AMENDED

47341/85 3

COMMONWEALTH of AUSTRALIA

PATENTS ACT 1952

598446

APPLICATION FOR A STANDARD PATENT

We FUJISAWA PHARMACEUTICAL CO., LTD.

of No. 3,4-chome, Doshomachi, Higashi-ku, Osaka, Japan

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 10-4-90

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

"QUINOLIZINONE COMPOUND, PROCESSES FOR PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME"

which is described in the accompanying ~~provisional~~ complete specification.

Details of basic application(s):—

Number	Convention Country	Date
8429710	GREAT BRITAIN	NOVEMBER 23, 1984
712,435	UNITED STATES OF AMERICA	MARCH 18, 1985
770,953	UNITED STATES OF AMERICA	AUGUST 30, 1985

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 8th day of OCTOBER, 1985

To: THE COMMISSIONER OF PATENTS

E. A. Pennington

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

Davies & Collison, Melbourne and Canberra.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

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

In support of the Application made for a patent for an invention entitled: "QUINOLIZINONE COMPOUND, PROCESSES FOR PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME"

Insert title of invention.

~~I/We~~ I, Tomokichiro Fujisawa,
of FUJISAWA PHARMACEUTICAL CO., LTD.
of No. 3,4-chome, Doshomachi, Higashi-ku,
Osaka, Japan

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

do solemnly and sincerely declare as follows :–

1. (a) ~~I am/We are the applicant for the patent~~

Cross out whichever of paragraphs 1(a) or 1(b) does not apply

1(a) relates to application made by individual(s)
1(b) relates to application made by company; insert name of applicant company.

or (b) I am authorized by
FUJISAWA PHARMACEUTICAL CO., LTD.
the applicant for the patent to make this declaration on ~~its~~ behalf.

2. (a) ~~I am/We are the actual inventor of the invention~~

Cross out whichever of paragraphs 2(a) or 2(b) does not apply

2(a) relates to application made by inventor(s)
2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventors.

or (b) Yoshihiko KITAURA of No. 2-148, Heiwaoka, Meitou-ku, Nagoya, Japan;
Teruo OKU of No. 2-23-406, Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka, Japan;
Hideo HIRAI of No. 2-1-20-204, Takasu-cho, Nishinomiya, Japan;
Tosiyuki YAMAMOTO of No. 2-2-10, Midorigaoka, Ikeda, Japan; and
Masashi HASHIMOTO of No. 1-6-17, Satsukidai, Nakayama, Takarazuka, Japan
~~are~~ the actual inventors of the invention and the facts upon which the applicant ~~is~~ entitled to make the application are as follows :–

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

The actual inventors have 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~~s~~ as defined by Section 141 of the Act ~~was~~ were made
in Great Britain on the 23rd November, 1984
by FUJISAWA PHARMACEUTICAL CO., LTD.
in United States of America on the 18th March, 1985
by FUJISAWA PHARMACEUTICAL CO., LTD.
in United States of America on the 30th August, 1985
by FUJISAWA PHARMACEUTICAL CO., LTD.

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

Insert place and date of signature.

Declared at Osaka this 18th day of SEPTEMBER, 1985

Signature of declarant(s) (no attestation required)

Tomokichiro Fujisawa

Tomokichiro Fujisawa, President

Note: Initial all alterations.

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-47341/85
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 598446

(54) Title
QUINOLIZIN-4-ONE DERIVATIVES

International Patent Classification(s)
(51)[4] C07D 455/02 C07D 455/00 C07D 455/04 C07D 455/06

(21) Application No. : 47341/85 (22) Application Date : 11.09.85

(30) Priority Data

(31) Number	(32) Date	(33) Country
8429710	23.11.84	GB UNITED KINGDOM
712435	18.03.85	US UNITED STATES OF AMERICA
770953	30.08.85	US UNITED STATES OF AMERICA

(43) Publication Date : 29.05.86

(44) Publication Date of Accepted Application : 28.06.90

(71) Applicant(s)
FUJISAWA PHARMACEUTICAL CO., LTD.

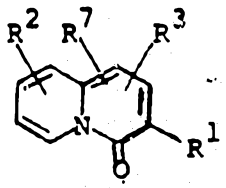
(72) Inventor(s)
YOSHIHIKO KITAURA; TERUO OKU; HIDEO HIRAI; TOSIYUKI YAMADO; MASASHI HASHIMOTO

(74) Attorney or Agent
DAVIES & COLLISON, MELBOURNE

(56) Prior Art Documents
AU 49241/85 C07D 455/02

(57) Claim

1. A compound of the formula :



(I)

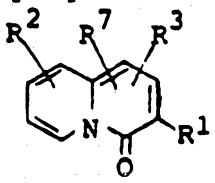
wherein R^1 is carboxy;
CONH R^{10} wherein R^{10} is hydrogen; pyridyl; pyrimidinyl; pyrimidinyl substituted with lower alkyl; pyrazinyl; phenyl; phenyl substituted with hydroxy; thiazolyl; triazinyl; triazolyl; triazolyl substituted with amino; pyridazinyl; pyridazinyl substituted with halogen; or tetrazolyl;
cyano, thiocarbamoyl, or tetrazolyl;
R^7 is hydrogen or aryl;
R^2 is hydrogen, hydroxy, lower alkyl or lower alkoxy; and
R^3 is hydrogen, hydroxy, lower alkyl, lower

.../2

alkoxy, carboxy, lower alkoxycarbonyl, lower alkenyloxy; aryl optionally substituted with halogen, lower alkyl or lower alkoxy; arylthio, aroyl, ar(lower)alkyl, arenesulfonyl, N-lower alkylanilino or aryloxy;

and pharmaceutically acceptable salts thereof.

8. A process for preparing a compound of the formula :



(I)

wherein R^1 is carboxy;
CONH R^{10} wherein R^{10} is hydrogen; pyridyl; pyrimidinyl; pyrimidinyl substituted with lower alkyl; pyrazinyl; phenyl; phenyl substituted with hydroxy; thiazolyl; triazinyl; triazolyl; triazolyl substituted with amino; pyridazinyl; pyridazinyl substituted with halogen; or tetrazolyl; cyano, thiocarbamoyl, or tetrazolyl;

R^7 is hydrogen or aryl;

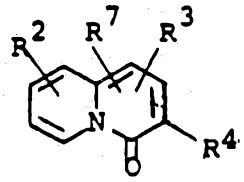
R^2 is hydrogen, hydroxy, lower alkyl or lower alkoxy; and

R^3 is hydrogen, hydroxy, lower alkyl, lower alkoxy, carboxy, lower alkoxycarbonyl, lower alkenyloxy; aryl optionally substituted with halogen, lower alkyl or lower alkoxy; arylthio, aroyl, ar(lower)alkyl, arenesulfonyl, N-lower alkylanilino or aryloxy;
arylthio, aroyl, ar(lower)alkyl, arenesulfonyl, N-lower alkylanilino or aryloxy;

or a salt thereof which comprises

(1) subjecting a compound of the formula :

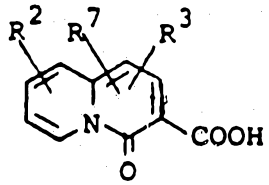
.../3



wherein R^7, R^2 and R^3 are each as defined above, and

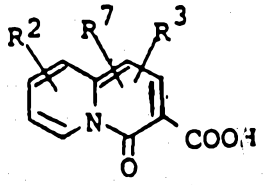
R^4 is protected carboxy,

or a salt thereof, to elimination reaction of the carboxy protective group, to give a compound of the formula :

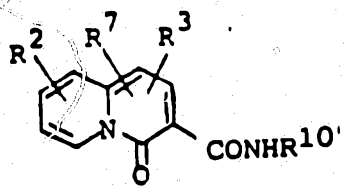


wherein R^7, R^2 and R^3 are each as defined above, or a salt thereof; or

(2) reacting a compound of the formula:

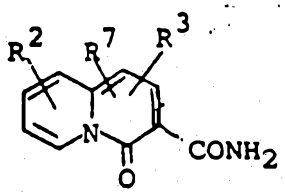


wherein R^7, R^2 and R^3 are each as defined above, or its reactive derivative at the carboxy group or a salt thereof, with $H_2N\text{-}R^{10}$ wherein R^{10} is as defined above, to give a compound of the formula:

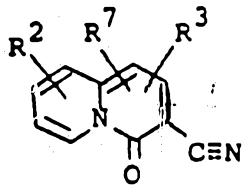


wherein R^7, R^{10}, R^2 and R^3 are each as defined above,
or a salt thereof; or

(3) subjecting a compound of the formula :

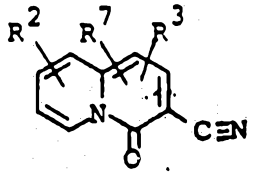


wherein R^7, R^2 and R^3 are each as defined above,
or a salt thereof, to dehydration reaction,
to give a compound of the formula :

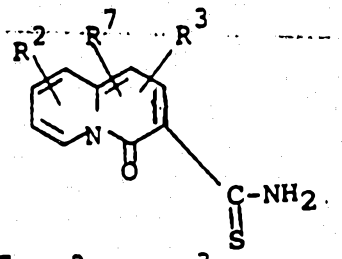


wherein R^7, R^2 and R^3 are each as defined above,
or a salt thereof; or

(4) reacting a compound of the formula :

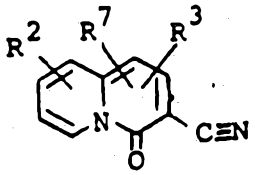


wherein R^7, R^2 and R^3 are each as defined above,
or a salt thereof, with hydrogen sulfide,
to give a compound of the formula :

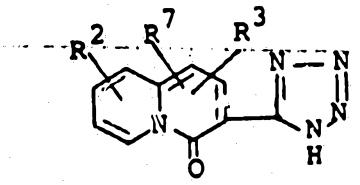


wherein R^7, R^2 and R^3 are each as defined above, or a salt thereof; or

(5) subjecting a compound of the formula :

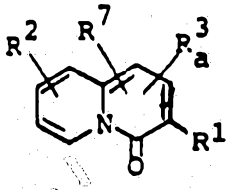


wherein R^7, R^2 and R^3 are each as defined above, or a salt thereof, to the formation reaction of a tetrazole group, using a combination of alkali methal azide and ammonium halide, to give a compound of the formula :



wherein R^7, R^2 and R^3 are each as defined above,
or a salt thereof, or

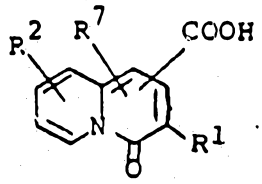
(6) subjecting a compound of the formula :



wherein R^1, R^2 and R^7 are each as defined above,

and

R^3_a is lower alkoxycarbonyl, or a salt thereof, to elimination reaction of lower alkyl, to give a compound of the formula :



wherein R^1, R^2 and R^7 are each as defined above, or a salt thereof.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION 598446

(Original)

FOR OFFICE USE

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the amendments made under Section 49 and is correct for printing.

47341/85.

Name of Applicant: FUJISAWA PHARMEACEUTICAL CO., LTD.

Address of Applicant: No. 3,4-chome, Doshomachi,
Higashi-ku, Osaka,
JAPAN

Actual Inventor(s): YOSHIHIKO KITAURA
TERUO OKU
HIDEO HIRAI
TOSIYUKI YAMAMOTO
MASASHI HASHIMOTO

Address for Service: DAVIES & COLLISON, Patent Attorneys,
1 Little Collins Street, Melbourne, 3000.

Complete specification for the invention entitled:

"QUINOLIZINONE COMPOUND, PROCESSES FOR PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME"

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

QUINOLIZINONE COMPOUND, PROCESSES FOR PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

This invention relates to quinolizinone compound and a salt thereof. More particularly, it relates to a new quinolizinone compound and a pharmaceutically acceptable salt thereof which have inhibitory activities on allergy and ulcer, to processes for preparation thereof, and to a pharmaceutical composition comprising the same.

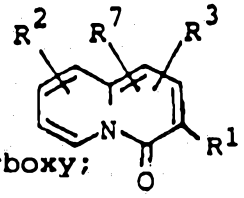
Accordingly, one object of this invention is to provide the new and useful quinolizinone compound and a pharmaceutically acceptable salt thereof.

Another object of this invention is to provide processes for preparation of said quinolizinone compound and the salt thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said quinolizinone compound or the pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a therapeutical method for treatment of allergic disease and ulcer in human being and animals.

The quinolizinone compound of this invention can be represented by the following formula (I) :



(I)

wherein R^1 is carboxy;

$CONHR^{10}$ wherein R^{10} is hydrogen; pyridyl; pyrimidinyl; pyrimidinyl substituted with lower alkyl; pyrazinyl; phenyl; phenyl substituted with hydroxy; thiazolyl; triazinyl; triazolyl; triazolyl substituted with amino; pyridazinyl; pyridazinyl substitued with halogen; or tetrazolyl;

cyano, thiocarbamoyl, or tetrazolyl

R^7 is hydrogen or aryl;

R^2 is hydrogen, hydroxy, lower alkyl or lower alkoxy; and

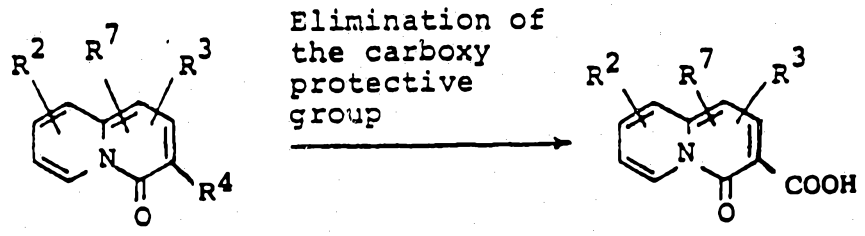
R^3 is hydrogen; hydroxy; lower alkyl; lower alkoxy; carboxy; lower alkoxycarbonyl; lower alkenyloxy;

aryl optionally substituted with halogen, lower alkyl or lower alkoxy;

arylthio, aroyl, ar(lower)alkyl, arenesulfonyl, N-lower alkylanilino; or aryloxy.

According to this invention, the object compound (I) can be prepared by the processes as illustrated by the following schemes.

Process 1 :



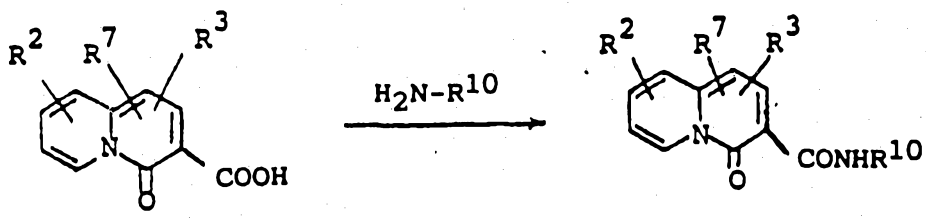
(II)

or a salt thereof

(Ia)

or a salt thereof

Process 2 :



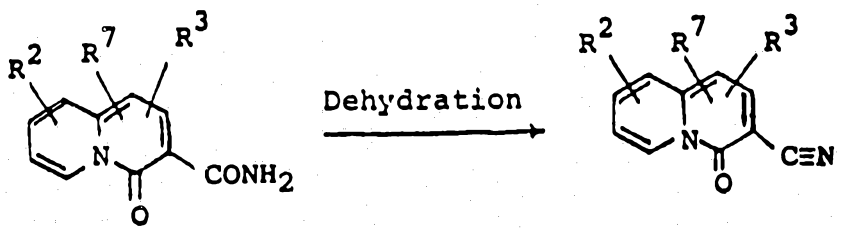
(Ia)

or its reactive derivative at the carboxy group or a salt thereof

(Ib)

or a salt thereof

Process 3 :



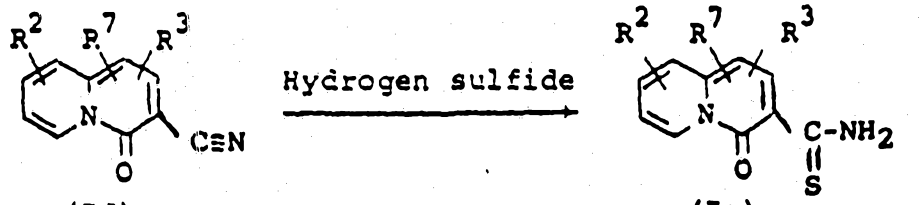
(Ic)

or a salt thereof

(Id)

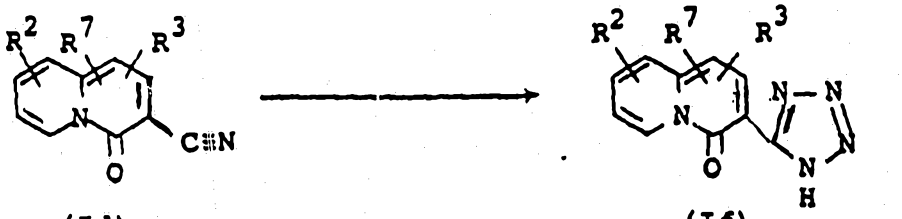
or a salt thereof

Process 4 :



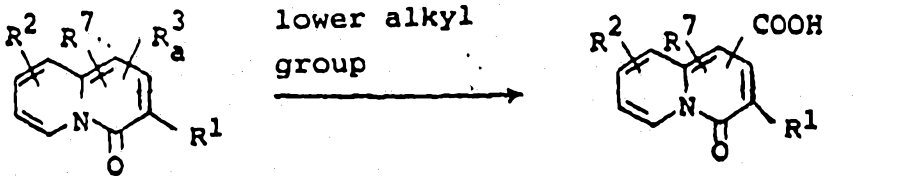
(Id) or a salt thereof — (Ie) or a salt thereof

Process 5 :



(Id) or a salt thereof — (If) or a salt thereof

Process 6 :

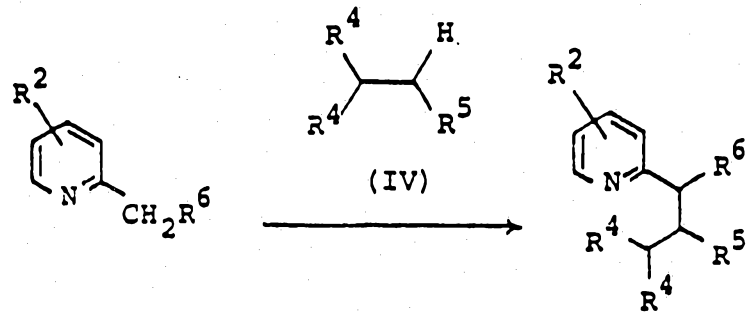


(Ig) or a salt thereof — (Ih) or a salt thereof

wherein R^2, R^3, R^7 and R^{10} are each as defined above,
R^4 is protected carboxy, and
R^3_a is lower alkyoxycarbonyl.

Among the starting compounds in the present invention, the compound (II) can be prepared by the processes which are illustrated in the following schemes.

Process A - (1) :



(III)

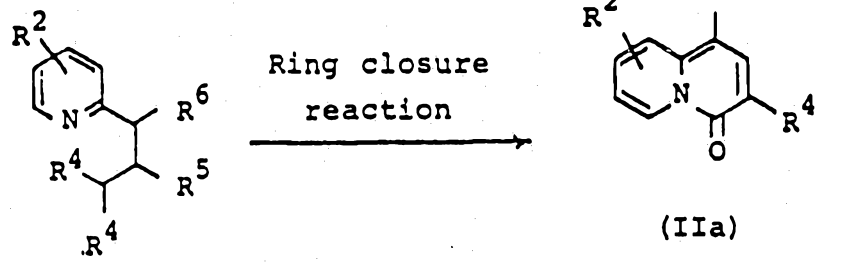
or a salt thereof

(IV)

(V)

or a salt thereof

Process A - (2) :



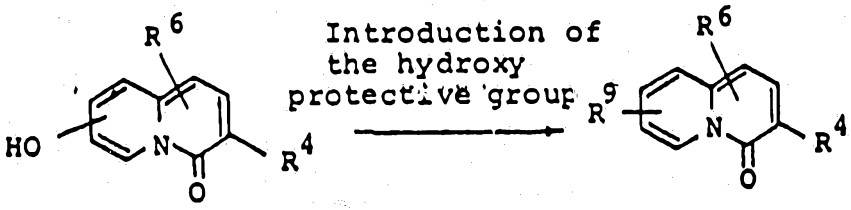
(V)

or a salt thereof

(IIa)

or a salt thereof

Process B :



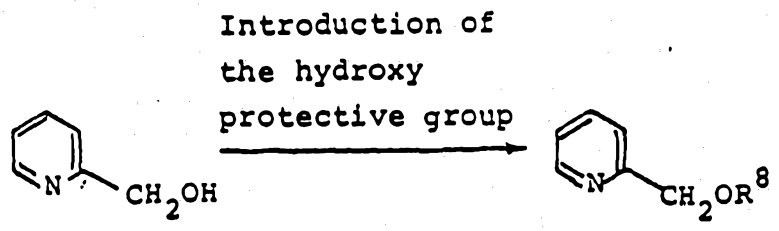
(IId)

or a salt thereof

(IIe)

or a salt thereof

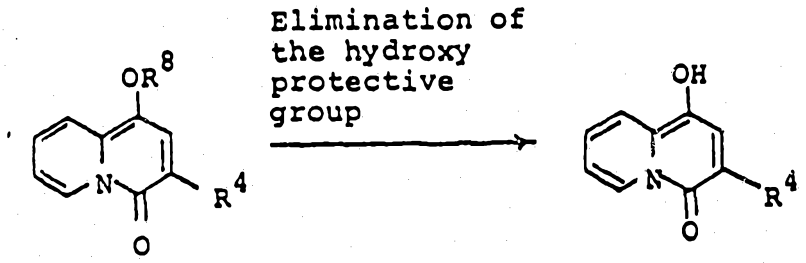
Process C :



(IIId) or a salt thereof

(IIIe) or a salt thereof

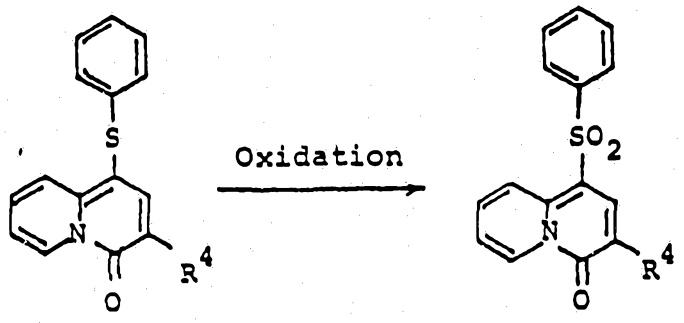
Process D :



(IIh) or a salt thereof

(IIi) or a salt thereof

Process E :



(IIj) or a salt thereof

(IIk) or a salt thereof

(to be continued to the next page.)

wherein R^2, R^4 and R^7 are each as defined above,
R^5 is lower alkoxy,
R^6 is hydrogen; protected hydroxy; lower alkyl; lower alkoxy; carboxy; lower alkoxycarbonyl; lower alkenyloxy; aryl optionally substitued with halogen, lower alkyl or lower alkoxy; arylthio; aroyl; ar(lower)alkyl; arenesulfonyl; arylamino optionally substituted with N-lower alkylanilino; or aryloxy,
R^8 is hydroxy protective group,
R^9 is protected hydroxy and
n is 1 or 2.

Suitable pharmaceutically acceptable salts of the object compounds (I) are conventional non-toxic salt and include and acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, nitrate, phosphate), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt) an an alkaline earth metal salt (e.g. calcium salt, magnesium salt), an ammonium salt or an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt.

In the above and subsequent decriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" and "lower alkyl" moiety in "ar(lower)alkyl" includes straight or branched, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl or hexyl.

Suitable "lower alkoxy" includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy and hexyloxy, preferably one having 1 to 4 carbon atom(s).

Suitable "lower alkenyloxy" includes vinyloxy, 1-propenyloxy, allyloxy, 1-butenyloxy, 2-butenyloxy and 2-pentenyloxy, preferably ones having 2 to 4 atoms.

Suitable "lower alkoxycarbonyl" includes methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl and 1-cyclopropylethoxycarbonyl.

Suitable "triazolyl" includes 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl and 2H-1,2,3-triazolyl.

Suitable "tetrazolyl" includes 1H-tetrazolyl and 2H-tetrazolyl.

Suitable "triazinyl" includes 1,2,3-triazinyl, 1,2,4-triazinyl and 1,3,5-triazinyl.

Suitable "halogen" includes chlorine, bromine, iodine and fluorine.

Suitable "protected hydroxy" includes a hydroxy group protected by a conventional hydroxy-protective group, for example, lower alkyl (e.g. methyl, ethyl, propyl, n-butyl), lower alkenyl (e.g. vinyl, allyl), ar(lower)alkyl such as mono- or di- or triphenyl (lower)alkyl (e.g. benzyl, benzhydryl, trityl, trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, isopropyldimethylsilyl, tert-butyldimethylsilyl, diisopropylethylsilyl), triarylsilyl (e.g. triphenylsilyl) and triar(lower)alkylsilyl tribenzylsilyl).

Suitable "aryl" includes phenyl, tolyl, xylyl, cumenyl, naphthyl and biphenylyl which may have one or more suitable substituent(s) such as halogen (e.g. fluorine, chlorine, bromine, iodine), lower alkyl or lower alkoxy.

Suitable "aryl" moiety in the terms "arylthio" and "ar(lower)alkyl" can be referred to the ones as exemplified above.

Suitable "aroyl" includes benzoyl, toluoyl and naphthoyl.

Suitable "arenesulfonyl" includes benzenesulfonyl and p-toluenesulfonyl.

Suitable "aryloxy" includes phenoxy and tolyloxy.

Suitable "hydroxy protective group" can be referred to the ones as exemplified above.

The processes for preparing the object compounds (I) of the present invention are explained in detail in the following.

Process 1 :

The object compound (Ia) or a salt thereof can be prepared by subjecting the compound (II) or a salt thereof to elimination reaction of the carboxy protective group.

Suitable salt of the compound (II) can be referred to the acid addition salt exemplified for the compound (I) and suitable salt of the compound (Ia) can be referred to the ones as exemplified for the compound (I).

In the present elimination raction, all conventional methods used in the elimination reaction of the carboxy protective group, for example, hydrolysis, reduction, elimination using Lewis acid are applicable. When the carboxy protective group is an ester, it can be eliminated by hydrolysis or elimination using Lewis acid. The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base includes, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate), alkali metal acetate (e.g. sodium acetate,

potassium acetate), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate) or alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate), and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo [4,3,0] non-5-one, 1,4-diazabicyclo [2,2,2]octane or 1,5-diazabicyclo[5,4,0]undecene-5. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid).

The present hydrolysis is usually carried out in an organic solvent, water or a mixed solvent thereof.

The reaction temperature is not critical, and it may suitably selected in accordance with the kind of the carboxy protective group and the elimination method.

The elimination using Lewis acid is preferable to eliminate substituted or unsubstituted ar(lower)alkyl ester and carried out by reacting the compound (II) or a salt thereof with Lewis acid such as boron trihalide (e.g. boron trichloride, boron trifluoride), titanium tetrahalide (e.g. titanium tetrachloride, titanium tetrabromide), tin tetrahalide (e.g. tin tetrachloride, tin tetrabromide), aluminium halide (e.g. aluminum chloride, aluminum bromide) or trihaloacetic acid (e.g. trichloroacetic acid, trifluoroacetic acid). This elimination reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol) and is usually carried out in a solvent such as nitroalkane (e.g. nitromethane, nitroethane), alkylene halide (e.g. methylene chloride,

ethylene chloride, diethyl ether, carbon disulfide or any other solvent which does not adversely affect the reaction. These solvents may be used as a mixture thereof.

The reduction elimination can be applied preferably for elimination of the protective group such as halo(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl) ester or ar(lower)alkyl (e.g. benzyl) ester.

The reduction method applicable for the elimination reaction may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam) or a salt of chromium compound (e.g. chromous chloride, chromous acetate) and an organic or an inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid); and conventional catalytic reduction in the presence of a conventional metallic catalyst (e.g. palladium carbon, Raney nickel).

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

The present elimination reaction of the carboxy protective group includes, within its scope, the case that another protected carboxy are converted into free carboxy during the reaction or the post-treating step of the present process.

Process 2 :

This objection compound (Ib) or a salt thereof can be prepared by reacting the compound (Ia) or its reactive derivative at the carboxy group or a salt thereof with $H_2N\text{-}R^{10}$.

Suitable salt of the compound (Ib) can be referred to the salt exemplified for the compound (I).

Suitable reactive derivative at the carboxy group of the compound (Ia) may include and acid halide, an acid anhydride, and an activated ester. The suitable example may be an acid chloride, an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialklyphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid), dialkylphosphorous acid, sulforous acid, thiosulfuric acid, sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid) or a aromatic carboxylic acid (e.g. benzoic acid); a symmetrical acid anhydride; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide and 1-hydroxy-6-chloro-1H-benzotriazole.

When the compound (Ia) is used in a free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethyl carbodimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, 1,1'-carbonyldiimidazole, thionyl chloride, oxalyl chloride, lower alkoxycarbonyl halide [e.g. ethyl chloroformate, isobutyl chlorofomate or 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuan, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction in the presence of a condensing agent is usually carried out in an anhydrous, but not critical conditions.

The reaction may be carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide), an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate), an alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate), tri(lower)alkylamine (e.g. trimethylamine, triethylamine) or pyridine or its derivative (e.g. picoline, lutidine, 4-dimethylaminopyridine). In case that the base or the condensing agent to be used is in liquid, it can be used also as a solvent.

The reaction temperature is not critical, and the reaction is usually carried out under heating or under warming, preferably under heating.

Process 3 :

The object compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof

to dehydration reaction.

The dehydrating agent to be used in this dehydration reaction may include phosphoryl chloride, thionyl chloride, phosphorus pentoxide, phosphorus pentachloride, phosphorus pentabromide and the like.

The present reaction is usually carried out in a solvent such as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, dimethylformamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out at ambient temperature, under warming or heating.

Process 4 :

The object compound (Ie) or a salt thereof can be prepared by reacting the compound (Id) or a salt thereof with hydrogen sulfide.

The present reaction is usually carried out in a solvent such as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, dimethylformamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out at ambient temperature, under warming or heating.

Process 5 :

The object compound (If) or a salt thereof can be prepared by subjecting the compound (Id) or a salt thereof

to the formation reaction of a tetrazole group.

Suitable salt of the compound (If) and (Id) can be referred to the acid addition salt exemplified for the compound (I).

The agent to be used in the present reaction may include conventional ones such as combination of alkali metal azide (e.g., potassium azide, sodium azide) and ammonium halide (e.g. ammonium chloride)

The present reaction is usually carried out in a solvent such as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, dimethylformamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming or heating.

Process 6 :

The compound (Ih) or a salt thereof can be prepared by subjecting the compound (Ig) or a salt thereof to elimination reaction of the carboxy protective group.

Suitable salts of the compounds (Ig) and (Ih) can be referred to the salts exemplified for the compound (I).

The present reaction can be carried out in a similar manner to that of Process 1 as mentioned above, and therefore the reaction modes and conditions (e.g. reaction temperature, solvent) are referrred to those of Process 1.

Process A - (1) :

The compound (V) or a salt thereof can be prepared by reacting the compound (III) or a salt thereof with the compound (IV).

Suitable salts of the compounds (III) and (V) can be referred to the acid addition salts exemplified for the compound (I).

The present reaction can be preferably carried out in the presence of alkyl lithium (e.g., n-butyl lithium), lithium diisopropylamide and alkalimetal alkoxide (e.g., sodium methoxide, sodium ethoxide).

The present reaction is usually carried out in a solvent such as acetone, dioxane, acetonitrile, dimethylformamide, benzene, hexane, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

Process A - (2) :

The compound (IIa) or a salt thereof can be prepared by subjecting the compound (V) or a salt thereof to ring closure reaction.

Suitable salt of the compound (V) can be referred to the acid addition salt exemplified for the compound (I).

The present reaction may preferably be carried out in the presence of a suitable agent such as the mixture of diphenyl and diphenylether, which is used as heating medium.

The reaction temperature is not critical and the reaction is usually carried out under heating.

Process B :

The object compound (IIe) or a salt thereof can be prepared by subjecting the compound (IId) or a salt thereof to introduction reaction of the hydroxy protective group.

Suitable salt of the compounds (IId) and (IIe) can be referred to the acid addition salts as exemplified for the compound (I).

In case the protective group to be introduced are lower alkyl or lower alkenyl, the reaction can be carried out by reacting the compound (IId) with lower alkylating agent or lower alkenylating agent.

The lower alkylating agent or lower alkenylating agent to be used in the present reaction may include conventional one such as mono(or di)lower alkyl sulfate (e.g. dimethyl sulfate), lower alkyl(lower) - alkanesulfonate (e.g. methyl methanesulfonate), halo(lower)alkane (e.g. bromomethane, iodomethane, iodoethane, iodobutane) or halo(lower)alkene (e.g. iodopropene).

When lower alkyl ester of an acid is used as a lower alkylating agent, the reaction is usually carried out in a solvent such as water, acetone, tetrahydrofuran, ethanol, ether, dimethylformamide or any other solvent which does not adversely influence the reaction.

The present reaction is preferably carried out in the present of a conventional base such as an inorganic base or an organic base.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating around boiling point of the solvent.

Process C :

The compound (IIIe) or a salt thereof can be prepared by subjecting the compound (IIId) or a salt thereof to introduction reaction of the hydroxy protective group.

The present reaction can be carried out in a conventional manner.

In case that the protective group to be introduced is a silyl group, the present reaction is carried out by reacting the compound (IIId) or a salt thereof with the compound of the formula :

$$Ra - X \qquad (VI)$$

wherein Ra is a trisubstituted silyl and
X is an acid residue.

Suitable acid residue may include halogen (e.g., chlorine or bromine).

The present reaction is preferably carried out in the presence of imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under warming.

Process D :

The compound (IIi) or a salt thereof can be prepared by subjecting the compound (IIh) or a salt thereof to elimination reaction of the hydroxy protective group.

The present elimination reaction is carried out in accordance with a conventional method such as Process E.

The present reaction is preferably carried out in the presence of a mild reagent such as tetra-n-butylammonium fluoride.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under warming.

The object compound (IIk) or a salt thereof can be prepared by oxidizing the compound (IIj) or a salt thereof.

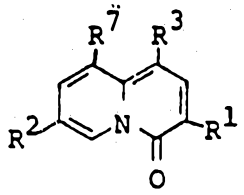
The oxidizing agent to be used in this reaction may include an inorganic peracid or a salt thereof (e.g. periodic acid, persulfuric acid, or sodium or potassium salt thereof), an organic peracid or a salt thereof (e.g. perbenzoic acid, m-chloroperbenzoic acid, performic acid, peracetic acid, chloroperacetic acid, trifluoroperacetic acid, or sodium or potassium salt thereof), ozone, hydrogen peroxide, urea-hydrogen peroxide, N-halosuccinimide (e.g. N-bromosuccinimide, N-chlorosuccinimide), hypochlorite compound (e.g. tert-butyl hypochlorite), permanganate (e.g. potassium permanganate), or any other conventional oxidizing agent which can oxidide a sulfinyl group to a sulfonyl group.

The present reaction can also be carried out in the presence of a compound comprising Group Vb or VIb metal in the Periodic Table of elements, for example, tungstic acid, molybdic acid, vanadic acid, etc., or an alkali or an alkaline earth metal salt thereof.

The present oxidation reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetic acid, chloroform, methylene chloride, acetone, methanol, ethanol or a mixture thereof.

The reaction temperature is not critical and the reaction is preferably carried out under cooling to at ambient temperature.

Particularly, the compounds (I) possessing the most potent antimicrobial activity can be represented by the following formula:



wherein R^1, R^2, R^3 and R^7 are each as defined above, and more particularly, R^1 is tetrazolylamido, R^2 and R^7 are each hydrogen, and R^3 is aryloxy or aroyl.

(to be continued to the next page.)

For the purpose of showing pharmaceutical utility of the quinolizinone compound (I), pharmaceutical test data thereof are illustrated in the following.

[1] Test compound :

N-[5-(1H-Tetrazolyl)]-4H-quinolizin-4-one-3-carboxamide (hereinafter referred to as compound (A))

N-[5-(1H-Tetrazolyl)]-1-phenyl-4H-quinolizin-4-one-3-carboxamide (hereinafter referred to as compound (B))

[2] Test :

(A) Inhibition on stress ulcer

(1) Test Method :

Sprague-Dawley rats weighing about 200 g were used. Each animal was immobilized in a small cage and put in a water bath allowing to respire. The temperature of the water bath kept at 22°C. The test compound (A) and (B) were administered orally just before the immobilization. Seven hours later, the animals were sacrificed and their stomachs were removed. The stomach was then fixed with 2% formalin. The area of ulcers was measured for each animal. The mean area (mm^2) in the test animals was compared with that in the control animals.

② Test Result :

Treatment	No.	Ulcer index		Inh. %
		mm^2	Mean ± S.E.	
Control	1	19	19.2 ± 2.8	-
	2	26		
	3	12		
	4	14		
	5	25		
Compound (A) 32 mg/kg	1	18	6.2 ± 3.0	67.7
	2	5		
	3	3		
	4	4		
	5	1		

Treatment	No.	Ulcer index		Inh. %
		mm^2	Mean ± S.E.	
Control	1	50	48.4 ± 8.3	-
	2	52		
	3	58		
	4	17		
	5	65		
Compound (B) 32 mg/kg	1	10	8.4 ± 1.9	83.7
	2	11		
	3	3		
	4	5		
	5	11		

(B) Effect on passive cutaneous anaphylaxis (PCA).

(1) Test Method

Recipient animals for PCA reactions were female Sprague-Dawley rats, 7 weeks old, 180g-200g (Nihon Kurea). Each experiment included 5 observations.

Five times crystallized ovalbumin (OVA) (Sigma Lot, 31F-8061) was used as antigen.

Female BDF1 mice, 7 weeks old (Nihon Kurea), were given a primary injection (left foot pad, s.c.) of 100 mcg OVA in 0.05ml saline and after 20 days a booster injection by the same route. Blood was collected 28 days after the primary injection and the sera were stored at -80°C.

The animals were shared with an electric clipper in advance and prepared for Passive Cutaneous Anaphylaxis (PCA) by injecting 0.05ml of mouse antiserum dilutions (1/16, 1/32) in each side of the dorsal skin.

They were then challenged 48 hours later with an intravenous injection of 1 ml of 0.5% Evans Blue containing 5 mg OVA. Fifty minutes later, they were killed and the lesions (diameter) measured.

A minimal skin response was one with a 5 mm or greater diameter blue spot measured on the dermal side of reflected skin. Drug activity was estimated using the following formula;

$$\% \text{ inhibition} = \left(1 \frac{\text{drug treated (dia;mm)}}{\text{Saline treated (dia;mm)}}\right) \times 100$$

Drugs were suspended in 0.1% methyl cellulose/saline and given intravenously with the antigen.

(2) Test Result :

	Dose mg/kg	Inhibition (%)	
		Antiserum concentration 1/16	1/32
Compound (A)	1	97.2	100
	10	94.5	100

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains an active substance of this invention in admixture with an organic or inorganic carrier or excipient suitable for external, oral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, collidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The pharmaceutical compositions can also contain preservative or bacteriostatic agents to keep the active ingredient in the desired preparations stable in activity. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired therapeutic effect upon the

process or condition of diseases.

For applying this composition to humans, it is preferably to apply it by intravenous, intramuscular or oral administration. While the dosage or therapeutically effective amount of the object compound of this invention varies from and also depends upon the age and condition of each individual patient to be treated, a daily doses of about 0.05-5 mg of the active ingredient/kg of a human being or an animal in generally give for treating diseases, and an average, single dose of about 2.5 mg, 25 mg and 250 mg in generally administered.

The following preparations and examples are given for purpose of illustrating this invention.

Preparation 1

To a solution of 2-methylpyridine (7 ml) in tetrahydrofuran (140 ml) was added dropwise a solution of n-butyl lithium (49 ml of 1.59 mol solution in hexane) with ice-cooling. The resulting dark red solution was allowed to warm to ambient temperature and stirred for an hour. After cooling to -78°C, a solution of diethyl ethoxymethylenemalonate (15.68 ml) in tetrahydrofuran (50 ml) was added over a period of 30 minutes. The reaction mixture was allowed to warm to -20°C and stirred for 30 minutes at -20°C. Acetic acid (4.48 ml) was added. The solvent was distilled off, the residue was dissolved in ethyl acetate and washed with 10% aqueous solution of sodium bicarbonate, water and saturated aqueous sodium chloride, After drying over magnesium sulfate, the ethyl acetate extract was filtered and evaporated to give an oil (27 g). The residue was chromatographed on silica gel (Merck 70 - 230 mesh, 270 g)

eluting with chloroform to give ethyl 3-ethoxy-2-ethoxycarbonyl-4-(2-pyridyl)butyrate (19 g) as an oil.

IR (film) : 1730, 1590, 1470, 1440, 1370 cm^{-1}

NMR ($CDCl_3$) δ : 0.97 (t, 3H, J=8Hz), 1.26 (t, 6H, J=8Hz), 3.12 (d, 1H, J=8Hz), 3.2-3.6 (m, 2H), 3.62 (d, 1H, J=8Hz), 4.21 (q, 4H, J=8Hz), 4.47 (q, 2H, J=8Hz), 6.97-7.80 (m, 3H), 8.42-8.67 (m, 1H)

Preparation 2

A mixture of ethyl 3-ethoxy-2-ethoxycarbonyl-4-(2-pyridyl)butyrate (18.9 g), diphenyl (48.85 g) and diphenyl ether (135.8 g) was heated to 250°C for 40 minutes. The reaction mixture was cooled to ambient temperature and chromatographed on silica gel (Merck 70-230 mesh, 620 g) eluting with hexane and then a mixture of ethanol and chloroform (1:49) to give a crude oil, which was crystallized from a mixture of ether and hexane (1:1) to give 3-ethoxycarbonyl-4H-quinolizin-4-one (11.48 g) as yellow crystal.

IR (Nujol) : 1670, 1625, 1490 cm^{-1}

NMR ($CDCl_3$) δ : 1.42 (t, 3H, J=7Hz), 4.42 (q, 2H, J=7Hz), 6.62 (d, 1H, J=8Hz), 7.02-7.38 (m, 1H), 7.53-7.68 (m, 2H), 8.33 (d, 1H, J=8Hz), 9.23-9.47 (m, 1H)

Preparation 3

The following compounds were obtained according to a similar manner to that of Preparation 1.

(1) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-[2-(5-ethylpyridyl)]butyrate.

IR (film) : 1750, 1730 cm^{-1}

(2) Ethyl 4-phenyl-3-ethoxy-2-ethoxycarbonyl-4-(2-pyridyl)butyrate.

IR (film) : 1750 (sh), 1730 cm^{-1}

(3) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-[2-(5-hydroxypyridyl)]butyrate.

IR (film) : 2550, 1730, 1490, 1270, 1160, 1090, 1025 cm^{-1}

NMR ($CDCl_3$) δ : 0.97 (t, 3H, J=7Hz), 1.25 (t, 6H, J=7Hz), 3.07 (d, 2H, J=5Hz), 3.20-4.77 (m, 8H), 6.47 (m, 1H), 7.07-7.37 (m, 2H), 8.17 (m, 1H)

(4) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-[2-(3-methylpyridyl)]butyrate.

IR (Nujol) : 1750, 1735, 1575, 1440, 860, 790 cm^{-1}

NMR ($CDCl_3$) δ : 0.92 (t, 3H, J=5Hz), 1.27 (t, 6H, J=5Hz), 2.37 (s, 3H), 3.08-3.60 (m, 4H), 3.70 (d, 1H, J=5Hz), 4.18 (q, 2H, J=5Hz), 4.22 (q, 2H, J=5Hz), 4.52 (m, 1H), 7.05 (dd, 1H, J=6Hz and 3Hz), 7.45 (d, 1H, J=6Hz), 8.42 (d, 1H, J=3Hz)

(5) Ethyl 3-ethoxy-2-carboethoxy-4-[2-(4-methylpyridyl)]butyrate.

IR (film) : 1750, 1730, 1600, 1240, 1150, 1020 cm^{-1}

NMR ($CDCl_3$) δ : 0.97 (t, 3H, J=7Hz), 1.27 (t, 6H, J=7Hz), 2.32 (s, 3H), 3.10 (d, 2H, J=5.5Hz), 3.28-3.58 (m, 2H), 4.20 (q, 3H, J=7Hz), 4.23 (q, 3H, J=7Hz), 6.87-7.13 (m, 2H), 8.40 (d, 1H, J=6Hz)

(6) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-[2-(6-methylpyridyl)]butyrate.

IR (film) : 1650, 1630, 1590, 1580, 1270, 1150, 1090 cm^{-1}

NMR ($CDCl_3$) δ : 0.97 (t, 3H, J=7Hz), 1.25 (t, 6H, J=7Hz), 2.48 (s, 3H), 3.07 (d, 2H, J=5.5Hz), 3.60 (q, 2H, J=7Hz), 3.23-3.57 (m, 1H), 4.18 (q, 4H, J=7Hz), 4.33-4.67 (m, 1H), 6.85-7.15 (m, 2H), 7.33-7.66 (m, 1H)

(7) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-(2-pyridyl)-pentanoate.

IR (film) : 1750, 1730, 1590, 1300, 1090, 1020 cm^{-1}

NMR ($CDCl_3$) δ : 1.00 (t, 3H, J=7Hz), [1.35 (t, J=7Hz), 1.25 (t, J=7Hz), 1.25 (s) 9H], 3.00-3.75 (m, 4H), 3.93-4.58 (m, 5H), 6.98-7.60 (m, 2H), 7.65 (m, 1H), 8.58 (m, 1H)

(8) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-[2-(5-methylpyridyl)]butyrate.

IR (film) : 1740, 1730, 1600, 1480, 1150, 1090, 1025 cm^{-1}

NMR ($CDCl_3$) δ : 1.00 (t, 3H, J=7Hz), 1.27 (t, 6H, J=7Hz), 2.32 (s, 3H), 3.00-3.77 (m, 4H), 4.22 (q, 3H, J=7Hz), 4.25 (q, 3H, J=7Hz), 7.03-7.50 (m, 2H), 8.37 (m, 1H)

(9) Ethyl 3-ethoxy-4-methoxy-4-(2-pyridyl)-2-ethoxycarbonylbutyrate.

IR (film) : 1750, 1730, 1590, 1365, 1090, 1025, 760 cm^{-1}

NMR ($CDCl_3$) δ : 0.78 (t, 3H, J=7Hz), 1.25 (t, 3H, J=7Hz), 1.28 (t, 3H, J=7Hz), 3.33 (d, 2H, J=4Hz), 3.60-4.60 (m, 9H), 7.07-7.90 (m, 3H), 8.62 (m, 1H)

Preparation 4

The following compounds were obtained according to a similar manner to that of Preparation 2.

(1) 7-Ethyl-3-ethoxycarbonyl-4H-quinolizin-4-one.
mp. 81-83°C.
IR (Nujol) : 1720, 1630 cm^{-1}
NMR ($CDCl_3$) δ : 1.32 (t, 3H, J=7Hz), 1.44 (t, 3H, J=7Hz), 2.76 (q, 2H, J=7Hz), 4.40 (q, 2H, J=7Hz), 6.60 (d, 1H, J=8Hz), 7.52 (s, 2H), 8.32 (d, 1H, J=8Hz), 9.20 (s, 1H)

(2) 1-Phenyl-3-ethoxycarbonyl-4H-quinolizin-4-one.
mp. 120-123°C.
IR (Nujol) : 1730, 1620 cm^{-1}
NMR ($CDCl_3$) δ : 1.36 (t, 3H, J=7Hz), 4.38 (q, 2H, J=7Hz), 7.04-7.76 (m, 7H), 8.32 (s, 1H), 9.48 (d, 1H, J=8Hz)

(3) 8-Hydroxy-3-ethoxycarbonyl-4H-quinolizin-4-one.
mp. 242°C. (dec.)
IR (Nujol) : 3300, 3200, 1680, 1660, 1620, 1300, 1140, 960, 900 cm^{-1}
NMR ($DMSO-d_6$) δ: 2.27 (t, 3H, J=7Hz), 4.23 (q, 2H, J=8Hz), 6.13 (d, 1H, J=8Hz), 7.58 (dd, 1H, J=2Hz, 8Hz), 7.90 (d, 1H, J=8Hz), 8.07 (d, 1H, J=8Hz), 8.82 (d, 1H, J=2Hz)
Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75
Found : C, 62.18; H, 5.05

(4) 9-Methyl-3-ethoxycarbonyl-4H-quinolizin-4-one.
mp. 125-126°C.

IR (Nujol) : 3090, 1725, 1645, 1590, 1125, 1100 cm^{-1}

NMR ($CDCl_3$) δ : 1.40 (t, 3H, J=7Hz), 2.50 (s, 3H), 4.42 (q, 2H, J=7Hz), 6.63 (d, 1H, J=9Hz), 7.07 (t, 1H, J=7Hz), 7.47 (d, 1H, J=7Hz), 8.35 (d, 1H, J=9Hz), 9.32 (d, J=7Hz, 1H)

Anal. Calcd for $C_{13}H_{13}NO_3$: C; 67.52, H; 5.67
Found : C; 67.51, H; 5.83

(5) 8-Methyl-3-ethoxycarbonyl-4H-quinolizin-4-one. mp. 146-148°C.

IR (Nujol) : 3060, 1720, 1660, 1640, 1245, 1155, 790 cm^{-1}

NMR ($CDCl_3$) δ : 1.40 (t, 3H, J=7Hz), 2.50 (s, 3H), 4.38 (q, 2H, J=7Hz), 6.50 (d, 1H, J=9Hz), 7.00 (dd, 1H, J=7Hz, 2Hz), 7.30 (d, 1H, J=2Hz), 8.32 (d, 1H, J=9Hz), 9.28 (d, 1H, J=7Hz)

Anal. Calcd for $C_{13}H_{13}NO_3$: C; 67.52, H; 5.67
Found : C; 67.38, H; 5.65

(6) 3-Ethoxycarbonyl-6-methyl-4H-quinolizin-4-one. mp. 90-93°C.

IR (Nujol) : 1720, 1650, 1620, 1590, 1265, 1120, 1100, 795 cm^{-1}

NMR ($CDCl_3$) δ : 1.35 (t, 3H, J=7Hz), 3.05 (s, 3H), 4.38 (q, 2H, J=7Hz), 6.38 (d, 1H, J=8Hz), 6.67 (m, 1H), 7.25 (d, 1H, J=4.5Hz), 8.18 (d, 1H, J=8Hz)

Anal. Calcd for $C_{13}H_{13}NO_3$:
C; 67.52, H; 5.67, N; 6.07
Found : C; 67.28, H; 5.63, N; 6.03

(7) 1-Methyl-3-ethoxycarbonyl-4H-quinolizin-4-one. mp. 142-143°C.

IR (Nujol) : 1720, 1650, 1620, 1595, 1300, 1230, 1160, 1120, 775 cm^{-1}

NMR ($CDCl_3$) δ : 1.42 (t, 3H, J=7Hz), 2.40 (s, 3H), 4.43 (q, 2H, J=7Hz), 7.20 (m, 1H), 7.62-7.80 (m, 2H), 8.25 (s, 1H), 9.47 (m, 1H)

Anal. Calcd for $C_{13}H_{13}NO_3$:
C; 67.52, H; 5.67, N; 6.06
Found : C; 67.49, H; 5.94, N; 6.06

(8) 7-Methyl-3-ethoxycarbonyl-4H-quinolizin-4-one. mp. 146-149°C.

IR (Nujol) : 1720, 1620, 1145, 1110 cm^{-1}

NMR ($CDCl_3$) δ : 1.42 (t, 3H, J=7Hz), 2.45 (s, 3H), 4.43 (q, 2H, J=7Hz), 6.62 (d, 1H, J=8Hz), 7.47-7.57 (m, 2H), 8.33 (d, 1H, J=8Hz), 9.23 (m, 1H)

Anal. Calcd for $C_{13}H_{13}NO_3$:
C; 67.52, H; 5.62, N; 6.06
Found : C; 67.44, H; 5.85, N; 6.00

(9) 1-Methoxy-3-ethoxycarbonyl-4H-quinolizin-4-one. mp. 132-133°C.

IR (Nujol) : 1680, 1670, 1620, 1595, 1360, 1120, 1020, 770 cm^{-1}

NMR ($CDCl_3$) δ : 1.43 (t, 3H, J=7Hz), 3.93 (s, 3H), 4.45 (q, 2H, J=7Hz), 7.25 (m, 1H), 7.67 (m, 1H), 7.97-8.20 (m, 2H), 9.47 (d, 1H, J=7.5Hz)

Anal. Calcd for $C_{13}H_{13}NO_4$:
C; 63.15, H; 5.30, N; 5.66
Found : C; 62.80, H; 5.33, N; 5.63

Preparation(5):

To a stirred solution of 3-ethoxycarbonyl-7-hydroxy-4H-quinolizin-4-one (4.5 g) in dry N,N-dimethylformamide (90 ml) was added sodium hydride (60% in mineral oil, 0.93 g) at room temperature and the resulting solution was kept for 30 minutes at 50°C. The reaction mixture was treated with methyl iodide (4.13 g) and stirred for 30 minute at the same temperature. The reaction mixture was poured into dilute hydrochloric acid solution and extracted with chloroform. The organic layer was washed with water, dried over anhydrous magnesium sulfate and evaporated to give an oil (12.3 g) which was applied to a silica gel column. Elution with chloroform-methanol (99:1) gave 3-ethoxycarbonyl-7-methoxy-4H-quinolizin-4-one (3.75 g), mp, 156-158°C.

IR (Nujol) : 1720, 1620, 1500, 1140, 1100 cm^{-1}

NMR ($CDCl_3$) δ : 1.43 (t, 3H, J=7Hz), 3.93 (s, 3H), 4.43 (q, 2H, J=7Hz), 6.63 (d, 1H, J=8.5Hz), 7.23-7.70 (m, 2H), 7.28 (d, 1H, J=8.5Hz), 9.00 (m, 1H)

Anal. Calcd for $C_{13}H_{13}NO_4$: C; 63.15, H; 5.30

Found : C; 62.62, H; 5.52

Preparation(6)

The following compounds were obtained according to a similar manner to that of Preparation 5.

(1) 3-Ethoxycarbonyl-7-n-butoxy-4H-quinolizin-4-one. mp. 132-133°C.

IR (Nujol) : 1710, 1620, 1540, 1280, 1240, 1140, 845, 780 cm^{-1}

NMR ($CDCl_3$) δ : 1.00 (t, 3H, J=6Hz), 1.43 (t, 3H, J=7.5Hz), 1.50-2.33 (m, 4H), 4.10 (t, 2H, J=6Hz), 4.43 (q, 2H, J=7.5Hz), 6.63 (d, 1H, J=8Hz), 7.23-7.67 (m, 2H), 8.28 (d, 1H, J=8Hz), 8.97 (d, 1H, J=2Hz)

Anal. Calcd for $C_{16}H_{19}NO_4$:
C; 66.42, H; 6.62, N; 4.84
Found : C; 66.54, H; 6.52, N; 4.82

(2) 3-Ethoxycarbonyl-7-isopropoxy-4H-quinolizin-4-one. mp. 132-134°C

IR (Nujol) : 1725, 1625, 1240, 1140, 1100, 970, 840 cm^{-1}

NMR ($CDCl_3$) δ : 1.42 (d, 6H, J=6Hz), 1.43 (t, 3H, J=7.5Hz), 4.43 (q, 1H, J=7.5Hz), 4.65 (m, 2H), 6.62 (d, 1H, J=8.5Hz), 7.20-7.68 (m, 2H), 8.27 (d, 1H, J=8.5Hz), 9.00 (d, 1H, J=2Hz)

Anal. Calcd for $C_{15}H_{17}NO_4$:
C; 65.44, H; 6.22, N; 5.09
Found : C; 65.66, H; 6.15, N; 5.10

Preparation 7

The following compounds were obtained according to a similar manner to that of Preparation 1.

(1) Ethyl 4-phenyl-4-(2-quinolyl)-3-ethoxy-2-ethoxycarbonylbutyrate.

IR (Film) : 1750, 1730, 1590, 1500, 1150, 1090, 1030 cm^{-1}

NMR ($CDCl_3$, δ) : 0.82 (3H, t, J=7Hz), 1.20 (3H, t, J=7Hz), 1.28 (3H, t, J=7Hz), 3.12 (1H, m), 3.42-4.47 (6H, m), 4.67 (1H, m), 5.25 (1H, m), 7.12-8.27 (11H, m)

(2) Ethyl 4-(2-pyridyl)-4-(1-naphthyl)-3-ethoxy-2-ethoxycarbonylbutyrate.

IR (Film) : 1750, 1720, 1580, 780, 750 cm^{-1}

NMR ($CDCl_3$, δ) : 0.60 (3H, t, J=7Hz), 1.20 (6H, t, J=7Hz), 2.20-4.53 (8H, m), 5.33 (1H, m), 6.95-8.10 (10H, m), 8.58 (1H, m)

(3) Ethyl 4-(2-pyridyl)-4-(4-biphenylyl)-3-ethoxy-2-ethoxycarbonylbutyrate.

IR (Film) : 1750, 1730, 1590, 1485, 1300, 1150, 760 cm^{-1}

NMR ($CDCl_3$, δ) : 0.83 (3H, t, J=7Hz), 1.33 (6H, t, J=7Hz), 3.28 (1H, m), 3.63 (2H, q, J=7Hz), 4.25 (4H, q, J=7Hz), 4.50-5.30 (2H, m), 7.02-7.83 (2H, m), 8.65 (1H, m)

(4) Ethyl 4-phenoxy-4-(2-pyridyl)-3-ethoxy-2-ethoxycarbonylbutyrate.

IR (Film) : 1750, 1730, 1590, 1490, 1200, 1060, 750 cm^{-1}

NMR ($CDCl_3$, δ) : 0.80 (3H, t, J=7Hz), 1.03 (3H, t, J=7Hz), 1.28 (3H, t, J=7Hz), 2.73 (1H, m),

3.17-3.70 (2H, m), 3.80-4.40 (4H, m), 4.60 (1H, m), 5.55 (1H, m), 6.80-7.03 (3H, m), 7.10-7.40 (3H, m), 7.42-7.80 (2H, m), 8.65 (1H, m)

(5) Ethyl 4-(3-tolyl)-4-(2-pyridyl)-3-ethoxy-2-ethoxycarbonylbutyrate.

IR (Film) : 1750, 1730, 1600, 1590, 1100, 700 cm^{-1}

NMR (CCl_4, δ) : 0.72 (3H, t, J=7Hz), 1.07-1.45 (6H, m), 2.33 (3H, s), 3.12-3.73 (3H, m), 3.87-4.48 (5H, m), 4.95 (1H, m), 6.85-7.72 (7H, m), 8.58 (1H, m)

(6) Ethyl 4-(2-pyridyl)-4-(4-chlorophenyl)-3-ethoxy-2-ethoxycarbonylbutyrate.

IR (Film) : 1750, 1730, 1590, 1490, 1090, 750 cm^{-1}

NMR ($CDCl_3$, δ) : 0.63-0.97 (3H, m), 1.05-1.50 (6H, m), 3.03-3.82 (3H, m), 3.93-4.58 (5H, m), 4.93 (1H, m), 6.90-7.72 (7H, m), 8.53 (1H, m)

(7) Ethyl-4-(2-pyridyl)-4-(3-methoxyphenyl)-3-ethoxy-2-ethoxycarbonylbutyrate.

IR (Film) : 1750, 1730, 1590, 1470, 1440, 1370, 1160, 1100, 1040, 760, 700 cm^{-1}

NMR (CCl_4, δ) : 0.73 (3H, t, J=7Hz), 1.07-1.48 (6H, m), 2.85-4.53 (8H, m), 3.72 (3H, s), 4.93 (1H, m), 6.50-7.70 (7H, m), 8.60 (1H, m)

(8) Ethyl 4-(2-tolyl)-4-(2-pyridyl)-3-ethoxy-2-ethoxycarbonylbutyrate.

IR (Film) : 3060, 1740, 1720, 1590, 1440, 1090, 860, 750 cm^{-1}

NMR (CCl_4, δ) : 0.70 (3H, t, J=7Hz), 1.03-1.48 (6H, m), 2.4 (3H, m), 2.80-4.93 (9H, m), 6.80-7.60 (7H, m), 8.47 (1H, m)

(9) Ethyl 4-(2-pyridyl)-4-t-butyldimethylsiloxy-3-ethoxy-2-ethoxycarbonylbutyrate.

IR (Film) : 1750, 1730, 1590, 1580 cm^{-1}

Preparation 8

The following compounds were obtained according to a similar manner to that of Preparation 2.

(1) 1-(1-Naphthyl)-3-ethoxycarbonyl-4H-quinolizin-4-one.

mp : 161-163°C

IR (Nujol) : 1690, 1665, 1590, 1270, 1240, 780, 770 cm^{-1}

NMR ($CDCl_3$, δ) : 1.38 (3H, t, J=7Hz), 4.43 (2H, q, J=7Hz), 7.05-7.77 (8H, m), 7.80-8.10 (2H, m), 8.43 (1H, s), 9.58 (1H, m)

Anal. Calcd for $C_{22}H_{17}NO_3$:
C; 76.95, H; 4.99, N; 4.08

Found : C; 77.14, H; 5.27, N; 3.89

(2) 1-(4-Biphenylyl)-3-ethoxycarbonyl-4H-quinolizin-4-one.

mp : 183-184.5°C

IR (Nujol) : 1690, 1680, 1625, 1590, 1260, 770, 740 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (3H, t, J=7Hz), 4.50 (2H, q, J=7Hz), 7.08-8.02 (12H, m), 8.43 (1H, s), 9.55 (1H, m),

Anal. Calcd for $C_{24}H_{19}NO_3 \cdot 1/4H_2O$:
C; 77.09, H; 5.27, N; 3.75
Found : C; 77.04, H; 5.49, N; 3.60

(3) 1-Phenoxy-3-ethoxycarbonyl-4H-quinolizin-4-one.

mp : 108-109°C

IR (Nujol) : 1680, 1670, 1620, 1590, 1225, 1200, 1000 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (3H, t, J=7Hz), 4.42 (2H, q, J=7Hz), 6.78-7.48 (6H, m), 7.57-7.98 (2H, m), 8.23 (1H, s), 9.45 (1H, m)

Anal. Calcd for $C_{18}H_{15}NO_4$:
C; 69.89, H; 4.89, N; 4.53
Found : C; 70.18, H; 5.03, N; 4.51

(4) 1-(3-Tolyl)-3-ethoxycarbonyl-4H-quinolizin-4-one.

mp : 109-111°C

IR (Nujol) : 1725, 1645, 1620, 1595, 1240, 770 cm^{-1}

NMR ($CDCl_3$, δ) : 1.42 (3H, t, J=7Hz), 2.45 (3H, s), 4.45 (2H, q, J=7Hz), 7.08-7.48 (5H, m), 7.53-7.95 (2H, m), 8.42 (1H, s), 9.55 (1H, m)

Anal. Calcd for $C_{19}H_{17}NO_3 \cdot 1/5H_2O$:
C; 73.39, H; 5.64, N; 4.50
Found : C; 73.58, H; 5.62, N; 4.49

(5) 1-(4-Chlorophenyl)-3-ethoxycarbonyl-4H-quinolizin-4-one.

mp : 159-160°C

IR (Nujol) : 1680, 1670, 1490, 1295, 1260, 1240, 1130, 1020, 765 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (3H, t, J=7Hz), 4.43 (2H, q, J=7Hz), 6.97-7.87 (7H, m), 8.32 (1H, s), 9.48 (1H, m)

Anal. Calcd for $C_{18}H_{14}ClNO_3$:
C; 65.96, H; 4.31, N; 4.27

Found : C; 65.81, H; 4.49, N; 4.19

(6) 1-(3-Methoxyphenyl)-3-ethoxycarbonyl-4H-quinolizin-4-one.

mp : 155-157°C

IR (Nujol) : 3070, 1730, 1650, 1625, 1595, 1130, 1100, 780 cm^{-1}

NMR ($CDCl_3$, δ) : 1.42 (3H, t, J=7Hz), 3.80 (3H, s), 4.40 (2H, q, J=7Hz), 6.85-7.93 (7H, m), 8.35 (1H, s), 9.47 (1H, m)

Anal. Calcd for $C_{19}H_{17}NO_4 \cdot 1/4H_2O$:
C; 69.61, H; 5.38, N; 4.27

Found : C; 69.62, H; 5.29, N; 4.19

(7) 1-(2-Tolyl)-3-ethoxycarbonyl-4H-quinolizin-4-one.

mp : 97-98°C

IR (Nujol) : 1730, 1680, 1620, 1480, 1230, 1100, 785 cm^{-1}

NMR ($CDCl_3$, δ) : 1.45 (3H, t, J=7Hz), 2.10 (3H, s), 4.48 (2H, q, J=7Hz), 7.18-7.83 (7H, m), 8.42 (1H, s), 9.68 (1H, m)

Anal. Calcd for $C_{19}H_{17}NO_3$:
C; 74.25, H; 5.57, N; 4.56

Found : C; 74.50, H; 5.66, N; 4.50

(8) 1-t-Butyldimethylsiloxy-3-ethoxycarbonyl-4H-quinolizin-4-one.

mp : 80°C

IR (Nujol) : 1695, 1675, 1620, 1590 cm^{-1}

NMR ($CDCl_3$, δ) : 0.2 (6H, s), 1.10 (9H, s), 1.45 (3H, t, J=7Hz), 4.45 (2H, q, J=7Hz), 7.10-8.0 (3H, m), 8.10 (1H, s), 9.15 (1H, d, J=8Hz)

Anal. Calcd for $C_{18}H_{25}NO_4Si$:
C; 62.22, H; 7.25, N; 4.03

Found : C; 61.97, H; 7.04, N; 4.08

Preparation 9

A mixture of 2-hydroxymethylpyridine (19.3 ml), t-butyldimethylsilyl chloride (36.2 g) and imidazole (27.2 g) in dimethylformamide (190 ml) was stirred for two hours at room temperature. Water was added to the reaction mixture and extracted with n-hexane. The organic layer was washed with water, dried over magnesium sulfate and then evaporated. The residue was distilled to give 2-t-butyldimethylsiloxymethyl-pyridine (42.30 g).

IR (Film) : 1595, 1585, 1260, 1160, 1140 cm^{-1}

NMR ($CDCl_3$, δ) : 1.0 (6H, s), 1.83 (9H, s), 4.70 (2H, s), 6.85-7.20 (1H, m), 7.25-7.70 (2H, m), 8.20-8.30 (1H, m)

Preparation 10

To a solution of 1-t-butyldimethylsiloxy-3-ethoxycarbonyl-4H-quinolizin-4-one (3.32 g) in tetrahydrofuran (100 ml) was added a solution of tetra-n-butylammonium fluoride (1M, 11.47 ml) at 0°C. The mixture was stirred for one hour and the solvent was distilled off. The residue was dissolved in ethyl acetate, washed with water and saturated sodium

chloride solution. After drying over magnesium sulfate, the solvent was filtered and evaporated. The residue was chromatographed on silica gel eluting with chloroform to give 1-hydroxy-3-ethoxycarbonyl-4H-quinolizin-4-one (1.13 g).

mp : > 250°C

IR (Nujol) : 3 100, 1690, 1650, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30 (3H, t, J=7Hz), 4.25 (2H, q, J=7Hz), 7.20-7.60 (1H, m), 7.90-8.10 (2H, m), 9.20-9.30 (1H, m), 9.60 (1H, s)

Anal. Calcd for $C_{12}H_{11}NO_4$: C; 61.80, H; 4.75, N; 6.01

Found : C; 61.11, H; 4.58, N; 5.91

Preparation 11

The following compounds were obtained according to a similar manner to that of Preparation 1.

(1) Ethyl 4-phenyl-3-ethoxy-2-ethoxycarbonyl-4-(5-hydroxy-2-pyridyl)butyrate.

(2) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-(N-methylanilino)-4-(2-pyridyl)butyrate.
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7.2Hz), 1.14 (3H, t, J=7.2Hz), 1.30 (3H, t, J=7.2Hz), 3.03 (3H, s), 3.20-4.50 (7H, m), 5.00-5.60 (2H, m), 6.50-7.80 (8H, m), 8.57 (1H, d, J=4.4Hz)

(3) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-benzoyl-4-(2-pyridyl)butyrate.

(4) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-(2-pyridyl)-4-benzylbutyrate.
IR (film) : 1750, 1730, 1635, 1585, 1365, 1290, 1245, 1185, 1140, 1090, 1025, 745, 700 cm^{-1}
NMR ($CDCl_3$, δ) : 0.98-1.50 (9H, m), 2.93-4.67 (11H, m), 6.73-7.63 (8H, m), 8.48-8.63 (1H, m)

(5) Ethyl 3-ethoxy-2-ethoxycarbonyl-4-(2-pyridyl)-4-phenylthiobutyrate.
IR (film) : 1750, 1730, 1590, 1440, 1300, 1150, 1090, 1025, 760 cm^{-1}
NMR ($CDCl_3$, δ) : 0.83-1.40 (9H, m), 3.07-4.43 (7H, m), 4.53-4.92 (2H, m), 7.0-7.73 (8H, m), 8.53 (1H, m)

Preparation 12

The following compounds were obtained according to a similar manner to that of Preparation 2.

(1) 3-Ethoxycarbonyl-7-hydroxy-1-phenyl-4H-quinolizin-4-one.

IR (Nujol) : 1720, 1620, 1490, 1450 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30 (3H, t, J=7Hz), 4.26 (2H, q, J=7Hz), 7.46 (5H, m), 7.60-7.70 (2H, m), 7.97 (1H, s), 8.98 (1H, d, J=2Hz)

Anal. Calcd for $C_{18}H_{15}NO_4$:
C, 69.89; H, 4.89; N, 4.53
Found : C, 69.20; H, 5.30; N, 4.14

(2) 3-Ethoxycarbonyl-1-(N-methylanilino)-4H-quinolizin-4-one.

IR (Nujol) : 1690, 1680, 1600, 1510, 1380, 1235 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30 (3H, t, J=7Hz), 3.30 (3H, s), 4.28 (2H, q, J=7Hz), 6.50-8.10 (8H, m), 8.15 (1H, s), 9.40 (1H, d, J=7Hz)

Anal. Calcd for $C_{19}H_{18}N_2O_3$:
C, 70.79; H, 5.63; N, 8.69
Found : C, 71.00; H, 5.40; N, 8.56

mp : 129-132°C

(3) 3-Ethoxycarbonyl-1-benzoyl-4H-quinolizin-4-one.

mp : 176-178°C

IR (Nujol) : 1750, 1630, 1580, 1485, 1220, 1110, 785 cm^{-1}

NMR ($CDCl_3$, δ) : 1.37 (3H, t, J=7Hz), 4.38 (2H, q, J=7Hz), 7.20-8.07 (7H, m), 8.62 (1H, s), 8.82-9.10 (1H, m), 9.42-9.67 (1H, m)

Anal. Calcd for $C_{19}H_{15}NO_4$:
C, 71.02; H, 4.70; N, 4.36
Found : C, 70.76; H, 4.96; N, 4.33

(4) 3-Ethoxycarbonyl-1-benzyl-4H-quinolizin-4-one.
mp : 102-105°C
IR (Nujol) : 1690, 1670, 1625, 1595, 1320, 1235, 765, 725 cm^{-1}
NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7Hz), 4.23 (2H, s), 4.48 (2H, q, J=7Hz), 7.02-7.42 (6H, m), 7.52-7.78 (2H, m), 8.28 (1H, s), 9.45 (1H, m)
Anal. Calcd for $C_{19}H_{17}NO_3$:
C, 74.25; H, 5.57; N, 4.56
Found : C, 73.97; H, 5.72; N, 4.42

(5) 3-Ethoxycarbonyl-1-phenylthio-4H-quinolizin-4-one.
mp : 171-173°C
IR (Nujol) : 1740, 1660, 1625, 1575, 1280, 1220, 1140, 1120, 780, 750 cm^{-1}
NMR ($CDCl_3$, δ) : 1.40 (3H, t, J=7Hz), 4.42 (2H, q, J=7Hz), 6.68-7.47 (5H, m), 7.73 (1H, m), 8.33 (1H, m), 8.72 (1H, s), 9.52 (1H, m)
Anal. Calcd for $C_{18}H_{15}NO_3S$:
C, 66.44; H, 4.65; N, 4.30
Found : C, 66.17; H, 4.69; N, 4.28

Preparation 13

A mixture of 2-chloromethylpyridine (50 g), N-methylaniline (42 g), and potassium carbonate (120 g) in N,N-dimethylformamide (200 ml) was stirred for 4 hours at 120°C. The reaction mixture was cooled to room temperature, added to water (1 ℓ), and extracted with ether. The ether extract was washed with water and then treated with activated carbon. After drying over magnesium sulfate, the ether extract was filtered

and concentrated. The residue was crystallized from isopropyl alcohol to give N-methyl-N-(2-pyridylmethyl)-aniline (39 g).

mp : 60°C

IR (Nujol) : 1610, 1590, 1570, 1510, 1470, 1440, 1360 cm^{-1}

Preparation 14

To a solution of 2-methylpyridine (9.31 g) in tetrahydrofuran (200 ml) was added a 1.5M hexane solution of n-butyllithium (73.3 ml) at -20°C. The resulting solution was stirred for 30 minutes at room temperature and added to a solution of ethyl benzoate (15.02 g) in tetrahydrofuran (100 ml) at -60°C. After stirring for 2 hours at -60°C, acetic acid (15 ml) was added and the resulting mixture was allowed to warm to room temperature and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The aqueous layer was reextracted with ethyl acetate and the combined extracts were washed with water, 10% aqueous solution of sodium hydrogen carbonate, and saturated aqueous sodium chloride. After drying over magnesium sulfate, the ethyl acetate extracts were filtered and evaporated. The residue (20.5 g) was chromatographed on silica gel (Merck 70-230 mesh, 308 g) eluting with chloroform to give 2-pyridylmethyl phenyl ketone (10.86 g) as an oil.

IR (Nujol) : 1680, 1630, 1600, 1545, 1270, 1200, 1145, 1060, 800, 775, 690 cm^{-1}

NMR ($CDCl_3$, δ) : 4.43 (1.5H, s), 6.02 (0.5H, s), 6.83-8.65 (9H, m)

Preparation 15

(1) To a solution of 5-hydroxy-2-methylpyridine (10.66 g) in tetrahydrofuran (426 ml) was added

a solution of n-butyllithium (1.5M in hexane, 143 ml) at -30°~-10°C. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour at room temperature. After cooling to -78°C, cyclohexane (11.14 ml) was added dropwise and allowed to warm to 0°C and stirred for 30 minutes at 0°C. After addition of acetic acid (24.6 ml), the solvent was distilled off and the residue was diluted with ethyl acetate, and washed successively with water, 10% aqueous sodium hydrogen carbonate and aqueous saturated sodium chloride. After drying over magnesium sulfate, the ethyl acetate extract was filtered and evaporated. The residue was washed with ethyl acetate to give 5-hydroxy-2-[(1-hydroxycyclohexyl)methyl]pyridine (11.96 g).

IR (Nujol) : 1615, 1575, 1500, 1460 cm^{-1}

NMR (CD_3OD, δ) : 1.20-2.00 (10H, m), 2.90 (1H, s), 4.95 (2H, s), 7.20 (2H, m), 8.05 (1H, d, J=2.0Hz)

(2) A solution of 5-hydroxy-2-[(1-hydroxycyclohexyl)methyl]pyridine (1 g) in acetic acid (15 ml) containing sulfuric acid (5 ml) was heated to reflux for 1 hour. After cooling to room temperature, the reaction mixture was poured on an ice, basified with 10% aqueous sodium hydrogen carbonate, and extracted with ether. The combined ether extracts were washed with aqueous saturated sodium chloride, dried over magnesium sulfate, filtered, and concentrated. The residue was washed with isopropylalcohol to give 2-benzyl-5-hydroxypyridine (409 mg).

IR (Nujol) : 1560, 1450, 1370, 1280 cm^{-1}

NMR ($CDCl_3$, δ) : 4.07 (2H, s), 6.85-7.43 (7H, m), 8.08 (1H, d, J=3.0Hz), 10.30 (1H, broad s)

Preparation 16

To a solution of 1-phenylthio-3-ethoxycarbonyl-4H-quinolizin-4-one (1.0 g) in acetic acid (20 ml) and chloroform (7.5 ml), was added potassium permanganate (583 mg) at 0°C. After stirring for two hours at the same temperature, the reaction mixture was allowed to warm to room temperature and stirred further for one hour. Potassium permanganate (194 mg) was added and stirred overnight. To the resulting reaction mixture was added. Saturated aqueous sodium thiosulfate solution with ice-cooling and the mixture was extracted with chloroform. After drying over magnesium sulfate, the chloroform extract was filtered and evaporated. The residue was washed with diisopropyl ether to give 1-phenylsulfonyl-3-ethoxycarbonyl-4H-quinolizin-4-one (583 mg), mp 182°C.

IR (Nujol) : 1710, 1680, 1640, 1580, 1200, 1150 cm^{-1}

NMR ($CDCl_3$, δ) : 1.45 (3H, t, J=7Hz), 4.45 (2H, q, J=7Hz), 7.20-8.10 (7H, m), 8.60 (1H, d, J=8Hz), 9.18 (1H, s), 9.50 (1H, d, J=8Hz)

Anal. Calcd for $C_{18}H_{15}NO_5S$: C, 60.50; H, 4.23; N, 3.92

Found : C, 60.44; H, 4.51; N, 3.88

Preparation 17

To a solution of 3-ethoxycarbonyl-7-hydroxy-1-phenyl-4H-quinolizin-4-one (5 g) in N,N-dimethylformamide (100 ml) was added sodium hydride (63.6% in mineral oil, 732 mg) at 50°C. After stirring for 30 minutes at 50°C, n-butyliodide (2.77 ml) was added. After stirring for 1 hour at 50°C, the mixture was cooled to room temperature and added to a mixture of aqueous hydrogen chloride and an ice.

The mixture was extracted with chloroform and the chloroform extract was washed with 10% aqueous sodium hydrogen carbonate and aqueous saturated sodium chloride. After drying over magnesium sulfate, the chloroform extract was filtered and concentrated in vacuo. The residue was chromatographed on silica gel (Merck 70-230 mesh, 100 g), eluting with chloroform and then 10% methanol in chloroform to give 3-ethoxycarbonyl-7-(n-butoxy)-1-phenyl-4H-quinolizin-4-one (2.37 g).

mp : 94-95°C

IR (Nujol) : 1730, 1690, 1655, 1630, 1480 cm^{-1}

NMR ($CDCl_3$, δ) : 0.95 (3H, t, J=5Hz), 1.42 (3H, t, J=5Hz), 1.30-2.10 (4H, m), 4.13 (2H, t, J=5Hz), 4.45 (2H, q, J=5Hz), 7.30 (1H, d, J=7Hz), 7.42 (5H, m), 7.67 (1H, d, J=7Hz), 8.27 (1H, s), 9.08 (1H, d, J=2Hz)

Anal. Calcd for $C_{22}H_{23}NO_4$:
C, 72.31; H, 6.34; N, 3.83

Found : C, 71.74; H, 6.39; N, 3.80

Preparation 18

The following compound was obtained according to a similar manner to that of Preparation 5.

1-Allyloxy-3-ethoxycarbonyl-4H-quinolizin-4-one.

mp : 82-84°C

IR (Nujol) : 1690, 1680, 1660, 1620, 1580, 1320, 1235, 1100, 1015, 770 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7Hz), 4.42 (2H, q, J=7Hz), 4.50-4.75 (2H, m), 5.15-5.67 (2H, m), 5.78-6.47 (1H, m), 6.97-8.32 (4H, m), 9.47 (1H, d, J=7.5Hz)

Anal. Calcd for $C_{15}H_{15}NO_4$:
C, 65.93; H, 5.53; N, 5.13

Found : C, 66.11; H, 5.36; N, 4.94

Preparation 19

The following compound was obtained according to a similar manner to that of Preparation 14.

(5-Hydroxypyridin-2-yl)methyl phenyl ketone

NMR ($CDCl_3$, δ) : 4.44 (2H, broad s), 6.85-7.70 (5H, m), 7.70-8.30 (3H, m), 9.34 (2H, s)

Preparation 20

The following compound was obtained according to a similar manner to that of Preparation 1.

Ethyl 4-benzoyl-3-ethoxy-2-ethoxycarbonyl-4-(5-hydroxypyridin-2-yl)butyrate

IR (Nujol) : 1730, 1720, 1675, 1595 cm^{-1}

Preparation 21

The following compound was obtained according to a similar manner to that of Preparation 2.

1-Benzoyl-3-ethoxycarbonyl-7-hydroxy-4H-quinolizin-4-one.

IR (Nujol) : 1740, 1630, 1570, 1490 cm^{-1}

NMR (DMSO-d_6, δ) : 1.22 (3H, t, J=7Hz), 4.27 (2H, q, J=7Hz), 7.43-7.97 (6H, m), 8.22 (1H, s), 8.87 (1H, d, J=10Hz), 8.95 (1H, d, J=2Hz)

Preparation 22

The following compound was obtained according to a similar manner to that of Preparation 5.

1-Benzoyl-3-ethoxycarbonyl-7-n-butoxy-4H-quinolizin-4-one.

mp : 158-159°C

IR (Nujol) : 1740, 1680, 1630, 1580, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 0.98 (3H, t, J=5Hz), 1.23 (3H, t, J=7Hz), 1.30-2.10 (4H, m), 4.02-4.48 (4H, m), 7.37-8.18 (6H, m), 8.33 (1H, s), 8.88 (1H, d, J=10Hz), 9.03 (1H, d, J=2Hz)

Preparation 23

To a solution of sodium ethoxide (sodium, 151 mg) in ethanol (20 ml) was added ethyl pyrid-2-ylacetate (1 ml) at room temperature and the mixture was stirred for 1 hour at the same temperature. To the mixture was added diethyl ethoxymethylenemalonate (1.33 ml) at room temperature and the mixture was stirred at room temperature overnight. To the mixture was added acetic acid (0.75 ml) at room temperature and the precipitate was filtered and washed with water to give 1,3-diethoxycarbonyl-4H-quinolizin-4-one (896 mg).

mp : 130-131°C

IR (Nujol) : 1680, 1625, 1585 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (6H, t), 4.20-4.55 (4H, m), 7.20-7.46 (1H, m), 7.72-8.00 (1H, m), 9.15 (1H, s), 9.27-9.64 (2H, m).

Example 1

To a solution of 3-ethoxycarbonyl-4H-quinolizin-4-one (2.17 g) in methanol (65.2 ml) was added dropwise 6N aqueous sodium hydroxide (6.5 ml) at room temperature. After stirring for 20 minutes, water (10 ml) was added. After stirring for 20 minutes, water (30 ml) was also added. After stirring for an hour, the reaction mixture was acidified to pH 3 with 4N aqueous hydrochloric acid. The precipitate was filtered and washed with water to give 4H-quinolizin-4-one-3-carboxylic acid (1.75 g) as pale yellow crystal. mp 233°C.

IR (Nujol) : 1730, 1610, 1585, 1320 cm^{-1}

NMR (DMSO-d_6) δ : 7.26 (d, 1H, J=9Hz), 7.50-7.95 (m, 1H), 8.00-8.20 (m, 2H), 8.41 (d, 1H, J=9Hz), 9.20-9.40 (m, 1H)

Example 2

To a suspension of 4H-quinolizin-4-one-3-carboxylic acid (1.69 g) in N,N-dimethylformamide (16.9 ml) was added 1,1'-carbonyldiimidazole (2.17 g) at ambient temperature. The resulting suspension was heated to 100°C for 30 minutes and 5-amino-1H-tetrazole (1.06 g) was added at 100°C. After stirring for 20 minutes at 100°C, the reaction mixture was cooled to 0°C. The precipitate was filtered and washed with

pre-cooled N,N-dimethylformamide and then ether to give N-[5-(1H-tetrazolyl)]-4H-quinolizin-4-one-3-carboxamide (2.0 g) as yellow solid. mp > 260°C.

IR (Nujol) : 3200, 1660, 1620, 1500, 1310 cm^{-1}

NMR (CF_3COOH) δ : 7.42 (d, 1H, J=8Hz), 7.68-7.88 (m, 1H), 7.98-8.29 (m, 2H), 8.72 (d, 1H, J=8Hz), 9.48 (d, 1H, J=8Hz)

Analysis Calcd. for $C_{11}H_8O_2N_6$: C; 51.56, H; 3.15, N; 32.80

Found : C; 51.70, H; 3.22, N; 32.99

Example 3

The following compounds were obtained according to a similar manner to that of Example 1.

(1) 7-Ethyl-4H-quinolizin-4-one-3-carboxylic acid. mp. 193-195°C.

IR (Nujol) : 3100, 1725, 1700, 1605 cm^{-1}

NMR (CF_3COOH) δ : 1.52 (t, 3H, J=8Hz), 3.12 (q, 2H, J=8Hz), 7.92 (d, 1H, J=9Hz), 8.32 (s, 2H), 8.73 (d, 1H, J=9Hz), 9.30 (m. 1H).

Analysis Calcd. for $C_{12}H_{11}NO_3$: C; 66.35, H; 5.10, N; 6.45

Found : C; 66.40, H; 5.14, N; 6.46

(2) 1-Phenyl-4H-quinolizin-4-one-3-carboxylic acid. mp. 198°C.

IR (Nujol) : 3315, 1740, 1620 cm^{-1}

NMR (CF_3COOH) δ : 7.32-7.82 (m, 5H), 7.92-8.23 (m, 1H), 8.25-8.52 (m, 2H), 8.70 (s, 1H), 9.48-9.72 (m, 1H),

Analysis Calcd. for $C_{16}H_{11}NO_3 \cdot 5/4H_2O$: C; 66.78, H; 4.64, N; 4.87

Found : C; 66.89, H; 4.22, N; 4.59

(3) 7-Hydroxy-4H-quinolizin-4-one-3-carboxylic acid. mp. > 270°C

IR (Nujol) : 3120, 2690, 1690, 1590 cm^{-1}

NMR (CF_3COOH) δ : 7.87 (d, 1H, J=8.5Hz), 8.07-8.42 (m, 2H), 8.58 (d, 1H, J=8.5Hz), 9.07 (m, 1H)

Anal. Calcd for $C_{10}H_7NO_4 \cdot 1/4H_2O$:
C; 57.28, H; 3.61, N; 6.68
Found : C; 57.51, H; 3.60, N; 6.75

(4) 7-Methoxy-4H-quinolizin-4-one-3-carboxylic acid. mp. 215-216°C.

IR (Nujol) : 3150, 3100, 1700, 1610, 1590 cm^{-1}

NMR (CF_3COOH) δ : 4.18 (s, 3H), 7.88 (d, 1H, J=8.5Hz), 8.10-8.47 (m, 2H), 8.67 (d, 1H, J=8.5Hz), 8.88 (m, 1H)

Anal. Calcd for $C_{11}H_9NO_4$:
C; 60.27, H; 4.14, N; 6.39
Found : C; 59.90, H; 4.38, N; 6.48

(5) 9-Methyl-4H-quinolizin-4-one-3-carboxylic acid. mp. 259-260°C.

IR (Nujol) : 3100, 3020, 1740, 1610, 1590, 1120, 780 cm^{-1}

NMR (DMSO-d_6) δ : 2.92 (s, 3H), 7.90 (d, 1H, J=7.5Hz), 8.07 (d, 1H, J=9.5Hz), 8.05-8.38 (m, 1H), 8.82 (d, 1H, J=9.5Hz), 9.42 (d, 1H, J=7.5Hz)

Anal. Calcd for $C_{11}H_9NO_3$:
C; 65.02, H; 4.46, N; 6.89
Found : C; 64.92, H; 4.76, N; 6.89

(6) 8-Methyl-4H-quinolizin-4-one-3-carboxylic acid. mp. 228-230°C.

IR (Nujol) : 3090, 3030, 2700, 1630, 1620, 1580, 785 cm^{-1}

NMR (CF_3COOH) δ : 2.82 (s, 3H), 7.82 (d, 1H, J=9Hz), 7.92 (dd, 1H, J=7Hz, 2Hz), 8.17 (d, 1H, J=2Hz), 8.68 (d, 1H, J=9Hz), 9.37 (d, 1H, J=7Hz)

Anal. Calcd for $C_{11}H_9NO_3$: C; 65.02, H; 4.46, N;6.89
Found : C; 64.88, H; 4.79, N; 6.85

(7) 6-Methyl-4H-quinolizin-4-one-3-carboxylic acid.
mp. 185-187°C.
IR (Nujol) : 3100, 2700, 1720, 1615, 1595, 1295, 1040, 800 cm^{-1}
NMR (CF_3COOH) δ : 3.45 (s, 3H), 7.82 (d, 1H, J=9Hz), 7.58-7.97 (m, 1H), 8.10-8.30 (m, 2H), 8.68 (d, 1H, J=9Hz)
Anal. Calcd for $C_{11}H_9NO_3$: C; 65.02, H; 4.46, N; 6.89
Found : C; 64.60, H; 4.52, N; 6.91

(8) 1-Methyl-4H-quinolizin-4-one-3-carboxylic acid.
mp. 258-260°C.
IR (Nujol) : 1740, 1610, 1450, 780 cm^{-1}
NMR (CF_3COOH) δ : 2.87 (s, 3H), 8.15 (m, 1H), 8.35-8.77 (m, 3H), 9.66 (m, 1H)
Anal. Calcd for $C_{11}H_9NO_3$: C; 65.02, H; 4.46, N; 6.89
Found : C; 64.70, H; 4.56, N; 6.86

(9) 7-Methyl-4H-quinolizin-4-one-3-carboxylic acid. mp. 222-224°C
IR (Nujol) : 1720, 1600, 1590, 1320, 1125, 1110, 840 cm^{-1}
NMR (CF_3COOH) δ : 2.77 (s, 3H), 7.93 (d, 1H, J=9Hz), 8.22-8.38 (m, 2H), 8.73 (d, 1H, J=9Hz), 9.32 (s, 1H)
Anal. Calcd for $C_{11}H_9NO_3$: C; 65.02, H; 4.46, N; 6.89
Found : C; 65.04, H; 4.31, N; 6.91

(10) 1-Methoxy-4H-quinolizin-4-one-3-carboxylic acid. mp. 259-261°C.

IR (Nujol) : 3100, 1630, 1620, 1580, 1100, 1070, 780 cm^{-1}

NMR (CF_3COOH) δ : 4.27 (s, 3H), 8.00-8.67 (m, 3H), 8.90 (m, 1H), 9.52 (d, 1H, J=7.5Hz)

Anal. Calcd for $C_{11}H_9NO_4$: C; 60.28, H; 4.14, N; 6.39
Found : C; 59.64, H; 4.15, N; 6.30

(11) 7-n-Butoxy-4H-quinolizin-4-one-3-carboxylic acid. mp. 120-122°C.

IR (Nujol) : 1725, 1600, 1590, 1320, 1070, 1000 cm^{-1}

NMR (CF_3COOH) δ : 1.07 (t, 3H, J=6Hz), 1.30-2.20 (m, 4H), 4.40 (t, 2H, J=6Hz), 7.90 (d, 1H, J=9.5Hz), 8.13-8.43 (m, 2H), 8.67 (d, 1H, J=9.5Hz), 8.93 (d, 1H, J=2Hz)

Anal. Calcd for $C_{14}H_{15}NO_4$: C; 64.36, H; 5.79, N; 5.36
Found : C; 64.46, H; 5.80, N; 5.31

(12) 7-Isopropoxy-4H-quinolizin-4-one-3-carboxylic acid. mp. 218-219°C.

IR (Nujol) : 3140, 3090, 1720, 1620, 1120, 1060, 1000, 780 cm^{-1}

NMR (CF_3COOH) δ : 1.67 (d, 6H, J=6Hz), 4.97 (1H, J=6Hz), 7.88 (d, 1H, J=9Hz), 8.10-8.43 (m, 4H), 8.63 (d, 1H, J=9Hz), 8.90 (d, 1H, J=2Hz)

Anal. Calcd for $C_{13}H_{13}NO_4$: C; 63.15, H; 5.30, N; 5.66
Found : C; 63.28, H; 5.18, N; 5.65

Example 4

The following compounds were obtained according to a similar manner to that of Example 2.

(1) N-[3-(4H-1,2,4-Triazolyl)]-4H-quinolizin-4-one 3-carboxamide. mp. > 250°C.

IR (Nujol) : 3400, 3300, 1700, 1660, 1650, 1620 cm^{-1}

NMR (CF_3COOH) δ : 7.90-9.60 (m, 7H)

Anal. Calcd for $C_{12}H_9N_5O_2$:
C; 56.47, H; 3.55, N; 27.44
Found : C; 56.83, H; 3.79, N; 27.50

(2) N-[5-(1H-Tetrazolyl)]-9-methyl-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.

IR (Nujol) : 3200, 3100, 3080, 1660, 1620, 1590, 790 cm^{-1}

NMR (CF_3COOH) δ : 2.80 (s, 3H), 7.50-7.87 (m, 2H), 8.08 (d, 1H, J=7Hz), 8.78 (d, 1H, J=9Hz), 9.43 (d, 1H, J=7Hz)

Anal. Calcd for $C_{12}H_{10}N_6O_2$:
C; 53.33, H; 3.73, N; 35.10
Found : C; 55.28, H; 3.88, N; 31.35

(3) N-[5-(1H-Tetrazolyl)]-7-ethyl-4H-quinolizin-4-one-3-carboxamide. mp. > 250°C.

IR (Nujol) : 3200, 1660, 1640, 1620, 1590, 1490 cm^{-1}

NMR (CF_3COOH) δ : 1.50 (t, 3H, J=7Hz), 3.05 (q, 2H, J=7.5Hz), 7.45 (d, 1H, J=9Hz), 8.08 (s, 2H), 8.68 (d, 1H, J=9Hz), 9.33 (m, 1H)

Anal. Calcd for $C_{13}H_{12}N_6O_2$: C; 54.93, H; 4.25, N; 29.56
Found : C; 55.32; H; 4.32, N; 29.72

(4) N-[5-(1H-Tetrazolyl)]-1-phenyl-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.

IR (Nujol) : 3180, 3100, 1680, 1620, 1490 cm^{-1}

NMR (CF_3COOH) δ : 7.27-8.02 (m, 6H), 8.05-8.35 (m, 2H), 8.70 (s, 1H), 9.48-9.75 (m, 1H)

Anal. Calcd for $C_{17}H_{12}N_6O_2$:
C; 61.44, H; 3.64, N; 25.29

Found : C; 61.21, H; 3.80, N; 24.83

(5) N-[5-(1H-Tetrazolyl)]-7-hydroxy-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.

IR (Nujol) : 3120, 3090, 2530, 1670, 1640, 1540, 980 cm^{-1}

NMR (CF_3COOH) δ : 7.73-7.70 (m, 2H), 8.03 (m, 1H), 8.67 (m, 1H), 9.15 (m, 1H)

Anal. Calcd for $C_{11}H_8N_6O_3$:
C; 49.06, H; 3.32, N; 32.11

Found : C; 48.56, H; 3.47, N; 32.66

(6) N-[5-(1H-Tetrazolyl)]-7-methoxy-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.

IR (Nujol) : 3200, 3100, 1680, 1650, 1610 cm^{-1}

NMR (CF_3COOH) δ : 4.13 (s, 3H), 7.42 (d, 1H, J=9Hz), 7.73-8.17 (m, 2H), 8.58 (d, 1H, J=9Hz), 8.92 (m, 1H)

Anal. Calcd for $C_{12}H_{10}N_6O_3$:
C; 50.35, H; 3.52, N; 29.36

Found : C; 50.54, H; 3.55, N; 29.63

(7) N-(2-Thiazolyl)-4H-quinolizin-4-one-3-carboxamide. mp. 240°C.

IR (Nujol) : 3100, 1665, 1620, 1490, 1320 cm^{-1}

NMR (CF_3COOH) δ : 7.30-7.90 (m, 4H), 8.03-8.47 (m, 2H), 8.75 (d, 1H, J=9Hz), 9.42 (d, 1H, J=7Hz)

Anal. Calcd for $C_{13}H_9N_3OS$:
C; 57.56, H; 3.34, N; 15.49

Found : C; 57.25, H; 3.77, N; 15.24

(8) N-(2-Hydroxyphenyl)-4H-quinolizin-4-one-3-carboxamide. mp. 247°C.

IR (Nujol) : 1650, 1630, 1600 cm^{-1}

NMR ($CDCl_3$) δ : 6.80-7.50 (m, 5H), 7.70 (d, 2H, J=7Hz), 8.76 (d, 1H, J=8Hz), 9.40 (d, 1H, J=8Hz), 10.10 (s, 1H)

Anal. Calcd for $C_{16}H_{12}N_2O_3$:
C; 68.57, H; 4.32, N; 9.99
Found : C; 68.04, H; 4.48, N; 10.11

(9) N-(2-Pyrimidinyl)-4H-quinolizin-4-one-3-carboxamide. mp. 218°C.

IR (Nujol) : 1690, 1650, 1620 cm^{-1}

NMR (DMSO-d_6) δ : 7.10-8.20 (m, 5H), 8.50-8.80 (m, 3H), 9.20-9.40 (m, 1H)

Anal. Calcd for $C_{14}H_{10}N_4O_2$:
C; 63.15, H; 3.79, N; 21.04
Found : C; 61.20, H; 4.19, N; 20.76

(10) N-[5-(1H-Tetrazolyl)]-8-methyl-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C

IR (Nujol) : 3200, 3150, 1660, 1635, 1590, 780 cm^{-1}

NMR (CF_3COOH) δ : 2.73 (s, 3H), 7.35 (d, 1H, J=9Hz), 7.65 (dd, 1H, J=7Hz, 2Hz), 7.88 (d, 1H, J=2Hz), 8.65 (d, 1H, J=9Hz), 9.38 (d, 1H, J=7Hz)

Anal. Calcd for $C_{12}H_{10}N_6O_2$:
C; 53.33, H; 3.73, N; 31.10
Found : C; 54.03, H; 3.84; N; 30.38

(11) N-[5-(1H-Tetrazolyl)]-6-methyl-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.

IR (Nujol) : 3200, 1660, 1620, 1590, 1030, 820, 790 cm^{-1}

NMR (CF_3COOH) δ : 3.33 (s, 3H), 7.37 (d, 1H, J=9Hz), 7.37-7.62 (m, 1H), 7.87-8.07 (m, 2H), 8.60 (d, 1H, J=9Hz)

Anal. Calcd for $C_{12}H_{10}N_6O_2$:
C; 53.33, H; 3.73, N; 31.10
Found : C; 53.63, H; 3.92, N; 31.42

(12) N-[5-(1H-Tetrazolyl)]-1-methyl-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.
IR (Nujol) : 3180, 1665, 1640, 1620, 1595, 1500, 1040, 1020, 770 cm^{-1}
NMR (CF_3COOH) δ : 2.77 (s, 3H), 7.83-8.10 (m, 1H), 8.38 (d, 2H, J=3Hz), 8.72 (s, 1H), 9.65 (d, 1H, J=6Hz)
Anal. Calcd for $C_{12}H_{10}N_6O_2$:
C; 53.55, H; 3.73, N; 31.10
Found : C; 53.71, H; 4.04, N; 31.03

(13) N-[5-(1H-Tetrazolyl)]-7-methyl-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.
IR (Nujol) : 3200, 1670, 1610, 1580, 1500, 1310, 1060, 1040, 840 cm^{-1}
NMR (CF_3COOH) δ : 2.73 (s, 3H), 7.47 (d, 1H, J=9Hz), 8.03-8.50 (m, 2H), 8.70 (d, 1H, J=9Hz), 9.33 (s, 1H)
Anal. Calcd for $C_{12}H_{10}N_6O_2$:
C; 53.33, H; 3.73, N; 31.10
Found : C; 53.61, H; 3.69, N; 31.34

(14) N-[6-(1,2,4-Triazinyl)]-4H-quinolizin-4-one-3-carboxamide. mp. 263°C (dec.)
IR (Nujol) : 3100, 1690, 1620, 1580, 1520, 1500, 1040 cm^{-1}
NMR (CF_3COOH) δ : 7.33 (d, 1H, J=9Hz), 7.60-8.23 (m, 3H), 8.72 (d, 1H, J=9Hz), 9.10-9.17 (m, 1H), 9.27-9.68 (m, 2H)
Anal. Calcd for $C_{13}H_9N_5O_2 \cdot 1/4H_2O$:
C; 57.51, H; 3.59, N; 25.97
Found : C; 57.51, H; 3.52, N; 25.77

(15) N-pyrazinyl-4H-quinolizin-4-one-3-carboxamide. mp. > 250°C.

IR (Nujol) : 3400, 1675, 1620, 1580, 1520, 1500, 1400, 1320, 780 cm^{-1}

NMR (CF_3COOH) δ : 7.43 (d, 1H, J=9.5Hz), 7.78 (m, 1H), 8.00-8.23 (m, 2H), 8.77 (d, 9.5Hz), 8.83 (d, J=7.5Hz), 8.78-8.98 (m, 3H), 9.55 (d, 1H, J=7.5Hz), 9.82 (s, 1H)

Anal. Calcd for $C_{14}H_{10}N_4O_2 \cdot H_2O$:
C; 59.15, H; 4.25, N; 19.71

Found : C; 59.58, H; 4.03, N; 19.99

(16) N-(2-Pyridyl)-4H-quinolizin-4-one-3-carboxamide. mp. 228-230°C.

(17) N-[6-(3-Chloropyridazinyl)]-4H-quinolizin-4-one-3-carboxamide. mp. > 250°C.

IR (Nujol) : 3100, 1680, 1620, 1580, 1510, 1070, 780 cm^{-1}

NMR (CF_3COOH) δ : 7.38 (d, 1H, J=9Hz), 7.63-8.50 (m, 5H), 8.77 (d, 1H, J=9Hz), 9.48 (m, 1H).

Anal. Calcd for $C_{14}H_9ClN_4O_2$:
C; 55.92, H; 3.02, N; 18.63
Found : C; 55.65, H; 3.15, N; 19.14

(18) N-[5-(1H-Tetrazolyl)]-1-methoxy-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.

IR (Nujol) : 3200, 1660, 1650, 1620, 1290, 1015, 775 cm^{-1}

NMR (CF_3COOH) δ : 4.33 (s, 3H), 8.13 (m, 1H), 8.33 (s, 1H), 8.43-9.02 (m, 2H), 9.62 (d, 1H, J=7.5Hz)

Anal. Calcd for $C_{12}H_{10}N_6O_3$:
C; 50.35, H; 3.52, N; 29.36
Found : C; 50.46, H; 3.45, N; 29.39

(19) N-[2-(4,6-Dimethylpyrimidinyl)]-4H-q[illegible]zin-4-one-3-carboxamide. mp. 217-218°C.

IR (Nujol) : 3460, 3120, 1690, 1650, 1620, 1060, 790 cm^{-1}

NMR (CF_3COOH) δ : 2.87 (s, 6H), 7.38 (d, 1H, J=9Hz), 7.47-8.32 (m, 4H), 8.75 (d, 1H, J=9Hz), 9.63 (d, 1H, J=7.5Hz)

Anal. Calcd for $C_{16}H_{14}N_4O_2 \cdot 1/3H_2O$:
C; 63.99, H; 4.92, N; 19.04
Found : C; 63.99, H; 4.92, N; 18.66

(20) N-[5-(1H-Tetrazolyl)]-7-n-butoxy-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.

IR (Nujol) : 3200, 1665, 1640, 1625, 1590, 1000, 850, 780 cm^{-1}

NMR (CF_3COOH) δ : 1.10 (t, 3H, J=6.5Hz), 1.37-2.3 (m, 4H), 4.38 (t, 2H, J=6.5Hz), 7.53 (d, 1H, J=8.5Hz), 7.97-8.28 (m, 2H), 8.67 (d, 1H, J=8.5Hz), 9.03 (s, 1H)

Anal. Calcd for $C_{15}H_{16}N_6O_3$: C; 54.88, H; 4.91, N; 26.00
Found : C; 55.14, H; 4.89, N; 25.83

(21) N-[5-(1H-Tetrazolyl)]-7-isopropoxy-4H-quinolizin-4-one-3-carboxamide. mp. > 270°C.

IR (Nujol) : 3200, 1680, 1650, 1620, 1500, 1310, 780 cm^{-1}

NMR (CF_3COOH) δ : 1.77 (d, 6H, J=6Hz), 5.12 (sept, 1H, J=6Hz), 7.67 (d, 1H, J=8.5Hz), 8.02-8.37 (m, 2H), 8.80 (d, 1H, J=8.5Hz), 9.20 (s, 1H)

Anal. Calcd for $C_{14}H_{14}N_6O_3$:
C; 53.50, H; 4.49, N; 26.74
Found : C; 53.73, H; 4.41, N; 27.04

Example 5

(1) To a suspension of 4H-quinolizin-4-one-3-carboxylic acid (2.27 g) in dry N,N-dimethylformamide (22.7 ml) was added 1,1'-carbonyldiimidazole (2.92 g). The resulting suspension was heated to 100°C and kept for 30 minutes. After cooling to room temperature the resulting solution was treated with dry ammonia and stirred for 20 minutes. The crystals separated was collected by filtration and washed with water to give 4H-quinolizin-4-one-3-carboxamide (1.94 g).
mp. 230-232°C.

IR (Nujol) : 3350, 3120, 1660, 1630 cm^{-1}

NMR (CF_3COOH) δ : 7.58 (d, 1H, J=9Hz), 7.75-8.07 (m, 1H), 8.12 (m, 2H), 8.60 (d, 1H, J=9Hz) and 9.52 (d, 1H, J=7Hz).

Anal. Calcd for $C_{10}H_8N_2O_2$:
C; 63.83, H; 4.28, N; 14.89
Found : C; 63.96, H, 4.43, N; 14.90

(2) A mixture of 4H-quinolizin-4-one-3-carboxamide (1.0 g) and phosphorus oxychloride (50 ml) was refluxed for one hour. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in aqueous sodium bicarbonate solution and chloroform.

The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and then evaporated. The residue was chromatographed on silica gel (30 g) eluting with chloroform-methanol (50:1) to give 3-cyano-4H-quinolizin-4-one, which on recrystallization from ether gave crystals (800 mg), mp. 198-200°C.

IR (Nujol) : 2420, 1680, 1620 cm^{-1}

NMR (DMSO-d_6) δ : 6.93 (d, 1H, J=8Hz), 7.30-7.60 (m,1H), 7.86-8.20 (m, 3H), 9.13 (d, 1H, J=8Hz)

(3) To a solution of 3-cyano-4H-quinolizin-4-one (1.20 g) in a mixture of pyridine (50 ml) and triethylamine (30 ml) was bubbled hydrogen sulfide gas over a period of 30 minutes at room temperature. The resulting mixture was allowed to stand at ambient temperature for 3 days. The solvent was distilled off and the residue was washed with a hot mixture of chloroform and methanol (1: 1) and filtered. The filtrate was concentrated and the residue was washed again with a hot mixture of chloroform and methanol (9:1) and filtered. The filtered cake was washed well with a mixture of chloroform and methanol (9:1) to give 4H-quinolizin-4-one-3-thiocarboxamide (0.76 g).

mp. 220-230°C.

IR (Nujol) : 3300, 3100, 1650, 1620, 1500 cm^{-1}

NMR (DMSO-d_6) δ : 7.07 (d, 1H, J=8Hz), 7.36-7.67 (m, 1H), 7.80-8.10 (m, 2H), 9.13 (d, 1H, J=8Hz), 9.26 (d, 1H, J=8Hz), 9.80 (broad s, 1H)

(4) 3-Cyano-4H-quinolizin-4-one (4.21 g), sodium azide (1.77 g), and ammonium chloride (1.45 g) was dissolved in N,N-dimethyl-formamide (42 ml) and the resulting mixture was heated at 120°C for two days. The reaction mixture was evaporated and the residue was dissolved in

aqueous sodium bicarbonate solution and filtered. The filtrate was acidified with dilute hydrochloric acid to pH 1-2. The precipitates were filtered, washed with water and then cold N,N-dimethylformamide. The filtered solid was dissolved in hot N,N-dimethylformamide and filtered. The filtrate was treated with ether and kept at 0°C. The crystals separated were filtered and recrystallized from a mixture of ether and N,N-dimethylformamide to give 3-[5-(1H-tetrazolyl)]-4H-quinolizin-4-one (1.1 g).

mp. > 250°C.

IR (Nujol) : 3200, 3100, 3050, 1660, 1620, 1590 cm^{-1}

NMR (CF_3COOH) δ : 7.40 (d, 1H, J=8Hz), 7.60-8.30 (m, 3H), 8.60 (d, 1H, J=8Hz), 8.90 (s, 1H), 9.40-9.60 (m, 1H)

Anal. Calcd for $C_{10}H_7ON_5$:
C; 56.34, H; 3.31, N; 32.85
Found : C; 56.55, H, 3.87, N; 33.02

Example 6

(1) A suspension of 4H-quinolizin-4-one-3-carboxylic acid (196.7 mg) in 0.1N-aqueous sodium hydroxide solution (9.9 ml) was stirred for one hour at room temperature. The resulting reaction mixture was filtered and then the filtrate was lyophilized to give sodium 4H-quinolizin-4-one-3-carboxylate (201 mg).

IR (Nujol) : 1660 cm^{-1}

NMR (D_2O) δ : 6.80 (d, 1H, J=8Hz), 7.00-7.30 (m, 1H), 7.40-7.60 (m, 2H), 8.05 (d, 1H, J=8Hz), 8.96 (d, 1H, J=8Hz)

(2) The following compound was obtained according to a similar manner to that of Example 6 - (1).

N-[5-(1H-Tetrazolyl)]-4H-quinolizin-4-one-3-

carboxamide sodium salt.

IR (Nujol) : 1670 cm^{-1}

NMR (D_2O-DMSO-d_6) δ : 6.80 (d, 1H, J=8Hz), 7.20-7.40 (m, 1H), 7.40-7.60 (m, 2H), 8.10 (d, 1H, J=8Hz), 8.88 (d, 1H, J=8Hz)

Example 7

The following compounds were obtained according to a similar manner to that of Example 1.

(1) 1-(1-Naphthyl)-4H-quinolizin-4-one-3-carboxylic acid.

mp : >270°C

IR (Nujol) : 1730, 1720, 1610, 770 cm^{-1}

NMR (CF_3COOH, δ) : 7.10-8.37 (10H, m), 8.82 (1H, s), 9.62 (1H, m)

Anal. Calcd for $C_{20}H_{13}NO_3 \cdot 1/2H_2O$:
C; 74.07, H; 4.35, N; 4.32

Found : C; 74.12, H; 4.13, N; 4.22

(2) 1-(4-Biphenylyl)-4H-quinolizin-4-one-3-carboxylic acid.

mp : 261-263°C

IR (Nujol) : 3100, 1720, 1660, 1610, 1580, 1290, 890, 775 cm^{-1}

NMR (CF_3COOH, δ) : 7.20-8.47 (12H, m), 8.70 (1H, s), 9.53 (1H, m)

Anal. Calcd for $C_{22}H_{15}NO_3 \cdot 1/4H_2O$:
C; 76.40, H; 4.52, N; 4.05

Found : C; 76.41, H; 4.57, N; 3.93

(3) 1-Phenoxy-4H-quinolizin-4-one-3-carboxylic acid.

mp : 224-226°C

IR (Nujol) : 3100, 2650, 1725, 1640, 1620, 1580, 1210, 910 cm^{-1}

NMR (CF_3COOH, δ) : 7.20-7.37 (2H, m), 7.43-7.73 (3H, m), 8.78 (1H, s), 8.27 (1H, d, J=7.5Hz), 8.60 (1H, t, J=7.5Hz), 9.05 (1H, d, J=8.5Hz), 9.63 (1H, d, J=7.5Hz)

Anal. Calcd for $C_{16}H_{11}NO_4$: C; 68.33, H; 3.94, N; 4.98

Found : C; 68.45, H; 3.96, N; 4.96

(4) 1-(3-Tolyl)-4H-quinolizin-4-one-3-carboxylic acid.

mp : 176-178°C

IR (Nujol) : 3130, 1740, 1620, 1590, 1220, 770, 705 cm^{-1}

NMR (CF_3COOH, δ) : 2.52 (3H, s), 7.17-7.67 (4H, m), 7.90-8.50 (3H, m), 8.70 (1H, s), 9.58 (1H, m)

Anal. Calcd for $C_{17}H_{13}NO_3$: C; 73.11, H; 4.69, N; 5.02

Found : C; 73.11, H; 4.85, N; 5.13

(5) 1-(4-Chlorophenyl)-4H-quinolizin-4-one-3-carboxylic acid.

mp : 269-271°C

IR (Nujol) : 3140, 1740, 1620, 1490, 1320, 1290, 1090, 890, 825, 775 cm^{-1}

NMR (CF_3COOH, δ) : 7.35-7.78 (4H, m), 7.92-8.47 (3H, m), 8.73 (1H, s), 9.62 (1H, m)

Anal. Calcd for $C_{16}H_{10}ClNO_3$: C; 64.12, H; 3.36, N; 4.67

Found : C; 63.95, H; 3.33, N; 4.58

(6) 1-(2-Tolyl)-4H-quinolizin-4-one-3-carboxylic acid.

mp : 168-170°C

IR (Nujol) : 3400, 1720, 1610, 1290, 1070, 780 cm^{-1}

NMR (CF_3COOH, δ) : 2.17 (3H, s), 7.25-7.75 (4H, m), 7.98-8.63 (3H, m), 8.80 (1H, s), 9.72 (1H, m)

Anal. Calcd for $C_{17}H_{13}NO_3$: C; 73.11, H; 4.69, N; 5.02

Found : C; 72.95, H; 4.91, N; 5.01

(7) 1-(3-Methoxyphenyl)-4H-quinolizin-4-one-3-carboxylic acid.

mp : 222-224°C

IR (Nujol) : 3100, 1725, 1600, 1490, 1220, 1030, 780 cm^{-1}

NMR (CF_3COOH, δ) : 4.10 (3H, s), 7.15-8.62 (7H, m), 8.77 (1H, s), 9.62 (1H, m)

Anal. Calcd for $C_{17}H_{13}NO_4$: C; 69.15, H; 4.44, N; 4.74

Found : C; 69.67, H; 4.70, N; 4.67

(8) 1-Hydroxy-4H-quinolizin-4-one-3-carboxylic acid.

IR (Nujol) : 3200, 3100, 1690, 1620 cm^{-1}

NMR (CF_3COOH, δ) : 8.00-9.50 (5H, m),

Anal. Calcd for $C_{10}H_7NO_4$: C; 58.54, H; 3.44, N; 6.83

Found : C; 57.93, H; 3.56, N; 6.77

Example 8

The following compounds were obtained according to a similar manner to that of Example 2.

(1) N-[5-(1H-Tetrazolyl)]-(1-naphthyl)-4H-quinolizin-4-one-3-carboxamide.

mp : > 270°C

IR (Nujol) : 3280, 1665, 1640, 1620, 1290, 780, 770 cm^{-1}

NMR (CF_3COOH; δ) : 7.27-8.25 (10H, m), 8.77 (1H, s), 9.68 (1H, m)

Anal. Calcd for $C_{21}H_{14}N_6O_2$:
C; 65.96, H; 3.69, N; 21.98

Found : C; 60.51, H; 3.75, N; 21.91

(2) N-[5-(1H-Tetrazolyl)]-1-(4-biphenylyl)-4H-quinolizin-4-one-3-carboxamide.

mp : > 270°C

IR (Nujol) : 3180, 1670, 1625, 1590, 1100, 1035, 780, 730 cm^{-1}

Anal. Calcd for $C_{23}H_{16}N_6O_2$:
C; 67.64, H; 3.95, N; 20.58

Found : C; 68.04, H; 4.31, N; 20.39

(3) N-[5-(1H-Tetrazolyl)]-1-phenoxy-4H-quinolizin-4-one-3-carboxamide.

mp : > 270°C

IR (Nujol) : 3200, 3150, 1660, 1620, 1590, 1010, 780, 750 cm^{-1}

NMR (CF_3COOH, δ) : 7.08-7.67 (5H, m), 7.97 (1H, m),

8.22-8.47 (2H, m), 8.70 (1H, m), 9.67 (1H, m)

Anal. Calcd for $C_{17}H_{12}N_6O_3$:
C; 58.62, H; 3.47, N; 24.13

Found : C; 59.39, H; 3.54, N; 24.06

(4) N-[5-(1H-Tetrazolyl)]-1-(3-tolyl)-4H-quinolizin-4-one-3-carboxamide.

mp : > 270°C

IR (Nujol) : 3160, 1670, 1640, 1620, 1600, 1585 cm^{-1}

NMR (CF_3COOH, δ) : 2.52 (2H, s), 7.17-7.62 (m, 4H), 7.70-8.40 (3H, m), 8.73 (1H, s), 9.63 (1H, m)

Anal. Calcd for $C_{18}H_{14}N_6O_2$:
C; 62.42, H; 4.07, N; 24.26

Found : C; 63.03, H; 4.16, N; 24.56

(5) N-[5-(1H-Tetrazolyl)]-1-(4-chlorophenyl)-4H-quinolizin-4-one-3-carboxamide.

mp : > 270°C

IR (Nujol) : 3220, 1675, 1640, 1600, 1480, 1290, 1040, 770 cm^{-1}

Anal. Calcd for $C_{17}H_{11}ClN_6O_2$:
C; 55.67, H; 3.02, N; 22.91

Found : C; 57.45, H; 3.26, N; 21.47

(6) N-(2-Pyridyl)-1-phenyl-4H-quinolizin-4-one-3-carboxamide.

mp : 227-229°C

IR (Nujol) : 1680, 1620, 1550, 1480, 1300, 780, 770 cm^{-1}

NMR (CF_3COOH, δ) : 7.35-8.18 (10H, m), 8.35-8.77 (2H, m), 9.60 (1H, m)

Anal. Calcd for $C_{21}H_{15}N_3O_2$:
C; 73.89, H; 4.43, N; 12.31

Found : C; 74.17, H; 4.61, N; 12.26

(7) N-[5-(1H-Tetrazolyl)]-1-hydroxy-4H-quinolizin-4-one-3-carboxamide.

mp : > 250°C

IR (Nujol) : 3200 (sh), 1660, 1620, 1580 cm^{-1}

Anal. Calcd for $C_{11}H_8N_6O_3 \cdot 1/2H_2O$:
C; 46.97, H; 3.22, N; 29.85
Found : C; 46.48, H; 3.31, N; 29.57

(8) N-[5-(1H-Tetrazolyl)]-1-(3-methoxyphenyl)-4H-quinolizin-4-one-3-carboxamide.

mp : > 270°C

IR (Nujol) : 3150, 1680, 1640, 1620, 1590, 1490, 1300, 1210, 1030, 790, 780 cm^{-1}

NMR (CF_3COOH, δ) : 4.13 (3H, s), 7.17-7.52 (3H, m), 7.55-8.15 (2H, m), 8.18-8.43 (2H, m), 8.80 (1H, s), 9.67 (1H, m)

Anal. Calcd for $C_{18}H_{14}N_6O_3$:
C; 59.67, H; 3.89, N; 23.19
Found : C; 59.81, H; 4.19, N; 23.35

(9) N-[5-(1H-Tetrazolyl)]-1-(2-tolyl)-4H-quinolizin-4-one-3-carboxamide.

mp : > 270°C

IR (Nujol) : 3200, 3120, 1680, 1620, 1490, 1290, 1030, 780 cm^{-1}

NMR (CF_3COOH, δ) : 2.15 (3H, s), 7.25-7.70 (4H, m), 7.77-8.43 (3H, m), 8.77 (1H, s), 9.77 (1H, s)

Anal. Calcd for $C_{18}H_{14}N_6O_2$:
C; 62.42, H; 4.07, N; 24.26
Found : C; 62.75, H; 4.06, N; 24.35

Example 9

The following compounds were obtained according to a similar manner to that of Example 1.

(1) 7-(n-Butoxy)-1-phenyl-4H-quinolizin-4-one-3-carboxylic acid.
mp : 155-157°C
IR (Nujol) : 1720, 1610, 1495, 1425 cm^{-1}
NMR (DMSO-d_6, δ) : 0.95 (3H, t, J=5Hz), 1.3-2.0 (4H, m), 4.20 (2H, t, J=5Hz), 7.3-7.7 (5H, m), 7.80 (2H, s), 8.10 (1H, s), 8.80 (1H, s), 14.1 (1H, broad s)

(2) 1-Allyloxy-4H-quinolizin-4-one-3-carboxylic acid.
mp : 140-143°C
IR (Nujol) : 3100, 1730, 1720, 1610, 1580, 1420, 1095, 1065, 770 cm^{-1}
NMR (CF_3CO_2H, δ) : 4.90-5.13 (2H, m), 5.35-5.78 (2H, m), 5.90-6.57 (1H, m), 7.97-8.67 (3H, m), 8.77-9.03 (1H, m), 9.39-9.67 (1H, m)

(3) 1-(N-Methylanilino)-4H-quinolizin-4-one-3-carboxylic acid.
mp : 185°C (dec.)
IR (Nujol) : 1720, 1700 (sh), 1620 cm^{-1}
NMR (CF_3COOH, δ) : 3.58 (3H, s), 6.60-7.50 (5H, m), 7.80-8.60 (3H, m), 8.64 (1H, s), 9.50 (1H, d, J=7Hz)
Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52
Found : C, 69.03; H, 4.76; N, 9.31

(4) 1-Benzyl-4H-quinolizin-4-one-3-carboxylic acid.
mp : 221-223°C
IR (Nujol) : 3380, 1720, 1620, 1410, 1320, 1070, 1020, 780 cm^{-1}

Anal. Calcd for $C_{17}H_{13}NO_3$:
C, 73.11; H, 4.69; N, 5.02
Found : C, 73.72; H, 4.92; N, 5.04

(5) 1-Phenylthio-4H-quinolizin-4-one-3-carboxylic acid.
mp : 195-197°C
IR (Nujol) : 3350, 1720, 1620, 1400, 1285, 1065, 885, 780, 740 cm^{-1}
Anal. Calcd for $C_{16}H_{11}NO_3S'$:
C, 64.63; H, 3.73; N, 4.71
Found : C, 65.04; H, 3.90; N, 4.73

(6) 1-Phenylsulfonyl-4H-quinolizin-4-one-3-carboxylic acid.
mp : >250°C
IR (Nujol) : 1730, 1640, 1620, 1580, 1160, 1140 cm^{-1}.
NMR (DMSO-d_6, δ) : 7.30-8.50 (7H, m), 8.60 (1H, d, J=8Hz), 9.00 (1H, s), 9.50 (1H, d, J=8Hz)
Anal. Calcd for $C_{16}H_{11}NO_5S'$:
C, 58.35; H, 3.37
Found : C, 58.62; H, 3.31

Example 10

To a solution of 3-ethoxycarbonyl-1-benzoyl-4H-quinolizin-4-one (2.14 g) in chloroform (65 ml) was added dropwise trimethylsilyliodide (1.04 ml) at 0°C. After stirring for 30 minutes at 0°C, trimethylsilyliodide (1.04 ml) was added. After stirring for 1 hour at room temperature, trimethylsilyliodide (1.04 ml) was added. After stirring for 2 hours at room temperature, the reaction mixture was diluted with chloroform and washed with water. After drying over magnesium sulfate, the chloroform extract was filtered and concentrated. The precipitate was washed with a

cold chloroform to give 1-benzoyl-4H-quinolizin-4-one-3-carboxylic acid (1.252 g) as yellow crystals.

IR (Nujol) : 1735, 1630, 1610, 1455, 1440, 1370 cm^{-1}

NMR ($CDCl_3$, δ) : 6.70-8.30 (9H, m), 8.42-8.68 (1H, d, J=3Hz)

Anal. Calcd for $C_{17}H_{11}NO_4$: C, 69.62; H, 3.78; N, 4.78

Found : C, 62.89; H, 3.54; N, 3.70

Mass : m/e 293 (M^+)

Example 11

The following compounds were obtained according to a similar manner to that of Example 2.

(1) 7-(n-Butoxy)-1-phenyl-N-[5-(1H-tetrazolyl)]-4H-quinolizin-4-one-3-carboxamide.

mp : >205°C (dec.)

IR (Nujol) : 1670, 1635, 1580, 1370 cm^{-1}

NMR (DMSO-d_6, δ) : 1.00 (3H, t, J=5.6Hz), 1.02-2.10 (4H, m), 4.18 (2H, t, J=6Hz), 6.80-7.25 (2H, m), 7.30-7.65 (3H, m), 7.68-8.00 (2H, m), 8.20 (1H, s), 8.87 (1H, broad s)

(2) N-[5-(1H-Tetrazolyl)]-1-phenylthio-4H-quinolizin-4-one-3-carboxamide.

mp : >270°C

IR (Nujol) : 3180, 1660, 1640, 1620, 1285, 1035, 780, 730 cm^{-1}

Anal. Calcd for $C_{17}H_{12}N_6O_2S$: C, 56.04; H, 3.32; N, 23.06

Found : C, 56.61; H, 3.53; N, 23.48

(3) 1-(N-Methylanilino)-N-[5-(1H-tetrazolyl)]-4H-

quinolizin-4-one-3-carboxamide.

mp : >230°C

IR (Nujol) : 3200, 1660, 1640, 1620, 1290, 1030 cm^{-1}

NMR (CF_3COOH, δ) : 3.74 (3H, s), 6.80-7.60 (5H, m), 7.62-8.08 (1H, m), 8.15-8.40 (2H, m), 8.85 (1H, s), 9.65 (1H, d, J=7Hz)

(4) N-[5-(1H-Tetrazolyl)]-1-allyloxy-4H-quinolizin-4-one-3-carboxamide.

mp : >270°C (dec.)

IR (Nujol) : 3200, 1660, 1620, 1580, 1500, 1220, 1100, 1040, 1020, 955, 770 cm^{-1}

NMR (CF_3COOH, δ) : 4.90-5.17 (2H, m), 5.37-5.80 (2H, m), 5.90-6.55 (1H, m), 8.93-9.02 (4H, m), 9.50-9.73 (1H, m)

Anal. Calcd for $C_{14}H_{12}N_6O_3$: C, 53.85; H, 3.87; N, 26.91

Found : C, 54.20; H, 3.81; N, 26.93

(5) N-[5-(1H-Tetrazolyl)]-1-benzyl-4H-quinolizin-4-one-3-carboxamide.

mp : >270°C.

IR (Nujol) : 3140, 1660, 1620, 1595, 1490, 1295, 1040, 1005, 775, 720, 690 cm^{-1}

Anal. Calcd for $C_{18}H_{14}N_6O_2$: C, 62.42; H, 4.07; N, 24.26

Found : C, 62.88; H, 4.54; N, 24.52

(6) N-[5-(1H-Tetrazolyl)]-1-phenylsulfonyl-4H-quinolizin-4-one-3-carboxamide.

mp : >250°C

IR (Nujol) : 1680, 1640, 1620, 1590 cm^{-1}

Anal. Calcd for $C_{17}H_{12}N_6O_4S$: C, 51.51; H, 3.05; N, 21.20

Found : C, 51.71; H, 2.93; N, 21.83

(7) 1-Benzoyl-N-[5-(1H-tetrazolyl)]-4H-quinolizin-4-one-3-carboxamide.

mp : >250°C

IR (Nujol) : 1690, 1630, 1380, 1240, 1120 cm^{-1}

NMR (CF_3COOH, δ) : 7.40-8.25 (5H, m), 8.22-8.51 (1H, m), 8.70 (1H, broad s), 8.93 (1H, s), 9.12 (1H, d, J=9Hz), 9.73 (1H, d, J=7Hz)

Anal Calcd for $C_{18}H_{12}N_6O_3$: C, 60.00; H, 3.36; N, 23.32

Found : C, 56.90; H, 3.80; N, 24.97

Example 12

The following compounds were obtained according to a similar manner to that of Example 6-(1).

(1) 1-Benzoyl-N-[5-(1H-tetrazolyl)]-4H-quinolizin-4-one-3-carboxamide sodium salt.

mp : 248-250°C (dec.)

IR (Nujol) : 1670, 1610, 1550, 1480, 1450 cm^{-1}

(2) N-[5-(1H-Tetrazolyl)]-1-phenyl-4H-quinolizin-4-one-3-carboxamide sodium salt.

mp : >250°C

IR (Nujol) : 3150 (broad), 1660 (sh), 1650, 1640, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 7.40-8.00 (9H, m), 8.50 (1H, s), 9.30-9.60 (1H, m)

(3) N-[5-(1H-Tetrazolyl)]-1-phenoxy-4H-quinolizin-4-one-3-carboxamide sodium salt.

mp : >250°C

IR (Nujol) : 1660 cm^{-1}

NMR (DMSO-d_6, δ) : 6.9-7.8 (6H, m), 8.01 (2H, d, J=4Hz), 8.32 (1H, s), 9.42 (1H, d, J=7Hz), 12.30 (1H, s)

Anal. Calcd for $C_{17}H_{11}N_6NaO_3$:
C, 55.14; H, 2.99; N, 22.70
Found : C, 54.78; H, 3.63; N, 20.44

Example 13

The following compound was obtained according to a similar manner to that of Example 1.

1-Benzoyl-7-n-butoxy-4H-quinolizin-4-one-3-carboxylic acid

mp : 155-156°C

IR (Nujol) : 1720, 1620, 1580, 1495 cm^{-1}

NMR ($CDCl_3$, δ) : 1.03 (3H, t, J=6Hz), 1.30-2.17 (4H, m), 4.23 (2H, t, J=6Hz), 7.17-7.93 (6H, m), 8.70 (1H, s), 8.88 (1H, d, J=10Hz), 9.02 (1H, d, J=2Hz), 13.60 (1H, broad s)

Example 14

The following compounds were obtained according to a similar manner to that of Example 2.

(1) 1-Benzoyl-7-n-butoxy-N-(1H-tetrazol-5-yl)-4H-quinolizin-4-one-3-carboxamide

mp : 227°C

IR (Nujol) 1680, 1660, 1625, 1585, 1550, 1495 cm^{-1}

NMR (DMSO-d_6, δ) : 1.2-2.0 (4H, m), 4.23 (2H, t, J=6Hz), 7.08 (2H, broad s), 7.37-8.17 (6H, m), 8.43 (1H, s), 8.75 (1H, d, J=10Hz), 8.93 (1H, d, J=2Hz)

(2) N-(4H-5-Amino-1,2,4-triazol-3-yl)-7-n-butoxy-1-phenyl-4H-quinolizin-4-one-3-carboxamide

mp : 220°C

IR (Nujol) : 1690, 1650, 1490, 1465, 1450 cm^{-1}

NMR (DMSO-d_6, δ) : 0.80-1.10 (3H, t), 1.30-2.10 (4H, m), 4.18 (2H, t), 7.03 (1H, s), 7.40-7.65 (5H, m), 7.70 (1H, d, J=7Hz), 7.83 (1H, d, J=7Hz), 8.26 (1H, s), 8.87 (1H, s)

Mass : m/e 387 (M+)

(3) 1-Ethoxycarbonyl-N-(1H-tetrazol-5-yl)-4H-quinolizin-4-one-3-carboxamide

mp : >250°C

IR (Nujol) : 1665, 1640, 1610, 1595, 1580 cm^{-1}

Mass : m/e 328 (M^+)

Example 15

The following compounds were obtained according to a similar manner to that of Example 6-(1).

(1) 1-Benzoyl-7-n-butoxy-N-(1H-tetrazol-5-yl)-4H-quinolizin-4-one-3-carboxamide sodium salt

mp : 200-203°C

NMR (DMSO-d_6, δ) : 0.98 (3H, t, J=6Hz), 1.20-2.0 (4H, m), 4.25 (2H, t, J=6Hz), 7.32-8.17 (6H, m), 8.57 (1H, s), 8.75 (1H, d, J=10Hz), 9.02 (1H, d, J=2Hz), 11.87 (1H, broad s)

(2) 7-n-Butoxy-1-phenyl-N-(1H-tetrazol-5-yl)-4H-quinolizin-4-one-3-carboxamide sodium salt

IR (Nujol) : 1680, 1640, 1620, 1585 cm^{-1}

NMR (DMSO-d_6, δ) : 0.80-1.20 (3H, m), 1.30-2.10 (4H, m), 4.00-4.48 (2H, m), 7.43-7.68 (5H, m), 7.70-7.90 (2H, m), 8.40 (1H, s), 9.00 (1H, d, J=2Hz)

Example 16

To a solution of 1,3-diethoxycarbonyl-4H-quinolizin-4-one (1 g) in chloroform (20 ml) was added trimethylsilyl iodide (0.49 ml) at room temperature and the mixture was stirred for 4 hours and heated with reflux for 4 hours. After cooling to room temperature, the mixture was washed with water, aqueous sodium thiosulfate, and brine. Drying over magnesium sulfate and evaporation gave a crystalline residue, which was

washed with isopropyl alcohol to give 1-ethoxycarbonyl-4H-quinolizin-4-one-3-carboxylic acid (794 mg).

mp : 189°C

IR (Nujol) : 1735, 1710, 1635, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 1.34 (3H, t, J=7Hz), 4.33 (2H, q, J=7Hz), 7.45-7.95 (1H, m), 8.00-8.45 (1H, m), 8.90 (1H, s), 9.05-9.60 (2H, m),

Mass : m/e 261 (M^+)

Anal. Calcd. for $C_{13}H_{11}NO_5$:
C, 59.77; H, 4.24; N, 5.36

Found : C, 59.12; H, 4.59; N, 5.33

Example 17

To a solution of 1,3-diethoxycarbonyl-4H-quinolizin-4-one (896 mg) in methanol (9 ml) was added 6N aqueous sodium hydroxide (2.58 ml) at room temperature and the mixture was heated with reflux for an hour. After cooling to 0°C, the reaction mixture was acidified to pH 2 with 6N hydrochloric acid and the precipitate was filtered and washed with water to give 4H-quinolizin-4-one-1,3-dicarboxylic acid (202 mg).

mp : >250°C

IR (Nujol) : 1675, 1655, 1635 cm^{-1}

NMR (D_2O, NaOD, δ) : 7.30-8.10 8.65 (1H, s), 8.70-9.00 (1H, m), 9.30 (1H, d, J=7Hz)

Example 18

To a solution of 1-ethoxycarbonyl-N-(1H-tetrazol-5-yl)-4H-quinolizin-4-one-3-carboxamide (500 mg) in N,N-dimethylformamide (5 ml) was added 1N aqueous sodium hydroxide (6 ml) at room temperature and the mixture was heated at 100°C for an hour. After cooling to 0°C, the mixture was acidified to pH 2 with 6N hydrochloric acid and the precipitate was filtered and washed with

water to give 1-carboxy-N-(1H-tetrazol-5-yl)-4H-quinolizin-4-one-3-carboxamide (280 mg).

mp : >250°C

IR (Nujol) : 1670, 1640, 1615, 1590 cm^{-1}

NMR (D_2O-NaOD, δ) : 7.24-7.60 (1H, m), 7.60-8.07 (1H, m), 8.68-9.05 (1H, m), 8.84 (1H, s), 9.30 (1H, d, J=8Hz)

Mass : m/e 272 (M^+)

Anal. Calcd. for $C_{12}H_8N_6O_4 \cdot H_2O$: C, 45.29; H, 3.16; N, 26.41

Found : C, 45.29; H, 3.62; N, 26.56

Example 19

To a solution of pyridin-2-ylacetic acid hydrochloride (1 g) in N,N-dimethylformamide (10 ml) was added N,N'-carbonyldiimidazole (934 mg) at room temperature and the mixture was heated at 60°C for 20 minutes. To the mixture was added 2,2-dimethyl-1,3-dioxane-4,6-dione (830 mg) at 60°C and the mixture was stirred for 1 hour at the same temperature. The solvent was distilled off and the residue was diluted with chloroform and washed with water. The chloroform layer was extracted with aqueous sodium hydrogen carbonate and the aqueous layer was washed with chloroform and acidified to pH 2 with 6N hydrochloric acid at 0°C and extracted with chloroform. The chloroform layer was washed with brine, dried over magnesium sulfate, and evaporated to give 2-hydroxy-4H-quinolizin-4-one-3-carboxylic acid (220 mg).

mp : 194-195°C

IR (Nujol) : 1690, 1605, 1370, 1300 cm^{-1}

NMR (DMSO-d_6, δ) : 6.75 (1H, s), 7.15-7.45 (1H, m), 7.76 (2H, d), 8.90 (1H, d, J=6Hz)

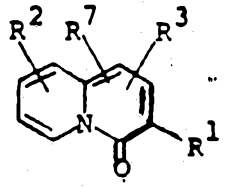
Mass : m/e 205 (M^+)

Anal. Calcd. for $C_{10}H_7NO_4$: C, 58,54; H, 3.44; N, 6.83

Found : C; 58.49; H, 3.17; N, 6.86

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula :



(I)

wherein R^1 is carboxy; CONH R^{10} wherein R^{10} is hydrogen; pyridyl; pyrimidinyl; pyrimidinyl substituted with lower alkyl; pyrazinyl; phenyl; phenyl substituted with hydroxy; thiazolyl; triazinyl; triazolyl; triazolyl substituted with amino; pyridazinyl; pyridazinyl substituted with halogen; or tetrazolyl; cyano, thiocarbamoyl, or tetrazolyl;

R^7 is hydrogen or aryl;

R^2 is hydrogen, hydroxy, lower alkyl or lower alkoxy; and

R^3 is hydrogen, hydroxy, lower alkyl, lower alkoxy, carboxy, lower alkoxycarbonyl, lower alkenyloxy; aryl optionally substituted with halogen, lower alkyl or lower alkoxy; arylthio, aroyl, ar(lower)alkyl, arenesulfonyl, N-lower alkylanilino or aryloxy;

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein

R^1 is carboxy, carbamoyl, pyridylcarbamoyl, pyrimidinylcarbamoyl, pyrimidinylcarbamoyl substituted with lower alkyl, pyrazinylcarbamoyl, phenylcarbamoyl, phenylcarbamoyl substituted with hydroxy, thiazolylcarbamoyl, triazinylcarbamoyl, triazolylcarbamoyl, triazolylcarbamoyl substituted with amino,

pyridazinylcarbamoyl, pyridazinylcarbamoyl substituted with halogen, tetrazolylcarbamoyl, cyano, thiocarbamoyl or tetrazolyl group,

R^7 is hydrogen or phenyl,

R^2 is hydrogen, hydroxy, lower alkyl, lower alkoxy, and

R^3 is hydrogen, hydroxy, lower alkyl, lower alkoxy, lower alkoxycarbonyl, carboxy, lower alkenyloxy, phenyl, naphthyl, biphenyl, phenyl substituted with lower alkyl, phenyl substituted with halogen, phenyl substituted with lower alkoxy, phenylthio, benzolyl, phenyl(lower)alkyl, benzenesulfonyl, N-lower alkylanilino, or phenoxy.

3. A compound of claim 2, wherein

R^1 is carboxy, carbamoyl, pyrid-2-ylcarbamoyl, 4,6-dimethylpyrimidin-2-ylcarbamoyl, pyrazinylcarbamoyl, phenylcarbamoyl, pyrimidin-2-ylcarbamoyl, 2-hydroxyphenylcarbamoyl, 4H-1,2,4-triazol-3-ylcarbamoyl, 4H-5-amino-1,2,4-triazol-3-ylcarbamoyl, 1H-tetrazol-5-yl-carbamoyl, thiazol-2-ylcarbamoyl, 1,2,4-triazin-6-ylcarbamoyl, pyrazinylcarbamoyl, 3-chloropyridazin-6-ylcarbamoyl, cyano, thiocarbamoyl or tetrazolyl group,

R^2 is hydrogen, hydroxy, methyl, ethyl or methoxy,

R^3 is hydrogen, hydroxy, methyl, methoxy, isopropoxy, n-butoxy, ethoxycarbonyl, carboxy, allyloxy, phenyl, naphthyl, biphenylyl, 3-methylphenyl, phenoxy, 4-chlorophenyl, 2-methylphenyl, 3-methoxyphenyl, benzyl, phenylthio, benzoyl, benzenesulfonyl or N-methylanilino.

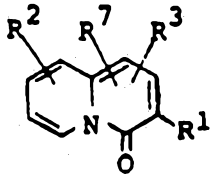
4. A compound of claim 3, which is N-[5-(1H-tetrazolyl)]-4H-quinolizin-4-one-3-carboxamide or its sodium salt.

5. A compound of claim 3, which is N-[5-(1H-tetrazolyl)]-1-phenyl-4H-quinolizin-4-one-3-carboxamide or its sodium salt.

6. A compound of claim 3, which is N-[5-(1H-tetrazolyl)]-1-phenoxy-4H-quinolizin-4-one-3-carboxamide or its sodium salt.

7. A compound of claim 3, which is N-[5-(1H-tetrazolyl)]-1-benzoyl-4H-quinolizin-4-one-3-carboxamide or its sodium salt.

8. A process for preparing a compound of the formula :



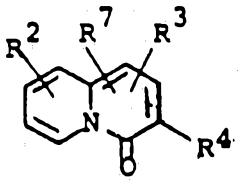
(I)

wherein R^1 is carboxy;
CONH R^{10} wherein R^{10} is hydrogen; pyridyl; pyrimidinyl; pyrimidinyl substituted with lower alkyl; pyrazinyl; phenyl; phenyl substituted with hydroxy; thiazolyl; triazinyl; triazolyl; triazolyl substituted with amino; pyridazinyl; pyridazinyl substituted with halogen; or tetrazolyl; cyano, thiocarbamoyl, or tetrazolyl;
R^7 is hydrogen or aryl;
R^2 is hydrogen, hydroxy, lower alkyl or lower alkoxy; and
R^3 is hydrogen, hydroxy, lower alkyl, lower alkoxy, carboxy, lower alkoxycarbonyl, lower alkenyloxy; aryl optionally substituted with halogen, lower alkyl or lower alkoxy; arylthio, aroyl, ar(lower)alkyl, arenesulfonyl, N-lower alkylanilino or aryloxy;

arylthio, aroyl, ar(lower)alkyl, arenesulfonyl, N-lower alkylanilino or aryloxy;

or a salt thereof which comprises

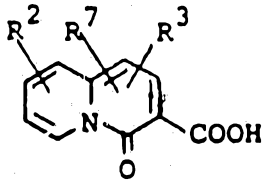
(1) subjecting a compound of the formula :



wherein R^7, R^2 and R^3 are each as defined above, and

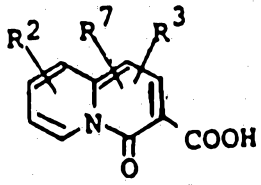
R^4 is protected carboxy,

or a salt thereof, to elimination reaction of the carboxy protective group, to give a compound of the formula :

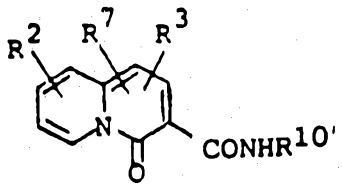


wherein R^7, R^2 and R^3 are each as defined above, or a salt thereof; or

(2) reacting a compound of the formula:

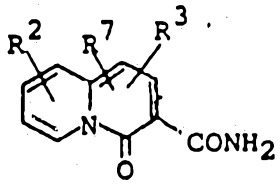


wherein R^7, R^2 and R^3 are each as defined above, or its reactive derivative at the carboxy group or a salt thereof, with $H_2N\text{-}R^{10}$ wherein R^{10} is as defined above, to give a compound of the formula:

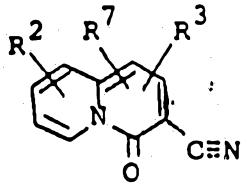


wherein R^7, R^{10}, R^2 and R^3 are each as defined above,
or a salt thereof; or

(3) subjecting a compound of the formula :

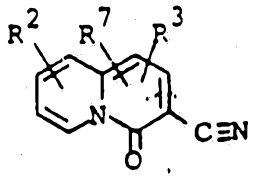


wherein R^7, R^2 and R^3 are each as defined above,
or a salt thereof, to dehydration reaction,
to give a compound of the formula :

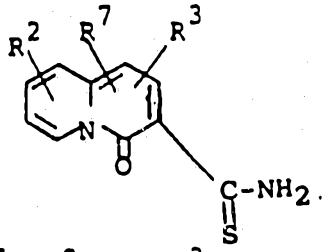


wherein R^7, R^2 and R^3 are each as defined above,
or a salt thereof; or

(4) reacting a compound of the formula :

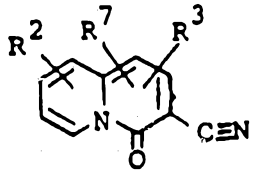


wherein R^7, R^2 and R^3 are each as defined above, or a salt thereof, with hydrogen sulfide, to give a compound of the formula :

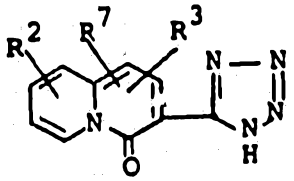


wherein R^7, R^2 and R^3 are each as defined above, or a salt thereof; or

(5) subjecting a compound of the formula :

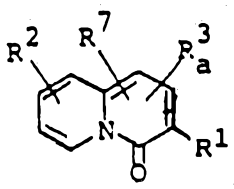


wherein R^7, R^2 and R^3 are each as defined above, or a salt thereof, to the formation reaction of a tetrazole group, using a combination of alkali methal azide and ammonium halide, to give a compound of the formula :



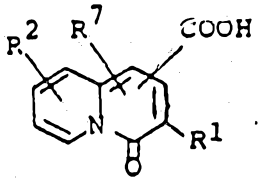
wherein R^7, R^2 and R^3 are each as defined above,
or a salt thereof, or

(6) subjecting a compound of the formula :



wherein R^1, R^2 and R^7 are each as defined above, and

R^3_a is lower alkoxycarbonyl, or a salt thereof, to elimination reaction of lower alkyl, to give a compound of the formula :



wherein R^1, R^2 and R^7 are each as defined above, or a salt thereof.

9. A pharmaceutical composition comprising an effective amount of a compound of claim 1 or pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

10. A method for the treatment of allergic and ulcer diseases which comprises administering to human beings and animals in need of such treatment a therapeutically effective amount of a compound of Claim 1.

11. A compound of Claim 1 substantially as hereinbefore described with reference to any one of the Examples.

12. A process for preparing a compound of Claim 1 substantially as hereinbefore described with reference to any one of the Examples.

13. A pharmaceutical composition containing a compound of Claim 1 substantially as hereinbefore described with reference to any one of the Examples.

DATED this day of 2nd April, 1990
FUJISAWA PHARMACEUTICAL CO., LTD
By Its Patent Attorneys
DAVIES & COLLISON