

COMMONWEALTH of AUSTRALIA
Patents Act 1952

APPLICATION FOR A STANDARD PATENT

615260

I/We

Shionogi & Co., Ltd.

of

1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541, Japan

hereby apply for the grant of a Standard Patent for an invention entitled:

2-substituted carbonylimidazo[4,5-c] quinolines

which is described in the accompanying complete specification.

Details of basic application(s):-

Number

Convention Country

Date

033270/1988

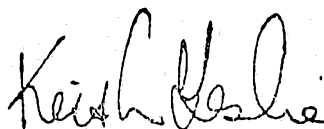
Japan

16 February 1988

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this FOURTEENTH day of FEBRUARY 1989

To: THE COMMISSIONER OF PATENTS



.....
a member of the firm of
DAVIES & COLLISON for
and on behalf of the
applicant(s)

Davies & Collison, Melbourne

MO06602 14/02/89

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A PATENT

Insert title of invention.

In support of the Application made for a patent for an invention
entitled: "2-substituted carbonylimidazo[4,5-c] quinolines"

Insert full name(s) and address(es)
of declarant(s) being the appli-
cant(s) or person(s) authorized to
sign on behalf of an applicant
company.

~~XXX~~

Kazuo Yoshitoshi of
Shionogi & Co., Ltd.,

presently of: 12, Doshomachi 3-chome,
Higashi-ku, Osaka 541 Japan
but about to become: 1-8 Doshomachi 3-chome,
Chuo-ku, Osaka 541 Japan

do solemnly and sincerely declare as follows :-

1. (a) ~~XXX~~ ~~the applicant~~ ~~for the patent~~
or (b) I am authorized by

Shionogi & Co., Ltd.

the applicant..... for the patent to make this declaration on ^{its} ~~XXX~~ behalf.

2. (a) ~~XXX~~ ~~the actual inventor~~ ~~of the invention~~
or (b)

1. Susumu TAKADA
2. Toshio FUJISHITA
3. Takashi SASATANI
4. Akira MATSUSHITA
5. Masami EIGYO

See over page for addresses

~~XXX~~ the actual inventor..S..... of the invention and the facts upon which the applicant.....
are
is
~~XXX~~ entitled to make the application are as follows :-

State manner in which applicant(s)
derive title from inventor(s)

The actual inventors assigned the invention to the
said applicant

Cross out paragraphs 3 and 4
for non-convention applications.
For convention applications,
insert basic country(s) followed
by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act ^{was} ~~XXX~~ made
in Japan..... on the 16th February 1988
by Shionogi & Co., Ltd.
in..... on the
by
in..... on the
by

4. The basic application..... referred to in paragraph 3 of this Declaration ^{was} ~~XXX~~
the first application..... made in a Convention country in respect of the invention the subject
of the application.

Insert place and date of signature.

Declared at Osaka, Japan this 24th day of January, 1989
Shionogi & Co., Ltd.

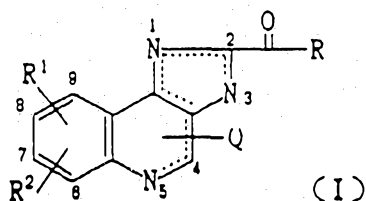
Signature of declarant(s) (no
attestation required)

Note Initial all alterations.

Kazuo Yoshitoshi
Kazuo Yoshitoshi,
Representative Director

(12) PATENT ABRIDGMENT (11) Document No. AU-B-29934/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 615260

- (54) Title
2-SUBSTITUTED CARBONYLIMIDAZO(4,5-C) QUINOLINES
- (51)⁴ International Patent Classification(s)
C07D 471/04 A61K 031/47
- (21) Application No. : 29934/89 (22) Application Date : 14.02.89
- (30) Priority Data
- (31) Number (32) Date (33) Country
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- (43) Publication Date : 17.08.89
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- (72) Inventor(s)
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- (74) Attorney or Agent
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- (56) Prior Art Documents
AU 64165/86 C07D 471/04/161
AU 581190 35402/84
- (57) Claim
1. A compound of the formula:



wherein R is (1) hydrogen; (2) hydroxy; (3) C₁-C₁₀ alkyl optionally substituted by halogen, C₁-C₅ alkylthio, C₁-C₅ alkyloxycarbonyl, or phenyl; (4) C₃-C₅ cycloalkyl optionally substituted by C₁-C₅ alkyl; (5) C₂-C₅ alkenyl optionally substituted by C₁-C₅ alkyl or di-C₁-C₅ alkyl; (6) C₁-C₅ alkoxy; (7) phenoxy; (8) amino optionally substituted by C₁-C₅ alkyl or di-C₁-C₅ alkyl; (9) phenyl optionally substituted by one or two members independently selected from the group consisting of halogen, trifluoromethyl, C₁-C₅ alkoxy, and C₁-C₅ alkylthio; or (10) 5- or 6-membered heterocyclic group selected from isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, thiadiazolyl, oxadiazolyl, thienyl, furyl and pyridyl optionally

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-2-

substituted by one or two members independently selected from the group consisting of halogen, C₁-C₅ alkyl, and phenyl; Q is hydrogen, C₁-C₅ alkyl, benzyl, benzhydryl, trityl, C₁-C₅ alkylsulfonyl, or C₆-C₁₂ arylsulfonyl, provided that Q is located at nitrogen atom of 1-, 3-, or 5-position; R¹ and R² each is hydrogen, C₁-C₅ alkyl, C₁-C₅ alkoxy, or halogen; and the dotted lines indicate the presence of three double bonds at the position of 2(3), 3a(9b), 4(5); 1(9b), 2(3), 3a(4); or 1(2), 3a(9b), 4(5);

or its pharmaceutically acceptable acid addition salts.

5. A method for treating a patient suffering from depression, convulsion, anxiety, amnesia, senile dementia, or cerebral disorder characterized by administering a pharmaceutical composition according to Claim 4 to the patient.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

615260

**NAME & ADDRESS
OF APPLICANT:**

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NAME(S) OF INVENTOR(S):

Susumu TAKADA
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Akira MATSUSHITA
Masami EIGYO

ADDRESS FOR SERVICE:

DAVIES & COLLISON
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1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

2-substituted carbonylimidazo[4,5-c] quinolines

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

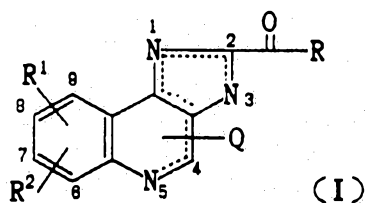
This invention relates to imidazo[4,5-c]quinolines substituted by carbonyl group at 2-position.

Prior Art

As to compounds having an imidazo[4,5-c]quinoline ring as a basic structure, Abbasi, et al. in Monatsh. Chem., 111, 963 (1980) have shown 3-hydroxy-2-hydroxymethyl-8-methoxy-9-nitro-4-styryl-2H-imidazo[4,5-c]quinoline derivatives as intermediates for synthesizing physiologically active substances. European Patent No. 145,340 discloses 2-hydroxyalkyl-1H-imidazo[4,5-c]quinolines as bronchodilators or antiviral drugs.

SUMMARY

This invention relates to compounds of the formula:



wherein R is (1) hydrogen; (2) hydroxy; (3) C₁-C₁₀ alkyl optionally substituted by halogen, C₁-C₆ alkylthio, C₁-C₆ alkyloxycarbonyl, or phenyl; (4) C₃-C₆ cycloalkyl optionally substituted by C₁-C₆ alkyl;

(5) C₂-C₅ alkenyl optionally substituted by C₁-C₅ alkyl or di-C₁-C₅ alkyl; (6) C₁-C₅ alkoxy; (7) phenoxy; (8) amino optionally substituted by C₁-C₅ alkyl or di-C₁-C₅ alkyl; (9) phenyl optionally substituted by one or two members independently selected from the group consisting of halogen, trifluoromethyl, C₁-C₅ alkoxy, and C₁-C₅ alkylthio; or (10) 5- or 6-membered heterocyclic group selected from isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, thiadiazolyl, oxadiazolyl, thienyl, furyl and pyridyl optionally substituted by one or two members independently selected from the group consisting of halogen, C₁-C₅ alkyl, and phenyl; Q is hydrogen, C₁-C₅ alkyl, benzyl, benzhydryl, trityl, C₁-C₅ alkylsulfonyl, or C₆-C₁₂ arylsulfonyl, provided that Q is located at nitrogen atom of 1-, 3-, or 5-position; R¹ and R² each is hydrogen, C₁-C₅ alkyl, C₁-C₅ alkoxy, or halogen; and the dotted lines indicate the presence of three double bonds at the position of 2(3), 3a(9b), 4(5); 1(9b), 2(3), 3a(4); or 1(2), 3a(9b), 4(5); or its pharmaceutically acceptable acid addition salts, and also relates to psychotropic agents containing the compound as an active ingredient.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Compounds having the aforementioned basic structure have been widely studied. However, none of them were found to have any psychotropic activity. The present inventors have found that the abovementioned imidazo-[4,5-c]quinoline derivatives have utility as psychotropic agents (e.g. US Pat. 4753951). In addition, they found that the compounds of the present invention having a carbonyl group at 2-



position have excellent psychotropic activity, based upon the activation of benzodiazepine receptor. Especially, these are expected as psychostimulants, based upon the potentiation of pentylenetetrazole (PTZ)-induced convulsions. So the compounds (I) of the present invention may be useful for treatment of depression, convulsion, anxiety, amnesia, senile dementia, or cerebral disorder etc.

The terms used in the above definitions are explained below.

As the alkyl, there are exemplified straight or branched alkyl, such as methyl, ethyl, propyl, butyl, isobutyl, t-butyl, sec-butyl, pentyl, neopentyl, etc.

As the alkoxy, there are, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, etc.; and as the alkylthio, there are, for example, methylthio, ethylthio, propylthio, butylthio, isobutylthio, neopentylthio, etc.

As the cycloalkyl, there are exemplified cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.

As the alkenyl, there are, for example, vinyl, 1-propenyl, 2-propenyl, 1-isobutenyl, butenyl, isopentenyl, pentenyl, etc.

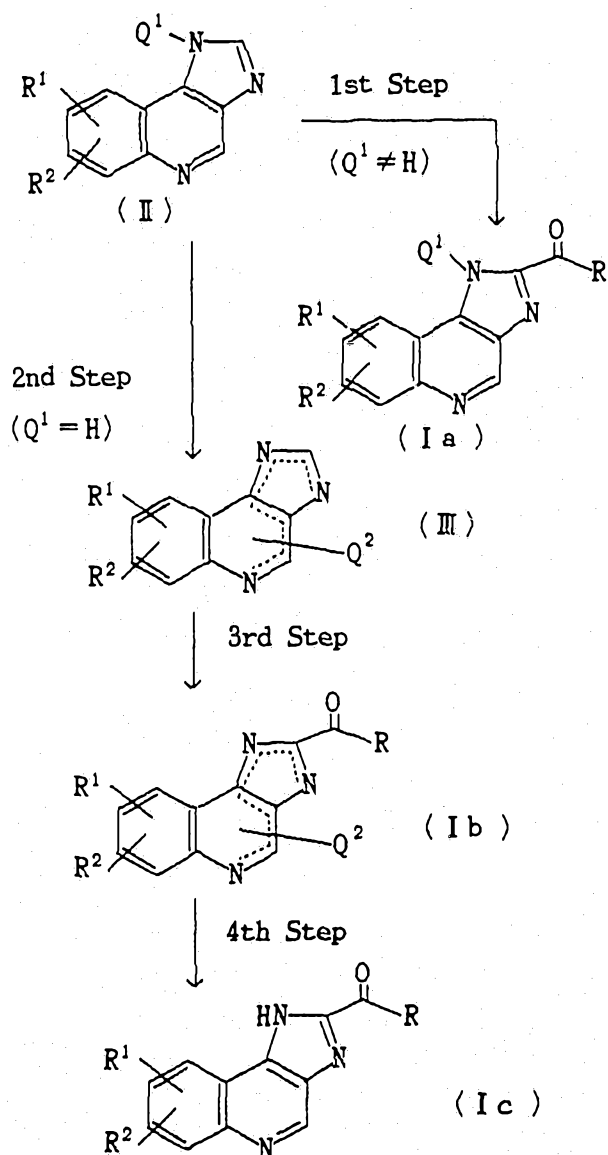
As the halogen, there are fluorine, chlorine, bromine and iodine.

~~As the 5- or 6-membered heterocyclic group, there are exemplified isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, thiadiazolyl, oxadiazolyl, thienyl, furyl, pyridyl, etc.~~

The compound (I) of the present invention can be obtained through the following four routes:



Route A



(wherein R, R¹ and R² have the same meaning as defined above; Q¹ is hydrogen or alkyl; and Q² is alkyl, benzyl, benzhydryl, or trityl.)

1st Step

The objective 2-carbonyl compound (I a) is obtained by reacting the starting material (II) with an acylating agent or carbamoylating agent in the presence of a lithium-type base such as n-BuLi, sec-BuLi, t-BuLi, or PhLi. This reaction is carried out at a low temperature (about -50 ~ about -80°C) usually in an appropriate solvent, using an acylating agent or carbamoylating agent corresponding to the required acyl or amide group, respectively.

As the solvent, ether-type solvents such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane and 1, 2-dimethoxyethane, etc. are exemplified

As the acylating agent, acid halide, carboxylate, acid anhydride, mixed acid anhydride, etc. may be used.

As the carbamoylating agent, there may be used dimethylcarbamoyl halide and isocyanates such as alkyl isocyanate and phenyl isocyanate.

2nd Step

The imidazo[4,5-c]quinoline (III) having a substituent at 1-, 3-, or 5-position is obtained by reacting the starting material (II) with an appropriate alkylating agent for several hours in a suitable solvent in the presence of a base.

As the alkylating agent, there are, for example, alkyl halide such as methyl iodide and ethyl iodide; benzyl halide such as benzyl

chloride; and benzhydryl bromide, trityl chloride, etc.

Comparatively bulky groups such as trityl are mainly introduced to the 3-position, while in case of less bulky alkyls such as methyl, ethyl, or propyl, compounds having substituents at the 1- or 5-position in addition to the 3-position are obtained as a mixture.

As the solvent, acetonitrile, tetrahydrofuran, ether, dioxane, dimethylformamide, etc. are exemplified.

As the base, triethylamine, pyridine, sodium ethylate, sodium hydride, etc are exemplified.

The reaction is completed in 5 ~ 30 hours if performed at about 0 ~ about 50°C , preferably at room temperature.

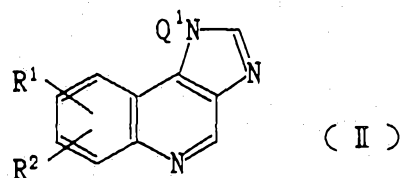
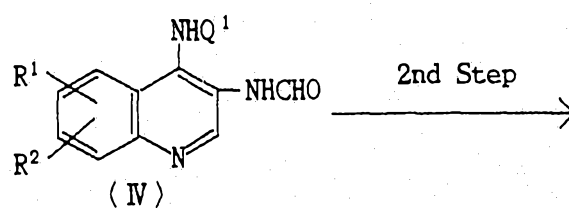
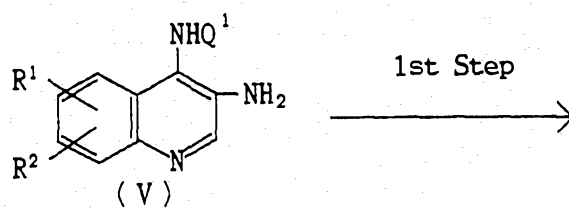
3rd Step

The objective compound (I b) is obtained by acylating or carbamoylating the compound (III) in the same manner as in the 1st Step.

4th Step

The above-mentioned 2-carbonyl compound (I b) is dealkylated by treating with a suitable reagent at about 0 ~ about 50°C, preferably at room temperature, whereby the objective compound (I c) is obtained. As the reagent for dealkylation, trifluoroacetic acid, hydrogen iodide, boron tribromide, etc. are preferable.

Preparation of the Starting Material (II)



(Wherein R¹, R², and Q¹ have the same meanings as defined above.)

1st Step

4-Amino-3-formylaminoquinoline (IV) is obtained by reacting 3, 4-diaminoquinoline (V) with formic acid under heating for several hours. The reaction may be carried out at about 80 ~ about 110°C for 1 - 3 hours.

However, when Q¹ is not H, the compound (II) is directly obtained by this reaction in some cases.

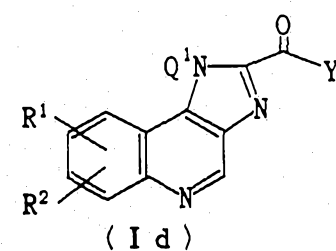
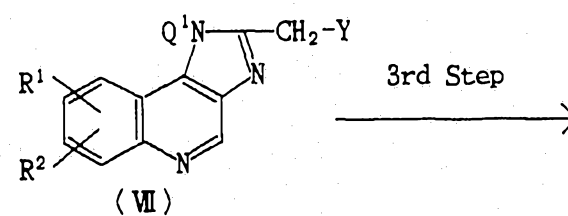
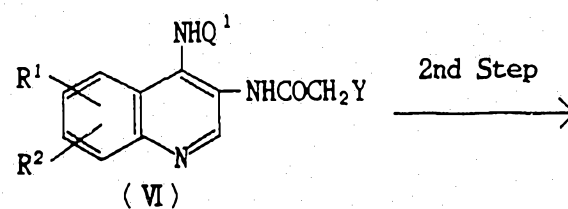
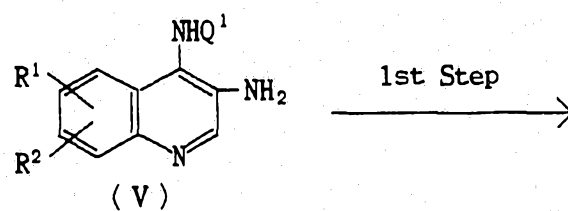
2nd Step

1H-Imidazo[4,5-c]quinoline compound (II) may be obtained by heating under reflux the above obtained compound (IV) obtained above in a solvent for several hours.

As the solvent, the solvents having high boiling point, for instance, alcohols such as ethylene glycol and ethers such as diglyme, and the like are exemplified.

The reaction may be carried out at about 100 ~ about 200°C for 1 - 5 hours.

Route B



(wherein R¹, R², and Q¹ have the same meanings as defined above; Y is alkyl, cycloalkyl or aryl.)

1st Step

4-Amino-3-substituted acetamidoquinoline (VI) is obtained by reacting a substituted acetyl halide with the compound (V) in an appropriate solvent.

As the solvent, there are exemplified hexamethylphosphoramide, acetonitrile, dimethylformamide, chloroform or a mixture thereof.

The reaction is completed in 0.5 ~ 5.0 hours if performed at about -50 ~ about 5°C, preferably at about -10 ~ about 0°C.

2nd Step

2-Substituted methyl-1H-imidazo[4, 5-c]quinoline compound (VII) is obtained by heating the amide (VI) above for several minutes under reflux in a solvent.

As the solvent, the solvents having high boiling point are preferable. They are, for instance, alcohols such as ethylene glycol, etc. and ethers such as diglyme, etc. The reaction is carried out for 10 ~ 40 minutes at about 100 ~ about 200°C.

3rd Step

The objective compound (I d) is obtained by heating the compound (VII) as obtained above with an oxidizing agent for several hours in an appropriate solvent.

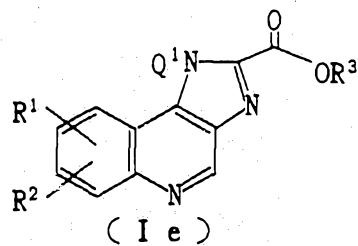
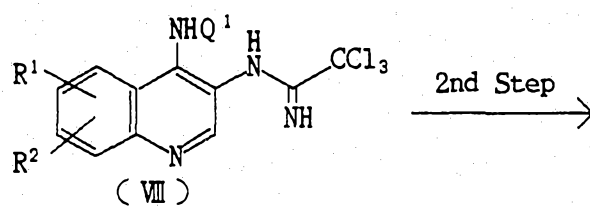
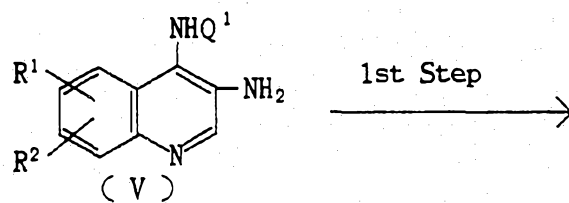
As the solvent, water, dioxane, 1, 2-dimethoxyethane, acetone, benzene, etc. are exemplified.

As the oxidizing agent, there are exemplified selenium dioxide, manganese dioxide, chromic anhydride, potassium permanganate, etc.

The reaction is completed in 1 - 3 hours if carried out at about 60 ~ about 90°C.

Route C

(When $R = OR^c$)



(wherein R^1 , R^2 , and Q^1 have the same meanings as defined above; R^3 is alkyl or aryl.)

1st Step

4-Amino-3-(trichloroacetimidoylamino)quinoline (VIII) is obtained by reacting methyltrichloroacetimidate with the compound (V) in an appropriate solvent, and then by stirring for several hours at room temperature.

As the solvent, acetic acid is preferable.

The reaction is carried out for 1 - 5 hours at about 0 ~ about 50°C, preferably at room temperature.

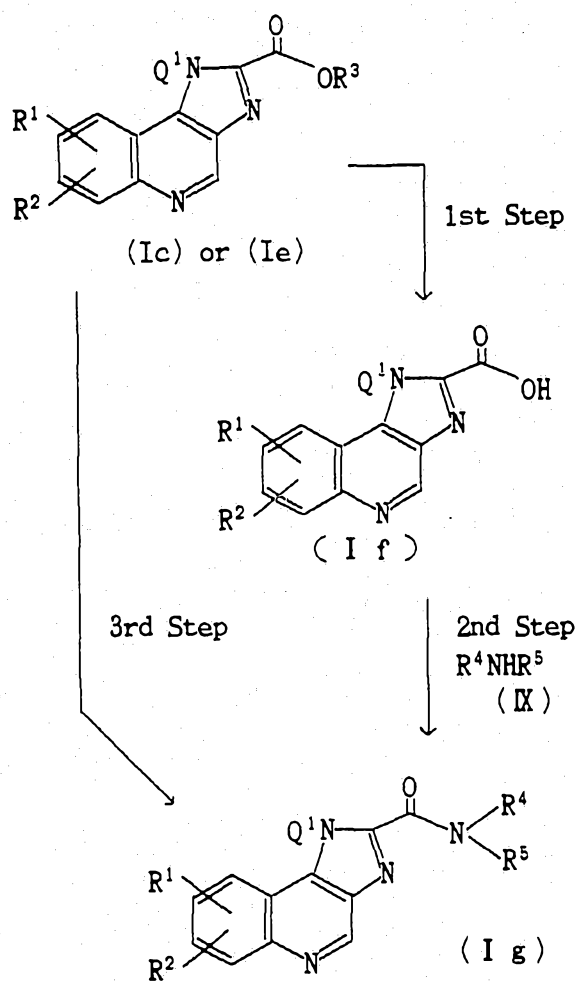
2nd Step

The objective compound (Ie) is obtained by reacting the compound (VIII) obtained above with a suitable alcohol or phenol under reflux or heating for several hours. As the alcohols there may be used, for example, methanol, ethanol, n-propyl alcohol, isopropyl alcohol, etc.

The phenols include cresols and naphthols as well as phenols.

The reaction is completed in 1 - 5 hours if carried out at about 60 ~ about 200°C.

Route D



(wherein R^1 , R^2 , and Q^1 have the same meanings as defined above; R^4 and R^5 each is hydrogen or alkyl.)

1st Step

The carboxylic acid (I f) is obtained by reacting the ester (I c) or (I e) with a base in an appropriate solvent for several hours.

As the solvent, there are exemplified methanol, ethanol, isopropanol, water or a mixture thereof. As the base, sodium hydroxide, potassium hydroxide, and the like are preferable.

This hydrolysis is carried out at about 10 ~ about 100 °C for 1 - 5 hours.

2nd Step

The carboxylic acid (I f) thus obtained is at first converted into an acid halogenide by the reaction with a halogenating agent such as thionyl chloride, etc. and the resulting halogenide is allowed to react with an appropriate amine (IX) to give the amide (I g).

As the amines, there are exemplified N, N-dimethylamine, N, N-diethylamine, monomethylamine, monobutylamine, etc.

The reaction is carried out at about 0 ~ about 50°C, preferably at room temperature for 10 ~ 40 minutes. The reaction of the 2nd step may follow the 1st Step successively without isolation of the compound (I f).

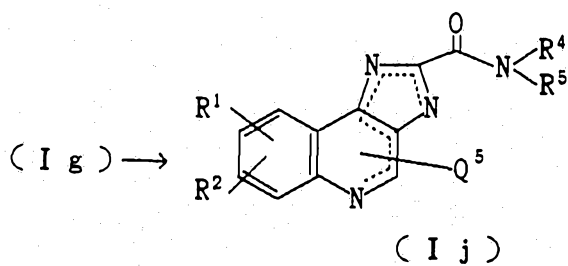
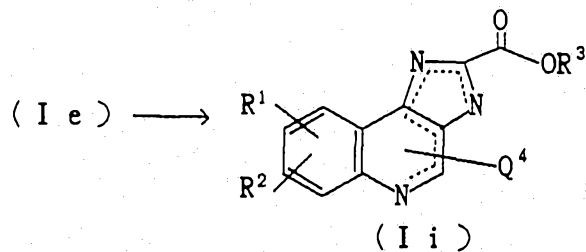
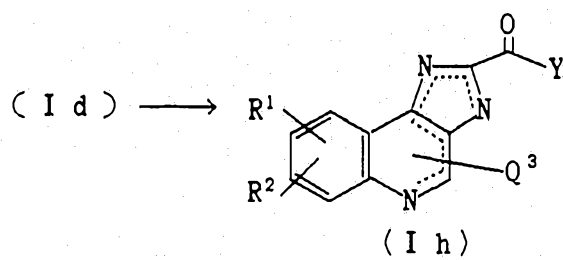
3rd Step

To a solution of the compound (I c) or (I e) in an appropriate solvent is added a suitable amine, and the mixture is heated at about 60 ~ about 150°C for 1 - 5 hours in a sealed tube, whereby the objective compound (I g) is obtained.

As the solvent, alcohols such as methanol and ethanol, etc. or

water are exemplified.

Route E



(wherein Q³, Q⁴, and Q⁵ each is alkyl, acyl, alkylsulfonyl or arylsulfonyl; and R¹, R², R³, R⁴, R⁵, and Y have the same meanings as defined above.)

The objective compound (I d), (I e) and (I g) obtained in the Routes B, C and D may be subjected to the reaction for introducing substituent Q if Q' is hydrogen.

This reaction may be carried out by treating the compound (I d), (I e) or (I g) with a suitable reagent in the presence of a base for several hours in an appropriate solvent.

As the reagent, alkyl halide such as methyl iodide and ethyl iodide, etc.; acid halide, acid anhydride, sulfonyl chloride, etc. are exemplified.

As the solvent, there are, for example, acetonitrile, tetrahydrofuran, ether, dioxane, dimethylformamide, etc.

As the base, triethylamine, sodium alcoholate, sodium hydride, etc. are exemplified.

The reaction is completed in 5 ~ 30 hours if performed at about 0 ~ about 50°C, preferably at room temperature.

The objective compound (I) can be converted into its pharmaceutically acceptable acid addition salts such as salts with inorganic acids including hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid, etc.; and organic acids including acetic acid, maleic acid, malic acid, citric acid, lactic acid, methanesulfonic acid, etc. The compounds (I) or the pharmaceutically acceptable acid addition salts show high affinities for benzodiazepine receptor and are useful as psychotropic agents such as psychostimulants or antianxiety agents.

The compounds (I) can be administered orally or parenterally to

humans or mammals. They may be formulated in a conventional manner into tablets, capsules, pills, granules, injections, suppositories and syrups. The pharmaceutically acceptable carriers, diluents, and excipients illustratively include lactose, sucrose, wheat starch, potato starch, magnesium stearate, gelatin, methyl cellulose, agar, water and the like. If necessary, stabilizers, emulsifiers, wet extenders, buffers and other pharmaceutical auxiliaries may appropriately be added. An optimum daily dosage is 0.1 ~ 500 mg orally, and 0.1 ~ 300 mg injectably, in one to three divided doses.

The present invention is explained in more detail by the following Examples, Referential Examples, which are not intended to limit the scope of the invention.

The reactions shown in the Examples and Referential Examples are usually carried out in an anhydrous solvent under a nitrogen atmosphere. For the drying of extracting solvents, anhydrous magnesium or sodium sulfate is used. For chromatography on a column of silica gel, Kiesel gel 60 (70 - 230 mesh) made by Merck is used.

Abbreviations used in the Examples, Referential Examples and Tables have the following meanings:

Tr : trityl; Me : methyl; Et : ethyl; THF : tetrahydrofuran;
MeOH : methanol; EtOH : ethanol; AcOEt : ethyl acetate; DMF:
dimethylformamide; HMPA: hexamethylphosphoramide; MeCN:
acetonitrile; (d) : decomposition; (s) : sublimation;

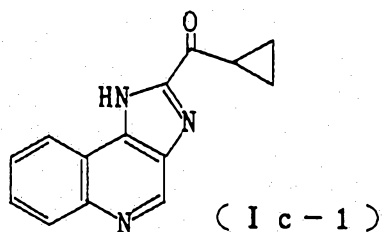
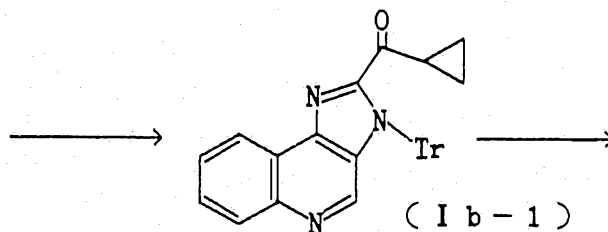
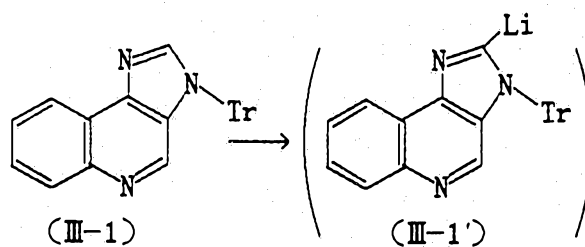
In the NMR spectrum, the indication of multiplicity is abbreviated as follows:

s : singlet; d : doublet; t : triplet; q : quartet;

m : multiplet

Example 1

2-Cyclopropylcarbonyl-1H-imidazo[4,5-c]quinoline (I c-1)



To a cold solution (-70°C) of 1.23 g of 3-trityl-3H-imidazo[4,5-

c]quinoline (III-1) in 25 ml of THF was added dropwise a mixture of 3 ml of 1.6 M solution of n-butyl lithium in hexane and 3 ml of THF while being kept at $-72 \sim -68^{\circ}\text{C}$. The mixture was stirred at the same temperature for 30 min., whereby a yellow solution of 2-lithio form (III-1') was obtained. All the 2-lithio form used in the Examples hereafter are prepared according to the same reaction conditions. To the yellow solution of the compound (III-1') was added 1.04 g of cyclopropanecarbonyl chloride all at once. The temperature of the reaction solution was gradually elevated to room temperature, and the solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and aqueous ammonia. The organic layer was washed with water and saturated brine, successively, and dried. The ethyl acetate was removed by evaporation, and the residue was crystallized from n-hexane - ethyl acetate to give 900 mg of the crude crystals (I b-1). The compound (I b-1) was deprotected by mixing with 4 ml of trifluoroacetic acid. After stirring for 30 min. at room temperature, the reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate. The organic layer was washed with water and saturated brine, and dried. The ethyl acetate was removed by evaporation, and the residue was chromatographed on a column of silica gel for purification. The fraction eluted with chloroform - methanol (30:1 v/v) was concentrated and crystallized from n-hexane to give 395 mg (yield : 56%) of the titled compound (I c-1). This was recrystallized from ethanol to give colorless

crystals melting at 230 °C (dec.).

Anal. Calcd. (%) for $C_{14}H_{11}N_3O$

: C, 70.87; H, 4.67; N, 17.71

Found (%) : C, 70.85; H, 4.84; N, 17.53

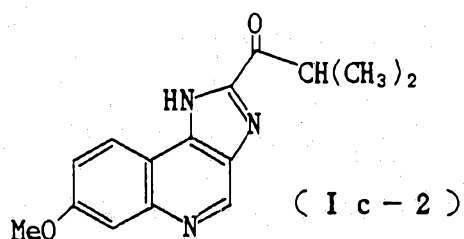
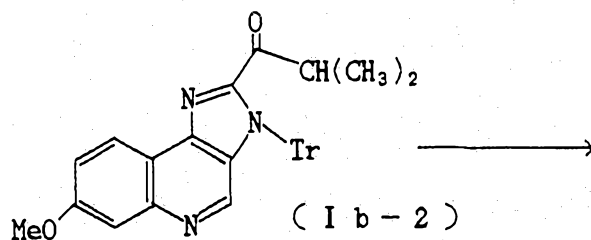
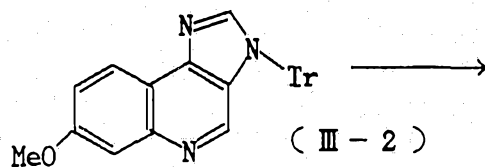
NMR (DMSO- d_6) δ : 1.23 (4H, d), 3.35 (1H, quintet),

7.60~7.85 (2H, m), 8.05~8.25 (1H, m), 8.55~8.75 (1H, m),

9.33 (1H, s)

Example 2

2-Isobutyryl-7-methoxy-1H-imidazo[4,5-c]quinoline (I c-2)



A solution of 1.32 g of 7-methoxy-3-trityl-3H-imidazo[4,5-c]-quinoline (III-2) in 30 ml of THF was reacted with a mixture of 2.5 ml of 1.6 M solution of n-butyl lithium in hexane and 2 ml of THF under the same conditions as in Example 1. To this was added 1.33 g of isobutyric anhydride. The reaction mixture was gradually warmed up to

room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and aqueous ammonia; and the organic layer was washed with water, then with saturated brine and dried. The ethyl acetate was removed by evaporation, and the residue was chromatographed on a column of silica gel for purification. The fraction eluted with ethyl acetate - n-hexane (1:2 v/v) was concentrated and crystallized from n-hexane to give 1.20 g of the objective compound (I b-2). The compound (I b-2) was dealkylated by mixing with 4 ml of trifluoroacetic acid. After treatment as in Example 1, the residue was chromatographed on a column of silica gel for purification. The fraction eluted with chloroform - methanol (30:1 v/v) was concentrated to give 580 mg (yield : 72%) of the titled compound (I c-2) as crystals. This was recrystallized from ethanol to give colorless crystals melting at 283 ~ 285°C.

Anal. Calcd. (%) for $C_{15}H_{16}N_3O_2$

: C, 66.90; H, 5.61; N, 15.60

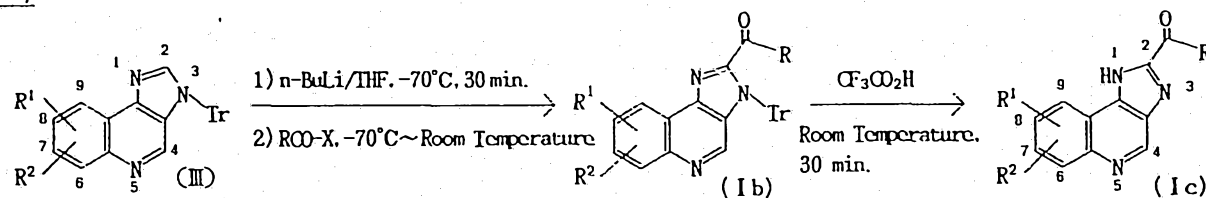
Found (%) : C, 67.07; H, 5.56; N, 15.74

NMR (DMSO- d_6) δ : 1.25 (6H, d), 3.93 (1H, septet), 3.97 (3H, s),
7.40 (1H, d, d), 7.57 (1H, d), 8.53 (1H, d), 9.28 (1H, s).

Examples 3 ~ 32

In the same manner as in Examples 1 or 2, the objective compounds (I c) were obtained under reaction conditions shown in Table 1. The physical properties of the objective compounds were shown in Tables 2-1 and 2-2.

Table 1 (No.1)



Ex No.	R	1st Step								2nd Step	Compound (Ic)		
		Amount of Compd. (III)				n-BuLi-THF (ml) (ml)		RCO-X		CF ₃ CO ₂ H (ml)	Yield		Compd. No.
		R ¹	R ²	(g)	Solvent THF(ml)			X	(g)		(mg)	(%)	
3	-CH ₃	H	H	1.23	30	4	4	-OCOCH ₃	1.3	6	290	46	I c-3
4	-C ₂ H ₅	H	H	1.23	25	2.5	2	Cl	0.75	4	295	44	I c-4
5	-C ₂ H ₅	7-OMe	H	1.32	30	2.5	2	Cl	0.75	4	365	48	I c-5
6	-(CH ₂) ₂ CH ₃	H	H	1.23	25	2.5	2	-OCO(CH ₂) ₂ CH ₃	1.26	4	265	37	I c-6
7	-(CH ₂) ₃ CH ₃	H	H	1.23	25	2.5	2	-OCO(CH ₂) ₃ CH ₃	1.50	4	450	61	I c-7
8	-(CH ₂) ₄ CH ₃	H	H	1.23	25	2.5	2	-OCO(CH ₂) ₄ CH ₃	1.85	4	355	44	I c-8
9	-(CH ₂) ₅ CH ₃	H	H	1.23	25	2.5	2	-OCO(CH ₂) ₅ CH ₃	2.10	4	580	69	I c-9
10	-(CH ₂) ₆ CH ₃	H	H	1.23	25	2.5	2	Cl	1.33	4	240	27	I c-10
11	-(CH ₂) ₇ CH ₃	H	H	1.23	25	2.5	2	Cl	1.47	3	260	29	I c-11
12	-(CH ₂) ₈ CH ₃	H	H	1.23	25	2.5	2	Cl	1.56	4	270	28	I c-12
13	-(CH ₂) ₉ CH ₃	H	H	1.23	25	2.5	2	Cl	1.65	4	290	29	I c-13
14	-CH(CH ₃) ₂	H	H	1.23	25	2.5	2	-OCOCH(CH ₃) ₂	0.95	4	150	21	I c-14

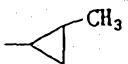
15	$-\text{CH}(\text{CH}_3)_2$	7-F H	1.42	70	2.8	2	C1	0.94	3	124	15	I c-15
16	$-\text{CH}(\text{CH}_3)_2$	8-F H	1.29	70	2.5	2	C1	0.85	4	240	31	I c-16
17	$-\text{CH}(\text{CH}_3)_2$	8-Me H	1.27	27	2.5	2	$-\text{OCOCH}(\text{CH}_3)_2$	1.33	4	550	73	I c-17
18	$-\text{CH} \begin{array}{l} \text{CH}_3 \\ \text{C}_2\text{H}_5 \end{array}$	H H	1.23	25	2.5	2	C1	0.99	4	350	46	I c-18
19	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H H	1.23	25	2.5	2	$-\text{OCOCH}_2\text{CH}(\text{CH}_3)_2$	1.50	4	470	62	I c-19
20		7-F H	1.72	80	3.2	2	C1	1.07	3	430	42	I c-20
21		8-F H	1.72	80	3.2	2.5	C1	1.07	4	580	57	I c-21
22		7-OMe H	1.32	30	2.5	2	C1	1.04	4	460	58	I c-22
23		8-Me H	1.27	27	2.5	2	C1	1.04	4	425	57	I c-23
24		H H	1.23	25	2.5	2	C1	0.95	3	350	47	I c-24

Table 1 (No. 3)

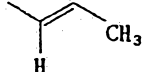
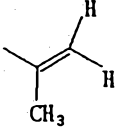
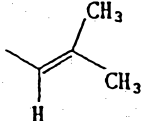
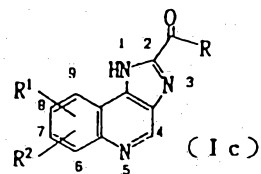
25		H	H	1.23	25	2.5	2	Cl	1.50	3	300	40	I c-25
26		H	H	1.23	25	2.5	2	Cl	1.00	4	290	37	I c-26
27		H	H	1.23	25	2.5	2	Cl	0.93	4	100	14	I c-27
28		H	H	1.23	25	2.5	2	Cl	0.90	2	110	15	I c-28
29		H	H	1.23	25	2.5	2	Cl	0.96	3	350	47	I c-29
30	$-(CH_2)_3Cl$	H	H	1.23	25	2.5	2	Cl	1.13	2	120	15	I c-30
31	$-(CH_2)_2SCH_3$	H	H	1.23	25	2.5	2	Cl	2.00	2	160	20	I c-31
32	$-(CH_2)_2$ 	H	H	1.23	25	2.5	2	Cl	1.20	2	195	22	I c-32

Table 2-1 (No. 1)



Compd. No.	R ¹	R ²	R	m.p. (°C)	Appearance	Recrystallizing Solvent	Molecular Formula	Elementary Analysis (%) Up (Calcd.), Down (Found)			
								C	H	N	
Ic-3	H	H	-CH ₃	247-250(d)	Colorless	EtOH	C ₁₁ H ₈ N ₂ O	68.24 67.99	4.29 4.35	19.89 19.56	
Ic-4	H	H	-C ₂ H ₅	230(d)	Colorless	EtOH	C ₁₃ H ₁₁ N ₂ O	69.32 69.41	4.92 4.99	18.65 18.56	
Ic-5	7-OMe	H	-C ₂ H ₅	295(d)	Light yellow	EtOH-CHCl ₃	C ₁₄ H ₁₁ N ₂ O ₂	65.87 65.71	5.13 5.23	16.46 16.45	
Ic-6	H	H	-(CH ₂) ₄ CH ₃	236-238	Colorless	EtOH	C ₁₆ H ₁₄ N ₂ O	70.26 70.27	5.48 5.57	17.56 17.51	
Ic-7	H	H	-(CH ₂) ₄ CH ₃	229-231	Colorless	EtOH	C ₁₆ H ₁₄ N ₂ O	71.13 71.36	5.97 6.05	16.59 16.60	
Ic-8	H	H	-(CH ₂) ₄ CH ₃	214-216	Colorless	AcOEt	C ₁₆ H ₁₄ N ₂ O	71.89 72.14	6.41 6.48	15.72 15.70	
Ic-9	H	H	-(CH ₂) ₄ CH ₃	205-206	Colorless	EtOH	C ₁₆ H ₁₄ N ₂ O	72.57 72.64	6.81 6.77	14.93 14.97	
Ic-10	H	H	-(CH ₂) ₄ CH ₃	196-198	Colorless	EtOH	C ₁₆ H ₁₄ N ₂ O	73.19 73.21	7.17 7.18	14.23 14.18	

Table 2-1 (No. 2)

I c-11	H H	$-(CH_2)_4CH_3$	193-195	Colorless	EtOH-CHCl ₃	C ₁₀ H ₂₂ N ₂ O	73.76 73.75	7.49 7.49	13.58 13.57	
I c-12	H H	$-(CH_2)_4CH_3$	190-192	Colorless	EtOH	C ₁₀ H ₂₂ N ₂ O	74.27 74.63	7.79 7.86	12.99 13.03	
I c-13	H H	$-(CH_2)_4CH_3$	185-186	Colorless	EtOH	C ₁₀ H ₂₂ N ₂ O	74.74 74.96	8.06 8.10	12.45 12.46	
I c-14	H H	$-CH(CH_3)_2$	274-276	Colorless	EtOH	C ₁₀ H ₂₁ N ₂ O	70.26 70.27	5.48 5.60	17.56 17.59	
I c-15	7-F H	$-CH(CH_3)_2$	278-281(d)	Colorless	MeOH-AcOEt	C ₁₀ H ₁₉ N ₂ OF	65.36 65.33	4.70 4.74	16.33 16.25	F 7.38 F 7.41
I c-16	8-F H	$-CH(CH_3)_2$	250-252(d)	Colorless	AcOEt-CH ₂ Cl ₃	C ₁₀ H ₁₉ N ₂ OF	65.36 65.44	4.70 4.96	16.33 16.13	F 7.38 F 7.49
I c-17	8-Me H	$-CH(CH_3)_2$	231-232	Light yellow	EtOH	C ₁₀ H ₂₁ N ₂ O	71.13 71.30	5.97 6.10	16.59 16.54	
I c-18	H H	$-CH \begin{matrix} \nearrow O^H \\ \searrow C_{21}H_{45} \end{matrix}$	243-244	Colorless	EtOH-CHCl ₃	C ₁₀ H ₂₁ N ₂ O	71.13 71.09	5.97 6.07	16.59 16.41	
I c-19	H H	$-CH_2CH(CH_3)_2$	259-261	Colorless	EtOH	C ₁₀ H ₂₁ N ₂ O	71.13 71.32	5.97 6.10	16.59 16.49	
I c-20	7-F H		267-270	Colorless	MeOH-CHCl ₃	C ₁₀ H ₁₉ N ₂ OF	65.87 65.81	3.94 4.13	16.46 16.38	F 7.44 F 7.59
I c-21	8-F H		273(d)	Colorless	MeOH-AcOEt	C ₁₀ H ₁₉ N ₂ OF	65.87 65.95	3.94 4.08	16.46 16.56	F 7.44 F 7.32
I c-22	7-OMe H		285(d)	Colorless	EtOH-CHCl ₃	C ₁₀ H ₂₁ N ₂ O ₂	67.41 67.56	4.90 4.95	15.72 15.77	

Table 2-1 (No. 3)

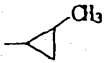
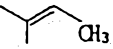
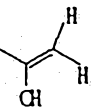
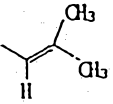
I c-23	8-Me H		245(d)	Colorless	EtOH	$C_{10}H_{11}N_2O$	71.70 71.86	5.21 5.23	16.72 16.86	
I c-24	H H		241-243(d)	Colorless	EtOH	$C_{10}H_{11}N_2O$	71.99 71.96	4.83 5.22	16.79 16.75	
I c-25	H H		246-248(d)	Colorless	EtOH	$C_{11}H_{13}N_2O$	71.70 71.83	5.21 5.30	16.72 16.59	
I c-26	H H		264(d)	Colorless	EtOH	$C_{12}H_{15}N_2O$	72.43 72.72	5.70 5.80	15.84 15.79	
I c-27	H H		224(d)	Light yellow	EtOH-CHCl ₃	$C_{11}H_{13}N_2O$	70.87 70.93	4.67 4.69	17.71 17.67	
I c-28	H H		225-227	Colorless	EtOH	$C_{11}H_{13}N_2O$	70.87 70.93	4.67 4.81	17.71 17.48	
I c-29	H H		272(d)	Colorless	EtOH-CHCl ₃	$C_{12}H_{15}N_2O$	71.70 71.87	5.21 5.30	16.72 16.68	
I c-30	H H	$-(CH_2)_3Cl$	175(d)	Colorless	EtOH	$C_{11}H_{13}N_2OCl$	61.43 61.44	4.42 4.41	15.35 15.17	Cl 12.95 Cl 13.09
I c-31	H H	$-(CH_2)_3SCH_3$	210(d)	Colorless	EtOH	$C_{12}H_{15}N_2OS$	61.97 61.97	4.83 4.76	15.49 15.23	S 11.82 S 11.60
I c-32	H H	$-(CH_2)_2$ 	251-253	Colorless	EtOH	$C_{11}H_{13}N_2O$	75.73 75.94	5.02 5.16	13.94 14.02	

Table 2-2 (No. 1)

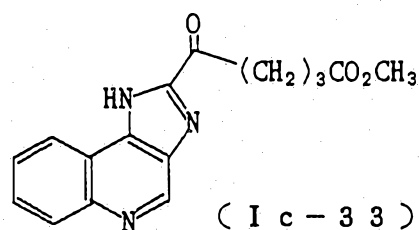
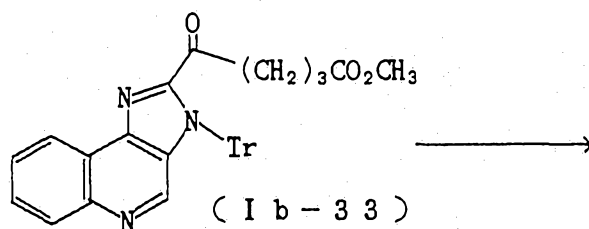
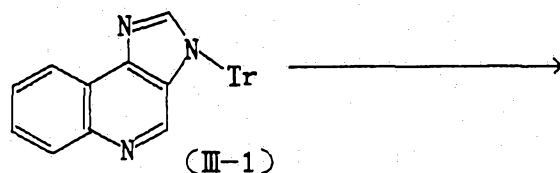
Compd. No	NMR (DMSO-d ₆) δ	Compd. No	NMR (DMSO-d ₆) δ
I c-3	2.80 (3H,s), 7.60~7.90 (2H,m), 8.05~8.30 (1H,m), 8.55~8.75 (1H,m), 9.33 (1H,s)	I c-13	0.83 (3H,t), 1.05~1.95 (16H,m), 3.25 (2H,t), 7.65~7.90 (2H,m), 8.10~8.30 (1H,m), 8.55~8.75 (1H,m), 9.33 (1H,s)
I c-4	1.20 (3H,t), 3.27 (2H,q), 8.60~8.90 (2H,m), 8.05~8.25 (1H,m), 8.55~8.75 (1H,m), 9.32 (1H,s)	I c-14	1.27 (6H,d), 3.98 (1H,septet), 7.70~7.90 (2H,m), 8.05~8.30 (1H,m), 8.55~8.80 (1H,m), 9.35 (1H,s)
I c-5	1.18 (3H,t), 3.27 (2H,q), 3.93 (3H,s), 7.37 (1H,d,d), 7.57 (1H,d), 8.53 (1H,d), 9.27 (1H,s)	I c-15	1.27 (6H,d), 3.96 (1H,septet), 7.62~7.73 (1H,m), 7.87~7.93 (1H,m), 8.64~8.71 (1H,m), 9.35 (1H,s)
I c-6	0.98 (3H,t), 1.55~1.98 (2H,t), 3.25 (2H,t), 7.65~7.90 (2H,m), 8.05~8.30 (1H,m), 8.55~8.80 (1H,m), 9.33 (1H,s)	I c-16	1.27 (6H,d), 3.96 (1H,septet), 7.61~7.71 (1H,m), 8.18~8.25 (1H,m), 8.30~8.43 (1H,m), 9.31 (1H,s)
I c-7	0.93 (3H,t), 1.15~1.90 (4H,m), 3.27 (2H,t), 7.65~7.90 (2H,m), 8.10~8.35 (1H,m), 8.55~8.80 (1H,m), 9.33 (1H,s)	I c-17	1.30 (6H,d), 3.97 (1H,septet), 7.55 (1H,d,d), 8.03 (1H,d), 8.40 (1H,d), 9.23 (1H,s)
I c-8	0.90 (3H,t), 1.10~1.90 (6H,m), 3.25 (2H,t), 7.60~7.90 (2H,m), 8.05~8.30 (1H,m), 8.55~8.80 (1H,m), 9.33 (1H,s)	I c-18	0.93 (3H,t), 1.25 (3H,d), 1.40~2.05 (2H,m), 3.55~4.10 (1H,m), 7.65~7.90 (2H,m), 8.10~8.30 (1H,m), 8.60~8.80 (1H,m), 9.37 (1H,s)
I c-9	0.87 (3H,t), 1.00~1.95 (8H,m), 3.27 (2H,t), 7.60~7.90 (2H,m), 8.10~8.30 (1H,m), 8.55~8.75 (1H,m), 9.33 (1H,s)	I c-19	1.00 (6H,d), 2.33 (1H,septet), 3.15 (2H,d), 7.65~7.90 (2H,m), 8.10~8.30 (1H,m), 8.55~8.75 (1H,m), 9.33 (1H,s)
I c-10	0.87 (3H,t), 1.15~2.00 (10H,m), 3.27 (2H,t), 7.65~7.95 (2H,m), 8.05~8.30 (1H,m), 8.55~8.80 (1H,m), 9.33 (1H,s)	I c-20	1.23~1.27 (4H,m), 3.28~3.43 (1H,m), 7.62~7.72 (1H,m), 7.87~7.94 (1H,m), 8.64~8.71 (1H,m), 9.36 (1H,s)
I c-11	0.83 (3H,t), 1.05~1.90 (12H,m), 3.25 (2H,t), 7.65~7.95 (2H,m), 8.05~8.25 (1H,m), 8.55~8.75 (1H,m), 9.33 (1H,s)	I c-21	1.24~1.28 (4H,m), 3.30~3.46 (1H,m), 7.60~7.71 (1H,m), 8.18~8.25 (1H,m), 8.31~8.38 (1H,m), 9.30 (1H,s)
I c-12	0.83 (3H,t), 1.05~1.90 (14H,m), 3.23 (2H,t), 7.65~7.90 (2H,m), 8.05~8.25 (1H,m), 8.55~8.75 (1H,m), 9.30 (1H,s)	I c-22	1.20 (4H,d), 3.37 (1H,quintet), 3.93 (3H,s), 7.37 (1H,d,d), 7.58 (1H,d), 8.53 (1H,d), 9.30 (1H,s)

Table 2-2 (No. 2)

Compd. No	NMR (DMSO-d ₆) δ
I c-23	1.23 (4H,d), 3.40 (1H,quintet), 3.57 (3H,s), 7.60 (1H,d,d), 8.05 (1H,d), 8.43 (1H,d), 9.27 (1H,s)
I c-24	1.00~1.90 (6H,m), 3.05~3.40 (1H,m), 7.60~7.90 (2H,m), 8.05~8.30 (1H,m), 8.50~8.75 (1H,m), 9.35 (1H,s)
I c-25	1.80~2.40 (6H,m), 4.23~4.60 (1H,m), 7.60~7.90 (2H,m), 8.05~8.30 (1H,m), 8.55~8.75 (1H,m), 9.30 (1H,s)
I c-26	1.50~2.30 (8H,m), 4.00~4.45 (1H,m), 7.65~7.90 (2H,m), 8.10~8.30 (1H,m), 8.55~8.75 (1H,m), 9.35 (1H,s)
I c-27	2.07 (3H,d), 7.30~7.95 (4H,m), 8.05~8.30 (1H,m), 8.55~8.80 (1H,m), 9.33 (1H,s)
I c-28	2.10 (3H,s), 6.27~6.40 (1H,m), 7.27 (1H,s), 7.65~7.95 (2H,m), 8.05~8.30 (1H,m), 8.55~8.70 (1H,m), 9.33 (1H,s)
I c-29	2.11 (3H,s), 2.35 (3H,s), 7.40~7.50 (1H,m), 7.60~7.85 (2H,m), 8.05~8.25 (1H,m), 8.50~8.75 (1H,m), 9.30 (1H,s)
I c-30	2.20 (2H,t,t), 2.47 (2H,t), 2.80 (2H,t), 7.60~7.95 (2H,m), 8.10~8.30 (1H,m), 8.55~8.75 (1H,m), 9.35 (1H,s)
I c-31	2.15 (3H,s), 2.93 (2H,t), 3.57 (2H,t), 7.65~7.90 (2H,m), 8.05~8.30 (1H,m), 8.55~8.80 (1H,m), 9.33 (1H,s)
I c-32	3.07 (2H,t), 3.60 (2H,t), 7.05~7.45 (5H,m), 7.60~7.90 (2H,m), 8.00~8.25 (1H,m), 8.50~8.75 (1H,m), 9.30 (1H,s)

Example 33

2-(4-Methoxycarbonylbutyl)-1H-imidazo[4,5-c]quinoline (I c-33)



To a mixture of 1.23 g of trytyl compound (III-1) in 25 ml of THF and a solution of 2.5 ml of n-butyl lithium - 2 ml of THF prepared in the same manner as in Example 1 was added 1.30 g of glutaric acid dimethyl ester. The mixture was stirred for 30 min. at -70°C and 240 mg

of acetic acid was added thereto. The reaction solution was elevated to room temperature and concentrated under reduced pressure. The residue obtained was distributed in ethyl acetate - saturated aqueous sodium hydrogencarbonate. The organic layer was washed with water and saturated brine, successively, and dried. The ethyl acetate was removed by evaporation, and the residue was chromatographed on a column of silica gel eluting with ethyl acetate - n-hexane (1:2 v/v) to give an oily substance (I b-33). The oily substance (I b-33) obtained was dealkylated by mixing with 4 ml of trifluoroacetic acid. After treating in the same manner as in Example 1, the residue was chromatographed on a column of silica gel for purification. The fraction eluted with chloroform - methanol (30:1 v/v) was concentrated and crystallized from n-hexane to give 245 mg (yield : 28%) of the titled compound (I c-33). This was recrystallized from ethanol to give colorless crystals melting at 207 ~ 208°C.

Anal. Calcd. (%) for $C_{16}H_{18}N_3O_3$

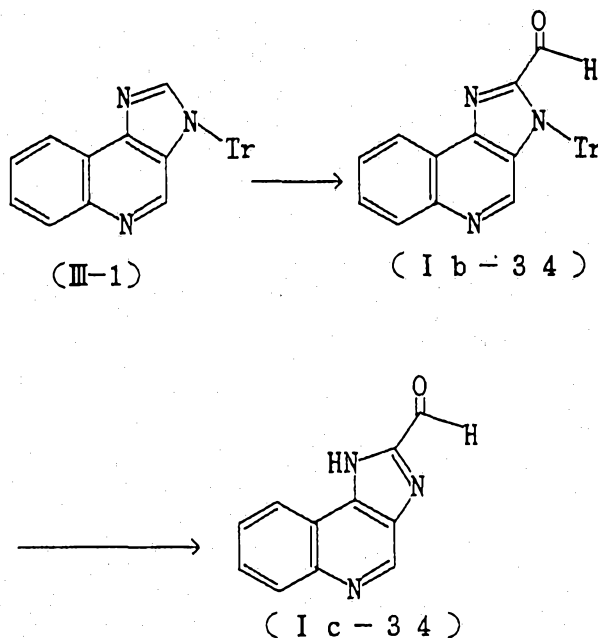
: C, 64.64; H, 5.09; N, 14.13

Found (%) : C, 64.68; H, 5.09; N, 13.99

NMR (DMSO- d_6) δ : 1.98 (2H, t, t), 2.47 (2H, t), 3.33 (2H, t),
3.63 (3H, s), 7.65~7.90 (2H, m), 8.05~8.25 (1H, m),
8.55~8.75 (1H, m), 9.30 (1H, s)

Example 34

2-Formyl-1H-imidazo[4,5-c]quinoline (I c-34)



To a mixture of 1.23 g of trityl compound (III-1) in 25 ml of THF and a solution of 2.5 ml of 1.6 M solution of n-butyl lithium in hexane - 2 ml of THF prepared in the same manner as in Example 1 was added dropwise 760 mg of DMF. After stirring the reaction mixture for 30 min. at - 70°C, 240 mg of acetic acid was added thereto, and the temperature of the mixture was elevated to room temperature. After treating in the same manner as in Example 33, the residue was chromatographed on a column of silica gel eluting with ethyl acetate - n-hexane (1:2 v/v) to give an oily substance (I b-34). The oily substance (I b-34) obtained was dealkylated by mixing with 4 ml of

trifluoroacetic acid. The reaction mixture was concentrated under reduced pressure. Saturated aqueous sodium hydrogencarbonate was added to the residue, and the resulting precipitate was collected by filtration, washed with water and dried. This was chromatographed on a column of silica gel eluting with ethyl acetate - methanol (20:3 v/v). The fraction obtained was concentrated and crystallized from ethanol to give 210 mg (yield : 36%) of the titled compound (Ic-34). This was crystallized from DMF to give colorless crystals melting at 254°C (d).

Anal. Calcd. (%) for $C_{11}H_7N_3O \cdot 1/10 H_2O$

: C, 66.39; H, 3.65; N, 21.12

Found (%) : C, 66.27; H, 3.87; N, 20.86

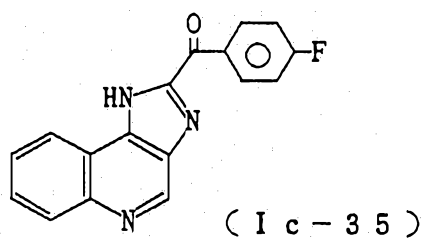
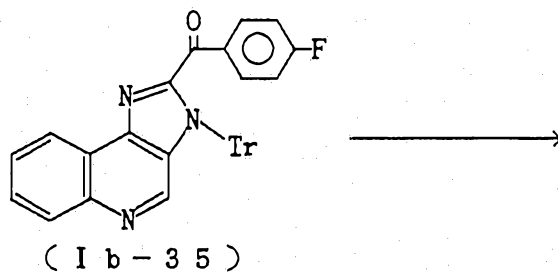
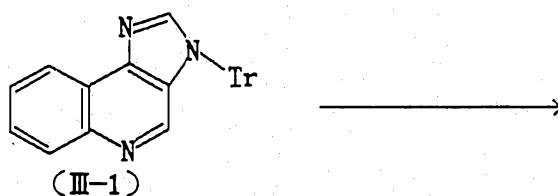
Mass spectrum: m/z 197 (M^+)

NMR (DMSO- d_6) δ : 7.60~7.95 (2H, m), 8.10~8.30 (2H, m),

8.50~8.70 (1H, m), 9.37 (1H, s), 10.08 (1H, s)

Example 35

2-(4-Fluorobenzoyl)-1H-imidazo[4,5-c]quinoline (I c-35)



To a mixture of 1.64 g of trytyl compound (III-1) in 20 ml of THF and a solution of 4 ml of n-butyl lithium and 10 ml of THF was added 2.55 g of 4-fluorobenzoic acid chloride. The reaction solution was

- 10 ml of THF was added 2.55 g of 4-fluorobenzoyl chloride. The reaction mixture was warmed to room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and aqueous ammonia. The organic layer was washed with water, then with brine and dried. The ethyl acetate was removed by evaporation and an oily substance obtained was chromatographed on a column of silica gel eluting with ethyl acetate - n-hexane (1:2 v/v). The fraction obtained was concentrated and crystallized from n-hexane to give 1.36 g of the titled compound (I b-35). The compound (I b-35) was suspended in 6 ml of trifluoroacetic acid and stirred for 30 min. at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was neutralized with saturated aqueous sodium hydrogencarbonate. The precipitate obtained was collected by filtration, washed with water and dried. This material was chromatographed on a column of silica gel eluting with chloroform - methanol (30:1 v/v) to give 740 mg (yield : 64%) of the titled compound (I c-35). This was recrystallized from ethanol - chloroform to give light yellow crystals melting at 305 ~ 307°C.

Anal. Calcd. (%) for $C_{17}H_{10}N_3OF$

: C, 70.10; H, 3.46; N, 14.43; F, 6.52

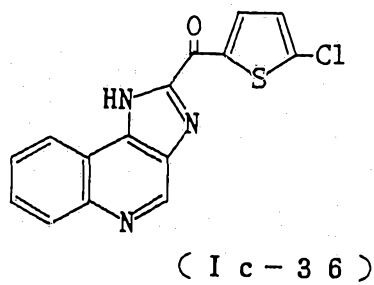
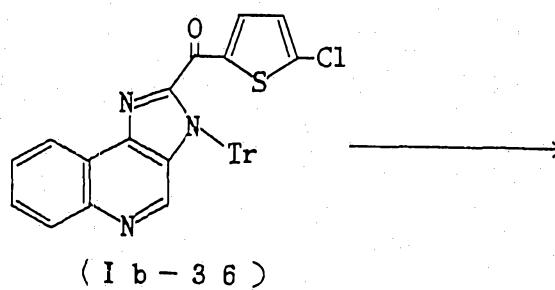
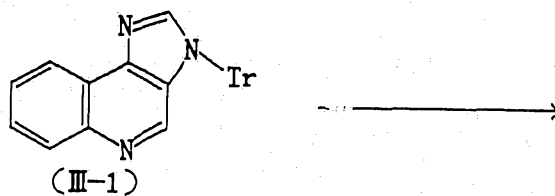
Found (%) : C, 70.25; H, 3.70; N, 14.34; F, 6.62

NMR (DMSO- d_6) δ : 7.30~7.95 (4H, m), 8.10~8.30 (1H, m),
8.57~8.90 (3H, m), 9.40 (1H, s).

Example 36

2-[(5-Chlorothiophen-2-yl)carbonyl]-1H-imidazo[4,5-c]quinoline

(I c-36)



A solution of 1.4 g of methyl 5-chloro-2-thiophencarboxylate in 2 ml of THF was added dropwise to a solution prepared in the same manner as in Example 1 from a solution of 1.23 g of the compound (III-1) in 25 ml of THF and a mixture of 2.5 ml of 1.6 M solution of n-butyl lithium in hexane - 2 ml of THF. After stirring for 30 min., 240 mg of acetic acid was added thereto, and the temperature was elevated to room temperature. After workup in the same manner as in Example 33, the residue was chromatographed on a column of silica gel eluting with ethyl acetate - n-hexane (1:2 v/v). The fraction was concentrated to give an oily substance (I b-36). The oily substance (I b-36) was dealkylated by mixing with 4 ml of trifluoroacetic acid. Crude crystals obtained by the same workup as in Example 35 were chromatographed on a column of silica gel for purification. When the fraction eluted with chloroform - methanol (30:1 v/v) was concentrated and crystallized from ethanol, 560 mg (yield : 61%) of the titled compound (I c-36) was obtained. This was recrystallized from ethanol - chloroform to give light yellow crystals melting at 320 - 322°C.

Anal. Calcd. (%) for $C_{15}H_9N_3OSCl$

: C, 57.42; H, 2.57; N, 13.39; S, 10.22; Cl, 11.30

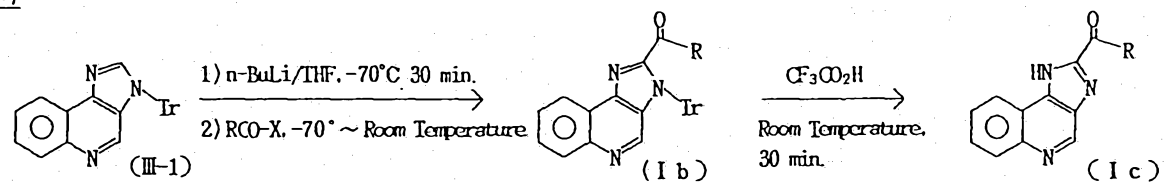
Found (%) : C, 57.17; H, 2.77; N, 13.17; S, 10.17; Cl, 11.24

NMR (DMSO- d_6) δ : 7.38 (1H, d), 7.60~7.90 (2H, m), 8.05~8.25 (1H, m), 8.53 (1H, d), 8.55~8.80 (1H, m), 9.33 (1H, s).

Examples 37 ~ 63

In the same manner as in Examples 35 or 36, the objective compounds (I c) were obtained under the reaction conditions shown in Table 3. The physical properties of the compounds were shown in Tables 4-1 and 4-2.

Table 3 (No. 1)



Ex No	R	1st Step							2nd Step	Compound (Ic)		
		Amount of Compd. (III-1) (g)	Solvent THF (ml)	n-BuLi-THF (ml) (ml)		RCO-X		Solvent THF (ml)	CF ₃ CO ₂ H (ml)	Yield from (III-1)		Compd. No.
						X	(g)			(mg)	(%)	
37		1.23	30	3	3	Cl	1.59	—	5	370	43	Ic-37
38		1.23	25	3	3	Cl	1.56	—	4	450	52	Ic-38
39		1.23	25	2.5	2	Cl	1.44	—	4	350	38	Ic-39
40		1.23	30	4	4	Cl	2.60	—	10	545	53	Ic-40
41		0.82	20	3	3	Cl	1.77	—	5	180	29	Ic-41
42		1.23	25	4	4	Cl	2.35	—	5	295	32	Ic-42
43		1.23	25	2.5	2	Cl	1.50	—	4	460	50	Ic-43

Table 3 (No. 2)

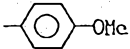
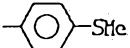
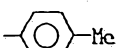
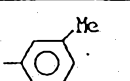
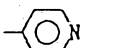
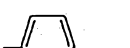
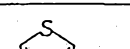
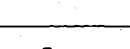
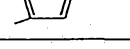
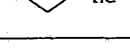
44		1.23	25	4 4	Cl	2.20	—	6	600	66	I c-44
45		1.23	25	2.5 2	OMe	1.32	4ml	4	560	59	I c-45
46		1.23	25	4 4	Cl	1.99	—	6	410	48	I c-46
47		1.23	25	2.5 2	Cl	1.29	—	4	520	61	I c-47
48		1.23	25	2.5 2	OEt	1.20	—	4	420	51	I c-48
49		1.23	25	2.5 2	OEt	1.30	2ml	4	300	37	I c-49
50		1.23	25	4 4	OEt	1.98	—	5	300	36	I c-50
51		1.23	25	2 2	Cl	0.70	2ml	4	310	37	I c-51
52		1.23	25	2.5 2	OMe	1.40	2ml	2	100	11	I c-52
53		1.23	25	2.5 2	OMe	1.25	2ml	4	430	49	I c-53
54		1.23	25	2.5 2	OMe	1.25	2ml	8	500	57	I c-54

Table 3 (No. 3)

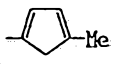
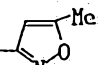
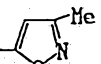
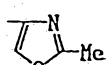
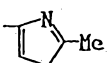
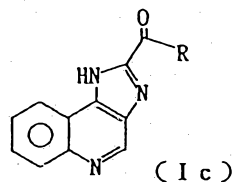
55		1.23	25	2.5 2	Cl	1.30	—	4	530	60	I c-55
56		1.23	25	2.5 2	Cl	1.06	—	5	415	53	I c-56
57		1.23	25	2.5 2	OMe	1.15	—	4	425	51	I c-57
58		1.23	25	2.5 2	Cl	1.04	—	4	485	62	I c-58
59		1.95	30	3 3	Cl	1.26	—	4	115	9	I c-59
60		1.23	25	3 3	Cl	1.40	—	6	470	57	I c-60
61		1.23	25	2.5 2	Cl	1.40	4ml	4	140	17	I c-61
62		1.23	25	2 2	OEt	1.00	2ml	2	220	26	I c-62
63		1.23	25	2.5 2	OEt	1.40	2ml	4	220	25	I c-63

Table 4-1 (No. 1)



Compd. No.	R	m.p. (°C)	Appearance	Recrystallizing Solvent	Molecular Formula	Elementary Analysis (%)			
						Up (Calcd.)	Down (Found)		
I c-37		263-265	Light yellow	EtOH	C ₁₇ H ₁₀ N ₂ OF	70.10	3.46	14.43	F 6.52
						69.85	3.68	14.38	F 6.64
I c-38		306-308	Light yellow	EtOH-CHCl ₃	C ₁₇ H ₁₀ N ₂ OF	70.10	3.46	14.43	F 6.52
						70.20	3.76	14.41	F 6.58
I c-39		287-289(d)	Light yellow	EtOH-CHCl ₃	C ₁₇ H ₈ N ₂ OF ₂	66.02	2.93	13.59	F 12.29
						66.03	3.16	13.55	F 12.26
I c-40		252-253	Colorless	EtOH-CHCl ₃	C ₁₈ H ₁₀ N ₂ OF ₃	63.85	2.95	12.31	F 16.70
						63.50	3.07	12.37	F 16.45
I c-41		310(s)	Yellow	EtOH-CHCl ₃	C ₁₇ H ₁₀ N ₂ OC1	66.35	3.28	13.65	Cl 11.52
						66.61	3.29	13.66	Cl 11.33
I c-42		298-300(d)	Light yellow	EtOH-CHCl ₃	C ₁₇ H ₁₀ N ₂ OC1	66.35	3.28	13.65	Cl 11.52
						66.04	3.58	13.35	Cl 11.42
I c-43		283-285	Light yellow	EtOH-CHCl ₃	C ₁₇ H ₁₀ N ₂ OC1	66.35	3.28	13.65	Cl 11.52
						66.43	3.34	13.65	Cl 11.82
I c-44		274-276	Colorless	EtOH	C ₁₈ H ₁₄ N ₂ O ₂	71.28	4.32	13.85	
						71.39	4.30	13.79	

Table 4-1 (No. 2)

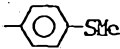
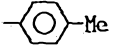
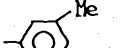
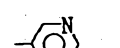
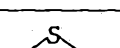
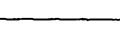
I c-45		275-277	Light yellow	EtOH-CHCl ₃	C ₁₁ H ₁₁ N ₃ OS	67.69 67.88	4.10 4.26	13.16 13.06	S 10.04 S 9.92
I c-46		286-287	Light yellow	EtOH-CHCl ₃	C ₁₁ H ₁₁ N ₃ O	75.25 75.17	4.56 4.59	14.62 14.52	
I c-47		246-248	Colorless	EtOH	C ₁₁ H ₁₁ N ₃ O	75.25 75.72	4.56 4.83	14.62 14.57	
I c-48		311-312	Yellow	EtOH-CHCl ₃	C ₁₁ H ₁₀ N ₄ O	70.07 70.02	3.68 3.86	20.43 20.22	
I c-49		330-333(d)	Yellow	EtOH-CHCl ₃	C ₁₁ H ₁₀ N ₄ O	70.07 70.36	3.68 3.91	20.43 20.39	
I c-50		315-317(d)	Colorless	EtOH-CHCl ₃	C ₁₁ H ₁₁ N ₃ OS	64.50 64.36	3.25 3.38	15.04 14.81	S 11.48 S 11.27
I c-51		300-302	Yellow	EtOH-CHCl ₃	C ₁₁ H ₁₁ N ₃ OS	64.50 64.50	3.25 3.43	15.04 14.99	S 11.48 S 11.39
I c-52		335(d)	Yellow	DMF	C ₁₁ H ₈ N ₃ OSCl	57.42 57.29	2.57 2.83	13.39 13.41	S 10.22, Cl 11.30 S 10.26, Cl 11.44
I c-53		320-323(d)	Yellow	EtOH-CHCl ₃	C ₁₁ H ₁₁ N ₃ OS	65.51 65.58	3.78 3.87	14.32 14.32	S 10.93 S 10.79
I c-54		306-308(d)	Yellow	EtOH-CHCl ₃	C ₁₁ H ₁₁ N ₃ OS	65.51 65.46	3.78 3.96	14.32 14.24	S 10.93 S 10.96

Table 4-1 (No. 3)

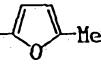
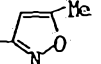
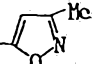
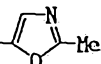
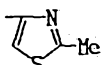
I c-55		291(d)	Yellow	EtOH-CHCl ₃	C ₁₅ H ₁₁ N ₃ O ₅	65.51 65.19	3.78 3.89	14.32 14.03	S 10.93 S 10.85
I c-56		305-307(d)	Yellow	EtOH-CHCl ₃	C ₁₅ H ₁₁ N ₃ O ₂	68.44 68.56	3.45 3.51	15.96 16.07	
I c-57		316-318(d)	Yellow	EtOH-CHCl ₃	C ₁₅ H ₁₁ N ₃ O ₂	69.31 69.31	4.00 3.94	15.15 15.16	
I c-58		295-297(d)	Colorless	EtOH	C ₁₅ H ₁₁ N ₃ O ₂	68.44 68.73	3.45 3.63	15.96 16.05	
I c-59		263-265(d)	Yellow	EtOH	C ₁₅ H ₁₁ N ₄ O ₂	63.63 63.74	3.05 3.23	21.20 20.96	
I c-60		276-278(d)	Yellow	EtOH-CHCl ₃	C ₁₅ H ₁₁ N ₄ O ₂	64.74 64.98	3.62 3.78	20.13 19.97	
I c-61		330(d)	Yellow	EtOH-CHCl ₃	C ₁₅ H ₁₁ N ₄ O ₂	64.74 64.65	3.62 3.60	20.13 19.97	
I c-62		291-293(d)	Light yellow	EtOH-CHCl ₃	C ₁₅ H ₁₁ N ₄ O ₂	64.74 65.05	3.62 3.75	20.13 19.79	
I c-63		325(d)	Light yellow	MeOH-CHCl ₃	C ₁₅ H ₁₁ N ₄ O ₅	61.21 61.29	3.42 3.62	19.04 18.71	S 10.89 S 10.69

Table 4-2 (No. 1)

Compd.No	NMR (DMSO-d ₆) δ
I c-37	7.30~7.97 (5H,m), 8.00~8.33 (2H,m), 8.53~8.80 (1H,m), 9.37 (1H,s)
I c-38	7.55~7.95 (4H,m), 8.07~8.27 (1H,m), 8.30~8.53 (2H,m), 8.60~8.80 (1H,m), 9.40 (1H,s)
I c-39	7.20~7.90 (4H,m), 8.10~8.45 (2H,m), 8.55~8.85 (1H,m), 9.33 (1H,s)
I c-40	7.70~8.30 (5H,m), 8.60~8.80 (1H,m), 8.83~9.03 (2H,m), 9.40 (1H,s)
I c-41	7.60~7.90 (4H,m), 8.05~8.25 (1H,m), 8.55~8.80 (3H,m), 9.37 (1H,s)
I c-42	7.50~8.00 (6H,m), 8.15~8.30 (1H,m), 8.50~8.80 (1H,m), 9.33 (1H,s)
I c-43	7.60~7.95 (4H,m), 8.10~8.35 (1H,m), 8.50~8.80 (3H,m), 9.40 (1H,s)
I c-44	3.93 (3H,s), 7.20 (2H,d), 7.65~7.93 (2H,m), 8.05~8.30 (1H,m), 8.60~8.85 (3H,m), 9.40 (1H,s)
I c-45	2.60 (3H,s), 7.47 (2H,d), 7.65~7.90 (2H,m), 8.10~8.30 (1H,m), 8.55~8.80 (3H,m), 9.37 (1H,s)
I c-46	2.45 (3H,s), 7.45 (2H,d), 7.65~7.90 (2H,m), 8.07~8.30 (1H,m), 8.50~8.80 (3H,m), 9.37 (1H,s)

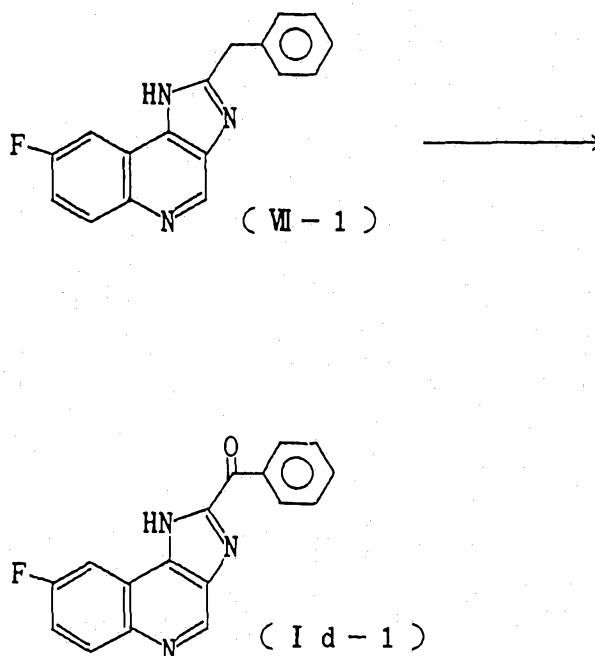
Compd.No	NMR (DMSO-d ₆) δ
I c-47	2.47 (3H,s), 7.45~7.90 (4H,m), 8.05~8.80 (4H,m), 9.40 (1H,s)
I c-48	7.65~7.90 (2H,m), 8.10~8.30 (1H,m), 8.33~8.47 (2H,m), 8.60~8.80 (1H,m), 8.90~9.05 (2H,m), 9.40 (1H,s)
I c-49	7.60~7.90 (3H,m), 8.10~8.25 (1H,m), 8.65~9.00 (3H,m), 9.40 (1H,s), 9.63~9.80 (1H,m)
I c-50	7.30~7.45 (1H,m), 7.60~7.90 (2H,m), 8.05~8.33 (2H,m), 8.55~8.90 (2H,m), 9.37 (1H,s)
I c-51	7.65~7.90 (3H,m), 7.95~8.30 (2H,m), 8.63~8.80 (1H,m), 9.37 (1H,s), 9.40~9.50 (1H,m)
I c-52	7.65~7.90 (2H,m), 7.97 (1H,d), 8.05~8.30 (1H,m), 8.65~8.80 (1H,m), 9.25 (1H,d), 9.35 (1H,s)
I c-53	2.60 (3H,s), 7.13 (1H,d), 7.65~7.85 (2H,m), 8.05~8.30 (1H,m), 8.60~8.80 (2H,m), 9.35 (1H,s)
I c-54	2.37 (3H,s), 7.65~7.90 (3H,m), 8.10~8.30 (1H,m), 8.60~8.80 (2H,m), 9.40 (1H,s)
I c-55	2.70 (3H,s), 7.20 (1H,d), 7.65~7.90 (2H,m), 8.05~8.30 (1H,m), 8.07 (1H,d), 8.60~8.80 (1H,m), 9.37 (1H,s)
I c-56	6.83~6.97 (1H,m), 7.63~7.90 (2H,m), 8.10~8.30 (2H,m), 8.50 (1H,d), 8.60~8.77 (1H,m), 9.37 (1H,s)

Table 4-2 (No. 2)

Compd. No.	NMR (DMSO-d ₆) δ
I c-57	2.47 (3H,s), 6.57 (1H,d), 7.65~7.90 (2H,m), 8.10~8.30 (1H,m), 8.45 (1H,d), 8.60~8.80 (1H,m), 9.35 (1H,s)
I c-58	7.23 (1H,d), 7.65~7.90 (2H,m), 7.97 (1H,m), 8.05~8.30 (1H,m), 8.60~8.85 (1H,m), 9.30 (1H,d), 9.37 (1H,s)
I c-59	7.57 (1H,d), 7.70~7.90 (2H,m), 8.10~8.30 (1H,m), 8.60~8.80 (1H,m), 7.30 (1H,d), 7.40 (1H,s)
I c-60	2.59 (3H,s), 7.23 (1H,s), 7.60~7.90 (2H,m), 8.05~8.30 (1H,m), 8.55~8.75 (1H,m), 9.37 (1H,s)
I c-61	* Not measured, as it was difficult to dissolve the compound
I c-62	2.53 (3H,s), 7.65~7.85 (2H,m), 8.05~8.25 (1H,m), 8.55~8.80 (1H,m), 9.31 (1H,s), 9.47 (1H,s)
I c-63	* Measuring solvent CDCl ₃ -CD ₃ OD, 2.85 (3H,s), 8.65~8.90 (2H,m), 8.10~8.30 (1H,m), 8.40~8.60 (1H,m), 9.30 (1H,s), 9.55 (1H,s)

Example 64

2-Benzoyl-8-fluoro-1H-imidazo[4,5-c]quinoline (Id-1)



To a suspension of 830 mg of 2-benzyl-8-fluoro-1H-imidazo[4,5-c]-quinoline (VII-1) in 50 ml of dioxane heated to 80°C was added 1.07 g of selenium dioxide. The reaction mixture was refluxed for 1.5 hours. The resulting precipitate was immediately removed by filtration and concentrated under reduced pressure, and the residue obtained was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate. The organic layer was washed with water and saturated brine, and dried. The ethyl acetate was removed and the residue was chromatographed on a column of silica gel for purification. After

elution with chloroform - methanol (30:1 v/v), 820 mg (yield 94%) of the compound (I d-1) was obtained as crystals. This was recrystallized from ethanol - chloroform to give light yellow crystals melting at 255 ~ 256 °C.

Anal. Calcd. (%) for $C_{17}H_{10}N_3OF$

: C, 70.10; H, 3.46; N, 14.43; F, 6.52

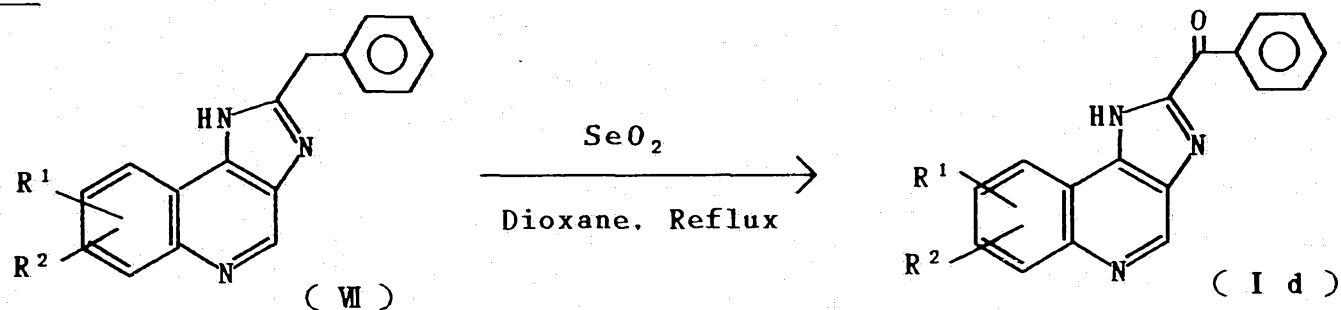
Found (%): C, 70.22; H, 3.57; N, 14.43; F, 6.64

NMR (DMSO- d_6) δ : 7.50~7.90 (4H, m), 8.07~8.47 (2H, m),
8.53~8.75 (2H, m), 9.31 (1H, s).

Examples 65 ~ 67

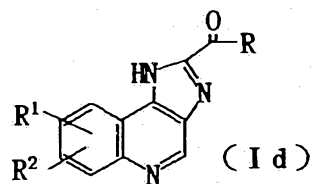
In the same manner as in Example 64, the objective compounds (I d) were obtained under the reaction conditions shown in Table 5. The physical properties of the compounds were shown in Tables 6-1 and 6-2.

Table 5



Ex.	Amount of Compound (VI)			Selenium dioxide	Dioxane	Reflux Time	Compound (Id)		
	No.	R ¹	R ²	(mg)	(ml)	(hr)	Yield		Compd. No.
							(mg)	(%)	
65		H	H	300	420	1	285	90	I d-2
66		7-F	H	700	1000	2	270	37	I d-3
67		7-OMe	H	500	615	1	335	64	I d-4

Table 6-1



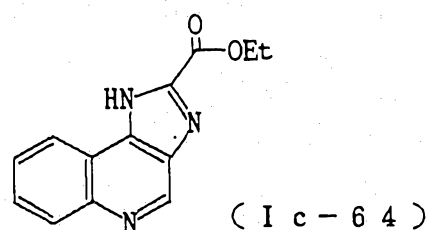
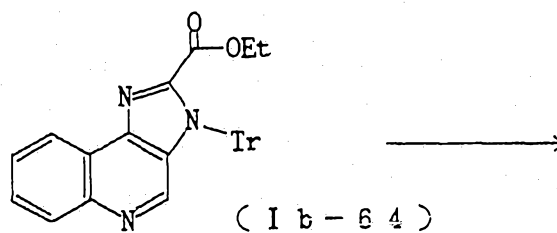
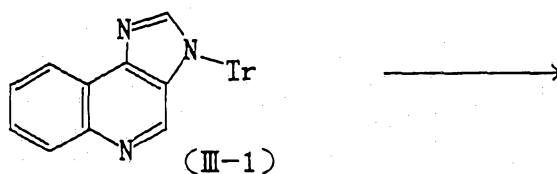
Compd. No.	R	R ¹	R ²	m. p. (°C)	Appearance	Solvent for Re-crystalln.	Molecular Formula	Elementary Analysis (%) Up (Calcd.), Down (Found)			
								C	H	N	
I d-2		H	H	285-287	Colorless	EtOH	C ₁₇ H ₁₁ N ₃ O	74.71 74.85	4.06 4.16	15.38 15.22	
I d-3		7-F	H	318-320(d)	Light yellow	EtOH-CHCl ₃	C ₁₇ H ₁₀ N ₃ OF	70.10 70.21	3.46 3.53	14.43 14.45	F 6.52 F 6.55
I d-4		7-OMe	H	322-324(d)	Colorless	EtOH-CHCl ₃	C ₁₈ H ₁₃ N ₃ O ₂	71.28 71.36	4.32 4.25	13.85 13.61	

Table 6-2

Compd. No.	NMR (DMSO-d ₆), δ
I d-2	7.53~7.90 (5H,m), 8.17~8.27 (1H,m), 8.53~8.70 (3H,m), 9.37 (1H,s)
I d-3	7.50~7.97 (5H,m), 8.53~8.85 (3H,m), 9.37 (1H,s)
I d-4	3.95 (3H,s), 7.30~7.90 (5H,m), 8.47~8.80 (3H,m), 9.33 (1H,s)

Example 68

2-Ethoxycarbonyl-1H-imidazo[4,5-c]quinoline (I c-64)



To a solution prepared in the same manner as in Example 1 from 410 mg of the compound (III-1) in 5 ml of THF and a mixture of 1 ml of 1.6 M solution of n-butyl lithium in hexane - 5 ml of THF was added 350 mg of ethyl chloroformate. The reaction mixture was warmed to

room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate. The organic layer was washed with water and saturated brine, and dried. After evaporating the ethyl acetate, the residue was crystallized from n-hexane to give 455 mg of the compound (I b-64) as crude crystals. The compound (I b-64) was dealkylated by mixing with 4 ml of trifluoroacetic acid. After treatment in the same manner as in Example 1, the crude product was chromatographed on a column of silica gel for purification. After elution with chloroform - methanol (10:1 v/v) and evaporation of the fraction obtained, the residue was crystallized from n-hexane to give 200 mg (yield : 83%) of the titled compound (I c-64). This was recrystallized from ethyl acetate to give colorless crystals melting at 198 ~ 200 °C.

Anal. Calcd. (%) for $C_{13}H_{11}N_3O_2$

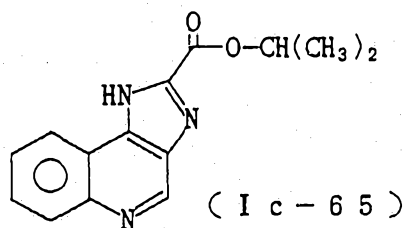
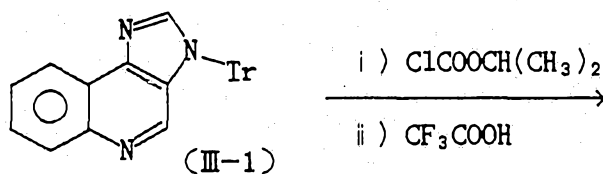
: C, 64.72; H, 4.60; N, 17.42

Found (%) : C, 64.74; H, 4.58; N, 17.43

NMR (DMSO- d_6) δ : 1.42 (3H, t), 4.50 (2H, q), 7.60~7.90 (2H, m),
8.05~8.30 (1H, m), 8.55~8.75 (1H, m), 9.33 (1H, s)

Example 69

2-Isopropyloxycarbonyl-1H-imidazo[4,5-c]quinoline (Ic-65)



In the same manner as in Example 68, isopropyl chloroformate was allowed to react with III-1 to give the titled compound (Ic-65) in 50 % yield. This was recrystallized from ethyl acetate to give colorless crystals melting at 245 ~ 247 °C.

Anal. Calcd. (%) for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2$

: C, 65.87; H, 5.13; N, 16.46

Found (%) : C, 65.80; H, 5.24; N, 16.42

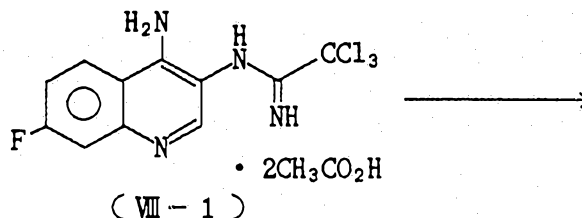
NMR (DMSO-d_6) δ : 1.43 (6H, d), 5.30 (1H, septet),

7.60~7.85 (2H, m), 8.05~8.25 (1H, m), 8.50~8.70 (1H, m),

9.30 (1H, s)

Example 70

2-Ethoxycarbonyl-7-fluoro-1H-imidazo[4,5-c]quinoline (I e-1)



A solution of 1.15 g of 4-amino-7-fluoro-3-(trichloroacetimidoyl-amino)quinoline diacetate (VII-1) in 120 ml of ethanol was heated under reflux for two hours. The reaction mixture was concentrated under reduced pressure, and the residue was added to ice-water. After being basified with 2 N aqueous ammonia, the mixture was extracted with chloroform. The extract was washed with water and brine, and then dried. The chloroform was removed by evaporation. The residue was chromatographed on a column of silica gel with chloroform - methanol (100:1 v/v), whereby 395 mg (yield : 59 %) of the titled compound (I e-1) was obtained as crystals. These were recrystallized

from chloroform - ethanol to give colorless crystals melting at 238 ~ 240 °C (d).

Anal. Calcd. (%) for $C_{13}H_{10}N_3O_2F$

: C, 60.23; H, 3.89; N, 16.21; F, 7.33

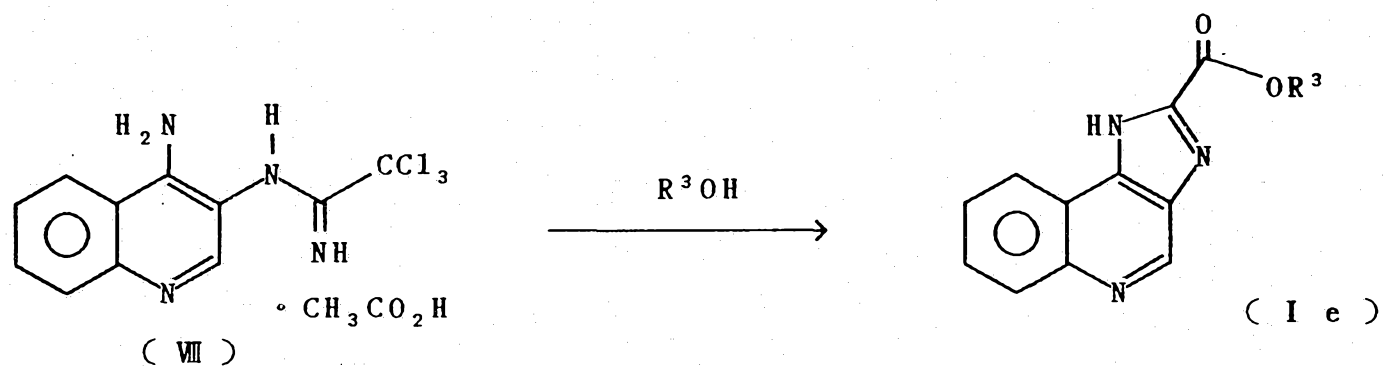
Found (%) : C, 60.16; H, 4.03; N, 16.29; F, 7.41

NMR (DMSO- d_6) δ : 1.41 (3H, t), 4.49 (2H, q), 7.50~8.10 (2H, m),
8.60~8.80 (1H, m), 9.33 (1H, s)

Examples 71 ~ 72

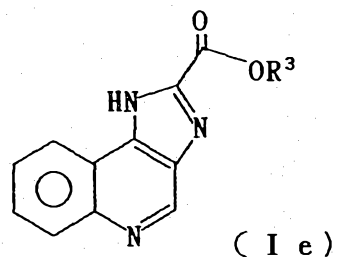
In the same manner as in Example 70, the objective compounds (I e) were obtained under reaction conditions shown in Table 7. The physical properties of the compounds were shown in Tables 8-1 and 8-2.

Table 7



Ex. No.	R ³	Amount of VIII (mg)	R ³ OH (ml)	Reaction Temp. (°C)	Reaction Time (hr)	Compound (I e)		
						Yield		Compd. No.
						(mg)	(%)	
71	-CH ₃	800	20	Reflux	16	234	47	I e-2
72	-(CH ₂) ₂ CH ₃	182	20	80	4	68	53	I e-3

Table 8-1



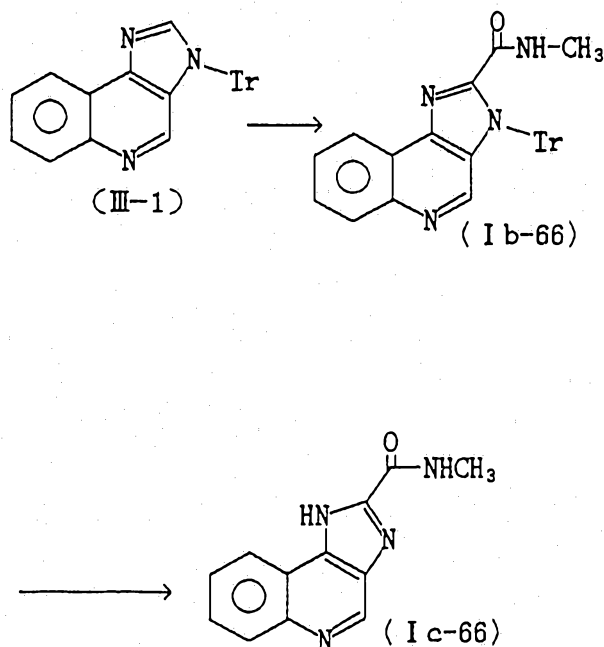
Compd. No.	R ³	m.p. (°C)	ap- pear- ance	Solvent for recrysta- lln.	Molecular Formula	Elementary Analysis (%) Up (Calcd.), Down (Found)		
						C	H	N
I e-2	-CH ₃	218-219(d)	Color- less	EtOH-CHCl ₃	C ₁₂ H ₉ N ₃ O ₂	63.42 63.14	3.99 3.99	18.49 18.21
I e-3	-(CH ₂) ₂ CH ₃	214-217	Color- less	EtOH-CHCl ₃	C ₁₄ H ₁₃ N ₃ O ₂	65.87 65.43	5.13 5.21	16.46 16.50

Table 8-2

Compd. No.	NMR (DMSO-d ₆), δ
I e-2	4.00 (3H,s), 7.60~8.70 (4H,m), 9.27 (1H,s)
I e-3	1.00 (3H,t), 1.80 (2H,m), 4.37 (2H,t), 7.60~8.80(4H,m), 9.27 (1H,s)

Example 73

2-Methylcarbamoyl-1H-imidazo[4,5-c]quinoline (I c-66)



To a solution prepared in the same manner as in Example 1 from 1.23 g of the compound (III-1) in 30 ml of THF and a mixture of 4 ml of 1.6 M solution of n-butyl lithium in hexane - 4 ml of THF was added 770 mg of methyl isocyanate. The reaction mixture was gradually warmed to room temperature and concentrated under reduced pressure. Water was added to the residue, and the product was extracted with ethyl acetate. The extract was washed with water and brine, and then dried. The ethyl acetate was removed and the residue was crystallized from ether to give 990 mg of the compound (I b-66) as crude crystals. The compound (I b-66) was dealkylated by mixing with 4 ml of tri-

fluoroacetic acid and stirred for 30 min. at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was neutralized with saturated aqueous sodium hydrogencarbonate. The crystals precipitated were collected by filtration, washed with water and ethanol, and then dried to give 410 mg (yield : 61%) of the titled compound (I c-66). The compound (I c-66) was recrystallized from ethanol - chloroform to give colorless crystals, m.p. at 322 °C (s).

Anal Calcd. (%) for $C_{12}H_{10}N_4C$

: C, 63.71; H, 4.46; N, 24.76

Found (%) : C, 63.60; H, 4.60; N, 24.48

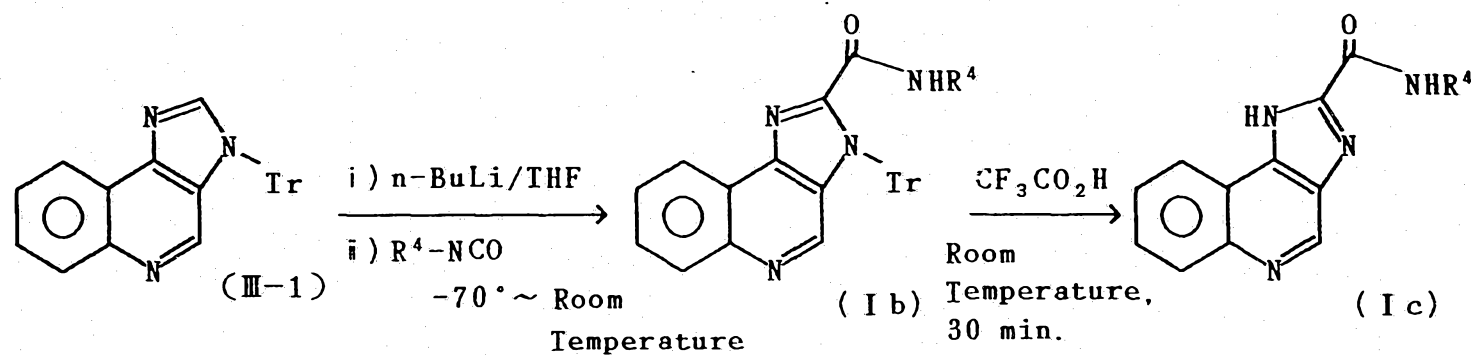
NMR (DMSO- d_6 - CD_3OD) δ : 3.93 (3H, s), 7.57~7.90 (2H, m),

8.07~8.30 (1H, m), 8.55~8.80 (1H, m), 9.27 (1H, s)

Examples 74 ~ 76

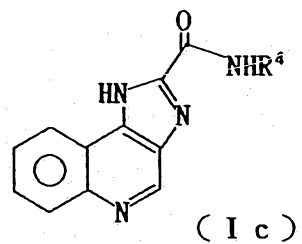
In the same manner as in Example 73, the objective compounds (I c) were obtained under the reaction conditions shown in Table 9. The physical properties of the compounds were shown in Tables 10-1 and 10-2.

Table 9



Ex. No.	R ⁴	1st Step				2nd Step	Compound (I c)			
		Amount of III -1 (g)	Solvent THF (ml)	n-BuLi-THF		R ⁴ NCO (g)	CF ₃ CO ₂ H (ml)	Yield		Compd. No.
				(ml)	(ml)			(mg)	(%)	
74	-C ₂ H ₅	1.23	25	2.5	2	0.63	4	300	42	I c-67
75	-(CH ₂) ₂ CH ₃	1.23	25	2.5	2	0.68	3	260	34	I c-68
76	-CH(CH ₃) ₂	1.23	25	2.5	2	0.69	4	540	71	I c-69

Table 10-1



Compd. No.	R ⁴	m.p. (°C)	Appear- ance	Solvent for Recrys- talln.	Molecular Formula	Elementary Analysis(%) Up (Calcd.), Down (Found)		
						C	H	N
I c-67	-C ₂ H ₅	296-297	Colorless	EtOH-CHCl ₃	C ₁₃ H ₁₂ N ₄ O	64.99 64.92	5.03 5.23	23.32 23.19
I c-68	-(CH ₂) ₂ CH ₃	253-254	Colorless	EtOH	C ₁₄ H ₁₄ N ₄ O	66.13 66.12	5.55 5.47	22.03 21.92
I c-69	-CH(CH ₃) ₂	263-264	Colorless	EtOH	C ₁₄ H ₁₄ N ₄ O	66.13 66.08	5.55 5.57	22.03 21.96

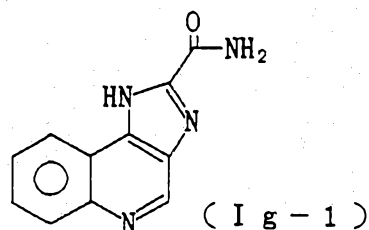
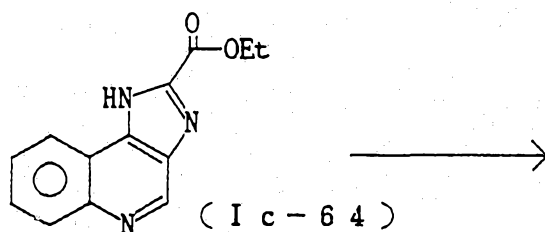
14 0000

Table 10-2

Compound No.	NMR (DMSO-d ₆) δ
I c-67	1.17 (3H,t), 3.20~3.57 (2H,m), 7.60~7.90 (2H,m), 8.05~8.30 (1H,m), 8.55~8.80 (1H,m), 9.13 (1H,t), 9.37 (1H,s)
I c-68	0.93 (3H,t), 1.65 (2H,t,q), 3.35 (2H,d,t), 7.60~7.90 (2H,m), 8.10~8.30 (1H,m), 8.55~8.80 (1H,m), 9.10 (1H,t), 9.30 (1H,s)
I c-69	1.27 (6H,d), 4.05~4.45 (1H,m), 7.65~7.90 (2H,m), 8.10~8.30 (1H,m), 8.10~8.30 (1H,m), 8.55~8.75 (1H,m), 8.87 (1H,d), 9.30 (1H,s)

Example 77

2-Carbamoyl-1H-imidazo[4,5-c]quinoline (I g-1)



A mixture of 30 ml of 28% aqueous ammonia and 1.00 g of the compound (I c-64) was heated at 100 °C for two hours in a sealed tube. The reaction mixture was concentrated to 20 ml of the volume, and the resulting crystals were washed successively with water, ethanol, and n-hexane, whereby 688 mg (yield : 74%) of the titled compound (I g-1) was obtained. This was recrystallized from methanol - chloroform to give colorless crystals, m.p. 326 ~ 328 °C.

Anal. Calcd. (%) for $C_{11}H_8N_4O \cdot \frac{2}{3} H_2O$

: C, 58.92; H, 4.20; N, 24.99

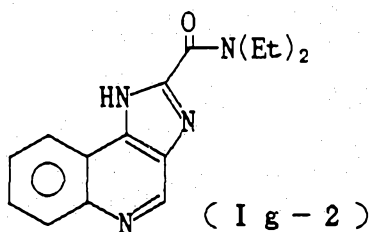
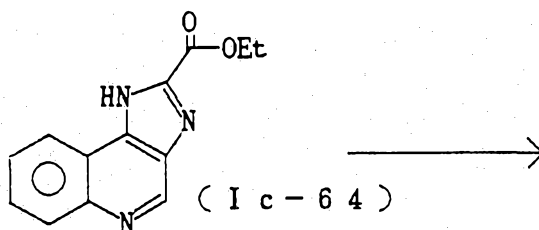
Found (%) : C, 58.95; H, 4.02; N, 24.95

Mass spectrum : m/z , 212 (M^+)

NMR ($DMSO-d_6$ - CD_3OD) δ : 7.55~7.85 (2H, m), 8.05~8.25 (1H, m),
8.55~8.75 (1H, m), 9.23 (1H, s)

Example 78

2-Diethylcarbamoyl-1H-imidazo[4,5-c]quinoline (I g-2)



To a solution of 560 mg of the compound (I c-64) in 10 ml of ethanol was added 4.8 ml of 1 N aqueous sodium hydroxide, and the mixture was refluxed for one hour. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 10 ml of water, and acidified with 5.2 ml of 1N aqueous hydrochloric acid.

The precipitated crystals were collected by filtration, washed with water and dried, whereby 440 mg of carboxylic acid were obtained as crude crystals. These were suspended in 8 ml of thionyl chloride, and the suspension was refluxed for 30 min. The excess thionyl chloride was evaporated under reduced pressure, and 10 ml of toluene was added to the residue. After stirring the mixture, the toluene was evaporated under reduced pressure. To a suspension of the resulting residue in 10 ml of dichloromethane was added 2 ml of diethylamine at room temperature, and the mixture was stirred vigorously for 30 min. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and then dried. The ethyl acetate was removed and the residue was chromatographed on a column of silica gel for purification. The fraction eluted with chloroform - methanol (10:1 v/v) was concentrated and the residue was crystallized from n-hexane to give 110 mg (yield : 10%) of the titled compound (I g-2). This was recrystallized from ethyl acetate - n-hexane to give colorless crystals melting at 179 ~ 181 °C.

Anal. Calcd. (%) for $C_{15}H_{16}N_4O$

: C, 67.15; H, 6.01; N, 20.88

Found (%) : C, 67.05; H, 6.00; N, 20.52

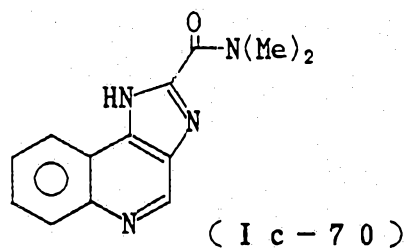
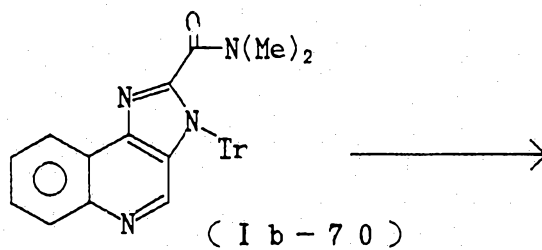
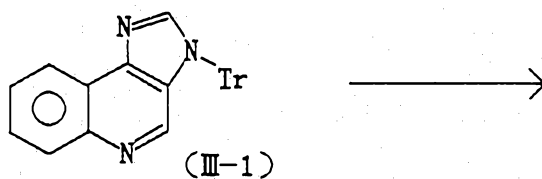
NMR (DMSO- d_6), δ : 1.23 (3H, t), 1.31 (3H, t), 3.57 (2H, q),

4.13 (2H, q), 7.60~7.90 (2H, m), 8.03~8.30 (1H, m),

8.53~8.80 (1H, m), 9.29 (1H, s)

Example 79

2-Dimethylcarbamoyl-1H-imidazo[4,5-c]quinoline (I c-70)



In the same manner as in Ex. 1, to a solution containing 1.23 g of the compound (III-1) in 25 ml of THF and a mixture of 2.5 ml of 1.6 M solution of n-butyl lithium in hexane - 2 ml of THF was added 930 mg of dimethylcarbonyl chloride, and the usual workup gave 610 mg of the compound (I b-70) as crude crystals. The compound (I b-70) was dealkylated by mixing with 3 ml of trifluoroacetic acid. The crude crystals were chromatographed on a column of silica gel with chloroform - methanol (30:1 v/v), whereby 280 mg (yield : 39%) of the titled compound (I c-70) was obtained. This was recrystallized from ethanol to give colorless crystals, m.p. 284 ~ 286 °C.

Anal. Calcd. (%) for $C_{13}H_{12}N_4O$

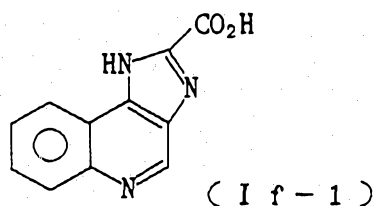
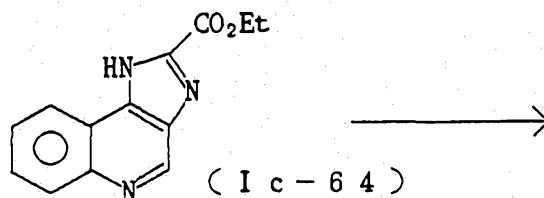
: C, 64.99; H, 5.03; N, 23.32

Found (%) : C, 65.17; H, 5.15; N, 23.25

NMR (DMSO- d_6), δ : 3.15 (3H, s), 3.67 (3H, s), 7.60~7.90 (2H, m), 8.05~8.25 (1H, m), 8.55~8.75 (1H, m), 9.27 (1H, s)

Example 80

2-Carboxy-1H-imidazo[4,5-c]quinoline (I f-1)



To a solution of 240 mg of the compound (Ic-64) in 4 ml of ethanol was added 2 ml of 1N aqueous sodium hydroxide, and the mixture was refluxed for one hour. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 5 ml of water, and acidified with 2.2 ml of 1N aqueous hydrochloric acid. The precipitated crystals were collected by filtration, washed with water, and dried at room temperature under reduced pressure to give 200 mg (yield : 94 %) of the titled compound (I f-1).

Melting point : 165 ~ 167 °C (d)

Anal. Calcd. (%) for C₁₁H₇N₃O₂

: C, 61.97; H, 3.31; N, 19.71

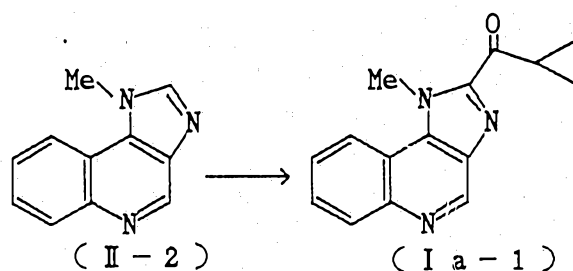
Found (%) : C, 61.88; H, 3.51; N, 19.65

NMR (DMSO- d_6) δ : 7.55~7.95 (2H, m), 8.05~ 8.35 (1H, m),

8.50~8.85 (1H, m), 9.30 (1H, s)

Example 81

2-Cyclopropylcarbonyl-1-methyl-1H-imidazo[4,5-c]quinoline (I a-1)



In the same manner as in Ex. 1, to a solution containing 550 mg of 1-methyl-1H-imidazo[4,5-c]quinoline (II-2) in 25 ml of THF and a mixture of 2.2 ml of 1.6 M solution of n-butyl lithium in hexane - 2 ml of THF was added 0.75 g of cyclopropanecarbonyl chloride. The reaction mixture was gradually warmed to room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and aqueous ammonia. The organic layer was washed with water and brine, and then dried. The ethyl acetate was removed by evaporation, and the residue was chromatographed on a column of silica gel for purification. The fraction eluted with ethyl acetate was concentrated and the residue was crystallized from n-hexane to give

275 mg (yield : 36%) of the titled compound (I a-1). This was recrystallized from ethyl acetate -n-hexane to give colorless crystals melting at 156 ~ 158°C.

Anal. Calcd. (%) for $C_{16}H_{13}N_3O$

: C, 71.70; H, 5.21; N, 16.72

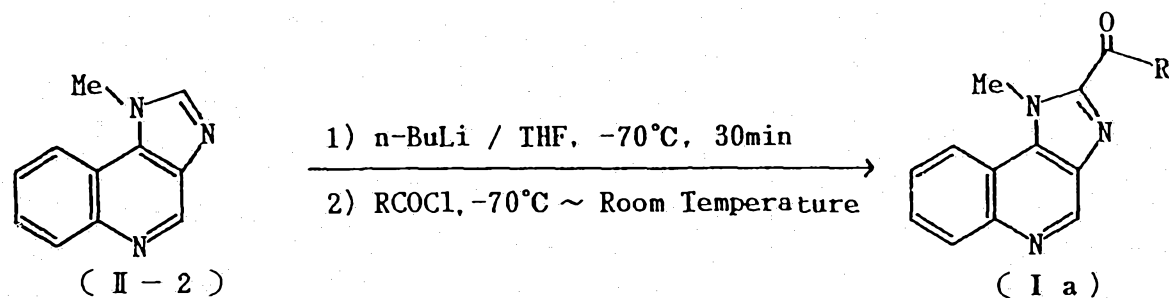
Found (%) : C, 71.62; H, 5.13; N, 16.64

NMR (DMSO- d_6) δ : 1.05~1.45 (4H, m), 3.45~3.75 (1H, m),
4.63 (3H, s), 7.55~7.85 (2H, m), 8.35~8.50 (2H, m),
9.40(1H, s)

Example 82 - 83

In the same manner as in Ex. 81, the objective compounds (I a) were obtained under the reaction conditions shown in Table 11. The physical properties of the compounds were shown in Tables 12-1 and 12-2.

Table 11



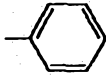
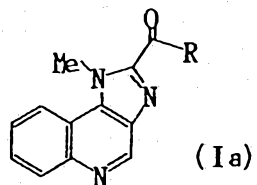
Ex. No.	Amount of Compd. II -2 (g)	Solvent THF (ml)	RCOCl		n-BuLi - THF		Compound (I a)		Compd. No.
			R	(g)	(ml)	(ml)	Yield		
							(mg)	(%)	
82	0.55	25		1.15	2.5	2	290	34	I a -2
83	0.55	25	-OEt	0.80	2.5	2	290	38	I a -3

Table 12-1

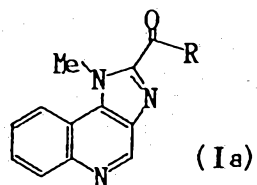


Compd. No.	R	m.p. (°C)	Appear- ance	Solvent for Recrysta- lln.	Molecular Formula	Elementary Analysis(%)		
						Up (Calcd.) Down (Found)		
						C	H	N
I a- 2		195-197	Color- less	AcOEt	C ₁₈ H ₁₃ N ₃ O	75.25	4.56	14.62
						75.55	4.56	14.66
I a- 3	-OEt	149-151	Color- less	AcOEt- n-Hexane	C ₁₄ H ₁₃ N ₃ O ₂	65.87	5.13	16.46
						65.87	5.10	16.42

Table 12-2

Compound No.	NMR (CDCl ₃) δ
I a- 2	4.60 (3H,s), 7.40~7.85 (5H,m), 8.20~8.50 (4H,m), 9.40 (1H,s)
I a- 3	1.50 (3H,t), 4.55 (2H,q), 4.63 (3H,s), 7.55~7.85 (2H,m), 8.20~8.45 (2H,m), 9.40 (1H,s)

Table 12-1



Compd. No.	R	m.p. (°C)	Appear- ance	Solvent for Recrysta- lln.	Molecular Formula	Elementary Analysis(%)		
						Up (Calcd.) Down (Found)	C	H
I a- 2		195-197	Color- less	AcOEt	C ₁₈ H ₁₃ N ₃ O	75.25	4.56	14.62
						75.55	4.56	14.66
I a- 3	-OEt	149-151	Color- less	AcOEt- n-Hexane	C ₁₄ H ₁₃ N ₃ O ₂	65.87	5.13	16.46
						65.87	5.10	16.42

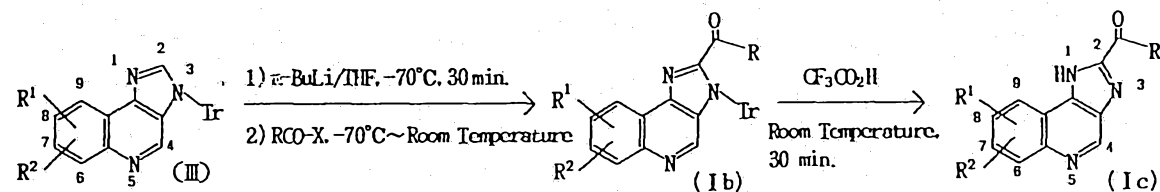
Table 12-2

Compound No.	NMR (CDCl ₃) δ
I a- 2	4.60 (3H,s), 7.40~7.85 (5H,m), 8.20~8.50 (4H,m), 9.40 (1H,s)
I a- 3	1.50 (3H,t), 4.55 (2H,q), 4.63 (3H,s), 7.55~7.85 (2H,m), 8.20~8.45 (2H,m), 9.40 (1H,s)

Examples 84 - 90

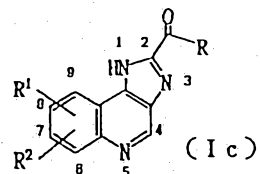
In the same manner as in Examples 1, 2, 35, or 36, the objective compounds (Ic) were obtained under the reaction conditions shown in Table 13. The properties of the compounds were shown in Tables 14-1 and 14-2.

Table 13



Ex No	R	1st Step								2nd Step	Compound (Ic)		
		Amount of Compd. (III)				n-BuLi-THF (ml) (ml)		RCO-X		CF ₃ CO ₂ H (ml)	Yield		Compd. No
		R ¹	R ²	(g)	Solvent THF(ml)			X	(g)		(mg)	(%)	
84		8-F	H	1.28	90	2	2	Cl	1.10	3	50	6	Ic-71
85		8-F	H	1.28	90	2	2	Cl	1.05	4	470	56	Ic-72
86		7-F	H	1.29	80	2.2	2	OMe	1.1	4	270	28	Ic-73
87		H	H	1.23	25	2.5	2	Cl	1.70	4	460	45	Ic-74
88	-(CH ₂) ₂ -Ph	7-F	H	1.29	80	2.2	2	Cl	1.36	3	155	16	Ic-75
89		8-OMe	H	1.32	30	2.5	2	Cl	1.04	4	310	39	Ic-76
90	-CH(CH ₃) ₂	8-OMe	H	1.32	30	2.5	2	-OCOCH(CH ₃) ₂	1.33	4	630	78	Ic-77

Table 14-1



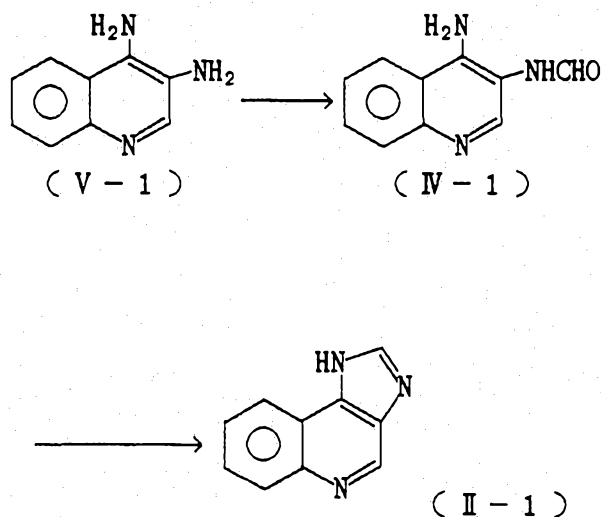
Compd. No.	R ¹	R ²	R	m.p. (°C)	Appearance	Recrystallizing Solvent	Molecular Formula	Elementary Analysis (%)			
								Up (Calcd.)	Down (Found)		
I c-71	8-F	H		275-277 (d)	Colorless	EtOH	C ₁₅ H ₁₁ N ₃ O ₂ F	60.81 61.02	3.06 3.28	18.91 18.81	F, 6.41 F, 6.47
I c-72	8-F	H		310-312	Light yellow	EtOH - CHCl ₃	C ₁₅ H ₁₁ N ₃ O ₂ F	64.06 64.03	2.87 2.93	14.94 14.92	F, 6.75 F, 6.73
I c-73	7-F	H		> 310	Light yellow	DMF	C ₁₅ H ₁₁ N ₃ O ₂ FS	61.73 61.56	3.24 3.40	13.50 13.44	F, 6.10 S, 10.30 F, 6.10 S, 10.30
I c-74	H	H		295-297 (d)	Light yellow	EtOH - CHCl ₃	C ₁₅ H ₁₁ N ₃ O ₂	70.58 70.78	3.55 3.69	16.46 16.26	
I c-75	7-F	H	-(CH ₂) ₂ -Ph	274-276	Colorless	EtOH - CHCl ₃	C ₁₅ H ₁₁ N ₃ OF	71.46 71.72	4.42 4.58	13.16 13.31	F, 5.95 F, 6.15
I c-76	8-OMe	H		185-187 (d)	Colorless	EtOH	C ₁₅ H ₁₁ N ₃ O ₂	67.41 67.16	4.90 4.79	15.72 15.58	
I c-77	8-OMe	H	-CH(CH ₂) ₂	188-190	Colorless	AcOEt	C ₁₅ H ₁₅ N ₃ O ₂	66.90 66.89	5.61 5.66	15.60 15.53	

Table 14-2

Compd. No	NMR (DMSO-d ₆) δ
I c-71	2.63 (3H,s), 7.23 (1H,s), 7.50~7.75 (1H,m), 8.10~8.40 (2H,m), 9.30 (1H,s)
I c-72	7.17 (1H,d), 7.47~7.77 (1H,m), 7.93 (1H,d), 8.05~8.45 (2H,m), 9.37 (2H,s)
I c-73	2.61 (3H,s), 7.13 (1H,d), 7.55~7.97 (2H,m), 8.65~8.85 (2H,m), 9.30 (1H,s)
I c-74	Measuring Solvent CDCl ₃ - CD ₃ OD 7.45~8.05 (8H,m), 8.10~8.30 (1H,m), 8.50~8.70 (1H,m), 9.40 (1H, s)
I c-75	3.07 (2H,t), 3.60 (2H,t), 7.10~7.45 (5H,m), 7.50~7.95 (2H, m), 8.55~8.80 (1H, m), 9.33 (1H, s)
I c-76	1.35 (4H,d), 3.37 (1H,quintet), 3.97 (3H,s) 7.37 (1H, d,d), 7.97~8.20 (2H,m), 9.27 (1H,s)
I c-77	1.30 (6H,d), 3.90 (1H,septet), 3.97 (3H,s), 7.37 (1H,d,d), 8.00~8.15 (2H,m), 9.15 (1H,s)

Referential Example 1

1H-Imidazo[4,5-c]quinoline (II-1)



A solution of 5.0 g of 3, 4-diaminoquinoline (V-1) in 15 ml of formic acid was refluxed for one hour. The reaction solution was concentrated under reduced pressure, and the residue obtained was neutralized with saturated aqueous sodium hydrogencarbonate. This was allowed to stand overnight. The precipitated crystals were collected by filtration, washed with water, and dried to give 5.6 g of crystals (IV-1). The crystals were suspended in 120 ml of diglyme, and the suspension was refluxed for 1.5 hours. The reaction mixture was cooled down and the precipitated crystals were collected by filtration, and washed with ethyl acetate and n-hexane, successively, to give 5.1 g (yield : 96%) of the titled compound (II-1). This was recrystallized from ethanol to give colorless crystals melting at 294 ~ 296 °C.

Anal. Calcd. (%) for $C_{10}H_7N_3$

: C, 70.99; H, 4.17; N, 24.84

Found (%) : C, 71.12; H, 4.27; N, 24.76

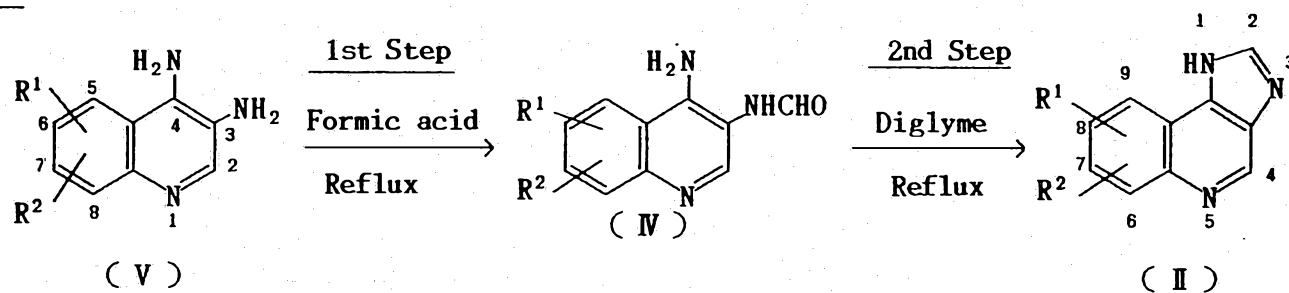
NMR (DMSO- d_6) δ : 7.50~7.85 (2H, m), 8.03~8.27 (1H, m),

8.33~8.57 (1H, m), 8.53 (1H, s), 9.27 (1H, s).

Referential Examples 2 - 6

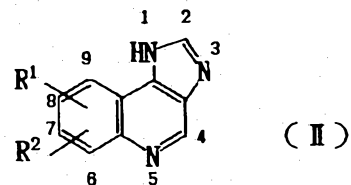
In the same manner as in Referential Example 1, the compounds (IV) were obtained under the reaction conditions shown in Table 15. The physical properties of the compounds (IV) were shown in Tables 14-1 and 14-2.

Table 15



Ref. Ex. No.	Amount of Compound (V)			1st Step		2nd Step		Compound (II)		
	R ¹	R ²	(g)	Formic acid (ml)	Reflux Time (hr)	Diglyme (ml)	Reflux Time (hr)	Yield		Compd. No.
								(g)	(%)	
2	7-OMe	H	4.55	14	1	150	4	4.34	90	II -2
3	6-F	H	4.00	12	1	90	2	3.71	88	II -3
4	7-F	H	5.00	12	1.5	120	1.5	4.97	94	II -4
5	6-Me	H	1.90	6	1	70	1.5	1.30	65	II -5
6	6-OMe	H	2.54	8	1	100	3.5	2.34	88	II -6

Table 16-1



Compd. No.	R ¹ R ²	m.p. (°C)	Appear- ance	Solvent for Recrysta- lln.	Mole- cular Formula	Elementary Analysis(%) Up (Calcd.). Down (Found)		
						C	H	N
II -2	7-OMe H	290-292(d)	Color- less	EtOH	C ₁₁ H ₉ N ₃ O	66.32 66.16	4.55 4.76	21.09 20.81
II -3	8-F H	325-327(d)	Color- less	MeOH-CHCl ₃	C ₁₀ H ₆ N ₃ F	64.16 64.56	3.23 3.48	22.44 22.43
II -4	7-F H	316-318(d)	Color- less	MeOH-CHCl ₃	C ₁₀ H ₆ N ₃ F	64.16 64.36	3.23 3.53	22.44 22.41
II -5	8-Me H	319-321(d)	Color- less	EtOH	C ₁₁ H ₉ N ₃	72.11 72.15	4.95 5.10	22.34 22.71
II -6	8-OMe H	280-282	Color- less	EtOH	C ₁₁ H ₉ N ₃ O	66.32 66.36	4.55 4.74	21.09 21.01

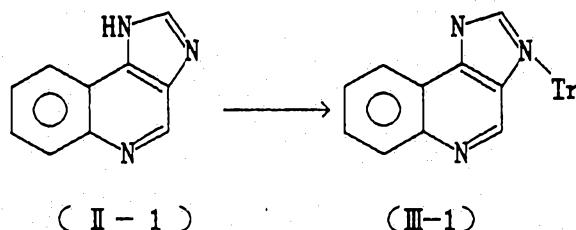
14 20 2004

Table 16-2

Compound No.	NMR (DMSO-d ₆) δ
II - 2	3.93 (3H,s), 7.35 (1H,d,d), 7.55 (1H,d), 8.33 (1H,d), 8.43 (1H,s), 9.17 (1H,s)
II - 3	7.42~7.66 (1H,m), 8.04~8.30 (2H,m), 8.53 (1H,s), 9.22 (1H,s)
II - 4	7.48~7.93 (2H,m), 8.40~8.57 (1H,m), 8.53 (1H,s), 9.27 (1H,s)
II - 5	2.57 (3H,s), 7.49 (1H,d,d), 8.03 (1H,d), 8.27 (1H,d), 8.47 (1H,s), 8.17 (1H,s)
II - 6	3.97 (3H,s), 7.30 (1H,d,d), 7.83 (1H,d), 8.05 (1H,d), 8.48 (1H,s), 9.10 (1H,s)

Referential Example 7

3-Trityl-3H-imidazo[4,5-c]quinoline (III-1)



To a suspension of 5.2 g of 1H-imidazo[4,5-c]quinoline (II-1) in 180 ml of MeCN were added 10.3 g of trityl chloride and 4.2 g of triethylamine, and the mixture was stirred at room temperature for 8 hours. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate. The organic layer was washed with water and brine, and then dried. The ethyl acetate was removed and the residue was chromatographed on a column of silica gel with ethyl acetate - n-hexane (1:1 v/v). Crystallization of the resulting oily substance from n-hexane gave 12.4 g (yield : 98%) of the titled compound (III-1). This was recrystallized from ethyl acetate - n-hexane to give colorless crystals melting at 190 ~ 192°C.

Anal. Calcd. (%) for $C_{21}H_{15}N_3$

: C, 84.64; H, 5.14; N, 10.21

Found (%) : C, 84.58; H, 5.23; N, 10.14

NMR (CDCl₃), δ : 7.10~7.50 (15H, m), 7.53~7.77 (2H, m),

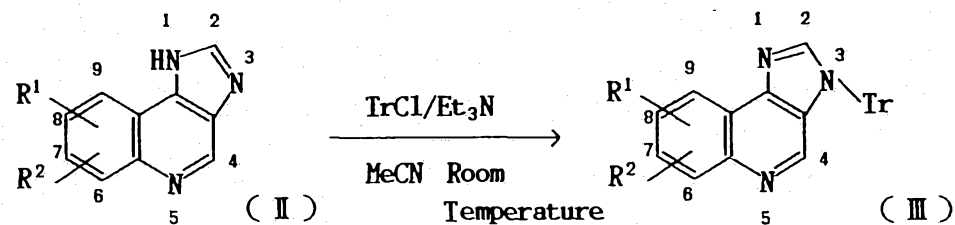
8.07 (1H, s), 8.10 (1H, s), 8.00~8.20 (1H, m),

8.53~8.73 (1H, m)

Referential Examples 8 - 12

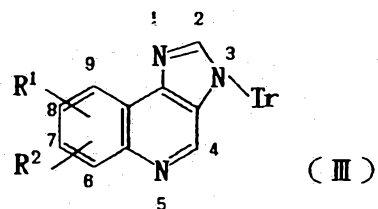
In the same manner as in Ref. Ex. 7, the compounds (III) were obtained under the reaction conditions shown in Table 17. The physical properties of the compounds were shown in Tables 18-1 and 18-2.

Table 17



Ref. Ex. No.	Amount of Compound (II)		TrCl (g)	Et ₃ N (g)	MeCN (ml)	Reaction Time (hr)	Compound (III)			
	R ¹	R ²					(g)	Yield		Compd. No.
								(g)	(%)	
8	7-OMe	H	4.18	7.10	3.00	75	8	8.60	93	III -2
9	8-F	H	3.35	5.99	2.35	130	15	6.81	88	III -3
10	7-F	H	4.50	8.05	3.16	160	24	9.01	88	III -4
11	8-Me	H	1.24	2.30	0.95	40	12	2.68	97	III -5
12	8-OMe	H	2.21	3.75	1.58	40	8	4.75	97	III -6

Table 18-1



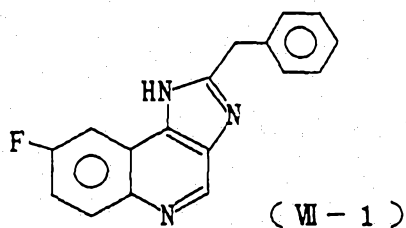
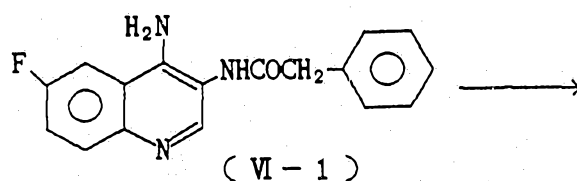
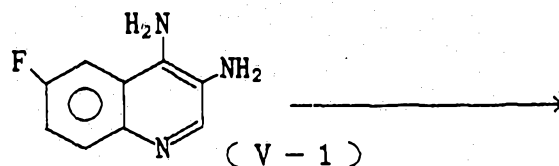
Compd. No.	R ¹ R ²	m. p. (°C)	Appear- ance	Solvent for Recrystalln.	Molecular Formula	Elementary Analysis(%)		
						Up (Calcd.) Down (Found)		
						C	H	N
III-2	7-OMe H	228-230	Color- less	AcOEt	C ₃₀ H ₂₃ N ₃ O	81.61 81.32	5.25 5.34	9.52 9.48
III-3	8-F H	267-269	Color- less	AcOEt-CH ₂ Cl ₂	C ₂₂ H ₂₀ N ₃ F	81.09 80.67	4.69 4.96	9.78 9.66
III-4	7-F H	226-228	Color- less	AcOEt	C ₂₂ H ₂₀ N ₃ F	81.09 81.18	4.69 4.78	9.78 9.84
III-5	8-Me H	270-272	Color- less	AcOEt	C ₃₀ H ₂₃ N ₃	84.68 84.74	5.45 5.44	9.87 9.93
III-6	8-OMe H	252-254	Color- less	AcOEt - n-hexane	C ₃₀ H ₂₃ N ₃ O	81.61 81.73	5.25 5.38	9.52 9.48

Table 18-2

Compd. No.	NMR (CDCl ₃) δ
III -2	3.91 (3H,s), 7.00~7.60 (17H,m), 8.01 (2H,s), 8.47 (1H,d)
III -3	7.13~7.52 (17H,m), 7.97 (1H,s), 8.03~8.23 (1H,s), 8.13 (1H,s)
III -4	7.10~7.50 (16H,m), 7.63~7.80 (1H,m), 8.07 (1H,s), 8.10 (1H,s), 8.52~8.68 (1H,m)
III -5	2.60 (3H,s), 7.10~7.60 (16H,m), 7.97 (1H,d), 8.03 (2H,s), 8.37 (1H,d)
III -6	4.00 (3H,s), 7.13~7.50 (17H,m), 7.90 (1H,d), 7.97 (1H,s), 8.03 (1H,s)

Referential Example 13

2-Benzyl-8-fluoro-1H-imidazo[4,5-c]quinoline (VI-1)



To a mixture of 10 ml of HMPA and 1 ml of MeCN was added 935 mg of phenylacetyl chloride at -10°C . After stirring at the same temperature for 15 min., 900 mg of 3,4-diamino-6-fluoroquinoline (V-1) was added and the mixture was stirred for 3 hours at $-5 \sim 0^{\circ}\text{C}$. The reaction mixture was diluted with ice water and neutralized with

saturated aqueous sodium hydrogencarbonate. The crystals precipitated were collected by filtration, dissolved in 200 ml of ethyl acetate and dried. The ethyl acetate was removed and the residue was crystallized from n-hexane to give 1.44 g of the compound (VI-1). The compound (VI-1) was suspended in 50 ml of ethylene glycol and refluxed for 30 min. The mixture was concentrated under reduced pressure. Water was added to the residue. The crystals precipitated were collected by filtration, washed with water, dissolved in 70 ml of ethyl acetate and dried. The ethyl acetate was removed and the residue was crystallized from n-hexane to give 1.3 g (yield : 92%) of the titled compound (VI-1). This was recrystallized from ethyl acetate to give colorless crystals melting at 226 ~ 228°C.

Anal. Calcd. (%) for $C_{11}H_{11}N_3F$

: C, 73.63; H, 4.36; N, 15.15; F, 6.85

Found (%) : C, 73.83; H, 4.30; N, 15.13; F, 6.55

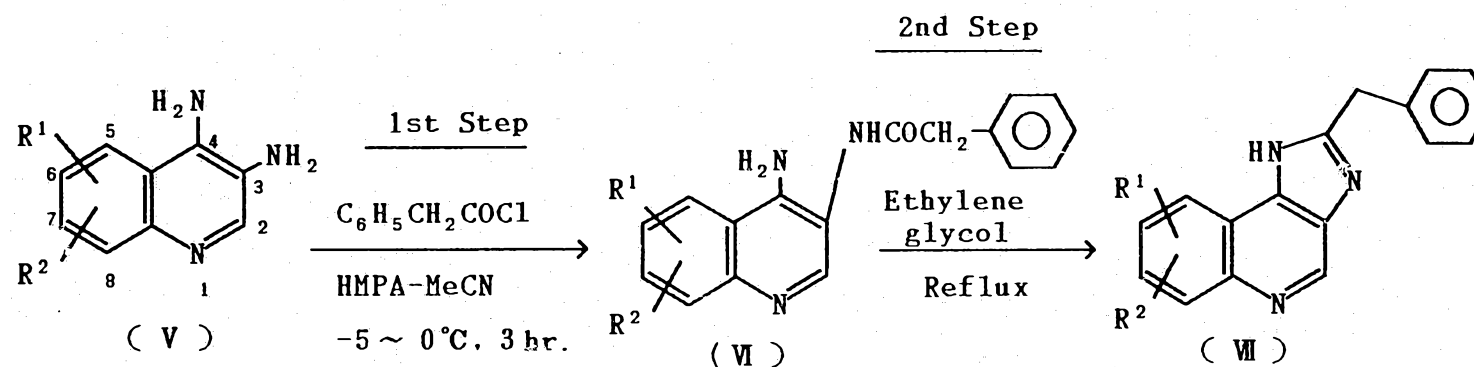
NMR (DMSO- d_6) δ : 4.33 (2H, s), 7.20~7.65 (6H, m),

7.93~8.25 (2H, m), 9.11 (1H, s)

Referential Examples 14 - 16

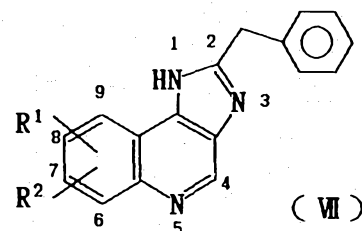
In the same manner as in Referential Example 13, the compounds (VII) were obtained under the reaction conditions shown in Table 19. The physical properties of the compounds were shown in Tables 20-1 and 20-2.

Table 19



Ref. Ex. No.	Amount of (V)		1st Step			2nd Step		Compound (VI)			
	R ¹	R ²	(g)	HMPA – MeCN		C ₆ H ₅ CH ₂ COCl (g)	Ethylene glycol (ml)	Reflux Time (hr)	Yield		Compd. No.
				(ml)	(ml)				(g)	(%)	
14	H	H	0.90	15	1.5	1.10	50	30	1.15	79	VI-2
15	7-F	H	0.90	10	1	0.94	50	10	1.26	90	VI-3
16	7-OMe	H	0.90	10	1	0.89	30	15	0.74	54	VI-4

Table 20-1



Compd. No.	R ¹	R ²	m.p.	Appear- ance	Solvent for Recrystalln.	Molecular Formula	Elementary Analysis(%)		
							Up (Calcd.)	Down (Found)	
							C	H	N
VI-2	H	H	212-214	Color- less	AcOEt	C ₁₇ H ₁₃ N ₃	78.74 78.46	5.05 5.04	16.20 15.88
VI-3	7-F	H	195-196	Color- less	AcOEt-n- hexane	C ₁₇ H ₁₂ N ₃ F	73.63 73.69	4.36 4.39	15.15 14.91
VI-4	7-OMe	H	211-213	Color- less	AcOEt	C ₁₈ H ₁₅ N ₃ O	74.72 74.63	5.23 5.20	14.52 14.39

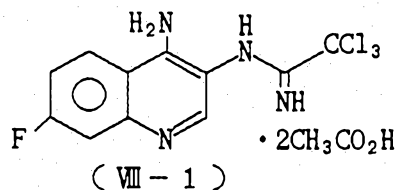
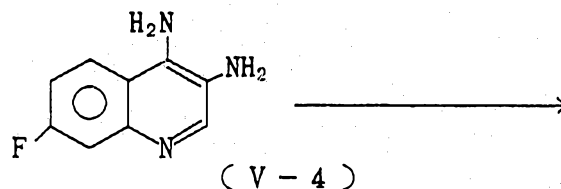
Table 20-2

Compound No.	NMR (DMSO-d ₆) δ
VI-2	4.33 (2H,s), 7.10~7.50 (5H,m), 7.53~7.80 (2H,m), 7.90~8.50 (2H,m), 9.13 (1H,s)
VI-3	4.35 (2H,s), 7.20~7.47 (5H,m), 7.53~7.95 (2H,m), 8.25~8.60 (1H,m), 9.17 (1H,s)
VI-4	3.90 (3H,s), 4.30 (2H,s), 7.20~7.57 (7H,m), 8.23 (1H,d), 9.07 (1H,s)

Referential Example 17

4-Amino-7-fluoro-3-(trichloroacetimidoylamino)quinoline diacetate

(VIII-1)



To a solution of 1.77 g of 3, 4-diamino-7-fluoro-quinoline (V-4) in 20 ml of acetic acid was added 1.94 g of methyl trichloroacetimidate and the mixture was stirred for two hours at room temperature. After concentration under reduced pressure, 10 ml of ethyl acetate was added to the residue, and the mixture was allowed to stand overnight. The crystals precipitated were collected by filtration and washed with ethyl acetate and then a small quantity of ethanol to give 3.75 g (yield : 87%) of the titled compound (VIII-1).

Melting point : 120 ~ 125 °C (d)

Anal. Calcd. (%) for $C_{15}H_{15}N_4O_4FCl_3$

: C, 40.79; H, 3.65; N, 12.68; F, 4.30; Cl, 24.08

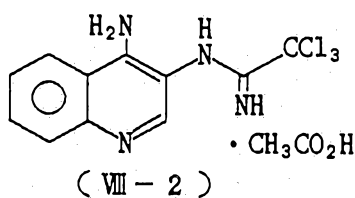
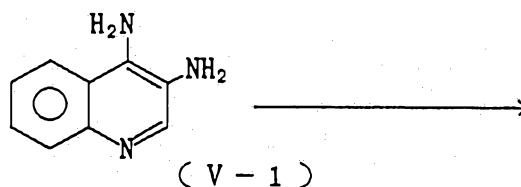
Found (%) : C, 40.42; H, 3.90; N, 12.79; F, 4.40; Cl, 24.56

NMR (DMSO- d_6) δ : 1.90 (6H, s), 7.20~7.60 (2H, m), 8.17 (1H, s),

8.24 (1H, m)

Referential Example 18

4-Amino-3-(trichloroacetimidoylamino)quinoline acetate (VIII-2)



In the same manner as in Ref. Ex. 17, 1.59 g of 3,4-diaminoquinoline (V-1) in 20 ml of acetic acid was treated with 1.9 g of methyl

trichloroacetimidate to give 3.13 g (yield : 80%) of the titled compound (VIII-2).

Melting point : 143 ~ 145°C (d)

Anal. Calcd. (%) for $C_{13}H_{13}N_4O_2Cl_3$

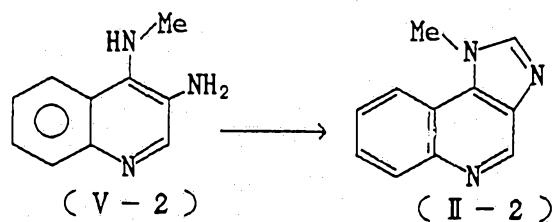
: C, 42.93; H, 3.60; N, 15.40; Cl, 29.24

Found (%) : C, 42.88; H, 3.68; N, 15.04; Cl, 29.19

NMR (DMSO- d_6), δ : 1.90 (3H, s), 7.30~7.90 (3H, m), 8.13 (1H, m),
8.17 (1H, s)

Referential Example 19

1-Methyl-1H-imidazo[4,5-c]quinoline (II-2)



A solution of 2.92 g of 3-amino-4-methylaminoquinoline (V-2) in 20 ml of formic acid was refluxed for 1.5 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between chloroform and saturated aqueous sodium hydrogen-carbonate. The organic layer was washed with brine and dried. The chloroform was removed and the residue was crystallized from n-hexane

to give 2.39 g (yield : 77%) of the titled compound (II-2). This was recrystallized from ethyl acetate to give colorless crystals melting at 146 ~ 148 °C.

Anal. Calcd. (%) for $C_{11}H_9N_3$

: C, 72.11; H, 4.95; N, 22.94

Found (%) : C, 72.25; H, 4.94; N, 22.86

NMR ($CDCl_3$), δ : 4.20 (3H, s), 7.45~7.80 (2H, m), 7.84 (1H, s),

8.15~8.40 (2H, m), 9.33 (1H, s)

Effect of the Invention

The compounds of the present invention show a high affinity for the benzodiazepine (BZ) receptor in brain. The BZ receptor ligands (compounds bound to the receptor) are thought to comprise a continuous spectrum of agents with a graduated range of pharmacological efficacies at the receptor: (1) full agonists (positive efficacy; anxiolytic/anticonvulsant), (2) partial agonists, selective anxiolytic), (3) antagonists (nil efficacy; antagonism towards the other classes), (4) partial inverse agonists (intermediate negative efficacy; proconvulsant, cognition enhancer), and (5) full inverse agonists (negative efficacy; anxiogenic/convulsant). The classification can be achieved mainly on the basis of inhibition or facilitation of the pentylenetetrazole-induced convulsions [C. Braestrup et al., Biochem. Pharmacol. 33, 859 (1984)]. The inverse agonist methyl β -carboline-3-carboxylate (β -CCM) enhances the performance in several animal models of learning and memory, whereas the agonist diazepam impairs such performance in humans, suggesting that partial inverse agonists may provide a new type of nootropic drugs [M. Sarter et al., TIINS 11, 13 (1988)]. Thus, agonists are expected to work as anxiolytic or anticonvulsant agents, antagonists as antidotes for benzodiazepine intoxication and accidental excessive uptake thereof, and partial inverse agonists as cognition enhancers or nootropic agents.

Experiments of the compounds of the present invention are shown below.

Experiment 1

Test on Binding to Benzodiazepine Receptor

This test was carried out by modifying partially a method of Möhler & Okada, Science, 198, 849-851 (1977). Receptor preparation was provided from the cerebral cortex of male Wistar rats (11 - 13 weeks age). Inhibitory action of the test compound on the specific binding of tritium-labeled diazepam to the receptor was evaluated as follows: 2nM tritium-labeled diazepam and an aqueous solution of the test compound in 5 or 6 different concentrations were incubated with the receptor preparation at 0°C for 60 minutes. The 50% inhibitory concentration (IC_{50}) was measured by the concentration-response curve. In addition, the inhibitory constant (K_i) of the test compound was calculated by dissociation constant (K_d) and concentration (L) of the tritium-labeled diazepam. The results are shown in the undermentioned table.

$$K_i = \frac{IC_{50}}{1 + \frac{L}{K_d}}$$

Test Compound	Ki (nM)
I c-1	0.357
I c-4	0.409
I c-6	0.432
I c-9	6.11
I c-14	1.24
I c-18	3.60
I c-21	0.50
I c-22	1.90
I c-27	13.1
I c-31	1.50
I c-37	2.21
I c-41	8.33
I c-45	3.20
I c-49	1.80
I c-50	0.819
I c-56	1.07
I c-60	0.373

Experiment 2

Antagonism of Pentylene-tetrazole-Induced Convulsion

Agonistic activity was evaluated in this Experiment. Pentylene-tetrazole was subcutaneously administered male mice (a group of 8-16 male mice was employed in each test) at a dose of 125 mg/kg immediately after intravenous injection of the test compound. The dose (ED_{50}) required to prevent tonic convulsion and death in 50% of the animals during subsequent 2-hour observation period was calculated by the probit method.

Test Compd.	ED_{50} (mg/kg)
I c-9	3.21
I c-27	2.47
I c-36	0.46
I c-38	1.12
I c-45	0.88
I d-2	1.06

Experiment 3

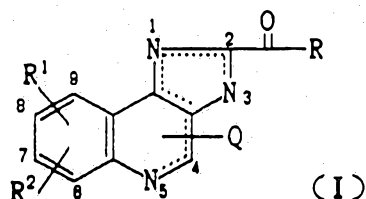
Potentiation of Pentylenetetrazole-Induced Convulsion

Inverse agonist activity was evaluated in this Experiment. Pentylenetetrazole was subcutaneously administered male mice (a group of 8-16 male mice was employed in each test) at a dose of 90 mg/kg immediately after intravenous injection of the test compound. The dose (ED_{50}) required to produce tonic convulsion and death in 50% of the animals during subsequent 2-hour observation period was calculated by the probit method.

Test Compd.	ED_{50} (mg/kg)
I c-6	1.00
I c-14	0.20
I c-22	0.15
I c-24	0.09
I c-60	0.71
I c-64	0.31
I c-67	0.35

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A compound of the formula:



10
 15
 20
 25
 30

wherein R is (1) hydrogen; (2) hydroxy; (3) C₁-C₁₀ alkyl optionally substituted by halogen, C₁-C₅ alkylthio, C₁-C₅ alkyloxycarbonyl, or phenyl; (4) C₃-C₅ cycloalkyl optionally substituted by C₁-C₅ alkyl; (5) C₂-C₅ alkenyl optionally substituted by C₁-C₅ alkyl or di-C₁-C₅ alkyl; (6) C₁-C₅ alkoxy; (7) phenoxy; (8) amino optionally substituted by C₁-C₅ alkyl or di-C₁-C₅ alkyl; (9) phenyl optionally substituted by one or two members independently selected from the group consisting of halogen, trifluoromethyl, C₁-C₅ alkoxy, and C₁-C₅ alkylthio; or (10) 5- or 6-membered heterocyclic group selected from isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, thiadiazolyl, oxadiazolyl, thienyl, furyl and pyridyl optionally substituted by one or two members independently selected from the group consisting of halogen, C₁-C₅ alkyl, and phenyl; Q is hydrogen, C₁-C₅ alkyl, benzyl, benzhydryl, trityl, C₁-C₅ alkylsulfonyl, or C₆-C₁₂ arylsulfonyl, provided that Q is located at nitrogen atom of 1-, 3-, or 5-position; R¹ and R² each is hydrogen, C₁-C₅ alkyl, C₁-C₅ alkoxy, or halogen; and the dotted lines indicate the presence of three double



bonds at the position of 2(3), 3a(9b), 4(5); 1(9b), 2(3), 3a(4); or 1(2), 3a(9b), 4(5);

or its pharmaceutically acceptable acid addition salts.

2. A compound claimed in Claim 1, namely 2-cyclopropylcarbonyl-7-fluoro-1H-imidazo[4,5-c]quinoline.

3. A compound claimed in Claim 1, namely 2-cyclopropylcarbonyl-7-methoxy-1H-imidazo[4,5-c]quinoline.

4. A pharmaceutical composition for treatment of depression, convulsion, anxiety, amnesia, senile dementia, or cerebral disorder, comprising a pharmacologically effective amount of a compound according to Claim 1 together with a carrier, diluent, and/or excipient.

5. A method for treating a patient suffering from depression, convulsion, anxiety, amnesia, senile dementia, or cerebral disorder characterized by administering a pharmaceutical composition according to Claim 4 to the patient.

6. Compounds of formula I, methods for their manufacture or pharmaceutical compositions or methods of treatment involving them, substantially as hereinbefore described with reference to the examples.

~~7. The steps, features, compositions and compounds disclosed herein or referred to or indicated in the specification and/or claims of this application, individually or collectively, and any and all combinations of any two or more of said steps or features.~~

DATED this FOURTEENTH day of FEBRUARY 1989

Shionogi & Co., Ltd.

by DAVIES & COLLISON

Patent Attorneys for the applicant(s)

