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Crystal and Molecular Structures of a New Anti-ulcer Agent, 3-[*p*-(*trans*-4-Aminomethylcyclohexylcarbonyl)phenyl]-propionic Acid Hydrochloride

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The crystal and molecular structures of 3-[*p*-(*trans*-4-aminomethylcyclohexylcarbonyl)phenyl]-propionic acid hydrochloride, which is an anti-ulcer agent, have been determined by X-ray analysis. The crystal belongs to space group $P2_1/n$, with lattice parameters $a=5.3443(2)$, $b=57.616(3)$, $c=5.5881(2)$ Å, $\beta=90.080(5)°$, and $Z=4$. The structure, in which the aminomethylcyclohexyl moiety and phenylpropionic acid moiety are connected by the planar carbonyl group, takes a rigid bent-rod like conformation. In the crystal the molecules are dimerized in a head-to-head fashion with hydrogen bonding between the carboxy groups at one end. Protonated amino groups at the other end of the molecules and the chloride ions gather at $y \simeq b/4$ and $(3/4)b$.

Keywords——X-ray analysis; crystal structure; molecular structure; 3-[*p*-(*trans*-4-aminomethylcyclohexylcarbonyl)phenyl]propionic acid; anti-ulcer agent

The title compound (**1**) is an anti-ulcer agent which promotes defensive factors such as gastric mucosal blood flow and glycoprotein production in the mucosal tissue.[1)] A synthetic route to **1** from *trans*-4-aminomethylcyclohexanecarboxylic acid (**2**) is outlined in Chart 1.[2)] An ambiguity remains in the conformation of **1**, since it is known that ring conversion of a substituted cyclohexane (1e, 4e, → 1a, 4e, or 1e, 4a, where e and a designate equatorial and axial, respectively) might occur during the reaction process.[3)] To establish the three-dimensional structure of **1**, the crystal of **1** has been subjected to X-ray analysis. On the basis of the determined structure, the possible conformations of some related compounds in solution are discussed.

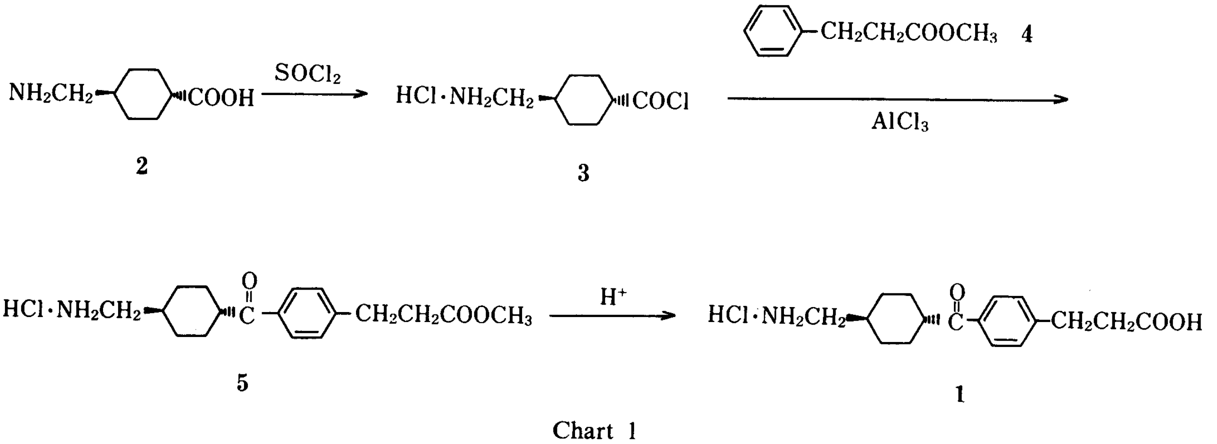

Chart 1

Experimental

X-Ray Structure Determination——**1** ($C_{17}H_{24}ClNO_3$) was recrystallized from water. Crystal data are: monoclinic, space group $P2_1/n$, $a=5.3443(2)$ Å. $b=57.616(3)$ Å $c=5.5881(2)$ Å, $\beta=90.080(5)^\circ$, cell volume· 1720.70(1) $Å^3$, $d_{\mathrm{measd}}=1.262\ \mathrm{g/cm^3}$ (flotation in CCl_4/n-heptane), $d_{\mathrm{calcd}}=1.258\ \mathrm{g/cm^3}$, and $Z=4$.

Intensity data were collected on a Rigaku automated four-circle diffractometer within the range of $2<2\theta<125^\circ$ with CuK_α radiation ($\lambda=1.54184$ Å). Since the value of b is very large, an ω scan mode was adopted instead of an ω–2θ mode. The size of the crystal used was 0.2 × 0.4 × 0.5 mm. A total of 2610 independent reflections were obtained. The standard deviation of each reflection was estimated from the equation $\sigma^2(F_o)=\sigma_p^2+qF^2$, where σ_p is obtained from counting statistics and q (2.6×10^{-4}) was derived from the variation among the monitored reflections.[4)]

The structure was solved by the direct method using MULTAN 78,[5)] and the atomic parameters were refined by

Table I. Fractional Coordinates (× 10^4) and Isotropic Thermal Parameters ($Å^2$) of **1** for Non-hydrogen Atoms with Estimated Standard Deviations in Parentheses

Atom	x	y	z	$B_{\mathrm{eq}}{}^{a)}$
Cl	581 (2)	7232 (0)	11422 (2)	4.1
N(1)	−4440 (5)	7252 (0)	8328 (5)	4.0
C(2)	−4640 (7)	7108 (1)	6101 (6)	4.3
C(3)	−4600 (6)	6849 (1)	6629 (6)	3.8
C(4)	−5216 (7)	6717 (1)	4328 (7)	5.0
C(5)	−5163 (8)	6457 (1)	4715 (7)	5.1
C(6)	−2659 (7)	6375 (1)	5683 (7)	4.5
C(7)	−2005 (7)	6506 (1)	7979 (7)	5.0
C(8)	−2087 (7)	6768 (1)	7600 (7)	4.5
C(9)	−2676 (7)	6116 (1)	6207 (7)	4.9
O(10)	−4086 (6)	6043 (0)	7740 (6)	7.8
C(11)	−928 (7)	5957 (1)	4933 (6)	4.0
C(12)	240 (7)	6020 (1)	2824 (6)	4.5
C(13)	1909 (8)	5869 (1)	1722 (7)	5.1
C(14)	2459 (7)	5657 (1)	2742 (7)	4.8
C(15)	1260 (8)	5594 (1)	4817 (7)	5.6
C(16)	−439 (8)	5739 (1)	5901 (7)	5.1
C(17)	4446 (9)	5510 (1)	1484 (8)	6.4
C(18)	5539 (8)	5304 (1)	2801 (8)	5.7
C(19)	7383 (8)	5175 (1)	1512 (8)	5.3
O(20)	8259 (7)	5002 (1)	2711 (6)	8.2
O(21)	8117 (6)	5224 (1)	−457 (6)	7.6

a) $B_{\mathrm{eq}}=(4/3)\sum_i\sum_j\beta_{ij}(\boldsymbol{a}_i\cdot\boldsymbol{a}_j)$.

Table II. Bond Lengths (Å) of **1**

Bond	Length	Bond	Length
N(1)–C(2)	1.501	C(11)–C(12)	1.382
C(2)–C(3)	1.520	C(11)–C(16)	1.394
C(3)–C(4)	1.531	C(12)–C(13)	1.387
C(3)–C(8)	1.521	C(13)–C(14)	1.380
C(4)–C(5)	1.512	C(14)–C(15)	1.374
C(5)–C(6)	1.518	C(14)–C(17)	1.532
C(6)–C(7)	1.528	C(15)–C(16)	1.373
C(6)–C(9)	1.524	C(17)–C(18)	1.474
C(7)–C(8)	1.525	C(18)–C(19)	1.506
C(9)–O(10)	1.217	C(19)–O(20)	1.289
C(9)–C(11)	1.490	C(19)–O(21)	1.203

The standard deviations are about 0.005 Å.

Table III. Bond Angles (°) of **1**

Atoms	Angle	Atoms	Angle
N(1)–C(2)–C(3)	112.5	C(9)–C(11)–C(16)	119.1
C(2)–C(3)–C(4)	108.9	C(12)–C(11)–C(16)	118.8
C(2)–C(3)–C(8)	112.4	C(11)–C(12)–C(13)	120.5
C(4)–C(3)–C(8)	109.6	C(12)–C(13)–C(14)	120.4
C(3)–C(4)–C(5)	111.7	C(13)–C(14)–C(15)	118.9
C(4)–C(5)–C(6)	111.9	C(13)–C(14)–C(17)	116.7
C(5)–C(6)–C(7)	110.3	C(15)–C(14)–C(17)	124.4
C(5)–C(6)–C(9)	111.5	C(14)–C(15)–C(16)	121.5
C(7)–C(6)–C(9)	109.0	C(11)–C(16)–C(15)	119.9
C(6)–C(7)–C(8)	111.5	C(14)–C(17)–C(18)	116.2
C(3)–C(8)–C(7)	112.2	C(17)–C(18)–C(19)	113.1
C(6)–C(9)–O(10)	118.6	C(18)–C(19)–O(20)	113.4
C(6)–C(9)–C(11)	120.5	C(18)–C(19)–O(21)	123.9
O(10)–C(9)–C(11)	120.8	O(20)–C(19)–O(21)	122.7
C(9)–C(11)–C(12)	122.1		

The standard deviations are about 0.3°.

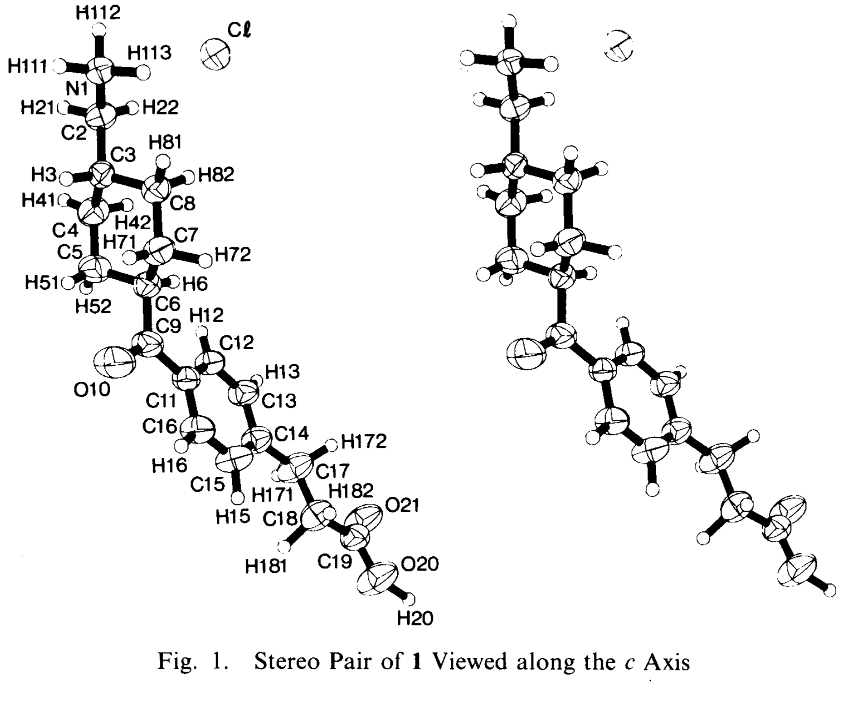

Fig. 1. Stereo Pair of **1** Viewed along the *c* Axis

a block-diagonal matrix least-squares method, including all the hydrogen atoms. The quantity minimized was $\Sigma\omega(|F_o|-|F_c|)^2$, where $\omega=1/\sigma^2(|F_o|)$. The refinement was terminated when the maximum shift in parameters of non-hydrogen atoms was 0.2σ. The final R value was 0.065 for 2523 reflections with $F>3\sigma(F_o)$ ($R_w=0.068$). Atomic scattering factors used were taken from ref. 6. Final atomic coordinates, bond lengths and angles are listed in Tables I—III. Numbering of atoms is shown in Fig. 1.

Results and Discussion

A stereo view of **1** with thermal ellipsoids drawn by DCMS 82[7)] is shown in Fig. 1. The conformation of the cyclohexyl moiety in **1** has been confirmed to be (1e, 4e), which is the same as that of the starting material **2**. The cyclohexyl and phenyl moieties subtend an angle of about 120° at the planar carbonyl linkage. The phenyl group is nearly coplanar with the carbonyl group. Side chains at both ends are fully extended and the carbonyl group on one

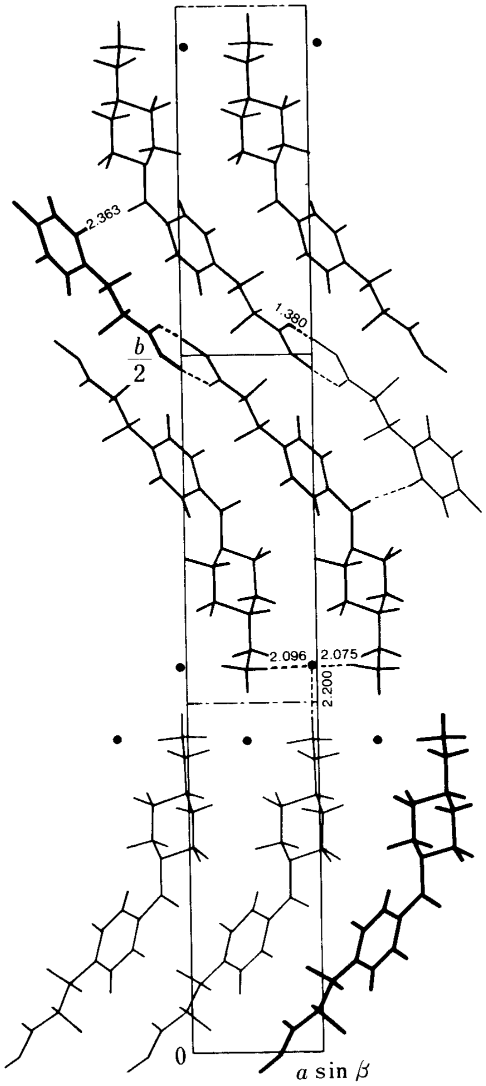

Fig. 2. Crystal Structure of **1**

Hydrogen bonds are depicted by dashed lines with the distance.

side takes a stable synplanar conformation. This molecular structure might be the most stable in general, and can be considered as an obtuse isosceles triangle. The molecules are associated to form a dimer around an inversion center by the hydrogen bonds between the carboxy groups at one end, as shown in Fig. 2. At the other end, protonated amino groups of three adjacent molecules share a chloride ion to form $NH^{+} \cdots Cl^{-}$ hydrogen bonds. There is also a weak interaction between the carbonyl group and a hydrogen of the phenyl ring at the middle of the two parallel molecules.

The fairly rigid isosceles triangle conformation of **1** can serve as a probe to explore the active conformation of related compounds. As a structural parameter for characterizing the conformation of the compounds, we take the distance between the amino group and carboxy group at the ends of the molecule and its range of fluctuation owing to torsional flexibility. As shown in Fig. 3, the latera of the isosceles triangle conformation of **1** are cyclohexyl C_2–C_9 and phenyl C_9–C_{17} moieties of equal length, 5.80 Å. Even if both the cyclohexyl and phenyl moieties rotate about each latus, the length of the base C_2–C_{17} is unchanged, and the distance between the two end groups changes only within the range of 10.1 and 11.3 Å due to free rotation of the C_{17}–C_{19} bonds adjacent to the carboxy end. Next, if the carbonyl group of **1** is replaced by carbon (**6**), the obtuse angle changes slightly from 120 to 109 °, and now wider free rotation about the obtuse angle is possible. However, the length of the base is unchanged, and the range of the distance between the end groups lies within 9.4–10.8 Å, which is comparable

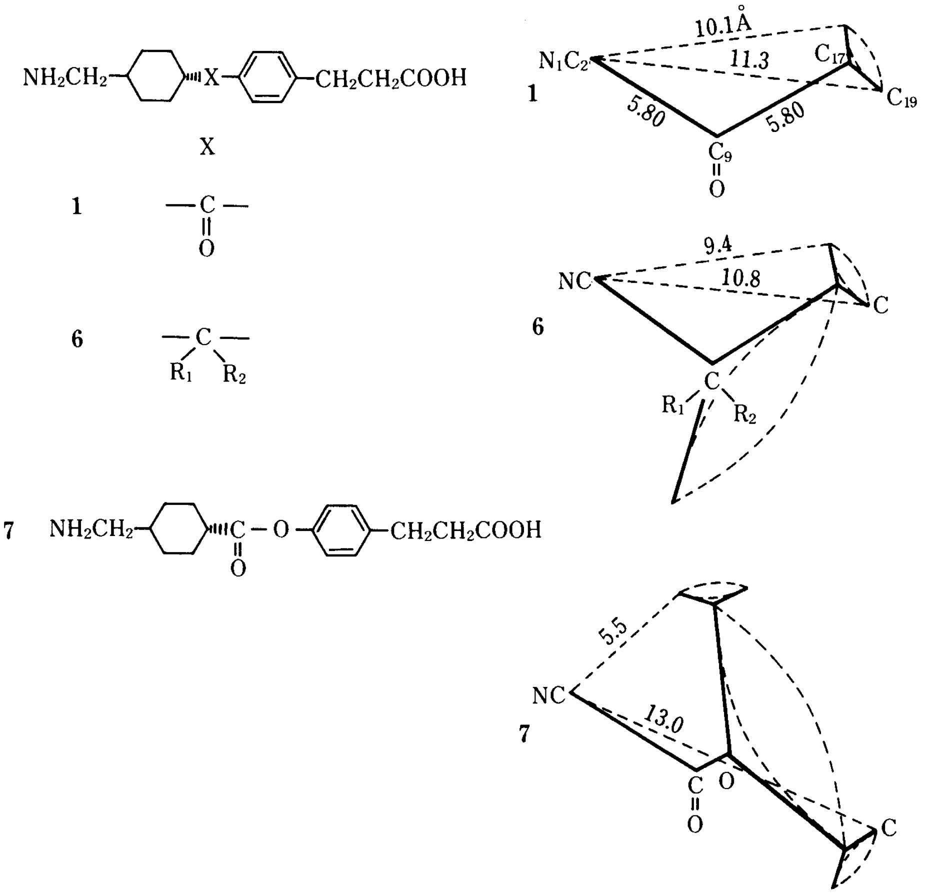

Fig. 3. Conformations of **1** and Related Compounds

with that of **1**. Finally, if an oxygen atom is inserted between the carbonyl group and the phenyl ring moiety of **1** to make an ester linkage, 4-[(*trans*-4-aminomethylcyclohexyl)carbonyloxy]benzenepropanoic acid (**7**) is obtained. In this case the distance between the end groups can vary over the widest range of 5.5—13.0 Å by free rotation about the C–O bond of the ester linkage, since the potential barrier of the rotation seems to be low.[8] However, the range includes those of **1** and **6**, and therefore the common range of the three is considered to represent the region of active conformation for molecules of this kind of anti-ulcer agent.

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