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(54) Title
NOVEL TETRAHYDROPYRIDINE DERIVATIVES

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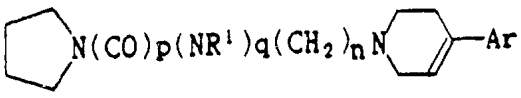
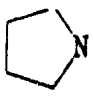
(56) Prior Art Documents
AU 31020/89
AU 21043/88
US 4704390

(57) Claim

1. A compound of the formula:



wherein Ar is phenyl which has identically or differently one or two substituents selected from the group consisting of lower alkyl, lower alkoxy, trifluoromethyl, hydroxy and phenyl, which latter phenyl may be substituted by hydroxy, lower alkyl, lower alkoxy or halogen, or Ar is phenyl which is substituted by two halogen atoms;
n is an integer of from 2 to 6;
R^1 is hydrogen or lower alkyl;
the group

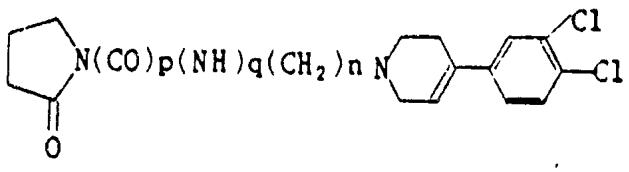


may have identically or differently 1 to 3 substituents selected from the group consisting of lower alkyl, halogen, oxo and phenyl, which phenyl may be substituted by hydroxy, lower alkyl, lower alkoxy or halogen; and

.../2

p and q each is an integer of 0 to 1, with the proviso that when p is 0, q is not 1; or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of the formula:



wherein n is an integer of from 2 to 6; p and q each is an integer of 0 or 1, with the proviso that when p is 0, q is not 1; or a pharmaceutically acceptable acid addition salt thereof.

6. A method for the treatment of psychosis which comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 4 to a subject in need thereof.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

643258

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COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

Novel tetrahydropyridine derivatives

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to novel tetrahydropyridine derivatives with psychotropic activities.

Prior Art

Antidopamine agents such as haloperidol (U. S. Pat. No. 3,438,991) are adopted for the antipsychotic agent. Adverse reactions in the extrapyramidal tract such as delayed dyskinesia are caused by them during the long-term therapy. Recently, safer drugs, rimcazole (JP. Pat. Publn. No.55-64,585) and BMY 148021 (GB Patent No. 2,155, 925), which show high affinity to σ receptors but low affinity to dopamine receptors, have been developed as psychotropic drugs. On the other hand, the exsistence of the binding site of dextromethorphan (DM) in the central nervous system has been reported (J. Musacchio, M.Klein and L.J.Santiago, The Journal of Pharmacology and Therapeutics 247 (2), 424 (1988), High Affinity Dextromethorphan Binding Sites in Guinea Pig Brain: Further Characterization and Allosteric Interactions). DM, which is one of the most popular antitussives, is thought to be effective for the ischemic encephalopathy (F.C.Tortella, M.Pellicano and N.G.Bowery, Trips,10(12), 501 (1989), Dextromethophan and neuromodulation: old drug coughs up new activities). It is also thought that the property of σ receptors, which is labeled with [3H]3PPP adopted in the present invention, resembles to the that of DM binding site (J.M.Musacchio, M. Klein and P.D.Cano 11, Life Sciences, 45, 1721 (1989), Dextromethorphan and Sigma Ligands: Common Sites but Diverse Effects).

SUMMARY OF THE INVENTION

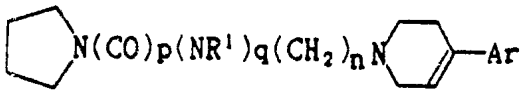
This invention relates to novel tetrahydropyridine derivatives with psychotropic activities. Furthermore, these compounds have high affinity and specificity to σ receptors, whereby these are thought to be effective for some psychoses such

as depression, mania, and acute and chronic schizophrenia, and cerebral ischemic disease.

DETAILED DESCRIPTION

The present invention relates to:

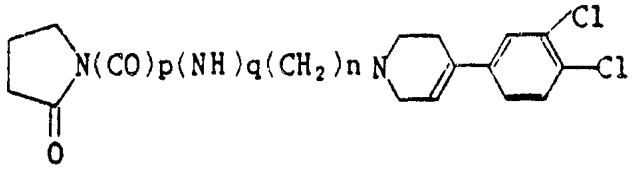
(a) a compound of the formula:



wherein Ar is phenyl which has identically or differently one or two substituents selected from the group consisting of lower alkyl, lower alkoxy, trifluoromethyl, hydroxy and phenyl, which latter phenyl may be substituted by hydroxy, lower alkyl, lower alkoxy or halogen, or Ar is phenyl which is substituted by two halogen atoms;
n is an integer of from 2 to 6;
R^1 is hydrogen or lower alkyl:
the group

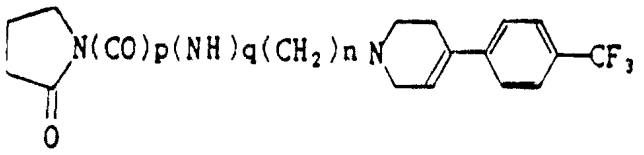
may have identically or differently 1 to 3 substituents selected from the group consisting of lower alkyl, halogen, oxo and phenyl, which phenyl may be substituted by hydroxy, lower alkyl, lower alkoxy or halogen; and
p and q each is an integer of 0 to 1, with the proviso that when p is 0, q is not 1;
or a pharmaceutically acceptable acid addition salt thereof;

(b) a compound of the formula:



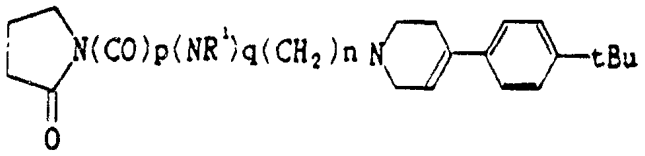
wherein n is an integer of from 2 to 6; p and q each is an integer of 0 or 1, with the proviso that when p is 0, q is not 1; or a pharmaceutically acceptable acid addition salt thereof;

(c) a compound of the formula:



wherein n is an integer of from 2 to 6; p and q each is an integer of 0 or 1, with the proviso that when p is 0, q is not 1; or a pharmaceutically acceptable acid addition salt thereof; and

(d) a compound of the formula:



wherein R^1 is hydrogen or lower alkyl; n is an integer of from 2 to 6; p and q each is an integer of 0 or 1, with the proviso that when p is 0, q is not 1; or a pharmaceutically acceptable acid addition salt thereof.

In this specification, the term "lower alkyl" refers to a straight or branched chain C_1 to C_6 alkyl including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 2-methylbutyl, n-hexyl, isohexyl and the like.

The term "lower alkoxy" refers to C_1 to C_6 alkoxy refers to methoxy, ethoxy, propoxy, butoxy, pentyloxy , hexyloxy and the like.

The term "halogen" refers to fluorine, chlorine, bromine, and iodine.

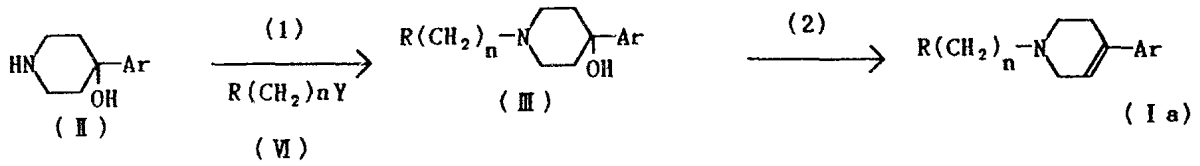
"Substituted phenyl" means phenyl substituted by one or more substituents, of which examples are hydroxy, lower alkyl, lower alkoxy, and halogen.

"5- or 6-membered heterocyclic group" may contain additional one or more heteroatoms including oxygen, sulfur, and nitrogen atoms, and examples of 5- or 6- membered heterocyclic group are isothiazole, pyrazole, pyridine, pyrimidine, imidazole, and isoxazole, preferably, pyrrolidine, piperidine, piperazine, imidazolidine, thiomorpholine, morpholine, pyrazolidine, and the like. And above mentioned heterocyclic group may be condensed with a benzene ring at any position. Further they may identically or differently have 1 to 3 substituents selected from the group consisting of lower alkyl, halogen, oxo, pyrimidine, and substituted or unsubstituted phenyl.

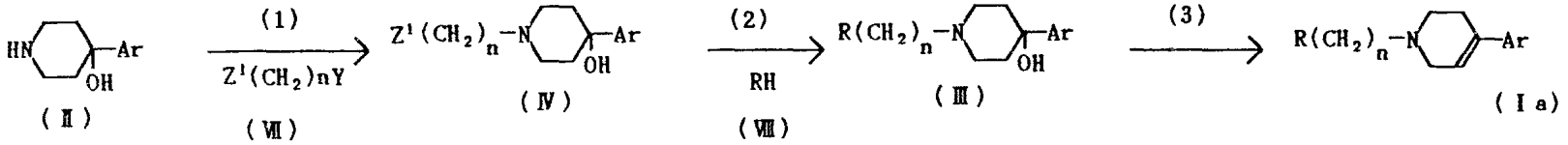
Pharmaceutically acceptable acid addition salt includes mineral acid salts such as hydrochloride, sulfate, nitrate, and phosphate, and organic acid salts such as acetate, fumarate, citrate, tartarate, maleate, and oxalate, most preferably hydrochloride, maleate and oxalate.

The compounds of this invention can be prepared by the following method.

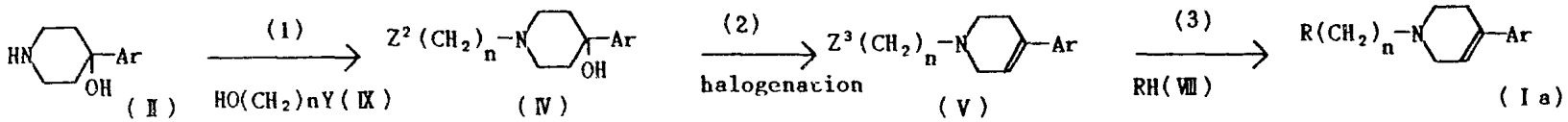
METHOD A



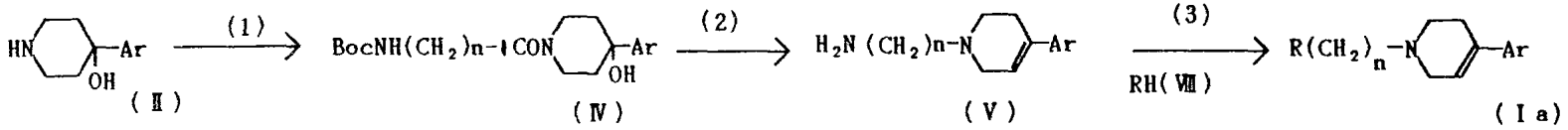
METHOD B



METHOD C



METHOD D



wherein Ar, R, X^1, X^2, and n each has the same meaning as defined above.

Y means halogen. Z^1 means phthaloyl or halogen.

Z^2 and Z^3 each means halogen, hydroxy, alkoxy, or carbonyl.

METHOD A

Step 1

The compound (Ⅱ) is reacted with the compound of the formula:

$$R(CH_2)nY \quad (Ⅵ)$$

wherein R, Y, and n each has the same meaning as defined above in an appropriate organic solvent, if necessary in the presence of the base to prepare the compound (Ⅲ).

The reaction is performed at a temperature of from 50 to 200 ℃, preferably from 85 to 120 ℃, for 1-15 hours, especially for 5-10 hours.

As organic solvents which may be used are alcohols such as methanol and ethanol, ethers such as diethylether and tetrahydrofuran, dimethylformamide, acetonitrile and the like, most preferably dimethylformamide.

As the base, sodium hydroxide, potassium hydroxide, calcium hydroxide, potassium carbonate, pyridine, triethylamine, and the like may be used.

Step 2

The compound (Ⅲ) is subjected to dehydration in an organic solvent in the presence of the acid to prepare the compound (Ⅰa).

The reaction is performed at a temperature of from 0 to 120℃, preferably at room temperature for 1-96 hours, especially for 3-72 hours.

The same organic solvent as mentioned in Step 1 may be used.

The acid includes hydrochloride, acetic acid, trifluoro-acetic acid and p-toluenesulfonic acid.

METHOD B

Step 1

The compound (Ⅱ) is reacted with the compound of the formula:

$$Z^1(CH_2)nY \quad (Ⅶ)$$

wherein Z^1, Y, and n each has the same meaning as defined above in an organic solvent in the presence of the base to prepare the

compound (Ⅳ).

The reaction is performed at 10-150 ℃, preferably from room temperature to 110 ℃, for 1-20 hours, especially for 3-7 hours.

The same organic solvent and the base as mentioned Method A (step 1) may be used.

The compound (Ⅶ) means phthalimide butylbromide, 3-bromo-1-chloropropane and the like.

Step 2

The compound (Ⅳ) is reacted with the compound of the formula:

RH (Ⅷ)

wherein R has the same meaning as defined above in an organic solvent, if necessary in the presence of the base to prepare the compound (Ⅲ).

The reaction is performed at 80-200℃, preferably at 100-130 ℃, for 1-24 hours, especially for 2-7 hours.

The same organic solvent and the base as mentioned Step 1 may be used.

Step 3

The compound (Ⅲ) is subjected to dehydration in the same manner as Method A (step 2) to prepare the compound (Ⅰa). Each condition is same as Method A (step 2).

METHOD C

Step 1

The compound (Ⅱ) is reacted with the compound of the formula:

$HO(CH_2)nY$ (Ⅸ)

wherein Y and n each has the same meaning as defined above preferably in the presence of the base to prepare the compound (Ⅳ).

The reaction is performed at 50-200 ℃, preferably at 120-150℃, for 3-20 hours, especially for 5-9 hours.

Step 2

The compound (Ⅳ) is reacted with chloride of nonmetal

element to prepare the compound (V).

The reaction is performed at 0-100 ℃, preferably at room temperature, for 1-48 hours, especially for 2-24 hours.

The chloride includes sulfur chloride, thionylchloride, hydrochloride, carbon tetrachloride, and the like.

Step 3

The compound (V) is reacted with RH (Ⅷ) to prepare the compound (Ⅲ).

The reaction is performed at 0-100℃, preferably from room temperatre to 50 ℃ for 1-96 hours, preferably for 3-72 hours.

Step 4

The compound (Ⅲ) is subjected to dehydration in the same manner as Method A (step 2) to prepare the compound (I a).

METHOD D

Step 1

The compound (Ⅱ) is reacted with N-protected-β-alanine, in the presence of the condensing agent such as 1,3-dicyclohexyl-carbodiimide, and 1-hydroxybenzotriazole in an appropriate organic solvent to prepare the compound (Ⅳ).

The reaction is performed at a temperature of from 10 to 150 ℃, preferably from room temperature to 70 ℃, for 1-20 hours, especially for 3-7 hours.

The same organic solvent as mentioned in METHOD A (Step 1) may be used.

Step 2

The compound (Ⅳ) is reacted in an appropriate solvent to exclude the amino-protecting group. Then the obtained compound is subjected to the reduction reaction in the presence of the reductant.

The former reaction is performed at a temperature of from 10 to 150 ℃, preferably from room temperature to 70 ℃, for 1-20 hours, especially for 3-7 hours.

The same organic solvent as mentioned in METHOD A (Step 1) may be used, most preferably trifluoroacetic acid.

The latter reduction reaction is performed in the ordinally

method in the presence of the reductant such as lithium aluminium hydride, hydro iodide, hydrogen sulfide, and sodium iodide at a temperature of from 0 to 100 °C, preferably room temperature, for 1 to 7 hours, especially for 2 to 4 hours.

Step 3

The compound (V) is reacted with RH (Ⅷ) to prepare the compound (I a).

The reaction is performed at a temperature of from 50 to 200 °C, preferably from 100 to 130 °C, for 30 minutes to 5 hours, especially for 1-3 hours.

The compound of the present invention can be administered orally or parenterally. For example, the compound of the present invention may be orally administered in the form of tablets, powders, capsuls, and granules, or liquid form such as syrup or elixir, and parenterally in the form of injection of aqueous or oily suspension.

These preparations can be prepared in a conventional manner by using excipients, binders, lubricants, aqueous or oily solubilizers, emulsifier, suspending agents, and the like. And further another preservatives and stabilizers can be used.

The dosages may be varied depending upon the administration route and age, weight, condition, and the kind of disease of the patients, usually 5-1000 mg/day, preferably 20-200 mg/day through the oral route, and 1-500 mg/day, preferably 5-50 mg/day through the parenteral route in a single or divided doses.

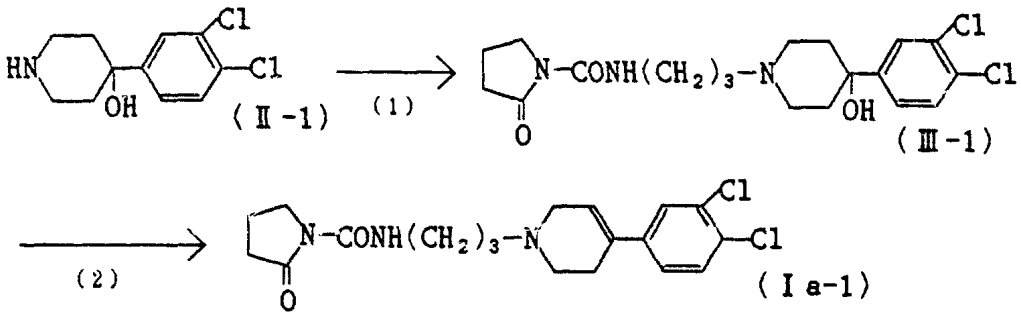
The present invention is illustrated by the following examples and reference examples, which are not to be considered as limiting.

The abbreviations used in exmaples and reference examples have the following meanings.

Me : methyl, Et: ethyl, t-Bu : tert-butyl,
iPr : isopropyl, Ph : phenyl, Ts : tosyl
DMF : dimethylformamide, aq. : aqueous

Example 1

1-[3-{4-(3,4-dichlorophenyl)-1,2,5,6-tetrahydropyridin-1-yl}-propylcarbamoyl]-2-oxopyrrolidine (I a-1)



(1) A solution of 3.0 g of 4-hydroxy-4-(3,4-dichlorophenyl)piperidine (II -1) and 2.50 g of 1-{(3-chloropropyl)carbamoyl-2-oxopyrrolidine in 35 ml of DMF is stirred at 105-110 °C for 6 hours in the presence of 2.74 g of NaI and 4.22 g of K_2CO_3 (reaction condition 1). The reaction mixture is poured into ice-water, and the solution is extracted with ethyl acetate. The organic layer is washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The obtained oily substance is subjected to column chromatography of silica gel eluting with methylene chloride/methanol (15/1-10/1 v/v) to prepare 4.20 g of the objective compound (III -1) as colorless needles.

mp. : 135.5-137.0°C

Anal Calcd. (%) for $C_{19}H_{25}N_3O_3Cl_2$:

: C, 54.90; H, 6.10; N, 10.16; Cl, 17.21

Found : C, 55.08; H, 6.08; N, 10.14; Cl, 17.11

IR ($CHCl_3$) : 3600, 3320, 1712, 1680, 1545, 1489, 1470

NMR ($CDCl_3$) δ (200MHz): 1.682 (dd, J_1=12Hz, J_2=2Hz, 2H); 1.772 (quint, J=7Hz, 2H); 2.042 (quint, J=8Hz, 2H); 2.062 (s, 1H); 2.191 (td, J_1=13Hz, J_2=4Hz, 2H); 2.409 (t, J=11Hz, 2H); 2.497 (t, J=7Hz, 2H); 2.628 (t, J=8Hz, 2H); 2.837 (dd, J_1=11Hz, J_2=2Hz, 2H); 3.394 (q, J=6Hz, 2H); 3.854 (t, J=7Hz, 2H); 7.393,7.401,7.716 (sx3,3H)

(2) A solution of 2.77 g of the compound (III -1) and 1.60 g

of p-toluenesulfonic acid in 300 ml of toluene is reflexed for 48 hours to separate water as azeotropic mixture of toluene. After removal of the solvent, the residue is dissolved in ethyl acetate and washed with aq.NaOH and water. The solution is dried over Na_2SO_4 and concentrated under reduced pressure. The oily residue is subjected to column chromatography of silica gel eluting with ethyl acetate-methylene chloride/methanol (20/1 v/v) to prepare 2.26 g (Yield : 89.3 %) of the objective compound (I a-1) as an oil. The maleate is recrystallized from i-PrOH to prepare 2.50 g colorless needles. mp. 135.5-136.5 °C

Anal Calcd. (%) for $C_{19}H_{23}N_3O_2Cl_2 \cdot C_4H_4O_4$:

C, 53.84; H, 5.32; N, 8.18; Cl, 13.93

Found : C, 53.91; H, 5.31; N, 8.20; Cl, 13.84

IR (Nujol) cm^{-1} :

3310, 1713. 1680, 1625, 1580, 1550 (sh), 1518, 1485, 1455

NMR ($CDCl_3$) δ (200MHz) :

1.829 (quint, J=7Hz, 2H); 2.039 (quint, J=8Hz, 2H); 2.50~2.55 (m, 4H); 2.612 (t, J=8Hz, 2H); 2.714 (t, J=6Hz, 2H); 3.171 (q, J=3.3 Hz, 2H); 3.398 (q, J=7Hz, 2H); 3.874 (t, J=7Hz, 2H); 6.100 (quint, J=2Hz, 1H); 7.224 (dd, J_1=8Hz, J_2=2Hz, 1H); 7.397 (d, J=8Hz, 1H); 7.463 (d, J=2Hz, 2H); 8.513 (brs, 1H)

Example 2-16

The reaction is performed in the same manner as Example 1 to prepare the compound (I a). The reaction conditions are shown in table 1 and 2, and pyhsical constants of the compound (III) are shown in table 3 and those of the compound (I a) are shown in table 4.

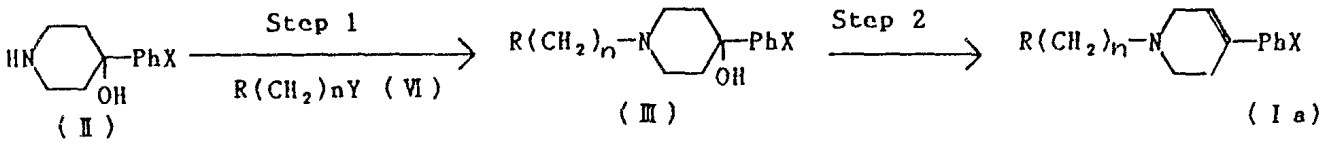


Table 1 (Step 1) (No.1)

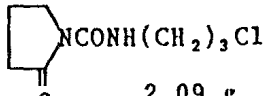
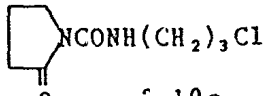
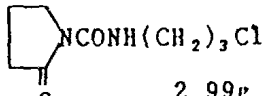
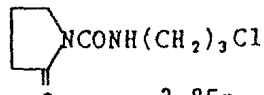
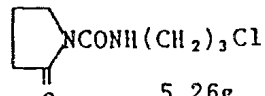
Ex. No.	(Ⅱ) X=	R(CH₂)nY(Ⅵ)	DMF (ml)	K_2CO_3 (g)	NaI (g)	reaction condition(1)	eluent condition	g (%) compd. No
2	CF_3(p) 2.50g (Ⅱ-2)	 2.09 g	25	2.28	2.29	105-110 7 hr.	CH_2Cl_2/MeOH =10/1	3.89 (92.2) (Ⅲ-2)
3	n-Pr(p) 2.25g (Ⅱ-3)	 2.10g	20	2.85	2.31	105 5 hr.	CH_2Cl_2/MeOH =10/1	2.98 (74.6) (Ⅲ-3)
4	Et(p) 3.00g (Ⅱ-4)	 2.99g	30	4.04	3.28	105 7 hr.	CH_2Cl_2/MeOH =10/1	4.10 (75.2) (Ⅲ-4)
5	Ph(p) 4.76g (Ⅱ-5)	 3.85g	57	5.19	4.22	105 24hr.	CH_2Cl_2/MeOH =20/1-10/1	7.31 (92.3) (Ⅲ-5)
6	t-Bu(p) 6.0g (Ⅱ-6)	 5.26g	60	7.11	5.78	105 10hr.	CH_2Cl_2/MeOH =10/1	8.36 (81.0) (Ⅲ-6)

Table 1 (No. 2)

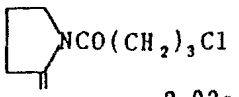
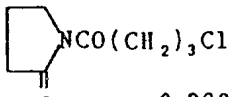
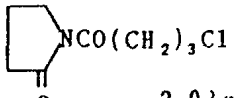
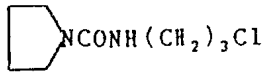
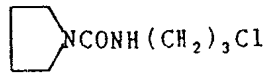
7	n-Pr(p) 1.95g (Ⅱ-3)	 0 2.02g	30	2.46	2.0	105℃ 9hr.	CH_2Cl_2/MeOH =20/1~10/1	2.0 (65.0) (Ⅲ-7)
8	t-Bu(p) 1.98g (Ⅱ-6)	 0 0.928g	20	1.35	1.10	100 ℃ 2.6 hr.	CH_2Cl_2/MeOH =19/1-9/1	0.853 (46.9) (Ⅲ-8)
9	CF_3(p) 2.33g (Ⅱ-2)	 0 2.02g	30	2.62	2.14	100-105℃ 8.5 hr.	CH_2Cl_2/MeOH =20/1-10/1	2.46 (65.0) (Ⅲ-9)
10	Ph 930mg (Ⅱ-5)	 0.70g	11	1.015	0.825	105℃ 5 hr.	CH_2Cl_2/MeOH /NH_4OH =128/16/1- 32/6/1	0.616 (41.0) (Ⅲ-10)
11	t-Bu(p) 844mg (Ⅱ-6)	 0.70g	11	1.00	0.813	100℃ 5.5hr.	CH_2Cl_2/MeOH /NH_4OH =128/16/1- 64/8/1	0.830 (57.3) (Ⅲ-11)

Table 1 (No. 3)

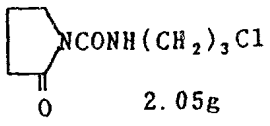
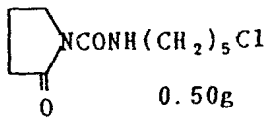
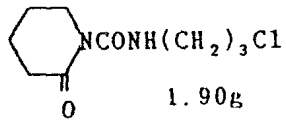
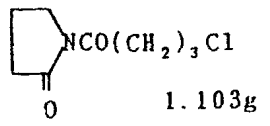
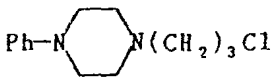
12	CF_3(m) 2.5g (Ⅱ-7)	 2.05g	25	2.76	2.25	100-105℃ 5.5hr.	CH_2Cl_2/MeOH =10/1	3.8 (90.2) (Ⅲ-12)
13	CF_3(p) 527mg (Ⅱ-2)	 0.50g	7	0.59	—	105℃ 7hr.	CH_2Cl_2/MeOH =20/1-10/1	0.82 (86.6) (Ⅲ-13)
14	t-Bu(p) 2.03g (Ⅱ-6)	 1.90g	20	2.40	1.95	105℃ 7.5hr.	CH_2Cl_2/MeOH =20/1-7/1	2.99 (82.8) (Ⅲ-14)
15	Me (p) 1.07g (Ⅱ-8)	 1.103g	26	1.61	1.31	95℃ 7hr.	CH_2Cl_2/MeOH =19/1-9/1	0.477 (24.8) (Ⅲ-15)
16	t-Bu (p) 980 mg (Ⅱ-6)	 1.0g	20	1.16	0.94	105℃ 6.5hr.	CH_2Cl_2/MeOH =10/1-5/1	1.69 (92.6) (Ⅲ-16)

Table 2 (Step 2) (No.1)

starting material	acid	solvent (ml)	reflux time	eluenting condition (2)	product (g)
(Ⅲ-2) 4.24g	TsOH・H_2O (3.90g)	toluene(280) dichloro-ethane (70)	48hr.	ethyl acetate-CH_2Cl_2/MeOH=20/1	Ⅰa-2 2.26g
(Ⅲ-3) 2.52g	CF_3COOH (25ml)	—	10hr.	toluene/ ethyl acetate=1/1 CH_2Cl_2/MeOH=20/1	Ⅰa-3 2.22g
(Ⅲ-4) 4.10g	CF_3COOH (35ml)	—	10hr.	ethyl acetate-CH_2Cl_2/MeOH =30/1-20/1	Ⅰa-4 3.41g
(Ⅲ-5) 2.73g	CF_3COOH (30ml)	—	9hr.	CH_2Cl_2/MeOH =30/1-20/1	Ⅰa-5 2.40g
(Ⅲ-6) 2.08g	CF_3COOH (25ml)	—	4hr.	ethyl acetate-CH_2Cl_2/MeOH =30/1-20/1	Ⅰa-6 1.90g (95.6)

Table 2 (No.2)

(Ⅲ-7) 2.67g	CF_3COOH (30ml)	—	7.5hr.	toluene/ethyl- ethyl acetate=1/1- ethyacetate	Ⅰa-7 0.24g (59.8)
(Ⅲ-8) 0.822g	CF_3COOH (2ml)	—	1.8hr.	toluene/acetone=2/1 CH_2Cl_2/MeOH=9/1	Ⅰa-8 0.697g (88.8)
(Ⅲ-9) 2.27g	CF_3COOH (25ml)	—	24.5hr.	toluene/ ethyl acetate=1/1 CH_2Cl_2/MeOH =20/1-10/1	Ⅰa-9 1.13g (52.1)
(Ⅲ-10) 0.766g	CF_3COOH (10ml)	—	1hr.	CH_2Cl_2/MeOH=9/1	Ⅰa-10* 0.572g (60.5)
(Ⅲ-11) 0.914g	CF_3COOH (10ml)	—	1hr.	CH_2Cl_2/MeOH=9/1	Ⅰa-11* 0.854g (75.4)

*: maleate

Table 2 (No.3)

(Ⅲ-12) 3.42g	CF_3COOH (35ml)	—	23hr.	toluene/ ethyl acetate=1/1 CH_2Cl_2/MeOH=20/1	Ⅰa-12 3.15g (96.0)
(Ⅲ-13) 3.45g	CF_3COOH (45ml)	—	72hr.	toluene/ ethyl acetate=1/1 CH_2Cl_2/MeOH=20/1	Ⅰa-13 2.96g (89.4)
(Ⅲ-14) 2.82g	CF_3COOH (35ml)	—	5hr.	CH_2Cl_2/MeOH=20/1	Ⅰa-14 2.62g (97.0)
(Ⅲ-15) 0.544g	CF_3COOH (1ml)	—	3hr. (room temperature)	toluene/acetone=2/1	Ⅰa-15 0.313g (59.6)
(Ⅲ-16) 1.50g	CF_3COOH (20ml)	—	4hr.	toluene/ ethyl acetate=1/1 CH_2Cl_2/MeOH =20/1-10/1	Ⅰa-16 1.40g (97.4)

Table 3 (No.1)

Compd. No.	mp. (℃) (solvent)	Anal. Calcd. (%) Found (%)	I R (cm^{-1})	NMR (δ)
Ⅲ-2	151.5-152.5 (CH_2Cl_2-Et_2O)	$C_{20}H_{26}N_3O_3F_3$: C. 57.92 (58.10) H. 6.26 (6.34) N. 10.15 (10.16) F. 13.57 (13.79)	($CHCl_3$) 3600, 3310, 1713 1680, 1605, 1510 1489	($CDCl_3$) 1.712 (d-d, J_1=12Hz, J_2=2Hz, 2H); 1.776 (quintJ=7Hz, 2H); 2.026 (quint, J=7Hz, 2H); 2.046 (s, 1H); 2.210 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.432 (t-d, J_1=11Hz, J_2=2Hz, 2H); 2.490 (t, J=7Hz, 2H); 2.601 (t, J=8Hz, 2H); 2.838 (d-d, J_1=11Hz, J_2=2Hz, 2H); 7.595 (d, J=8Hz, 2H); 7.679 (d, J=8Hz, 2H); 8.619 (brs, 1H)
Ⅲ-3	96.0-97.0 (ethyl-acetate -Et_2O	$C_{22}H_{33}N_3O_3$: C. 67.84 (68.18) H. 8.41 (8.58) N. 10.74 (10.84)	($CHCl_3$) 3600, 3320, 1713 1680, 1602, 1547 1490, 1460	($CDCl_3$) 1.634 (sextet, J=7Hz, 2H); 1.70~1.85 (m, 4H); 2.018 (quint, J=8Hz, 2H); 2.185 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.38~2.64 (m, 8H); 7.160 (d, J=8Hz, 2H); 7.343 (d, J=8Hz, 2H); 8.551 (brs, 1H)
Ⅲ-4	84.0-85.5		($CHCl_3$) 3600, 3320, 1713 1680, 1545	($CDCl_3$) 1.235 (t, J=8Hz, 3H); 1.72~1.83 (m, 4H); 2.022 (quint, J=7Hz, 2H); 2.191 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.4~2.7 (m, 8H); 2.819 (d-d, J_1=12Hz, J_2=1Hz, 2H); 3.375 (q, J=6Hz, 2H); 3.848 (t, J=7Hz, 2H); 7.186 (d, J=8Hz, 2H); 7.442 (d, J=8Hz, 2H); 8.555 (brs, 1H)
Ⅲ-5	155.5-156.5 (CH_2Cl_2-Et_2O)	$C_{26}H_{31}N_3O_3 \cdot 1/5H_2O$ C. 70.50 (70.63) H. 7.46 (7.82) N. 9.65 (9.88)	($CHCl_3$) 3600, 3320, 1713 1682, 1545	($CDCl_3$) 1.84~1.73 (m, 4H); 2.014 (quint, J=8Hz, 2H); 2.247 (t-d, J_1=14Hz, J_2=4Hz, 2H); 2.458 (t-d, J_1=14Hz, J_2=1H, 2H); 2.507 (t, J=7Hz, 2H); 2.595 (t, J=8Hz, 2H); 2.853 (d, J=11Hz, 2H); 3.386 (q, J=6Hz, 2H); 3.846 (t, J=7Hz, 2H); 7.25~7.65 (m, 9H); 8.577 (brs, 1H)
Ⅲ-6	149.5-150.5 (CH_2Cl_2-Et_2O)	$C_{23}H_{35}N_3O_3$ C. 68.48 (68.80) H. 8.69 (8.79) N. 10.39(10.46)	($CHCl_3$) 3600, 3320, 1713 1680, 1543	($CDCl_3$) 1.303 (s, 9H); 1.521 (s, 1H); 1.738 (d-d, J_1=11Hz, J_2=3Hz, 2H); 1.793 (quint, J=8Hz, 2H); 2.022 (quint, J=7Hz, 2H); 2.195 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.39~2.53 (m, 4H); 2.593 (t, J=8Hz, 2H); 2.823 (d, J=11Hz, 2H); 3.375 (q, J=7Hz, 2H); 3.851 (t, J=7Hz, 2H); 7.38, 7.43 (ABq, J=9Hz, 4H); 8.543 (brs, 1H)

Table 3 (No. 2)

Compd. No.	mp. (°C) (solvent)	Anal Calcd.(%) Found (%)	IR (cm^{-1})	NMR (δ)
Ⅲ-7	161.0~162.5 (CH_2Cl_2-ethyl-acetate)	$C_{22}H_{33}N_2O_3Cl \cdot 1/3H_2O$ C. 63.46 (63.68) H. 8.02 (8.18) N. 6.83 (6.75) F. 7.98 (8.54)	(Nujol) 3310, 2640, 2560 1730, 1680	($CDCl_3$) 0.939 (t, J=7Hz, 3H); 1.630 (sextet, J=7Hz, 2H); 1.781 (d, J=12Hz, 2H); 1.87-2.10 (m, 4H); 2.246 (t-d, J_1=12Hz, J_2=3Hz, 2H); 2.50-2.68 (m, 8H); 2.920 (d, J=12Hz, 2H); 2.957 (t, J=7Hz, 2H); 3.804 (t, J=7Hz, 2H); 7.156, 7.406 (ABq, J=8Hz, 4H)
Ⅲ-8	207.0-210.0 (CH_2Cl_2-Et_2O-n-hexane)	$C_{23}H_{34}N_2O_3$: C. 63.73 (71.47) H. 8.09 (8.87) N. 7.31 (7.25)	($CHCl_3$) 3663, 3598, 3345 2630, 2460, 2410 1740, 1692, 1611 1509, 1471, 1460	($CDCl_3$) 1.299 (s, 9H); 1.960 (d, J=14Hz, 2H); 1.95-2.13 (m, 4H); 2.17-2.35 (m, 2H); 2.606 (t, J=8Hz, 2H); 2.694 (t-d, J_1=14Hz, J_2=2Hz, 2H); 2.95-3.10 (m, 4H); 3.25-3.45 (m, 4H); 3.800 (t, J=7Hz, 2H); 7.368, 7.441 (ABq, J=8Hz, 4H)
Ⅲ-9	147.0~148.0 (CH_2Cl_2-Et_2O)	$C_{26}H_{35}N_2O_3F_3 \cdot 1/5H_2O$ C. 59.79 (59.75) H. 6.27 (6.97) N. 6.79 (6.37) F. 14.26 (14.18)	($CHCl_3$) 3600, 1738, 1693 1620	($CDCl_3$) 1.715 (d-d, J_1=14Hz, J_2=2Hz, 2H); 1.878 (s, 1H); 1.898 (quint, J=8Hz, 2H); 2.021 (quint, J=8Hz, 2H); 2.152 (t-d, J_1=14Hz, J_2=4Hz, 2H); 2.451 (t-d, J_1=15Hz, J_2=2Hz, 2H); 2.482 (t, J=8Hz, 2H); 2.584 (t, J=8Hz, 2H); 2.862 (d, J=15Hz, 2H); 2.936 (t, J=7Hz, 2H); 3.794 (t, J=7Hz, 2H) 7.579, 7.627 (ABq, J=8Hz, 4H)
Ⅲ-10	225.0~228.0 (CH_2Cl_2-MeOH-Et_2O)	$C_{25}H_{33}N_3O_2 \cdot 1/10H_2O$ C. 73.25 (73.35) H. 8.26 (8.18) N. 10.21 (10.27)	(Nujol) 3300, 3055, 3030 2810, 2770, 2670 1606, 1528, 1487 1471, 1456, 1448	($CDCl_3$) 1.775 (quint, J=7Hz, 2H); 1.845 (d, J=14Hz, 2H); 1.89-1.96 (m, 4H); 2.171 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.52-2.63 (m, 4H); 2.900 (d, J=12Hz, 2H); 3.25-3.38 (m, 4H); 7.30-7.70 (m, 9H)
Ⅲ-11	138.5~140.5 (CH_2Cl_2-Et_2O)	$C_{23}H_{37}N_3O_2 \cdot 2/5H_2O$ C. 70.07 (69.98) H. 9.54 (9.65) N. 10.66 (10.64)	(Nujol) 3350, 3150, 1631 1542, 1509, 1485 1460, 1441, 1388	($CDCl_3$) 1.322 (s, 9H); 1.76-1.94 (m, 8H); 2.262 (t-d, J_1=14Hz, J_2=4Hz, 2H); 2.50-2.65 (m, 4H); 2.951 (d, J=11Hz, 2H); 3.30-3.39 (m, 4H); 5.738 (brs, 1H); 7.378, 7.418 (ABq, J=8Hz, 4H)

Table 3 (No.3)

Compd. No.	mp. (°C) (solvent)	Anal Calcd.(%) Found (%)	IR (cm^{-1})	NMR (δ)
Ⅲ-12	113.5~114.5 (CH_2Cl_2-Et_2O)	$C_{20}H_{24}N_3O_3F_3$: C.57.90 (58.10) H. 6.26 (6.34) N.10.14 (10.16) F.13.49 (13.79)	($CHCl_3$) 3600, 3320, 1713 1680, 1545, 1490 1385, 1332	($CDCl_3$) 1.715 (d-d, J_1=12Hz, J_2=2Hz, 2H); 1.780 (quintJ=7Hz, 2H); 2.000 (s, 1H); 2.027 (quint, J=7Hz, 2H); 2.253 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.442 (d, J=12Hz, 2H); 2.504 (t, J=7Hz, 2H); 2.606 (t, J=8Hz, 2H);2.854 (d-d, J_1=11Hz, J_2=3Hz, 2H); 3.394 (quint, J=7Hz, 2H); 3.850 (t, J=7Hz, 2H); 7.474 (d, J=7Hz, 1H); 7.492 (t, J=7Hz, 1H); 7.746 (d, J=7Hz, 1H); 7.871 (s, 1H); 8.678 (brs, 1H)
Ⅲ-13	oil	——	——	($CDCl_3$) 1.30-1.44 (m, 2H); 1.584 (quint×2, J=7Hz, 4H); 1.747 (d, J=12Hz, 2H); 2.022 (quint, J=7Hz, 2H); 2.216 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.41-2.49 (m, 4H); 2.600 (t, J=8Hz, 2H); 2.773 (d, J=11Hz, 2H); 3.292 (q, J=7Hz, 2H); 3.837 (t, J=7Hz, 2H); 7.598, 7.662 (ABq, J=9Hz, 4H); 8.428 (brs, 1H)
Ⅲ-14	153.0~154.0 (CH_2Cl_2-Et_2O)	$C_{24}H_{37}N_3O_3$: C.69.29 (69.36) H. 8.93 (8.97) N.10.14 (10.11)	($CHCl_3$) 3600, 3280, 1702 (sh), 1697, 1645 1530, 1480, 1460 1400	($CDCl_3$) 1.319 (s, 9H); 1.623 (s, 1H); 1.71-1.86 (m, 8H); 2.190 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.39-2.58 (m, 6H); 2.824 (d, J=11Hz, 2H); 3.375 (q, J=7Hz, 2H); 3.75-3.82 (m, 2H); 7.463, 7.372 (ABq, J=9Hz, 4H); 9.479 (brs, 1H)
Ⅲ-15	~180 (CH_2Cl_2-Et_2O)	——	——	($CDCl_3$) 1.782 (d-d, J_1=14Hz, J_2=2Hz, 2H); 1.90-2.12 (m, 6H); 2.275 (t-d, J_1=14Hz, J_2=2Hz, 2H); 2.330 (s, 3H); 2.600 (t, J=8Hz, 4H); 2.965 (t,J=7Hz, 4H); 3.810 (t, J=7Hz, 2H); 7.163, 7.394 (ABq, J=8Hz, 4H)
Ⅲ-16	129.0~130.5 (CH_2Cl_2-Et_2O)	$C_{28}H_{41}N_3O \cdot 1/3H_2O$ C.76.08 (76.15) H. 9.41 (9.51) N. 9.63 (9.51)	($CHCl_3$) 3600, 1602, 1580 1505(sh), 1495, 1470, 1460(sh), 1455, 1400, 1380	($CDCl_3$) 1.661 (s, 1H); 1.77-1.94 (m, 4H); 2.285 (t-d, J_1=13Hz, J_2=2Hz, 2H); 2.460 (t, J=7Hz, 2H); 2.53-2.65 (m, 6H); 3.18-3.24 (m, 2H); 6.80-7.48 (m, 9H)

Table 4 (No. 1)

Compd. No.	mp. (°C) (solvent)	Anal Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
I a-2	187.0-188.5 (oxalate) (i-PrOH)	$C_{20}H_{24}N_3O_2F_3 \cdot C_2H_2O_4$ C. 54.45 (54.43) H. 5.38 (5.40) N. 8.76 (8.66) F. 12.26 (11.74)	($CHCl_3$) 3290, 2600 (br), 1710, 1685, 1615 1550, 1460	($CDCl_3$-CD_3OD=1/5) 2.00~2.20 (m, 4H): 2.620 (t, J=8Hz, 2H): 2.98~2.87 (brs, 2H): 3.292 (t, J=8Hz, 2H): 3.451 (t, J=7Hz, 2H): 3.556 (t, J=6Hz, 2H): 3.819 (t, J=7Hz, 2H): 3.977 (d, J=3Hz, 2H): 6.239 (t, J=3Hz, 1H): 7.646 (s, 4H)
I a-3	162.0-162.5 (maleate) (i-PrOH)	$C_{26}H_{35}N_3O_6$: C. 64.23 (64.31) H. 7.23 (7.27) N. 8.54 (8.65)	(Nujol) 3330, 1705 (s), 1695, 1620, 1575 1528	($CDCl_3$) 0.935 (t, J=7Hz, 3H): 1.629 (sextet, J=7Hz, 2H): 1.828 (quint, J=7Hz, 2H): 2.015 (quint, J=7Hz, 2H): 2.49~2.64 (m, 8H): 2.706 (t, J=6Hz, 2H): 3.158 (q, J=3Hz, 2H): 3.387 (q, J=7Hz, 2H): 3.858 (t, J=7Hz, 2H): 6.032 (quint, J=2Hz, 1H): 7.117 (d, J=8Hz, 2H): 7.302 (d, J=8Hz, 2H): 8.486 (brs, 1H)
I a-4	86.0-87.0 (ether)	$C_{21}H_{29}N_3O_2$ C. 70.97 (70.95) H. 8.11 (8.22) N. 11.97 (11.82)	($CHCl_3$) 3220, 1713, 1682 1545, 1488, 1460	($CDCl_3$) 1.227 (t, J=7Hz, 3H): 1.824 (quint, J=7Hz, 2H): 2.015 (quint, J=7Hz, 2H): 2.527 (t, J=8Hz, 2H): 2.561 (brs, 2H): 2.591 (t, J=8Hz, 2H): 2.629 (q, J=8Hz, 2H): 3.150 (q, J=3Hz, 2H): 3.386 (q, J=7Hz, 2H): 3.856 (t, J=7Hz, 2H): 6.017 (quint, J=2Hz, 1H): 7.141 (d, J=8Hz, 2H): 7.310 (d, J=8Hz, 2H): 8.490 (brs, 1H)
I a-5	144.0-146.0 (decom. point) (ethyl acetate)	$C_{25}H_{29}N_3O_2$ C. 74.32 (74.41) H. 7.21 (7.24) N. 10.49 (10.41)	($CHCl_3$) 3320, 1702, 1680 1600, 1545, 1485	($CDCl_3$) 1.840 (quint, J=7Hz, 2H): 2.019 (quint, J=8Hz, 2H): 2.555 (t, J=8Hz, 2H): 2.584 (br, 2H): 2.596 (t, J=8Hz, 2H): 2.733 (t, J=6Hz, 2H): 3.190 (q, J=3Hz, 2H): 3.398 (q, J=7Hz, 2H): 3.863 (t, J=7Hz, 2H): 6.128 (quint, J=3Hz, 1H): 7.26~7.63 (m, 9H): 8.504 (brs. 1H)
I a-6	173.0-174.0 (decom.) (maleate) (i-PrOH -MeOH)	$C_{23}H_{33}N_3O_2 \cdot C_4H_4O_4$ C. 64.68 (64.91) H. 7.48 (7.46) N. 8.38 (8.41)	(NUjol) 3320, 1712, 1690 1620, 1580, 1543	($CDCl_3$)(free) 1.314 (s, 9H): 1.837 (quint, J=7Hz, 2H): 2.022 (quint, J=7Hz, 2H): 2.5~2.6 (m, 6H): 2.717 (t, J=6Hz, 2H): 3.169 (q, J=3Hz, 2H): 3.387 (q, J=6Hz, 2H): 6.023 (q, J=2Hz, 1H): 7.332 (s, 4H): 8.496 (brs, 1H)

Table 4 (No. 2)

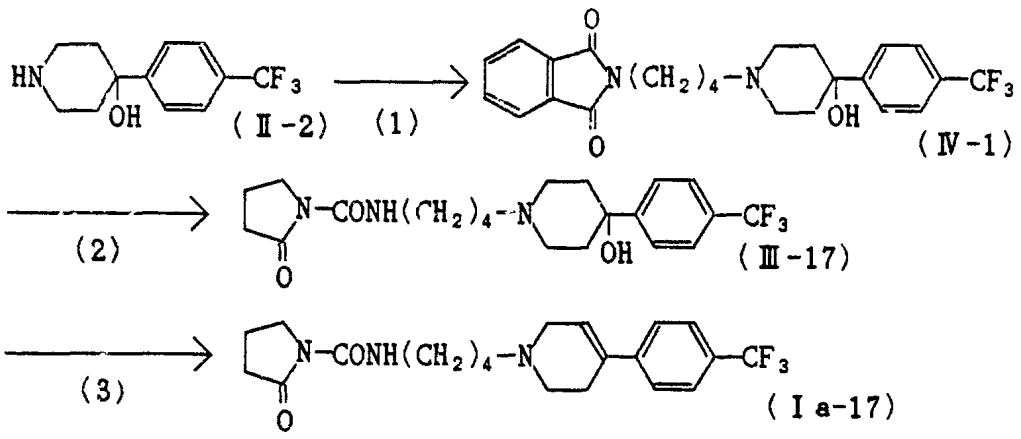
Compd. No.	mp. (°C) (solvent)	Anal Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
I a-7	190.0-191.0 (oxalate) (MeOH)	$C_{20}H_{24}N_3O_2F_3 \cdot C_2H_2O_4$ C. 64.39 (64.85) H. 6.27 (7.26) N. 6.12 (6.30)	(Nujol) 2500, 1732, 1725 (sh), 1685, 1610 (br)	($CDCl_3$) 0.935 (t, J=7Hz, 3H); 1.629 (sextet, J=8Hz, 2H); 1.978 (sextet, J=7Hz, 2H); 1.989 (sextet, J=7Hz, 2H); 2.52-2.60 (m, 8H); 2.745 (t, J=6Hz, 2H); 2.973 (t, J=7Hz, 2H); 3.195 (q, J=3Hz, 2H); 3.795 (t, J=7Hz, 2H); 6.022 (quint, J=2Hz, 1H); 7.120, 7.299 (ABq, J=8Hz, 4H)
I a-8	96.0-97.0 (Et_2O-n-hexane)	$C_{23}H_{32}N_2O_2$: C. 75.23 (74.96) H. 8.73 (8.75) N. 7.65 (7.60)	($CHCl_3$) 1737, 1692, 1508 1482, 1459, 1427 1364	($CDCl_3$) 1.317 (s, 9H); 1.962 (sextet, J=6Hz, 2H); 1.996 (sextet, J=6Hz, 2H); 2.570 (q, J=8Hz, 6H); 2.721 (t, J=5Hz, 2H); 2.972 (t, J=7Hz, 2H); 3.174 (q, J=3Hz, 2H); 3.801 (t, J=7Hz, 2H); 6.031 (quint, J=2Hz, 1H); 7.331 (s, 4H)
I a-9	149.5-150.5 (CH_2Cl_2-Et_2O)	$C_{20}H_{23}N_2O_2F_3$ C. 63.17 (63.15) H. 6.09 (6.09) N. 7.38 (7.36) F. 15.06 (14.98)	($CHCl_3$) 1738, 1692, 1615 1477, 1365, 1325	($CDCl_3$) 1.964 (sextet, J=7Hz, 2H); 2.001 (sextet, J=7Hz, 2H), 2.538 (q, J=8Hz, 6H); 2.745 (t, J=6Hz, 2H); 2.980 (t, J=7Hz, 2H); 3.207 (q, J=3Hz, 2H); 3.803 (t, J=7Hz, 2H); 6.160 (quint, J=3Hz, 1H); 7.472, 7.565 (ABq, J=8Hz, 4H)
I a-10	164.0-166.0 (malenate) (MeOH-Et_2O)	$C_{25}H_{31}N_3O \cdot C_4H_4O_4$ C. 68.89 (68.89) H. 6.97 (6.98) N. 8.30 (8.31)	(Nujol) 3403, 3037, 2330 1700, 1640, 1578 1537, 1498, 1457	(CD_3OD) 1.88-2.06 (m, 4H); 2.951 (brs, 2H); 3.20-3.40 (m, 6H); 3.557 (brs, 2H); 3.959 (brs, 2H); 6.220 (s, 1H); 6.248 (s, 2H); 7.30-7.70 (m, 9H)
I a-11	138.0-140.0 (malenate) (MeOH-Et_2O)	$C_{23}H_{33}N_3O \cdot C_4H_4O_4 \cdot 1/5H_2O$ C. 66.16 (66.29) H. 8.21 (8.12) N. 8.82 (8.59)	(Nujol) 3522, 3362, 2718 2350, 1701, 1630 1579, 1524, 1498	(CD_3OD) 1.316 (s, 9H); 1.87-2.08 (m, 6H); 2.896 (brs, 2H); 3.22-3.36 (m, 8H); 3.526 (brs, 2H); 3.918 (brs, 2H); 6.117 (quint, J=3Hz, 1H); 6.245 (s, 2H); 7.414 (s, 4H)

Table 4 (No. 3)

Compd. No.	mp. (°C) (solvent)	Anal Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
I a-12	128.0-129.0 (malenate) (i-PrOH -MeOH)	$C_{20}H_{24}N_3O_2F_3 \cdot C_4H_4O_4$ C. 56.35 (56.36) H. 5.55 (5.52) N. 8.21 (8.22) F. 11.08 (11.14)	(Nujol) 3300, 2300 (br), 1710, 1638, 1625 1570, 1530, 1500 1460, 1445	($CDCl_3$) 1.831 (quint, J=7Hz, 2H): 2.027 (quint, J=8Hz, 2H): 2.51-2.65 (m, 6H): 2.729 (t, J=6Hz, 2H): 3.186 (q, J=3Hz, 2H): 3.397 (q, J=7Hz, 2H): 3.865 (t, J=7Hz, 2H): 6.145 (quint, J=2Hz, 1H): 7.41-7.63 (m, 4H): 8.517 (brs, 1H)
I a-13	128.0-129.5 (oxalate) (MeOH- i-PrOH)	$C_{22}H_{24}N_3O_2F_3 \cdot C_2H_2O_4 \cdot 1/2PrOH$ C. 56.18 (56.35) H. 6.23 (6.39) N. 7.70 (7.73) F. 10.22 (10.49)	(Nujol) 3510, 3310, 1708 1690, 1680, 1615 1537, 1480, 1460	($CDCl_3$) 1.35-1.47 (m, 2H): 1.613 (quint×2, J=7Hz, 4H): 2.025 (quint, J=8 Hz, 2H): 2.44-2.65 (m, 6H): 2.716 (t, J=5Hz, 2H): 3.181 (q, J=3Hz, 2H): 3.312 (q, J=6Hz, 2H): 3.862 (t, J=7Hz, 2H): 6.157 (quint, J=2 Hz, 1H): 7.472, 7.563 (ABq, J=8Hz, 4H): 8.419 (brs, 1H)
I a-14	185.0-186.5 (malenate) (MeOH)	$C_{24}H_{35}N_3O_2 \cdot C_4H_4O_4$ C. 65.53 (65.48) H. 7.62 (7.65) N. 8.24 (8.18)	(Nujol) 3285, 1695, 1648 1620, 1580, 1523 1477, 1460, 1450	($CDCl_3$) 1.312 (s, 9H): 1.77-1.88 (m, 6H): 2.49-2.56 (m, 6H): 2.704 (t, J=6 Hz, 2H): 3.160 (q, J=3Hz, 2H): 3.380 (q, J=7Hz, 2H): 3.75-3.82 (m, 2H): 6.026 (quint, J=2Hz, 1H): 7.328 (s, 4H): 9.444 (brs, 1H)
I a-15	109.5-110.0 (Et_2O- n-hexane)	$C_{20}H_{16}N_2O_2$ C. 73.79 (73.59) H. 8.08 (8.03) N. 8.55 (8.58)	($CHCl_3$) 1738, 1692, 1512 1485, 1460, 1430 1367	($CDCl_3$) 1.939 (quint, J=7Hz, 2H): 2.007 (quint, J=7Hz, 2H): 2.328 (s, 3H): 2.49-2.63 (m, 4H): 2.713 (t, J=5Hz, 2H): 2.969 (t, J=7Hz, 2H): 3.153 (q, J=3Hz, 2H): 3.794 (t, J=7Hz, 2H): 6.018 (quint, J=2Hz, 1H): 7.115, 7.280 (ABq, J=8Hz, 4H)
I a-16	105.0-106.0 (malenate) (i-PrOH -Et_2O) 210.0-212.5 (MeOH)	$C_{28}H_{32}N_3O_2 \cdot C_4H_4O_4$ C. 66.49 (66.54) H. 7.26 (7.29) N. 6.59 (6.47)	(Nujol) 1710, 1622, 1598 1575, 1495(sh), 1480, 1462, 1450 1385, 1360	($CDCl_3$) 1.315 (s, 9H): 1.78-1.84 (m, 8H): 2.43-2.75 (m, 8H): 3.16-3.25 (m, 6H): 6.043 (quint, J=2Hz, 1H): 6.80-7.34 (m, 9H)

Example 17

1-[4-(4-(4-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridin-1-yl)-butylcarbamoyl]-2-oxopyrrolidine (I a-17)



(1) A solution of 2.00 g of 4-hydroxy-4-(4-trifluoromethylphenyl)piperidine (II -2) and 2.42 g of phthalimido butyl bromide in 20 ml of DMF in the presence of 2.26 g of K_2CO_3 is stirred at 105°C for 6 hours. The reaction mixture is poured into ice-water, and the solution is extracted with ethyl acetate. The organic layer is washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue is subjected to column chromatography of silia gel eluting with methylene chloride/methanol (20/1 v/v). The purified substance is recrystallized from methylene chloride/ether to prepare 3.0 g of the compound (IV -1). mp. 139.0-140.5 °C

Anal Calcd.(%) for $C_{24}H_{25}N_2O_3F_3$:

C, 64.23; H, 5.73; N, 6.10; F, 12.98

Found : C, 64.57; H, 5.64; N, 6.27; F, 12.77

IR ($CHCl_3$) : 3590, 1772, 1713, 1618, 1470, 1440, 1409(sh), 1389

NMR ($CDCl_3$) (200MHz) δ :

1.52-1.80 (m, 6H); 1.843 (s, 1H); 2.152 (td, J_1=13Hz, J_2=4Hz, 2H); 2.37-2.50 (m, 4H); 2.838 (dd, J_1=9Hz, J_2=2Hz, 2H); 3.728 (t, J=7 Hz, 2H); 7.613, 7.640 (ABq, J=9Hz, 4H) 7.7-7.9 (m, 4H)

(2) A solution of 2.56 g of the compound (Ⅳ-1) and 424 mg of hydrazine hydrate in 25 ml of ethanol is refluxed for 3 hours. After the excess agent is distilled off under reduced pressure, the residue is mixed with 1.15 g of 1-phenoxycarbonyl-2-oxopyrrolidine and heated at 105 °C for 1.5 hours. The reaction mixture is sub jected to column chromatography of silica gel eluting with methylene chloride/methanol=20/1-10/1 v/v. The obtained material is recrystallized from methylene chloride-ether to prepare 1.76 g (Yield: 73.5 %) of the objective compound (Ⅲ-17) as colorless needles. mp. 150.5-152.0°C

Anal Calcd. (%) for $C_{21}H_{26}N_3O_3F_3$:

C, 58.78; H, 6.51; N, 9.75; F, 13.56

Found : C, 59.01; H, 6.60; N, 9.83; F, 13.33

IR ($CHCl_3$) :

3590, 3320, 1713, 1680, 1618, 1545, 1489, 1460, 1409, 1385, 1328

NMR ($CDCl_3$) :

1.57-1.63 (m, 4H); 1.743 (d, J=12Hz, 2H); 2.019 (quint, J=7Hz, 2H); 2.189 (td, J_1=13Hz, J_2=4Hz, 2H); 2 341 (s, 1H); 2.42-2.55 (m, 4H); 2.595 (t, J=8Hz, 2H); 2.862 (dd, J_1=10Hz, J_2=2Hz, 2H); 3.311 (q, J=6Hz, 2H); 3.822 (t, J=7Hz, 2H); 7.591, 7.653 (ABq, J=9Hz, 4H); 8.438 (brs, 1H)

(3) A solution of 1.40 g of the compound (Ⅲ-17) in 20 ml of trifluoro acetic acid is refluxed for 72 hours. After removal of the excess reagent, the residue is poured into sodium hydroxide, and the solution is extracted with ethyl acetate. The organic layer is dried over $MgSO_4$ and concentrated under reduced pressure. The oily residue is subjected to column chromatography of silica gel eluting with methylene chloride/methanol (20/1 v/v) and recrystallized from i-PrOH-ether to prepare 1.31 g (Yield : 97.7%) of the objective compound (Ⅰa-17) as needles.

mp. 136.0-136.5 °C

Anal Calcd.(%) for $C_{21}H_{26}N_3O_2F_3$:

C, 61.87; H, 6.49; N, 10.26; F, 13.87

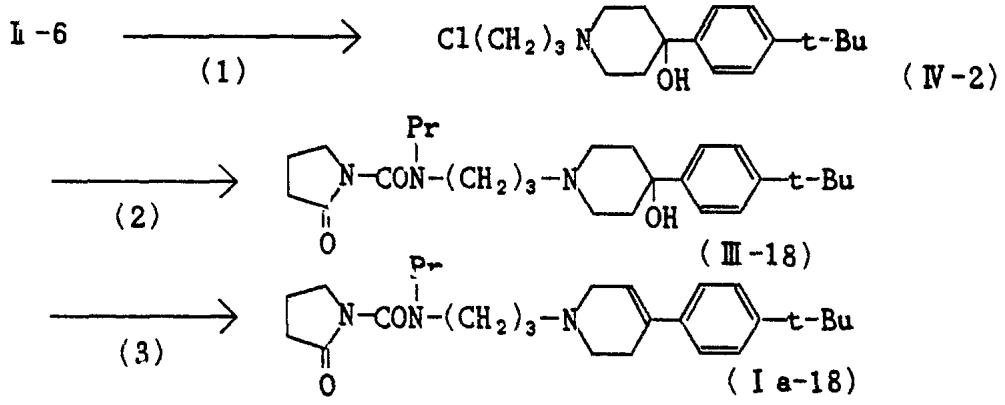
Found : C, 61.60; H, 6.40; N, 10.26; F, 13.92

IR ($CHCl_3$) : 3310, 1713, 1680, 1615, 1545, 1487, 1458, 1385, 1327

NMR ($CDCl_3$) (200MHz) δ : 1.55-1.67 (m, 4H); 2.031 (quint, J=8Hz, 2H); 2.47-2.65 (m, 6H); 2.725 (t, J=5Hz, 2H); 3.190 (q, J=3Hz, 2H); 3.344 (q, J=6Hz, 2H); 3.857 (t, J=8Hz, 2H); 6.154 (quint, J=2 Hz, 1H); 7.471, 7.564 (ABq, J=8Hz, 4H); 8.436 (brs, 1H)

Example 18

1-[N-propyl-N-[3-(4-(4-t-butylphenyl)-1,2,5,6-tetrahydropyridin-1-yl)-propylcarbamoyl]]-2-oxopyrrolidine (I a-18)



(1) A solution of 2.00 g of the compound (Ⅱ-6) and 1.42 g of 3-bromo-1-chloropropane in 30 ml of DMF is strried in the presence of 2.37 g of K_2CO_3 at room temperature for 3.5 hours. The reaction mixture is poured into ice-water, and the solution is extracted with ethyl acetate. The organic layer is washed with water, dried and concentrated uner reduced pressure to prepare 1.32 g of the compound (Ⅳ-2).

(2) A solution of 0.5 g of the compound (Ⅳ-2) and 0.44 ml of n-propyl in 1 ml of DMF is heated at 105 °C for 2 hours under stirring. The mixture is concentrated, and the residue is poured into aq.NaOH. The solution is extracted with methylene chloride, the organic layer is dried over $MgSO_4$ under reduced pressure. The oily residue is mixed with 310 mg of 1-phenoxycarbonyl-2-oxopyrrolidine and reacted at 115 °C for 2 hours. The reaction mixture is dissolved into methylene chloride, washed with aq. NaOH

and aq.NaCl in order, dried over Na_2SO_4, and concentrated under reduced pressure. The oily residue is subjected to column chromatography of silica gel eluting with methylene chloride/methanol (20/1-10/1 v/v) to prepare 500 mg (Yield : 70.0 %) of the compound (Ⅲ-18) as an oil.

IR ($CHCl_3$) :

3595, 1720, 1665, 1605, 1517, 1465(sh), 1460, 1425, 1400, 1375

NMR ($CDCl_3$) :

0.889 (t, J=7Hz, 3H); 1.316 (s, 9H); 1.594 (q, J=8Hz, 2H); 1.74-1.89 (m, 4H); 2.076 (quint, J=7Hz, 2H); 2.207 (t, J=15Hz, 2H); 2.435 (t, J=8Hz, 2H); 2.48-2.60 (m, 4H); 2.80-2.90 (m, 2H); 3.317 (t, J=4Hz, 2H); 3.421 (t, J=4Hz, 2H); 3.712 (t, J=7Hz, 2H); 7.368, 7.436 (ABq, J=8Hz, 4H)

(3) A solution of 1.40 g of the compound (Ⅲ-17) in 15 ml of trifluoroacetic acid is refluxed for 2.5 hours. The solution is concentrated, and the residue is poured into aq.NaOH. The solution is extracted with ethyl acetate, and the organic layer is dried over $MgSO_4$ and concetrated under reduced pressure. The oily residue is subjected to column chromatography of silica gel eluting with toluene/ethyl acetate (1/1 v/v) to prepare 1.07 g (Yield : 80 %) of the objective compound (Ⅰa-18) as an oil.

mp. 158.5-159.5 ℃ (dec.)

Anal Calcd. (%) for $C_{26}H_{38}N_2O_2 \cdot C_2H_2O_4 \cdot 1/2H_2O$:

: C, 64.38; H, 8.11; N, 8.05

Found : C, 64.10; H, 8.07; N, 8.01

IR (Nujol) :

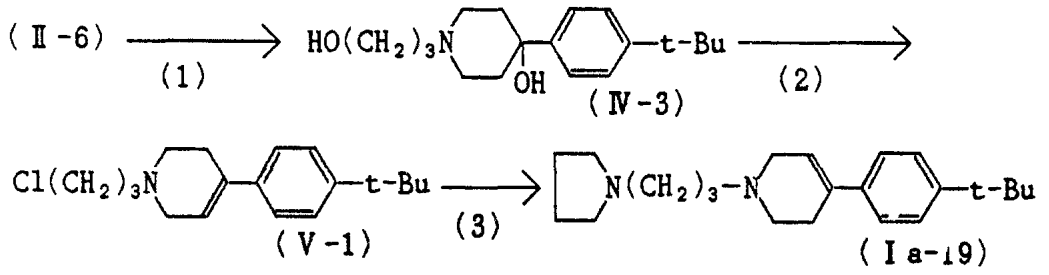
3420, 2720, 2590, 2500, 1715, 1692, 1675(sh), 1610(br), 1515, 1460

NMR (CD_3OD) (200MHz) δ :

0.894 (t, J=7Hz, 3H); 1.312 (s, 9H); 1.618 (q, J=7Hz, 2H); 2.117 (quint, J=7Hz, 4H); 2.458 (t, J=8Hz, 2H); 2.872 (brs, 2H); 3.28-3.37 (m, 4H); 3.49-3.56 (m, 4H); 3.695 (t, J=7Hz, 2H); 3.932 (brs, 2H); 6.089 (quint, J=2Hz, 1H); 7.402 (s, 4H)

Example 19

1-[3-(4-(4-tert-butylphenyl)-1,2,5,6-tetrahydropyridin-1-yl)propyl]pyrrolidine (Ⅰa-19)



(1) A mixture of 10.061 g of the compound (Ⅱ-6) and 5.41 ml of 3-chloro-1-propanol is stirred at 140 °C for 6 hours in the presence of 12.03 ml of Et_3N. The reaction mixture is recrystallized from methylene chloride-ether-n-hexane to prepare 9.357 g (Yield : 74.0 %) of the compound (Ⅳ-3). mp.122.5-123.5°C

Anal Calcd. (%) for $C_{18}H_{29}NO_2 \cdot 1/10H_2O$

: C,73.72; H,9.93; N,4.82

Found : C,73.73; H,10.04; N,4.78

IR ($CHCl_3$) cm^{-1} :

3600, 3225, 1509, 1472, 1437, 1424, 1399, 1372 (sh), 1366

NMR ($CDCl_3$) δ :

1.31 (s, 9H); 1.62-1.85 (m, 4H); 2.119 (td, J_1=13Hz, J_2=4Hz, 2H); 2.507 (td, J_1=12Hz, J_2=2Hz, 2H); 2.707 (t, J=6Hz, 2H); 2.973 (d, J=11Hz, 2H); 3.829 (t, J=6Hz, 2H); 7.367, 7.417 (ABq, J=8Hz, 4H)

(2) A mixture of 10.568 g of the compound (Ⅳ-3) and 26.4 ml of thionyl chloride is stirred at room temperature over night. Excess reagent is distilled off under reduced pressure, and the residue is poured into aq.Na_2CO_3. The solution is extracted with methylene chloride, and the organic layer is dried over $MgSO_4$ and concentrated. The residue is subjected to column chromatography of silica gel eluting with toluene/acetone (8/1-6/1 v/v) and recrystallized from n-hexane to prepare 2.167 g (Yield : 20.5%) of the compound (Ⅴ-1) as colorless crystals.

Anal Calcd. (%) for $C_{18}H_{28}NCl$:

: C, 73.86; H, 9.08; N, 4.96; Cl, 12.35

Found : C, 74.07; H, 8.98; N, 4.80; Cl, 12.15

IR ($CHCl_3$) : 1640, 1610, 1510, 1470, 1390, 1380

NMR($CDCl_3$) : 1.315 (s, 9H); 2.041 (quint, J=7Hz, 2H); 2.50-2.66 (m, 4H); 2.714 (t, J=5Hz, 2H); 3.169 (q, J=3Hz, 2H); 3.638 (t, J=7Hz, 2H); 6.032 (quint, J=3H, 1H); 7.334 (s, 4H)

(3) A mixture of 621 mg of the compound (V -1) and 1.78 ml of pyrrolidine is stirred at room temperature for 72 hours. The excess reagent is distilled off, and the residue is subjeced to column chromatography of silica gel eluting with methylene chloride/methanol/ammonia (128/16/1 v/v) to prepare 675 mg of the compound (I a-19) as an oil, which is crystallized as maleate and recrystallized from methanol to give 800 mg (yield : 67.3%) of colorless plates. mp. 190.0-191.0 °C (dec.)

Anal Calcd. (%) for $C_{22}H_{34}N_2O_2 \cdot C_4H_4O_4$:

: C, 64.74; H, 7.58; N, 5.11

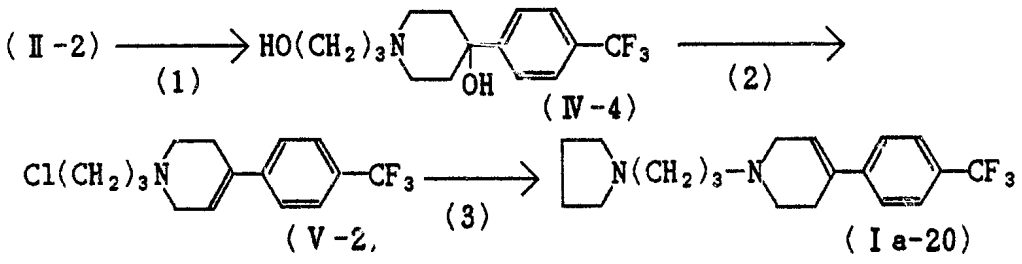
Found : C, 64.50; H, 7.58; N, 5.01

IR (Nujol) : 2355, 1711, 1620, 1577, 1543, 1479(sh), 1461, 1378

NMR (CD_3OD) δ : 1.314 (s, 9H); 2.122 (quint, J=3Hz, 2H); 2.20-2.37 (m, 2H); 2.907 (brs, 2H); 3.30-3.43 (m, 6H); 3.567 (t, J=6Hz, 2H); 3.949 (brs, 2H); 6.129 (brs, 1H); 6.269 (s, 2H); 7.416 (s, 4H)

Example 20

1-[3-(4-(4-trifluoromethyl)-1,2,5,6-tetrahydropyridin-1-yl)-propyl]pyrrolidine (I a-20)



(1) A mixture of 5.00 g of the compound (Ⅱ -2) and 2.22 ml of 3-chloro-1-propanol is stirred in the presence of 4.27 ml of Et_3N at 140°C for 8 hours. The mixture is subjected to column chromatography of silica gel eluting with methylene chloride/

methanol/ammonium=64/8/1-32/6/1 v/v. The obtaind purified substance is recrystallized from ether-n-hexane to prepare 5.155 g (Yield : 75.7 %) of the compound (Ⅳ-4). mp. 116.0-116.5°C

Anal Calcd. (%) for $C_{15}H_{20}NO_2F_3$:

C, 59.31; H, 6.59; N, 4.69; F, 18.70

Found : C, 59.40; H, 6.65; N, 4.62; F, 18.79

IR (Nujol) : 3335, 3075, 2773, 1617, 1462, 1436, 1407, 1378

NMR ($CDCl_3$) δ : 1.73-1.83 (m, 4H); 2.119 (td, J_1=13Hz, J_2=4Hz, 2H); 2.494 (td, J_1=12Hz, J_2=3Hz, 2H); 2.716 (t, J=6Hz, 2H); 3.009 (d-d, J_1=12Hz, J_2=2Hz, 2H); 3.836 (t, J=6Hz, 2H); 7.612 (s, 4H)

(2) The compound (Ⅳ-4) 4.892 g is treated in the same manner as Example 19(2) to prepare 3.357 g of the compound (Ⅴ-2) as an oil.

IR ($CHCl_3$) : 1608, 1453, 1439, 1399, 1368(sh), 1319

NMR ($CDCl_3$) : 2.036 (quint, J=7Hz, 3H); 2.54-2.62 (m, 2H); 2.636 (t, J=7Hz, 2H); 2.733 (t, J=6Hz, 2H); 3.192 (q, J=3Hz, 2H); 3.635 (t, J=7Hz, 2H); 6.152 (quint, J=2Hz, 1H); 7.466, 7.562 (ABq, J=8 Hz, 4H)

(3) A mixture of 1.05 g of the compound (Ⅴ-2) and 1.44 ml of pyrrolidine is stirred at room temperatrue for 32.5 hours, and the reaction mixture is treated in the same manner as Example 19 (3) to prepare 1.15 g (Yield : 98.2%) of the objective compound (Ⅰa-20) as crystals. The malenate is recrystallized from methanol to prepare 1.04 g (Yield : 98.2%) of colorless needles. mp.175.0-178.0 (dec.)

Anal. Calcd. (%) for $C_{19}H_{25}N_2F_3O_2 \cdot C_4H_4O_4$

C, 57.92; H, 5.74; N, 4.97; F, 10.05

Found : C, 56.84; H, 5.83; N, 4.91; F, 9.99

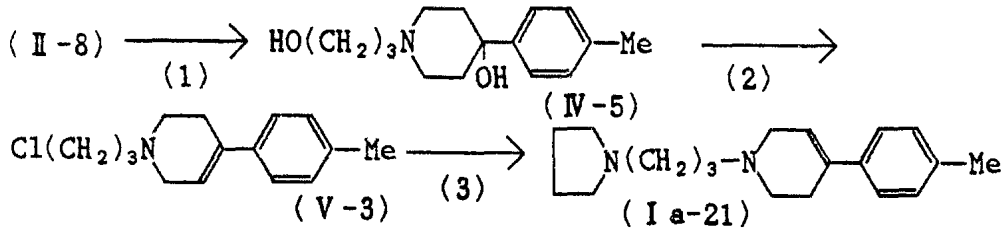
IR (Nujol) : 2590, 2360, 2160, 1711, 1620, 1560, 1535(sh), 1483, 1458, 1378, 1359

NMR (CD_3OD) : 2.119 (quint, J=3Hz, 4H); 2.20-2.37 (m, 2H); 2.927 (brs, 2H); 3.28-3.50 (m, 8H); 3.566 (t, J=6Hz, 2H); 3.971 (q, J=2Hz, 2H); 6.266 (s, 4H); 6.295 (brs, 1H); 7.681 (s, 4H)

Example 21

1-[3-(4-(4-methylphenyl)-1,2,5,6-tetrahydropyridin-1-yl)-

propyl]pyrrolidine (I a-21)



(1) A mixture of 10.20 g of the compound (Ⅱ-8) and 5.51 ml of 3-chloro-1-propanol is stirred in the presence of 11 ml of Et_3N at 140 °C for 5.5 hours. The reaction mixture is recrystallized from methylene chloride-ether to prepare 8.51 g (Yield : 64.0 %) of the compound (Ⅳ-5). mp. 110.5-111.5 °C

Anal Calcd. (%) for $C_{18}H_{23}NO_2$:

: C, 72.01; H, 9.25; N, 5.58

Found : C, 72.25; H, 9.30; N, 5.62

IR ($CHCl_3$) : 3597, 3220, 1513, 1470, 1452, 1437, 1423, 1397

NMR ($CDCl_3$) δ : 1.67-1.81 (m, 4H); 2.087 (td, J_1=13Hz, J_2=4Hz, 2H); 2.337 (s, 3H); 2.479 (td, J_1=15Hz, J_2=3Hz, 2H); 2.693 (t, J=6 Hz, 2H); 2.952 (d, J=11Hz, 2H); 3.828 (t, J=5Hz, 2H); 7.168, 7.372 (ABq, J=8Hz, 4H)

(2) A solution of 12.82 g of the compound (Ⅳ-5) in 38 ml of trifluoroacetic acid is refluxed for 3.1 hours. The reaction mixture is concentrated, and the residue is poured into aq.$NaHCO_3$. The mixture is extracted with ethyl acetate, and the organic layer is dried over $MgSO_4$ and concentrated under reduced pressure. The oily substance is subjected to column chromatography of silica gel eluting with methylene chloride/methanol/NH_4OH (128/16/1 v/v). A mixture of 870 mg of the product and 8.01 ml of thionyl chloride is stirred at room temperature for 2 hours. The excess reagent is distilled away under reduced pressure. The residue is washed with ether and dried under reduced pressure to give 1.067 g (Yield : 99.2 %) of the objective compound (V-3) as a light yellowish powder.

IR ($CHCl_3$) : 1600, 1510, 1460, 1410

NMR ($CDCl_3$) : 2.046 (quint, J=7Hz, 2H); 2.334 (s, 3H); 2.54, 2.64 (m, 2H); 2.629 (t, J=7Hz, 2H); 2.723 (t, J=5Hz, 2H); 3.173 (q, J=2Hz, 2H); 3.630 (t, J=7Hz, 2H); 6.023 (quint, J=2Hz, 1H); 7.123, 7.287 (ABq, J=8Hz, 4H)

(3) A mixture of 466 mg of the compound (V-3) and 0.78 ml of pyrrolidine is stirred at 50 °C for 3 hours and treated in the same manner as Example 19(3) to give the maleate of the objective compound (Ia-21). It is recrystallized from methanol-iPrOH to prepare 225 mg (Yield : 42.5%) of the compound (Ia-21) as needles. mp.180.0-181.0 °C (dec.)

Anal Calcd. (%) for $C_{19}H_{28}N_2 \cdot 2C_4H_4O_4$

: C, 62.84; H, 6.99; N, 5.48

Found : C, 62.78; H, 7.02; N, 5.42

Example 22-29

The compound (V-1), (V-2) and (V-3), each of which were obtained in Step 1 of Example 19-21, are reacted with amine (VIII) in the same manner as Step 3 in Example 19-21 to prepare the compound (Ia). The reaction conditions and physical constants are shown in table 5 and 6.

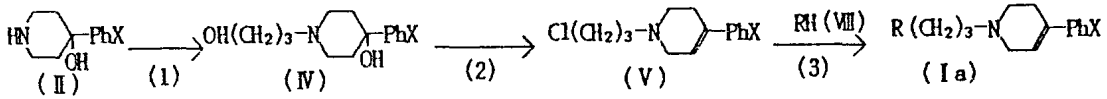
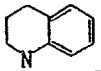
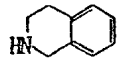
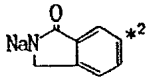
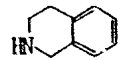


Table 5

Ex. No.	starting material	RH	reaction condition	purification condition	product mg (%)
22	(V-1) 0.628g	$HN(i\text{-}Bu)_2$ 3.76ml	33 hours reflux	CH_2Cl_2/MeOH =49/1-19/1	Ia-22*1 685mg (51.1%)
23	(V-2) 0.602g	$HN(i\text{-}Bu)_2$ 1.50g	32 hours reflux	CH_2Cl_2/MeOH =49/1-19/1	Ia-23*1 338mg (27.1%)
24	(V-3) 0.517g	$HN(i\text{-}Bu)_2$ 1.36g	20 hours reflux	CH_2Cl_2/MeOH =49/1	Ia-24*1 457mg (38.4%)
25	(V-3) 0.924g	 2.32ml	150°C 8.15 hours	toluene/ acetone =19/1-9/1	Ia-25*1 930mg (54.4%)
26	(V-3) 0.624g		150°C 4.1 hours	CH_2Cl_2/MeOH =19/1	Ia-26*1 963mg 66.6%)
27	(V-2) 1.02g	 *2	100°C 25 hours (in DMF)	toluene/ acetone =3/11/1	Ia-27*1 266mg (15.3%)
28	(V-2) 0.645g	$H_2N\text{-}i\text{-}Bu$ 1.1ml	15.6hours reflux	CH_2Cl_2:MeOH :NH_4OH=64/8/1	Ia-28 461mg (63.8%)
29	(V-1) 0.828g		150°C 3 hours	CH_2Cl_2/MeOH =29/1-19/1	Ia-29*1 773mg (70.2%)

*1: separated as maleate
*2: prepared by the reaction with 492 mg of isoindoline and 162 mg of 60% NaH in 5 ml of DMF at 100 °C for 1 hour.

Table6(No. 1)

Compd. No.	mp.(°C) Rec. sol.*1	Anal Cald. (%) Found (%)	IR (cm^{-1})	NMR (δ) (200MHz)
I a-22	(maleate) 176.5~178.0 (MeOH-Et_2O) needleshaped crystals	$C_{28}H_{44}N_2O_2 \cdot C_4H_4O_4$ C. 63.46 (63.68) H. 8.02 (8.18) N. 6.83 (6.75) F. 7.98 (8.54)	(Nujol) 2620, 2510, 1690 1657, 1618, 1579 1533, 1488, 1460 1409, 1378	(CD_3OD) 1.083 (d, J=7Hz, 12H); 1.314 (s, 9H); 2.158 (7tet, J=7Hz, 2H); 2.20-2.37 (m, 2H); 2.913 (brs, 2H); 3.042 (d, J=7Hz, 4H); 3.25-3.37 (m, 4H); 3.588 (t, J=6Hz, 2H); 3.974 (s, 2H); 6.131 (s, 1H); 6.272 (s, 4H); 7.419 (s, 4H)
I a-23	(maleate) 135.0~136.5 (MeOH-Et_2O) needleshaped crystals	$C_{23}H_{33}N_2F_3O_2 \cdot C_4H_4O_4$ C. 59.12 (59.23) H. 6.76 (6.89) N. 4.35 (4.46) F. 9.05 (9.07)	(Nujol) 2420, 1707, 1616 1572, 1485, 1456 1377	(CD_3OD) 1.071 (d, J=7Hz, 12H); 2.05-2.35 (m, 4H); 2.90-3.30 (m, 4H); 3.20-3.30 (m, 4H); 3.559 (brs, 2H); 3.972 (brs, 2H); J=7Hz, 2H) 2.54-2.61 (m, 2H); 2.747 (t, J=5Hz, 2H); 6.260 (s, 5H); 7.674 (s, 4H)
I a-24	(maleate) 140.5~142.5 (MeOH-Et_2O) needleshaped crystals	$C_{23}H_{38}N_2 \cdot C_4H_4O_4$ C. 64.67 (64.79) H. 7.99 (8.07) N. 4.69 (4.87)	(Nujol) 2710, 2500, 1706 1572, 1480, 1455 1375	($CDCl_3$) 0.872 (d, J=7Hz, 12H); 1.685 (quint, J=7Hz, 4H); 2.059 (d, J=7Hz, 4H); 2.329 (s, 3H); 2.33-2.60 (m, 6H); 2.712 (t, J=5Hz, 2H); 3.161 (q, J=3Hz, 2H); 6.021 (quint, J=2Hz, 1H); 7.116, 7.283 (ABq, J=9 Hz, 4H)
I a-25	(maleate) 148.0~150.0 (iPrOH-Et_2O)	$C_{24}H_{30}N_2O_2 \cdot C_4H_4O_4$ C. 72.65 (72.70) H. 7.36 (7.41) N. 6.11 (6.06)	(Nujol) 2720, 2575(sh), 2490(sh), 2330, 1708, 1652, 1600 1571, 1502, 1459	(CD_3OD) 1.80-2.01 (m, 4H); 2.331 (s, 3H); 2.48-2.63 (m, 4H); 2.712 (t, J=7Hz, 2H); 2.747 (t, J=7Hz, 2H); 3.162 (q, J=3Hz, 2H); 3.283 (t, J=6Hz, 2H); 3.329 (t, J=7Hz, 2H); 6.026 (quint, J=2Hz, 1H); 6.50-6.64 (m, 2H); 6.91-7.32 (m, 6H)
I a-26	(maleate) 191.0~192.0 (MeOH-H_2O) needleshaped crystals	$C_{24}H_{36}N_2O_2 \cdot C_4H_4O_4$ C. 66.48 (66.42) H. 6.61 (6.62) N. 4.92 (4.84)	(Nujol) 3030, 2720, 2278 1711, 1623, 1572 1532, 1513(sh), 1485, 1463, 1435	($CDCl_3$) 1.322 (s, 9H); 1.76-1.94 (m, 8H); 2.262 (t-d, J_1=14Hz, J_2=4Hz, 2H); 2.50-2.65 (m, 4H); 2.951 (d, J=11Hz, 2H); 3.30-3.39 (m, 4H); 5.738 (brs, 1H); 7.378, 7.418 (ABq, J=8Hz, 4H)

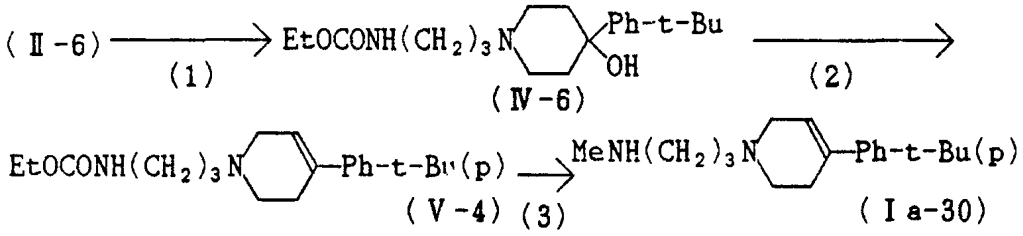
Table 6 (No.2)

Compd. No.	mp. (°C) Rec. sol.*1	Anal Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ) (200MHz)
I a-27	(maleate) 152.5~154.0 ($MeOH-Et_2O$) needleshaped crystals	$C_{23}H_{23}F_3N_2O \cdot C_4H_4O_4$ C. 62.64 (62.79) H. 5.29 (5.27) N. 5.48 (5.42) F. 11.00 (11.03)	($CHCl_3$) 2700-1750 (br): 1695, 1663, 1619 1532, 1463, 1412 1378, 1358	(CD_3OD) 2.236 (quint, J=7Hz, 2H): 2.934 (brs, 2H): 3.334 (t, J=7Hz, 2H): 2.369 (t, J=5Hz, 2H): 3.808 (t, J=7Hz, 2H): 4.010 (s, 2H): 4.606 (s, 2H): 6.230 (brs, 2H): 6.298 (brs, 1H): 7.51-7.81 (m, 9H)
I a-28	(maleate) 182.5~184.0 ($MeOH-Et_2O$) needleshaped crystals	$C_{19}H_{27}N_2F_3 \cdot C_4H_4O_4$ ———	(Nujol) 3483, 2723, 2679 2587, 2415, 1703 1618, 1579, 1478 1460, 1412, 1382	($CDCl_3$) 0.952 (d, J=7Hz, 6H): 2.093 (quint, J=7Hz, 3H): 2.636 (brs, 2H): 2.727 (d, J=7Hz, 2H): 2.771 (t, J=6Hz, 2H): 2.898 (t, J=6Hz, 2H): 3.149 (t, J=6Hz, 2H): 3.29-3.33 (m, 2H): 6.184 (quint, J=2Hz, 1H): 7.474, 7.587 (ABq, J=8Hz, 4H)
I a-29	(maleate) 183.5~185.0 ($CHCl_3$-MeOH) needleshaped crystals	$C_{27}H_{36}N_2 \cdot 2C_4H_4O_4 \cdot 1/10H_2O$ C. 67.29 (67.59) H. 7.08 (7.16) N. 4.56 (4.50)	(Nujol) 2340, 1708, 1619 1568, 1528(sh), 1485, 1461	(CD_3OD) 1.330 (s, 9H): 2.424 (brs, 2H): 2.867 (brs, 2H): 3.204 (brs, 2H): 3.370 (brs, 4H): 3.544 (brs, 4H): 3.948 (s, 2H): 4.403 (s, 2H): 6.060 (s, 1H): 6.252 (s, 4H): 7.15-7.44 (m, 8H)

*1 : a solvent for recrystallization

Example 30

1-[(3-methylamino)propyl]-4-(4-tert-butylphenyl)-1,2,5,6-tetrahydropyridine (Ⅰa-30)



(1) A solution of 3.60 g of the compound (Ⅱ-6) and 2.80 g of 1-ethoxycarbonylamino-3-chloropropane in 30 ml of DMF is reacted in the presence of 4.26 g of K_2CO_3 and 3.46 g of NaI at 105-110 ℃ for 6 hours. The reaction mixture is poured into ice water and extracted with ethyl acetate. The ethyl acetate layer is washed wih water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue is subjected to column chromatography of silica gel eluting with methylene chlorde/methanol (10/1-5/1 v/v) to give 4.60 g (Yield : 82.0%) of the compound (Ⅳ-6) as crystals. Recrystallization from methylene chloride-ether gives colorless needles. mp. 111.5-113.0 ℃

Anal Calcd. (%) for $C_{21}H_{34}N_2O_3 \cdot 1/5H_2O$:

: C, 68.92; H, 9.37; N, 7.78

Found : C, 68.89; H, 9.47; N, 7.65

IR (Nujol) : 3320, 1715, 1700, 1535

NMR ($CDCl_3$) δ : 1.242 (t, J=7Hz, 3H); 1.320 (s, 9H); 1.66-1.84 (m, 4H); 2.210 (td, J_1=13Hz, J_2=4Hz, 2H) 2.45-2.60 (m, 4H); 2.877 (d, J=12Hz, 2H); 3.286 (q, J=6Hz, 2H); 4.103 (q, J=7Hz, 2H); 5.929 (brs, 1H); 7.376,7.443 (ABq, J=8Hz, 4H)

(2) A solution of 4.30 g of the compound (Ⅳ-6) obtained above in 35 ml of trifluoroacetic acid is refluxed for 5 hours and treated in the same manner as Example 7(2) to prepare 4.05 g (Yield . 99.0%) of the compound (Ⅴ-4) as an oil.

(3) To a suspension of 146 mg of lithium aluminium

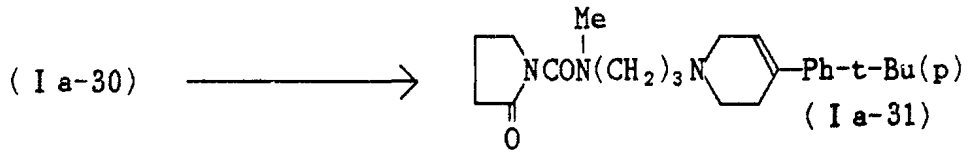
hydride in 15 ml of dry ether is added dropwise a solution of 530 mg of the compound (V -4) in 15 ml of THF under stirring. After reflux for 8 hours, the excess reagents are decomposed by careful addition of aq. NaOH and filtered off. The resulting organic layer is dried and evaporated under reduced pressure to prepare 420 mg (Yield : 95.2 %) of the compound (I a-30) as an oil.

IR ($CHCl_3$) : 3290, 1602, 1510, 1470, 1445

NMR($CDCl_3$) : 1.321 (s, 9H); 1.780 (quint, J=7Hz, 2H); 2.444 (s, 3 H); 2.48-2.62 (m, 2H); 2.532 (t, J=7Hz, 2H); 2.672 (t, J=7Hz, 2H); 3.152 (q, J=3Hz, 2H); 6.039 (quint, J=2Hz, 1H); 7.333 (s, 4H)

Example 31

1-[N-methyl-N-[3-{4-(4-tert-butylphenyl)-1,2,5,6-tetrahydropyridin-1-yl}propylcarbamoyl]]-2-oxopyrrolidine (I a-31)



A mixture of 400 mg of the compound (I a-30) obtained in Example 30 and 280 mg of 1-phenoxycarbonyl-2-oxopyrrolidine is heated at 115°C for 2 hours. The reaction mixture is subjected to column chromatography of silica gel eluting with toluene/ethyl acetate (1/1)-methylene chloride/methanol (20/1) to prepare 370 mg (Yield : 68.5%) of the compound (I a-31) as an oil. The tosylate is recrystallized from ethyl acetate/methanol to prepare needles.

mp. 128.0-134.0°C

Anal Calcd. (%) for $C_{24}H_{35}N_3O_2 \cdot C_7H_8O_3S \cdot H_2O$

: C, 63.51; H, 7.56; N, 7.16; S, 5.37

Found : C, 63.35; H, 7.72; N, 7.15; S, 5.45

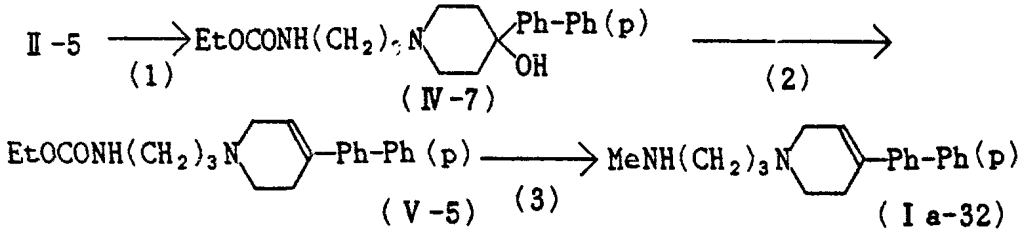
IR (Nujol) cm^{-1}: 3570, 3500, 2740, 2630, 1720, 1690, 1675(sh), 1663, 1475, 1120, 1033

NMR ($CDCl_3$) δ : 1.314 (s, 9H); 1.895 (quint, J=7Hz, 2H); 2.071 (quint, J=7Hz, 2H); 2.454 (t, J=8Hz, 2H); 2.50-2.60 (m, 4H); 2.720 (t, J=5Hz, 2H); 2.995 (s, 3H); 3.174 (q, J=3Hz, 2H); 3.461 (t, J=7

Hz, 2H), 3.735 (t, J=7Hz, 2H); 6.024 (quint, J=2Hz, 1H); 7.244, 7.348 (ABq, J=8Hz, 4H)

Example 32

1-[(3-methylamino)propyl]-4-(4-phenylphenyl-1,2,5,6-tetrahydropyridine (Ⅰa-32)



(1) A solution of 3.20 g of the compound (Ⅱ-5) and 2.30 g of 1-ethoxycarbonylamino-3-chloropropane in 30 ml of DMF is reacted in the presence of 3.48 g of K_2CO_3 and 2.83 g of NaI at 105 °C for 41 hours. The reaction mixture is poured into ice water and extracted with ethyl acetate. The ethyl acetate layer is washed wih water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue is subjected to column chromatography of silica gel eluting with methylene chloride/methanol (10/1-5/1v/v). The resulting purified substance is recrystallized from methylene chloride to prepare 2.46 g (Yield : 51.0%) of the compound (Ⅳ-7).

mp. 138.0-139.0 °C

Anal Calcd.(%) for $C_{23}H_{30}N_2O_3$

: C, 72.22; H, 7.84; N, 7.30

Found : C, 72.22; H, 7.91; N, 7.32

IR ($CHCl_3$) cm^{-1}: 3600, 3450, 1705, 1602, 1512, 1490

NMR ($CDCl_3$) δ : 1.240 (t, J=7Hz, 3H); 1.60-1.80 (m, 4H); 1.830 (s, 1H); 2.195 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.480 (d-d, J_1=14Hz, J_2=2 Hz, 2H); 2.524 (t, J=7Hz, 2H); 2.850 (d, J=14Hz, 2H); 3.280(q, J=6 Hz, 2H); 4.101 (q, J=7Hz, 2H); 6.962 (brs, 1H); 7.25-7.70 (m, 9H) 9H)

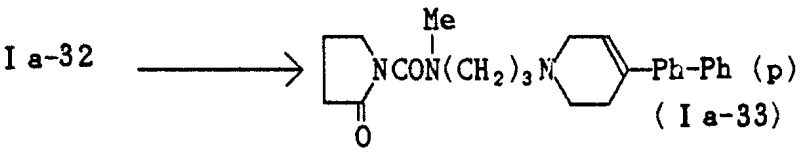
(2) A solution of 2.29 g of the compound (Ⅳ-7) in 25 ml of trifluoroacetic acid is refluxed for 9.5 hours and treated in

the same manner as Exmaple 7 (2) to prepare 2.08 g (Yield : 95.3%) of the compound (V -5). mp. 135.0-138.0 °C

(3) To a solution of 1.80 g of the compound (V -5) in 26 ml of THF is added dropwise 375 mg of lithium alminium hydride. After reflux for 8 hors, the reaction mixture is treated in the same manner as Example 29 (3) to prepare (I a-32) as an oil.

Example 33

1-[3-{4-(4-phenylphenl)-1,2,5,6-tetrahydropyridin-1-yl} propylmethylcarbamoyl]-2-oxopyrrolidine (I a-33)



To the compound (I a-32) obtained Example 32 is added dropwise 810 mg of 1-phenoxycarbonyl-2-oxopyrrolidine, and the mixture is heated at 115-120°C for 5 hours. The reaction mixture is subjected to column chromatography of silica gel eluting with methylene chloride/methanol (20/1 v/v) to prepare 650 mg (Yield : 31.5 %) of the compound (I a-33). The oxalate is recrystallized from i-PrOH to give needles. mp.186.0-187.0 °C (dec.)

Anal Calcd. (%) for $C_{26}H_{31}N_3O_2 \cdot C_2H_2O_4 \cdot 1/2H_2O$

: C, 64.71; H, 6.52; N,7.97

Found : C, 65.10; H, 6.63; N,8.13

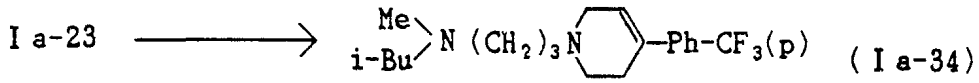
IR (Nujol) :

3500(br), 2720, 2600, 1720, 1665, 1485, 1455, 1405, 1405, 1375

NMR ($CDCl_3$) δ : 1.900 (quint, J=7Hz, 2H); 2.107 (quint, J=7Hz, 2H); 2.455 (t, J=8Hz, 2H); 2.55-2.64 (m, 4H); 2.741 (t, J=5Hz, 2H); 3.002 (s, 3H); 3.198 (q, J=3Hz, 2H); 3.469 (t, J=7Hz, 2H); 3.737 (t, J=7Hz, 2H); 6.124 (quint, J=2Hz, 1H) 7.3-7.6 (m, 9H)

Example 34

1-[3-(N-methyl-N-isobutyl)aminopropyl]-4-(4-trifluoro-methylphenyl)-1,2,5,6-tetrahydropyridine (I a-34)



(I a-34)

A mixture of 342 mg of the compound (I a-23), 1ml of formaldehyde, and 1 ml of formic acid is stirred at 70°C for 3hour and 40 minutes. The reaction mixture is concentrated, and the residue is poured into aq.$NaHCO_3$. The solution is extracted with methylene chloride-methanol, and the organic layer is dried over $MgSO_4$ and evaporated under reduced pressure. The resulting oily substance is subjected to column chromatography of silica gel eluting with methylene chloride/methanol (19/1-5/1 v/v) to prepare 252 mg of the objective compound (I a-34). The maleate is recrystallized from ethnol-ether to prepare 325 mg (Yield : 55.2 %) of colorless needles. mp. 182.0-183.5°C

Anal Calcd. (%) for $C_{20}H_{21}N_2F_3 \cdot 2C_4H_4O_4$

: C, 57.16; H, 6 .32; N, 4.82; F, 9.46

Found : C, 57.33; H, 6.36; N, 4.78; F, 9.72

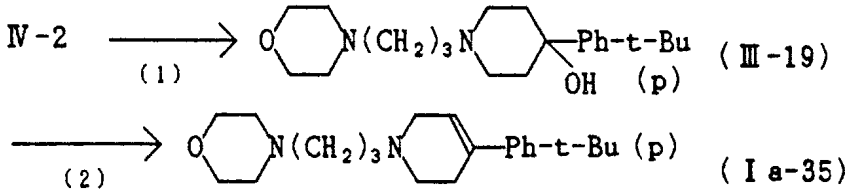
IR (Nujol) :

2360, 1708, 1621, 1570, 1533, 1481, 1460, 1447(sh), 1377, 1359

NMR ($CDCl_3$) : 0.938 (d, J=7Hz, 6H); 1.826 (quint, J=7Hz, 3H); 2.212 (d, J=7Hz, 2H); 2.309 (s, 3H); 2.513 (t, J=7Hz, 2H); 2.548 (t, J=7Hz, 2H); 2.58, 2.63 (m, 2H); 2.747 (t, J=5Hz, 2H); 3.208 (q, J=3Hz, 2H); 6.161 (quint, J=2Hz, 1H); 7.474, 7.567 (ABq, J=8Hz, 4H)

Example 35

4-[3-(4-(4-tert-butylphenyl)-1,2,5,6-tetrahydropyridin-1-yl)propyl]morpholine (I a-35)



(1) A mixture of 1.09 g of the compound (Ⅳ-2) obtained in Example 18 and 1.4 g of morpholine is refluxed for 4 hours. After removal of the excess reagent under reduced pressure, the residue is poured into aq.Na_2SO_4 and evaporated. The residue is purified by column chromatography of silic gel eluting with mthylene chloride/methanol (20/1 v/v). The hydrochloride of the compound (Ⅲ-19) is crystallized from methylene chloride-ether to prepare 850 mg (Yield : 66.3%) of needles. mp. 242°C (dec.)

NMR ($CDCl_3$ • CD_3OD=10/1):

1.307 (s, 9H); 2.10-2.22 (m, 2H); 2.48-2.55 (m, 4H); 2.760 (td, J_1=15Hz, J_2=4Hz, 2H); 3.06-3.15 (m, 4H); 3.25-3.50 (m, 4H); 3.731 (t, J=5Hz, 4H); 7.387, 7.454 (ABq, J=9Hz, 4H)

(2) A solution of 880 mg of the compound (Ⅲ-19) in 10 ml of trifluoroacetic acid is refluxed for 8 hours and evaporated under reduced pressure. The residue is poured into aq. sodium hydrogencarbonate, and extracted with methylene chloride. The organic layer is washed with saline dried over Na_2SO_4 and evaporated. The residue is purified by column chromatography followed by crystallization as the maleate. Recrystallization from methanol gives 760 mg (Yield : 97.5%) of redish needles.

mp. 213.0-214.5°C (dec.)

Anal Calcd.(%) for $C_{22}H_{34}N_2O \cdot 2C_4H_4O_4$

: C, 62.63; H, 7.35; N, 4.93

Found : C, 62.70; H, 7.37; N, 4 .87

IR (Nujol) :

2300 (br); 1717, 1622, 1675, 1535, 1500, 1465, 1458, 1450(sh)

NMR ($CDCl_3$) : 1.314 (s, 9H); 1.783 (quint, J=7Hz, 2H); 2.36, 2.63

(m, 8H); 2.709 (t, J=5Hz, 2H); 3.164 (q, J=3Hz, 2H); 3.725 (t, J=5 Hz, 2H); 6.031 (quint, J=1Hz, 1H); 7.330 (s, 4H)

Example 36-71

The reaction is performed in the same manner as Example 1 to prepare the compound (I a). The reaction conditions are shown in Table 7 and 8. Further the physical constants of the compound (I a) obtained in Example 36-71 are shown in Table 9.

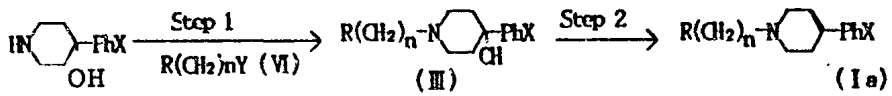


Table 7 (Step 1) (No.1)

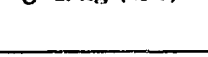
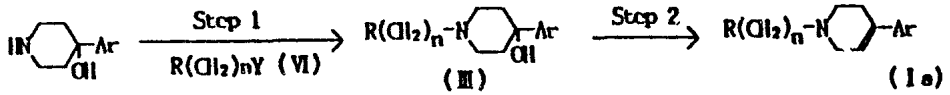
Exam. No.	starting material X=	R(CH₂)nY(VI)	DMF (ml)	K_2CO_3 (g)	NaI (g)	reaction condition(1) (°C, hr.)	purification condition	g (%) Compd. No.	m.p. (°C)	IR (cm^{-1})
36	Me(p) 2.50g (II-8)	 2.49g (VI-7)	35	4.53	2.95	105-110 7 hr.	CH_2Cl_2/MeOH =10/1	3.46 (76.4) (III-20)	116.0~ 117.0	(CHCl₃) 3600. 3320. 1713. 1688 (sh). 1680. 1545. 1490
37	Me(p) 2.34g (II-8)	 2.50g (VI-1)	25	4.21	2.74	105 6 hr.	toluene/ ethyl acetate =20/1-10/1	3.07 (70.0) (III-21)	143.5~ 144.5	(CHCl₃) 3600. 3320. 1715. 1618. 1550-1520
38	Me(m) 1.85g (II-9)	(VI-1) 2.35 g	30	3.18	2.59	105-110 8 hr.	CH_2Cl_2/MeOH =10/1	1.70 (49.0) (III-22)	—	(CHCl₃) 3600. 3320. 1715. 1680. 1608. 1545. 1490. 1470
39	Me(o) 2.50g (II-10)	(VI-1) 2.68 g	35	4.53	2.95	105-110 7 hr.	CH_2Cl_2/MeOH =10/1	3.18 (67.5) (III-23)	—	(CHCl₃) 3600. 3320. 1712. 1680. 1600. 1545. 1489. 1470. 1460
40	3.4-di-Me 2.10g (II-11)	(VI-1) 2.09 g	35	2.82	2.29	105 7 hr.	CH_2Cl_2/MeOH =10/1	2.56 (67.2) (III-24)	—	—
41	3.5-di-Me 2.82g (II-12)	(VI-1) 2.81 g	35	3.79	3.08	105°C 6 hr.	CH_2Cl_2/MeOH =10/1	3.81 (74.4) (III-25)	—	(CHCl₃) 3595. 3310. 1715. 1680. 1590. 1565. 1545. 1489. 1470 1460.
42	Cl(m) 2.70g (II-13)	(VI-1) 2.49 g	30	4.18	2.72	105-110°C 7hr.	CH_2Cl_2/MeOH =20/1-10/1	3.78 (81.8) (III-26)	90.5~ 91.5	(CHCl₃) 3600. 3220. 1713. 1658. 1595. 1545. 1490. 1470. 1460

Table 1 (No. 2)

4 3	Cl(m) 2.70g (II-13)	(VI-7) 2.31 g	30	4.18	2.72	105-110°C 7 hr.	CH_2Cl_2/MeOH =10/1	3.30 (74.3) (III-27)	94.0-98.0	(Nujol) 3280. 2720-2520. 1713. 1685. 1600. (sh). 1588. 1560
4 4	Cl(o) 2.50g (II-14)	(VI-1) 2.42 g	30	4.08	2.65	105-110 6 hr.	ethyl acetate /toluene=1/1 CH_2Cl_2/MeOH =15/1	2.10 (46.7) (III-28)	——	($CHCl_3$) 3580. 3320. 1715. 1680. 1547
4 5	Cl(o) 1.45g (II-14)	(VI-7) 1.28 g	20	2.32	1.51	105-110 6 hr.	CH_2Cl_2/MeOH =15/1	0.840 (34.1) (III-29)	——	($CHCl_3$) 3580. 3220. 1715. 1680. 1545(sh). 1540(sh). 1525
4 6	3.5-diCl 3.86g (II-15)	(VI-1) 3.0 g	35	4.04	3.28	105°C 7.0hr.	CH_2Cl_2/MeOH =10/1	5.25 (86.8) (III-30)	138.0-140.0	($CHCl_3$) 3595. 3310. 1715. 1680. 1590. 1565. 1545
4 7	Br (p) 2.57 g (II-16)	(VI-1) 1.96 g	25	2.64	2.15	105°C 8hr.	CH_2Cl_2/MeOH =10/1	3.16 (77.9) (III-31)	——	($CHCl_3$) 3590. 3310. 1713. 1680. 1545. 1489. 1460
4 8	F (p) 4.00g (II-17)	(VI-1) 4.20 g	50	7.08	4.61	105-110°C 6.0 hr.	CH_2Cl_2/MeOH =15/1-8/1	4.96 (66.5) (III-32)	102.5-104.0	($CHCl_3$) 3600. 3320. 1713. 1680. 1545. 1510. 1489
4 9	F (p) 2.30g (II-17)	(VI-7) 2.25 g	25	4.08	2.65	105°C 6 hr.	CH_2Cl_2/MeOH =10/1	2.78 (67.4) (III-33)	118.0-119.0	($CHCl_3$) 3600. 3320. 1713. 1680. 1605. 1545. 1510. 1489
5 0	CF_3(m) Cl (p) 3.50 g (II-18)	(VI-1) 2.56g	50	3.46	2.81	105-110°C 9 hr.	CH_2Cl_2/MeOH =20/1-10/1	5.20 (92.9) (III-34)	238.5-240.5	(Nujol) 3350. 2650. 2525. 2450. 1720. 1677. 1557
5 1	CF_3(m) Cl(p) 3.50g (II-18)	(VI-7) 2.38 g	50	3.46	2.81	105-110 15 hr.	CH_2Cl_2/MeOH =20/1-10/1	4.75 (87.6) (III-35)	255.0-257.0	(Nujol) 3400. 3260. 2640. 2500. 2430. 1713. 1672. 1547

Table 7



5 2	2.80g (II-19) *1	(VI-1) 2.64 g	36	4.46	2.90	105-110 8 days	CH_2Cl_2/MeOH =10/1	3.55 (71.3) (III-36)	122.0-123.0	($CHCl_3$) 3590. 3320. 1713. 1680. 1544. 1490. 1470. 1460(sh). 1450
5 3	2.10g (II-20) *2	(VI-1) 1.70 g	30	1.73	2.50	105 7 days	CH_2Cl_2/MeOH =10/1	3.00 (85.7) (III-37)	—	($CHCl_3$) 3600. 3320. 1712. 1680. 1543

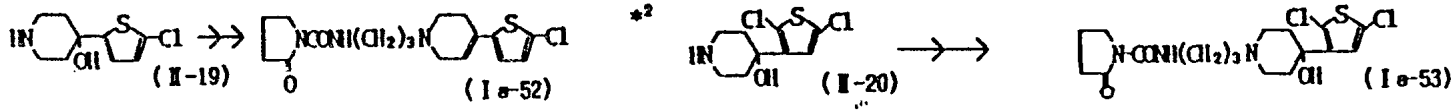


Table 7 (No. 3)

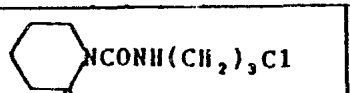
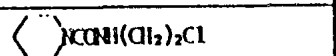
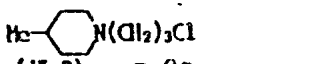
5 4	Cl(p) 1.00g (II-21)	 1.90g	10	1.63	1.06	90 12hr.	CH_2Cl_2/MeOH =20/1-10/1	1.37 (74.0) (III-38)	111.5-112.0	($CDCl_3$) 3600. 3280. 1702. 1698. 1530. 1645. 1495. 1480. 1463
5 5	Cl (p) 2.0 g (II-21)	 (VI-8)2.32g	25	3.26	2.12	90-95 10hr.	CH_2Cl_2/MeOH =10/1	1.75 (48.9) (III-39)	128.0-129.0	($CDCl_3$) 3600. 3280. 1525. 1492. 1480. 1460
5 6	t-Bu(p) 1.00g (II-6)	 (VI-9) 0.90g	10	K_2CO_3 1.184	NaI 0.96	100°C 3hr.	CH_2Cl_2/MeOH /NH_4OH =64/8/1	1.13 (71.0) (III-40)	—	($CHCl_3$) 3590. 2498. 1510. 1470. 1455. 1399
5 7	Me (p) 1.00g (II-8)	(VI-9) 1.10 g	10	K_2CO_3 1.45	NaI 1.18	100 °C 2.5 hr.	CH_2Cl_2/MeOH /NH_4OH =64/8/1	1.445 (83.6) (III-41)	—	($CHCl_3$) 3580. 2498. 1510. 1463. 1450. 1375

Table 7 (No. 4)

5 8	tBu(p) 0.81g (II-6)	MeN⟨⟩N(CH₂)₃Cl 0.67g	12	K₂CO₃ 0.96	NaI 0.78	100 °C 2.7 hr.	CH₂Cl₂/MeOH /NH₄OH =64/8/1.	1.053 (84.6) (III-42)	—	(CHCl₃) 3580. 2498. 1510. 1463. 1450. 1375
5 9	tBu(p) 0.727g (II-6)	⟨⟩N(CH₂)₃Cl 0.66g	11	K₂CO₃ 0.86	NaI 0.70	100°C 2.5 hr.	—	0.736 (62.4) (III-43)	—	(CHCl₃) 3630. 3590. 3390. 2499. 1506. 1467. 1440. 1421. 1399
6 0	Me (p) 10.2g (II-8)	HO(CH₂)₃Cl (VI-12) 5.81 ml	—	Et₃N 11.16ml		140°C 4.0hr.	CH₂Cl₂/MeOH =9/1	8.51g (64.0) (III-44)	183.0~ 184.0	(CHCl₃) 3597. 3220. 1513. 1470. 1452. 1437. 1423. 1397
6 1	Me (p) 0.964g (II-8)	⟨⟩NCONH(CH₂)₃Cl 0.70g	15	K₂CO₃ 1.40g	NaI 1.14g	105 °C 5.75hr.	CH₂Cl₂/MeOH =9/1 CH₂Cl₂/MeOH /NH₄OH=64/8/1	0.74 g (41.7) (III-45)	170.0~ 172.5	(CHCl₃) 3675. 3599 3465. 3285. 2465. 1631. 1521. 1488. 1478. 1462. 1457(sh). 1439(sh). 1402
6 2	Ph(p) 0.93g (II-5)	⟨⟩NCONH(CH₂)₃Cl 0.70g	11	K₂CO₃ 1.02g	NaI 0.83g	105°C 5.75hr.	CH₂Cl₂/MeOH =10/1 CH₂Cl₂/MeOH /NH₄OH=128/16 /1=32/8/1	616mg (41.0) (III-46)	225.0~ 228.0 (dec.)	(Nujol) 3300. 3055. 3030. 2810. 2770. 2670. 1606. 1528. 1487. 1471. 1456. 1448
6 3	CF₃ (p) 1.50g (II-2)	⟨N,N⟩-N⟨⟩NCO(CH2)3Cl (VI-13) 1.50g	20	K₂CO₃ 1.69g	NaI 1.38mg	105°C 8.0hr.	CH₂Cl₂/MeOH =20/1~10/1	0.56 g (19.1) (III-47)	142.5~ 144.0	(CHCl₃) 3690. 3600. 1637(sh) 1632. 1587. 1552. 1510(sh). 1495. 1440
6 4	Me (p) 1.44g (II-8)	⟨⟩NCO(CH2)2Cl (VI-14) 1.63g	CH₂Cl₂ 20	Et₃N 1.16 ml		room temperature 92hr.	CH₂Cl₂/MeOH /NH₄OH =128/10/1 ~64/8/1	2.11 g (88.4) (III-48)	—	—

Table 7 (No. 5)

Exam. No.	(II)	R(CH$_2$)nY (VI)	DMF ml	K_2CO_3 g	NaI g	reaction condition	purification condition (1)	g (%) (III)	m.p. (°C)
65	(II-6) 3.67 g	(VI-7) 3.00g	45	4.35	3.54	105°C, 8hr.	CH_2Cl_2/MeOH =29/1~9/1	4.90 (73.5) (III-49)	219.0~222.0
66	(II-1) 3.60 g	(VI-7) 3.07g	45	4.04	3.28	105°C., 9hr.	CH_2Cl_2/MeOH =10/1	5.57 (95.0) (III-50)	232.0~239.0
67	(II-2) 4.70 g	(VI-7) 3.34g	45	4.83	3.93	105°C. 9hr.	CH_2Cl_2/MeOH =15/1~10/1	6.11 (87.4) (III-51)	266.0~268.0
68	(II-16) 3.36 g	(VI-7) 2.50g	35	3.62	2.95	105°C. 12hr.	CH_2Cl_2/MeOH =10/1	4.50 (83.7) (III-52)	230.0~232.0
69	(II-5) 3.99 g	(VI-7) 3.00g	45	4.35	3.54	105°C. 8hr.	CH_2Cl_2/MeOH =39/1~19/1	5.61 (80.3) (III-53)	233.0~238.0
70	(II-3) 3.45 g	(VI-1) 3.00g	45	4.35	3.54	105°C. 6.5hr	CH_2Cl_2/MeOH =39/1~9/1	5.34 (82.7) (III-54)	203.0~207.5
71	(II-22)* 2.60 g	(VI-1) 2.23g	30	3.01	2.44	105°C. 8.5hr	CH_2Cl_2/MeOH =10/1~5/1	1.35 (30.5) (III-55)	95.0~96.5

*: (II-22)

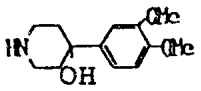


Table 8 (Step 2) (No.1)

(Ⅲ) (g)	acid	solvent (ml)	reflux time	purification condition (2)	Product g (%)
(Ⅲ-20) 2.53g	TsOH・H₂O (2.68g)	toluene(60) CH_2Cl_2 (20)	13hr.	ethyl acetate CH_2Cl_2/MeOH=10/1	Ⅰa-36 2.17g (90.3)
(Ⅲ-21) 2.66g	TsOH・H₂O (2.93g)	toluene(300) CH_2Cl_2 (50)	30hr.	CH_2Cl_2/MeOH=20/1	Ⅰa-37 2.27g (90.0)
(Ⅲ-22) 3.30g	TsOH・H₂O (3.49g)	toluene(300)	48hr.	ethyl acetate CH_2Cl_2/MeOH=20/1	Ⅰa-38 2.50g (80.0)
(Ⅲ-23) 3.18g	TsOH・H₂O (4.21g)	toluene(250) CH_2Cl_2 (60)	69hr.	toluene/ ethyl acetate=1/1 CH_2Cl_2/MeOH=20/1	Ⅰa-39 2.96g (Quantitative)
(Ⅲ-24) 2.56g	CF_3COOH (27ml)	—	8hr.	toluene/ ethyl acetate =30/1	Ⅰa-40 2.40g (98.0)
(Ⅲ-25) 3.80g	CF_3COOH (26ml)	—	8.5hr.	CH_2Cl_2/MeOH=30/1	Ⅰa-41 3.50g (96.8)

Table 8 (No. 2)

(Ⅲ-26) 3.16g	TsOH·H₂O (3.16g)	toluene(250) CH_2Cl_2 (70)	27hr.	CH_2Cl_2/MeOH=20/1	Ⅰa-42 2.20g (73.1)
(Ⅲ-27) 2.45g	TsOH·H₂O (2.55g)	toluene(200) CH_2Cl_2 (50)	48hr.	toluene/ ethyl acetate=1/1 CH_2Cl_2/MeOH=20/1	Ⅰa-43 1.87g (80.2)
(Ⅲ-28) 2.10g	TsOH·H₂O (1.60g)	toluene(100)	29hr.	CH_2Cl_2/MeOH=20/1 ethyl acetate	Ⅰa-44 1.480g (73.8)
(Ⅲ-29) 0.84g	TsOH·H₂O (0.52g)	toluene(60)	31hr.	CH_2Cl_2/MeOH=15/1	Ⅰa-45 0.80g (Quantitative)
(Ⅲ-30) 2.10g	CF_3COOH (10ml)	—	39hr.	CH_2Cl_2/MeOH=30/1	Ⅰa-46 1.34g (70.2)
(Ⅲ-31) 3.51g	CF_3COOH (36ml)	—	8 hr.	CH_2Cl_2/MeOH=20/1	Ⅰa-47 2.80g (92.9)
(Ⅲ-32) 4.14g	TsOH·H₂O (3.25g)	toluene(250)	26.5hr.	CH_2Cl_2/MeOH=20/1	Ⅰa-48 3.16g (80.3)

Table 8 (No.3)

(Ⅲ-33) 1.93	$TsOH \cdot H_2O$ (2.10g)	toluene(160) CH_2Cl_2 (60)	16hr.	CH_2Cl_2/MeOH=15/1	Ⅰa-49 1.50g (81.9)
(Ⅲ-34) 3.10g	CF_3COOH (35ml)	—	25hr.	CH_2Cl_2/MeOH =30/1-20/1	Ⅰa-50 2.80g (94.1)
(Ⅲ-35) 2.70g	CF_3COOH (35ml)	—	19.5hr.	CH_2Cl_2/MeOH =50/1-20/1	Ⅰa-51 2.40g (92.7)
(Ⅲ-36) 4.09g	$TsOH \cdot H_2O$ (4.03g)	toluene(280) CH_2Cl_2 (70)	26hr.	toluene= ethyl acetate=3/1 CH_2Cl_2/MeOH=20/1	Ⅰa-52 3.76g (96.4)
(Ⅲ-37) 3.00g	CF_3COOH (30ml)	—	8 hr.	CH_2Cl_2/MeOH=25/1	Ⅰa-53 2.57g (89.5)
(Ⅲ-38) 2.86g	$TsOH \cdot H_2O$ (2.76g)	benzene(150) CH_2Cl_2 (50)	23hr.	CH_2Cl_2/MeOH =10/1-20/1	Ⅰa-54 1.48g (48.7)
(Ⅲ-39) 1.00g	$TsOH \cdot H_2O$ (1.00g)	benzene(150) toluene(100)	25hr.	toluene/ ethyl acetate=1/1 CH_2Cl_2/MeOH=20/1	Ⅰa-55 0.93g (97.7)

Table 8 (No. 4)

(Ⅲ-40) 1.134g	CF_3COOH (10ml)	1.0hr.	CH_2Cl_2/MeOH/NH_4OH =64/8/1	Ⅰa-56 1.416g (79.3)
(Ⅲ-41) 1.445g	CF_3COOH (10ml)	1.5hr.	CH_2Cl_2/MeOH/NH_4OH =64/8/1	Ⅰa-57* 1.787g (75.1)
(Ⅲ-42) 1.002g	CF_3COOH (10ml)	50min.	CH_2Cl_2/MeOH/NH_4OH =64/8/1	Ⅰa-58* 1.117g (69.8)
(Ⅲ-43) 0.722g	CF_3COOH (6 ml)	1hr.	CH_2Cl_2/MeOH/NH_4OH =128/12/1-64/8/1	Ⅰa-59* 0.881g (64.6)
(Ⅲ-44) 12.82g	CF_3COOH (38.3ml)	3.17hr.	CH_2Cl_2/MeOH/NH_4OH =128/16/1-32/6/1	Ⅰa-60 7.719g (64.9)
(Ⅲ-45) 721mg	CF_3COOH (10ml)	1.5hr.	CH_2Cl_2/MeOH/NH_4OH =128/16/1	Ⅰa-61* 664mg (73.1)
(Ⅲ-46) 766mg	CF_3COOH (10ml)	1hr.	CH_2Cl_2/MeOH =19/1~9/1	Ⅰa-62* 572mg (60.5)
(Ⅲ-47) 540mg	CF_3COOH (8ml)	48hr.	CH_2Cl_2/MeOH =30/1~10/1	Ⅰa-63 529mg (69.2)
(Ⅲ-48) 2.105g	CF_3COOH (5ml)	1.25hr. room Temperature	CH_2Cl_2/MeOH=19/1	Ⅰa-64 1.693g (85.3)

*: malcate

Table 8 (No.5)

(Ⅲ-49) 2.87g	CF_3COOH (35ml)	50min.	CH_2Cl_2/MeOH=49/1	Ⅰa-65 2.61g (76.7)
(Ⅲ-50) 2.85g	CF_3COOH (30ml)	8hr.	CH_2Cl_2/MeOH =20/1-10/1	Ⅰa-66 2.70g (98.6)
(Ⅲ-51) 3.85g	CF_3COOH (50ml)	3 days.	CH_2Cl_2/MeOH =15/1-10/1	Ⅰa-67 3.53g (96.0)
(Ⅲ-52) 1.75g	CF_3COOH (25ml)	7hr.	CH_2Cl_2/MeOH=20/1	Ⅰa-68 1.54g (92.0)
(Ⅲ-53) 2.98g	CF_3COOH (34ml)	50min.	CH_2Cl_2/MeOH=49/1	Ⅰa-69 2.71g (87.1)
(Ⅲ-54) 2.62g	CF_3COOH (33ml)	50min.	toluene/acetone =9/1-3/1	Ⅰa-70 2.41g (87.5)
(Ⅲ-55) 1.58g	CF_3COOH (20ml)	2.5hr.	CH_2Cl_2/MeOH= 15/1-7/1	Ⅰa-71 1.28g (49.5)

*: maleate

Table 9 (No.1)

Compd. No.	m.p. (°C) (solvent*)	Anal. Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
I a-36	130.5-132.0 (CH_2Cl_2-Et_2O)	$C_{11}H_{22}N_2O_2$: C.69.42 (69.70) H. 7.65 (7.70) N.12.76 (12.63)	($CHCl_3$) 3310. 1713. 1680 1545. 1489. 1460	($CDCl_3$) 2.020 (quint. J=8Hz. 2H): 2.329 (s. 3H. J=7Hz. 2H): 2.56-2.59 (m. 4H): 2.671 (t. J=7Hz. 2H): 2.766 (t. J=6Hz. 2H): 3.217 (q. J=3Hz. 2H): 3.510 (q. J=7Hz. 2H): 3.859 (t. J=7Hz. 2H): 6.016 (quint. J=3 Hz. 1H): 7.116 (d. J=8Hz. 2H): 7.284 (d. J=8Hz. 2H): 8.596 (br. 1H)
I a-38	161.5-163.0 (iPrOH) (Oxalate)	$C_{21}H_{32}N_2O_6$: C.60.83 (61.24) H. 6.79 (6.77) N.9.51 (9.74)	(Nujol) 3330. 2600. 2500 1717. 1645. 1605 1533. 1485. 1460	($CDCl_3$) 1.782 (quint. J-7Hz. 2H): 1.969 (quint. J=8Hz. 2H): 2.302 (s. 3H): 2.44-2.59 (m. 6H): 2.658 (t. J=6Hz. 2H): 3.111 (q. J=3Hz. 2H): 3.347 (q. J=7Hz. 2H): 3.813 (t. J=7Hz. 2H): 5.999 (quint. J=3Hz. 1H): 6.00-7.02 (m. 1H): 7.14-7.16 (m. 3H): 8.456 (brs. 1H)
I a-39	146.0-147.0 (iPrOH) (oxalate)	$C_{21}H_{32}N_2O_6$: C.61.08 (61.24) H. 6.70 (6.77) N.9.71 (9.74)	(Nujol) 3300. 2600(br). 1708. 1683. 1548 1490(sh). 1460	($CDCl_3$) 1.873 (quint. J=7Hz. 2H): 2.030 (quint. J=8Hz. 2H): 2.297 (s. 3H): 2.38-2.48 (m. 2H): 2.593 (t. J=7Hz. 2H): 2.606 (t. J=8Hz. 2H): 2.746 (t. J=6Hz. 2H): 3.184 (q. J=3Hz. 2H): 3.402 (quint. J=7Hz. 2H): 5.531 (quint. J=?Hz. 1H): 7.11-7.17 (m. 4H): 8.519 (brs. 1H)
I a-40	146.5-147.5 (iPrOH) (maleate)	$C_{15}H_{22}N_2O_6$ C.53.40 (63.68) H. 6.99 (7.05) N. 3.87 (8.91)	(Nujol) 3330. 2420-2300. 1700. 1620. 1575 1530. 1460. 1450 (sh)	($CDCl_3$) 1.825 (quint. J=8Hz. 2H): 2.020 (quint. J=7Hz. 2H): 2.240 (s. 3H): 2.254 (s. 3H): 2.48-2.56 (m. 4H): 2.594 (t. J=8Hz. 2H): 2.697 (t. J=5Hz. 2H): 3.147 (q. J=3Hz. 2H): 3.390 (q. J=7Hz. 2H): 3.859 (t. J=7Hz. 2H): 6.002 (quint. J=2Hz. 1H): 7.04-7.16 (m. 3H): 8.489 (brs. 1H)
I a-41	159.0-160.0 (iPrOH) (maleate)	$C_{15}H_{22}N_2O_6$ C.63.71 (63.38) H. 7.05 (7.05) N. 8.86 (8.91)	(Nujol) 3290. 2400-2300. 1720(sh). 1710. 1685. 1620. 1600 (sh). 1577. 1550 1513	($CDCl_3$) 1.821 (quint. J=7Hz. 2H): 2.013 (quint. J=8Hz. 2H): 2.300 (s. 6H): 2.48-2.55 (m. 4H): 2.592 (t. J=7Hz. 2H): 2.690 (t. J=6Hz. 2H): 3.142 (q. J=3Hz. 2H): 3.385 (q. J=7Hz. 2H): 3.855 (d-d. J_1=8Hz. J_2=7Hz. 2H): 6.014 (quint. J=2Hz. 1H): 6.878 (s. 1H): 6.998 (s. 2H)

Table 9 (No. 2)

Compd. No.	m.p. (°C) (solvent*)	Anal. Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
I a-42	155.5-157.0 (iPrOH) (maleate)	$C_{22}H_{24}N_2O_6Cl$ C. 57.74 (57.80) H. 5.84 (5.90) N. 8.78 (8.79) Cl. 7.14 (7.42)	(Nujol) 3310. 2350. 2260 1715. 1682. 1585 1520. 1485(sh). 1455	(CDCl$_3$) 1.825 (quint. J=7Hz. 2H): 2.022 (quint. J=8Hz. 2H): 2.49-2.56 (m. 4H): 2.538 (t. J=7Hz. 2H): 2.709 (t. J=6Hz): 3.159 (q. J=3Hz. 2H): 3.389 (q. J=7Hz. 2H): 3.861 (t. J=7Hz. 2H) : 6.084 (quint. J=2Hz. 1H): 7.18-7.30 (m. 3H): 7.346 (s. 1H): 8.499 (brs. 1H)
I a-43	102.0-103.5 (ethyl acetate/ Et_2O)	$C_{21}H_{22}N_2O_6Cl$ C. 61.99 (62.15) H. 6.31 (6.37) N. 12.07 (12.08) Cl. 9.96 (10.19)	(CHCl$_3$) 3310. 1715. 1680 1595. 1545. 1489 1460	(CDCl$_3$) 2.024 (quint. J=7Hz. 2H): 2.55-2.64 (m. 4H): 2.673 (t. J=7Hz. 2H): 2.766 (t. J=6Hz. 2H): 3.218 (q. J=3Hz. 2H): 3.504 (q. J=6Hz. 2H): 3.860 (t. J=7Hz. 2H): 6.082 (quint. J=2Hz. 1H): 7.19-7.27 (m. 3H): 7.361 (s. 1H): 8.615 (brs. 1H)
I a-44	140.5-142.0 (iPrOH) (maleate)	$C_{22}H_{24}N_2O_6Cl \cdot 1/5H_2O$ C. 57.35 (57.37) H. 5.87 (5.94) N. 8.67 (8.37) Cl. 7.72 (7.36)	(Nujol) 3280. 2580 2360 1715. 1690. 1620 1580. 1545. 1490 (sh). 1460	(CDCl$_3$) 1.846 (quint. J=7Hz. 2H): 2.048 (quint. J=8Hz. 2H): 2.47-2.51 (m. 2H): 2.566 (t. J=8Hz. 2H): 2.606 (t. J=8Hz. 2H): 2.728 (t. J=6Hz. 2H): 3.172 (q. J=3Hz. 2H): 3.397 (q. J=7Hz. 2H): 3.865 (t. J=7Hz. 2H): 5.656 (quint. J=2Hz): 7.15-7.37 (m. 4H): 8.510 (brs. 1H)
I a-45	142.0-143.5 (maleate)	$C_{22}H_{24}N_2O_6Cl$ C. 56.54 (56.96) H. 5.89 (5.65) N. 8.79 (9.06) Cl. 7.98 (7.64)	(Nujol) 3300. 2580-2400. 1710. 1682. 1617 1565. 1528	(CDCl$_3$) 2.007 (t. quint. J=7Hz. 2H): 2.35-2.57 (m. 2H): 2.610 (t. J=8Hz): 2.746 (t. J=7Hz. 2H): 2.830 (t. J=6Hz. 2H): 3.723 (q. J=3Hz. 2H): 3.544 (q. J=6Hz. 2H): 3.869 (t. J=7Hz. 2H): 5.656 (q. J=2Hz. 1H): 7.15-7.37 (m. 4H): 8.626 (brs. 1H)
I a-46	216.0-217.5 (MeOH) (oxalate)	$C_{21}H_{22}N_2O_6Cl_2 \cdot 1/5H_2O$ C. 51.31 (51.48) H. 5.15 (5.23) N. 8.53 (8.58) Cl. 14.65 (14.47)	(Nujol) 3340. 1710. 1645 1588. 1562. 1538 1488. 1460. 1420	(CDCl$_3$) 1.807 (quint. J=7Hz. 2H): 2.027 (quint. J=8Hz. 2H): 2.48-2.56 (m. 4H): 2.599 (t. J=8Hz. 2H): 2.689 (t. J=6Hz. 2H): 3.155 (q. J=3Hz. 2H): 3.383 (q. J=7Hz. 2H): 3.859 (t. J=7Hz. 2H): 6.111 (quint. J=2 Hz. 1H): 7.20-7.25 (m. 3H): 8.510 (brs. 1H)

Table 9 (No. 3)

Compd. No.	m.p. (°C) (solvent*)	Anal. Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
I a-47	99.0-100.0 (CH_2Cl_2-Et_2O)	$C_{17}H_{14}N_3O_2Br$: C. 56.32 (56.16) H. 6.04 (5.95) N. 10.35 (10.34) Br. 19.59 (19.67)	($CHCl_3$) 3320, 1712, 1680 1545, 1489, 1465 (sh), 1460, 1440	($CDCl_3$) 1.819 (quint, J=7Hz, 2H); 2.023 (quint, J=7Hz, 2H); 2.49-2.56 (m, 4H); 2.598 (t, J=7Hz, 2H); 2.699 (t, J=6Hz, 2H); 3.145 (q, J=3Hz, 2H); 3.386 (q, J=6Hz, 2H); 3.861 (t, J=7Hz, 2H); 6.064 (quint, J=2Hz, 1H); 7.247 (d, J=8Hz, 2H); 7.462 (d, J=8Hz, 2H); 8.495 (brs, 1H)
I a-48	97.5-98.5 (CH_2Cl_2-Et_2O)	$C_{17}H_{14}N_3O_2F$: C. 65.89 (66.07) H. 7.03 (7.00) N. 12.07 (12.16) F. 5.57 (5.50)	($CHCl_3$) 3320, 1713, 1682 1605, 1545, 1510 1490, 1460	($CDCl_3$) 1.825 (quint, J=7Hz, 2H); 2.021 (quint, J=8Hz, 2H); 2.49-2.56 (m, 4H); 2.597 (t, J=8Hz, 2H); 2.705 (t, J=6Hz); 3.152 (q, J=3Hz, 2H); 3.389 (q, J=7Hz, 2H); 3.862 (t, J=7Hz, 2H); 5.998 (quint, J=2Hz, 1H); 6.992 (t, J=8Hz, 2H); 7.343 (d-d, J_1=8Hz, J_2=5Hz, 2H); 8.495 (brs, 1H)
I a-49	136.0-136.5 (iPrOH) (maleate)	$C_{21}H_{18}N_3O_6F$: C. 59.13 (59.05) H. 5.85 (5.86) N. 9.31 (9.39) F. 4.48 (4.25)	(Nujol) 3300, 2600(br) 1720, 1675, 1610 1602, 1570, 1535 1515	($CDCl_3$) 2.028 (quint, J=8Hz, 2H); 2.50-2.60 (m, 4H); 2.674 (t, J=7hz, 2H); 2.741 (t, J=5Hz, 2H); 3.216 (q, J=3Hz, 2H); 3.551 (q, J=6Hz, 2H); 3.866 (t, J=7Hz, 2H); 5.993 (quint, J=2Hz, 1H); 6.997 (t, J=9Hz, 2H); 7.350 (d-d, J_1=9Hz, J_2=5Hz, 2H); 8.615 (brs, 1H)
I a-50	185.0-188.0 (iPrOH-MeOH-Et_2O) (hydrochloride)	$C_{17}H_{14}N_3O_2ClF_2 \cdot HCl \cdot 1/5H_2O$ C. 50.92 (51.11) H. 5.15 (5.23) N. 8.71 (8.94) Cl. 14.95 (15.08) F. 11.83 (12.12)	(Nujol) 3320, 2670, 2550 2420, 1710	($CDCl_3$) 1.822 (quint, J=7Hz, 2H); 2.030 (quint, J=8Hz, 2H); 2.544 (t, J=8Hz, 2H); 2.55-2.60 (m, 2H); 2.602 (t, J=8Hz, 2H); 2.718 (t, J=5Hz, 2H); 3.177 (q, J=2Hz, 2H); 3.393 (q, J=7Hz, 2H); 3.865 (t, J=7Hz, 2H); 6.10-6.18 (m, 1H); 7.40-7.50 (m, 2H); 7.679 (brs, 1H); 8.511 (brs, 1H)
I a-51	213.0-215.0 (iPrOH-MeOH) (hydrochloride)	$C_{17}H_{14}N_3O_2ClF_2 \cdot HCl$ C. 50.38 (50.45) H. 4.90 (4.90) N. 9.22 (9.29) Cl. 15.65 (15.68) F. 12.61 (12.60)	(Nujol) 3500, 2520, 1704 1683, 1548, 1493 1462	($CDCl_3$) 2.030 (quint, J=7Hz, 2H); 2.50-2.60 (m, 2H); 2.597 (t, J=8Hz, 2H); 2.678 (t, J=6Hz, 2H); 2.777 (t, J=6Hz, 2H); 3.236 (q, J=3Hz, 2H); 3.504 (q, J=6Hz, 2H); 3.864 (t, J=7Hz, 2H); 6.10-6.16 (m, 1H); 7.40-7.50 (m, 2H); 7.685 (brs, 1H); 8.625 (brs, 1H)

Table 9 (No. 4)

Compd. No.	m.p. (°C) (solvent*)	Anal. Calcd. Found (%)	IR (cm^{-1})	NMR (δ)
I a-52	83.0-84.0 (CH_2Cl_2-Et_2O)	$C_{17}H_{22}N_3O_2SCl$ C. 55.38 (55.50) H. 5.96 (6.03) N. 11.51 (11.42) S. 8.69 (8.71) Cl. 9.69 (9.64)	($CHCl_3$) 3320, 1712, 1680 1545	($CDCl_3$) 1.801 (quint, J=7Hz, 2H); 2.024 (quint, J=7Hz, 2H); 2.50 (brs, 2H) 2.520 (t, J=7Hz, 2H); 2.596 (t, J=8Hz, 2H); 2.670 (t, J=6Hz, 2H); 3.119 (q, J=3Hz, 2H); 3.376 (q, J=7Hz, 2H); 3.857 (t, J=7Hz, 2H); 5.953 (quint, J=2Hz, 1H); 6.688 (d, J=4Hz, 1H); 6.756 (d, J=4Hz, 2H); 8.485 (brs, 1H)
I a-53	156.5-157.5 (iPrOH) (maleate)	$C_{21}H_{28}N_3O_6SCl_2$: C. 48.58 (48.65) H. 4.89 (4.86) N. 8.02 (8.11) S. 5.92 (6.18)	(Nujol) 3300, 1708, 1680 1585, 1535	($CDCl_3$) 1.808 (quint, J=7Hz, 2H); 2.030 (quint, J=7Hz, 2H); 2.48-2.56 (m, 4H); 2.604 (t, J=8Hz, 2H); 2.659 (t, J=6Hz, 2H); 3.136 (q, J=3Hz, 2H); 3.383 (q, J=7Hz, 2H); 3.862 (t, J=7Hz, 2H); 5.995 (quint, J=2Hz, 1H); 6.712 (s, 1H); 8.497 (brs, 1H)
I a-54	144.0-145.0 (iPrOH) (maleate)	$C_{24}H_{33}N_3O_6Cl$ C. 58.44 (58.59) H. 6.05 (6.15) N. 8.52 (8.54) Cl. 7.33 (7.21)	(Nujol) 3280, 2400-2280, 1692, 1650, 1622 1575, 1522, 1495	($CDCl_3$) 1.78-1.91 (m, 6H); 2.45-2.60 (m, 6H); 2.703 (t, J=6Hz, 2H); 3.161 (q, J=3Hz, 2H); 3.383 (q, J=7Hz, 2H); 3.76-3.83 (m, 2H); 6.056 (quint, J=2Hz, 1H); 7.264, 7.322 (ABq, J=9Hz, 4H); 9.449 (brs, 1H)
I a-55	134.0-135.5 (CH_2Cl_2-Et_2O)	$C_{19}H_{24}N_3O_2Cl$ C. 62.84 (63.06) H. 6.67 (6.68) N. 11.41 (11.61) Cl. 10.05 (9.80)	($CHCl_3$) 3280, 1795, 1645 1527, 1495, 1480 1463, 1450	($CDCl_3$) 1.78-1.85 (m, 4H); 2.45-2.60 (m, 4H); 2.680 (t, J=7Hz, 2H); 2.770 (t, J=6Hz, 2H); 3.238 (q, J=2Hz, 2H); 3.513 (q, J=7Hz, 2H); 3.80-3.83 (m, 2H); 6.051 (quint, J=2Hz, 1H); 7.24-7.35 (m, 4H); 9.521 (brs, 1H)
I a-56	192.5-193.5 (CH_2Cl_2-MeOH-iPrOH) (di-maleate)	$C_{24}H_{32}N_2 \cdot 2C_4H_4O_4$ C. 65.32 (65.51) H. 7.84 (7.90) N. 4.77 (4.77)	(Nujol) 2340, 1916, 1707 1619, 1563, 1542 1481, 1460, 1446 1378	($CDCl_3$)(free) 0.966 (d, J=5Hz, 3H); 1.314 (s, 9H); 1.43-1.57 (m, 3H); 1.67-1.78 (m, 2H); 1.930 (quint, J=7Hz, 2H); 2.239 (t, J=12Hz, 2H); 2.49-2.58 (m, 2H); 2.528 (t, J=7Hz, 2H); 2.63-2.74 (m, 4H); 3.14-3.21 (m, 4H); 6.027 (quint, J=1Hz, 1H); 7.330 (ABq, J=8Hz, 4H)

Table 9 (No.5)

Compd. No.	m.p. (°C) (solvent*)	Anal. Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
I a-57	191.5-193.0 (CH_2Cl_2-MeOH-iPrOH) (di maleate)	$C_{21}H_{32}N_2 \cdot 2C_4H_4O_4$ C. 63.75 (63.95) H. 7.31 (7.40) N. 5.16 (5.14)	(Nujol) 2340. 1995. 1709 1621. 1525(sh). 1510(sh). 1483. 1462. 1449(sh). 1379	($CDCl_3$) 0.980 (d. J=5Hz. 3H): 1.48-1.66 (m. 3H): 1.70-1.82 (m. 2H): 1.953 (quint. J=7Hz. 2H): 2.333 (s. 3H): 2.357 (t. J=12Hz. 2H): 2.544 (t. J=7Hz. 4H): 2.715 (t. J=8Hz. 2H): 2.78-2.84 (m. 2H): 3.160 (q. J=3Hz. 2H): 3.298 (d. J=12Hz): 6.013 (quint. J=1Hz. 1H): 7.123.7.2 84 (ABq. J=8Hz. 4H)
I a-58	190.0-192.0 (MeOH-iPrOH) (di-maleate)	$C_{23}H_{36}N_2 \cdot 2C_4H_4O_4$ C. 64.92 (65.02) H. 7.68 (7.74) N. 4.91 (4.89)	(Nujol) 2360. 1997. 1708 1619. 1570. 1535 1480. 1457. 1448 (sh). 1379	($CDCl_3$) 1.324 (s. 9H): 1.50-2.00 (m. 8H): 2.50-2.80 (m. 12H): 3.200 (q. J= 3Hz. 2H): 6.056 (s. 1H): 7.347 (ABq. J=8Hz. 4H)
I a-59	193.0-195.0 ($CHCl_3$-MeOH) (tri-maleate)	$C_{23}H_{37}N_3 \cdot 3C_4H_4O_4$ C. 59.39 (59.58) H. 6.95 (7.03) N. 6.01 (5.96)	(Nujol) 2335. 1995. 1706 1621. 1568. 1542 (sh). 1478. 1460 1439. 1380(sh)	($CDCl_3$) 1.313 (s. 9H): 1.786 (quint. J=7Hz. 2H): 2.296 (s. 3H): 2.37-2.60 (m. 17H): 2.703 (t. J=5Hz. 2H): 3.158 (q. J=3Hz. 2H): 6.028 (quint. J=1Hz. 1H): 7.382 (ABq. J=8Hz. 4H)
I a-60	75.0-77.0 (Et_2O-n-hexane)	$C_{16}H_{21}NO$ C. 77.94 (77.88) H. 9.16 (9.15) N. 6.22 (6.05)	(Nujol) 3110. 3023. 2773 1518. 1467. 1412 1397. 1379	($CDCl_3$) 1.791 (quint. J=7Hz. 2H): 2.332 (s. 3H): 2.50-2.60 (m. 2H): 2.735 (t. J=6Hz. 2H): 2.775 (t. J=6Hz. 2H): 3.221 (q. J=3Hz. 2H): 3.834 (t. J=5Hz. 2H): 6.001 (quint. J=2Hz. 1H): 7.123.7.272 (ABq. J=8Hz. 4H)
I a-61	115.0-116.0 (iPrOH-Et_2O) (maleate)	$C_{28}H_{39}N_3O \cdot C_4H_4O_4$ C. 64.88 (64.99) H. 7.54 (7.50) N. 9.42 (9.47)	(Nujol) 3405. 2720. 2570 2295. 1642. 1580 1538. 1499. 1457 1411. 1380	(CD_3OD) 1.87-12.05 (m. 6H): 2.333 (s. 3H): 2.886 (brs. 2H): 3.21-3.36 (m. 1H): 3.522 (brs. 2H): 3.913 (s. 2H) 6.099 (s. 1H): 6.245 (s. 2H): 7.188.7.369 (ABq. J=9Hz. 4H)

Table 9 (No. 6)

Compd. No.	m.p. (°C) (solvent*)	Anal. Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
I a-62	164.0-166.0 (MeOH-Et_2O) (maleate)	$C_{25}H_{31}N_3O \cdot C_4H_4O_4$ C. 68.89 (68.89) H. 6.97 (6.98) N. 8.30 (8.31)	(Nujol) 3403, 3037, 2330 1700, 1640, 1578 1537, 1498, 1457 (sh), 1449, 1409	(CD_3OD) 1.88-2.06 (m, 4H): 2.951 (brs, 2H): 3.20-3.40 (m, 6H): 3.557 (brs, 2H): 3.959 (brs, 2H): 6.220 (s, 1H): 6.248 (s, 2H): 7.30-7.70 (m, 9H)
I a-63	150.0-151.5 (CH_2Cl_2 -Et_2O)	$C_{24}H_{28}N_3OF_3$ C. 62.55 (62.73) H. 6.08 (6.14) N. 15.13 (15.24) F. 12.36 (12.40)	($CHCl_3$) 1632, 1617(sh), 1588, 1552, 1495 1437	($CDCl_3$) 1.940 (quint, J=7Hz, 2H): 2.450 (t, J=8Hz, 2H): 2.547 (t, J=7Hz, 2H): 5.565 (brs, 2H): 2.727 (t, J=6Hz, 2H): 6.142 (s, 1H): 6.515 (t, J=5Hz, 1H): 7.448, 7.540 (ABq, J=8Hz, 4H): 8.301 (d, J=5Hz, 2H)
I a-64	108.0-109.0 (CH_2Cl_2-Et_2O -n-hexane)	$C_{19}H_{24}N_2O$ C. 76.26 (76.47) H. 8.70 (8.78) N. 9.32 (9.39)	($CHCl_3$) 1625, 1512, 1466 1448, 1378	($CDCl_3$) 1.78-2.04 (m, 4H): 2.332 (s, 3H): 2.574 (t, J=8Hz, 4H): 2.765 (t, J=6Hz, 2H): 2.881 (t, J=8Hz, 2H): 3.211 (q, J=3Hz, 2H): 3.448 (t, J=6Hz, 2H): 3.477 (t, J=6Hz, 2H): 6.02 (quint, J=2Hz, 1H): 7.122, 7.285 (ABq, J=8Hz, 4H)
I a-65	183.0-190.0 (MeOH-Et_2O) (hydrochloride)	$C_{22}H_{31}N_3O_2 \cdot HCl$ C. 65.06 (65.09) H. 8.04 (7.95) N. 10.38 (10.35) Cl. 8.46 (8.73)	(Nujol) 3310, 2725, 2670 2405, 1709, 1688 1549, 1519, 1488 1459, 1430, 1412 1392	($CDCl_3$) 1.313 (s, 9H): 2.018 (quint, J=8Hz, 2H): 2.52-2.64 (m, 6H): 2.678 (t, J=7Hz, 2H): 2.774 (t, J=6Hz, 2H): 3.212, 3.242 (ABq, J=3Hz, 2H) 3.545, 3.484 (ABq, J=7Hz, 2H): 3.859 (t, J=7Hz, 2H): 6.029 (quint, J=2Hz, 1H): 7.332 (s, 4H): 8.604 (brs, 1H)
I a-66	216.0-219.0 (MeOH-Et_2O) (hydrochloride)	$C_{18}H_{27}N_3O_2Cl_2 \cdot HCl$ C. 51.66 (51.63) H. 5.34 (5.30) N. 10.01 (10.03) Cl. 25.12 (25.40)	(Nujol) 3290, 2510, 1712 1672, 1521	($CDCl_3$) 2.024 (quint, J=7Hz, 2H): 2.45-2.55 (m, 2H): 2.594 (t, J=8Hz, 2H): 2.665 (t, J=7Hz, 2H): 2.754 (t, J=6Hz, 2H): 3.214 (q, J=3Hz, 2H): 3.497 (q, J=6Hz, 2H): 3.860 (t, J=7Hz, 2H): 6.0-6.14 (m, 1H): 7.208 (dd, J_1=8Hz, J_2=2Hz, 1H): 7.365 (d, J=8Hz, 1H): 7.450 (d, J=2Hz, 1H): 8.615 (brs, 1H)

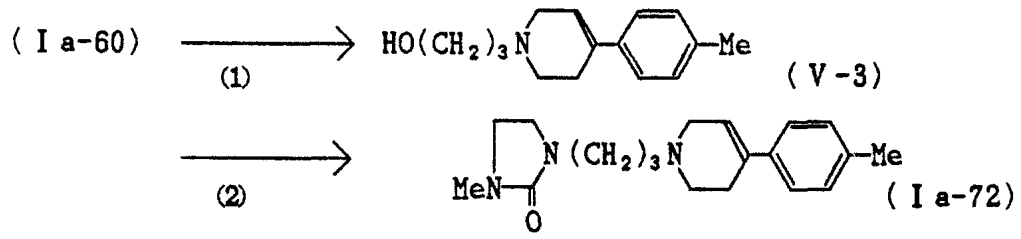
Table 9 (No. 7)

Compd. No.	m.p. (°C) (solvent*)	Anal. Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
I a-67	238.0-248.0 (MeOH-Et_2O) (Hydro-chloride)	$C_{19}H_{22}N_3O_2F_3 \cdot HCl$ C. 54.43 (54.61) H. 5.59 (5.55) N. 9.89 (10.06) Cl. 8.45 (8.48) F. 13.68 (13.64)	(Nujol) 3310, 2930, 2860 2460, 1711, 1687 1617, 1541	($CDCl_3$) 2.032 (quint, J=8Hz, 2H); 2.50-2.66 (m, 4H); 2.69 (t, J=6Hz, 2H); 2.722 (t, J=6Hz, 2H); 3.256 (q, J=3Hz, 2H); 3.518 (q, J=6Hz, 2H); 3.868 (t, J=7Hz, 2H); 6.14-6.17 (m, 1H); 7.478, 7.567 (ABq, J=9Hz, 4H); 8.625 (brs, 1H)
I a-68	228.0-232.0 (MeOH-Et_2O) (Hydro-chloride)	$C_{18}H_{22}N_3O_2Br \cdot HCl$ C. 50.89 (50.42) H. 5.58 (5.41) N. 9.90 (9.80) Cl. 8.22 (8.27)	(Nujol) 3320, 2920, 2860 2460, 1710, 1685 1537	(CD_3OD) 2.029 (quint, J=8Hz, 2H); 2.50-2.60 (m, 2H); 2.598 (t, J=8Hz, 2H); 2.675 (t, J=7Hz, 2H); 2.769 (t, J=6Hz, 2H); 3.216 (q, J=3Hz, 2H); 3.509 (q, J=6Hz, 2H); 3.865 (t, J=7Hz, 2H); 6.04-6.08 (m, 1H); 7.429, 7.247 (ABq, J=9Hz, 4H); 8.611 (brs, 1H)
I a-69	205.0-210.0 (MeOH-Et_2O) (Hydro-chloride)	$C_{24}H_{27}N_3O_2 \cdot HCl$ C. 67.72 (67.67) H. 6.64 (6.63) N. 9.80 (9.87) Cl. 8.10 (8.32)	(Nujol) 3305, 3045, 2415 2405, 1702, 1679 1578, 1540, 1488 1457, 1444, 1420 1392	($CDCl_3$) 2.205 (quint, J=8Hz, 2H); 2.54-2.66 (m, 4H); 2.695 (t, J=7Hz, 2H); 2.803 (t, J=6Hz, 2H); 3.261 (q, J=3Hz, 2H); 3.558, 3.497 (ABq, J=7Hz, 2H); 3.865 (t, J=7Hz, 2H); 6.128 (quint, J=2Hz, 1H); 7.28-7.67 (m, 9H); 8.624 (brs, 1H)

*: a solvent for recrystallization

Example 72

1-{3-(1-Methyl-2-oxo-imidazolidin-1-yl)propyl}-4-(4-tolyl)-1,2,5,6-tetrahydropyridine (I a-72)



(1) A mixture of 870 mg of the compound (I a-60) and 8.0 ml of thionylchloride is stirred at room temperature for 2 hours. After removal of the excess reagent under reduced pessure, the residue was washed with Et_2O and dried under reduced pressure to prepare 1.067 g (Yield : 99.2%) of the compound (V -3) as pale yellow powder.

IR($CHCl_3$) cm^{-1} : 1600, 1510, 1460, 1410

NMR ($CDCl_3$) : 2.046 (quint, J=7Hz, 2H); 2.334 (s, 3H); 2.54-2.64 (m, 2H); 2.629 (t, J=7H, 2H); 2.723 (t, J=5Hz, 2H); 3.173 (q, J=2 Hz, 2H); 3.630 (t, J=7Hz, 2H); 6.023 (quint, J=2Hz, 1H); 7.123, 7.287 (ABq, J=8Hz, 4H)

(2) To a solution of 266 mg of 1-methyl-2-oxo-imidazolidine in 5 ml of DMF was added 115 mg of 60% NaH under ice-cooling. After stirring at room temperature for 20 minutes, a solution of 553 mg of the compound (V -3) in 4 ml of DMF was added to the reaction mixture and stirred at room temperature for 90.5 hours. The reaction mixture was concentrated under reduced pressure and poured into d-HCl. The aqueous layer is made alkaline with $NaHCO_3$, extracted with $CHCl_3$-MeOH (19/1), dried over $MgSO_4$, and evaporated. The residue is subjected to column chromatography of silica gel eluting with $CHCl_3$-MeOH (19/1) to prepare 491 mg of the compound (I a-72). The maleate is recrystallized from iPrOH-Et_2O to prepare 439 mg (Yield : 45.8%) of colorless needles. mp. 126.5-128.0 °C.

Anal Calcd. (%) for $C_{19}H_{27}N_3O \cdot C_4H_4O_4 \cdot 1/5H_2O$:

: C, 63.73; H, 7.20; N, 9.61

Found : C, 63.78; H, 7.31; N, 9.70

IR ($CHCl_3$) :

2450, 2340, 1910, 1689, 1622, 1502, 1451, 1409, 1382

NMR ($CDCl_3$) : 1.797 (quint, J=8Hz, 2H); 2.329 (s, 3H); 2.46-2.62 (m, 4H); 2.712 (t, J=5Hz, 2H); 2.790 (s, 3H); 3.166 (q, J=3Hz, 2H); 3.255 (t, J=7Hz, 2H); 3.295 (s, 4H); 6.014 (quint, J=2Hz, 1H); 7.117, 7.283 (ABq, J=8Hz, 4H)

Example 73-91

The compounds (V) obtained in Example 19-21 are reacted in the same manner as Example 72 to prepare the compound (I a). The reaction conditions are shown in Table 10.

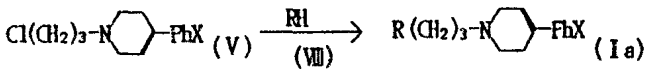


Table 10 (No.1)

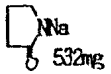
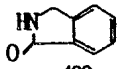
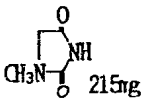
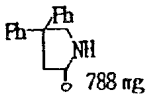
Ex. No.	(V)	(VII)	solvent	reaction condition	purification condition	product mg (Yield)	m.p.(°C)	IR
73	(V-3) 742mg	 532mg	DMF 5ml	100 °C 47min.	CH_2Cl_2/MeOH =19/1	Ia-73*1 602mg (46.2%)	119.0-121.0 (iPrOH)	($CHCl_3$) 2455. 2310. 1677 1622. 1512. 1497 1464. 1380. 1351
74	(V-2) 1.02g	 492mg	DMF 10ml	100 °C 25hr.	toluene/ acetone =3/1-1/1	Ia-74*1 266mg (15.3%)	152.0-154.0 (MeOH-Et_2O)	(Nujol) 2700-1750(br). 1695. 1663. 1619 1532. 1463. 1412 1378. 1358
75	(V-3) 500mg	 215mg	DMF 8ml	70 °C 10hr.	CH_2Cl_2/MeOH =39/1	Ia-75 409mg (62.4%)	98.0-100.0 ($CDCl_3$-MeOH)	($CHCl_3$) 3690. 1771. 1602 1511. 1488. 1454 1429. 1416. 1384
76	(V-3) 500mg	H_2NPh 0.192 ml (K_2CO_3 576mg, NaI 468mg, Pyridine 178ml)	DMF 8ml	80 °C 15hr.	toluene/ acetone=4/1	Ia-76*1 130mg (72.1%)	154.0-155.5 (MeOH-Et_2O)	(Nujol) 3050. 2660. 2615 2570. 2480. 2410 1606. 1590. 1578 1517. 1498. 1479 1447. 1423. 1398 1376
77	(V-3) 650mg	 788mg (Pyridine 231mg, NaI 608mg)	DMF 6ml	100°C 5hr.	toluene/ acetone=9/1	Ia-77*1 1.08g (71.4%)	174.0-176.0 (dec.) (MeOH-Et_2O)	($CHCl_3$) 3685. 3495. 3350 2700-1800 (br). 1778. 1707. 1621 1511. 1496. 1446 1395
78	(V-2) 440mg	CH_3NHPh 0.20ml (Pyridine 0.157ml, NaI 412mg)	DMF 8ml	110°C 6hr.20min.	toluene/ acetone=9/1	Ia-78*1 135mg (17.6%)	149.0-151.0 (MeOH-Et_2O)	($CHCl_3$) 3575. 3338

Table 10 (No.2)

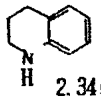
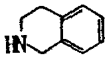
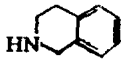
Ex. No.	(V)	(VIII)	solvent	reaction condition	purification condition	Product mg (Yield)	m.p.(°C)	IR
79	(V-3) 0.828g	NaOPh 207 mg	DMF 8ml	70°C 3hr.10min.	toluene/ acetone=9/1	Ia-79*1 562mg (66.3%)	148.0-150.0 (MeOH-Et$_2$O-iPrOH)	(Nujol) 2720. 2370. 1701 1620. 1598. 1584 1499. 1467. 1458(sh). 1387
80	(V-3) 942mg	 2.34ml	——	150°C 8hr.15min.	toluene/ acetone =19/1-9/1	Ia-80*1 930mg (54.4%)	148.0-150.0 (iPrOH-Et$_2$O)	(Nujol) 2720. 2575(sh). 2490(sh). 2330. 1708. 1652. 1600 1571. 1502. 1459
81	(V-3) 624mg	 1.56ml	——	150 °C 4hr.10min.	CH_2Cl_2/MeOH =19/1	Ia-81*1 963mg (66.6%)	191.0-192.0 (dec.) (MeOH-Et$_2$O)	(Nujol) 3030. 2720. 2278 1711. 1623. 1572 1532. 1513(sh). 1485. 1463. 1435
82	(V-3) 517mg	HN(iBu)$_2$ 1.358g	——	20hr. reflux	CH_2Cl_2/MeOH =49/1	Ia-82*1 457mg (38.4%)	140.5-142.5 (CH_2Cl_2-Et$_2$O)	(Nujol) 2710. 2500. 1706 1572. 1480. 1455 1375
83	(V-3) 511mg	H$_2$N(iBu) 1.02ml	——	10.5hr. reflux	CH_2Cl_2/MeOH /NH_4OH =128/12/1	Ia-83*1 471mg (44.4%)	179.5-182.5 (CH_2Cl_2-Et$_2$O)	(Nujol) 3340. 2780. 2545 2460. 1699. 1618 1577. 1474. 1458 1441. 1381
84	(V-3) 466mg	 0.78ml	——	50°C 3hr.	CH_2Cl_2/MeOH /NH_4OH =128/16/1 -32/4/0.5	Ia-84*1 225mg (42.4%)	180.0-181.0	(Nujol) 2340. 1709. 1550 1458. 1377. 156
85	(V-3) 511mg	H$_2$N(CH$_2$)$_2$N(iPr)$_2$ 1.054 g	——	105°C 7hr.	CH_2Cl_2/MeOH /NH_4OH =128/16/1 -64/8/1	Ia-85*1 436mg (32.0%)	125.0-127.0	(Nujol) 2668. 2500. 2400 (sh). 1702. 1619 1570. 1462. 1378
86	(V-2) 654mg	HN(iBu)$_2$ 1.50g	——	32hr. reflux	CH_2Cl_2/MeOH =49/1-19/1	Ia-86*1 338mg (27.1%)	135.0-136.5	(Nujol) 2420. 1707. 1616 1572. 1485. 1456 1377

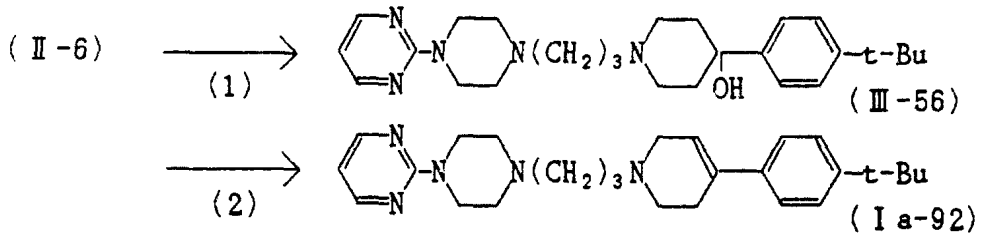
Table 10 (No.3)

Ex. No.	(V)	(VII)	solvent	reaction condition	purification condition	product mg (Yield)	m.p. (°C)	IR
87	(V-2) 645mg	HN(iBu)$_2$ 1.1ml	———	32hr. reflux	CH_2Cl_2/MeOH =49/1-19/1	I a-87*1 338mg (27.1%)	135.0-136.0 (MeOH-Et_2O)	(Nujol) 2420. 1707. 1616 1572. 1485. 1456 1377
88	(V-2) 1.05g		———	room temperature 32.5hr.	CH_2Cl_2/MeOH /NH_4OH =128/16/1 -32/4/0.5	I a-88*1 1.034g (52.4%)	176.0-178.0 (MeOH)	(Nujol) 3483. 2723. 2679 2587. 2415. 1703 1608. 1579. 1478 1460. 1412. 13[illegible]
89	(V-2) 621mg		———	room temperature 5days	CH_2Cl_2/MeOH /NH_4OH =128/16/1	I a-89*1 800mg (67.3%)	190.0-191.0 (dec.) (MeOH)	(Nujol) 2355. 1711. 162[illegible] 1577. 1543. 1479 (sh). 1461. 1378
90	(V-1) 828mg		———	150°C 3hr.	CH_2Cl_2/MeOH =29/1-19/1	I a-90*1 1.025g (58.0%)	183.5-185.0 ($CHCl_3$-MeOH)	(Nujol) 2340. 1708. 1619 1568. 1528(sh). 1485. 1461
91	(V-1) 628mg	HN(iBu)$_2$ 3.76ml	———	33hr. reflux	CH_2Cl_2/MeOH =49/1-19/1	I a-91*1 685mg (51.6%)	176.5-178.0 (dec.) (MeOH-Et_2O)	(Nujol) 2620. 2510. 1690 1657. 1618. 1579 1533. 1488. 1460 1409. 1378

*1: malcate

Example 92

4-(4-tert-Butylphenyl)-1-[3-(4-(pyrimidin-2-yl)piperazin-1-yl)propyl]-1,2,5,6-tetrahydropyridine (I a-92)



(1) A mixture of 1.1g of 3-(4-(pyrimidin-2-yl)piperazin-1-yl)propylchloride, 1.07g of the compound (Ⅱ-6), 1.26g of K_2CO_3, and 1.03g of NaI in 12 ml of DMF is stirred at 100 °C for 4 hours. The reaction mixture is poured into ice-water and extracted with ethyl acetate. The organic layer is washed with water, dried and evaporated. The residue is purified by silica gel chromatography (CH_2Cl_2/MeOH=10/1) followed by recrystallization from CH_2Cl_2-Et_2O to prepare 1.70g (Yield : 85%) of the compound (Ⅲ-56).
mp. 215.0-225.0 °C (dec.)

(2) A solution of 1.58 g of the compound (Ⅲ-56) in 15 ml of CF_3COOH is refluxed for 3.5 hours. After removal of the excess reagent, the residue is poured into ice-cooled aq.$NaHCO_3$ and extracted. The organic layer is dried over Na_2SO_4 and evaporated under reduced pressure. The oily residue is purified by column chromatography of silica gel eluting with CH_2Cl_2/MeOH (10/1-5/1) to prepare 1.44 g (Yield : 95%) of the compound (I a-92) as crystals(mp.79.0-81.0°C). The maleate is recrystallized from methanol to prepare colorless needls.
mp. 209.0-211.0 °C (dec.)

Example 93-94

The reactions are performed in the same manner as Example 92 to prepare the compound (Ⅲ) and (I a). The reaction conditions and physical constants are shown in Table 11 and 12.

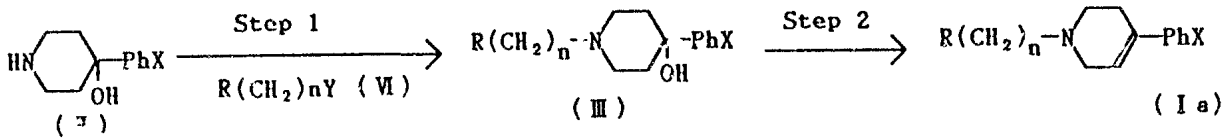


Table 11 (Step 1)

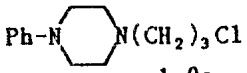
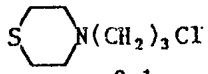
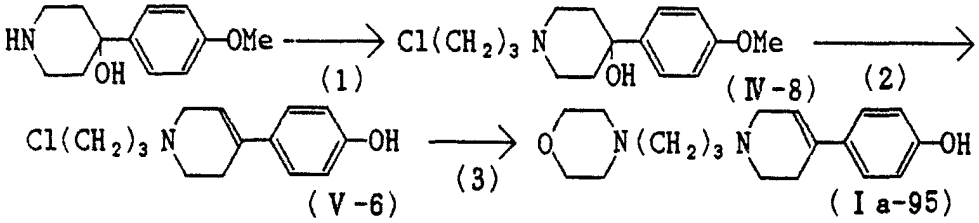
Ex. No.	(II)	R(CH₂)nY (VI)	DMF (ml)	K_2CO_3 (g)	NaI (g)	reaction condition (1)	purification condition (1)	g(Yield) Compd.No	m.p. (°C)
93	(II-6) 980mg	 1.0g	20	1.16	0.94	105 6.5 hr.	CH_2Cl_2/MeOH =10/1-5/1	1.69 (92.6) (III-57)	129.0-130.5 (CH_2Cl_2-Et_2O) (malcate)
94	(II-6) 2.67g	 2.1g	20	3.18	2.60	95-100 17 hr.	CH_2Cl_2/MeOH =20/1-10/1	4.04 (93.3) (III-58)	137.0-138.5 (CH_2Cl_2-Et_2O) (malcate)

Table 12 (Step 2)

(Ⅲ) (g)	CF_3COOH	reflux time	purification condition	(Ⅰa) g(Yield)	m.p.(°C)	IR
(Ⅲ-57) 1.50g	20ml	4hr.	CH_2Cl_2/MeOH =20/1-10/1	Ⅰa-93 1.40g (97.4)	105-106 (MeOH)	(Nujol) 1710, 1622, 1598, 1575, 1495 (sh), 1480, 1462, 1450, 1385, 1360
(Ⅲ-58) 0.88g	10ml	8hr.	CH_2Cl_2/MeOH=20/1	Ⅰa-94 maleate 0.74g (97.5)	213.0-214.5 (MeOH)	(Nujol) 2300, 1717, 1622, 1575, 1535, 1500, 1465, 1458, 1450

Example 95

4-(4-Hydroxyphenyl)-1-(3-(4-morpholinyl)propyl)-1,2,5,6-tetrahydropyridine (I a-95)



(1) A mixture of 2.829 g of 4-(4-methoxyphenyl)-4-hydroxypiperidine, 2.02 ml of 3-bromopropylchloride, and 3.773 g of K_2CO_3 in 30 ml of DMF is stirred at room temperature for 3 hours. The reaction mixture is poured into ice-water and extracted with ethyl acetate. The organic layer is dried and evaporated under reduced pressure to prepare 4.525 g of pale yellow solid. Purification by column chromatography of silica gel eluting with CH_2Cl_2/MeOH (29/1 -5/1) to prepare 3.316 g (Yield : 85.6%) of the compound (Ⅳ-8) as solid which is recrystallized from n-hexane-Et_2O to prepare colorless needles. mp. 103.5-105.0 °C

Anal Calcd.(%) for $C_{15}H_{22}ClNO_2$

: C,63.48; H,7.81; N,4.94; Cl,12.49

Found : C,63.47; H,7.78; N,5.01; Cl,12.45

IR($CHCl_3$): 3595, 1610, 1582, 1510, 1468, 1462, 1454, 1441, 1375

NMR ($CDCl_3$) δ : 1.761 (d-d, J_1=14Hz, J_2=3Hz, 2H); 1.998 (quint, J=7Hz, 2H); 2.121 (t-d, J_1=13Hz, J_2=4Hz, 2H); 2.475 (t-d, J_1=12Hz, J_2=3Hz, 2H); 2.560 (t, J=7Hz, 2H); 2.782 (d-d, J_1=14Hz, J_2=3Hz, 2H); 3.618 (t, J=7Hz 2H); 3.805 (s, 3H); 6.886, 7.427 (ABq, J=9 Hz, 4H)

(2) To a solution of 3.176 g of the compound (Ⅳ-8) is added 3.17 ml of BBr_3 with stirring under ice-cooling. After refluxing for 1.5 hours, the reaction mixture is poured into ice-water and the aqueous layer is made alkaline with c.NH_4OH and extracted with CH_2Cl_2/MeOH (4/1). The organic layer is dried and

evaporated to dryness. The crude product is dissolved in 20 ml of CF_3COOH and refluxed for 1 hour. The reaction mixture is concentrated under reduced pressure and poured into ice-water. The aqueous layer is made alkaline with c.NH_4OH and extracted with CH_2Cl_2/MeOH (4/1). The organic layer is dried and evaporated to prepare 1.701 g (Yield : 57.2%) of the compound (V-6) as solid, which is recrystallized from MeOH-n-hexane to prepare the compound (V-6) as pale orange plates. mp. 208.0-209.0°C

Anal Calcd. (%) for $C_{14}H_{18}ClNO$

: C,66.79; H,7.21; N,5.56; Cl,14.08

Found : C,66.79; H,7.26; N,5.52; Cl,14.25

IR(Nujol) :

3025, 2773, 2650, 2560, 1607, 1578, 1515, 1453, 1429, 1382

NMR ($CDCl_3$-CD_3OD) δ : 2.66 (quint, J=8Hz, 2H); 2.47-2.76 (m, 4H); 2.774 (t, J=6Hz, 2H); 3.200 (q, J=2Hz, 2H); 3.637 (t, J=6Hz, 2H); 5.972 (s, 1H); 6.803, 7.275 (ABq, J=9Hz, 4H)

(3) A stirred mixture of 1.482 g of the compound (V-6) and 2.57 ml of morpholine is refluxed for 2hr.15min. After removal of the reagent, the residue is purified by column chromatography of silica gel eluting with CH_2Cl_2/MeOH/NH_4OH (128/16/1-64/8/1) to give 1.047 g (Yield : 58.8%) of the compound (Ia-95) as a solid. The maleate is recrystallized from MeOH-Et_2O to prepare pale yellow plates. mp. 166.0-167.5°C (d.)

Anal Calcd. (%) for $C_{18}H_{26}N_2O_2 \cdot 2C_4H_4O_4$

: C,58.22; H,6.48; N,5.35

Found : C,58.42; H,6.41; N,5.24

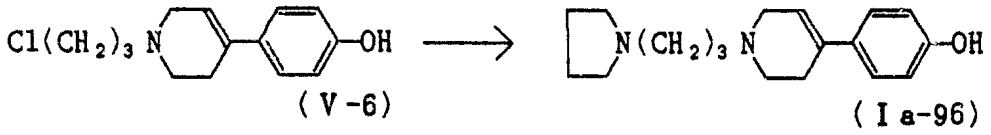
IR (Nujol):

3230, 3063, 2725, 2355, 1715, 1625, 1579, 1519, 1464, 1387

NMR (CD_3OD) δ : 2.13-2.35 (m, 2H); 2.866 (brs, 2H); 3.03-3.25 (m, 6H); 3.25-3.40 (m, 2H); 3.564 (t, J=6Hz, 3H); 3.883 (t, J=5Hz, 4H); 3.953 (brs, 2H); 5.999 (brs, 1H); 6.264 (s, 4H); 6.778, 7.320 (ABq, J=9Hz, 4H)

Example 96

4-(4-Hydroxyphenyl)-1-{3-(1-pyrrolidinyl)propyl}-1,2,5,6-tetrahydropyridine (Ia-96)



(V -6)　　(I a-96)

A mixture of 1.50 g of the compound (V -6) and 4.97 ml of pyrrolidine is stirred at room temperature for 18.5 hours and treated in the same manner as Example 95 (3) to prepare 2.041 g (Yield : 66.1%) of the maleate of the compound (I a-96) as needles. mp. 145.0-147.0°C (dec.)

Anal Calcd. (%) for $C_{18}H_{26}N_2O \cdot 2C_4H_4O_4$

: C, 60.03; H, 6.42; N, 5.50

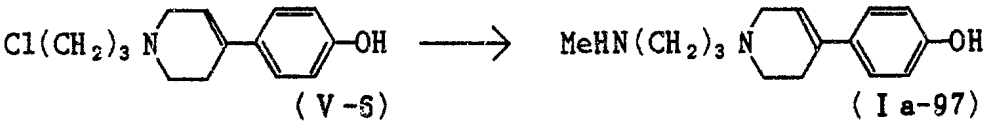
Found : C, 60.22; H, 6.61; N, 5.40

IR (Nujol) : 3230, 3041, 2710(sh), 2590, 2360, 1709, 1622, 1578, 1518, 1461, 1377

NMR (CD_3OD) δ : 2.00-2.175 (m, 4H); 2.175-2.375 (m, 2H); 2.859 (brs, 2H); 3.23-3.48 (m, 8H); 3.542 (t, J=6Hz, 3H); 3.992 (brs, 2H); 5.995 (brs, 1H); 6.257 (s, 4H); 6.778, 7.320 (ABq, J=8Hz, 4H)

Example 97

1-(3-(N-methylamino)propyl)-4-(4-hydroxyphenyl)-1,2,5,6-tetrahydropyridine (I a-97)



(V -6)　　(I a-97)

A mixture of 3.00 g of the compound (V -6) and 11.84 ml of $BuNH_2$ is refluxed for 5hours, and treated in the same manner as Example 96 to prepare 2.188 g (Yield : 63.7%) of the compound (I a-97) as needles. mp.233.0-236.0°C (dec.)

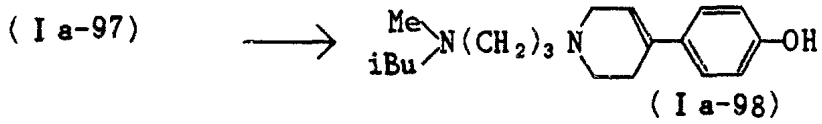
IR (Nujol) : 3425, 3055, 2778, 2670, 2582, 1665, 1613, 1590, 1515, 1471, 1453, 1439, 1428

NMR ($CDCl_3$) : 0.920 (d, J=7Hz, 6H); 1.92-2.18 (m, 3H); 2.554 (brs,

2H); 2.692 (d, J=7Hz, 2H); 2.751 (t, J=6Hz, 2H); 2.854 (t, 2H); 2.854 (t, J=6Hz, 2H); 3.134 (t, J=6Hz, 2H); 3.247 (brs, 2H); 5.922 (brs, 1H); 6.818, 7.194 (ABq, J=9Hz, 4H)

Example 98

1-{3-(N-isobutyl-N-methylamino)propyl}-4-(4-hydroxyphenyl)-1,2,5,6-tetrahydropyridine (I a-98)



(I a-97) (I a-98)

Treatment of 2.138 g of the compound (I a-97) in the same manner as Example 34 prepares 1.528 g (Yield : 70.1%) of the compound (I a-98) as solid, which is crystallized as maleate and recrystallized from MeOH-Et_2O to prepare pale yellow plates.

mp.150.0-153.0 ℃ (dec.)

Anal Calcd.(%) for $C_{19}H_{30}N_2O \cdot 2C_4H_4O_4$

: C, 60.38; H, 7.16; N, 5.38

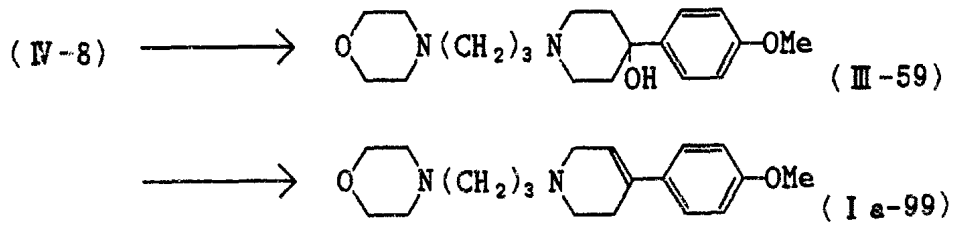
Found : C, 60.66; H, 7.16; N, 5.24

IR (Nujol) : 3235, 2700(sh), 2400, 1618, 1576, 1517, 1459, 1380 (sh), 1372(sh), 1359

NMR (CD_3OD) δ : 1.051 (d, J=7Hz, 6H); 2.025-2.400 (m, 3H); 2.852 (brs, 2H); 2.916 (s, 3H); 3.026 (d, J=7Hz, 2H); 3.15-3.38 (m, 4H); 3.533 (t, J=6Hz, 2H); 3.917 (brs, 2H); 5.995 (brs, 1H); 6.257 (s, 4H); 6.777,7.318 (ABq, J=9Hz, 4H)

Example 99

4-(4-Methoxyphenyl)-1-{3-(4-morpholinyl)propyl}-1,2,5,6-tetrahydropyridine (I a-99)



(Ⅳ-8) (Ⅲ-59) (I a-99)

A stirred mixture of 1.147 g of the compound (Ⅳ-8) and 1.76 ml of morpholine is refluxed for 1 hour. After removal of the reagent, the residue is purified by silica gel column chromatography (CH_2Cl_2/MeOH/NH_4OH=64/8/1-32/6/1) to prepare 1.34 g of the compound (Ⅲ-59) as oily substance. The oily product is dissolved in 10 ml of CF_3COOH and refluxed for 1 hour. After removal of the reagent, the residue is poured into aq. NH_4OH and extracted with methylene chloride. The organic layer is dried and evaporated under reduced pressure to preprare 1.012 g of the oily product. The oily product is subjected to column chromatograpy of silica gel eluting with CH_2Cl_2/MeOH(19/1). The eluate is recrystallized from Et_2O-n-hexane to prepare of 637 mg (Yield : 50.2 %) of the compound (Ⅰa-99) as colorless needles.

mp. 69.0-70.5 ℃

Anal Calcd.(%) for $C_{19}H_{28}N_2O_2$

: C, 72.12; H, 8.92; N, 8.85

Found : C, 72.01; H, 8.88; N, 9.05

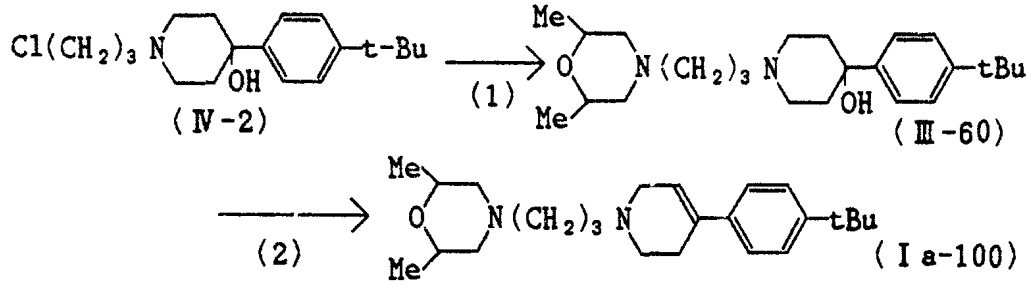
IR ($CHCl_3$) :

2490, 1610, 1572, 1512, 1466, 1446, 1417, 1402, 1378

NMR ($CHCl_3$) δ : 1.779 (quint, J=7Hz, 2H); 2.33-2.63 (m, 10H); 2.706 (t, J=5Hz, 2H); 3.151 (q, J=4Hz, 2H); 3.725 (t, J=5Hz, 4H); 3.802 (s, 3H); 5.969 (quint, J=2Hz, 1H); 6.851, 7.322 (ABq, J=9Hz, 4H)

Example 100

4-(4-tert-Butylphenyl)-1-{3-(2,6-dimethylmorpholino)-propyl}-1,2,5,6-tetrahydropyridine (Ⅰa-100)



(1) A mixture of 1.150 g of the compound (Ⅳ-2) and 2.29 ml of cis 2,6-dimethylmorpholine is stirred at 103-135 °C for 4 hours. After removal of the reagent, the residue is poured into aq.NaOH and extracted with methylene chloride. The organic layer is dried and evaporated under reduced pressure. The residue is purified by column chromatography of silica gel eluting with CH_2Cl_2-MeOH (15/1-5/1) to prepare 1.37 g (Yield : 95.0%) of the compound (Ⅲ-60) as crystals. mp. 137.5-138.0 °C (dec.)
IR ($CHCl_3$) : 3610, 3010, 2970, 2870, 2820, 1780, 1605, 1512 cm^{-1}
NMR ($CDCl_3$) δ : 1.161 (d, J=6Hz, 6H); 1.319 (s, 9H); 1.63-1.88 (m, 7H); 2.215 (td, J_1=13Hz, J_2=4Hz, 2H); 2.30-2.60 (m, 6H); 2.753 (dd, J_1=12Hz, J_2=2Hz, 2H); 2.875 (dd, J_1=11Hz, J_2=2Hz, 2H); 3.60-3.75 (m, 2 H); 7.377,7.451 (ABq, J=9Hz, 4H)

(2) A solution of 1.35 g of the compound (Ⅲ-60) in 10 ml of CF_3COOH is refluxed for 4 hour. After removal of the reagent, the residue is poured into aq.$NaHCO_3$ and extracted with ethyl acetate. The organic layer is washed with water, dried and evaporated under reduced pressure. The oily residue is purified by column chromatography of silica gel eluting with CH_2Cl_2/MeOH (25/1-15/1) to prepare 1.29 g (Yield : 86.8%) of the compound (Ⅰa-100) as an oil. The maleate is recrystallized from MeOH-iPrOH to prepare colorlees needles. mp. 192.0-193.0 °C
Anal Calcd.(%) for $C_{24}H_{38}N_2O \cdot 2C_4H_4O_4$
: C, 63.58; H, 7.79; N, 4.64
Found : C, 63.77; H, 7.69; N, 4.65

IR (Nujol) : 1707, 1618 cm^{-1}

NMR ($CDCl_3$) : 1.260 (d, J=7Hz, 6H); 1.330 (s, 9H); 2.20-2.40 (m, 2H); 2.491 (t, J=12Hz, 2H); 2.80-2.95 (m, 2H); 3.111 (t, J=8Hz, 2H); 3.28-3.40 (m, 4H); 3.542 (t, J=6Hz, 2H); 3.80-4.00 (m, 4H); 3.542 (t, J=6Hz, 2H); 3.80-4.00 (m, 4H); 6.02-6.08 (m, 1H); 6.283 (s, 2H); 7.355,7.422 (ABq, J=9Hz, 4H)

Example 101-104

The reaction is performed in the same manner as Exempl 100 to prepare the compoun (I a). The reaction condition are shown in Table 13 and 14.

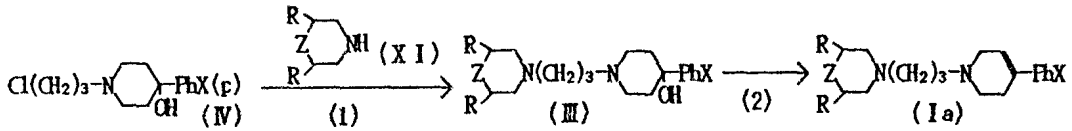


Table 13

Ex. No.	(Ⅳ)	(XI)	solvent	reaction condition	purification condition	product g (Yield)	m.p.(°C)	IR
101	X=Me 3.55g	Z=O, R=H 5.77g	———	2hr. reflux	/MeOH 15/1-5/1	Ⅲ-61 4.23g (96.0%)	103.0-104.5	(CHCl3) 3600, 3020, 2950, 2920, 2820, 1513, 1472
102	X=Cl 5.1g	Z=O, R=H 7.71g	———	130-135°C 2.5hr.	———	Ⅲ-62 5.97g (99.5%)	236.0-237.0	(Nujol) 3440, 2930, 2870, 2640, 2550, 2460
103	X=t-Bu 2.35g	Z=NH, R=Me 1.73g	DMF 20ml	95-100°C 2hr.	CH_2Cl/MeOH /NH_4OH =30/6/1	Ⅲ-63 1.92g (65.3%)	—	(CHCl3) 3000, 3330, 2960, 2820, 2470, 1665, 1635, 1605, 1590, 1510
104	X=Cl 2.05g	Z=NH, R=Me 1.62g	DMF 15ml	80-85°C 3.5hr.	CH_2Cl/MeOH /NH_4OH =32/6/1	Ⅲ-64 2.10g (80.9%)	—	(CHCl3) 3590, 3160, 2930, 2810, 2490, 1677, 1596, 1492

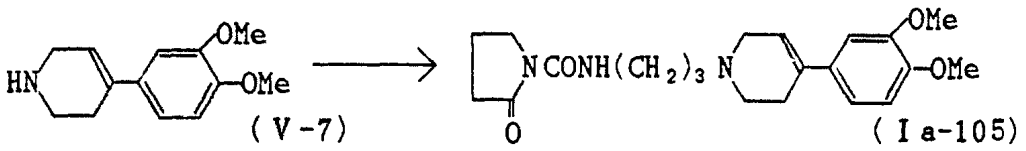
Table 14

Ex. No.	(Ⅲ)	CF_3COOH	reaction condition	purification condition	product g (Yield)	m.p.(°C)	IR
101	(Ⅲ-61) 4.45g	45ml	2.5hr. reflux	CH_2Cl_2/MeOH =15/1-5/1	I a-101 3.99g (92.0%)	186.5-188.5*1	(Nujol) 1709, 1621
102	(Ⅲ-62) 3.78g	45ml	7hr. reflux	CH_2Cl_2/MeOH =15/1-5/11	I a-102 3.00g (84.2%)	185.5-186.5*1	(Nujol) 2300 (br), 1709, 1622
103	(Ⅲ-63) 1.92g	20 ml	room temperature 2.5hr.reflux	CH_2Cl_2/MeOH /NH_4OH =128/16/1	I a-103 1.60g (87.4%)	235.0-250.0*2	(Nujol) 3440, 3410, 2670, 2580, 2470 2420, 1658, 1555, 1507
104	(Ⅲ-64) 2.10g	25 ml	room temperature 15hr. reflux	CH_2Cl_2/MeOH /NH_4OH =128/16/1	I a-104 1.79g (89.6%)	179.0-181.0*2	(Nujol) 3600, 2680, 2530, 2440, 1642 1597,1496

*1: maleate *2: hydrochloride

Example 105

1-[3-{4-(3,4-Dimethoxyphenyl)-1,2,5,6-tetrahydropyridin-1-yl}propylcarbamoyl]-2-oxopyrrolidine (I a-105)



To a solution of 3.76 g of 4-(3,4-dimethoxyphenyl)-1,2,5,6-tetrahydropyridine (V -7), which was prepared by the reaction of 4-hydroxy-4-(3,4-dimethoxyphenyl)piperidine and p-toluenesulfonic acid, and 2.94 g of 1-(3-chloropropylcarbamoyl)-2-oxopyrrolidine in 35 ml of DMF is added 3.98 g of K_2CO_3 and 3.22 g of NaI. The reaction mixture is stirred at 100-105 °C for 6 days under nitrogen gas. After cooling to room temperaure, the mixture is diluted with ethyl acetate, washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue is subjected to column chromatography of silica gel eluting with CH_2Cl_2/MeOH (20/1) to prepare 1.78 g (Yield : 33.4%) of the compound (I a-105) as solid. The oxalate is recrystallized from iPrOH-MeOH to prepare needles. mp. 178.0-182.0 °C

Anal Calcd.(%) for $C_{23}H_{31}N_3O_6 \cdot 1/5H_2O$

: C, 57.35; H, 6.33; N, 8.67

Found : C, 57.42; H, 6.58; N, 8.73

IR (Nujol) :

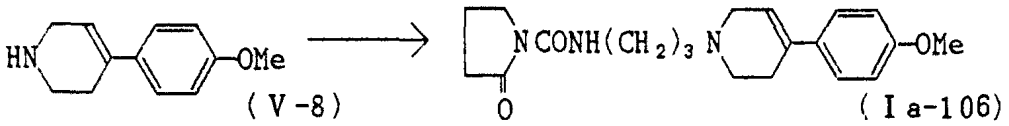
3310, 1725(sh), 1708, 1682, 1675, 1600, 1580, 1545, 1545, 1520

NMR ($CDCl_3$) : 1.764 (quint, J=7Hz, 2H); 1.954 (quint, J=8Hz, 2H); 2.44-2.51 (m, 4H); 2.530 (t, J=8Hz, 2H); 2.646 (t, J=5Hz, 2H); 3.094 (q, J=3Hz, 2H); 3.328 (q, J=7Hz, 2H); 3.795 (t, J=7Hz, 2H); 3.809, 3.827 (sx2, 6H); 5.915 (quint, J=3Hz, 1H); 6.755 (d, J=9Hz, 2H); 6.84-6.89 (m, 2H); 8.434 (brs, 1H)

Example 106

1-[3-{4-(4-Methoxyphenyl)-1,2,5,6-tetrahydropyridin-1-yl}-

propylcarbamoyl]-2-oxopyrrolidine (I a-106)



(V-8)　　(I a-106)

The compound (V-8) is reacted in the same manner as Example 105 to prepare the compound (I a-106).

mp.199.5-200.0℃ (dec.)

Anal Calcd.(%) for $C_{22}H_{29}N_3O_7$

: C, 58.81; H, 6.31; N, 9.32

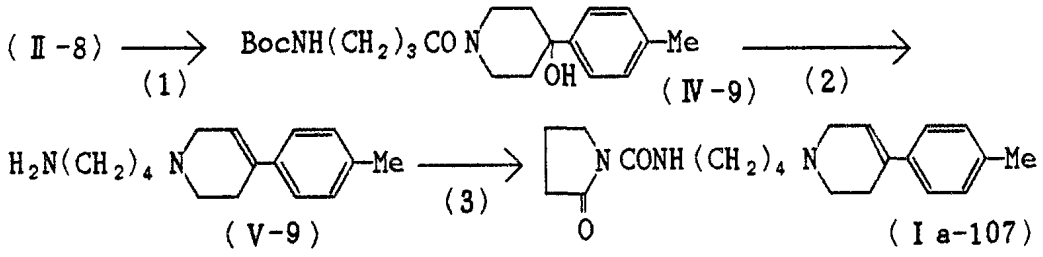
Found : C, 59.02; H, 6.53; N, 9.39

IR (Nujol) : 3300, 2730, 2620, 1700, 1685, 1612, 1548, 1529, 1465

NMR ($CDCl_3$) : 1.90-2.10 (m, 4H); 2.590 (t, J=7Hz, 2H); 2.80-2.86 (m, 2H); 3.23-3.30 (m, 2H); 3.33-3.52 (m, 4H); 3.778 (s, 3H); 3.898 (m, 2H); 5.995 (s, 1H); 6.893, 7.379 (ABq, J=8Hz, 4H)

Example 107

1-[4-(4-Tolyl)-1,2,5,6-tetrahydropyridin-1-yl}butyl-carbamoyl]-2-oxopyrrolidine (I a-107)



(V-9)　　(I a-107)

(1) To a solution of 4.00 g of the compound (II-8) and 4.675 g of N-Boc-β-alanine in 90 ml of THF are added 5.178 g of 1,3-dicyclohexylcarbodiimide and 848 mg of 1-hydroxybenzotriazole hydrate. The reaction mixture is stirred at room temperature for 2 hour and 10 minutes. After removal of precipitates, the reaction mixture is concentrated under reduced pressure. The residue is poured into d.HCl and extracted with CH_2Cl_2. The organic layer is

washed with aq.$NaHCO_3$ and water in order, dried over $MgSO_4$ and evaporated under reduced pressure. The residue is subjected to column chromatography of silica gel eluting with toluene/acetone (3/1-2/1) to prepare 6.862 g of crystalline residue. It is recrystallized from methylene chloride-ether-n-hexane to prepare 6.674 g (Yield : 84.8%) of the compound (Ⅳ-9) as colorless needles. mp. 161.5-163.0 °C

Anal calcd. (%) for $C_{21}H_{32}N_2O_4$

: C, 67.18; H, 8.46; N, 7.50

Found : C, 66.99; H, 8.57; N, 7.44

IR ($CHCl_3$) : 3597, 3457, 1709, 1628, 1508, 1474, 1448, 1393, 1369

NMR ($CDCl_3$) δ : 1.432 (s, 9H); 1.75,2.05 (m, 8H); 2.344 (s, 3H); 2.147 (t, J=7Hz. 2H); 3.04,3.20 (m, 3H); 3.560 (td, J_1=12Hz, J_2=4 Hz, 1H); 3.737 (d, J=14Hz, 1H); 4.548 (d, J=13Hz, 1H); 4.833 (brs, 1H); 7.177,7.353 (ABq, J=8Hz, 4H)

(2) A solution of 6.654 g of the compound (Ⅳ-9) in 13 ml of CF_3COOH is stirred at room temperature for 2.5 hours. After removal of the excess reagent, 6.36 g of the crystaline resiude is obtained. The residue is recrystallized from MeOH-Et_2O to prepare 5.798 g of colorless plates. Then to a solution of 4.818 g of the plates in 30 ml of methanol is added 5 ml of triethylamine. After removal of the solvent to dryness, the resulting solid is dropwise added to a stirred suspention of 737 mg of $LiAlH_4$ in 80 ml of THF at room temperature and stirred at the same temperature for 2.5 hours. After decomposition of the excess reagent by careful addition of water, the resulting precipitate is filtered off. The organic layer is evaporated to dryness to prepare 3.612 g of the yellow oily residue. The residue is subjected to column chromatography of silica gel eluting with $CHCl_3$/MeOH/c.NH_4OH (32/4/0.5-32/6/1) to prepare 1.341 g (Yield : 42.4%) of the compound (Ⅴ-9).

(3) A mixture of 1.341 g of the compound (Ⅴ-9) and 1.126 g of 1-phenoxycarbonyl-2-oxopyrrolidine is heated at 115 °C for 1 hour 43 minutes. The reaction mixture is purified by column chromatography of silica gel eluting with toluene/acetone (2/1-

1/1) followed by recrystallization from Et_2O-n-hexane to prepare 540 mg (Yield : 24.7%) of the compound (I a-107) as prisms.

mp. 104.0-104.5°C

Anal Calcd. (%) for $C_{21}H_{29}N_3O_2$

: C, 71.05; H, 8.22; N, 11.84

Found : C, 70.95; H, 8.22; N, 11.82

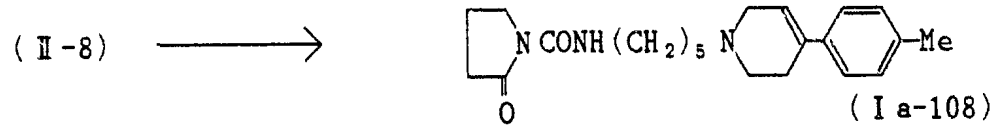
IR ($CHCl_3$) :

3325, 1714, 1682, 1602, 1548, 1516, 1490, 1461, 1442, 1387

NMR ($CDCl_3$) δ : 1.62,1.66 (m, 4H); 2.025 (quint, J=7Hz, 2H); 2.330 (s, 3H); 2.30-2.73 (m, 8H); 3.145 (q, J=3Hz, 2H); 3.338 (q, J=6Hz, 2H); 3.858 (t, J=7Hz, 2H) ; 6.016 (quint, J=2Hz, 1H); 7.117, 7.283 (ABq, J=8Hz, 4H); 8.430 (brs, 1H)

Example 108

1-[(5-(4-Tolyl)-1,2,5,6-tetrahydropyridin-1-yl)pentylcarbamoyl]-2-oxopyrroridine (I a-108)



(I a-108)

A mixture of 4.675 g of $BocNH(CH_2)_4COOH$ and 4.00 g of the compound (Ⅱ-8) is treated in the same manner as Example 107 (1)-(3) to prepare 392 mg (Yield : 15.0%) of the compound (I a-108).

mp.58.5-59.5°C.

Anal Calcd. (%) for $C_{22}H_{31}N_3O_2$

: C, 71.23; H, 8.42; N, 11.46

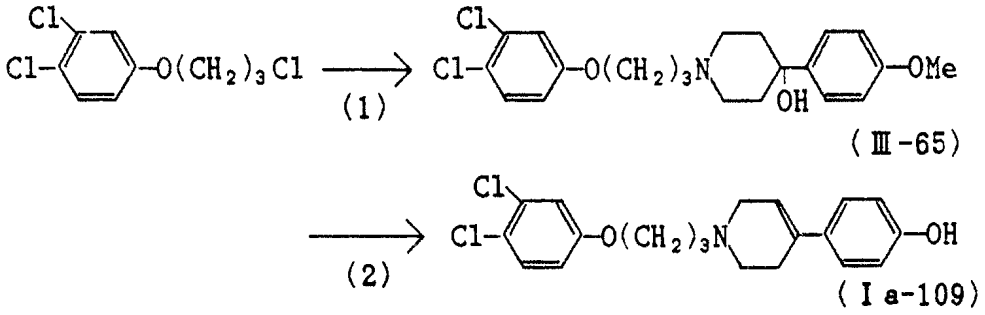
Found : C, 71.51; H, 8.46; N, 11.37

IR ($CHCl_3$) : 3321, 1714, 1681, 1548, 1516, 1489, 1461, 1387

NMR ($CDCl_3$-CD_3OD) δ : 1.32-1.45 (m, 2H); 1.52-1.70 (m, 4H); 2.039 (quint, J=7Hz, 2H); 2.333 (s, 3H); 2.429-2.507 (m, 2H); 2.615 (t, J=8Hz, 4H); 2.723 (t, J=6Hz, 2H); 3.161 (q, J=3Hz, 2H); 3.303 (q, J=6Hz, 2H); 3.854 (t, J=7Hz, 2H); 6.032 (s, 1H); 7.126, 7.292 (ABq, J=8Hz, 4H); 8.460 (brs, 1H)

Example 109

1-(3-(3,4-Dichlorophenoxy)propyl)-4-(4-hydroxyphenyl)-1,2,5,6-tetrahydropyridine (I a-109)



(1) A mixture of 3.6 g of 3-(3,4-dichlorophenoxy)propyl-chloride, which was prepared by the reaction of 3,4-dichorophenol with 3-bromopropylchloride, and 3.12 g of 4-hydroxy-4-(4-methoxyphenyl)piperidine, 4.15 g of K_2CO_3, and 3.37 g of NaI in 35 ml of DMF is stirred at 105 ℃ for 10 hour. The reaction mixture is poured into ice-water, and the resulting precipitates are extracted with methylene chloride. The organic layer is dried and evaporated under reduced pressure. The residue is purified by column chromatography of silica gel eluting with CH_2Cl_2/MeOH (20/1 -10/1) followed by recrystallization from methylene chloride to prepare 5.86 g (Yield : 95.2 %) of the compound (Ⅲ-65) as colorless needles. mp. 131.0-132.0 ℃

Anal Calcd. (%) for $C_{21}H_{25}N_2O_3Cl_2$

: C, 61.39; H, 6.20; N, 3.55; Cl, 17.28

Found : C, 61.47; H, 6.14; N, 3.41; Cl, 17.30

IR ($CHCl_3$) : 3600, 1612, 1595, 1568, 1513, 1480(sh), 1468

NMR ($CDCl_3$) δ : 1.563 (s, 1H); 1.772 (dd, J_1=14Hz, J_2=3Hz, 2H); 1.999 (quint, J=6Hz, 2H); 2.137 (td, J_1=13Hz, J_2=4Hz, 2H); 2.478 (td, J_1=12Hz, J_2=2Hz, 2H); 2.575 (t, J=7Hz, 2H); 2.811 (J_1=11Hz, J_2=3Hz, 2H); 3.803 (s, 3H); 4.004 (t, J=6Hz, 2H); 6.760 (dd, J_1=9Hz, J_2=3Hz, 1H); 6.887 (d, J=9Hz, 2H); 7.013 (d, J=3Hz, 1H); 7.308 (d, J=9Hz, 1H); 7.438 (d, J=9Hz, 2H)

(2) To a stirred solution of 2.08 g of the compound (Ⅲ-65

) in 50 ml of methylene chloride is added 1.44 ml of BBr_3 under ice-cooling. After removal of the reagent, the residue is poured into aq.$NaHCO_3$ and extracted with ethyl acetate. The organic layer is washed with water, dried and evaporated under reduced pressure. The resulting oily residue 1.91 g is dissolved in 20 ml of CF_3COOH and refluxed for 2 hour. After removal of the reagent, the residue is poured into aq.$NaHCO_3$ and extracted with ethyl-acetate. The organic layer is washed, dried and evaporated. The residue is purified by column chromatography of silica gel(toluene /ethyl acetate(1/1)-CH_2Cl_2/MeOH (20/1)) to prepare 270 mg (Yield : 33 %) of the compound (I a-109) as a solid. The maleate is recry-stallized from MeOH-iPrOH to prepare needles.

mp. 167.0-168.0 °C (dec.)

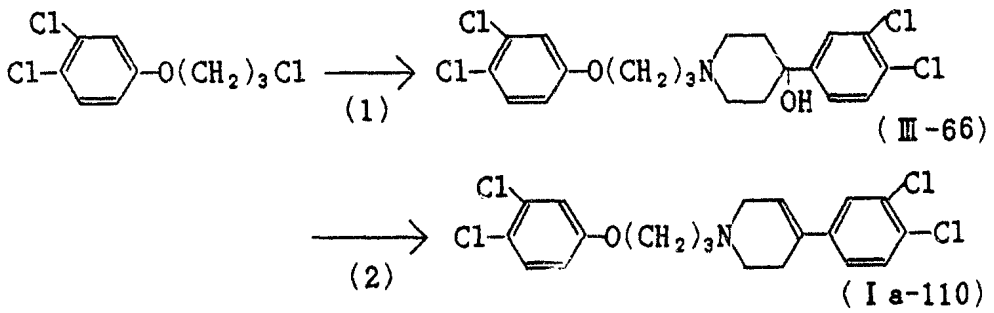
Anal Calcd. (%) for $C_{20}H_{21}NO_2Cl_2$

: C,58.08; H,5.05; N,2.93; Cl,14.55

Found: C,58.31; H,5.10; N,2.83; Cl,14.34

Example 110

1-{3-(3,4-Dichlorophenoxy)propyl}-4-(3,4-dichlorophenyl)-1,2,5,6-tetrahydropyridine (I a-110)



(1) 3-(3,4-dichlorophenoxy)propylchloride 1.38 g and 4-hydroxy-4-(3,4-dichlorophenyl)piperidine 1.35 g are reacted in the same manner as Example 109 (1) to prepare 2.40g (Yield :97.5%) of 1-{3-(3,4-dichlorophenoxy)propyl}-4-hydroxy-4-(3,4-dichlorophenyl) piperidine (III-66). mp.118.0-118.5 °C

(2) A solution of 1.61 g of the compound (III-66) in 20 ml

of trifluoroacetic acid is refluxed for 3.5hours. After removal of the reagent, the residue is poured into aq.$NaHCO_3$ and extracted with methylene chloride. The organic layer is washed, dried and evaporated. The residue is purified by column chromatography of silica gel eluting with CH_2Cl_2/MeOH(25/1) to prepare 1.45 g (Yield : 94.0%) of the compound (I a-110) as oxalate. The oxalate is recrystallized from MeOH-iPrOH to prepare the compound (I a-110) as needles. mp. 163.5-165.0 °C (dec.)

Anal Calcd. (%) for $C_{20}H_{19}NO_2Cl_4$

: C, 50.43; H, 4.09; N, 2.72; Cl, 27.15

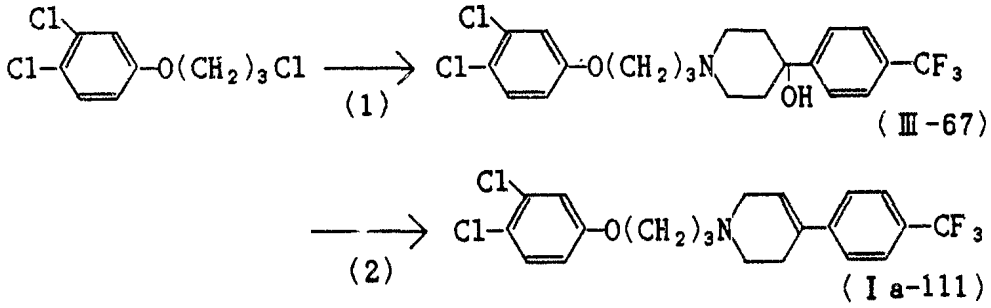
Found : C, 50.70; H, 4.06; N, 2.69; Cl, 27.21

IR (Nujol) : 2930, 1713, 1695(sh), 1615, 1597, 1563

NMR ($CDCl_3$) : 2.045 (quint, J=7Hz, 2H); 2.657 (t, J=8Hz, 2H); 2.554 (m, 2H); 2.745 (t, J=5Hz, 2H); 3.202 (q, J=3Hz, 2H); 4.026 (t, J=6Hz, 2H); 6.110 (m, 1H); 6.766 (dd, J_1=19Hz, J_2=3Hz, 1H); 7.0 15 (d, J=3Hz, 1H); 7.19-7.47 (m, 4H)

Example 111

1-{3-(3,4-Dichlorophenoxy)propyl}-4-(4-trifluoromethyl-phenyl)-1,2,5,6-tetrahydropyridine (I a-111)



(1) 3-(3,4-dichlorophenoxy)propylchloride 2.00 g and 4-hydroxy-4-(4-trifluoromethylphenyl)piperidine 1.95 g are reacted in the same manner as Example 109 (1) to prepare 3.16 g (Yield : 88.7%) of the compound (Ⅲ-67). mp. 196.0-196.5 °C

(2) A solution of 2.65 g of the compound (Ⅲ-67) in 30 ml of trifluoroacetic acid is refluxed for 41 hours. After removal

of the reagent, the residue is poured into aq.$NaHCO_3$ and extracted with ethyl acetate. The organic layer is dried and evaporated. The residue is purified by column chromatography of silica gel (toluene/ethyl acetate (3/1), CH_2Cl_2/MeOH(25/1)) to prepare 1.65 g (Yield : 65.9%) of the compound (I a-111) as a solid, which is recrystallized from Et_2O to prepare colorless needles, mp.83.5-84.0°C. The oxalate melts at mp. 195.5-196.0 °C

Anal Calcd. (%) for $C_{21}H_{20}NO_2Cl_2F_3 \cdot C_2H_2O_4$

: C, 52.93; H, 4.33; N, 2.71; Cl, 13.42; F, 11.08

Found : C, 53.09; H, 4.26; N, 2.69; Cl, 13.65; F, 10.95

IR ($CHCl_3$) : 2950, 2930, 2830, 2790, 1618, 1597, 1469

NMR ($CDCl_3$) : 2.052 (quint, J=7Hz, 2H); 2.52-2.65 (m, 2H); 2.661 (t, J=7Hz, 2H); 2.759 (t,J=6Hz, 2H); 3.222 (q, J=3Hz, 2H); 6.171 (m, 1H); 6.765 (dd, J_1=9Hz, J_2=3Hz, 1H); 7.015 (d, J=3Hz, 1H); 7.312 (d, J=9Hz, 1H); 7.479, 7.574 (ABq, J=8Hz, 4H)

Reference Example 1

4-Hydroxy-4-(3,4-dichlorophenyl)piperidine (Ⅱ -1)

A mixture of 64.2 g of 1-ethoxycarbonyl-4-hydroxy-4-(3,4-dichlorophenyl)piperidine (Ⅹ -1) and a solution of 72.4 g of KOH in 700 ml of nBuOH is refluxed for 2 hours and evaporated. The reaction mixture is concentrated under reduced pressure and extracted with ethyl acetate. The organic layer is washed with water, dried and evaporated. The resulting crystalline residue is recrystallized from ethyl acetate to prepare 44.7 g (Yield : 90.0 %) of the compound (Ⅱ -1). mp. 144.5-146.0 ℃

Anal Calcd. (%) for $C_{14}H_{17}NO_3Cl_2$:

: C, 53.62; H, 5.26; N, 5.68; Cl, 28.98

Found : C, 53.68; H, 5.32; N, 5.69; Cl, 28.81

IR (Nujol) : 3320, 3100, 1438

NMR (CD_3OD) δ : 1.651 (dd, J_1=12Hz, J_2=2Hz, 2H); 1.936 (td, J_1=12 Hz, J_2=5Hz, 2H); 1.651 (dd, J_1=12Hz, J_2=2Hz, 2H); 3.074 (td, J_1=12 Hz, J_2=3Hz, 2H); 7.402 (dd, J_1=8Hz, J_2=2Hz, 1H); 7.480 (d, J=8Hz, 1H); 7.662 (d, J=2Hz, 1H)

Reference Example 2-19

The reaction is performed in the same manner as Reference Example 1 to prepare the compound (Ⅱ). The reaction conditions and physical constants are shown in Table 15 and 16.

(X) (II)

Table 15 (No. 1)

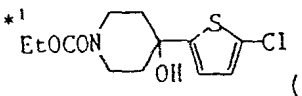
Ref. Ex. No.	(X) X =	Base	sovlent	reflux time	(II) g (Yield) m.p. (°C)
2	CF_3(p) 27.3g (X-2)	KOH (28.07g)	EtOH (450ml)	5 hours	(II-2) 13.24g (63.0%)
3	n-Pr(p) 44.0g (X-3)	KOH (49.3g)	n-BuOH (640ml)	5.5 hours	(II-3) 30.47g (92.0%)
4	Et(p) 22.42g (X-4)	KOH (26.37g)	n-BuOH (500ml)	2 days	(II-4) 13.88g (83.7%)
5	Ph(p) 18.65g (X-5)	KOH (18.70g)	n-BuOH (500ml)	15 hours	(II-5) 13.44g (92.6%)
6	t-Bu(p) 46.67g (X-6)	KOH (50.9g)	n-BuOH (700ml)	5.5 hours	(II-6) 33.64g (92.0%)

Table 15 (No. 2)

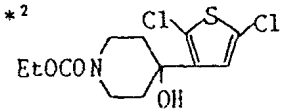
Ref. Ex. No.	(X) X =	Base	solvent	reflux time	(II) g (Yield) m.p. (°C)	I R
7	CH_3(p) 49.86g (X-7)	KOH (61.8g)	BuOH (700ml)	3.5 hours	(II-8) 33.20g (92.0%) 135.5-137.5	(Nujol) 3310. 1598. 1502. 1490 1445
8	CH_3(m) 21.2g (X-8)	KOH (26.3g)	EtOH (450ml)	6 days	(II-9) 10.25g (66.6%) 154.5-155.5	(Nujol) 3440. 3280. 3220. 3179 1606. 1590. 1490. 1475
9	CH_3(o) 14.7g (X-9)	KOH (18.21g)	EtOH (350ml)	5 days	(II-10) 7.90g (74.0%) 141.0-142.0	(Nujol) 3440. 3280. 3220. 3170 1608. 1590. 1490
10	3.4-diMe 20.2g (X-10)	KOH (23.76g)	EtOH (500ml)	10 days	(II-11) 13.97g (93.5%) ——	(Nujol) 3590. 3380. 1600. 1502 1467. 1448
11	3.5-diMe 22.7g (X-11)	KOH (26.7g)	EtOH (650ml)	12 days	(II-12) 14.85g (88.4%) 182.0-183.0	(Nujol) 3280. 3120(br). 1605 1415
12	Cl (m) 22.2g (X-12)	KOH (25.5g)	EtOH (350ml)	2 days	(II-13) 13.68g (82.6%) 100.0-101.0	(Nujol) 3220. 3080. 1595. 1570 1432. 1408
13	Cl (o) 9.2g (X-13)	NaOH (3.89g)	THF/H_2O (10ml/20ml)	5 days	(II-14) 4.95g (72.0%) 166.5-167.5	(KBr) 3440. 3280. 3060. 1475 1442. 1430

Table 15 (No.3)

Ref. Ex.No.	(X) X =	Base	solvent	reflux time	(II) g (Yield) m.p. (°C)	IR
14	3.5-diCl 25.11g (X-14)	KOH (25.74g)	EtOH (550ml)	11 days	(II-15) 15.5g (79.8%) 213.0-214.0	(Nujol) 3310. 3100. 3080. 1591 1568. 1450. 1425. 1410
15	Br (p) 21.0g (X-15)	KOH (20.87g)	EtOH (500ml)	10 days	(II-16) 9.23g (56.3%) 159.5~161.5	(Nujol) 3280. 3050. 1588. 1492 1478. 1420
16	F (p) 23.2g (X-16)	KOH (17.36g)	Dioxane/H_2O (170/70ml)	6 days	(II-17) 9.82g (58.8%) ——	(Nujol) 3280. 3130. 1602. 1512 1455
17	CF_3 (m) Cl (p) 41.8g (X-17)	KOH (42.7g)	nBuOH (580ml)	2 hours	(II-18) 22.30g (67.0%) 135.0-136.5	($CHCl_3$) 3595. 2950. 2850. 1607 1576. 1483
18	*1 (X-18) 27.1g	KOH (18.30g)	EtOH (350ml)	2 days	(II-19) 11.88g 149.5-150.0	(Nujol) 3290. 1540. 1417
19	*2 (X-19) 19.7g	KOH (19.82g)	nBuOH (500ml)	2 days	(II-20) 9.51g (62.1%) 151.0-152.5	(Nujol) 3280. 1640. 1540

*1 

(X-18)

*2 

(X-19)

Table 16

Compd. No.	m.p. (°C) (solvent*)	Anal Calcd. (%) Found (%)	IR (cm^{-1})	NMR (δ)
II-2	136.0-137.0 (ethyl acetate)	$C_{12}H_{14}NOF_3$: C. 58.83 (58.77) H. 5.74 (5.75) N. 5.73 (5.71) F. 23.13 (23.2.)	(Nujol) 3290, 1619, 1443 1439, 1422, 1410	(CD_3OD) 1.680 (d-d, J_1=14Hz, J_2=2Hz, 2H): 2.004 (t-d, J_1=14Hz, J_2=5Hz, 2H): 2.866 (d-d, J_1=13Hz, J_2=2Hz, 2H): 3.107 (t-d, J_1=13Hz, J_2=2Hz, 2H): 7.625 (d, J=9Hz, 2H): 7.698 (d, J=9Hz, 2H)
II-3	178.5-179.5 (oxalate) (i-PrOH)	$C_{14}H_{21}NO \cdot C_2H_2O_4$ C. 61.77 (62.12) H. 7.42 (7.49) N. 4.50 (4.53)	($CHCl_3$) 3600, 3350(br), 1593, 1510, 1468 1422	($CDCl_3$) 0.933 (t, J=7Hz, 3H): 1.620 (sextet, J=8Hz, 2H): 1.876 (J=14Hz, 2H): 2.330 (t-d, J_1=14Hz, J_2=4Hz, 2H): 2.564 (t, J=7Hz, 2H): 3.244 (d, J=12Hz, 2H): 3.367 (t, J=12Hz, 2H): 7.164 (d, J=8Hz, 2H): 7.40 (d, J=8Hz, 2H)
II-4	119.0-120.0 (Et_2O-ethyl acetate)	$C_{13}H_{19}NO$ C. 75.97 (76.05) H. 9.33 (9.33) N. 6.78 (6.82)	($CHCl_3$) 3600, 1510, 1469 1440, 1420, 1410 (sh)	(CD_3OD) 1.204 (t, J=7Hz, 3H): 1.676 (d-d, J_1=14Hz, J_2=2Hz, 2H): 1.933 (t-d, J_1=14Hz, J_2=5Hz, 2H): 2.616 (q, J=8Hz, 2H): 2.852 (d-d, J_1=12 Hz, J_2=3Hz, 2H): 3.084 (t-d, J_1=12Hz, J_2=3Hz, 2H): 7.156 (d, J=8 Hz, 2H): 7.397 (d, J=8Hz, 2H)
II-5	182.5-184.0 (MeOH-CH_2Cl_2)	$C_{17}H_{19}NO \cdot 1/6H_2O$ C. 79.84 (79.65) H. 7.48 (7.60) N. 5.44 (5.46)	(Nujol) 3320, 1595, 1581 1563, 1490, 1450	($CDCl_3$-CD_3OD=4/1) 1.804 (d, J=12Hz, 2H): 2.052 (t-d, J_1=14Hz, J_2=5Hz, 2H): 2.096 (d-d, J_1=13Hz, J_2=2Hz, 2H): 3.172 (t-d, J_1=12Hz, J_2=3Hz, 2H): 7.29-7.63 (m, 9H)
II-6	185.0-186.0 ($CHCl_3$-MeOH)	$C_{15}H_{23}NO \cdot H_2O$ C. 71.18 (71.67) H. 9.86 (10.02) N. 5.67 (5.57)	(Nujol) 3480(sh), 3390, 3320, 3290, 3090 1668, 1508, 1470	(CD_3OD) 1.301 (s, 9H): 1.684 (d-d, J_1=14Hz, J_2=2Hz, 2H): 1.839 (t-d, J_1=14 Hz, J_2=4Hz, 2H): 2.857 (d-m, J_1=12Hz, 2H): 3.086 (t-d, J_1=13Hz, J_2 =3Hz, 2H): 7.360 (d, J=9Hz, 2H): 7.404 (d, J=9Hz)

*: a solvent for recrystallization

Evaluation of biological activity

Experiment

After the decapitation of rats, the objective tissues were rapidly removed and each was weighed. Each tissue was homogenized with twenty-fold amount of ice-cold 50mM Tris-HCl buffer (pH7.8), homogenized, and centrifuged at 40,000×g for 10 minutes. The supernatant was removed and pellets were then resuspended in the buffer and recentrifuged. The procedure is repeated 3 times. Then these obtained samples were freeze-dried in liquid nitrogen and preserved at -80°C. On the test day, the sample was thawed at room temperature and centrifuged at 40,000 × g for 10 minutes, the pellets were then suspended in the incubation buffer and used as the receptor preparation. The preparation was added to the mixture containing the labelled ligand and the test drug, and filtered through Whatman GF/C filters and washed to terminate the reaction. Radioactivity on filters was determined by liquid scintillation counter and Ki value was calculated.

1. σ receptor

Sigma receptor binding was initiated by the addition of the receptor preparation (cortex tissue, 0.7 mg protein/ml) to a mixture containing 5nM of [^{3}H]3PPP [3-hydroxyphenyl-N-(1-propyl)-piperidine] and the test compound dissolved in 50 mM Tris-HCl buffer (pH 7.8). Incubation was carried out at 25°C for 90 minutes. Specific sigma receptor binding was defined as the difference in amount of [^{3}H]3PPP bound to the tissue in the presence or the absence of 10 μM haloperidol.

2. DA2 receptor

DA2 receptor binding was initiated by the addition of the receptor preparation (striatal tissue, 0.3 mg protein/ml) to a mixture containing 0.2nM of [^{3}H]spiroperidol and the test compound dissolved in 50 mM Tris-HCl buffer containing 100mM-NaCl and 5mM-KCl (pH 7.4). Incubation was carried out at 37°C for 10 minutes. Specific DA2 receptor binding was defined as the difference in amount of [^{3}H]spiroperidol bound to the tissue in the presence or

the absence of 10 μM haloperidol.

3. 5HT2 receptor

5HT2 receptor binding was initiated by the addition of the receptor preparation (cortex tissue, 0.5 mg protein/ml) to a mixture containing 1nM of [^{3}H]spiroperidol and the test compound dissolved in 50 mM Tris-HCl buffer (pH 7.4). Incubation was carried out at 37°C for 15 minutes. Specific 5HT2 receptor binding was defined as the difference in amount of [^{3}H] spiroperidol bound to the tissue in the presence or the absence of 1 mM serotonin.

4. PCP receptor

PCP receptor binding was initiated by the addition of the receptor preparation (cortex tissue, 0.2 mg protein/ml) to a mixture containing 5nM of [^{3}H]TCP and the test compound dissolved in 5 mM Tris-HCl buffer (pH 7.8). Incubation was carried out at 25°C for 30 minutes. Specific PCP receptor binding was defined as the difference in amount of [^{3}H]TCP bound to the tissue in the presence or the absence of 10 μM PCP.

The test results were shown in Table 17.

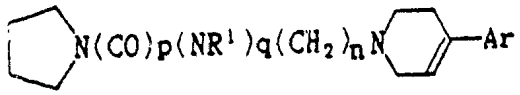
Table 17

Test compound	Ki (μM) PCP	σ	DA2	5-HT2
Ia-2	31	0.0041	4.7	0.55
Ia-3	16	0.0095	4.0	1.70
Ia-6	49	0.0027	2.2	2.50
Ia-8	>62	0.0013	1.20	2.90
Ia-9	33	0.0061	1.60	1.20
Ia-11	23	0.0026	4.50	4.40
Ia-13	26	0.0022	0.32	0.77
Ia-24	32	0.0058	1.10	0.38
Ia-30	>63	0.0013	2.00	3.70
Ia-35	18	0.0018	4.60	3.20
Ia-56	44	0.0065	4.50	8.90
Ia-57	44	0.0063	2.40	0.14
Ia-94	27	0.0013	1.40	1.90
Ia-101	>63	0.00031	1.80	7.70
Ia-102	>71	0.00071	3.20	5.70
Ia-111	>63	0.0029	0.63	0.39
Ia-112	>63	0.0025	>21	2.60

From the above mentioned, the compound of the present invention has low affinity to DA2 receptor and high affinity to σ receptor, and has useful activity as psychotropic agents.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

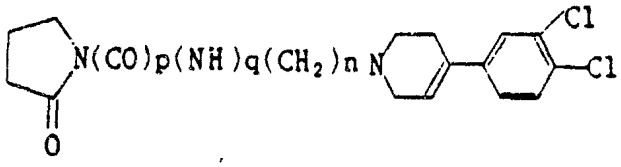
1. A compound of the formula:



wherein Ar is phenyl which has identically or differently one or two substituents selected from the group consisting of lower alkyl, lower alkoxy, trifluoromethyl, hydroxy and phenyl, which latter phenyl may be substituted by hydroxy, lower alkyl, lower alkoxy or halogen, or Ar is phenyl which is substituted by two halogen atoms;
n is an integer of from 2 to 6;
R^1 is hydrogen or lower alkyl;
the group

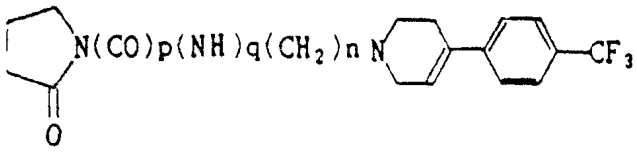
may have identically or differently 1 to 3 substituents selected from the group consisting of lower alkyl, halogen, oxo and phenyl, which phenyl may be substituted by hydroxy, lower alkyl, lower alkoxy or halogen; and
p and q each is an integer of 0 to 1, with the proviso that when p is 0, q is not 1;
or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of the formula:



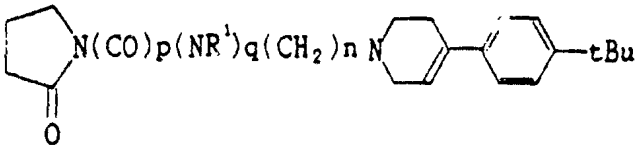
wherein n is an integer of from 2 to 6; p and q each is an integer of 0 or 1, with the proviso that when p is 0, q is not 1; or a pharmaceutically acceptable acid addition salt thereof.

3. A compound of the formula:



wherein n is an integer of from 2 to 6; p and q each is an integer of 0 or 1, with the proviso that when p is 0, q is not 1; or a pharmaceutically acceptable acid addition salt thereof.

4. A compound of the formula:



wherein R^1 is hydrogen or lower alkyl; n is an integer of from 2 to 6; p and q each is an integer of 0 or 1, with the proviso that when p is 0, q is not 1; or a pharmaceutically acceptable acid addition salt thereof.

5. A pharmaceutical composition comprising a pharmacologically effective amount of a compound according to any one of claims 1 to 4 together with a pharmaceutically acceptable carrier, diluent or excipient.

6. A method for the treatment of psychosis in instances of sigma receptor disfunction which comprises administering a therapeutically effective amount of a compound according to any one of claims 1 to 4 to a subject in need thereof.

7. A method according to claim 6 wherein the psychosis is depression, mania, acute and chronic schizophrenia or cerebral ischemic disease.

8. Compounds according to any one of claims 1 to 4, methods for their manufacture, pharmaceutical compositions containing them or methods of treatment involving them, substantially as hereinbefore described with reference to the Examples.

DATED this 2nd day of August, 1993

SHIONOGI & CO., LTD.
By its Patent Attorneys
DAVIES COLLISON CAVE