclohexane ring, calculated as the least-squares plane of the 6 atoms constituting the ring, is 67° in A and 81° in B.

2. The carboxyl group and C(2) atom lie on the opposite side of the indan plane in A, whereas they are located on the same side of the plane in B. As a result, the angle of tilt of the C(1)—C(10) bond to the indan plane is 56° in A and 33° in B.

The molecules A and B are associated together through the dimeric hydrogen bond between their carboxyl groups. Distances between $O(1)_A$–$O(2)_B$ and $O(2)_A$–$O(1)_B$ are 2.65 and 2.60Å, respectively. Other intermolecular short contacts are not found and molecules are mainly packed with van der Waals forces.

Stereochemical Structure and Biological Activity

As already mentioned, the absolute configuration at C-1 of *d*-TAI-284 was assigned to the sinister series. In several nonsteroidal antiinflammatory agents (III–VII) containing an asymmetric carbon at the position α to the carboxyl group,[9–11] their activities are known to reside mostly in the dextrorotatory isomer with *S* configuration. Interestingly, antiinflammatory corticosteroids such as hydrocortisone (VIII), prednisolone (IX), dichlorisone (X) and fluocortolone (XI) have the same configuration at C-17. The configurational coincidence of *d*-TAI-284 with these known agents may render a further support for the idea that the configuration exerts influence on a stereospecific drug-receptor interaction.[3,10]

6) J.M. Bijvoet, A.F. Peerdeman, and A.J. van Bommel, *Nature*, **168**, 271 (1951).
7) "International Tables for X-ray Crystallography," Vol. 3, Kynoch Press, Birmingham, 1962, p. 214.
8) C(2) atom is omitted from the calculation of the least-squares plane.
9) T.Y. Shen, *Angew. Chem. Intern. Ed. Engl.*, **11**, 460 (1972).
10) P.F. Juby, W.R. Goodwin, T.W. Hudyma, and R.A. Partyka, *J. Med. Chem.*, **15**, 1297 (1972).
11) I.T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, and J.H. Fried, *J. Med. Chem.*, **13**, 203 (1970).

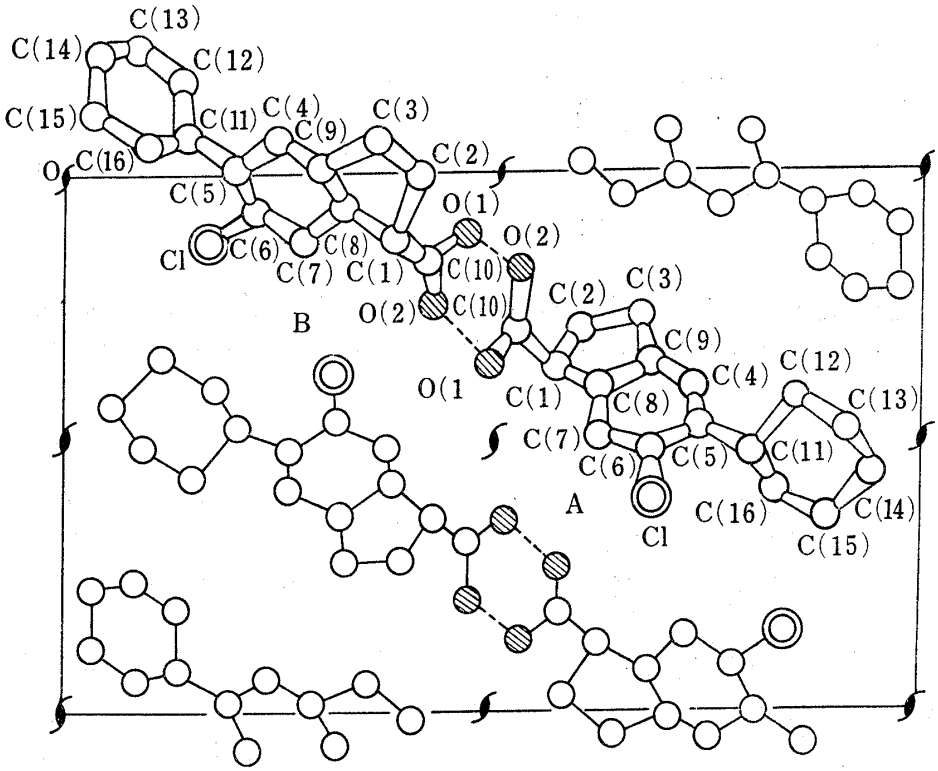


Fig. 1. The Contents of the Unit Cell as Seen along the *b* Axis

Broken lines show hydrogen bonds.

Crystal structure of indomethacin has been reported by Kistenmacher and Marsh.[12] Fig. 3 shows the conformation of indomethacin molecule viewed along the normal to the least-squares plane of the indole ring. From the comparison of this figure with Fig. 2, it will be clearly seen that the spatial arrangement of the carboxyl group and cyclohexane ring with respect to the planar part in *d*-TAI-284 molecule resembles to that of the carboxyl group and the benzene ring to the plane of the indole ring in indomethacin molecule. Their topochemical proximity will

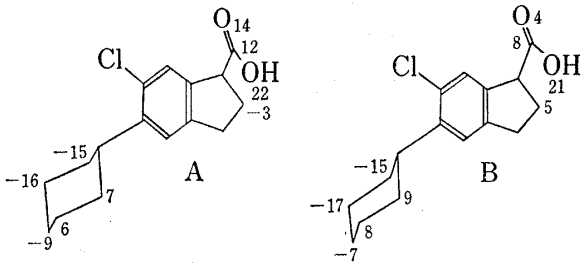
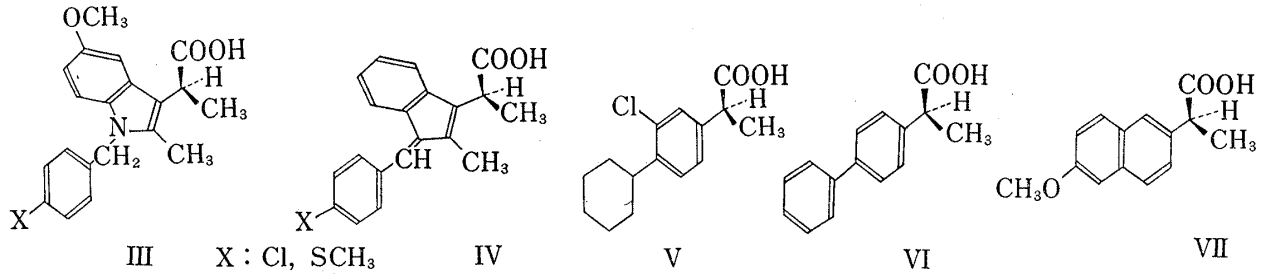


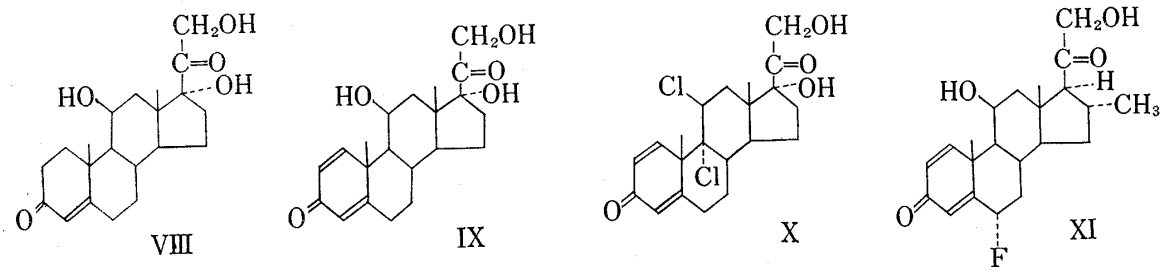
Fig. 2. Conformational Comparison of 2 Independent Molecules of *d*-TAI-284 in an Asymmetric Unit (A and B)

Each molecule is projected on the least-squares plane of the indan ring. Displacements of atoms from the plane are shown in 10×Å units.



be more clearly seen in Fig. 4, which is drawn by projecting the molecules along the plane of the indan ring (*d*-TAI-284) and the indole ring (indomethacin). It is also noticeable that the aforementioned angles between the normals to the best plane of the cyclohexane ring and to

12) T.J. Kistenmacher and R.E. Marsh, *J. Am. Chem. Soc.*, **94**, 1340 (1972).



the plane of the indan ring in two independent *d*-TAI-284 molecules are comparable to the angle (68°) between the normals to the benzene and to the indole ring of indomethacin molecule.

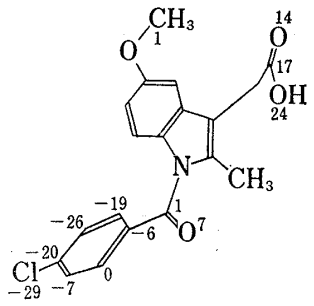


Fig. 3. Projection of Indomethacin Molecule on the Least-Squares Plane of the Indole Ring

calculated from data of Kistenmacher and Marsh[12]

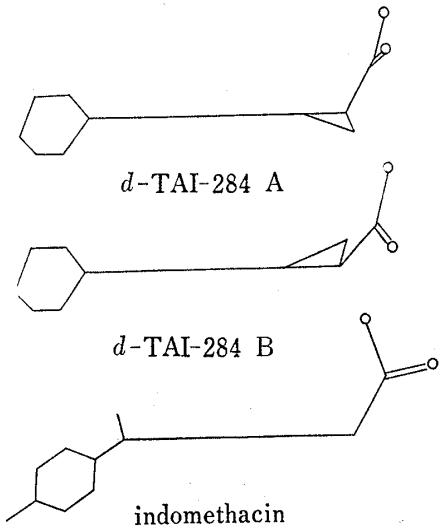


Fig. 4. Projection of Molecules along Planes of the Indan Ring (*d*-TAI-284) and the Indole Ring (Indomethacin)

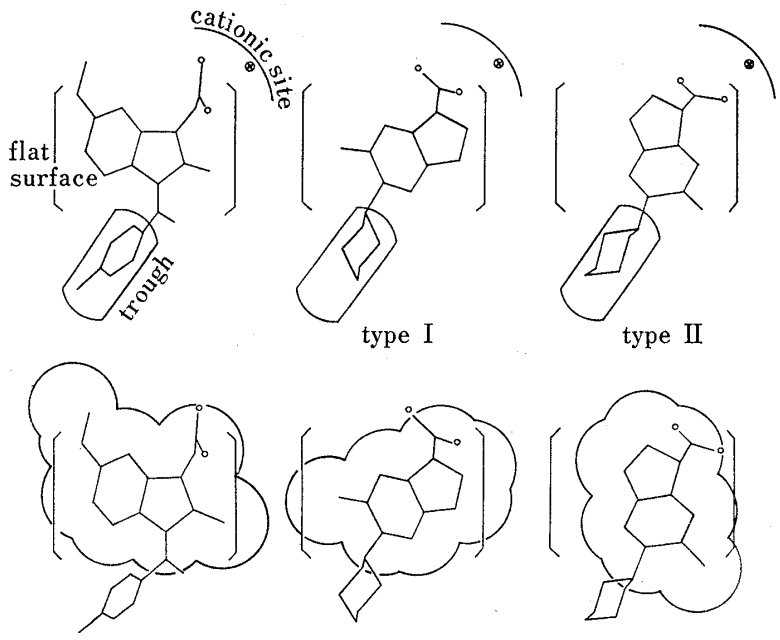


Fig. 5. Possible Structures of *d*-TAI-284 and Indomethacin Molecules bound to the Receptor Model[13]

In lower drawings, van der Waals contours of planar parts of the molecules are compared.

A hypothetical antiinflammatory "receptor" model for the indomethacin type non-steroidal agents has been proposed by Shen.[13] As the binding sites to the indole group, the carboxyl group and the benzene ring of indomethacin molecule, he assumed a flat surface (5×6 Å), a cationic site and a trough, respectively, in the receptor model. The molecule of *d*-TAI-284 determined in the present study seems to fit the model in 2 ways (types I and II in Fig. 5). In type II, the spatial arrangement of the chlorine atom in *d*-TAI-284 molecule is very similar to that of the carboxyl oxygen of the benzoyl group in indomethacin molecule, whereas in type I, the chlorine atom is merely taken as a part of aromatic moiety. However the lower drawings of Fig. 5 reveal that the contour of the van der Waals radii of the planar part of *d*-TAI-284 molecule in type I geometrically more coincides with that of indomethacin molecule than in type II.

From these considerations, it is suggested that indomethacin and *d*-TAI-284, which are not closely related chemically with each other, may be able to interact with the same receptor. This finding supports the idea that conformational structure may be one of the important factors in determining antiinflammatory activities.

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13) T.Y. Shen, "Topics in Medicinal Chemistry," Vol. 1, ed. by J.L. Rabinowitz, and R.M. Myerson, John Wiley and Sons, Inc., New York, 1967, p. 53.