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X-RAY CRYSTALLOGRAPHIC ANALYSIS OF TAUTOMERIC DIHYDROPYRIMIDINE DERIVATIVES

Hidetsura Cho[1*], Yoshihiro Hamamoto[1], Keiyuu Shima[1], and Zenei Taira[2]
*1 Suntory Institute for Biomedical Research, 1-1-1, Wakayamadai, Shimamoto-cho, Mishima-gun, 618, Osaka, Japan
*2 Department of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima-shi, 770, Tokushima, Japan

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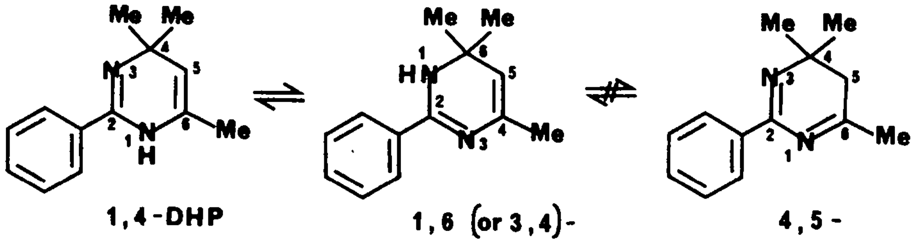
Abstract---X-ray crystallographic analysis of various dihydropyrimidine tautomers was carried out. 4-(2-Chlorophenyl)-5-ethoxycarbonyl-2,6-dimethyldihydropyrimidine 1 exists in an electron-localized 1,4-dihydro form with a flat boat conformation in the crystalline state. 6-Chloro-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-methyldihydropyrimidine 2 synthesized as 1/2 HCl salt after extractive work-up under basic conditions consists of two different molecules with Cl atoms;the molecules of electron-localized 1,4-dihydro form 2a and electron-delocalized form 2b. Both forms are linked by hydrogen bonding around the center of symmetry in the unit cell. X-ray analysis of compound 2c prepared by the addition of excess HCl-Et_2O to a solution of compound 2 exhibits an electron-delocalized structure of different molecular arrangement.

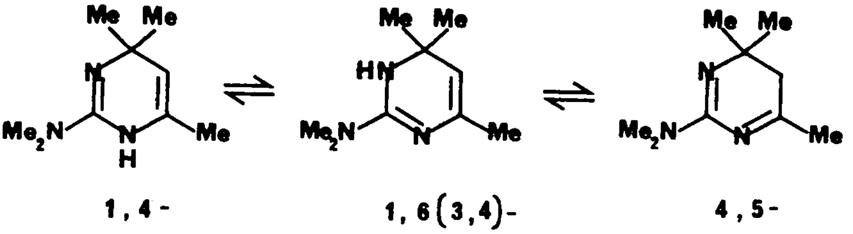
Introduction

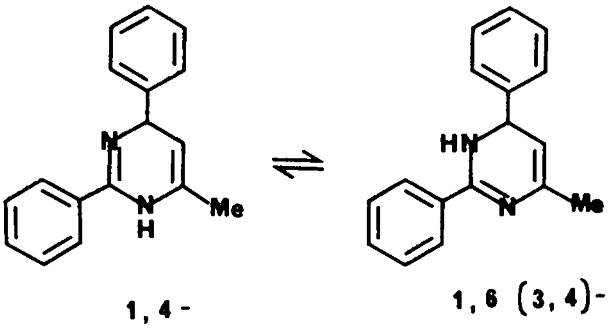
Only a few papers on the synthesis[1,2] and structure determination[1,3] of dihydropyrimidine derivatives have been reported. This is because the chemical structure becomes ambiguous and complicated due to tautomerism and isomerization of the double bond. Substituents on the dihydropyrimidine skeleton influence the location of the two double bonds. For example, Silversmith reported[1a] that 4,4,6-trimethyl-2-phenyldihydropyrimidine existed as a 1,4- or 3,4(1,6)-dihydropyrimidine,[4] while Traube reported it uncorrectly as a 4,5-dihydropyrimidine.[1b] (See Figure I) Also, 2-amino-4,4,6-trimethyl-4,5-dihydropyrimidine was revised to be a 3,4(1,6)-dihydropyrimidine.[1c] Kashima observed the novel tautomeric equilibrium between a 4,5- and a 3,4(1,6)-dihydropyrimidine in the 2-dimethylamino-4,6,6-trimethyldihydropyrimidine system besides a 1,4-dihydropyrimidine.[1d] Weis and Frolow reported interesting results concerning the X-ray crystallographic analysis of 6-methyl-2,4-diphenyl-dihydropyrimidine, whereby it was shown to exist in the 1,4-dihydro form with a flat boat conformation in the crystalline state as a single tautomeric entity. However, in solution it isomerizes to an equilibrium mixture of a 1,4- and a 3,4(1,6)-dihydropyrimidine.

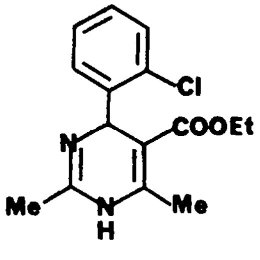
We are interested in studying the ambiguous molecular structure and the instability of dihydropyrimidine derivatives and recently synthesized a series of compounds with an ester group at position-5. To determine whether this additional substituent influences the location of the two double bonds, two different compounds, 4-(2-chlorophenyl)-5-ethoxycarbonyl-2,6-dimethyl-dihydropyrimidine 1 and 6-chloro-4-(2-chlorophenyl)-5-ethoxycarbonyl-2-methyldihydropyrimidine 2 were chosen for X-ray analysis.

Figure I

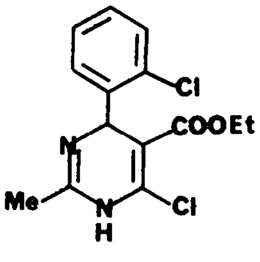

1,4-DHP
1,6 (or 3,4)-
4,5-
Me
N
Ph
Me₂N


1,4-
1,6(3,4)-
4,5-
Me₂N
HN
Me


1,4-
1,6 (3,4)-
Me
HN


Cl
COOEt
Me
N
H

1


Cl
COOEt
Me
N
H
Cl

2

Since an interesting arrangement of electron-localized and/or delocalized molecules in the unit cell was found, we now wish to disclose three remarkable examples of X-ray crystallographic analysis in detail.

Results and Discussions

Compound 1 was synthesized as described in the experimental.

The final molecular geometry (bond lengths, bond angles and torsion angles) and an ORTEP drawing[5] of compound 1 are given in Figure II.

The bond lengths of C(2)-N(3) (1.285 Å) and C(5)-C(6) (1.342 Å) are clearly shorter than the other bond lengths (1.412-1.538 Å).

This finding indicates that the tautomeric double bond is localized between C(2) and N(3) and the other double bond is located between C(5) and C(6).

This observation is also confirmed by the bond angles.

Therefore, compound 1 does not exist in the 3,4(1,6)-dihydropyrimidine but in the 1,4-dihydro form with a flat boat conformation in the crystalline state.

The ORTEP drawing of 1 showed that the dihydropyrimidine ring bears the phenyl ring almost perpendicularly by the observation of the dihedral angle 85.2° between the best planes of the two six-membered rings, and that chlorine atom on the phenyl ring faces to the methine proton at position-4 (syn relationship).

Compound 2 was formed as the HCl salt by the reaction of 6-(2-chlorophenyl)-5-ethoxycarbonyl-2-methyl-dihydropyrimidin-4-one with $POCl_3$, and the reaction mixture was worked up under basic conditions as described in the experimental section. The final molecular geometry (bond lengths, bond angles, and torsion angles) of the two crystallographically independent molecules of compound 2 are exhibited in Figure III. In molecule 2a, the bond length of C(2)-N(3) (1.301 Å) is shorter than that of N(1)-C(2) (1.341 Å) and the bond angles related to these bonds are close to sp^2 angle as 124.6° for the angle C(2)-N(3)-C(4), 121.3° for N(1)-C(2)-N(3), 120.3° for C(2)-N(1)-C(6). These findings indicate that the double bond related to tautomerism is localized on the bond C(2)-N(3). The ring takes a flat boat conformation in which a plane of the ring twisted about the bond N(1)-C(6) with the torsion angle 4.9°. The dihedral angle between the best planes of the two six-membered rings is 90.0°.

On the other hand, the molecule 2b should have the electron-delocalized double bond between N(1) and N(3), because the bond lengths of N(1)-C(2) (1.323 Å) and C(2)-N(3) (1.321 Å) are equal within experimental error and the bond angles around the bonds are close to that of the double bond angle.

The ring conformation is a flat boat form similar to the molecule 2a. The dihedral angle between the best planes of the two six-membered rings is 92.9°.

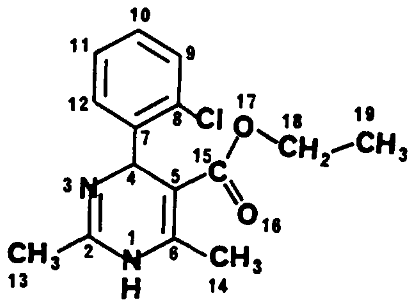
The crystal packing drawing of 2 is given in Figure IV. The four molecules of dihydropyrimidine 2a and 2b are associated with each other by hydrogen bonding around the center of symmetry and the groups of these four molecules are stacked in the crystal.

Compound 2 was dissolved in $CHCl_3$ and treated with excess $HCl-Et_2O$ solution to afford the hydrochloride 2c.

X-ray analysis of 2c reveals that four molecules of compound 2 and four molecules of HCl are arranged in the unit cell and the molecules of hydrochloride 2c exist in the electron-delocalized structure. (See Figure V) The bond lengths, the bond angles, and the position of chlorine atom of 2c is apparantly different from 2b. The chlorine atom of 2c is rather close to the nitrogen atom at position-1 while it is located near the nitrogen atom at position-3 in the case of compound 2b.

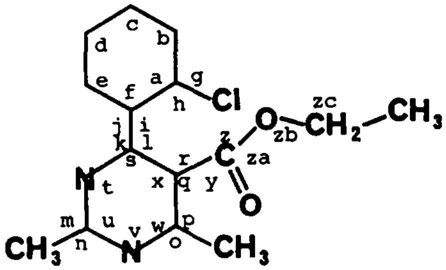
The molecular geometry are given in Figure V.

Figure II 1,4-Dihydropyrimidine 1



Bond Lengths Å

N(1)-C(2) 1.413(09), C(2)-N(3) 1.285(09), N(3)-C(4) 1.505(09), C(4)-C(5) 1.538(10), C(5)-C(6) 1.342(10), N(1)-C(6) 1.412(08), C(2)-C(13) 1.479(09), C(6)-C(14)1.439(10) C(4)-C(7) 1.467(10), C(7)-C(8) 1.435(11), C(8)-C(9) 1.332(11), C(9)-C(10) 1.482(13) C(10)-C(11) 1.315(13), C(11)-C(12) 1.413(12), C(7)-C(12) 1.402(11), C(8)-Cl 1.761 (08), C(5)-C(15) 1.532(12), C(15)-O(16) 1.261(11), C(15)-O(17) 1.206(11), O(17)-C (18) 1.507(11), C(18)-C(19) 1.356(14).



Bond Angles °

a: 125.3(7)°
b: 118.0(8)
c: 119.8(8)
d: 120.6(7)
e: 121.7(7)
f: 114.4(7)
g: 117.2(6)
h: 117.5(6)
i: 125.8(7)
j: 119.5(6)
k: 107.7(6)
l: 113.0(6)
m: 121.1(6)
n: 115.7(6)
o: 112.9(6)
p: 129.9(6)
q: 124.4(6)
r: 112.7(6)
s: 112.1(5)
t: 120.3(5)
u: 123.1(6)
v: 122.0(5)
w: 117.2(6)
x: 122.9(6)
y: 115.2(7)
z: 114.8(8)
Za: 129.8(9)
zb: 120.4(7)
zc: 111.8(9)

Torsion Angles °

C(4)-N(3)-C(2)-N(1)	9.7°
N(3)-C(2)-N(1)-C(6)	3.0
C(2)-N(1)-C(6)-C(5)	-5.7
N(1)-C(6)-C(5)-C(4)	-4.2
N(3)-C(4)-C(5)-C(6)	15.1
C(5)-C(4)-N(3)-C(2)	-17.6
C(8)-C(7)-C(4)-N(3)	107.8
C(8)-C(7)-C(4)-C(5)	-127.8
C(12)-C(7)-C(4)-N(3)	-65.0
C(12)-C(7)-C(4)-C(5)	59.4

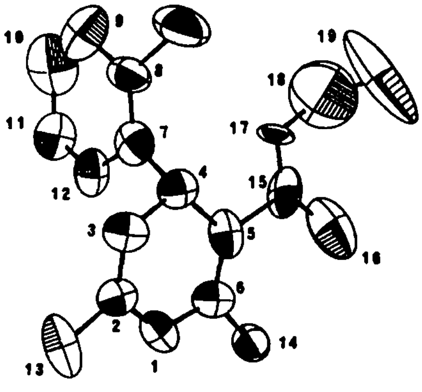
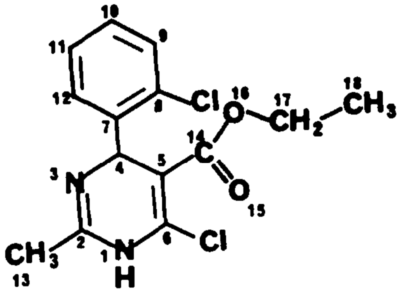
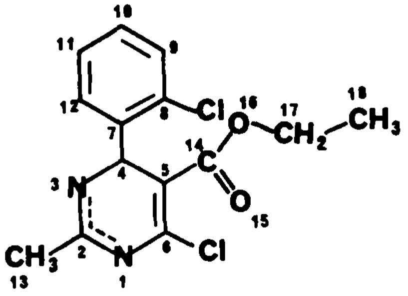


Figure III 1,4-Dihydropyrimidine 2a and 1,4(3,4)-dihydropyrimidine 2b



2a

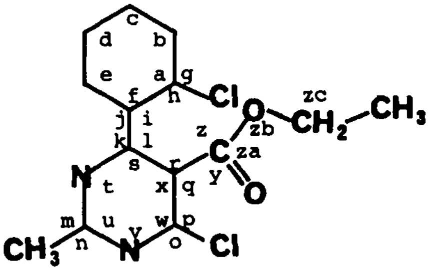


2b

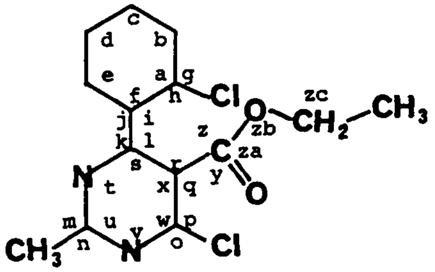
Bond Lengths Å

C(8)-Cl 1.748(6), C(8)-C(9) 1.357(11), C(9)-C(10) 1.379(9), C(10)-C(11) 1.406(9), C(11)-C(12) 1.387(11), C(7)-C(12) 1.377(7), C(7)-C(8) 1.402(7), C(4)-C(7) 1.515(9), N(3)-C(4) 1.472(6), C(2)-N(3) 1.301(6), N(1)-C(2) 1.341(7), N(1)-C(6) 1.384(6), C(5)-C(6) 1.327(7), C(4)-C(5) 1.524(8), C(2)-C(13) 1.485(7), C(5)-C(14) 1.484(7), C(14)-O(15) 1.180(6), C(14)-O(16) 1.312(7), O(16)-C(17) 1.461(7), C(17)-C(18) 1.483(9), C(11)-Cl 1.717(6).

C(8)-Cl 1.744(6), C(8)-C(9) 1.360(8), C(9)-C(10) 1.380(10), C(10)-C(11) 1.380(9), C(11)-C(12) 1.398(8), C(12)-C(7) 1.371(8), C(7)-C(8) 1.388(8), C(4)-C(7) 1.513(7), N(3)-C(4) 1.491(6), C(2)-N(3) 1.321(7), N(1)-C(2) 1.323(8), N(1)-C(6) 1.377(6), C(5)-C(6) 1.343(7), C(4)-C(5) 1.516(8), C(2)-C(13) 1.491(7), C(5)-C(14) 1.469(7), C(14)-O(15) 1.196(8), C(14)-O(16) 1.332(7), O(16)-C(17) 1.471(6), C(17)-C(18) 1.512(10) C(6)-Cl 1.717(6).



2a



2b

Bond angles°

a: 123.1(5)°
b: 119.2(5)
c: 119.9(8)
d: 119.2(6)
e: 121.6(4)
f: 117.1(6)
g: 117.4(3)
h: 119.6(5)
i: 122.2(4)
j: 120.5(4)
k: 107.3(5)
l: 113.6(5)
m: 120.3(4)
n: 118.4(4)
o: 110.7(3)
p: 126.5(4)
q: 128.0(5)
r: 112.0(4)
s: 110.9(4)
t: 124.6(4)
u: 121.3(4)
v: 120.3(4)
w: 122.9(5)
x: 119.6(4)
y: 121.2(5)
z: 114.4(4)
za: 124.4(5)
zb: 116.7(4)
zc: 107.0(4)

a: 122.3(5)°
b: 120.0(5)
c: 119.6(6)
d: 119.0(6)
e: 121.9(5)
f: 117.1(5)
g: 117.3(5)
h: 120.4(4)
i: 123.3(5)
j: 119.6(5)
k: 108.9(4)
l: 112.5(4)
m: 116.6(6)
n: 118.7(5)
o: 111.3(4)
p: 123.3(3)
q: 124.2(5)
r: 116.4(4)
s: 109.8(4)
t: 122.9(5)
u: 124.7(5)
v: 116.7(4)
w: 125.4(5)
x: 119.5(4)
y: 126.6(5)
z: 110.6(5)
za: 122.8(4)
zb: 115.6(4)
zc: 105.4(5)

Torsion angles°	2a	2b
N(1)-C(2)-N(3)-C(4)	5.9°	-7.9°
C(2)-N(3)-C(4)-C(5)	-8.2	11.6
N(3)-C(4)-C(5)-C(6)	4.2	-7.5
C(4)-C(5)-C(6)-N(1)	1.7	-0.4
C(5)-C(6)-N(1)-C(2)	-4.9	5.5
C(6)-N(1)-C(2)-N(3)	1.0	-1.3

	2a	2b
N(3)-C(4)-C(7)-C(8)	102.8	-108.0
N(3)-C(4)-C(7)-C(12)	-72.3	72.1
C(5)-C(4)-C(7)-C(12)	50.6	-49.9
C(5)-C(4)-C(7)-C(8)	-134.3	130.0

Figure IV crystal 2 (2a and 2b)

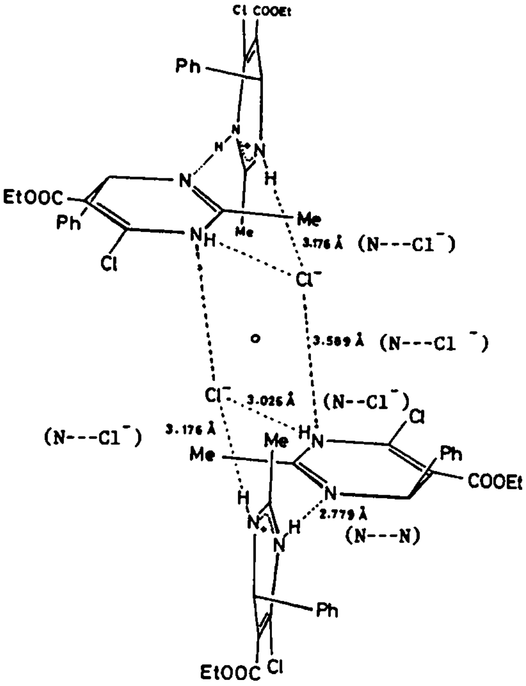
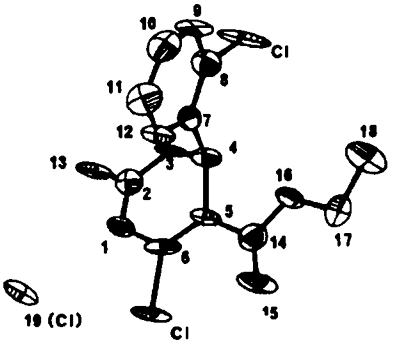


Figure V

compound 2c

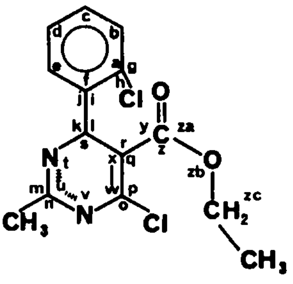


Bond lengths Å

N(1)-C(2)	1.339(9),	C(2)-N(3)	1.312(9)
C(2)-C(13)	1.44(1) ,	N(3)-C(4)	1.477(9)
C(4)-C(5)	1.52(1) ,	C(5)-C(6)	1.32(1)
C(5)-Cl	1.723(8),	C(6)-N(1)	1.396(9)
C(4)-C(7)	1.52(1) ,	C(7)-C(8)	1.41(1)
C(7)-C(12)	1.37(1) ,	C(8)-C(9)	1.36(1)
C(8)-Cl	1.741(8),	C(9)-C(10)	1.36(1)
C(10)-C(11)	1.38(1) ,	C(11)-C(12)	1.40(1)
C(5)-C(14)	1.47(1) ,	C(14)-O(15)	1.19(1)
C(14)-O(16)	1.32(1) ,	O(16)-C(17)	1.45(1)
C(17)-C(18)	1.50(2) ,	N(1)-Cl(19)	2.579(6)

Bond angles °

a: 123.0(7)	b: 119.5(8)	c: 120.8(8)	d: 118.3(8)
e: 122.8(7)	f: 115.5(7)	g: 118.5(6)	h: 118.5(6)
i: 121.6(6)	j: 122.9(7)	k: 111.7(6)	l: 112.0(6)
m: 120.8(7)	n: 120.6(6)	o: 111.1(5)	p: 125.6(6)
q: 125.4(7)	r: 117.7(6)	s: 110.0(6)	t: 123.8(6)
u: 118.6(6)	v: 120.0(6)	w: 123.3(7)	x: 116.9(6)
y: 124.7(7)	z: 111.0(6)	za:124.2(7)	zb:117.4(6)
zc:106.6(8)			



Torsion angles °

N(1)-C(2)-N(3)-C(4): -7.4
C(2)-N(3)-C(4)-C(5): 26.6
N(3)-C(4)-C(5)-C(6): -24.1
C(4)-C(5)-C(6)-N(1): 4.9
C(5)-C(6)-N(1)-C(2): 17.0
C(6)-N(1)-C(2)-N(3): -15.7
N(3)-C(4)-C(7)-C(8): -80.7
N(3)-C(4)-C(7)-C(12):100.4
C(5)-C(4)-C(7)-C(8): 155.3
C(5)-C(4)-C(7)-C(12):-23.6

In conclusion, substitution at position-5 does not influence the location of the two double bonds and compound 1 exists in the 1,4-dihydropyrimidine form as well as Frolow's.[3] To our knowledge, this is the first report that the novel unit cell with the centro-symmetrical arrangement of the electron-localized and the electron-delocalized molecules was found in X-ray crystallographic analysis of tautomer.

Experimental

1) Synthesis of compound 1.[2b]

To a stirred solution of 1.6 g of acetamidine hydrochloride in 15 ml of EtOH was added 1.1 g of NaOEt at r.t. After 15 min, a solution of 3.6 g of ethyl 2-acetyl-3-(*o*-chlorophenyl)-2-propenoate in 15 ml of EtOH was added. The mixture was stirred at r.t. for 45 min. After removal of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. To the residue in 30 ml of benzene was added 5.4 g of *p*-TsOH-H_2O. The mixture was refluxed for 1 h. After addition of excess $CHCl_3$, the solution was washed with saturated aqueous K_2CO_3, dried over $MgSO_4$ and evaporated to leave 4.0 g of compound 1, which was recrystallized from AcOEt, mp 195-197°.

2) Synthesis of compound 2.[2a]

A solution of 1.46 g of 5-ethoxycarbonyl-2-methyl-6-(*o*-chlorophenyl)-5,6-dihydropyrimidin-4-one in 60 ml of $POCl_3$ was refluxed under argon for 30 min. Removal of excess $POCl_3$ gave a residue, which was diluted with $CHCl_3$ and washed with saturated aqueous K_2CO_3. The organic layer was dried and evaporated to give 1.7 g of the residue. Purification on SiO_2 column chromatography yielded 677 mg of pale yellow crystals, which were recrystallized from AcOEt-Et_2O-*n*-hexane, mp 126-127°.

3) Crystal data of compound 1.

$C_{15}H_{17}ClN_2O_2$, mw=292.76. The crystals were recrystallized from AcOEt;mp 195-197°, colorless needles, tetragonal, space group $I4_1cd$, a=b=19.089(8), c=16.555(5) Å, U=6031.6(6) Å^3, Z=16, D_C=1.29 g/cm^3, F(000)=2460, Mo K_α (monochromated by a graphite plate), λ=0.71069 A, μ(Mo K_α)=0.260 mm^{-1}. The solution and refinement of the structure was as follows:The intensity data were obtained on a Rigaku AFC-6B four circle diffractometer (graphite monochromated Mo $K_\alpha$radiation) and ω scan mode was applied with scan speed 4°/min. The measurements were monitored using three standard reflections, without significant variations during data collection. Of the 3038 reflections collected up to 2θ= 50°, 666 independent reflections with |F| >6σ (F) were observed. The structure was solved by direct methods using the MULTAN program[7];all non-hydrogen atoms were found in an E map and refined by block-diagonal least-square calculations with anisotropic thermal parameters. The hydrogen atoms calculated with the standard geometry were included in the structure factor calculations. The final R values were 0.089 and 0.091 (w=1.0).

4) Crystal data of compound 2.

$C_{14}H_{14}Cl_2N_2O_2$ 1/2HCl, mw=313.18. The crystals were recrystallized from AcOEt-MeOH;mp 84-87°[6], pale yellow prisms, triclinic, space group $P\bar{1}$, a= 11.577(8), b=14.859(7), c=10.595(6) Å, α=116.08(8), β=99.53(5), γ=99.10(7)°, U=1558.5(32) Å^3, Z=4, D_C=1.26 g/cm^3, F(000)=616, λ=0.71069 Å, μ(Mo K_α)=0.334 mm^{-1}. The solution and refinement of the structure was as follows:The intensity data were obtained on a Rigaku AFC-6B four circle diffractometer (graphite monochromated Mo K_α radiation) and ω scan mode was applied with scan speed 4°/min. The measurements were monitored using three standard reflections, without significant variations during data collection. Of the 5716 independent reflections measured up to 2θ<50°, 4119 reflections with |F|>6σ(F) were observed. The structure was solved by direct methods using the MULTAN program[7];all non-hydrogen atoms were found in an E map and refined by block-diagonal least-square calculations with anisotropic thermal parameters. Most of hydrogen atoms were located on a difference map, although hydrogen atom of hydrochloride could not be determined on the map; Because an enough peak hight compared with those of the other hydrogen atoms was not observed on the map, the hydrogen atom of hydrochloride was not included in the following structure factor calculations. The refinement converged to R=0.059, R_w=0.075 (w=1.0). The calculations for the structure determination of the crystal were performed on a PANAFACOM U-1400 by the MULTAN, RASA and X-STANP programs. All atomic scattering factors were taken from reference 8. The structure factor table is included in Supplimentary Publication No.

5) Crystal data of compound 2c.

$C_{14}H_{14}Cl_2N_2O_2$ HCl, mw=349.54. The crystals were recrystallized from MeOH-Et_2O;mp 187-191°, colorless prisms, monoclinic, space group $P2_1/a$, a=12.720(1), b=17.914(2), c=7.209(1) Å, β=99.28(1)°, U=1621.3(4) $Å^3$, Z=4, D_C= 1.43 g/cm^3, F(000)=180, μ(Cu K_α)=5.28 mm^{-1}.

X-ray diffraction intensity data from the crystal (0.1x0.05x0.2 mm) was obtained on the Rigaku AFC diffractometer equipped with the rotating anode X-ray generator (50 kV-200mA), using graphite-monochromated Cu K_α radiation (λ=1.5418 Å).

A total of 2626 independent reflections with $2\theta \leq 126°$ were collected by ω scanning mode ($2\theta < 45°$) and $\omega/2\theta$ scanning mode ($2\theta \geq 45°$).

The structure was solved by the direct method MULTAN84.[9] Hydrogen atoms were determined by difference fourier synthesis. The refinement was carried out by the block-diagonal least-squares method with anisotropic thermal parameters for non-H atoms and with isotropic thermal parameters for H atoms. R factor was reduced to 0.046 using 1120 reflections with $|F| > 3\sigma(F)$. All calculations were performed on PANAFACOM U-1200 II of the Rigaku RASA-5RP system.

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References and Notes

1) a) E. F. Silversmith, J. Org. Chem., 27, 4090 (1962).
   b) W. Traube and R. Schwartz, Chem. Ber., 32, 3163 (1899).
   c) Y. H. Kim, C. M. Yoon, and N. J. Lee, Heterocycles, 16, 49 (1981).
   d) C. Kashima, M. Shimizu, and Y. Omote, Tetrahedron Lett., 26, 5057 (1985).
2) a) H. Cho, M. Ueda, Y. Ohnaka, and M. Hayashimatsu, Heterocycles, 22, 1959 (1984).
   b) H. Cho, K. Shima, M. Hayashimatsu, Y. Ohnaka, A. Mizuno, and Y. Takeuchi, J. Org. Chem., 50, 4227 (1985)
3) A. Weis and F. Frolow, J. Chem. Soc. Chem. Comm., 89 (1982).
4) The formal name of 3,4-dihydropyrimidine is 1,6-dihydropyrimidine.
5) C. K. Johnson, A FORTRAN thermal ellipsoid plot program for crystal structure illustrations. ORNL-5138. Oak Ridge National Laboratory, Oak Ridge (1976).
6) Since the crystals (mp 124-126° from benzene) were not suitable for X-ray analysis, recrystallization was carried out from AcOEt and small amount of MeOH to yield the pale yellow crystals, mp 84-87°.
7) G. Germain, P. Main, M. M. Woolfson, Acta Crystallogr., A27, 368 (1971).
8) International Tables for X-Ray Crystallography, 2nd Edn., Kynoch Press, Birmingham (1974).
9) P. Main, G. Germain, M. M. Woolfson. MULTAN84. A computer program for the automatic solution of crystal structures from X-ray diffraction data. Univ. of York, York, England, and Louvain, Belgium. (1984)