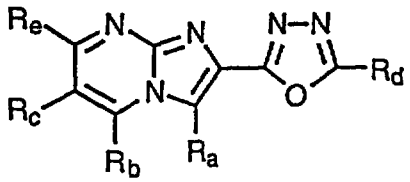
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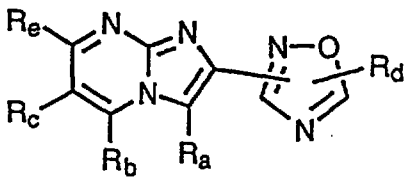
3-OXADIAZOLYL-1,6-NAPHTHYRIDINE DERIVATIVES

The present invention relates to a 3-oxadiazolyl-5,6,7,8-tetrahydro-1,6-naphthyridine derivative which is useful as a medicine, a process for preparing the same, use of the same as a medicine, and an intermediate thereof.

Benzodiazepine (BZP) compounds such as diazepam have widely been used as anxiolytic drugs or in the treatment of insomnia. However, these compounds show various side effects such as ataxia, sleepiness, muscular relaxation, or deterioration of recognition or reflex movement, and they also have various defects, for example, they cause drug-resistance or drug-dependence in patients. In order to solve these problems, studies have been made on non-benzodiazepine compounds having affinity for BZP receptor in the brain.

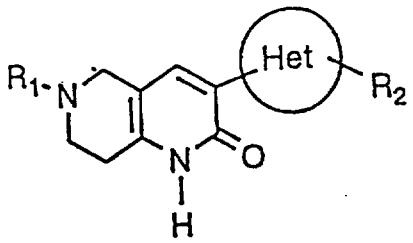
Such non-benzodiazepine compounds having the following formulae are disclosed in Journal of Medicinal Chemistry, Vol. 34, p. 2060 (1991).





wherein R_a is hydrogen atom, R_b to R_d are each, for example, a methyl group, and R_e is, for example, a methoxy group.

The present invention provides a 3-oxadiazolyl-5,6,7,8-tetrahydro-1,6-naphthyridine derivative of the following formula (I) or a pharmaceutically acceptable acid addition salt thereof, which has an affinity for benzodiazepine receptor and is useful as a medicine.



(I)

wherein Het is an oxadiazole ring, R_1 is hydrogen atom, an acyl group, a lower alkyl group or a group of the formula: $-CH_2R_1'$ (in which R_1' is a cyclo-lower alkyl group, a lower alkenyl group, a lower alkynyl group, benzyl group, an aryl group or a heteroaromatic group), R_2 is a lower alkyl group, a cyclo-lower alkyl group, a lower alkenyl group, a lower alkynyl group, an aryl group, a heteroaromatic group, a halogeno-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a lower alkenyloxy group, a phenoxy group or a lower alkylthio group, or a pharmaceutically acceptable acid addition salt thereof.

The invention also provides a process for preparing the compound of the formula (I), as later described, and a pharmaceutical composition containing said compound as an active ingredient and a pharmaceutically acceptable additive.

According to other aspects the invention provides a compound of the above formula (I), or a pharmaceutically acceptable salt thereof for use as a pharmaceutical and use of such a compound, or a pharmaceutically acceptable acid addition salt thereof, in the preparation of a medicament having a benzodiazepine receptor binding capacity.

According to a further aspect, the invention provides a synthetic intermediate for preparing the compound of the formula (I) as later described.

The compounds of the present invention have the above formula (I), but are more preferably compounds of the formula (I) wherein Het is 1,2,4-oxadiazole ring or 1,3,4-oxadiazole ring, R_1 is a group of the formula: $-CH_2R_1'$, R_1' is an aryl group or a hetero-aromatic group, R_2 is a lower alkyl group, a cyclo-lower alkyl group, a lower alkenyl group, an aryl group, a heteroaromatic group or a lower alkoxy group. Particularly preferable compounds of the present invention are compounds of the formula (I) wherein Het is 1,3,4-oxadiazole ring, R_1 is a group of the formula: $-CH_2R_1'$, R_1' is phenyl group or a phenyl group substituted by 1 to 2 halogen atoms, R_2 is an alkyl group having 2 to 3 carbon atoms, cyclopropyl group or methoxy group.

Throughout the specification, the terms "lower alkyl", "lower alkoxy" and "lower alkylthio" denote straight chain or branched chain alkyl, alkoxy and alkylthio having 1 to 5 carbon atoms, respectively. The terms "lower alkenyl", "lower alkynyl" and "lower alkenyloxy" denote straight chain or branched chain alkenyl, alkynyl, and alkenyloxy having 2 to 5 carbon atoms, respectively. The term "cyclo-lower alkyl" denotes cycloalkyl having 3 to 6 carbon atoms. The "acyl" group may be, for example, a straight chain or branched chain alkanoyl having 1 to 5 carbon atoms, benzoyl or naphthoyl. The "aryl

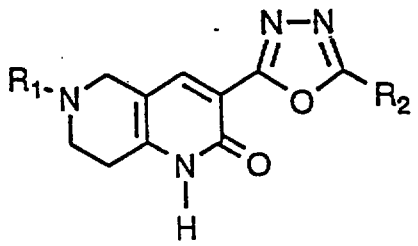
group" may be, for example, a phenyl group or naphthyl group, and these groups may optionally have 1 to 5, preferably 1 to 3, substituents each independently selected from a halogen atom, a lower alkyl group, a trifluoromethyl group, a lower alkoxy group and a nitro group. The "heteroaromatic group" includes a 5- or 6-membered heteroaromatic group containing 1 to 2 heteroatoms selected from a nitrogen, oxygen or sulfur atom, for example, thienyl, furyl, pyridinyl or isoxazolyl, and these heteroaromatic groups may optionally have 1 to 2 substituents each independently selected from a halogen atom, a lower alkyl group, a trifluoromethyl group and a lower alkoxy group.

The pharmaceutically acceptable acid addition salts of the compounds (I) are, for example, salts with an inorganic acid (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate) or salts with an organic acid (e.g. oxalate, maleate, fumarate, malonate, lactate, malate, citrate, tartrate, benzoate, methane-sulfonate, tosylate).

The compounds of the present invention may be prepared by various processes as mentioned below.

Process 1

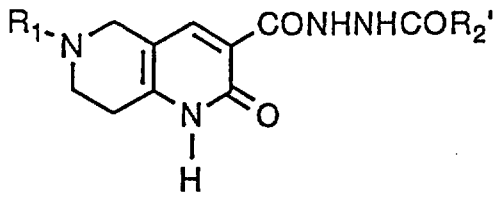
Among the compounds (I) of the present invention, the compound of the formula (Ia):



(Ia)

where R_1 is the same as defined above, and R_2 is a group other than

a lower alkylthio group can be prepared by subjecting a compound of the formula (II):



(II)

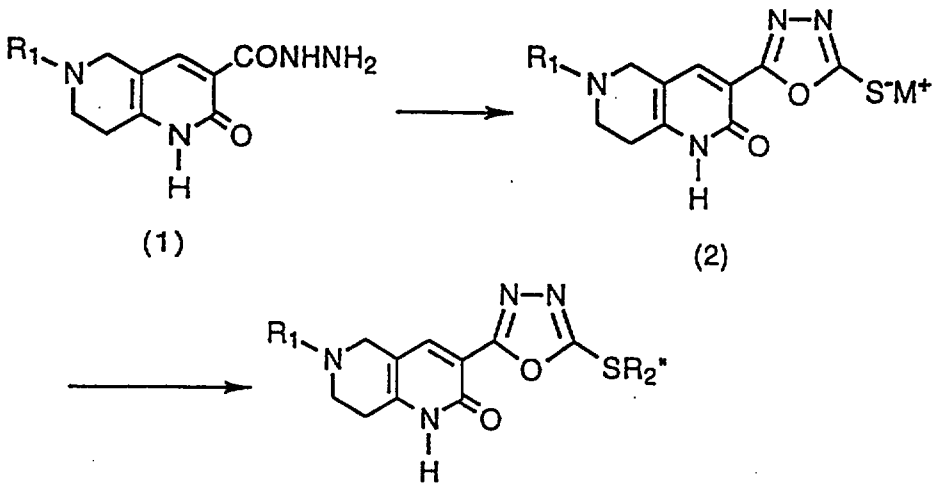
wherein R_2' is the same as R_2 except a lower alkylthio group, and R_1 is the same as defined above, to intramolecular cyclodehydration.

This cyclization reaction is usually carried out by treating the compound (II) with a dehydrating agent. The dehydrating agent is, for example, a combination of a phosphorus (III) compound (e.g. triphenylphosphine, etc.) and a dialkyl azodicarboxylate, or a phosphorus (V) compound (e.g. polyphosphoric acid, phosphorus oxychloride, etc.), but is preferably a combination of a phosphorus (III) compound and a dialkyl azodicarboxylate. The reaction may be carried out in a solvent or without a solvent, but is usually carried out in an inert solvent which does not affect the reaction. The solvent includes, for example, ethers (e.g. tetrahydrofuran, dioxane), aromatic hydrocarbons (e.g. benzene, toluene) and halogenated hydrocarbons (e.g. dichloromethane, chloroform). These solvents can be used either alone or in a mixture of two or more solvents. When the reaction is carried out by using a combination of a phosphorus (III) compound and a dialkyl azodicarboxylate, the reaction is preferably carried out in the presence of a base. The base includes organic bases such as triethylamine, tributylamine, diisopropylamine, N-methyl-

morpholine and pyridine. The reaction temperature varies according to the type of the starting compound, but is usually in a range of 0°C to 110°C, preferably in a range of 0°C to 70°C. When the compound of the formula (II) wherein R_1 is hydrogen atom is used in the reaction, the compound (II) may be protected by a suitable protecting group which can be removed after the cyclization reaction. The protecting group is, for example, a lower alkanoyl group (e.g. formyl group, acetyl group, etc.), a lower alkoxycarbonyl group and benzyloxycarbonyl group. The cyclization reaction with a phosphorus (III) compound and a dialkyl azodicarboxylate is a novel reaction.

Process 2

Among the compounds (I) of the present invention, the compound of the formula (I) wherein R_2 is a lower alkylthio group can be prepared by a process as shown in the following reaction scheme.

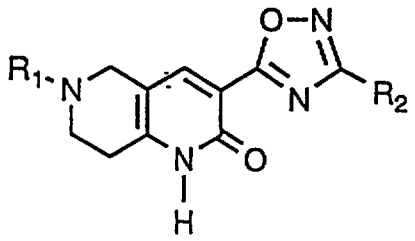


wherein R_2" is a lower alkyl group, M is sodium or potassium, and R_1 is the same as defined above.

The compound (1) is reacted with carbon disulfide in the presence of a base according to the method disclosed in Journal of Heterocyclic Chemistry, Vol. 19, p. 541 (1982) to give the compound (2), and then, the compound (2) is reacted with an alkylating agent (e.g. a lower alkyl halide) according to the method disclosed in Journal of Indian Chemical Society, Vol. 68, p. 108 (1991) to give the compound (1a') which is a compound of the formula (1a) wherein R_2 is a lower alkylthio group. When R_1 in the compound (I) is a hydrogen atom, it may be protected by a suitable protecting group, which may be removed after the reaction, as in the above Process 1.

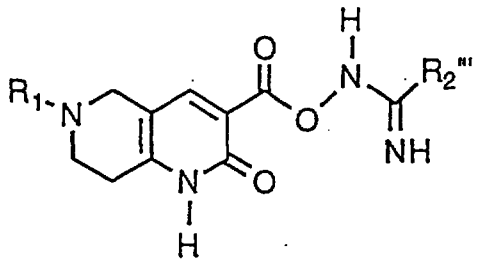
Process 3

Among the compounds (I) of the present invention, the compound of the formula (Ib):



(Ib)

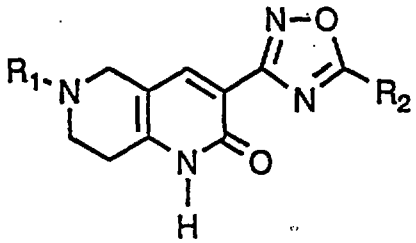
wherein R_2 is a group other than a lower alkoxy group, a lower alkenyloxy group, phenoxy group and a lower alkylthio group and R_1 is the same as defined above, can be prepared by subjecting a compound of the formula (III):



(III)

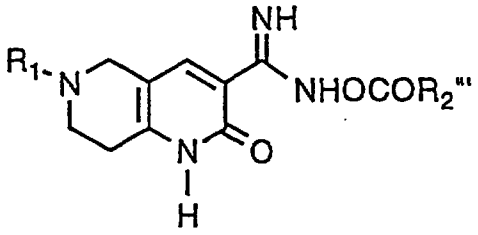
wherein R_2''' is the same as R_2 other than a lower alkoxy group, a lower alkenyloxy group, phenoxy group and a lower alkylthio group, and R_1 is the same as defined above, to intramolecular cyclodehydration.

In addition, among the compounds (I) of the present invention, the compound of the formula (Ic):



(Ic)

wherein R_2 is a group other than a lower alkoxy group, a lower alkenyloxy group, phenoxy group and a lower alkylthio group, and R_1 is the same as defined above, can be prepared by subjecting a compound of the formula (IV):



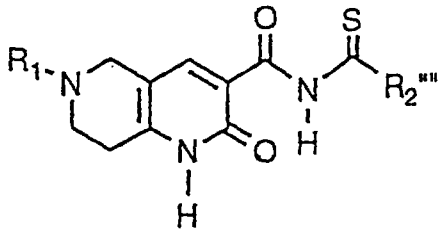
(IV)

wherein R_1 and R_2''' are the same as defined above, to intramolecular cyclodehydration.

The cyclization reaction of the compound (III) and the compound (IV) may be carried out by treating the compound with a dehydrating agent, usually with heating in a suitable solvent which does not affect the reaction. The solvent includes, for example, aromatic hydrocarbons (e.g. benzene, toluene, xylene) and ethers (e.g. tetrahydrofuran, dioxane). These solvents may be used either alone or in a mixture of one or more solvents. The reaction temperature varies according to the type of the starting compound, but it is usually in a range of 50°C to 150°C, preferably in a range of 80°C to 120°C. When the compound (III) and the compound (IV) wherein R_1 is hydrogen atom are used in these reactions, the compound (III) and the compound (IV) may be protected by a suitable protecting group, which can be removed after the cyclization reaction. The protecting group includes, for example, a lower alkanoyl group (e.g. formyl group, acetyl group), a lower alkoxycarbonyl group and a benzyloxycarbonyl group.

Process 4

Among the compounds (I) of the present invention, a compound of the formula (Ib) wherein R_2 is a lower alkoxy group, a lower alkenyloxy group, phenoxy group or a lower alkylthio group and R_1 is the same as defined above can be prepared by reacting a compound of the formula (V):



(V)

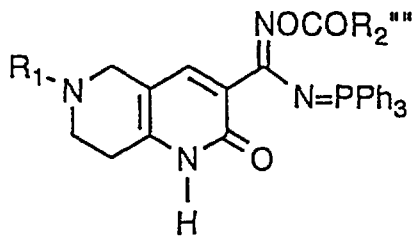
wherein R_2'''' is a lower alkoxy group, a lower alkenyloxy group, phenoxy group or a lower alkylthio group, and R_1 is the same as defined above, with hydroxylamine according to the method disclosed in Journal of Heterocyclic Chemistry, Vol. 18, p. 1197 (1981).

The reaction is usually carried out in a suitable solvent, for example, alcohols (e.g. methanol, ethanol) and water.

The reaction temperature varies according to the type of the starting compound, but it is usually in a range of 50°C to 90°C.

Process 5

Among the compounds (I) of the present invention, a compound of the formula (Ic) wherein R_2 is a lower alkoxy group, a lower alkenyloxy group, a phenoxy group or a lower alkylthio group and R_1 is the same as defined above can be prepared according to the method disclosed in Synthesis, p. 843 (1986), that is, by subjecting a compound of the formula (VI):



(VI)

wherein R_1 and R_2'''' are the same as defined above and Ph means phenyl group, to intramolecular cyclization.

The cyclization reaction may be carried out by heating in a suitable solvent, for example, aromatic hydrocarbons (e.g. benzene, toluene, xylene) and ethers (e.g. tetrahydrofuran, dioxane). The reaction temperature varies according to the type of the starting compound, but it is usually in a range of 50°C to 150°C, preferably 80°C to 120°C.

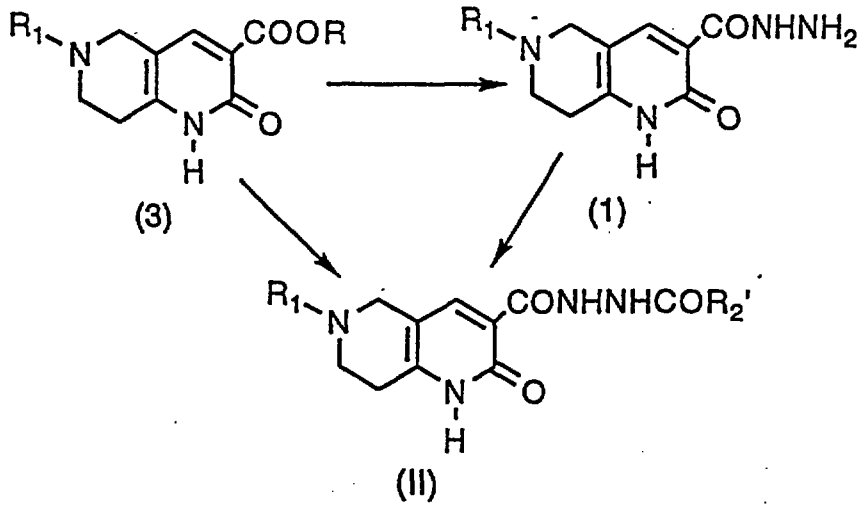
The present compounds (I) prepared by the above mentioned processes 1 to 5 may be isolated and purified by a conventional method such as chromatography, recrystallization and reprecipitation.

The compounds (I) of the present invention may be obtained either in a free form or in the form of an acid addition salt thereof, depending, for example on the type of the starting compound to be used and on the reaction conditions. The acid addition salt can be converted into a free base by a conventional method, for example, by treating it with a base such as alkali metal carbonates, alkaline earth metal carbonates, alkali metal hydroxides and alkaline earth metal hydroxides. The free base can be converted into an acid addition salt thereof by a conventional method, for example,

treating it with an inorganic or organic acid.

Process for preparing the starting compound

The compounds (II) used in the above mentioned Process 1 are novel compounds, and can be prepared by a process as shown in the following reaction scheme.



wherein R is hydrogen atom or a lower alkyl group, and R_1 and R_2' are the same as defined above.

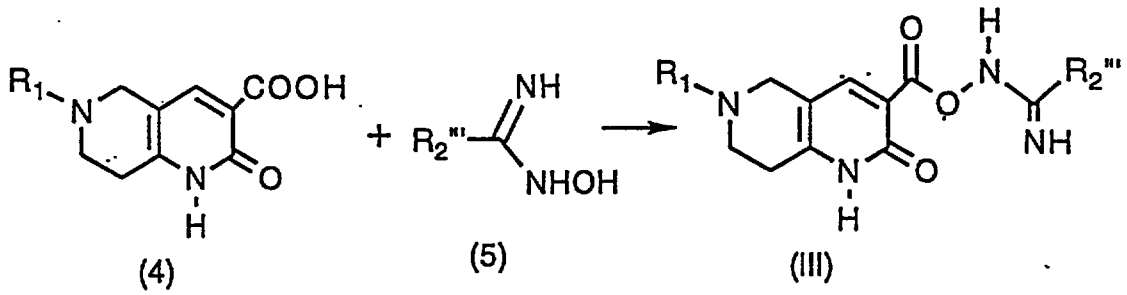
The synthesis of the compound (II) from the compound (3) may be carried out by reacting the compound (3) or a reactive derivative at the carboxyl group thereof with a hydrazide compound of the formula: $H_2NNHCOR_2'$ (R_2' is the same as defined above) by a conventional amidation reaction.

Alternatively, a compound (II) may also be prepared by two steps, that is, by reacting the compound (3) or a reactive derivative at the carboxyl group thereof with hydrazine by a conventional amidation reaction, followed by acylating the product with a reactive derivative of a carboxylic acid of the formula:

$R_2'COOH$.

The compound (3) may be prepared according to the method disclosed in Arkiv foer Kemi 26 (41), pp. 489-495 (1967) [Chemical Abstract Vol. 67, 32611z (1967)], or may also be prepared by other various processes as described hereinafter.

The compounds (III) used in Process 3 are a novel compounds, and may be prepared by a process as shown in the following reaction scheme.

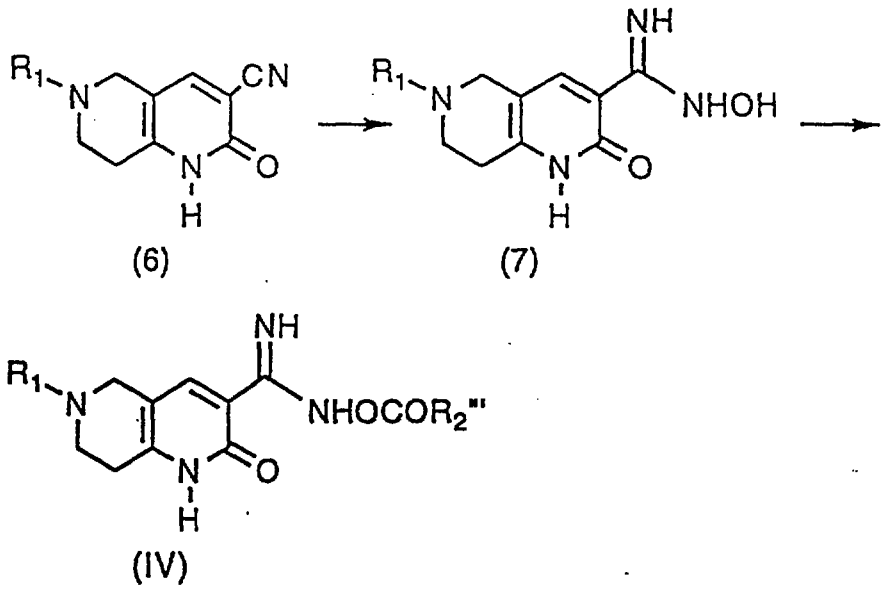


(4) (5) (III)

wherein R_1 and R_2''' are the same as defined above.

The compound (III) may be prepared by reacting the compound (4) or a reactive derivative at the carboxyl group thereof with an amidoxime (5) under the conditions for a conventional amidation reaction. When R_1 in the compound (4) is a hydrogen atom, the compound (4) may be protected by a protecting group as mentioned hereinbefore.

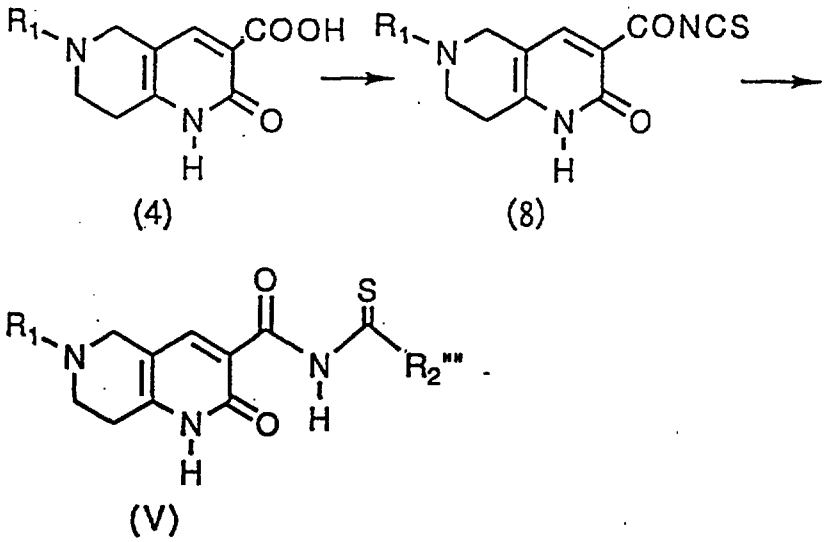
The compounds (IV) prepared by Process 3 are also novel compounds, and may be prepared by a process as shown in the following reaction scheme.



wherein R_1 and R_2''' are the same as defined above.

The compound (6) is reacted with hydroxylamine by a conventional method to give the compound (7), which is further reacted with a reactive derivative at the carboxyl group of a carboxylic acid of the formula: $R_2'''COOH$ (R_2''' is the same as defined above) in the presence of a base to give the compound (IV). When the compound (7) wherein R_1 is hydrogen atom is used, the R_1 group may be protected by a protecting group as mentioned hereinbefore.

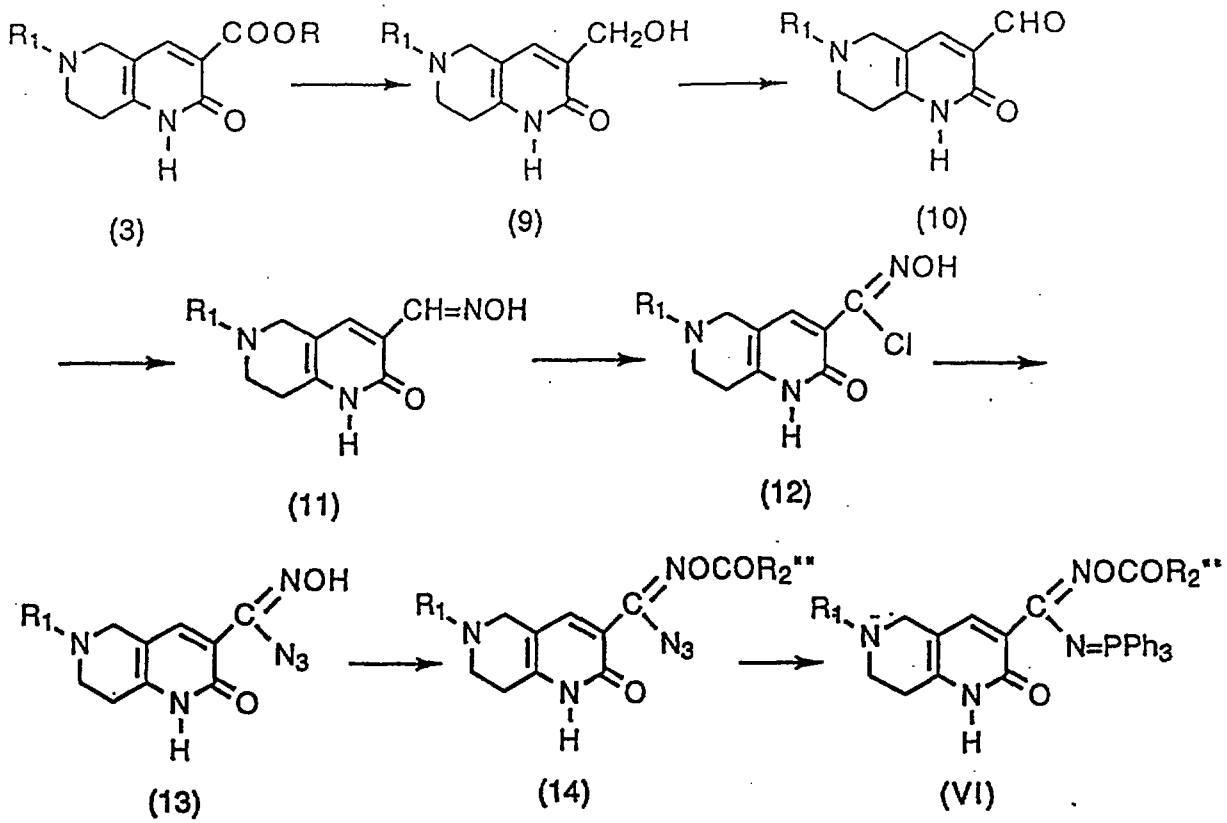
The compound (V) used in Process 4 may be prepared by a process as shown in the following reaction scheme.



wherein R_1 and R_2'''' are the same as defined above.

The compound (4) or a reactive derivative at the carboxyl group thereof is reacted with an alkali metal salt or ammonium salt of thiocyanic acid in a suitable solvent to give the compound (8), which is further subjected to alcoholysis, or alternatively, treated with a lower alkylthiol or a alkali metal salt thereof in a suitable solvent, to give the compound (V). When the compound (8) wherein R_1 is a hydrogen atom is used, the R_1 group may be protected with a protecting group as mentioned hereinbefore.

The compounds (VI) used in Process 5 are novel compounds, and may be prepared by a method as shown in the following reaction scheme.



wherein R, R_1 and R_2"" are the same as defined above, and Ph means a phenyl group.

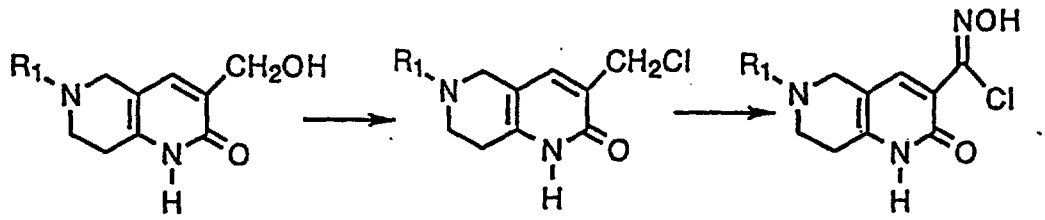
The compound (3) is reduced with a reducing agent such as sodium borohydride, tetrabutylammonium borohydride, lithium aluminum hydride in a suitable solvent which does not affect the reaction to give the compound (9), which is further subjected to oxidation with active manganese dioxide in a suitable solvent to give the compound (10).

The compound (10) is reacted with hydroxylamine under the conditions for a conventional oxime forming reaction to give the compound (11), which is reacted with N-chlorosuccinimide according to the method disclosed in Journal of Organic Chemistry, Vol. 45, p. 3916 (1980) to give the compound (12).

The compound (12) is reacted with sodium azide in a suitable solvent according to the method disclosed in Synthesis, p. 102 (1979) to give the compound (13).

The compound (13) is reacted with a haloformic acid ester or a reactive derivative of S-lower alkylthiocarboxylic acid ester in a suitable solvent according to the method disclosed in Synthesis, p. 843 (1986) to give the compound (14), which is further reacted with triphenylphosphine to give the compound (VI).

The compound (12) can also be prepared according to the method disclosed in Synthesis, p. 102 (1979) as shown in the following reaction scheme.

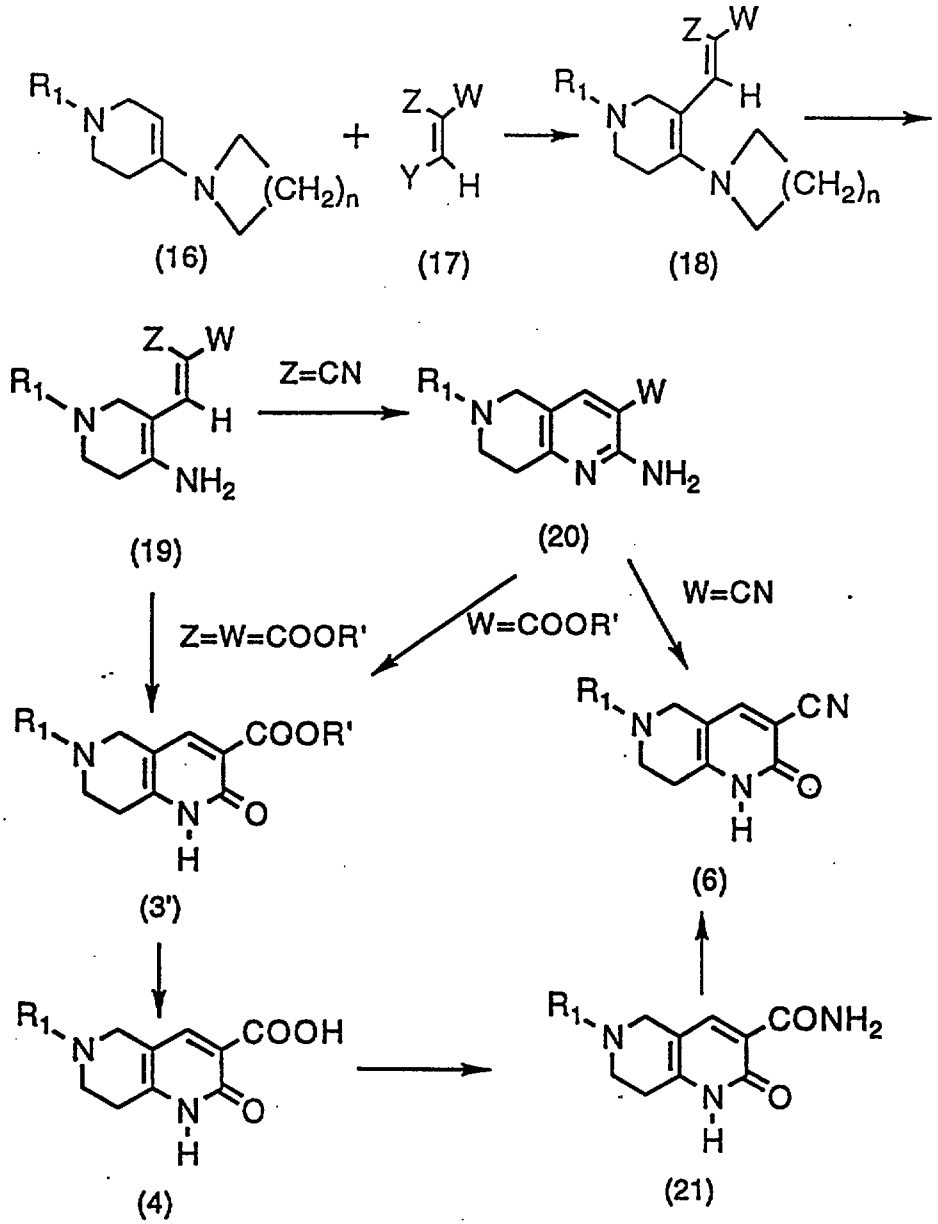


(9) (15) (12)

wherein R_1 is the same as defined above.

The compound (9) is reacted with a phosphorus compound (e.g. phosphorus trichloride, phosphorus oxychloride) . or a thionyl chloride in a suitable solvent to give the compound (15), which is further reacted with an alkyl nitrite in the presence of an acid in a suitable solvent to give the compound (12).

The compound (3), compound (4) and compound (6), which are converted into the compounds (II) - (VI), may be prepared according to the method disclosed in Arkiv foer Kemi 26 (41), 489-495 (1967) [Chemical Abstract Vol. 67, 32611z (1967)], or prepared by a process as shown in the following reaction scheme.



wherein Y is a halogen atom, a lower alkoxy group or a di-lower alkylamino group, W and Z are the same or different and each cyano group or a lower alkoxycarbonyl group, R' is a lower alkyl group, n is an integer of 1 to 3, and R_1 is the same as defined above.

The starting compound (16) in the above reaction scheme can be prepared according to the method disclosed in Journal of American Chemical Society, Vol. 85, p. 207 (1963). The compound

(16) thus prepared is reacted with the compound (17) in a solvent such as alcohols (e.g. methanol, ethanol), ethers (e.g. tetrahydrofuran, dioxane), aromatic hydrocarbons (e.g. benzene, toluene) at a temperature from 0°C to 120°C to give the compound (18), which is further reacted with ammonia or an ammonium salt (e.g. ammonium acetate) in a solvent such as alcohols (e.g. methanol, ethanol), ethers (e.g. tetrahydrofuran, dioxane) and acetonitrile at a temperature from 0°C to 100°C to give the compound (19).

When both W and Z in the compound (19) are a lower alkoxycarbonyl group, the compound (19) is heated in a solvent such as alcohols (e.g. methanol, ethanol) ethers (e.g. tetrahydrofuran, dioxane) and aromatic hydrocarbons (e.g. benzene, toluene, xylene) at a temperature from 50°C to 120°C to give the compound (3'), which is further hydrolyzed under an acidic or basic condition by a conventional method to give the compound (4).

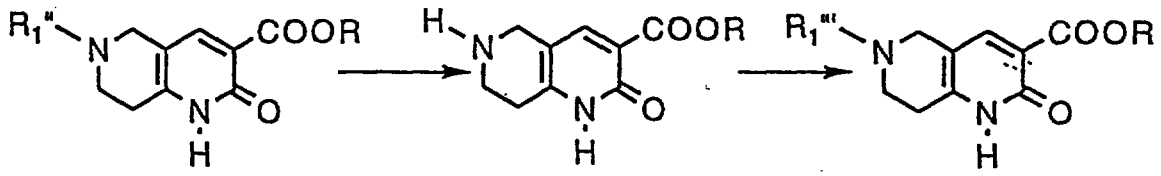
When in the compound (19) Z is cyano group, the compound (19) is treated in the presence of a base in a suitable solvent such as alcohols (e.g. methanol, ethanol) and ethers (e.g. tetrahydrofuran, dioxane) at a temperature from 0°C to 100°C to give the compound (20), which is further reacted with sodium nitrite under acidic conditions, for example, in 5 to 10 % aqueous hydrochloric acid solution or 5 to 20 % aqueous sulfuric acid solution, at a temperature from 0°C to 20°C to give the compound (3') when W in the compound (20) is an ester group, or

the compound (6) when W in the compound (20) is cyano group.

The compound (6) is prepared by reacting the compound (21) with a dehydrating agent (e.g. thionyl chloride, phosphorus pentachloride, phosphorus oxychloride, polyphosphoric acid) in a solvent, such as ethers (e.g. tetrahydrofuran, dioxane), aromatic hydrocarbons (e.g. benzene, toluene), halogenated hydrocarbons (e.g. dichloromethane, chloroform, 1,2-dichloroethane).

The compound (21) is prepared by reacting a reactive derivative at the carboxyl group of the compound (4) with ammonia by a conventional method.

The compound (3) can also be prepared by a process as shown in the following reaction scheme.



(3") (22) (3'")

wherein R_1" is a lower alkyl group, a benzyl group, a lower alkoxycarbonyl group or a benzyloxycarbonyl group, R_1'" is a group, other than a hydrogen atom and an acyl group, defined for R_1, and R is the same as defined above.

The substituent R_1" in the compound (3") and the substituent R_1'" in the compound (3'") can be converted from one to the other via the compound (22). The compound (3") wherein R_1" is a lower alkyl group or benzyl group is converted into the compound (22) by treating it, for example, with 1-chloroethyl chlorocarboxylate, according to

the method disclosed in Journal of Organic Chemistry, Vol. 49, p. 2081 (1984).

The compound (3") wherein R_1" is benzyl group or benzyloxycarbonyl group is converted into the compound (22) by treating it with hydrogen in the presence of a catalyst (e.g. Raney nickel, palladium-carbon), under atmospheric pressure or under pressure at a temperature from 25°C to 80°C in a suitable solvent, such as water, methanol, ethanol, acetic acid, dioxane and ethyl acetate.

The compound (3") wherein R_1" is a lower alkoxycarbonyl group or benzyloxycarbonyl group is also converted into the compound (22) by treating it with an acid or a base in a suitable solvent. For example, the compound (3") wherein R_1" is tert-butoxycarbonyl group is treated with trifluoroacetic acid at a temperature from 25°C to 80°C in a solvent such as dichloro-methane and chloroform, to give the compound (22).

The thus obtained compound (22) is then converted into the compound (3"') by reacting the compound (22) with an alkylating agent corresponding to R_1"' wherein R_1"' is, for example, a lower alkyl, allyl, propargyl, benzyl, naphthalenemethyl, or heteroaromatic methyl group in the presence of a basic compound, such as inorganic salts, for example, alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide), alkali metal carbonates (e.g. sodium carbonate, potassium carbonate) and alkali metal hydrogen carbonates (e.g. sodium hydrogen carbonate, potassium hydrogen

carbonate.), or organic bases, for example, pyridine, triethylamine and tributylamine, in a suitable solvent such as acetone, methyl ethyl ketone, diethyl ketone, dimethylformamide, benzene, toluene and acetonitrile, at a temperature from 25°C to 100°C. These alkylating agents may be any conventional ones such as alkyl halides.

The pharmacological properties of the compounds (I) of the present invention are illustrated by the following experiments with representative compounds.

Experiment 1 Benzodiazepine Receptor Binding Assay

According to the method disclosed in Life Science Vol. 20, p. 2101 (1977), the benzodiazepine receptor binding assay was carried out.

A crude synaptosome membrane fraction prepared from brains of Wistar rats (age: 7 to 8 weeks) was suspended in 15 mM Tris-HCl buffer (pH 7.4) containing 118 mM sodium chloride, 4.8 mM potassium chloride, 1.28 mM calcium chloride and 1.2 mM magnesium sulfate in a concentration of 1 g (wet weight) of brain per 20 ml of buffer to give a receptor membrane source. [^{3}H]-diazepam was used as a labelled ligand.

A test compound (a known amount), [^{3}H]-diazepam (final concentration; 1.5 nM), receptor membrane and the above buffer were added to a test tube (final volume: 1 ml). The reaction was started by addition of the receptor membrane. The test tube was incubated at 0°C for 20 minutes, and the reaction mixture was terminated by rapid filtration through Whatman GF/B glass fiber

filter attached to a Cell-harvester (manufactured by Brandell). Immediately, the collected labelled ligand-bound receptor membrane was washed three times with ice-cold 50 mM Tris-HCl buffer (pH 7.7, each 5 ml). The radioactivity on the filter was measured by a liquid scintillation counter to determine the amount of the [^{3}H]-diazepam bound to the receptor membrane (total binding). Separately, the same procedures were repeated except 1 μM diazepam was added, and thereby the amount of [^{3}H]-diazepam bound to the receptor membrane (non-specific binding) was measured likewise. This non-specific binding was deducted from the total binding to give the specific binding. Based on the specific binding thus obtained, the inhibitory activity (IC_{50}) of the test compound was determined by probit method. The IC_{50} means the concentration of the test compound to be required to decrease the specific binding of the labelled ligand by 50 %. The results are shown in the following Table 1.

Table 1 Benzodiazepine receptor binding assay

Ex. No.	IC_{50} (nM)	Ex. No.	IC_{50} (nM)
6	9.91	7	13.5
10	6.95	26	14.1
29	5.46	32	2.49
38	4.55	52	19.3
55	3.91	56	35.1
58	14.6	60	1.58
61	6.25	62	13.8

64	4.09	66	10.1
81	5.17	82	8.98
86	7.91	88	4.62
91	23.1	115	50.3
119	1.29	120	4.40
121	62.4	122	5.96
123	12.5	124	5.40
125	8.63	141	22.8
142	3.24	143	2.19
145	8.64	146	9.11
147	2.50	152	4.90
153	3.51	154	11.0
155	6.08	156	6.68
157	2.71	158	3.73
159	8.15	160	3.75

Experiment 2 Activity on pentylenetetrazole-induced clonic convulsion (anti-PTZ activity)

The activity on pentylenetetrazole-induced clonic convulsion of the test compound was tested according to the method of E. A. Swinyard (cf. Anticonvulsant Drugs. Mercier, J., Ed., pp. 47-65, Pergamon Press, New York (1973)). In this test, petit mal-type antiepileptics and most of benzodiazepine drugs show positive results.

A test compound was administered orally to Std-ddY male

mice (weight; 20-25 g, five mice/group). Two hours later, pentylenetetrazole (85 mg/kg) was injected subcutaneously into the mice, and immediately, the mice were put into a plastic cage, and the appearance of clonic convulsion was observed for 30 minutes. When no clonic convulsion was observed, it was determined that the test compound had antagonistic activity. The results are shown in the following Table 2.

Table 2 Anti-PTZ activity

Ex. No.	Dose of test compd. (mg/kg)	Number of mice having antagonistic activity/number of test mice	Ex. No.	Dose of test compd. (mg/kg)	Number of mice having antagonistic activity/number of test mice
6	50	5/5	7	50	5/5
10	20	5/5	13	20	5/5
17	20	3/5	23	10	4/5
26	2	3/5	33	10	4/5
35	2	5/5	36	2	5/5
38	2	4/5	52	10	5/5
55	50	5/5	56	50	4/5
60	50	5/5	66	50	5/5
80	50	4/5	83	50	5/5
85	50	4/5	89	50	5/5
91	50	5/5	111	50	5/5
119	10	5/5	120	10	9/10
122	10	10/10	124	10	3/5
142	10	4/5	143	10	3/5

As is shown in the above results, compounds embodying the present invention showed an apparent affinity for benzodiazepine receptor, and also showed excellent antagonistic activity against pentylenetetrazole-induced clonic convulsion. Accordingly, compounds embodying the present invention are useful as benzodiazepine receptor agonists, for example, as anxiolytics, antiepileptics, or hypnotics

Pharmaceutical use of the compounds of the present invention

The compounds of the present invention may be administered either orally, parenterally or intrarectally when used as benzodiazepine receptor agonist, but oral administration is preferable. The dosage of the present compound varies according to the route of the administration, conditions, and ages of the patients, or the types of the treatment (e.g. prophylaxis or treatment), but it is usually in the range of 0.01 to 10 mg/kg/day, preferably in the range of 0.02 to 5 mg/kg/day.

The present compounds may be administered in the form of a conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier or diluent. The pharmaceutically acceptable carrier or diluent may be any conventional one which is used in this field and does not react with the present compound, for example, lactose, glucose, mannitol, dextran, starch, white sugar, magnesium aluminate metasilicate, synthetic aluminum silicate, crystalline cellulose, sodium

carboxymethylcellulose, calcium carboxymethylcellulose, ion-exchange resin, methyl cellulose, gelatin, gum arabic, hydroxypropyl cellulose, lower-substituted hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, light silicic anhydride, magnesium stearate, talc, carboxyvinyl polymer, titanium oxide, sorbitan fatty acid ester, sodium laurylsulfate, glycerin, glycerin fatty acid ester, purified lanolin, glycerogelatin, polysorbate, macrogol, vegetable oil, wax, liquid paraffin, white petrolatum, nonionic surfactant, propylene glycol and water.

Pharmaceutical preparations are, for example, tablets, capsules granules, powders, syrups, suspensions, suppositories, gels and injection preparations. These preparations may be prepared by a conventional method. When a liquid preparation is prepared, it may previously be in the form of a solid preparation which is dissolved or suspended in water or a solvent when used. Besides, tablets or granules may be coated by a conventional method, and injection preparations prepared by dissolving the compound of the present invention or an acid addition salt thereof in distilled water for injection, or a physiological saline solution, but if necessary, it may be dissolved in a isotonic solution, and further, a pH adjustor, a buffer or a preservative may be added thereto.

These pharmaceutical preparations may contain the present compound in an amount of more than 0.01 % by weight, preferably 0.05 to 70 % by weight, and may contain other pharmacologically active ingredients.

Examples

The present invention is illustrated in more detail by the following Examples and Reference Examples.

Example 1

Preparation of ethyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylate:

(1) A solution of 1-benzyl-4-piperidone (19 g, 0.1 mole) and pyrrolidine (10.7 g, 0.15 mole) in toluene (200 ml) is refluxed for 5 hours during which water is removed by evaporation. The reaction solution is concentrated to dryness under reduced pressure, and anhydrous toluene (200 ml) is added to the residue. To the mixture is added dropwise and gradually a solution of ethyl ethoxymethylenecyanoacetate (17 g, 0.1 mole) in anhydrous toluene (50 ml) under ice-cooling. The mixture is warmed to room temperature, and stirred overnight, and thereto is added dropwise conc. hydrochloric acid (13 ml) under ice-cooling. The hydrochloride thus obtained is collected by filtration, and washed successively with ethyl acetate and isopropyl ether. The hydrochloride is dissolved in ethanol (300 ml), and thereto is blown ammonia gas under ice-cooling to saturate. The mixture is warmed to room temperature, and allowed to stand overnight, and then, concentrated to dryness under reduced pressure. To the residue is added isopropanol, and the precipitated crystals are collected by filtration, and dried to give the crude crystals (10 g).

The above mentioned crystals are dissolved in ethanol (100

ml), and thereto is added dropwise 10 % aqueous sodium hydroxide solution under ice-cooling. The mixture is warmed to room temperature, and stirred for 30 minutes, and thereto is added water (100 ml) under ice-cooling. The precipitated crystals are collected by filtration, and washed with water, and recrystallized from isopropanol to give ethyl 2-amino-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate (8.5 g) as a colorless solid.

Yield: 27.3 %

mp. 141-143°C.

(2) To a solution of the above ester compound (10 g, 32 mmole) in 10 % aqueous sulfuric acid solution (100 ml) is added dropwise and gradually a solution of sodium nitrite (4.5 g, 65 mmole) in water (20 ml) under ice-cooling. After addition, the mixture is stirred for 2 hours. The mixture is alkalified with 20 % aqueous sodium hydroxide solution with stirring under ice-cooling, and extracted with chloroform. The extract is dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The resulting crystals are recrystallized from isopropanol to give a colorless solid (6.8 g).

Yield: 68 %

mp. 168-170°C

Example 2

Preparation of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylic acid hydrochloride:

(1) A mixture of ethyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylate (6.8 g, 22 mmole) and

20 % aqueous hydrochloric acid solution (70 ml) is refluxed for 3 hours. After cooling, the precipitated crystals are collected by filtration, washed with water, and recrystallized from methanol-water to give the desired compound (7.0 g) as a colorless solid.

Yield: 99.2 %

m.p. 260-263°C

(2) A solution of 1-benzyl-4-piperidone (100 g, 0.53 mole) and pyrrolidine (70 ml, 0.795 mole) in toluene (1.5 liter) is refluxed for 5 hours with distilling off water. The mixture is concentrated to dryness under reduced pressure, and to the residue is added dioxane (1 liter). To the mixture is added diethyl ethoxymethylenemalonate (126 g, 0.58 mole) under ice-cooling, and the mixture is refluxed for 6 hours. The mixture is cooled to room temperature, and thereto is added ammonium acetate (82 g, 1.06 mole), and the mixture is refluxed with stirring for one hour. The reaction solution is concentrated to dryness under reduced pressure to give ethyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylate, which is used in the subsequent step without isolation or further purification.

To the above ethyl ester is added 20 % aqueous hydrochloric acid solution (600 ml), and the mixture is refluxed for 3 hours. After cooling, the precipitated crystals are collected by filtration, washed with water, and recrystallized from methanol-water to give the desired compound as a colorless solid (105 g).

Yield: 61.9 %

m.p. 260-263°C

Example 3

Preparation of ethyl 5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylate acetate:

To a solution of ethyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylate (8 g) in glacial acetic acid (360 ml) is added 10 % palladium-carbon catalyst (200 mg), and the mixture is subjected to catalytic hydrogenation at room temperature under hydrogen gas. After the theoretical amount of hydrogen gas is consumed, the catalyst is removed by filtration. The filtrate is concentrated to dryness under reduced pressure. To the residue is added ethanol, and the precipitated crystal is collected by filtration, and recrystallized from ethanol-water to give a colorless solid (6.8 g).

Yield: 94 %

m.p. 125-130°C

Example 4

Ethyl 6-(3-fluorobenzyl)-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylate:

A suspension of ethyl 5,6,7,8-tetrahydro-2(1H)-oxo-1,6-napthyridine-3-carboxylate acetate (2.0 g, 7.1 mmole), 3-fluorobenzyl bromide (1.7 g, 9 mmole) and sodium hydrogen carbonate (2.0 g, 24 mmole) in methyl ethyl ketone (100 ml) is refluxed for 16 hours. The insoluble materials are removed by filtration, and the filtrate is concentrated to dryness under reduced pressure. The residue is purified by medium-pressure column chromatography packed with Diaion CHP-20P (high porous

polystyrene resin, manufactured by Mitsubishi Kasei Corporation, Japan) (solvent; acetonitrile and water, with concentration gradient), and recrystallized from ethanol to give a colorless solid (1.91 g).

Yield: 81.4 %

m.p. 276-280°C

Example 5

Preparation of 6-(2-fluorobenzyl)-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylic acid hydrochloride:

(1) To phenylphosphonic dichloride (1 ml) is added ethyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylate (1.0 g, 3.2 mmole) at room temperature, and the mixture is stirred at 150°C for one hour. After cooling, to the mixture is added diisopropyl ether, and the precipitated crystals are collected by filtration. The crystals are suspended in chloroform, and the mixture is alkalified by adding thereto gradually 28 % aqueous ammonia with stirring under ice-cooling. The organic layer is separated, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The resulting oily product is purified by silica gel column chromatography (solvent; chloroform : methanol = 200 : 1) to give ethyl 6-benzyl-2-chloro-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate (0.7 g) as a colorless oil.

Yield: 66.1 %

(2) To a solution of the above ester (20.0 g, 60 mmole) in methylene chloride (200 ml) is added dropwise 1-chloroethyl

chloroformate (10.4 g, 72 mmole) at room temperature, and the mixture is refluxed for 20 hours. The mixture is concentrated to dryness under reduced pressure, and to the resulting residue is added methanol (200 ml). The mixture is heated with stirring at 40°C for 2 hours. The reaction mixture is concentrated to dryness under reduced pressure, and isopropyl ether is added to the residue. The precipitated crystals are collected by filtration, and recrystallized from ethanol to give ethyl 2-chloro-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate hydrochloride (21.2 g) as a colorless solid.

Yield: 85.8 %

m.p. 153-156°C

(3) To a solution of the above hydrochloride (5.0 g, 18 mmole) and triethylamine (4.0 g, 40 mmole) in N,N-dimethylformamide (DMF) (50 ml) is added 2-fluorobenzyl bromide (3.1 g, 21 mmole), and the mixture is heated with stirring at 60°C for 15 hours. The reaction solution is concentrated to dryness under reduced pressure, and the residue is dissolved in chloroform. The mixture is washed successively with 10 % aqueous potassium carbonate solution and water. The organic layer is dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to remove the solvent. The resulting oily product is purified by silica gel column chromatography (solvent; chloroform : methanol = 100 : 1) to give ethyl 2-chloro-6-(2-fluorobenzyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate (4.6 g) as a colorless oil.

Yield: 73.3 %

(4) A solution of the above ester (4.6 g, 13 mmole) in 20 % aqueous hydrochloric acid solution (80 ml) is refluxed for 24 hours. After cooling, the precipitated crystals are collected by filtration, washed, and recrystallized from ethanol to give the desired compound (3.4 g) as a colorless solid.

Yield: 77.2 %

m.p. 273-276°C

Example 6

Preparation of 6-benzyl-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one:

(1) A solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylic acid hydrochloride (3.0 g, 9.4 mmole) and N,N'-carbonyldiimidazole (2.3 g, 14 mmole) in DMF (50 ml) is heated with stirring at 70°C for 3 hours. To the solution is added methyl carbazate (1.0 g, 11 mmole), and the mixture is stirred at the same temperature for 2 hours. The reaction solution is concentrated to dryness under reduced pressure, and to the residue are added isopropanol and triethylamine. The precipitated crystals are collected by filtration, and recrystallized from methanol to give N'-methoxycarbonyl-6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbohydrazide (2.4 g) as a colorless solid.

Yield: 71.6 %

m.p. 240-242°C

(2) To a solution of the above product (2.0 g, 5.6 mmole),

triphenylphosphine (3.0 g, 11 mmole) and triethylamine (2.0 g, 20 mmole) in anhydrous tetrahydrofuran (THF) (50 ml) is added dropwise with stirring a solution of diisopropyl azodicarboxylate (2.2 g, 11 mmole) in anhydrous tetrahydrofuran (10 ml) under ice-cooling. The mixture is stirred at room temperature for one hour, and thereto is added a small amount of water, and the mixture is concentrated to dryness under reduced pressure. To the residue is added isopropanol, and the precipitated crystals are collected by filtration, and recrystallized from acetonitrile to give the desired compound (0.8 g) as a colorless solid.

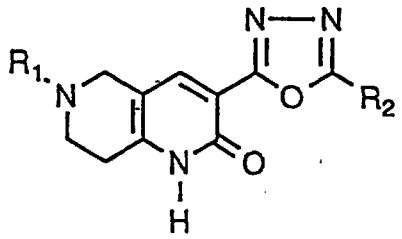
Yield: 43 %

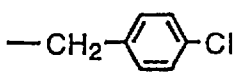
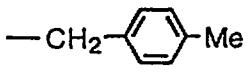
m.p. 176-178°C

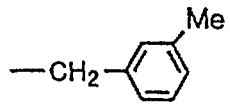
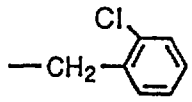
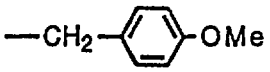
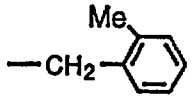
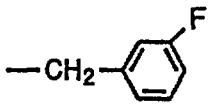
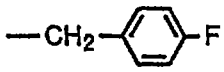
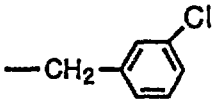
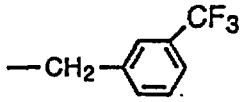
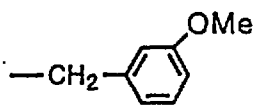
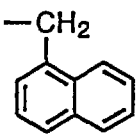
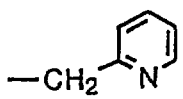
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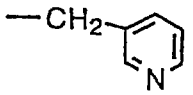
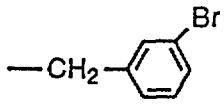
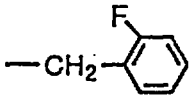
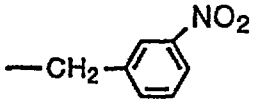
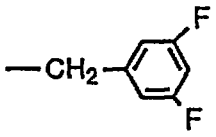
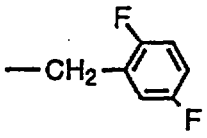
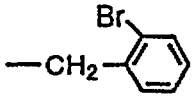
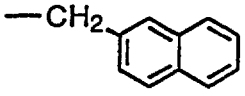
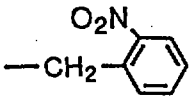
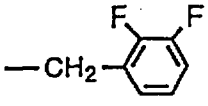
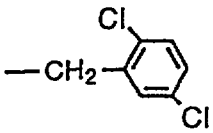
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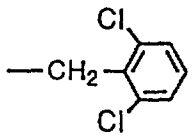
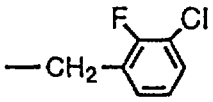
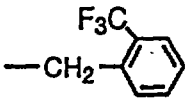
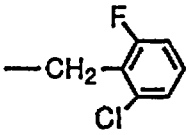
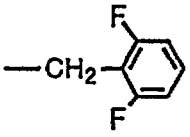
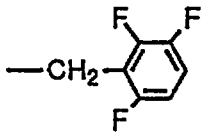
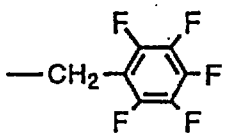
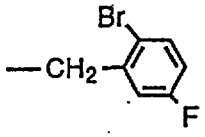
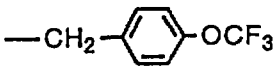
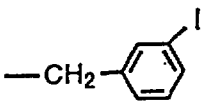
Table 3

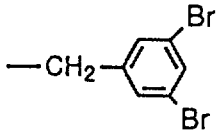
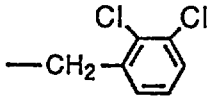
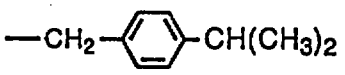
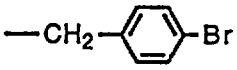
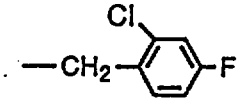
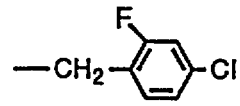
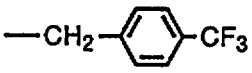
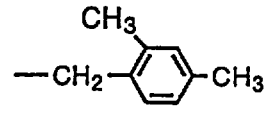
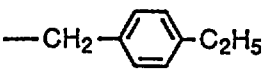
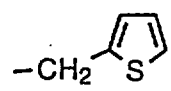
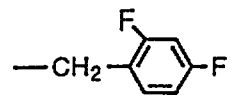


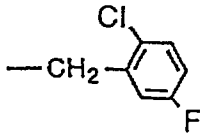
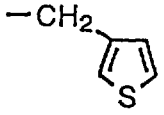
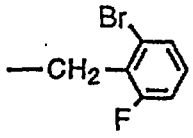
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7		-OCH_3	182-184	Ethanol
8		-OCH_3	183-185	Ethanol

9		-OCH_3	187-189	Ethanol
10		-OCH_3	189-191	Ethanol
11		-OCH_3	183-185	Ethanol
12		-OCH_3	179-181	Ethanol
13		-OCH_3	184-186	Ethanol
14		-OCH_3	203-205	Ethanol
15		-OCH_3	184-185	Ethanol
16		-OCH_3	192-194	Methanol
17		-OCH_3	178-180	Ethanol
18		-OCH_3	178-180	Ethanol
19		-OCH_3	171-173	Acetonitrile

20		-OCH_3	167-169	Acetonitrile
21		-OCH_3	185-187	Ethanol
22		-OCH_3	174-176	Ethanol
23		-OCH_3	185-187	Ethanol
24		-OCH_3	206-208	Ethanol
25		-OCH_3	202-204	Ethanol
26		-OCH_3	191-193	Ethanol
27		-OCH_3	203-205	Methanol
28		-OCH_3	194-196	Methanol
29		-OCH_3	195-197	Ethanol
30		-OCH_3	193-195	Methanol

31		$-OCH_3$	199-201	Methanol
32		$-OCH_3$	177-179	Ethanol
33		$-OCH_3$	189-191	Methanol
34		$-OCH_3$	187-189	Ethanol
35		$-OCH_3$	186-188	Ethanol
36		$-OCH_3$	199-201	Ethanol
37		$-OCH_3$	210-212	Methanol
38		$-OCH_3$	208-210	Methanol
39		$-OCH_3$	213-215	Ethanol
40		$-OCH_3$	185-187	Ethanol

41		$-OCH_3$	219-221	Methanol
42		$-OCH_3$	193-195	Methanol
43		$-OCH_3$	195-197	Acetonitrile
44		$-OCH_3$	191-193	Ethanol
45		$-OCH_3$	194-196	Ethanol
46		$-OCH_3$	190-192	Ethanol
47		$-OCH_3$	207-209	Ethanol
48		$-OCH_3$	181-183	Ethanol
49		$-OCH_3$	181-183	Acetonitrile
50		$-OCH_3$	153-155	Acetonitrile
51		$-OCH_3$	196-198	Ethanol

52		$-OCH_3$	209-211	Ethanol
53		$-OCH_3$	156-158	Acetonitrile
54		$-OCH_3$	187-189	Ethanol

Example 55

Preparation of 6-benzyl-3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one:

(1) A solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylic acid hydrochloride (1.5 g, 4.7 mmole) and N,N'-carbonyldiimidazole (1.14 g, 7 mmole) in DMF (30 ml) is heated with stirring at 70°C for 3 hours. To the solution is added cyclopropanecarbohydrazide (0.51 g, 5.2 mmole), and the mixture is stirred at the same temperature for 2 hours. The reaction solution is concentrated to dryness under reduced pressure, and to the residue are added isopropanol and triethylamine. The precipitated crystals are collected by filtration, and recrystallized from methanol to give N'-cyclopropanecarbonyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbohydrazide (1.2 g) as a colorless solid.

Yield: 66.1 %

m.p. 256-258°C

(2) To a solution of the above product (1.1 g, 2.9 mmole), triphenylphosphine (1.62 g, 6.2 mmole) and triethylamine (1.05 g, 10 mmole) in anhydrous THF (75 ml) is added dropwise with stirring a solution of diethyl azodicarboxylate (1.05 g, 6 mmole) in anhydrous THF (5 ml) under ice-cooling. The mixture is heated with stirring at 60°C for 2 hours, and thereto is added a small amount of water, and concentrated to dryness. The residue is purified by medium-pressure column chromatography of Diaion CHP-20P (solvent; acetonitrile and water, with concentration gradient), and recrystallized from acetonitrile to give a colorless solid (0.31 g).

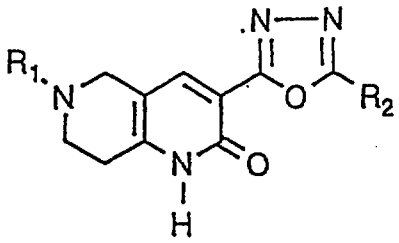
Yield: 44.5 %

m.p. 212-214°C

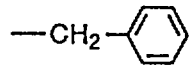
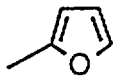
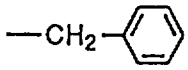
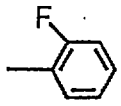
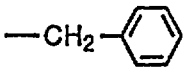
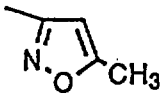
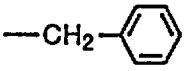
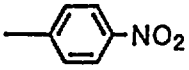
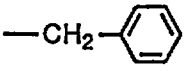
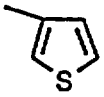
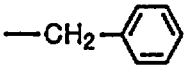
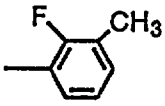
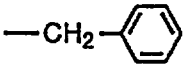
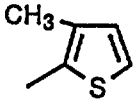
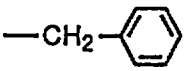
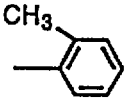
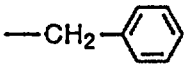
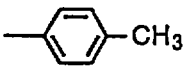
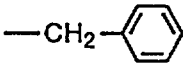
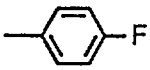
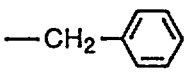
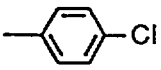
Examples 56-110

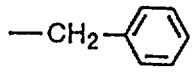
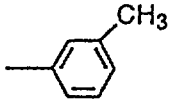
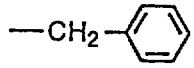
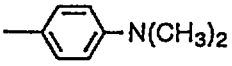
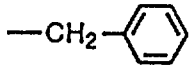
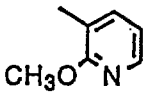
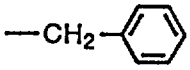
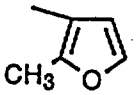
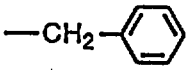
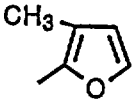
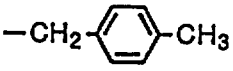
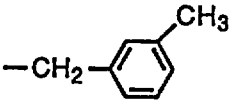
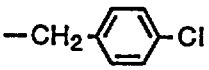
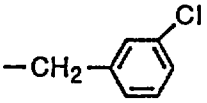
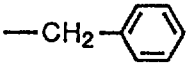
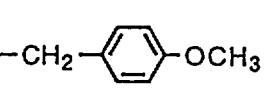
In the same manner as described in Example 55, there are prepared the compounds listed in Table 4.

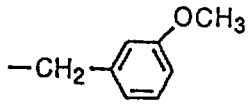
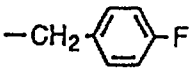
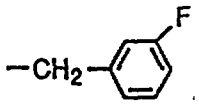
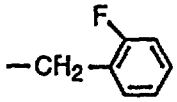
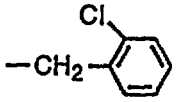
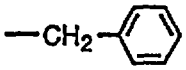
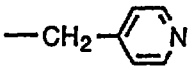
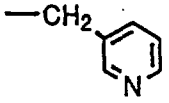
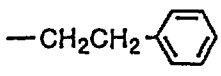
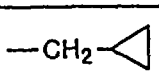
Table 4

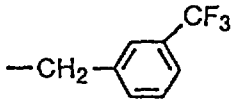
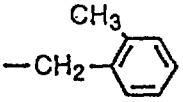
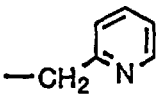
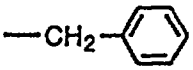
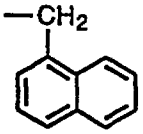
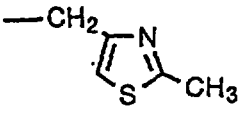
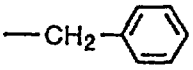
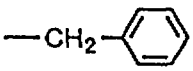


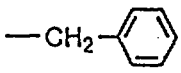
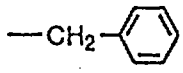
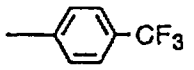
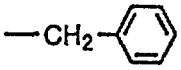
Ex. No.	R_1	R_2	m.p. (°C)	Solvent for recrystal.
56	—CH_2—	-$CH(CH_3)_2$	246-250	Methanol
57	—CH_2—	-OC_2H_5	211-213	Ethanol
58	—CH_2—	—	258-260	Methanol
59	—CH_2—	N	252-255	Methanol
60	—CH_2—	S	239-242	Ethanol
61	—CH_2—	Cl	227-230	Methanol
62	—CH_2—	-$(CH_2)_2CH_3$	219-221	Ethanol
63	—CH_2—	-OCH_3	221-224	Methanol

64			224-227	Ethanol
65			229-231	Methanol
66			247-250	Methanol
67			224-226	THF
68			207-209	Acetonitrile
69			232-234	THF
70			234-236	Methanol
71			231-233	Methanol
72			239-241	Methanol
73			230-232	Methanol
74			241-243	THF

75			258-260	Chloroform
76			224-226	Methanol
77			216-218	Methanol
78			259-261	Methanol
79			228-230	Methanol
80			214-216	Acetonitrile
81			224-226	Ethanol
82			222-224	Acetonitrile
83			221-223	Acetonitrile
84		-CH_3	226-228	Ethanol
85			184-186	Acetonitrile

86			212-214	Acetonitrile
87			212-214	Acetonitrile
88			219-221	Ethanol
89			210-212	Acetonitrile
90			225-227	Ethanol
91		$-C_2H_5$	213-215	Ethanol
92			230-232	Acetonitrile
93			209-211	Acetonitrile
94	$-CH_2CH=CH_2$		205-207	Acetonitrile
95			214-216	Acetonitrile
96			206-208	Acetonitrile

97			220-222	Acetonitrile
98			192-194	Acetonitrile
99			213-215	Ethanol
100	$-(CH_2)_2CH_3$		197-199	Acetonitrile
101		$-CH_2OCH_3$	187-189	Acetonitrile
102			218-220	Acetonitrile
103			197-199	Acetonitrile
104	$-CH(CH_3)_2$		201-203	Acetonitrile
105	$-CH_2CH(CH_3)_2$		223-225	Acetonitrile
106		$-(CH_2)_3CH_3$	195-197	Ethanol
107			253-256	Methanol

108			242-244	Ethanol
109			254-256	Chloroform
110		$-CH_2CH_2CF_3$	224-226	Ethanol

Example 111

Preparation of 6-benzyl-3-(5-isopropenyl-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one:

(1) To a solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbohyrazide (1.49 g, 5 mmole) in pyridine (20 ml) is added with stirring methacryloyl chloride (0.57 g, 5.5 mmole) under ice-cooling. The mixture is warmed to room temperature, and stirred for 2 hours, and concentrated to dryness under reduced pressure. To the residue is added 10 % aqueous potassium carbonate solution, and the mixture is extracted with chloroform. The organic layer is dried over anhydrous sodium sulfate, and evaporated under reduced pressure to remove the solvent. To the residue is added isopropanol, and the precipitated crystals are collected by filtration, and recrystallized from methanol to give N'-methacryloyl-6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbohyrazide (1.21 g) as a colorless solid.

Yield: 66 %

m.p. 245-248°C

(2) To a solution of the above product (0.92 g, 2.5 mmole), triphenylphosphine (1.35 g, 5 mmole) and triethylamine (0.87 g, 8.6 mmole) in anhydrous THF (50 ml) is added dropwise with stirring a solution of diethyl azodicarboxylate (0.87 g, 5 mmole) in anhydrous THF (5 ml) under ice-cooling. The mixture is heated with stirring at 60°C for 2 hours, and thereto is added a small amount of water, and concentrated to dryness under reduced pressure. To the residue is added isopropanol, and the precipitated crystals are collected by filtration, and recrystallized from acetonitrile to give a colorless solid (0.39 g).

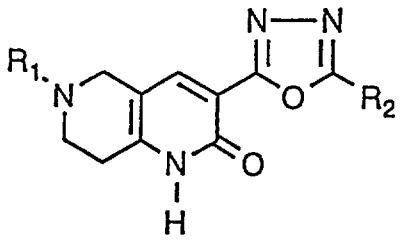
Yield: 44.8 %

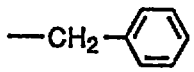
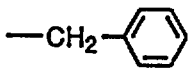
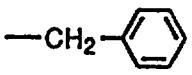
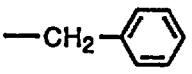
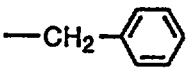
m.p. 221-223°C

Examples 112-116

In the same manner as described in Example 111, there are prepared the compounds listed in Table 5.

Table 5



Ex. No.	R_1	R_2	m.p. (°C)	Solvent for recrystal.
112	—CH_2—	-CH=CHCH$_3$	210-212	Acetonitrile
113	—CH_2—	-OCH(CH$_3$)$_2$	209-211	Ethanol
114	—CH_2—	—O—	230-232	Methanol
115	—CH_2—	-CF$_3$	230-232	Acetonitrile
116	—CH_2—	—O—C(CH$_3$)=CH$_2$	190-192	Acetonitrile

Example 117

Preparation of 6-benzyl-3-(5-methylthio-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one:

(1) To a solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbohydrazide (1.49 g, 5 mmole) in ethanol (20 ml) is added a solution of potassium hydroxide (0.29 g) in water (1 ml), and further thereto is added with stirring carbon disulfide (0.46 g, 6 mmole) under ice-cooling, and the mixture is

refluxed for 7 hours. After cooling, the precipitated crystals are collected by filtration to give 2-(6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridin-3-yl)-1,3,4-oxadiazole-5-thiol potassium salt (1.88 g) as a colorless solid.

Yield: 99 %

(2) To a solution of the above product (1.14 g, 3 mmole) in methanol (500 ml) is added methyl iodide (0.51 g, 3.6 mmole), and the mixture is stirred at room temperature for 3 hours. The reaction solution is concentrated to dryness under reduced pressure, and to the residue is added isopropanol. The precipitated crystals are collected by filtration, and recrystallized from ethanol to give the desired compound (0.59 g) as a colorless solid.

Yield: 55.5 %

m.p. 215-217°C

Example 118

Preparation of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbonitrile:

(1) A solution of 1-benzyl-4-piperidone (26.8 g, 0.14 mole) and pyrrolidine (20 g, 0.28 mole) in toluene (300 ml) is refluxed for 4 hours with distilling off water. The reaction solution is concentrated to dryness under reduced pressure, and to the residue is added anhydrous dioxane (300 ml). To the mixture is added dropwise gradually with stirring a solution of ethoxymethylenemalononitrile (19 g, 0.16 mole) in anhydrous dioxane (40 ml) under ice-cooling. The mixture is warmed to room temperature, and stirred for one hour. To the mixture is added

ammonium acetate (22 g, 0.29 mole), and the mixture is stirred at 70°C overnight, and concentrated to dryness under reduced pressure. To the residue is added isopropanol, and the precipitate crystals are collected by filtration, washed with water, and dried to give 2-amino-6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitrile (18.3 g, yield; 49 %), which is used in the subsequent reaction without purification.

(2) To a solution of the above product (15 g, 56.7 mmole) in 10 % aqueous sulfuric acid solution (150 ml) is added dropwise with stirring sodium nitrite (7.83 g, 113 mmole) under ice-cooling, and then, the mixture is stirred for 2 hours. The mixture is alkalified by adding 20 % aqueous sodium hydroxide solution thereto with stirring under ice-cooling. The mixture is extracted with chloroform, and the extract is dried over anhydrous sodium sulfate, and evaporated under reduced pressure to remove the solvent. To the residue is added isopropanol, and the precipitated crystals are collected by filtration, and recrystallized from acetonitrile to give the desired compound (10 g) as a colorless solid.

Yield: 66 %

m.p. 230-233°C

Example 119

Preparation of 6-benzyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one:

(1) To a solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbonitrile (1.6 g, 6 mmole) in ethanol (30 ml) are added hydroxylamine hydrochloride (0.52 g, 7.5 mmole)

and sodium carbonate (0.8 g, 7.5 mmole), and the mixture is refluxed with stirring overnight. The reaction solution is concentrated to dryness under reduced pressure, and water is added to the residue. The precipitated crystals are collected by filtration, washed with isopropanol, and dried to give amide oxime (1.4 g) as a colorless solid, which is used in the subsequent reaction without purification.

(2) To a suspension of the above product (1.19 g, 4 mmole) and potassium carbonate (0.66 g, 4.2 mmole) in methyl ethyl ketone (50 ml) is added dropwise with stirring a solution of cyclopropanecarbonyl chloride (0.44 g, 4.2 mmole) in methyl ethyl ketone (3 ml) under ice-cooling. The mixture is warmed to room temperature, and the mixture is stirred for 2 hours. The reaction solution is concentrated to dryness under reduced pressure, and water is added to the residue. The precipitated crystals are collected by filtration, and washed successively with water and isopropanol. A mixture of the crystals thus obtained and toluene (50 ml) is refluxed for 24 hours, and concentrated to dryness under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform : methanol = 100 : 3), and recrystallized from acetonitrile to give the desired compound (0.93 g) as a colorless solid.

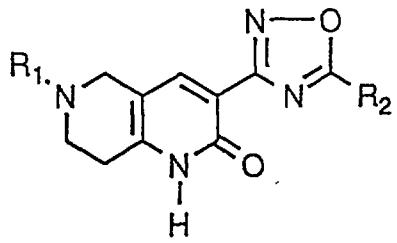
Yield: 66.7 %

m.p. 187-190°C

Examples 120-140

In the same manner as described in Example 119, there are prepared the compounds listed in Table 6.

Table 6

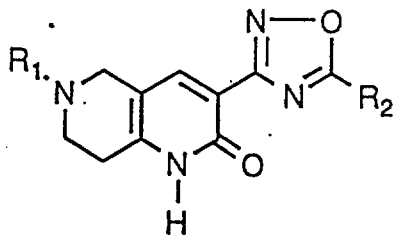


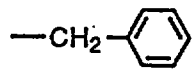
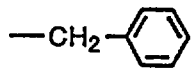
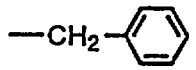
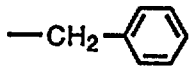
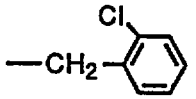
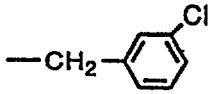
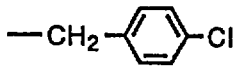
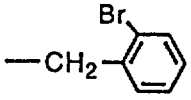
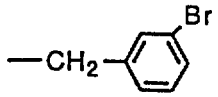
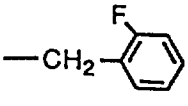
Ex. No.	R_1	R_2	m.p. (°C)	Solvent for recrystal.
120	—CH_2—	$-C_2H_5$	230-232	Acetonitrile
121	—CH_2—	—	239-241	Ethanol
122	—CH_2—	$-CH_3$	232-235	Ethanol
123	—CH_2—	S	230-233	Chloroform/ Ethanol
124	—CH_2—	$-CH(CH_3)_2$	191-194	Ethanol
125	—CH_2—	$-(CH_2)_2CH_3$	175-177	Ethanol

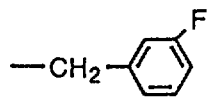
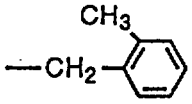
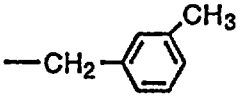
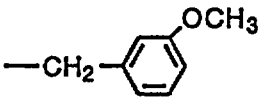
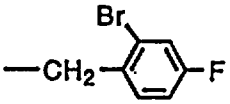
Examples 126-140

Using the suitable starting compounds, the same procedures as Example 119 are repeated to give the compounds listed in Table 7.

Table 7



Ex. No.	R_1	R_2
126		$-CH_2CH=CH_2$
127		$-C(CH_3)=CH_2$
128		$-CH=CHCH_3$
129		
130		
131		
132		
133		
134		
135		

136		
137		
138		
139		
140		

Example 141

Preparation of 6-benzyl-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one:

(1) To a suspension of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylic acid hydrochloride (1.6 g, 5 mmole) and triethylamine (0.56 g, 5.5 mmole) in 1,2-dichloroethane (50 ml) is added N,N'-carbonyldiimidazole (1.22 g, 7.5 mmole), and the mixture is heated with stirring at 70°C for 3 hours. The mixture is cooled to room temperature, and thereto is added benzamide oxime (0.82 g, 6 mmole), and the mixture is stirred for 2 hours. The reaction solution is concentrated to dryness under reduced pressure, and to the residue is added isopropanol. The precipitated crystals are collected by filtration to give a colorless solid (1.4 g, yield; 70 %), which is used in the subsequent reaction without purification.

(2) A solution of the above product (1.4 g) in toluene (50 ml) is refluxed overnight. The reaction solution is concentrated to dryness under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; chloroform : methanol = 100 : 3), and recrystallized from chloroform/methanol to give the desired compound (0.91 g) as a colorless solid.

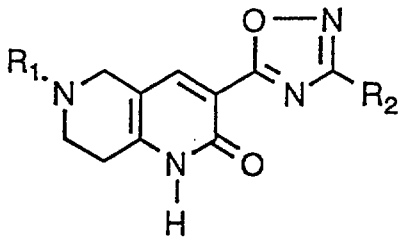
Yield: 68 %

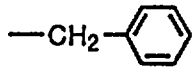
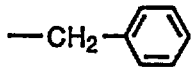
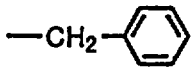
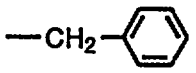
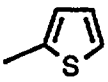
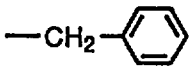
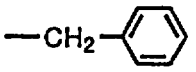
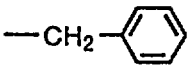
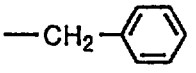
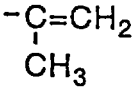
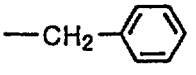
m.p. 231-233°C

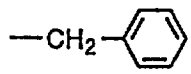
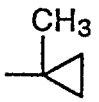
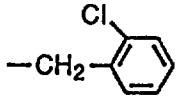
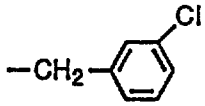
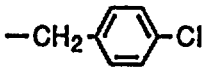
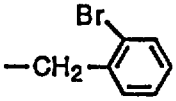
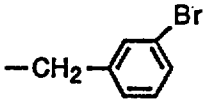
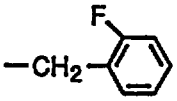
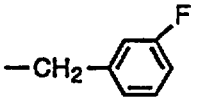
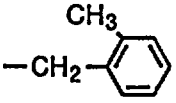
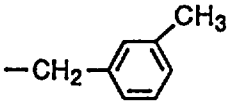
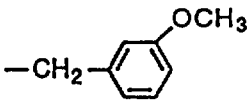
Examples 142-167

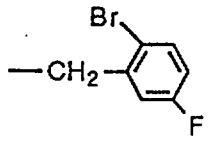
Using the corresponding starting compounds, the same procedures as in Example 141 are repeated to give the compounds listed in Table 8.

Table 8



Ex. No.	R_1	R_2	m.p. (°C)	Solvent for recrystal.
142	—CH_2—	-C_2H_5	232-235	Methanol
143	—CH_2—		198-235	Ethanol
144	—CH_2—	-CH_3	231-234	Methanol
145	—CH_2—		226-229	Methanol
146	—CH_2—	-$CH(CH_3)_2$	206-208	Ethanol
147	—CH_2—	-$(CH_2)_2CH_3$	185-187	Ethanol
148	—CH_2—	-$CH_2CH=CH_2$		
149	—CH_2—			
150	—CH_2—	-$CH=CHCH_3$		

151				
152			226-228	Ethanol
153			224-226	Ethanol
154			239-241	Ethanol
155			229-231	Ethanol
156			219-221	Ethanol
157			205-207	Ethanol
158			200-202	Ethanol
159			232-234	Ethanol
160			226-229	Ethanol
161				

162				

Example 163

Preparation of 6-benzyl-3-(5-methoxy-1,2,4-oxadiazol-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one:

(1) To a mixture of O-methoxycarbonyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-azidoxime (3.8 g, 10 mmole) and dichloromethane (40 ml) is added dropwise with stirring a solution of triphenylphosphine (2.7 g, 10 mmole) in dichloromethane (20 ml) under ice-cooling. The reaction solution is allowed to cool in a refrigerator overnight, and concentrated to dryness under reduced pressure. The resulting crystals are used in the subsequent reaction without purification.

(2) The above product is dissolved in anhydrous toluene (40 ml), and the mixture is refluxed for 15 hours. The reaction solution is concentrated to dryness under reduced pressure, and isopropanol is added to the residue. The precipitated crystals are collected by filtration, and recrystallized from methanol to give the desired compound as a colorless solid.

Using the corresponding starting compounds, the same procedure as Example 163 are repeated to give the following compounds of Examples 164-165.

Example 164

6-Benzyl-3-(5-ethoxy-1,2,4-oxadiazol-3-yl)-5,6,7,8-

tetrahydro-1,6-naphthyridin-2(1H)-one

Example 165

6-Benzyl-3-(5-isopropoxy-1,2,4-oxadiazol-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one

Example 166

Preparation of 6-benzyl-3-(3-methoxy-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one:

A suspension of N-methoxythiocarbonyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxyamide (3.6 g, 10 mmole) and hydroxylamine hydrochloride (1.4 g, 20 mmole) in pyridine (20 ml) is refluxed overnight. The reaction solution is concentrated to dryness under reduced pressure, and water is added to the residue. The precipitated crystals are collected by filtration, and recrystallized from methanol to give a colorless solid.

Using the corresponding starting compounds, the same procedures as Example 166 are repeated to give the following compounds of Examples 167-168.

Example 167

6-Benzyl-3-(3-ethoxy-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one

Example 168

6-Benzyl-3-(3-isopropoxy-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one

Reference Example 1

Preparation of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbohydrazide:

A solution of ethyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylate (5.6 g, 18 mmole) and hydrazine monohydrate (2.7 g, 54 mmole) in ethanol (300 ml) is refluxed for 3 hours. After cooling, the precipitated crystals are collected by filtration, and recrystallized from ethanol to give a colorless solid (5.2 g).

Yield: 96.8 %

m.p. 218-220°C

Reference Example 2

Preparation of 1-methyl-1-cyclopropanecarbohydrazide:

A mixture of ethyl 1-methyl-1-cyclopropanecarboxylate (10 g, 7.8 mmole) and hydrazine monohydrate (5.1 g, 0.1 mole) is heated with stirring at 100°C for 4 hours. To the reaction solution is added toluene (50 ml), and the mixture is refluxed for 3 hours while distilling off water. After cooling, the precipitated crystals are collected by filtration, and washed with diisopropyl ether to give the desired compound (8.9 g) as a colorless crystal.

Yield: 99 %

m.p. 85-87°C

Reference Example 3

Preparation of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-methanol:

A mixture of ethyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylate (20 g, 64 mmole), tetramethylammonium borohydride (25 g, 97 mmole) and 1,2-dichloroethane (200 ml) is refluxed for 4 hours. The reaction

solution is concentrated to dryness under reduced pressure. Water is added to the residue, and the mixture is refluxed overnight, and cooled with ice. The precipitated crystals are collected by filtration, and dried to give the desired compound.

Reference Example 4

Preparation of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbaldehyde:

To a solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-methanol (2.7 g, 10 mmole) in chloroform (100 ml) is added active manganese dioxide (13.5 g), and the mixture is refluxed for 5 hours. After cooling, the insoluble materials are removed by filtration, and the filtrate is concentrated to dryness under reduced pressure. The residue is purified by medium-pressure column chromatography of Diaion CHP-20P (solvent; acetonitrile and water, with concentration gradient) to give the desired compound.

Reference Example 5

Preparation of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-aldoxime:

A solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carbaldehyde (5.4 g, 20 mmole) and hydroxylamine hydrochloride (2.8 g, 40 mmole) in ethanol (50 ml) is refluxed for 3 hours. After cooling, the precipitated crystals are collected by filtration, and dried to give the desired compound.

Reference Example 6

Preparation of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-hydroxyiminoyl chloride:

To a solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-aldoxime (2.8 g, 10 mmole) in DMF (30 ml) is added N-chlorosuccinimide (1.4 g, 10 mmole) in portions at room temperature, and the mixture is stirred for 5 hours. The reaction solution is poured into ice-water, and the precipitated crystals are collected by filtration, and dried to give the desired compound.

Reference Example 7

Preparation of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-azidoxime:

A mixture of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-hydroxyiminoyl chloride (3.2 g, 10 mmole), sodium azide (0.65 g, 10 mmole) and DMF (30 ml) is stirred at room temperature for 6 hours. The reaction solution is poured into ice-water, and the precipitated crystals are collected by filtration, and dried to give the desired compound.

Reference Example 8

Preparation of O-methoxycarbonyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-azidoxime:

To a solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-azidoxime (3.2 g, 10 mmole) and triethylamine (1.1 g, 10 mmole) in dichloromethane (60 ml) is added dropwise with stirring a solution of methyl chloroformate (1.0 g, 10 mmole) in dichloromethane (5 ml) under ice-cooling. The mixture is warmed to room temperature, and stirred for 3 hours. The reaction solution is concentrated to dryness under reduced pressure, and water is added to the residue. The precipitated crystals are collected by

filtration, and dried over to give the desired compound.

Reference Example 9

Preparation of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboisothiocyanate:

(1) To a solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxylic acid hydrochloride (3.2 g, 10 mmole) and triethylamine (3.1 g, 30 mmole) in dichloromethane (50 ml) is added dropwise with stirring a solution of thionyl chloride (1.3 g, 10 mmole) in dichloromethane (5 ml) under ice-cooling. After the addition, the mixture is warmed to room temperature, and stirred for one hour, and is concentrated under reduced pressure to give an acid chloride as an oil.

(2) To a solution of the above oily product in 2N aqueous sodium hydroxide solution (25 ml) is added potassium thiocyanate (1.5 g, 15 mmole), and the mixture is stirred at room temperature for 20 hours. The mixture is extracted with chloroform, and the extract is dried over anhydrous sulfuric acid, and concentrated to dryness under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform ; methanol = 5 : 1) to give the desired compound as a colorless solid.

Reference Example 10

Preparation of N-methoxythiocarbonyl 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboxamide:

To a solution of 6-benzyl-5,6,7,8-tetrahydro-2(1H)-oxo-1,6-naphthyridine-3-carboisothiocyanate (3.3 g, 10 mmole) in absolute methanol (30 ml) is added sodium methoxide (1.1 g, 20

mmole), and the mixture is refluxed for 20 hours. The reaction solution is concentrated under reduced pressure, and ethanol is added to the residue. The precipitated crystals are collected by filtration, and dried to give the desired compound.

Preparation 1

Capsules:

6-Benzyl-3-(3-methoxy-1,3,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one	5 g
Corn starch	57 g
Lactose	10 g
Crystalline cellulose	25 g
Hydroxypropyl cellulose	2 g
Light silicic anhydride	0.5 g
Magnesium stearate	0.5 g

According to a conventional method, the above components are mixed and kneaded to give the granules, which are packed into 1000 capsules to give a capsule preparation (each 100 mg).

Preparation 2

Tablets:

6-Benzyl-3-(3-methoxy-1,3,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one	5 g
Corn starch	20 g
Lactose	30 g
Hydroxypropyl cellulose	5 g
Low-substituted hydroxypropyl cellulose	10 g

According to a conventional method, the above components are mixed and kneaded, and thereto are added light silicic anhydride and magnesium stearate, and the mixture is tabletted to give tablets containing 10 mg of the active ingredient in each tablet.

Preparation 3

Powders:

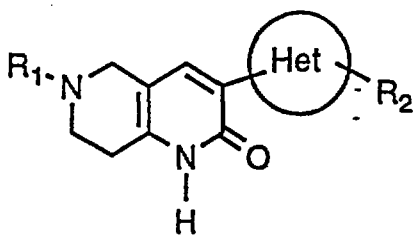
6-Benzyl-3-(3-methoxy-1,3,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one	5 g
Corn starch	173 g
Lactose	300 g
Hydroxypropyl cellulose	20 g

According to a conventional method, the above components are mixed and kneaded, pulverized, and thereto is added light silicic anhydride (q.s.) to give 50-trituration.

3-OXADIAZOLYL-1, 6-NAPHTHYRIDINE DERIVATIVES

CLAIMS:

1. A 3-oxadiazolyl-5,6,7,8-tetrahydro-1,6-naphthyridine derivative of the formula (I):



(I)

wherein Het is an oxadiazole ring, R_1 is hydrogen atom, an acyl group, a lower alkyl group or a group of the formula: $-CH_2R_1'$ (in which R_1' is a cyclo-lower alkyl group, a lower alkenyl group, a lower alkynyl group, benzyl group, an aryl group or a heteroaromatic group), R_2 is a lower alkyl group, a cyclo-lower alkyl group, a lower alkenyl group, a lower alkynyl group, an aryl group, a heteroaromatic group, a halogeno-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a lower alkenyloxy group, a phenoxy group or a lower alkylthio group, or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1, wherein R_1 is a group of the formula: $-CH_2R_1'$ (in which R_1' is phenyl group, a substituted phenyl group, or a 5-membered heteroaromatic group), R_2 is a lower alkyl group, a cyclo-lower alkyl group, a lower alkenyl group, phenyl group or a substituted phenyl group, a 5-membered heteroaromatic group or a lower alkoxy group, or a pharmaceutically acceptable acid addition salt thereof.

3. A compound according to claim 1 or claim 2, wherein R_2 is an alkyl group having 1 to 3 carbon atoms, a cyclopropyl group, or an alkoxy group having 1 to 3 carbon atoms, or a pharmaceutically acceptable acid addition salt thereof.

4. A compound according to any preceding claim, wherein Het is a 1,3,4-oxadiazole ring, or a pharmaceutically acceptable acid addition salt thereof.

5. A compound according to claim 1, 2 or 3, wherein Het is 1,2,4-oxadiazole ring, or a pharmaceutically acceptable acid addition salt thereof.

6. A 3-oxadiazolyl compound, which is

6-benzyl-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-(2-chlorobenzyl)-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-(4-chlorobenzyl)-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-(2-bromobenzyl)-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-(2-chloro-5-fluorobenzyl)-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-(2-bromo-5-fluorobenzyl)-3-(5-methoxy-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-benzyl-3-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-benzyl-3-(5-ethyl-1,3,4-oxadiazol-2-yl)-5,6,7,8-

tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-benzyl-3-(5-isopropyl-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-benzyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

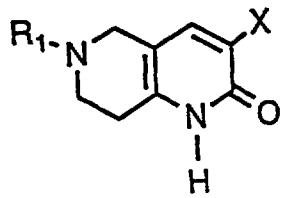
6-benzyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-benzyl-3-(5-ethyl-1,2,4-oxadiazol-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

6-benzyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one; or

a pharmaceutically acceptable acid addition salt of any said compound.

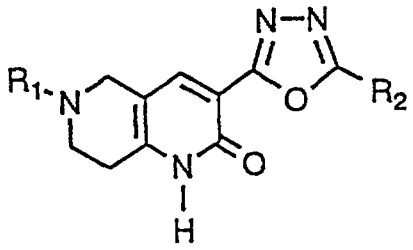
7. A 5,6,7,8-tetrahydro-1,6-naphthyridine derivative of the formula:



wherein R_1 is hydrogen atom, an acyl group, a lower alkyl group or a group of the formula: $-CH_2R_1'$ (in which R_1' is a cyclo-lower alkyl group, a lower alkenyl group, a lower alkynyl group, benzyl group, an aryl group or a heteroaromatic group), X is carboxyl group, a lower alkoxycarbonyl group, benzyloxycarbonyl group or nitrile group, provided that R_1 is not methyl), or a salt thereof.

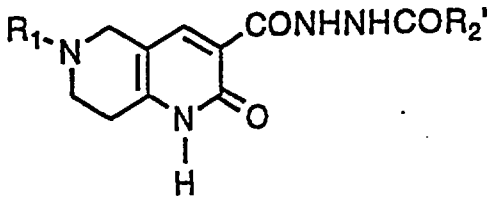
8. A process for preparing a 1,6-naphthyridine

derivative of the formula (Ia):



(Ia)

wherein R_1 and R_1 are the same as defined above, or a salt thereof, which comprises subjecting a compound of the formula (II):



(II)

wherein R_1 is the same as defined above, and R_2' is the same group defined for R_2 except a lower alkylthio group, to intramolecular cyclodehydration.

9. A 3-oxadiazolyl compound according to any one of claims 1 to 6 for use as a pharmaceutical.

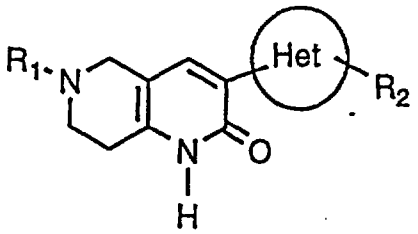
10. A pharmaceutical composition comprising a 3-oxadiazolyl compound according to any one of claims 1 to 6 and a pharmaceutically acceptable additive.

11. Use of a 3-oxadiazolyl compound according to any one of claims 1 to 6 in the preparation of a medicament having a benzodiazepine receptor binding capacity.

3-OXADIAZOLYL-1,6-NAPHTHYRIDINE DERIVATIVES

ABSTRACT

A 3-Oxadiazolyl-5,6,7,8-tetrahydro-1,6-naphthyridine derivative of the formula (I):



(I)

wherein Het is an oxadiazole ring, R_1 is hydrogen atom, an acyl group, a lower alkyl group or a group of the formula: $-CH_2R_1'$ (in which R_1' is a cyclo-lower alkyl group, a lower alkenyl group, a lower alkynyl group, benzyl group, aryl group or a heteroaromatic group), R_2 is a lower alkyl group, a cyclo-lower alkyl group, a lower alkenyl group, a lower alkynyl group, aryl group, a heteroaromatic group, a halogeno-lower alkyl group, a lower alkoxy-lower alkyl group, a lower alkoxy group, a lower alkenyloxy group, a phenoxy group or a lower alkylthio group, or a pharmaceutically acceptable acid addition salt thereof, is useful as benzodiazepine receptor agonist.