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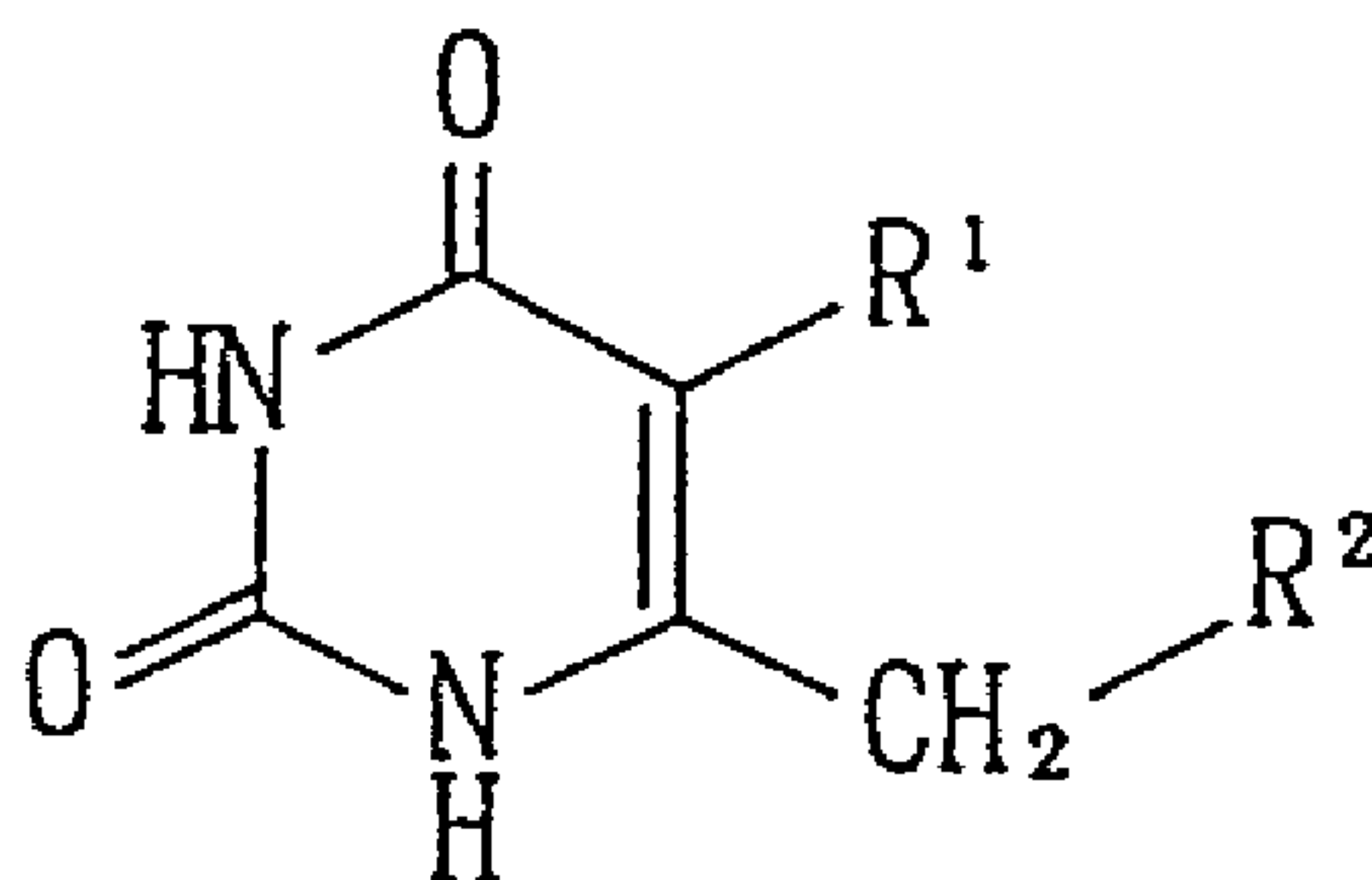
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(54) Titre : INHIBITEURS DE METASTASES CANCEREUSES CONTENANT DES DERIVES D'URACILE

(54) Title: CANCEROUS METASTASIS INHIBITORS CONTAINING URACIL DERIVATIVES



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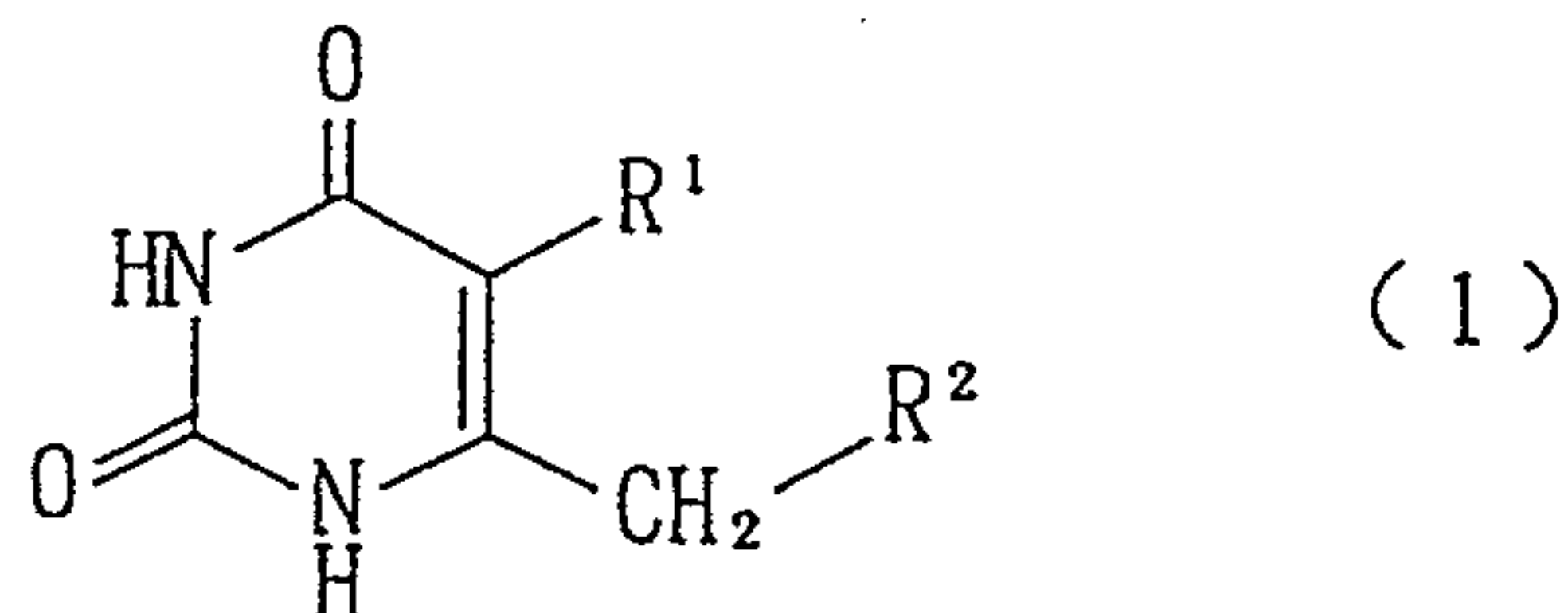
(57) Abrégé/Abstract:

Drugs having an inhibitory activity on thymidine phosphorylases and inhibiting cancerous metastasis, which contain as the active ingredient uracil derivatives represented by general formula (1) or salts thereof, wherein R¹ represents chlorine, bromine, iodine, cyano or lower alkyl; and R² represents an optionally substituted 4- to 8-membered heterocycle having nitrogen, optionally substituted amidinothio, guanidino, lower alkylamidino, amino, etc.

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ABSTRACT

This invention provides a drug which has inhibitory activities against thymidine phosphorylase and inhibits metastasis of a cancer. Specifically, this invention relates to a cancerous metastasis inhibitor comprising, as an active ingredient, a uracil derivative represented by the following formula (1):



wherein R^1 represents a chlorine, bromine or iodine atom or a cyano or lower alkyl group and R^2 represents a substituted or unsubstituted 4-8 membered heterocyclic group having nitrogen atoms or a substituted or unsubstituted amidinothio, guanidino, (lower alkyl)-amidino, amino or like group, or a salt thereof.

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DESCRIPTION

CANCEROUS METASTASIS INHIBITORS
CONTAINING URACIL DERIVATIVES

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Technical Field

This invention relates to a cancerous metastasis inhibitor which contains a uracil derivative having thymidine phosphorylase inhibiting activity.

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Background Art

Cancer treatments have achieved an innovative level of progress in recent years and, especially, an improvement in the success rate of primary carcinoma removal by surgery or radiotherapy has significantly contributed to the progress in cancer treatments. Nonetheless, there are not but a few cases of death by relapse due to metastases of cancers in spite of complete removal of primary carcinomas. A limitation is therefore imposed on the complete prevention of advances of cancers by surgery or radiotherapy.

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There is accordingly a growing recognition that the prevention of metastasis of a cancer is an important theme to be achieved for the treatment of the cancer, and clinical tests of cancerous metastasis in-

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hibitors are now under way in the United States, Great Britain, etc.

As a mechanism of hematogenous metastasis of a cancer, the metastasis is assumed to take place through a process which comprises (1) growth of carcinoma cells in a primary carcinoma lesion, (2) development of blood vessels, (3) infiltration of developed blood vessels by malignant carcinoma cells, followed by their penetration into the blood vessels, (4) circulation through the body, (5) arrival at and bonding to a target site, (6) infiltration to the outside of the blood vessels, (7) growth in a target organ, and (8) formation of a metastasized lesion.

As a cancerous metastasis inhibitor, it is generally desirable not only to prevent metastasis of carcinoma cells beforehand but also to prevent proliferation and metastasis of a small metastasized lesion already formed. Those currently available as chemotherapeutic agents for cancers (antitumor agents) on the market are used as drugs effective for the phase (1) in that they exhibit direct growth inhibition and cytocidal activity against carcinoma cells while bringing about size reductions of tumors. They are however not satisfactory drugs as cancerous metastasis inhibitors in that they cause various side effects led by

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myelotoxicity and exhibit substantially no activity against the other metastasis phases.

Accordingly, drugs of such a new type as having less side effects and permitting long-term administration in view of the process of metastasis are highly
5 valued as cancerous metastasis inhibitors. Clinically, there is also a demand for such drugs.

The blood vessel development phase (2) has therefore been attracting interests as an important target
10 phase for the inhibition of metastasis in recent years in that, except for the growth of a cancer, it takes place only in special cases such as wound healing, resulting in active developments of angiogenesis-inhibiting drugs as metastasis inhibitors.

15 Various factors are considered to take part in angiogenesis. Platelet-derived endothelial cell growth factor (PD-ECGF) [Nature, 338, 557-562 (1989)], one of such factors, has been reported to be genetically identical human thymidine phosphorylase in recent years
20 [Nature, 356, 668 (1992)]. Thymidine phosphorylase is an enzyme essential for the metabolism of thymidine, and its development in various tissues (livers, lungs, small intestines, large intestines, placentas, etc.) of human and diverse animals has been confirmed. It has
25 also been reported that in a malignant tumor, its de-

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velopment is promoted in the tumored part compared with its adjacent normal tissue [Biochimica et Biophysica Acta, 1034, 107-113 (1992)] and that this thymidine phosphorylase is also developed very often in clinical
5 samples of human tumors and its development is in a positive correlation with the number of blood vessels in a tumor [Cancer Letters, 95, 57-62 (1995)]. As is appreciated from the foregoing, thymidine phosphorylase/PD-ECGF is considered to have close con-
10 nection with angiogenesis associated with the growth of a tumor. For the induction of angiogenesis by thymidine phosphorylase, its enzymatic activity has been proven to be indispensable, thereby indicating the possibility of suppression of angiogenesis by inhibit-
15 ing the enzymatic activity [Cancer Research, 55, 1687-1690 (1995)]. Reported as thymidine phosphorylase inhibitors to date include 6-amino-5-bromo-uracil and 6-aminothimine [Biochemical Pharmacology, 29, 1059 (1980)], 6-amino-5-chlorouracil and 3-cyano-2,6-
20 dihydroxypyridine [JP Kokai 63-250324], and acyclo-thymidine [JP Kokai 5-213761]. Their inhibitory effects are however not sufficient, and it is the current circumstances that no metastasis inhibitor has been found yet for the suppression of angiogenesis induced
25 by thymidine phosphorylase.

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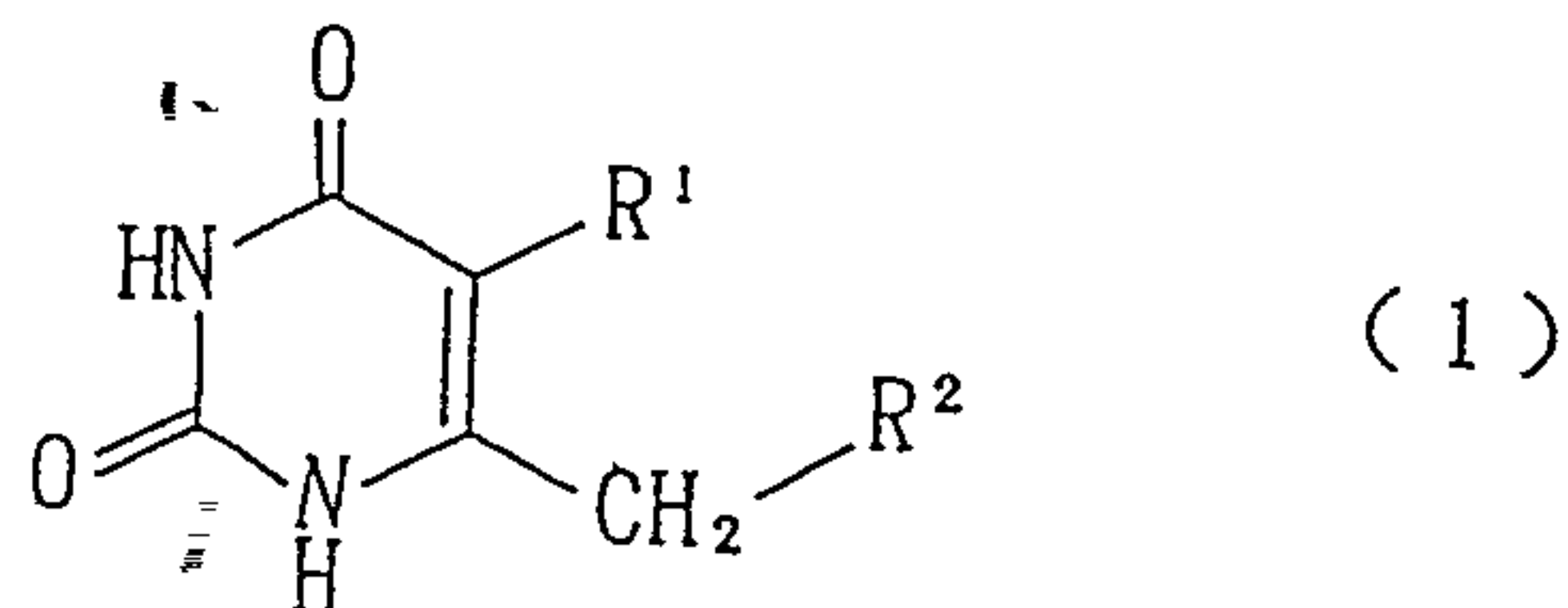
Accordingly, an object of the present invention is to provide a cancerous metastasis inhibitor having excellent inhibitory activity against thymidine phosphorylase.

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Disclosure of the Invention

With the foregoing circumstances in view, the present inventors have proceeded with an investigation from various viewpoints about pharmacological effects of uracil derivatives of a specific type which have heretofore been known to have neither angiogenesis inhibiting effects nor cancerous metastasis inhibiting effects. As a result, these compounds have been found to have extremely good thymidine phosphorylase inhibiting activity and, based on this activity, angiogenesis and cancerous metastasis inhibiting activities, leading to the completion of the present invention.

Accordingly, the present invention relates to a cancerous metastasis inhibitor comprising, as an active ingredient, a uracil derivative represented by the following formula (1):



wherein R¹ represents a chlorine, bromine or iodine

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atom or a cyano or lower alkyl group; and R^2 represents a 4-8 membered heterocyclic group having 1-3 nitrogen atoms, which may be substituted by one or more lower alkyl, imino, hydroxyl, hydroxymethyl, methanesulfonyloxy, amino or nitro groups; an amidinothio group, one or more of the hydrogen atom(s) on one or both of the nitrogen atoms of which may each be substituted by a lower alkyl group; a guanidino group, one or more of the hydrogen atom(s) on one, two or all of the nitrogen atoms of which may each be substituted by a lower alkyl or cyano group; a (lower alkyl)amidino group; an amino group, one or both of the hydrogen atoms on the nitrogen atom of which may each be substituted by a lower alkyl group; a group $-\text{CH}_2\text{N}(\text{R}^a)\text{R}^b$ in which R^a and R^b may be the same or different and each represents a hydrogen atom or a lower alkyl group or R^a and R^b may form a pyrrolidine ring together with the nitrogen atom to which R^a and R^b are bonded; a group $-\text{NH}-(\text{CH}_2)_m-\text{Z}$ in which Z represents an amino group, one or both of the hydrogen atoms on the nitrogen atom of which may each be substituted by a lower alkyl group, or a cyano group, and m stands for an integer of from 0 to 3; a group $\text{NR}^c(\text{CH}_2)_n-\text{OH}$ in which R^c represents a hydrogen atom or a lower alkyl group, and n stands for a natural number of from 1 to 4; a group $-\text{X}-\text{Y}$ in which X

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represents S or NH, and Y represents a 2-imidazolin-2-yl, 2-imidazolyl, 1-methylimidazol-2-yl, 1,2,4-triazol-3-yl, 2-pyrimidyl or 2-benzimidazolyl group which may be substituted by one or more lower alkyl groups; or a
5 ureido or thioureido group, one or more of the hydrogen atom(s) on one or both of the nitrogen atoms of which may each be substituted by a lower alkyl group; or a salt thereof.

The present invention is also concerned with a
10 cancerous metastasis inhibitor composition comprising the uracil derivative (1) or the salt thereof and a pharmaceutically acceptable carrier.

Further, the present invention pertains to use of the uracil derivative (1) or the salt thereof for the
15 production of a cancerous metastasis inhibitor.

The present invention also relates to a method for the inhibition of metastasis of a cancer, which comprises administering to a patient an effective amount of the uracil derivative (1) or the salt there-
20 of.

Best Mode for Carrying Out the Invention

Illustrative of the lower alkyl group represented by R¹ and R² in the formula (1) are linear or branched
25 alkyl groups having 1 to 4 carbon atoms. Specific ex-

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amples include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl groups. Among these, a methyl group is particularly preferred.

Illustrative of the 4-8 membered heterocyclic group containing 1-3 nitrogen atoms and represented by R^2 are 1-azetidiny1, 1-pyrrolidinyl, 2-pyrrolin-1-yl, 3-pyrrolin-1-yl, 1-pyrrolyl, 1-pyrazolidiny1, 2-pyrazolin-1-yl, 3-pyrazolin-1-yl, 4-pyrazolin-1-yl, 1-pyrazolyl, 1-imidazolidiny1, 2-imidazolin-1-yl, 3-imidazolin-1-yl, 4-imidazolin-1-yl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, piperidino, 1-piperazyl, morpholino, 1-perhydroazepiny1 and 1-perhydroazociny1 groups. Further, these heterocyclic groups may contain one or two substituent groups on their rings. Examples of such substituent groups include lower alkyl, imino, hydroxyl, hydroxymethyl, methanesulfonyloxy, amino and nitro groups. Specific examples of the heterocyclic group which may contain such substituent groups include 1-azetidiny1, 1-pyrrolidinyl, 2,5-dimethylpyrrolidin-1-yl, 2-imino-pyrrolidin-1-yl, 3-hydroxypyrrolidin-1-yl, 2-hydroxymethylpyrrolidin-1-yl, 3-methanesulfonyloxypyrrolidin-1-yl, 3-aminopyrrolidin-1-yl, 2-pyrrolin-1-yl, 3-pyrrolin-1-yl, 2-imino-3-pyrrolin-1-yl, 1-pyrrolyl, 1-pyrazolidiny1, 2-methylpyrazolidin-1-yl, 4-imino-

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pyrazolidin-1-yl, 2-pyrazolin-1-yl, 3-pyrazolin-1-yl,
2-methyl-3-pyrazolin-1-yl, 5-imino-3-pyrazolin-1-yl, 4-
pyrazolin-1-yl, 2-methyl-4-pyrazolin-1-yl, 3-imino-4-
pyrazolin-1-yl, 1-pyrazolyl, 1-imidazolidinyl, 3-
5 methylimidazolidin-1-yl, 2-iminoimidazolidin-1-yl, 2-
imino-3-methylimidazolidin-1-yl, 2-imino-3-ethyl-
imidazolidin-1-yl, 2-imino-3-isopropylimidazolidin-1-
yl, 2-imidazolin-1-yl, 3-imidazolin-1-yl, 4-imidazolin-
1-yl, 3-methyl-4-imidazolin-1-yl, 2-imino-4-imidazolin-
10 1-yl, 2-imino-3-methyl-4-imidazolin-1-yl, 2-imino-3-
ethyl-4-imidazolin-1-yl, 2-imino-3-isopropyl-4-
imidazolin-1-yl, 1-imidazolyl, 2-methylimidazol-1-yl,
2-nitroimidazol-1-yl, 4-nitroimidazol-1-yl, 1,2,3-
triazol-1-yl, 1,2,4-triazol-1-yl, 3-nitro-1,2,4-
15 triazol-1-yl, piperidino, 1-piperazyl, 4-methyl-
piperazin-1-yl, morpholino, 1-perhydroazepinyl and 1-
perhydroazocinyl groups. Preferred examples include 1-
azetidiny, 1-pyrrolidinyl, 2-iminopyrrolidin-1-yl, 2-
iminoimidazolidin-1-yl, 2-imino-3-methylimidazolidin-1-
20 yl, 2-imino-3-ethylimidazolidin-1-yl, 2-imino-3-
isopropylimidazolidin-1-yl, 2-imidazolin-1-yl, 2-imino-
3-methyl-4-imidazolin-1-yl, 2-imino-3-ethyl-4-
imidazolin-1-yl and 1-imidazolyl groups.

Illustrative of the amidinothio group represented
25 by R^2 , one or more of the hydrogen atom(s) on one or

- 10 -

both of the nitrogen atoms of which may each be substituted by a lower alkyl group, are those in which one to three of the three hydrogen atoms on the nitrogen atoms of an amidino group may be substituted by the
5 above lower alkyl group or groups. Especially, amidinothio, N¹-methyamidinothio and N¹,N²-dimethylamidinothio groups are preferred.

Illustrative of the guanidino group, one or more of the hydrogen atom(s) on one, two or all of the
10 nitrogen atoms of which may each be substituted by a lower alkyl or cyano group, are those in each of which one to four of the four hydrogen atoms in a guanidino group may be substituted by the above lower alkyl or cyano group or groups. Especially, 1-guanidino, 1-
15 methylguanidino, 3-methylguanidino, 2,3-dimethylguanidino and 2-cyano-3-methylguanidino groups are preferred.

Illustrative of the (lower alkyl)amidino group are those formed of amidino groups and the lower alkyl
20 groups bonded thereto, respectively. Of these, an acetoamidino group is preferred.

Illustrative of the amino group, one or both of the hydrogen atoms on the nitrogen atom of which may each be substituted by a lower alkyl group, are those
25 in each of which one or two of the two hydrogen atoms

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on an amino group may be substituted by the above lower alkyl group or groups. Of these, amino, N-methylamino, N,N-dimethylamino, N-ethylamino, N,N-diethylamino, N-propylamino and N-isopropylamino groups are preferred.

5 Preferred examples of the group represented by $-\text{CH}_2\text{N}(\text{R}^a)\text{R}^b$ include N-methylaminomethyl, N,N-dimethylaminomethyl and 1-pyrrolidinylmethyl groups.

Preferred examples of the group represented by $-\text{NH}-(\text{CH}_2)_m-\text{Z}$ include N,N-dimethylhydrazino, N-(2-aminoethyl)amino, N-(2-(N,N-dimethyl)aminoethyl)amino, N-(3-aminopropyl)amino and N-(2-cyanoethyl)amino groups.

10

Preferred examples of the group $\text{NR}^c(\text{CH}_2)_n-\text{OH}$ include N-(2-hydroxyethyl)-N-methylamino, N-(3-hydroxypropyl)amino and N-(4-hydroxybutyl)amino groups.

15 Preferred examples of the group represented by $-\text{X}-\text{Y}$ include 2-imidazolin-2-thio, 2-imidazolin-2-amino, imidazol-2-thio, 1-methylimidazol-2-thio, 1,2,4-triazol-3-thio, pyrimidin-2-thio and benzimidazol-2-thio groups.

20 Preferred examples of the ureido or thioureido group, one or more of the hydrogen atom(s) on one or both of the nitrogen atoms of which may each be substituted by a lower alkyl group, include ureido and 3-methylthioureido groups.

25 Preferred examples of the group represented by R^2

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in the formula (1) include 4-8 membered heterocyclic groups having 1-3 nitrogen atoms, which may each be substituted by one or more lower alkyl, imino, hydroxyl, hydroxymethyl, methanesulfonyloxy, amino or nitro groups; amidinothio groups, one or more of the hydrogen atom(s) on one or both of the nitrogen atoms of each of which may each be substituted by a lower alkyl group; guanidino groups, one or more of the hydrogen atom(s) on one, two or all of the nitrogen atoms of each of which may each be substituted by a lower alkyl or cyano group; or (lower alkyl)amidino groups.

Among the groups represented by R^2 , preferred specific examples include 1-azetidiny1, 1-pyrrolidinyl, 2-iminopyrrolidin-1-yl, 2-iminoimidazolidin-1-yl, 2-imino-3-methylimidazolidin-1-yl, 2-imino-3-ethylimidazolidin-1-yl, 2-imino-3-isopropylimidazolidin-1-yl, 2-imidazolin-1-yl, 2-imino-3-methyl-4-imidazolin-1-yl, 2-imino-3-ethyl-4-imidazolin-1-yl, 1-imidazolyl, amidinothio, N^1 -methy1amidinothio, N^1,N^2 -dimethylamidinothio, 1-guanidino, 1-methylguanidino, 3-methylguanidino, 2,3-dimethylguanidino and acetoamidino groups.

Preferred examples of the uracil derivative represented by the formula (1) include those containing

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a chlorine or bromine atom or a cyano group as R^1 and a 1-pyrrolidinyl, 1-azetidiny, 2-iminopyrrolidin-1-yl, 2-iminoimidazolidin-1-yl, 1-imidazolyl, amidinothio or 1-guanidino group as R^2 .

5 Examples of the salt of the uracil derivative (1) can include, but are not particularly limited to, acid-addition salts and/or base salts which have been obtained by causing pharmacologically acceptable acids or basic compounds to act respectively. Examples of these
10 acid addition salts include salts with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid and hydrobromic acid as well as salts with organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid,
15 acetic acid, p-toluenesulfonic acid and methanesulfonic acid, with the salt with hydrochloric acid or p-toluenesulfonic acid being preferred. Exemplary base salts include salts with alkali metals and alkaline earth metals such as sodium, potassium, magnesium and
20 calcium as well as salts with amines such as ammonia, methylamine, dimethylamine, piperidine, cyclohexylamine and triethylamine.

Particularly preferred specific examples of the uracil derivative (1) or its salt include:

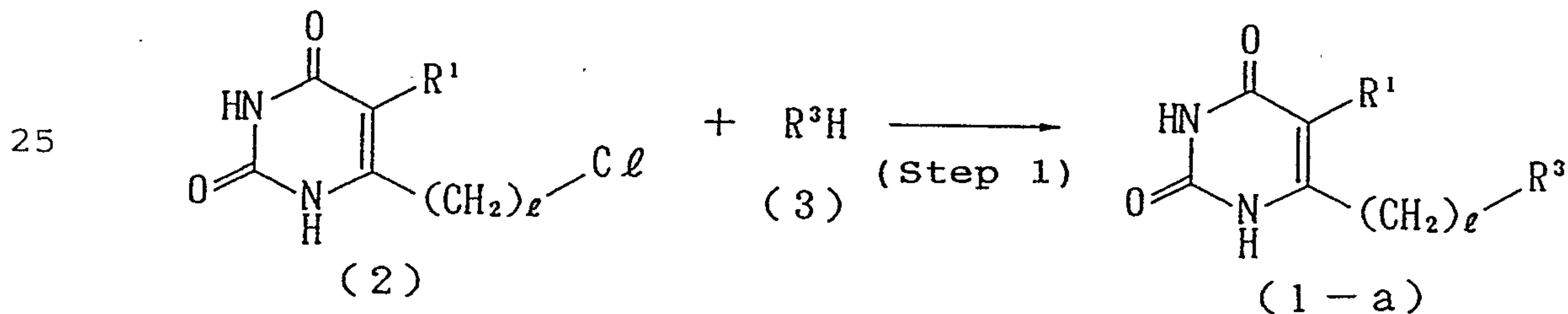
25 5-chloro-6-(1-pyrrolidinylmethy)uracil,

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- 5-bromo-6-(1-pyrrolidinylmethyl)uracil,
 5-chloro-6-(1-azetidinylmethyl)uracil,
 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil
 hydrochloride,
 5
 5-bromo-6-(1-(2-iminopyrrolidinyl)methyl)uracil
 hydrochloride,
 5-cyano-6-(1-(2-iminopyrrolidinyl)methyl)uracil,
 5-chloro-6-(1-(2-iminoimidazolidinyl)methyl)
 uracil,
 10
 5-bromo-6-(1-(2-iminoimidazolidinyl)methyl)
 uracil,
 5-chloro-6-(1-imidazolylmethyl)uracil
 hydrochloride,
 15
 2-(5-chlorouracil-6-ylmethyl)isothiourea
 hydrochloride,
 2-(5-cyanouracil-6-ylmethyl)isothiourea
 hydrochloride,
 5-chloro-6-(1-guanidino)methyluracil
 hydrochloride.

20 The uracil derivative (1) of the present inven-
 tion can be prepared, for instance, in accordance with
 the following Processes A to M, using various compounds
 as raw materials:

[Process A]



wherein R^1 has the same meaning as defined above, ℓ

- 15 -

stands for a number of 1 or 2, and R^3 represents a 4-8 membered heterocyclic group having 1-3 nitrogen atoms, which may be substituted by one or more lower alkyl, imino, hydroxyl, hydroxymethyl, amino or nitro groups; a group $-NH-(CH_2)_m-Z$ in which Z represents an amino group, one or both of the hydrogen atoms on the nitrogen atom of which may each be substituted by a lower alkyl group, or a cyano group, and m stands for an integer of from 0 to 3; or a group $NR^C(CH_2)_n-OH$ in which R^C represents a hydrogen atom or a lower alkyl group, and n stands for a natural number of from 1 to 4.

(Step 1)

The compound represented by the formula (1-a) can be prepared by reacting the compound represented by the formula (2), which is obtained by the below-described preparation processes (Process N) and (Process O), and the known compound represented by the formula (3), which is disclosed in literature [Journal of Organic Chemistry, 32, 738 (1967); Journal of Medicinal Chemistry, 15, 415 (1972)] or is commercially available, in a suitable solvent in the presence or absence of a basic compound.

No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the

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reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; amines such as pyridine and triethylamine; alkyl ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone; alcohols such as methanol, ethanol and propanol; and water.

Illustrative basic compounds include organic basic compounds, e.g., tertiary amines such as triethylamine, diisopropylethylamine, tributylamine, pyridine, dimethylaminopyridine and 1,8-diazabicyclo-[5.4.0]undec-7-ene; and inorganic basic compounds, e.g., alkali metal carbonates such as sodium carbonate and potassium carbonate, alkali metal bicarbonates such as sodium bicarbonate and potassium bicarbonate, alkali metal hydroxides such as sodium hydroxide and potassium hydroxide, alkali metals such as sodium and potassium, alkali metal alkoxides such as sodium methoxide, sodium ethoxide and potassium t-butoxide, and alkali metal hydrides such as sodium hydride.

As proportions of the raw materials, it is preferred to use the compound of the formula (3) in an

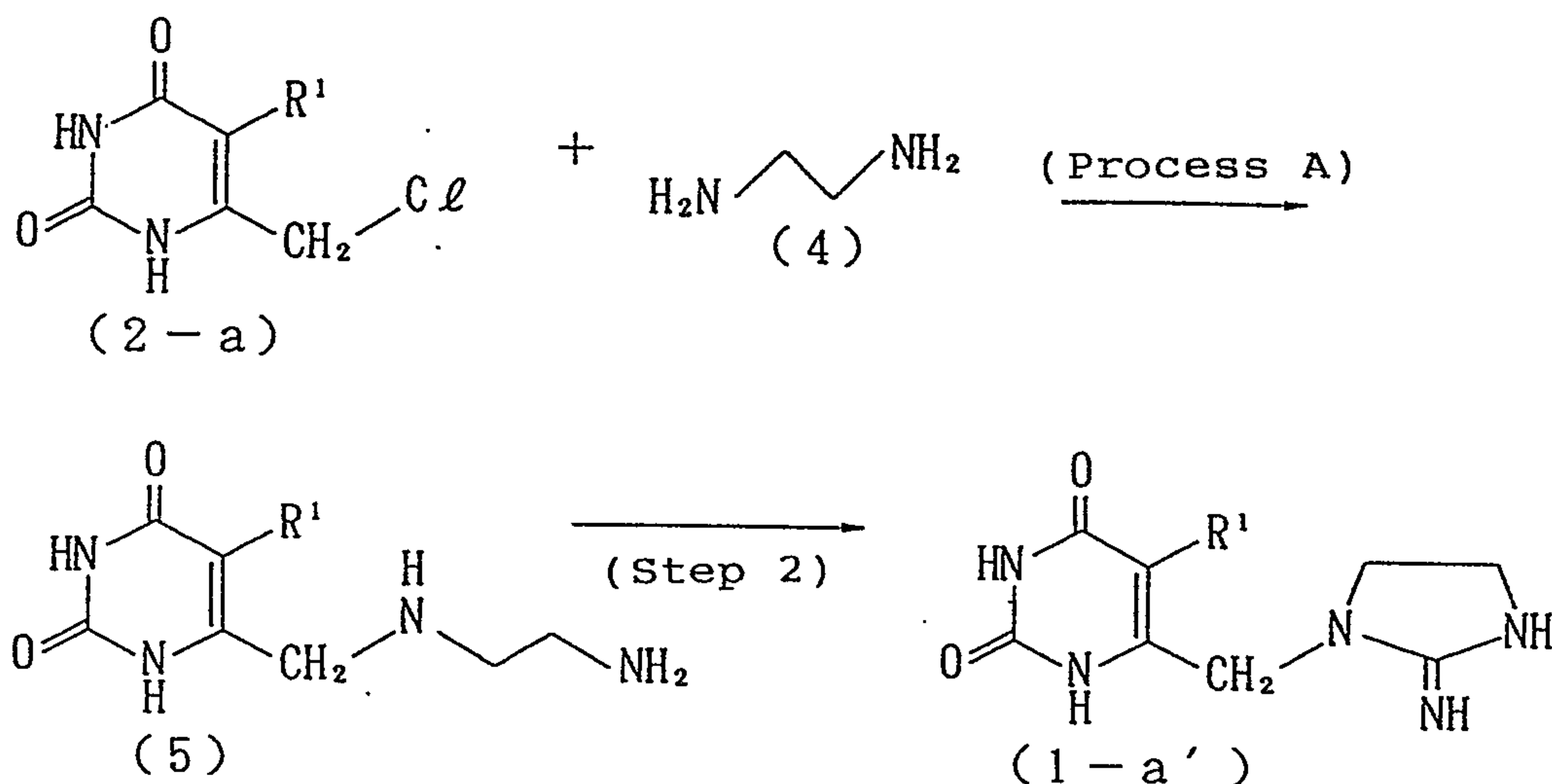
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amount of from 1 to 10 mole equivalents, preferably from 1 to 5 mole equivalents and the basic compound in an amount of from 1 to 5 mole equivalents, both per mole of the compound of the formula (2). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 0°C to 80°C. The reaction time may range from 0.1 to 48 hours, preferably from 0.5 to 24 hours.

When R^3 is a heterocycle having a hydroxyl group in the compound represented by the formula (1-a), the hydroxyl group can be converted further into a methanesulfonyloxy group by a usual method. Described specifically, the methanesulfonyloxy derivative can be obtained by using N,N-dimethylformamide, dimethylsulfoxide, dichloromethane, pyridine or the like as a solvent, triethylamine, pyridine, dimethylaminopyridine or the like as a basic compound and methanesulfonyl chloride as a mesylating agent, employing the mesylating agent in an amount of from 1 to 2 mole equivalents and the basic compound in an amount of from 1 to 5 mole equivalents, both per mole of the compound of the formula (1-a), and reacting them at a reaction temperature of from 0°C to the boiling point of the solvent or so for 0.5 to 48 hours.

[Process B]

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wherein R¹ has the same meaning as defined above.

More specifically, the step shown in the above
 5 reaction formula can be practiced as will be described
 hereinafter.

(Step 2)

The compound represented by the formula (1-a')
 can be prepared by reacting the compound represented by
 10 the formula (5), which is obtained by reacting the com-
 pound of the formula (2-a) and ethylenediamine (4) in
 accordance with Process A, with cyanogen bromide in a
 suitable solvent.

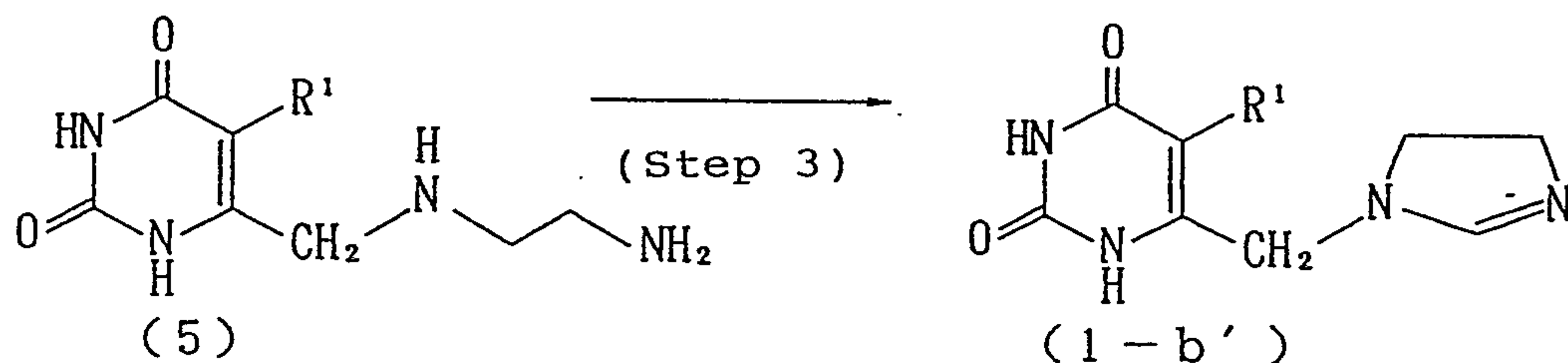
No particular limitation is imposed on the sol-
 15 vent to be used here insofar as it takes no part in the
 reaction. Examples of the solvent include aprotic
 polar solvents such as N,N-dimethylformamide, N,N-

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dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; 5 alcohols such as methanol, ethanol and propanol; and water.

In this reaction, it is preferred to conduct the reaction by using cyanogen bromide in an amount of from 1 to 2 mole equivalents per mole of the compound of the 10 formula (5). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 0°C to 80°C. The reaction time may range from 0.5 to 48 hours, preferably from 1 to 24 hours.

15 [Process C]



wherein R¹ has the same meaning as defined above.

More specifically, the step shown in the above reaction formula can be practiced as will be described 20 hereinafter.

- 20 -

(Step 3)

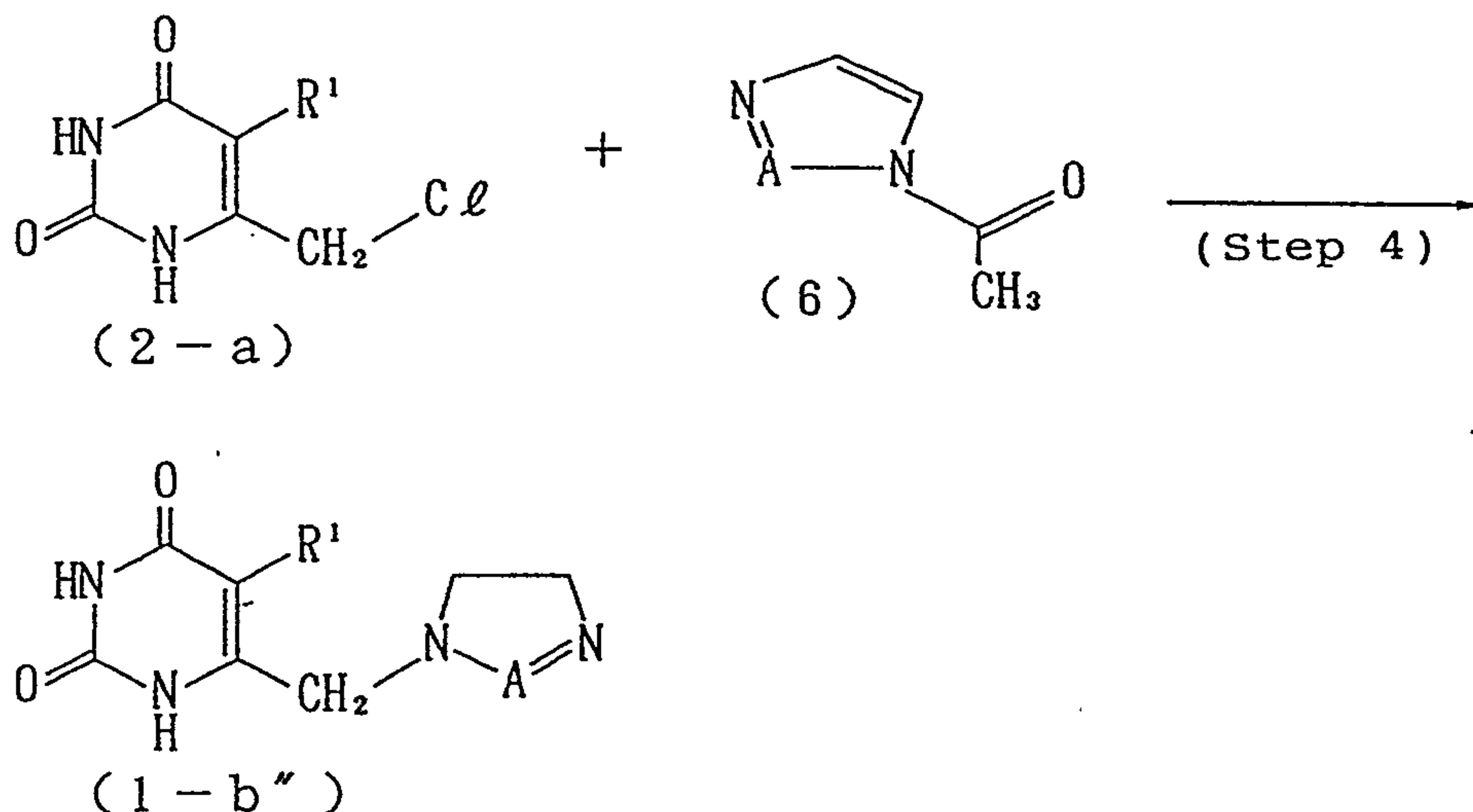
The compound represented by the formula (1-b') can be prepared by reacting the compound represented by the formula (5) with trimethyl orthoformate in a suitable solvent.

No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; alcohols such as methanol, ethanol and propanol; and acetic acid, formic acid and water.

In this reaction, it is preferred to use the trimethyl orthoformate in an amount of from 1 to 2 mole equivalents per mole of the compound of the formula (5). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 80°C to 130°C. The reaction time may range from 0.5 to 12 hours, preferably from 1 to 4 hours.

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[Process D]



wherein R^1 has the same meaning as defined above, and A
 5 represents CH or N.

More specifically, the step shown in the above
 reaction formula can be practiced as will be described
 hereinafter.

(Step 4)

10 The compound represented by the formula (1-b'')
 can be prepared by reacting the compound represented by
 the formula (2-a) with the compound represented by the
 formula (6) in a suitable solvent.

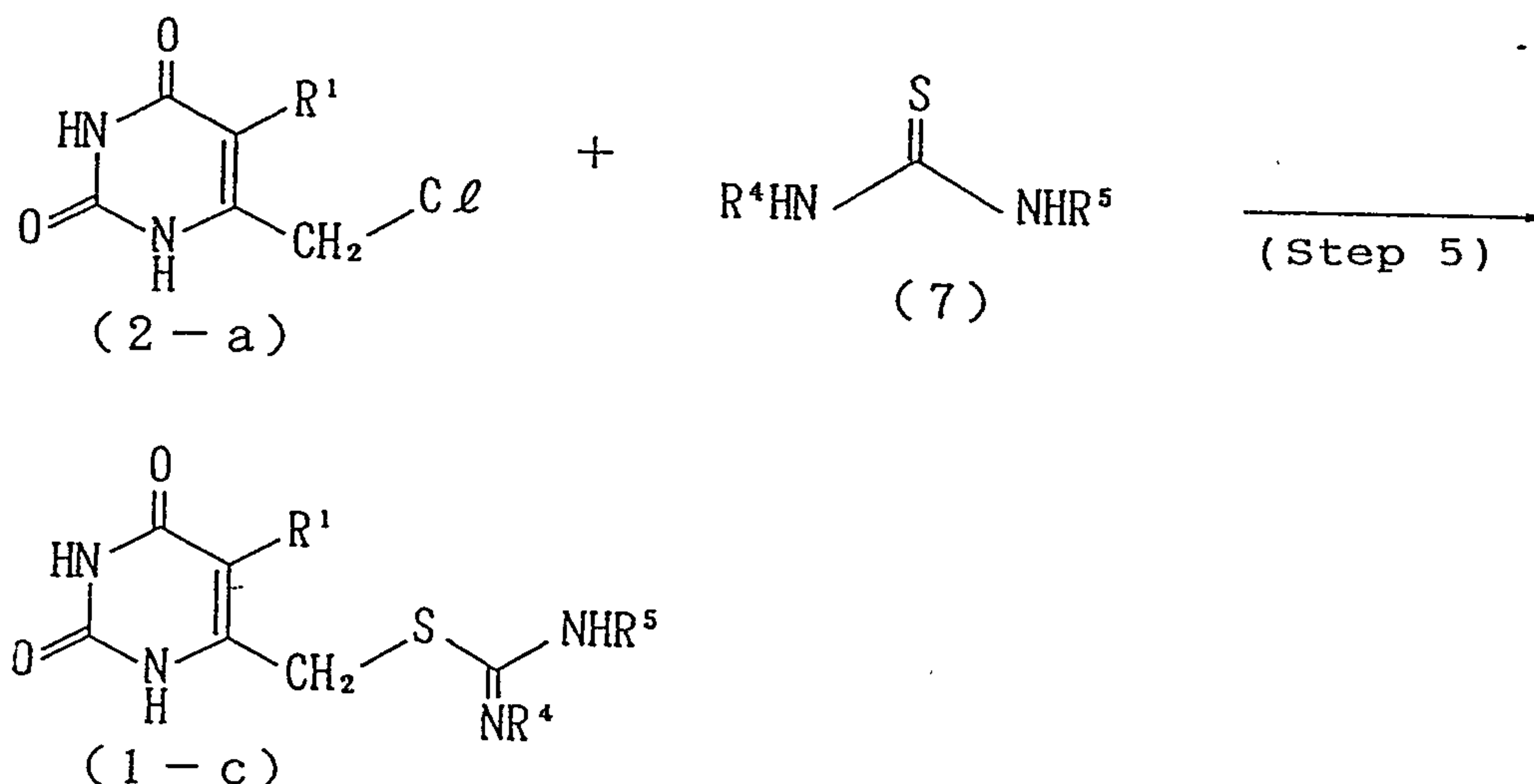
15 No particular limitation is imposed on the sol-
 vent to be used here insofar as it takes no part in the
 reaction. Examples of the solvent include aprotic
 polar solvents such as N,N-dimethylformamide, N,N-

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dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; alkyl ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone; alcohols such as methanol, ethanol and propanol; and water.

In this reaction, it is preferred to use the compound of the formula (6) in an amount of from 1 to 2 mole equivalents per mole of the compound of the formula (2-a). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 50°C to 120°C. The reaction time may range from 0.5 to 72 hours, preferably from 1 to 48 hours.

[Process E]



- 23 -

wherein R¹ has the same meaning as defined above, and R⁴ and R⁵ may be the same or different and each represents a hydrogen atom or a lower alkyl group.

More specifically, the step shown in the above
5 reaction formula can be practiced as will be described hereinafter.

(Step 5)

The compound represented by the formula (1-c) can be prepared by reacting the compound represented by the
10 formula (2-a) with the commercially-available compound represented by the formula (7) in a suitable solvent.

No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic
15 polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform;
20 alkyl ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone; alcohols such as methanol, ethanol and propanol; and water.

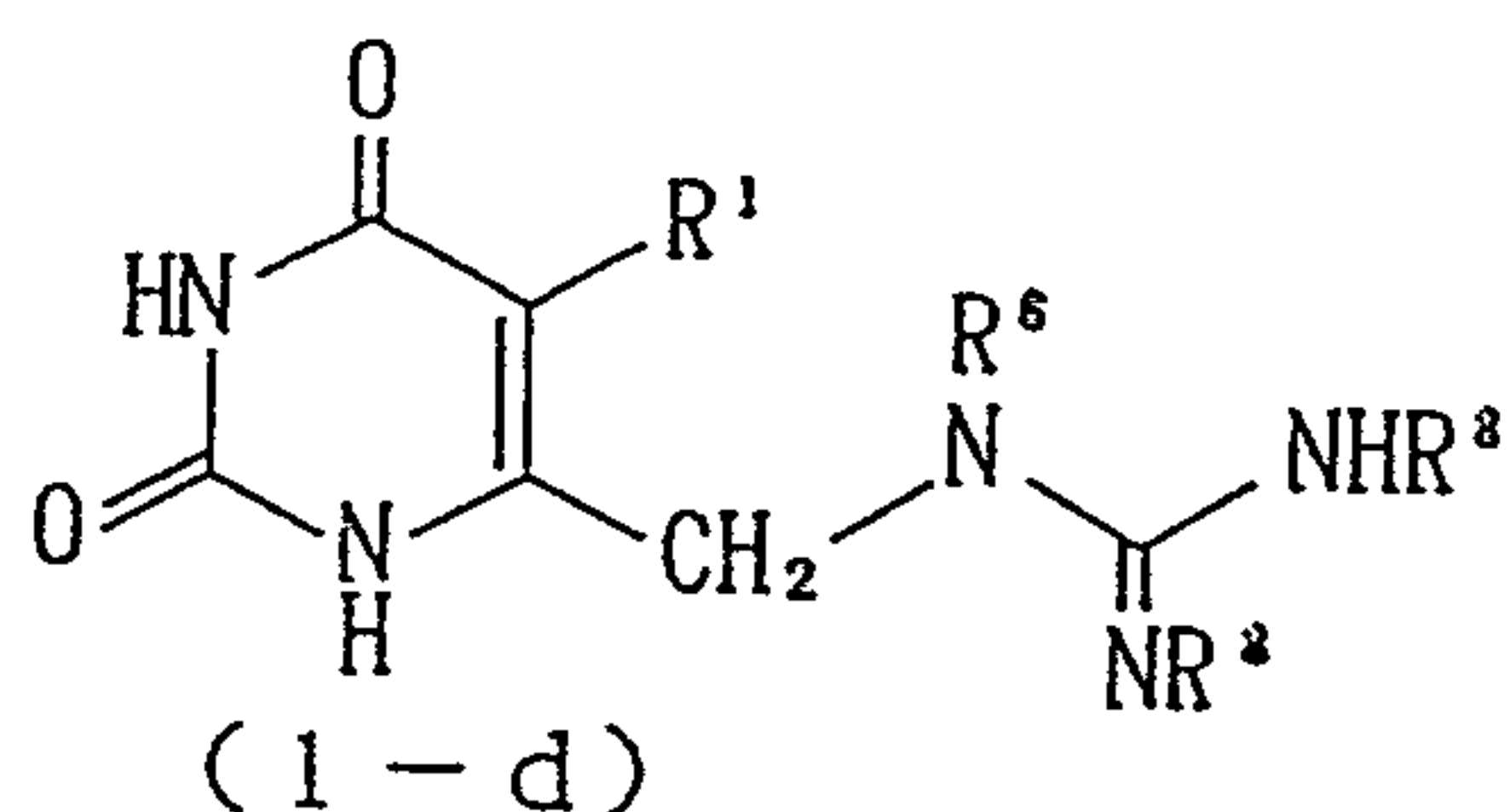
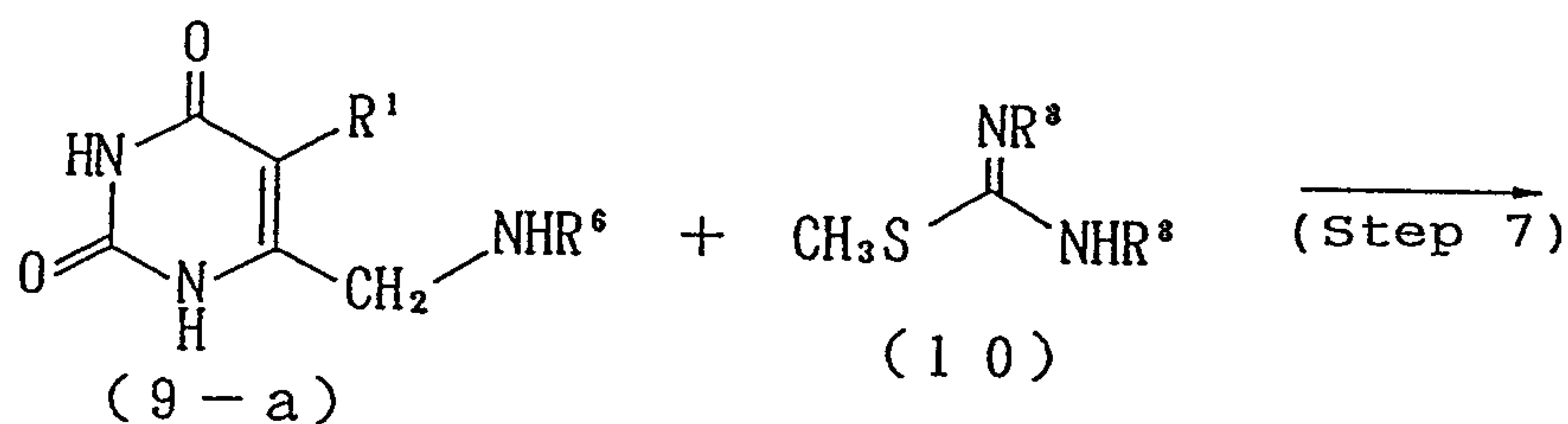
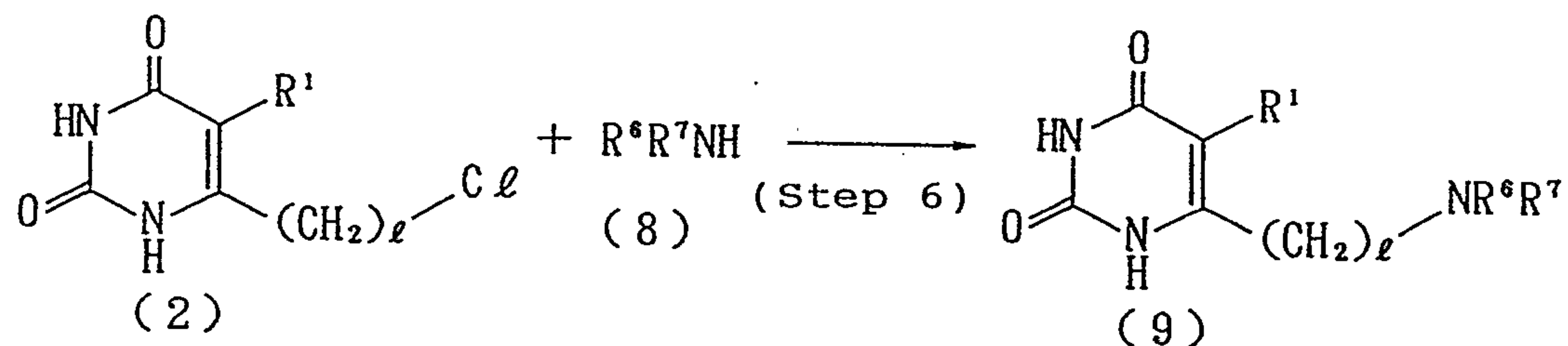
For this reaction, it is preferred to use the compound of the formula (7) in an amount of from 1 to 2
25 mole equivalents per mole of the compound of the for-

- 24 -

mula (2-a). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 50°C to 120°C. The reaction time may range from 0.5 to 24 hours, preferably from 1 to 8

5

[Process F]



wherein R¹ and ℓ have the same meanings as defined above, R⁶ and R⁷ may be the same or different and each represents a hydrogen atom or a lower alkyl group, and R⁸s each represents a hydrogen atom or a lower alkyl

10

- 25 -

group or two R⁸s represent a 2-imidazolin-2-yl group together with the nitrogen atom to which they are bonded.

5 More specifically, the individual steps shown in the above reaction scheme can be practiced as will be described hereinafter.

(Step 6)

10 The compound represented by the formula (9) can be prepared by reacting the compound represented by the formula (2) with the commercially-available compound represented by the formula (8) in a suitable solvent.

15 No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as tetrahydrofuran and dioxane; alcohols such as methanol, ethanol and propanol; and water.

20 In this reaction, it is preferred to use the compound of the formula (8) in an amount of from 1 to 50 mole equivalents, preferably from 1 to 10 mole equivalents per mole of the compound of the formula (2). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 0°C to
25

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80°C. The reaction time may range from 0.5 to 168 hours, preferably from 1 to 96 hours.

The compound of the formula (9) available by the above reaction can be used in Step 7 with or without isolation.

(Step 7)

The compound represented by the formula (1-d) can be prepared by reacting the compound represented by the formula (9-a) and the known compound represented by the formula (10), which is disclosed in literature [Analytical Biochemistry, 57, 310 (1974)] or is commercially available, in a suitable solvent in the presence or absence of a basic compound.

No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as tetrahydrofuran and dioxane; alcohols such as methanol, ethanol and propanol; and water.

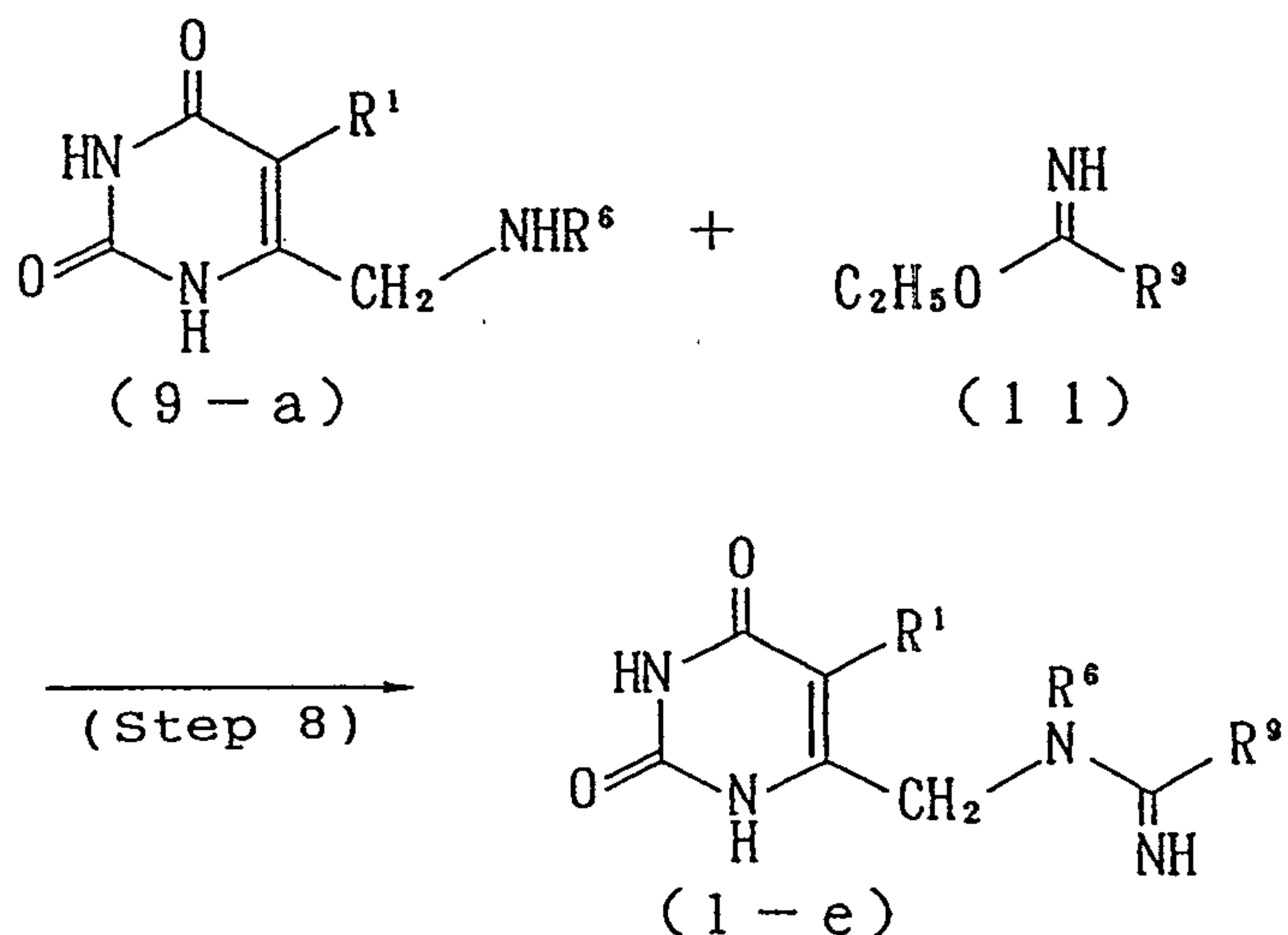
Illustrative basic compounds include inorganic basic compounds, e.g., alkali metal carbonates such as sodium carbonate and potassium carbonate, alkali metal bicarbonates such as sodium bicarbonate and potassium

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bicarbonate, alkali metal hydroxides such as sodium hydroxide and potassium hydroxide, alkali metals such as sodium and potassium, alkali metal alkoxides such as sodium methoxide, sodium ethoxide and potassium t-butoxide, and alkali metal hydrides such as sodium hydride.

In this reaction, it is preferred to use the compound of the formula (10) in an amount of from 1 to 2 mole equivalents and the basic compound in an amount of from 1 to 5 mole equivalents, both per mole of the compound of the formula (9-a). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 0°C to 80°C. The reaction time may range from 0.5 to 48 hours, preferably from 1 to 24 hours.

[Process G]



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wherein R¹ and R⁶ have the same meanings as defined above, and R⁹ represents a lower alkyl group.

More specifically, the step shown in the above reaction formula can be practiced as will be described hereinafter.

(Step 8)

The compound represented by the formula (1-e) can be prepared by reacting the compound represented by the formula (9-a) and the compound represented by the formula (11), which is disclosed in literature [Organic Syntheses Collective, 1, 5 (1941)], in a suitable solvent.

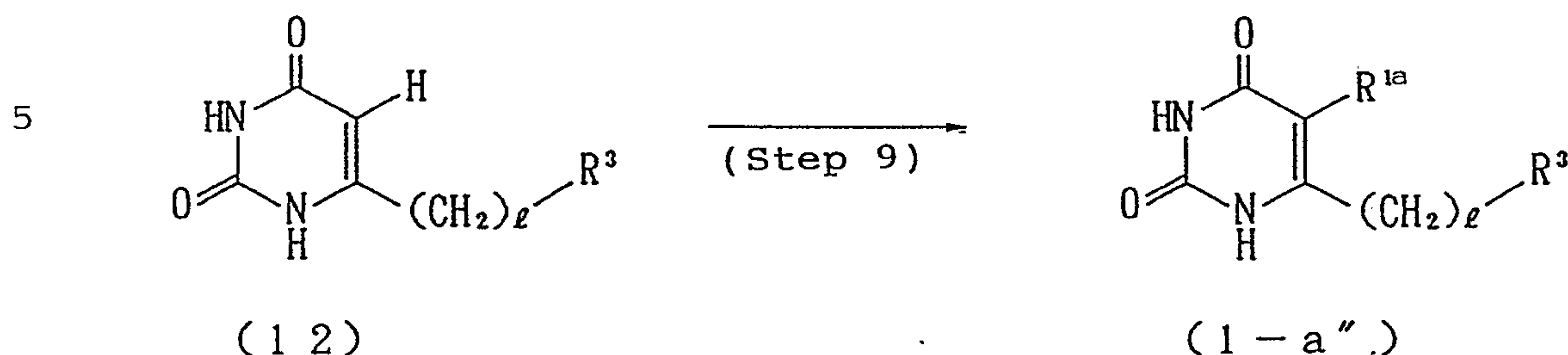
No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as tetrahydrofuran and dioxane; alcohols such as methanol, ethanol and propanol; and water.

In this reaction, it is preferred to use the compound of the formula (11) in an amount of from 1 to 2 mole equivalents per mole of the compound of the formula (9-a). The reaction temperature may range from 0°C to the boiling point of the solvent or so,

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preferably from 0°C to 80°C. The reaction time may range from 0.5 to 48 hours, preferably from 1 to 24 hours.

[Process H]



wherein R^{1a} represents a chlorine, bromine or iodine atom, and R³ and *l* have the same meanings as defined above.

10 More specifically, the step shown in the above reaction formula can be practiced as will be described hereinafter.

(Step 9)

15 The compound represented by the formula (1-a'') can be prepared by reacting the compound represented by the formula (12), which is obtained in accordance with the below-described preparation process (Process P), with a chlorinating agent, brominating agent or iodating agent in a suitable solvent.

20 No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic

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polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as tetrahydrofuran and dioxane; alcohols such as methanol, ethanol and propanol; and acetic acid, formic acid, concentrated sulfuric acid and water.

Illustrative of the chlorinating agent are chlorine, N-chlorosuccinimide, sulfuryl chloride and sodium hypochlorite.

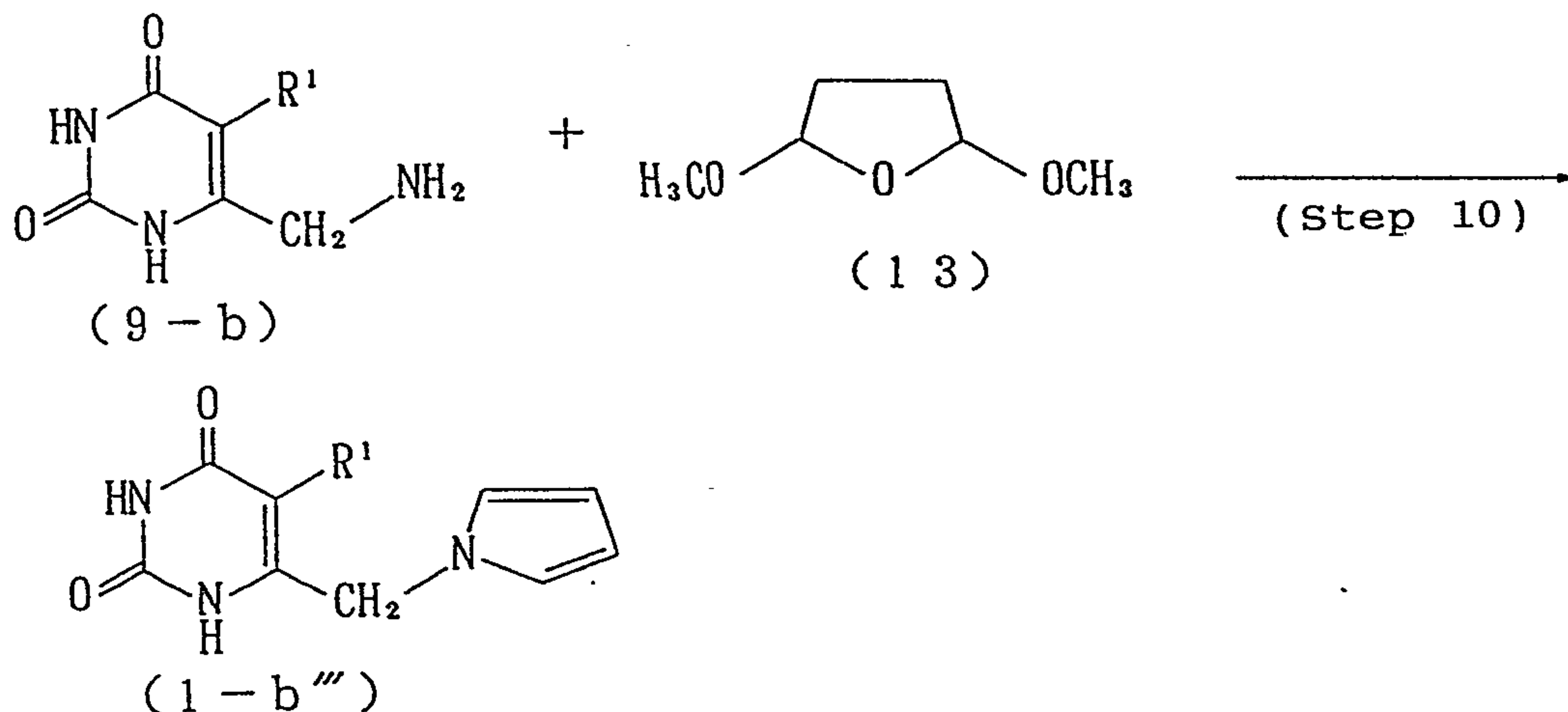
Illustrative of the brominating agent are bromine, N-bromosuccinimide and pyridiniumbromide perbromide.

Illustrative of the iodating agent are iodine and N-iodosuccinimide.

In this reaction, it is preferred to use the chlorinating agent, brominating agent or iodating agent in an amount of from 1 to 3 mole equivalents per mole of the compound of the formula (12). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 0°C to 80°C. The reaction time may range from 0.5 to 48 hours, preferably from 1 to 12 hours.

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[Process I]



wherein R^1 has the same meaning as defined above.

5 More specifically, the step shown in the above reaction formula can be practiced as will be described hereinafter.

(Step 10)

10 The compound represented by the formula (1-b''') can be prepared by reacting the compound represented by the formula (9-b) and 2,5-dimethoxytetrahydrofuran (13) in a suitable solvent.

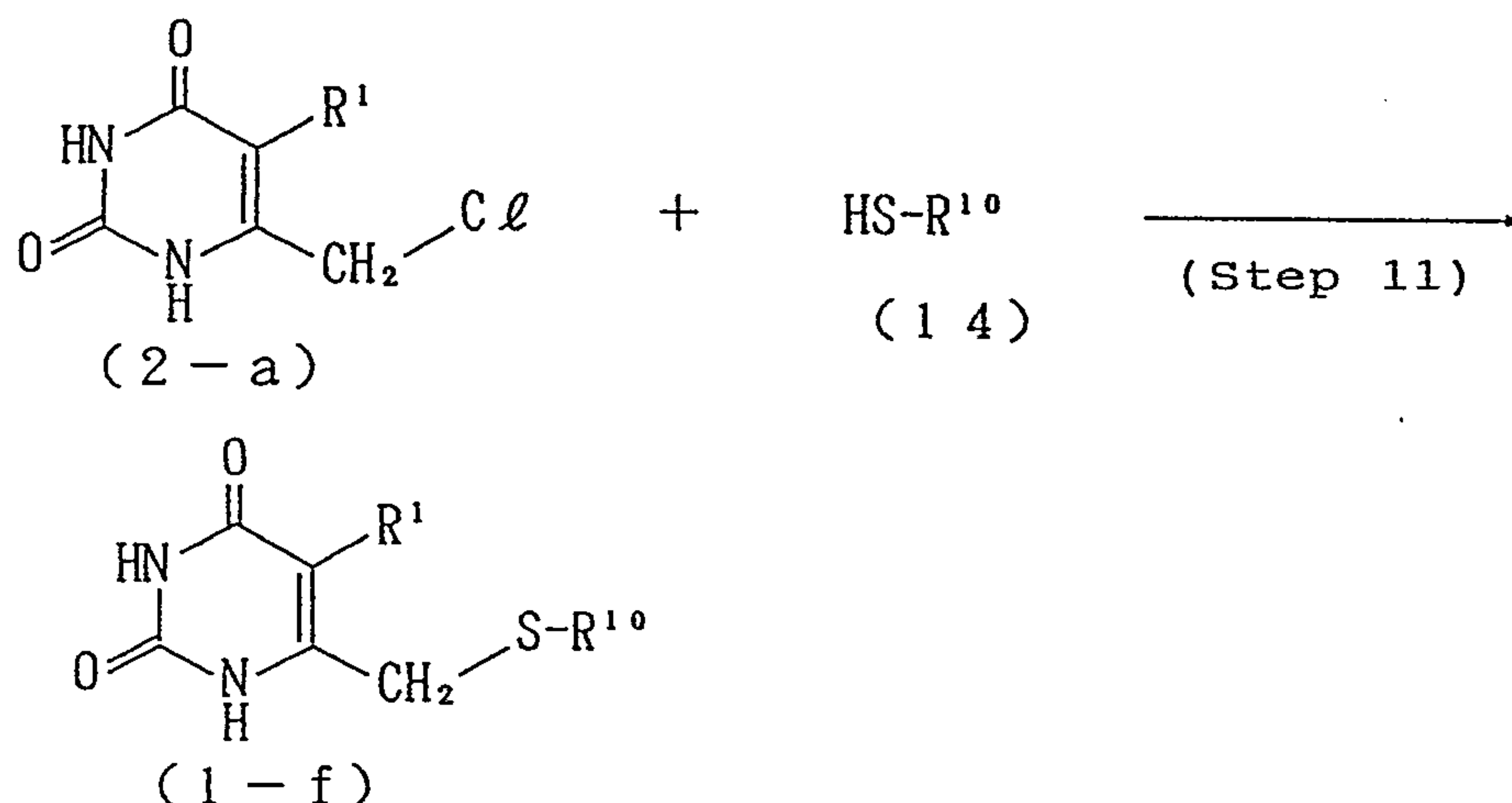
15 No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and

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hexamethylphosphoric triamide; ethers such as diethyl ether, tetrahydrofuran and dioxane; alcohols such as methanol, ethanol and propanol; and acetic acid, formic acid, concentrated sulfuric acid and water.

5 In this reaction, it is preferred to use 2,5-dimethoxytetrahydrofuran (13) in an amount of from 1 to 5 mole equivalents, preferably from 1 to 2 mole equivalents per mole of the compound of the formula (9-b). The reaction temperature may range from 0°C to the
10 boiling point of the solvent or so, preferably from 0°C to 120°C. The reaction time may range from 0.5 to 48 hours, preferably from 1 to 24 hours.

[Process J]



15 wherein R¹ has the same meaning as defined above, and R¹⁰ represents a 2-imidazolin-2-yl, 2-imidazolyl,

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1,2,4-triazol-3-yl, 1-methylimidazol-2-yl, 2-pyrimidyl or 2-benzimidazolyl group.

More specifically, the step shown in the above reaction formula can be practiced as will be described hereinafter.

(Step 11)

The compound represented by the formula (1-f) can be prepared by reacting the compound represented by the formula (2-a) and the commercially-available compound represented by the formula (14) in a suitable solvent.

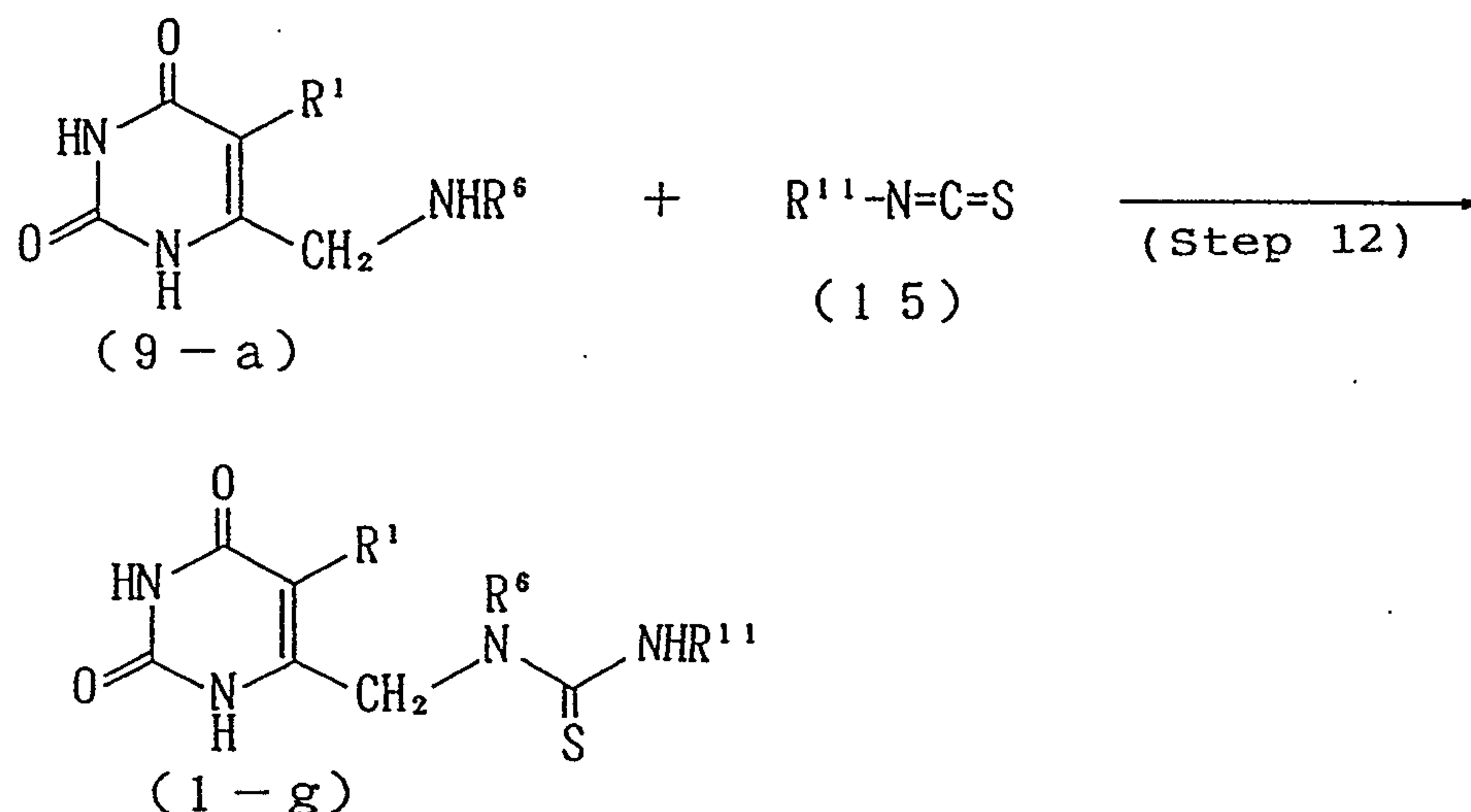
No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; alkyl ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone; alcohols such as methanol, ethanol and propanol; and water.

In this reaction, it is preferred to use the compound of the formula (14) in an amount of from 1 to 3 mole equivalents per mole of the compound of the formula (2-a). The reaction temperature may range from

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0°C to the boiling point of the solvent or so, preferably from 0°C to 100°C. The reaction time may range from 0.5 to 24 hours, preferably from 1 to 8 hours.

5 [Process K]



wherein R¹ and R⁶ have the same meanings as defined above, and R¹¹ represents a lower alkyl group.

10 More specifically, the step shown in the above reaction formula can be practiced as will be described hereinafter.

(Step 12)

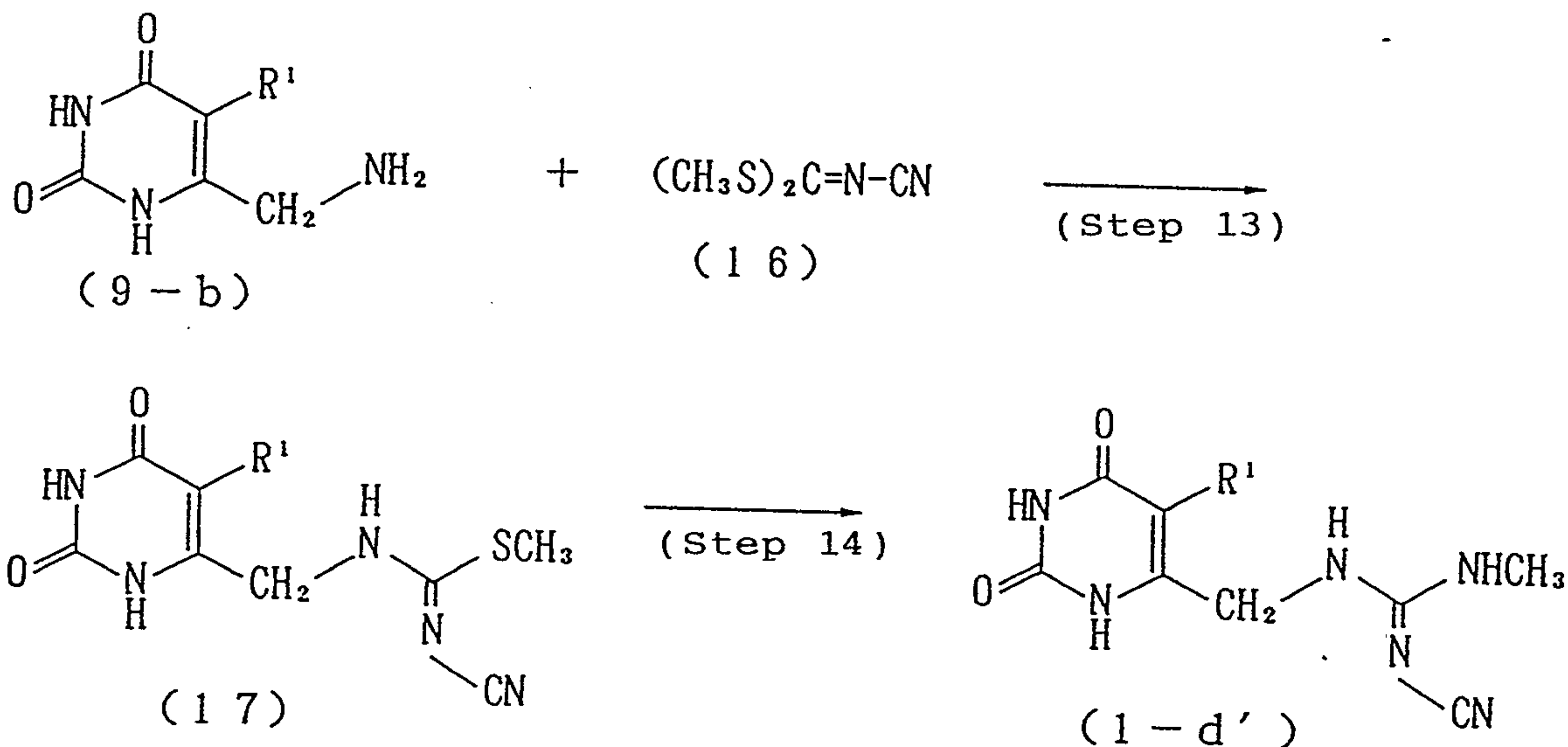
15 The compound represented by the formula (1-g) can be prepared by reacting the compound represented by the formula (9-a) and the compound represented by the formula (15) in a suitable solvent.

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No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; and ethers such as tetrahydrofuran and dioxane.

In this reaction, it is preferred to use the compound of the formula (15) in an amount of from 1 to 2 mole equivalents per mole of the compound of the formula (9-a). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 0°C to 80°C. The reaction time may range from 0.5 to 48 hours, preferably from 1 to 24 hours.

[Process L]



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wherein R¹ has the same meaning as defined above.

More specifically, the step shown in the above reaction formula can be practiced as will be described hereinafter.

5 (Step 13)

The compound represented by the formula (17) can be prepared by reacting the compound represented by the formula (9-b) and S,S'-dimethyl N-cyanodithioimino-carbonate (16), which is a compound commercially avail-
10 able on the market, in a suitable solvent.

No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-
15 dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; amines such as pyridine and triethylamine; alkyl
20 ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone; alcohols such as methanol, ethanol and propanol; and water.

In this reaction, it is preferred to use S,S'-dimethyl N-cyanodithioiminocarbonate (16) in an amount
25 of from 1 to 5 mole equivalents, preferably from 1 to 2

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mole equivalents per mole of the compound of the formula (9-b). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 60°C to 130°C. The reaction time may
5 range from 0.5 to 24 hours, preferably from 1 to 8 hours.

The compound of the formula (17) available by the above reaction can be used in Step 14 with or without isolation.

10 (Step 14)

The compound represented by the formula (1-d') can be prepared by reacting the compound represented by the formula (17) and methylamine in a suitable solvent.

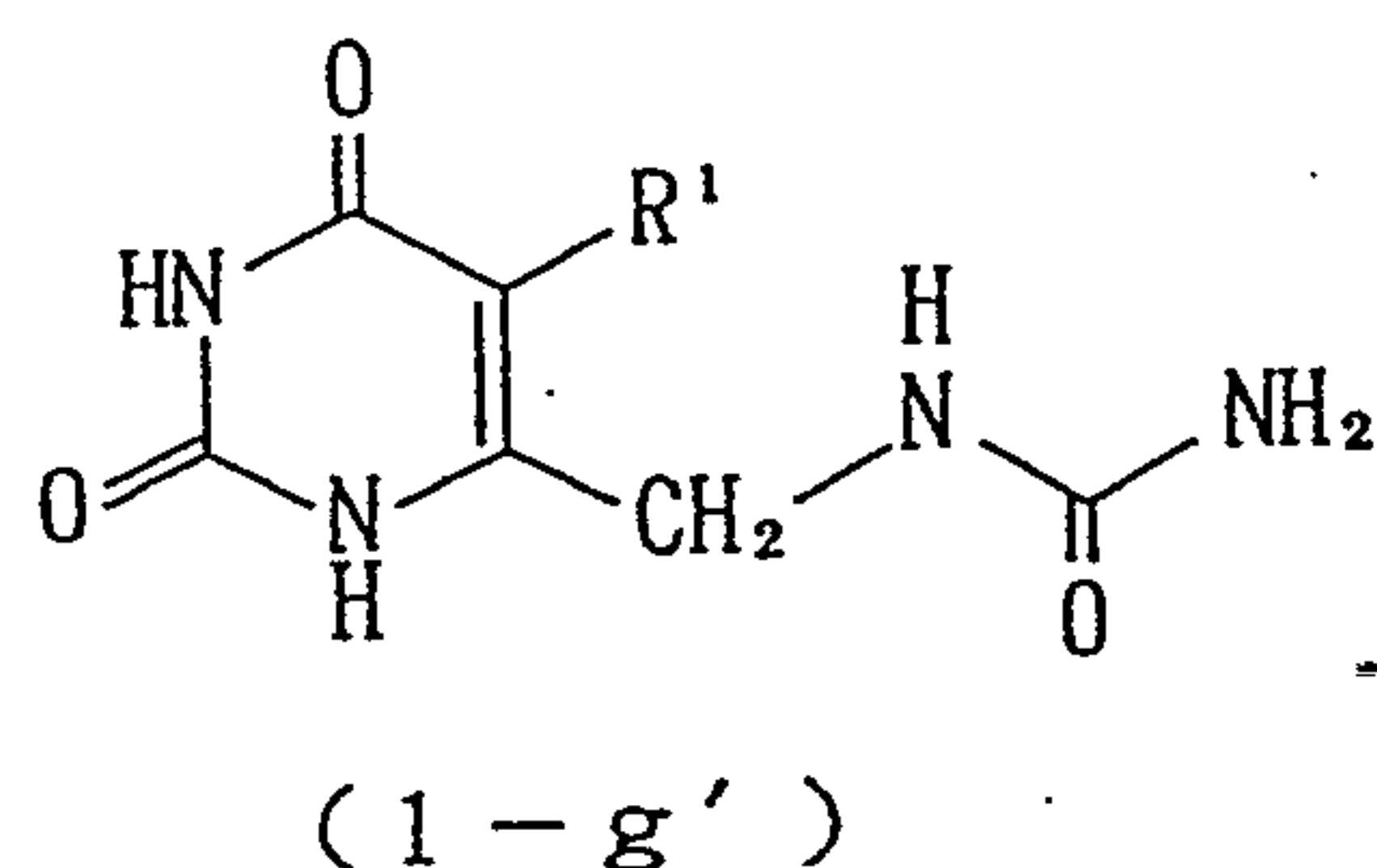
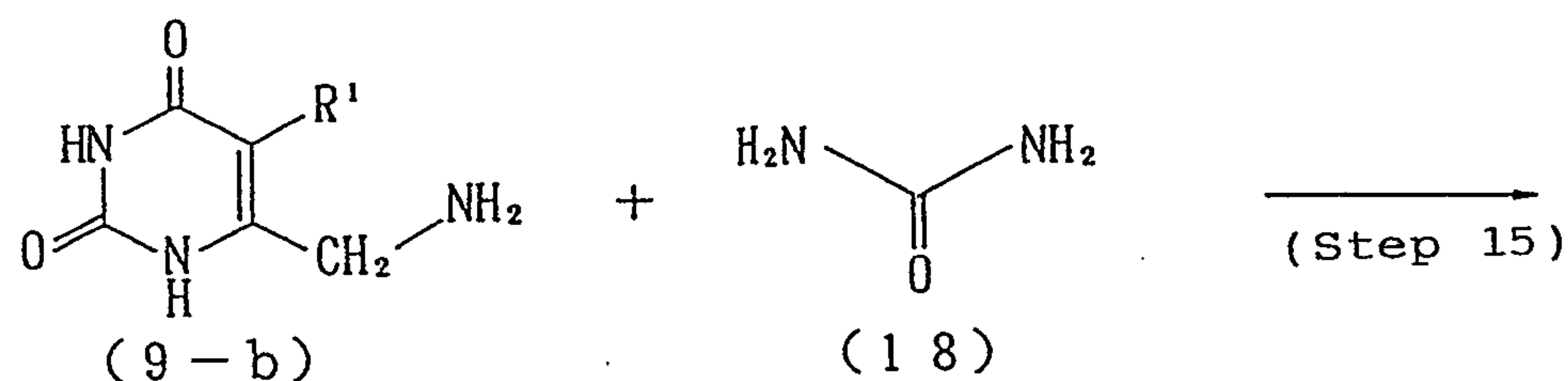
No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the
15 reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as diethyl
20 ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; alcohols such as methanol, ethanol and propanol; and water.

In this reaction, it is preferred to use methyl-
25 amine in an amount of from 1 to 100 mole equivalents

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per mole of the compound of the formula (17). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 0°C to 80°C. The reaction time may range from 0.5 to 24 hours, preferably from 1 to 8 hours.

[Process M]



wherein R¹ has the same meaning as defined above.

More specifically, the step shown in the above reaction formula can be practiced as will be described hereinafter.

(Step 15)

The compound represented by the formula (1-g') can be prepared by reacting the compound represented by the formula (9-b) and urea (18) in a suitable solvent.

No particular limitation is imposed on the sol-

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vent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and
5 hexamethylphosphoric triamide; ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; amines such as pyridine and triethylamine; alkyl ketones such as acetone, methyl ethyl ketone and methyl
10 isobutyl ketone; alcohols such as methanol, ethanol and propanol; and water.

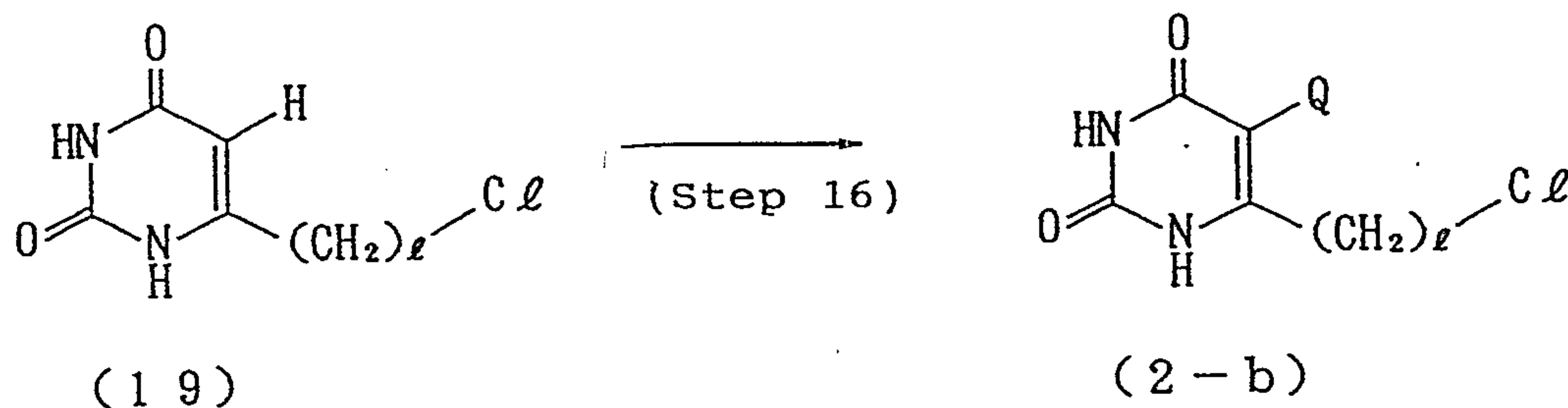
In this reaction, it is preferred to use urea in an amount of from 1 to 2 mole equivalents per mole of the compound of the formula (9-b). The reaction
15 temperature may range from 0°C to the boiling point of the solvent or so. The reaction time may range from 0.5 to 48 hours, preferably from 1 to 24 hours.

The compounds represented by the formula (2), which are raw materials for the above-described Process
20 A, Process B, Process D, Process E, Process F and Process J, can be prepared from various compounds as raw materials, for example, in accordance with Process N or Process O which will be described below. On the other
25 hand, 6-chloromethylthymine can be prepared by the process disclosed in literature [Journal of the American

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Chemical Society, 35, 596 (1913)].

[Process N]

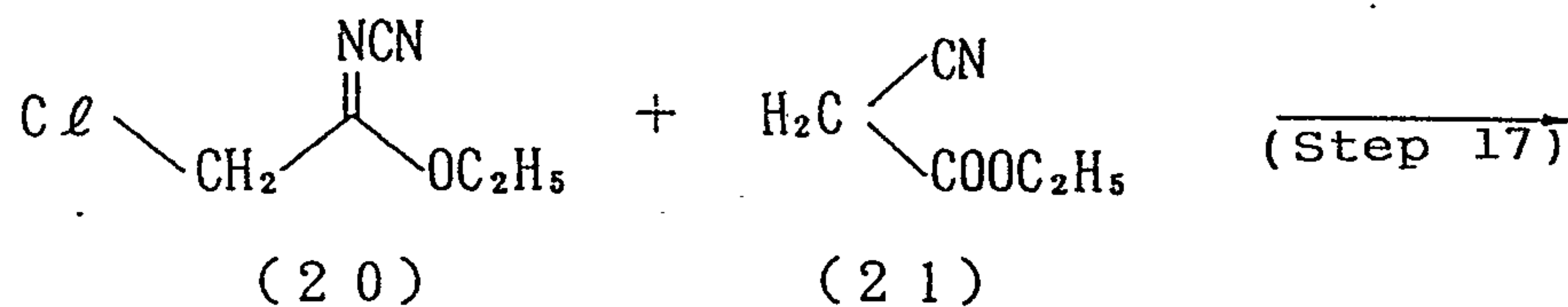


wherein Q represents a chlorine, bromine or iodine
 5 atom, and l stands for 1 or 2.

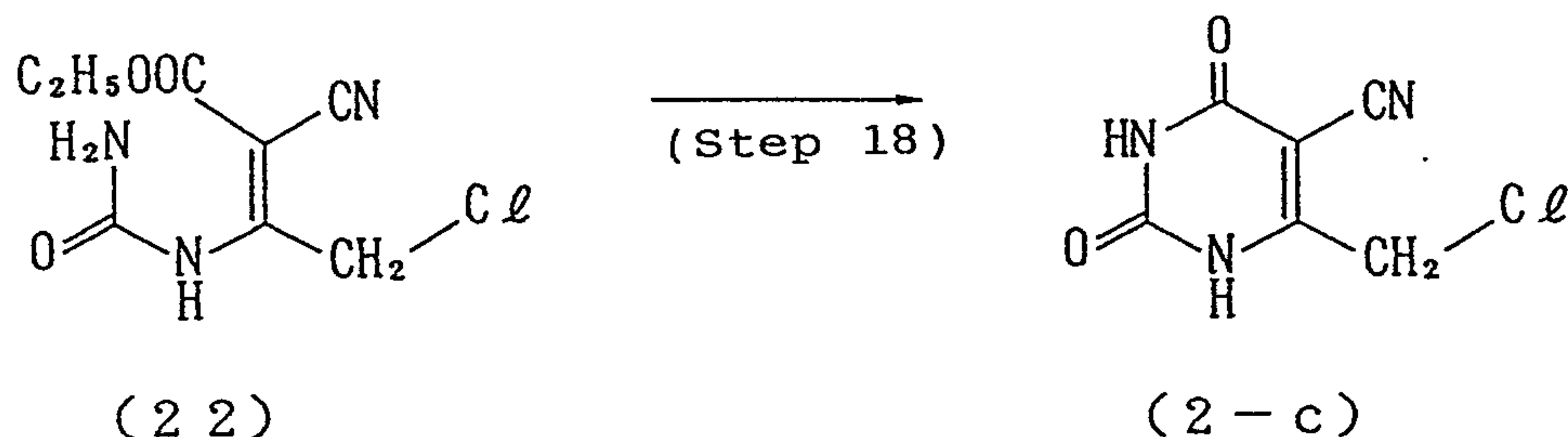
(Step 16)

The compound represented by the formula (2-b) can
 be prepared following Step 9 of Process H, using as a
 raw material 6-chloromethyluracil, a commercially-
 10 available compound, or 6-(2-chloroethyl)uracil, a com-
 pound already known from Journal of Heterocyclic
 Chemistry, 16, 239 (1979).

[Process O]



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More specifically, the step shown in the above reaction formula can be practiced as will be described hereinafter.

5 (Step 17)

The compound (22) can be prepared by reacting ethyl 2-chloro-N-cyanoacetoimidate (20) disclosed in literature [Journal of Organic Chemistry, 28, 1816 (1963)] and ethyl cyanoacetate (21) in a suitable solvent in the presence of a basic compound in accordance with the process disclosed in literature [Journal of the Chemical Society Chemical Communications, 350 (1974)].

10

No particular limitation is imposed on the solvent to be used here insofar as it takes no part in the reaction. Examples of the solvent include aprotic polar solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, dimethyl sulfoxide and hexamethylphosphoric triamide; ethers such as tetrahydrofuran and dioxane; and alcohols such as methanol, ethanol and propanol.

15

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Illustrative basic compounds include inorganic basic compounds, e.g., alkali metal carbonates such as sodium carbonate and potassium carbonate, alkali metal bicarbonates such as sodium bicarbonate and potassium bicarbonate, alkali metal hydroxides such as sodium hydroxide and potassium hydroxide, alkali metals such as sodium and potassium, alkali metal alkoxides such as sodium methoxide, sodium ethoxide and potassium t-butoxide, and alkali metal hydrides such as sodium hydride.

In this reaction, it is preferred to use ethyl cyanoacetate (21) in an amount of from 1 to 2 mole equivalents and the basic compound in an amount of from 1 to 2 mole equivalents, both per mole of ethyl 2-chloro-N-cyanoacetoimide (20). The reaction temperature may range from 0°C to the boiling point of the solvent or so, preferably from 0°C to 80°C. The reaction time may range from 0.5 to 48 hours, preferably from 1 to 24 hours.

The compound of the formula (22) available by the above reaction can be used in Step 18 with or without isolation.

(Step 18)

The compound (2-c) can be prepared by reacting the compound (22) with sodium hydroxide in water in ac-

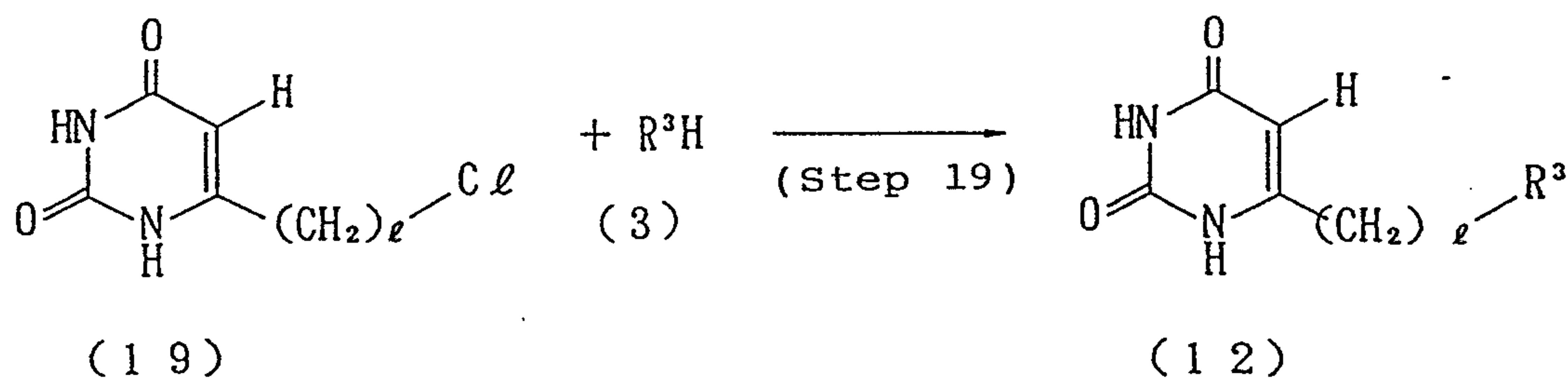
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cordance with the process disclosed in literature
[Journal of the Chemical Society Chemical Communica-
tions, 350 (1974)].

In the above reaction, it is preferred to use
5 sodium hydroxide in an amount of from 1 to 100 mole
equivalents per mole of the compound (22). The reac-
tion temperature may range from 0°C to the boiling
point of the solvent or so, preferably from 0°C to
50°C. The reaction time may range from 0.5 to 24
10 hours, preferably from 1 to 6 hours.

Further, the compound according to the present
invention represented by the formula (12), which is the
raw material for Process H, can be prepared, for exam-
ple, by the below-described Process P, using various
15 compounds as raw materials.

[Process P]



wherein R^3 and ℓ have the same meanings as defined
above.

20 (Step 19)

The compound represented by the formula (12) can

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be prepared following Step 1 of Process A, using 6-chloromethyluracil or 6-(2-chloroethyl)uracil (19) as a raw material.

5 The compounds (1) according to the present invention, which have been obtained by Process A, Process B, Process C, Process D, Process E, Process F, Process G, Process H, Process I, Process J, Process K, Process L and Process M, can be used after isolating and purifying them by conventional separation methods, for example, column chromatography, recrystallization, vacuum
10 distillation or the like.

The uracil derivative (1) or its salt according to the present invention, which has been obtained as described above, has excellent human thymidine
15 phosphorylase inhibiting effects and is useful as an effective ingredient for a cancerous metastasis inhibitor.

Incidentally, concerning 5-bromo-4-aminomethyluracil of the formula (1) in which R^1 is a bromine atom and R^2 is an amino group, a synthesis process of its
20 hydrochloride is reported in Acta Poloniae Pharmaceutica, 27(4), 329 (1970). This report however makes no mention about the inhibitory effects against human-derived thymidine phosphorylase.

25 Upon administration of the cancerous metastasis

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inhibitor according to the present invention to mammals including human, it can be formulated into various pharmacological dosage forms depending on the purposes of treatments. Specifically, it can be formulated into oral preparations such as tablets, coated tablets, pills, powders, granules, capsules, solutions, suspensions and emulsions; and parenteral preparations such as injections, suppositories, ointments and plasters. These dosable preparations can each be formulated by a common formulation method generally known in the present field of art while using a pharmaceutically acceptable carrier or the like.

Upon formulation into the form of tablets, usable examples of carriers include excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and silicic acid; binders such as water, ethanol, propanol, corn starch, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, potassium phosphate and polyvinyl pyrrolidone; disintegrators such as dried starch, sodium alginate, powdered agar, powdered laminarin, sodium bicarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium

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lauryl sulfate, stearic acid monoglyceride, starch and lactose; disintegration suppressors such as sucrose, stearic acid, cacao butter and hydrogenated oils; absorbefaciants such as quaternary ammonium bases and sodium lauryl sulfate; humectants such as glycerin and starch; adsorbents such as starch, lactose, kaolin, bentonite and colloidal silicic acid; and lubricants such as purified talc, stearate salts, powdered boric acid and polyethylene glycol. Further, tablets may be formed into those applied with conventional coatings as needed, for example, sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double-layer tablets and multi-layer tablets.

Examples of carriers usable upon formulation into the form of pills include excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin and talc; binders such as powdered gum arabic, powdered tragacanth, gelatin and ethanol; and disintegrators such as laminarin and agar.

Capsules can be formulated by mixing the uracil derivative (1) or its salt with one or more of the above-exemplified various carriers and then filling the resultant mixture in hard gelatin capsules, soft capsules or the like.

To formulate liquid preparations for oral admin-

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istration, liquid preparation for internal use, syrups and elixirs can be formulated by methods known *per se* in the art, using taste corrigents, buffers, stabilizers and smell corrigents. Illustrative of the taste corrigents are sucrose, bitter orange peel, citric acid and tartaric acid, illustrative of the buffers is sodium citrate, and illustrative of the stabilizers are tragacanth gum, gum arabic and gelatin.

As a carrier upon formulation into the form of suppositories, it is possible to use, for example, polyethylene glycol, cacao butter, a higher alcohol, an ester of a higher alcohol, gelatin, semisynthetic glyceride or the like.

To formulate injections, it is preferred to sterilize solutions, emulsions or suspensions and to make them isotonic with blood. Usable examples of diluents upon formulation into the form of these injections include water, an aqueous lactic acid solution, ethyl alcohol, propylene glycol, Macrogol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol and polyoxyethylene sorbitan fatty acid esters. In this case, such pharmaceutical preparations may contain sodium chloride, glucose or glycerin in an amount sufficient to prepare isotonic solutions. Further, conventional solubilizing aids, buffers, soothing agents,

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and the like may also be added.

Examples of diluents usable upon formulation into the form of ointments, for example, pastes, creams and gels include white petrolatum, paraffin, glycerin, cellulose derivatives, polyethylene glycol, silicone and bentonite.

For the formulation of a plaster, it is only necessary to coat a conventional backing material with the above-described ointment, cream, gel, paste or the like by a method known *per se* in the art. Suitable examples of the backing material include woven fabrics or nonwoven fabrics of cotton, rayon or chemical fibers, and films or foamed sheets of soft PVC, polyethylene or polyurethane.

To the above-described preparations, a coloring matter, a preservative, a perfume, a corrigent, a sweetening and/or the like as well as another pharmaceutical can also be added as needed.

No particular limitations are imposed on the amounts of the uracil derivative (1) or the salt thereof, which are contained in each preparation according to the present invention, and suitable amounts can be chosen as needed. In general, however, it is preferred to control the content of each of them at about 1 to 70 wt.% in each preparation.

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No particular limitation is imposed on the administration method for the each preparation according to the present invention. An administration method is determined as desired depending on the form of the preparation, the age, sex and other conditions of the patient, the severity of a symptom of the patient, and the like. For example, oral administration is used for tablets, pills, powders, granules, capsules, solutions, suspensions and emulsions. Injections are intravenously administered either by themselves or as mixtures with a usual fluid replacement such as glucose or amino acids, and if necessary, are also administered by themselves intra-arterially, intramuscularly, intracutaneously, subcutaneously or intraperitoneally. Suppositories are administered intrarectally. Ointments are coated on the skin, the oral mucosa or the like, whereas plasters are applied on the skin.

The dose of the active ingredient in each preparation according to the present invention can be suitably chosen depending on the administration method, the age, sex and other conditions of the patient, the severity of the disease, and the like. As a general standard, the dose of the uracil derivative (1) or the salt thereof may range from about 0.1 to 100 mg/kg/day, preferably from about 0.5 to 50 mg/kg/day. These prep-

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arations according to the present invention can each be administered once a day or in about 2 to 4 portions in a day.

5 Cancerous metastases which can be inhibited by the administration of preparations according to the present invention are not limited to any particular ones but include, for example, liver metastasis, lung metastasis, lymph node metastasis or the like of esophageal carcinoma, gastric cancer, gallbladder and
10 bile duct cancers, pancreas cancer, colon cancer, rectum cancer, head and neck cancers, breast cancer, cervical cancer, ovarian cancer, bladder cancer, prostatic cancer, testis tumor, osteochondroma, skin cancer and the like.

15 Examples

The present invention will hereinafter be described more specifically by the following Referential Examples, Examples and Tests but shall not be limited thereto.

20 [Synthesis of the Compound (2-b) by Process N]
Referential Example 1

Synthesis of 5-chloro-6-chloromethyluracil

To a suspension of 6-chloromethyluracil (163 g) in acetic acid (500 ml), sulfuryl chloride (120 ml)
25 was added dropwise at room temperature over 20 minutes,

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followed by stirring at the same temperature for 3 hours. The reaction mixture was poured into ice water (500 ml), and a crystallized matter was collected by filtration, whereby 182.3 g of the title compound were
5 obtained (yield: 92%).

Melting point: 225°C min. (decomposed).

NMR spectrum (DMSO-d₆) δ :

4.46(2H,s), 11.57(1H,s), 11.71(1H,s).

Table 1

Elemental analysis (as C₅H₄N₂O₂Cl₂)

	C	H	N
Calculated	30.80	2.07	14.37
Found	30.85	1.99	14.41

Referential Example 2

10 Synthesis of 5-bromo-6-chloromethyluracil

A reaction was conducted in a similar manner as Referential Example 1 except that N-bromosuccinimide was used instead of sulfuryl chloride, whereby the title compound was obtained in a yield of 70%.

15 Melting point: 245°C min. (decomposed).

NMR spectrum (DMSO-d₆) δ :

4.47(2H,s), 11.61(1H,s), 11.66(1H,s).

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Table 2

Elemental analysis (as $C_5H_4N_2O_2BrCl$)

	C	H	N
Calculated	25.08	1.68	11.70
Found	24.81	1.67	11.57

Referential Example 3

Synthesis of 5-iodo-6-chloromethyluracil

A reaction was conducted in a similar manner as Referential Example 1 except that N-iodosuccinimide was used instead of sulfuryl chloride, whereby the title compound was obtained in a yield of 77%.

Melting point: 225°C min. (decomposed).

NMR spectrum (DMSO- d_6) δ :

4.49(2H,s), 11.52(1H,s), 11.58(1H,s).

Table 3

Elemental analysis (as $C_5H_4N_2O_2ClI$)

	C	H	N
Calculated	20.96	1.41	9.78
Found	21.10	1.36	9.87

10 Referential Example 4

Synthesis of 5-chloro-6-(2-chloroethyl)uracil

A reaction was conducted in a similar manner as Referential Example 1 except that 6-(2-chloroethyl)-

- 53 -

uracil was used instead of 6-chloromethyluracil, whereby the title compound was obtained in a yield of 77%.

Melting point: 225°C min. (decomposed).

5 NMR spectrum (DMSO-d₆) δ :

3.01(2H,t,J=6.9Hz),

3.88(2H,t,J=6.9Hz),

11.28(1H,s), 11.60(1H,s).

Table 4

Elemental analysis (as C₆H₆N₂O₂Cl₂·2/5H₂O)

	C	H	N
Calculated	33.89	3.03	13.18
Found	34.27	3.02	12.75

[Synthesis of the Compound (2-c) by Process O]

10 Referential Example 5

Synthesis of ethyl 4-chloro-2-cyano-3-ureido-crotonate (22)

15 A solution of 20 g of ethyl 2-chloro-N-cyanoacetoimide (20), 16.6 g of ethyl cyanoacetate (21) and 9.28 g of sodium ethoxide in ethanol (350 ml) was stirred at room temperature for 3 hours. After the reaction mixture was distilled, 140 ml of 2 N hydrochloric acid were added, followed by stirring under ice cooling for 1 hour. After the reaction mixture was

- 54 -

neutralized with a 2 N aqueous solution of sodium hydroxide, the resultant mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue so obtained was purified by chromatography on a silica gel column while using gradient elution with hexane-ethyl acetate, whereby 5.66 g of the title compound were obtained (yield: 18%).

10 Melting point: 175-177°C.

NMR spectrum (DMSO-d₆) δ :

1.27 (3H, t, J=6.9Hz) ,

4.26 (2H, q, J=6.9Hz) ,

5.38 (2H, s) , 10.05 (1H, s) .

Table 5

Elemental analysis (as C₈H₁₀N₃O₂Cl)

	C	H	N
Calculated	41.48	4.35	18.14
Found	41.87	4.44	17.78

15 Referential Example 6

Synthesis of 5-cyano-6-chloromethyluracil (2-b)

Dissolved in 17 ml of a 2 N aqueous solution of sodium hydroxide were 3.88 g of the ethyl 4-chloro-2-cyano-ureidocrotonate (22) obtained in Referential Ex-

- 55 -

ample 5. The resulting mixture was stirred at room temperature for 1 hour and under ice cooling, was neutralized with 2 N hydrochloric acid. A crystallized matter was collected by filtration, whereby 1.16 g of the title compound were obtained (yield: 37%).

Melting point: 229°C min. (decomposed).

NMR spectrum (DMSO-d₆) δ :

4.45(2H,s), 10.05 (1H,s).

Table 6

Elemental analysis (as C₆H₄N₃O₂Cl·1/10H₂O)

	C	H	N
Calculated	38.46	2.26	22.43
Found	38.72	2.20	22.07

[Synthesis of the Compound (12) by Process P]

Referential Example 7

Synthesis of 6-(1-pyrrolidinylmethyl)uracil

To a solution of 1.78 g of pyrrolidine in water (20 ml), 1.33 g of 6-chloromethyluracil were added. The resulting mixture was stirred at room temperature for 24 hours and neutralized with acetic acid. The reaction mixture was then concentrated under reduced pressure. The residue so obtained was washed with methanol and then filtered, whereby 466 mg of the title compound were obtained (yield: 29%).

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Melting point: 176-178°C.

NMR spectrum (DMSO-d₆) δ:

1.68-1.76(4H,m), 2.42-2.55(4H,m),

3.49(2H,s), 5.44(1H,s),

10.90(2H,br-s).

5

Table 7

Elemental analysis (as C₉H₁₃N₃O₂·4/5H₂O)

	C	H	N
Calculated	51.57	7.02	20.04
Found	51.59	6.94	19.73

Physical properties of compounds obtained in the following Examples are presented in Table 9 to Table 28.

[Synthesis of the compound (1-a) by Process A]

10 Example 1

Synthesis of 5-chloro-6-(1-pyrrolidinylmethyl)uracil
(Compound 1)

15 To a solution of 32.8 g of pyrrolidine in water (300 ml), 30.0 g of the 5-chloro-6-chloromethyluracil obtained in Referential Example 1 were added. After the resultant mixture was stirred at room temperature for 24 hours, an insoluble matter was removed by filtration. The filtrate was concentrated under reduced pressure. The residue so obtained was washed with

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methanol and collected by filtration, whereby 14.2 g of the title compound were obtained (yield: 40%).

Example 2

Syntheses of Compounds 2 to 21

5 Compounds 2 to 21, which are shown in Table 9 to Table 11 and Table 19 to Table 21, were synthesized in a similar manner as in Example 1 by using appropriate starting raw materials.

Example 3

10 Synthesis of 5-chloro-6-(1-(3-methanesulfonyloxy)-pyrrolidinylmethyl)uracil (Compound 22)

 To a solution of 702 mg of the 5-chloro-6-(1-(3-hydroxy)pyrrolidinylmethyl)uracil (Compound 8), which had been obtained in Example 2, in pyridine (5 ml),
15 350 mg of methanesulfonyl chloride were added. After the resultant mixture was stirred at room temperature for 24 hours, the reaction mixture was purified by chromatography on a silica gel column (chloroform-methanol elution), whereby 220 mg of the title compound
20 were obtained (yield: 24%).

Example 4

 Synthesis of 5-chloro-6-(3-nitro-1,2,4-triazol-1-ylmethyl)uracil (Compound 23)

 To a solution of 0.88 g of 3-nitro-1,2,4-triazole
25 in a 1 N aqueous solution of KOH (10 ml), 0.50 g of 5-

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chloro-6-chloromethyluracil was added, followed by heating at 80°C for 2.5 hours under stirring. The reaction mixture was neutralized with 6 N hydrochloric acid. A precipitate was collected by filtration and then washed with water and methanol, whereby 510 mg of the title compound were obtained (yield: 73%).

Example 5

Syntheses of Compounds 24 to 28

Compounds 24 to 28, which are shown in Table 11 to Table 12 and Table 21 to Table 22, were synthesized in a similar manner as in Example 4 by using appropriate starting raw materials.

Example 6

Synthesis of 5-chloro-6-(1-(2-iminopyrrolidinyl)-methyl)uracil hydrochloride (Compound 29)

A solution of 5.0 g of 5-chloro-6-chloromethyluracil, 6.14 g of 2-iminopyrrolidine and 5.24 g of sodium ethoxide in N,N-dimethylformamide (50 ml) was stirred at room temperature for 14 hours. A crystallized matter was collected by filtration and then suspended in 30 ml of water. After the suspension was neutralized with acetic acid and then washed, an insoluble matter was collected by filtration and then dissolved in 60 ml of 1 N hydrochloric acid. Activated carbon was added to the resultant solution,

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followed by filtration. The filtrate was concentrated under reduced pressure, and the residue so obtained was washed with ethanol and collected by filtration, whereby 2.68 g of the title compound were obtained (yield: 38%).

Example 7

Synthesis of 5-chloro-6-(1-(2-iminopyrrolidinyl)-methyl)uracil p-toluenesulfonate (Compound 30)

A reaction was conducted in a similar manner as in Example 6 except that p-toluenesulfonic acid was used instead of 1 N hydrochloric acid, whereby the title compound was obtained in a yield of 26%.

Example 8

Syntheses of Compounds 31 to 36

Compounds 31 to 36, which are shown in Table 12 and Table 22, were synthesized in a similar manner as in Example 6 by using appropriate starting raw materials.

Example 9

Synthesis of 6-N-(2-aminoethyl)aminomethyl-5-chloro-uracil (Compound 37)

To a solution of 60 g of anhydrous ethylenediamine in water (200 ml), 39 g of the 5-chloro-6-chloromethyluracil obtained in Referential Example 1 were added. The resulting mixture was stirred at room

- 60 -

temperature for 24 hours. A crystallized matter was collected by filtration, whereby 28.35 g of the title compound were obtained (yield: 65%).

Example 10

5 Synthesis of 6-N-(2-aminoethyl)aminomethyl-5-bromo-
 uracil (Compound 38)

 A reaction was conducted in a similar manner as
 in Example 9 except that 5-bromo-6-chloromethyluracil
 was used instead of 5-chloro-6-chloromethyluracil,
10 whereby the title compound was obtained in a yield of
 46%.

Example 11

 Synthesis of 6-N-(2-aminoethyl)aminomethyl-5-iodo-
 uracil (Compound 39)

15 A reaction was conducted in a similar manner as
 in Example 9 except that 5-iodo-6-chloromethyluracil
 was used instead of 5-chloro-6-chloromethyluracil,
 whereby the title compound was obtained in a yield of
 69%.

20 Example 12

 Syntheses of Compounds 40 to 43

 Compounds 40 to 43, which are shown in Table 13
 and Table 23, were synthesized in a similar manner as
 in Example 9 by using appropriate starting raw
25 materials.

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Example 13

Synthesis of 5-chloro-6-(3-hydroxypropylamino)uracil
(Compound 44)

To a solution of 580 mg of 3-hydroxypropylamine
5 in water (20 ml), 500 mg of the 5-chloro-6-chloro-
methyluracil obtained in Referential Example 1 were
added, followed by stirring at room temperature for 19
hours. The reaction mixture was concentrated under
reduced pressure and a crude product so obtained was
10 purified by chromatography on a silica gel column
(chloroform-methanol-triethylamine elution), whereby
70 mg of the title compound were obtained (yield: 12%).

Example 14

Syntheses of Compounds 45 and 46

15 Compounds 45 and 46, which are shown in Table 13
to Table 14 and Table 23 to Table 24, were synthesized
in a similar manner as in Example 13 by using ap-
propriate starting raw materials.

[Synthesis of Compound (1-a') by Process B]

20 Example 15

Synthesis of 5-chloro-6-(1-(2-iminoimidazolidinyl)-
methyl)uracil (Compound 47)

To a solution of 3.6 g of cyanogen bromide in
water (50 ml), 7.0 g of 6-N-(2-aminoethyl)aminomethyl-
25 5-chlorouracil obtained in Example 9 were added, fol-

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lowed by stirring at room temperature for 3.5 hours. A crystallized matter was collected by filtration, washed with N,N-dimethylformamide and then suspended in 50 ml of water. The suspension was neutralized with a 1 N aqueous solution of sodium hydroxide and an insoluble matter was collected by filtration, whereby 2.65 g of the title compound were obtained (yield: 34%).

Example 16

Syntheses of Compounds 48 and 49

Compounds 48 and 49, which are shown in Table 14 and Table 24, were synthesized in a similar manner as in Example 15 by using appropriate starting raw materials.

[Synthesis of Compound (1-b) by Process C]

Example 17

Synthesis of 5-chloro-6-(2-imidazolin-1-ylmethyl)-uracil hydrochloride (Compound 50)

To a solution of 1.0 g of the 6-N-(2-aminoethyl)-aminomethyl-5-chlorouracil, which had been obtained in Example 9, in acetic acid (3 ml), 0.56 ml of triethyl orthoformate was added, followed by heating for 1 hour under reflux. To the reaction mixture, 0.1 ml of concentrated hydrochloric acid and 2 ml of acetic acid were added. The resultant mixture was then allowed to cool down. A crystallized matter was collected by fil-

- 63 -

tration and then washed with N,N-dimethylformamide, whereby 220 mg of the title compound were obtained (yield: 18%).

[Synthesis of Compound (1-b') by Process D]

5 Example 18

Synthesis of 5-chloro-6-(1-imidazolylmethyl)uracil hydrochloride (Compound 51)

To a solution of 4.3 g of N-acetylimidazole in methanol (100 ml), 5.0 g of 5-chloro-6-chloromethyl-
10 uracil were added, followed by heating for 2 days under reflux. After the reaction mixture was allowed to cool down, a crystallized matter was collected by filtration and then washed with a 10% solution of hydrochloric acid in methanol, whereby 4.32 g of the title compound
15 were obtained (yield: 64%).

Example 19

Synthesis of 5-chloro-6-(1,2,3-triazol-1-ylmethyl)-uracil (Compound 52)

A reaction was conducted in a similar manner as
20 in Example 18 except that N-acetyl-1,2,3-triazole was used instead of N-acetylimidazole, whereby the title compound was obtained in a yield of 58%.

[Synthesis of Compound (1-c) by Process E]

Example 20

25 Synthesis of 2-(5-chlorouracil-6-ylmethyl)isothio-

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urea hydrochloride (Compound 53)

To a solution of 140 mg of thiourea in ethanol (3 ml), 300 mg of 5-chloro-6-chloromethyluracil were added, followed by heating for 6 hours under reflux.

5 After the reaction mixture was allowed to cool down, a crystallized matter was collected by filtration, whereby 337 mg of the title compound were obtained (yield: 81%).

Example 21

10 Syntheses of Compounds 54 to 58

Compounds 54 to 58, which are shown in Table 14 to Table 15 and Table 24 to Table 25, were synthesized in a similar manner as in Example 20 by using appropriate starting raw materials.

15 [Synthesis of Compound (9) by Process F]

Example 22

Synthesis of 6-aminomethyl-5-chlorouracil (Compound 59)

20 To 400 ml of a 25% aqueous solution of ammonia, 10 g of the 5-chloro-6-chloromethyluracil obtained in Referential Example 1 were added, followed by stirring at room temperature for 4 days. A crystallized matter was collected by filtration, whereby 7.3 g of the title compound were obtained (yield: 81%).

25

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Example 23

Synthesis of 5-chloro-6-N-methylaminomethyluracil
(Compound 60)

To 150 ml of a 40% aqueous solution of
5 methylamine, 6 g of the 5-chloro-6-chloromethyluracil
obtained in Referential Example 1 were added. The
resulting mixture was stirred at room temperature for
4.5 hours and then concentrated under reduced pressure.
The residue so obtained was washed with methanol and
10 then collected by filtration, whereby 5.38 g of the
title compound were obtained (yield: 92%).

Example 24

Syntheses of Compounds 61 to 67

Compounds 61 to 67, which are shown in Table 15
15 to Table 16 and Table 25 to Table 26, were synthesized
in a similar manner as in Example 23 by using ap-
propriate starting raw materials.

[Synthesis of Compound (1-d) by Process F]

Example 25

20 Synthesis of 5-chloro-6-(1-guanidino)methyluracil
hydrochloride (Compound 68)

Subsequent to addition of 455 mg of 2-methyl-
isothiourea sulfate to 33 ml of a 0.1 N aqueous solu-
tion of potassium hydroxide under ice cooling, 600 mg
25 of the 6-aminomethyl-5-chlorouracil obtained in Example

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22 were added, followed by heating for 2 hours at 80°C under stirring. After the reaction mixture was allowed to cool down, a crystallized matter was collected by filtration and washed with 2 N hydrochloric acid, whereby 287 mg of the title compound were obtained (yield: 33%).

Example 26

Syntheses of Compounds 69 to 72

Compounds 69 to 72, which are shown in Table 16 and Table 26, were synthesized in a similar manner as in Example 25 by using appropriate starting raw materials.

[Synthesis of Compound (1-e) by Process G]

Example 27

Synthesis of N-(5-chlorouracil-6-ylmethyl)-acetamidine hydrochloride (Compound 73)

To a solution of 705 mg of ethyl acetoimidate hydrochloride in N,N-dimethylformamide (12 ml), 500 mg of 6-aminomethyl-5-chlorouracil were added, followed by stirring at room temperature for 13 hours. After the reaction mixture was allowed to cool down, a crystallized matter was collected by filtration and then washed with a 10% solution of hydrochloric acid in methanol, whereby 190 mg of the title compound were obtained (yield: 26%).

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[Synthesis of Compound (1-a'') by Process H]

Example 28

Synthesis of 5-bromo-6-(1-pyrrolidinylmethyl)uracil
(Compound 2)

5 To a solution of 1.0 g of the 6-(1-pyrrolidinyl-
methyl)uracil, which had been obtained in Referential
Example 7, in acetic acid (10 ml), 1.0 g of bromine
was added dropwise, followed by stirring at room
temperature for 20 hours. A crystallized matter was
10 collected by filtration and then washed with methanol,
whereby 560 mg of the title compound were obtained
(yield: 40%). The melting point and NMR spectrum of
the thus-obtained compound were in full conformity with
those of Compound 2 synthesized by Process A in Example
15 2.

Table 8

Elemental analysis (as $C_9H_{12}N_3O_2Br$)

	C	H	N
Calculated	39.44	4.41	15.33
Found	39.48	4.47	15.43

[Synthesis of Compound (1-b''') by Process I]

Example 29

Synthesis of 5-chloro-(1-pyrrolylmethyl)uracil (Com-
pound 74)

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To a solution of 500 mg of the 6-aminomethyl-5-chlorouracil, which had been obtained in Example 22, in acetic acid (8 ml), 577 mg of 2,5-dimethoxytetrahydrofuran were added, followed by heating at 110°C for 2 hours under stirring. The temperature of the reaction mixture was cooled back to room temperature. After an insoluble matter was filtered off, the filtrate was concentrated under reduced pressure. The residue so obtained was purified by chromatography on a silica gel column (chloroform-methanol elution), whereby 155 mg of the title compound were obtained (yield: 24%).

[Synthesis of Compound (1-f) by Process J]

Example 30

Synthesis of 5-chloro-6-(2-imidazolylthiomethyl)-uracil (Compound 75)

A reaction was conducted in a similar manner as in Example 20 except that 2-mercaptoimidazole was used instead of thiourea, whereby the title compound was obtained in a yield of 77%.

Example 31

Syntheses of Compounds 76 to 80

Compounds 76 to 80, which are shown in Table 17 to Table 18 and Table 27 to Table 28, were synthesized in a similar manner as Example 30 by using appropriate starting raw materials.

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[Synthesis of Compound (1-g) by Process K]

Example 32

Synthesis of N-methyl-N'-(5-chlorouracil-6-yl-methyl)thiourea (Compound 81)

5 A suspension of 0.50 g of 5-chloro-6-chloro-methyluracil and 0.22 g of methyl isothiocyanate in N,N-dimethylformamide (3 ml) was heated at 70°C for 4 hours under stirring. Water (50 ml) was added to the reaction mixture. A crystallized matter was collected
10 by filtration and then washed with water and methanol, whereby 435 mg of the title compound were obtained (yield: 61%).

[Synthesis of Compound (1-d') by Process L]

Example 33

15 Synthesis of N-cyano-N'-methyl-N''-(5-chlorouracil-6-ylmethyl)guanidine (Compound 82)

 A suspension of 1.0 g of the 6-aminomethyl-5-chlorouracil obtained in Example 22 and 0.926 g of S,S'-dimethyl-N-cyanodithioiminocarbonate in N,N-dimethylformamide (20 ml) was heated at 120°C for 3.5
20 hours under stirring. The reaction mixture was concentrated under reduced pressure. Methanol was added to the residue, followed by filtration. The filtrate was concentrated under reduced pressure. The residue
25 was purified by chromatography on a silica gel column

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(chloroform-methanol elution), whereby 190 mg of N-cyano-N'-(5-chlorouracil-6-ylmethyl)-S-methylisothio-urea were obtained.

5 Next, 150 mg of the N-cyano-N'-(5-chlorouracil-6-ylmethyl)-S-methylisothiourea were suspended in ethanol (3 ml), followed by the addition of 2 ml of a 30% solution of methylamine in ethanol. The resulting mixture was heated at 50°C for 3.5 hours under stirring. After an insoluble matter was filtered off, the filtrate was allowed to cool back to room temperature. A precipitate from the filtrate was collected by filtration, whereby 12 mg of the title compound were obtained (yield: 9%).

[Synthesis of Compound (1-g') by Process M]

15 Example 34

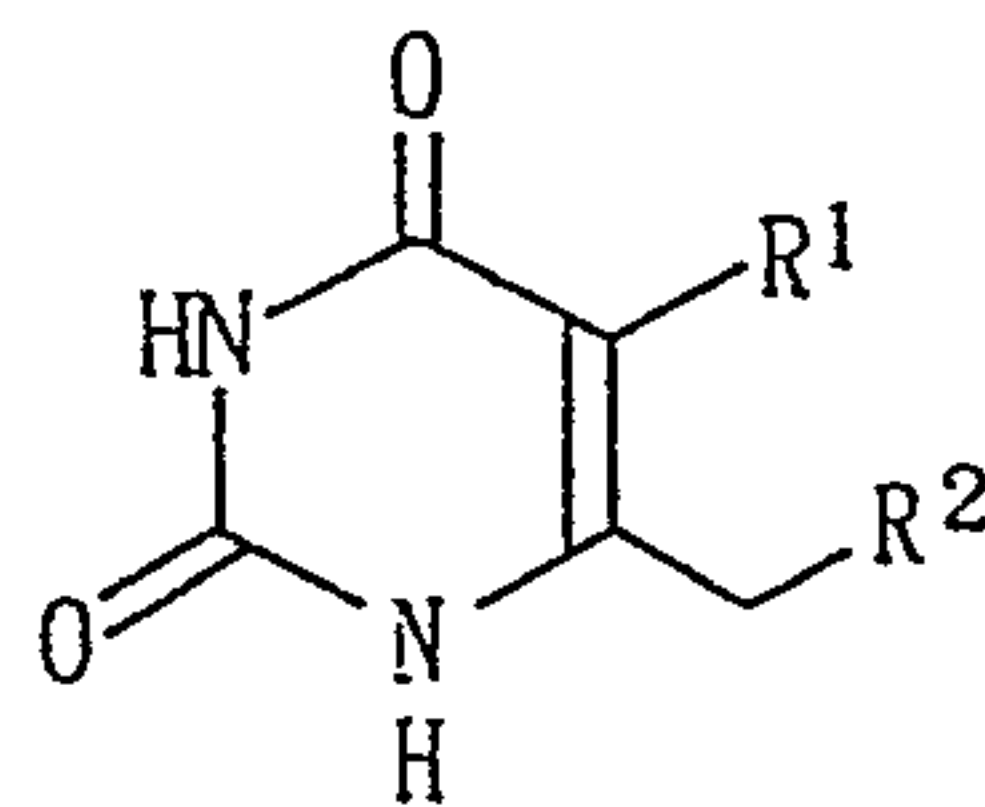
Synthesis of 5-chloro-6-(ureidomethyl)uracil (Compound 83)

6-Aminomethyl-5-chlorouracil (300 mg) obtained in Example 22 was suspended in 2 N hydrochloric acid (10 ml), followed by concentration under reduced pressure. To the residue, 188 mg of urea and 15 ml of water were added, followed by heating for 24 hours under reflux. After an insoluble matter was filtered off, the filtrate was allowed to cool back to room temperature. A precipitate was collected by filtration

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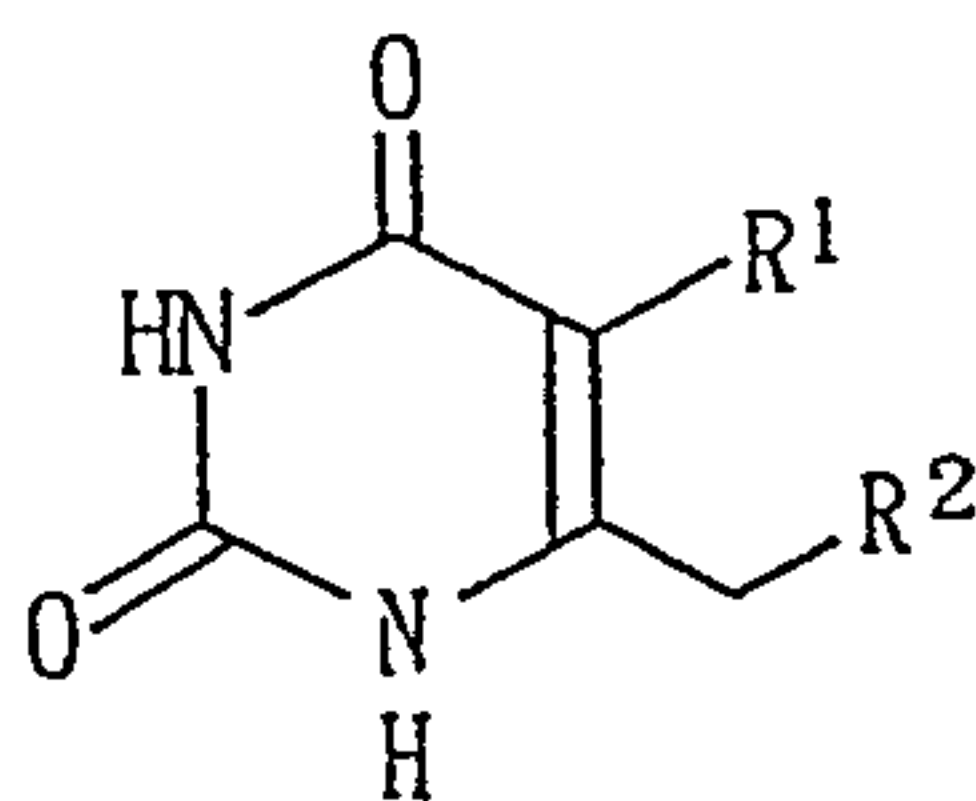
and then recrystallized from water, whereby 33 mg of the title compound were obtained (yield: 9%).

Table 9



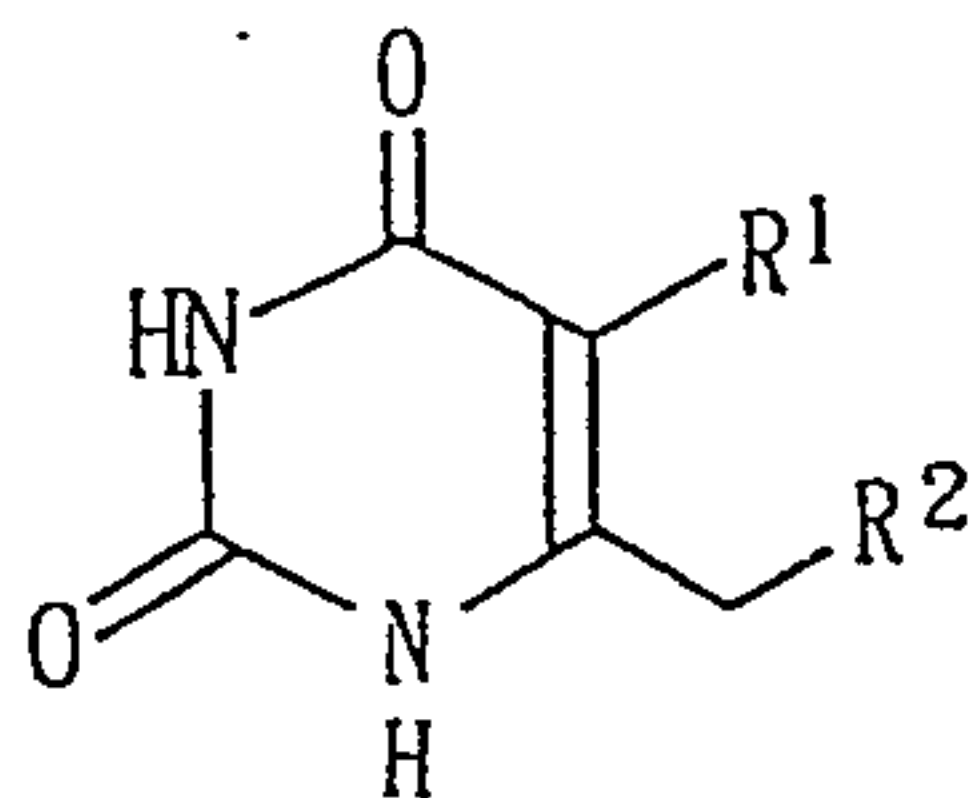
Compound No.	R ¹	R ²	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%) Calculated (Found) C H N
1	Cl		207-209 C ₉ H ₁₂ N ₃ O ₂ Cl	40	47.07 5.27 18.30 (46.97 5.36 18.15)
2	Br		213-215 C ₉ H ₁₂ N ₃ O ₂ Br	60	39.44 4.41 15.33 (39.54 4.44 15.49)
3	I		≥178 (decomp'd) C ₉ H ₁₂ N ₃ O ₂ I	17	33.66 3.77 13.09 (33.73 3.89 13.05)
4	CN		≥205 (decomp'd) C ₁₀ H ₁₂ N ₄ O ₂ H ₂ O	17	50.41 5.92 23.52 (50.70 5.57 23.29)
5	CH ₃		196-198 C ₁₀ H ₁₅ N ₃ O ₂ 1/5H ₂ O	25	56.43 7.29 19.74 (56.39 7.36 19.62)
6	Cl		190-191 C ₈ H ₁₀ N ₃ O ₂ Cl	40	44.56 4.67 19.49 (44.34 4.72 19.35)
7	Cl		≥220 (decomp'd) C ₁₁ H ₁₆ N ₃ O ₂ Cl	9	51.27 6.26 16.30 (51.13 6.41 16.34)
8	Cl		≥190 (decomp'd) C ₉ H ₁₂ N ₃ O ₃ Cl	22	44.00 4.92 17.10 (44.06 5.08 16.94)
9	Cl		165-167 C ₁₀ H ₁₄ N ₃ O ₃ Cl	53	46.25 5.43 16.18 (46.23 5.60 15.99)

Table 10



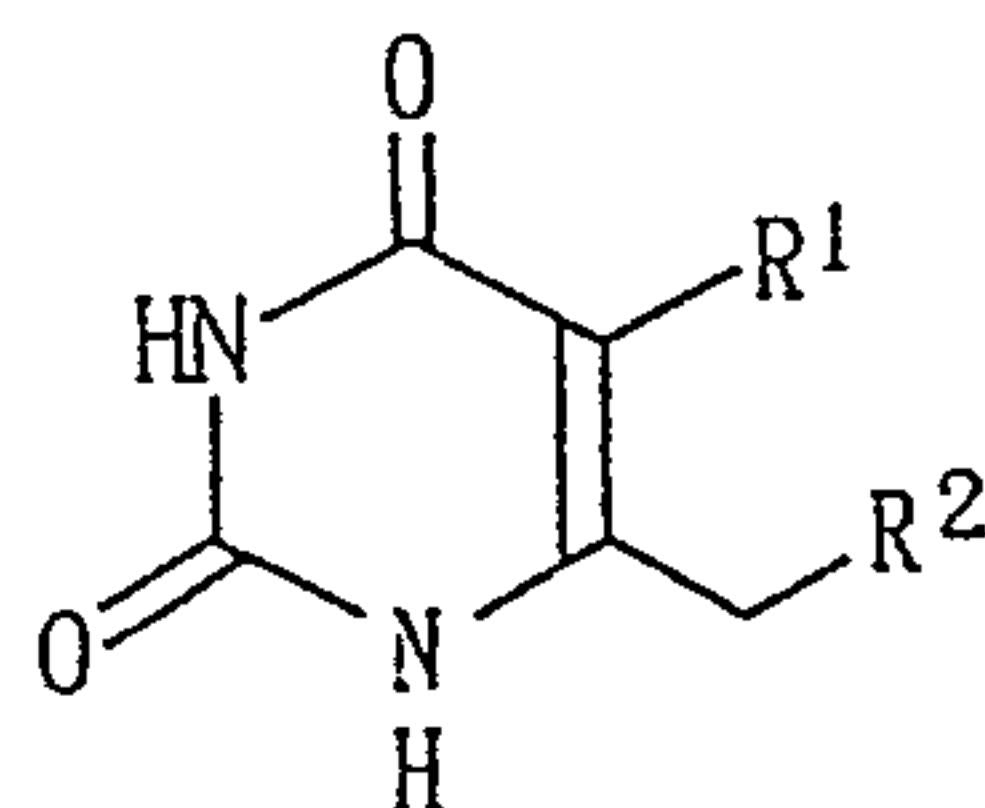
Compound No.	R ¹	R ²	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%)		
					Calculated	(Found)	
					C	H	N
10	Cℓ		165-167 C ₁₀ H ₁₄ N ₃ O ₃ Cℓ	22	46.25 (46.46)	5.43 (5.65)	16.18 (16.10)
11	Cℓ		≥220 (decomp'd) C ₉ H ₁₃ N ₄ O ₂ Cℓ 2HCl 1/5H ₂ O	91	33.65 (33.65)	4.83 (4.93)	17.44 (17.41)
12	Cℓ		233-236 C ₈ H ₉ N ₄ O ₂ Cℓ	99	42.03 (41.72)	3.97 (3.86)	24.50 (24.10)
13	Cℓ		≥195 (decomp'd) C ₁₀ H ₁₄ N ₃ O ₂ Cℓ	61	49.29 (49.37)	5.79 (5.83)	17.24 (17.15)
14	Br		≥215 (decomp'd) C ₁₀ H ₁₄ N ₃ O ₂ Br	30	41.68 (41.70)	4.90 (5.00)	14.58 (14.54)
15	Cℓ		≥205 (decomp'd) C ₁₀ H ₁₅ N ₄ O ₂ Cℓ	1	46.43 (46.44)	5.84 (6.05)	21.66 (21.53)
16	Cℓ		245 C ₉ H ₁₂ N ₃ O ₃ Cℓ 1/10H ₂ O	78	43.68 (43.68)	4.97 (4.81)	16.98 (16.89)
17	Cℓ		≥200 (decomp'd) C ₁₁ H ₁₆ N ₃ O ₂ Cℓ	47	51.27 (51.39)	6.26 (6.50)	16.30 (16.37)
18	Cℓ		≥175 (decomp'd) C ₁₂ H ₁₈ N ₃ O ₂ Cℓ	46	53.04 (53.03)	6.68 (7.03)	15.46 (15.39)

Table 11



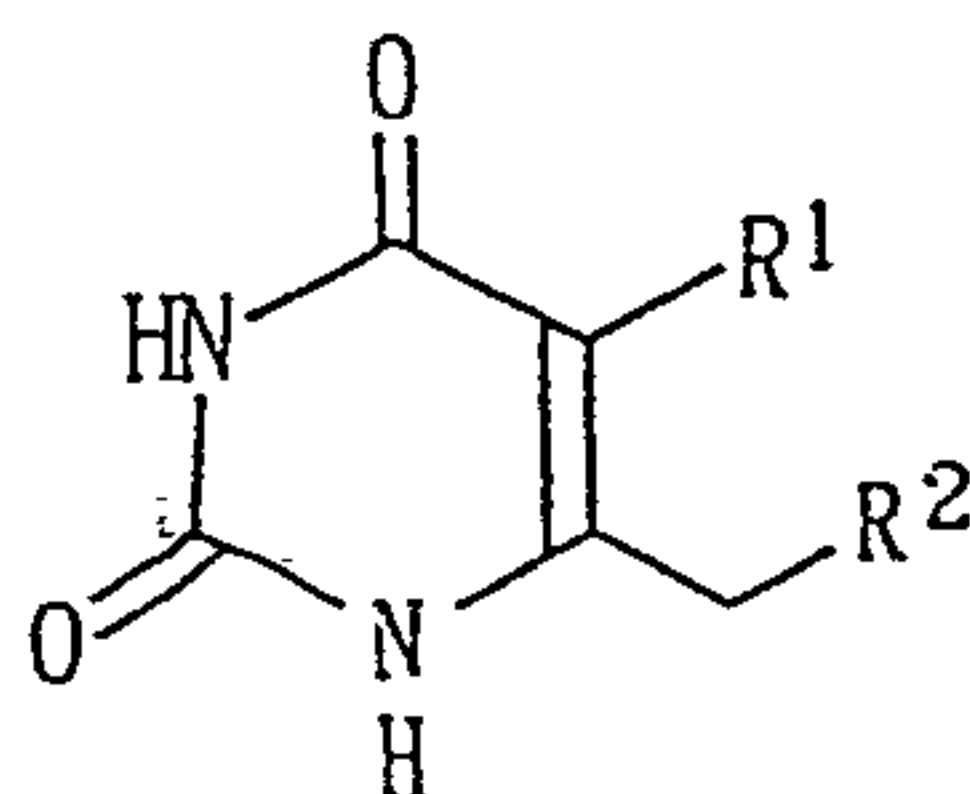
Compound No.	R ¹	R ²	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%) Calculated (Found) C H N
19	Cℓ	-CH ₂ -N	≥270 (decomp'd) C ₁₀ H ₁₄ N ₃ O ₂ Cℓ	14	49.29 5.79 17.24 (49.00 6.02 16.90)
20	Cℓ	 HN · HCℓ	≥250 (decomp'd) C ₉ H ₁₀ N ₅ O ₂ Cℓ 1/4H ₂ O	24	36.44 3.91 23.61 (36.41 3.86 23.55)
21	Cℓ	 HN · HCℓ	≥235 (decomp'd) C ₁₀ H ₁₂ N ₅ O ₂ Cℓ H ₂ O	7	37.05 4.66 21.60 (37.33 4.33 21.52)
22	Cℓ		≥175 (decomp'd) C ₁₀ H ₁₄ N ₃ O ₅ SCℓ	47	37.10 4.36 12.98 (36.93 4.40 12.80)
23	Cℓ		≥230 (decomp'd) C ₇ H ₅ N ₆ O ₄ Cℓ	73	30.84 1.85 30.83 (30.34 1.76 31.12)
24	Cℓ		≥220 (decomp'd) C ₈ H ₇ N ₄ O ₂ Cℓ	17	42.40 3.11 24.72 (42.01 3.05 24.39)
25	Cℓ	 N · HCℓ CH ₃	≥240 (decomp'd) C ₉ H ₉ N ₄ O ₂ Cℓ HCℓ 5/4H ₂ O	8	36.08 4.20 18.71 (36.03 3.94 18.44)
26	Cℓ		≥185 (decomp'd) C ₈ H ₆ N ₅ O ₄ Cℓ	50	35.38 2.23 25.78 (35.27 2.22 25.68)
27	Cℓ		155-158 C ₈ H ₆ N ₅ O ₄ Cℓ 5/4H ₂ O	12	32.67 2.91 23.81 (32.87 2.73 23.60)

Table 12



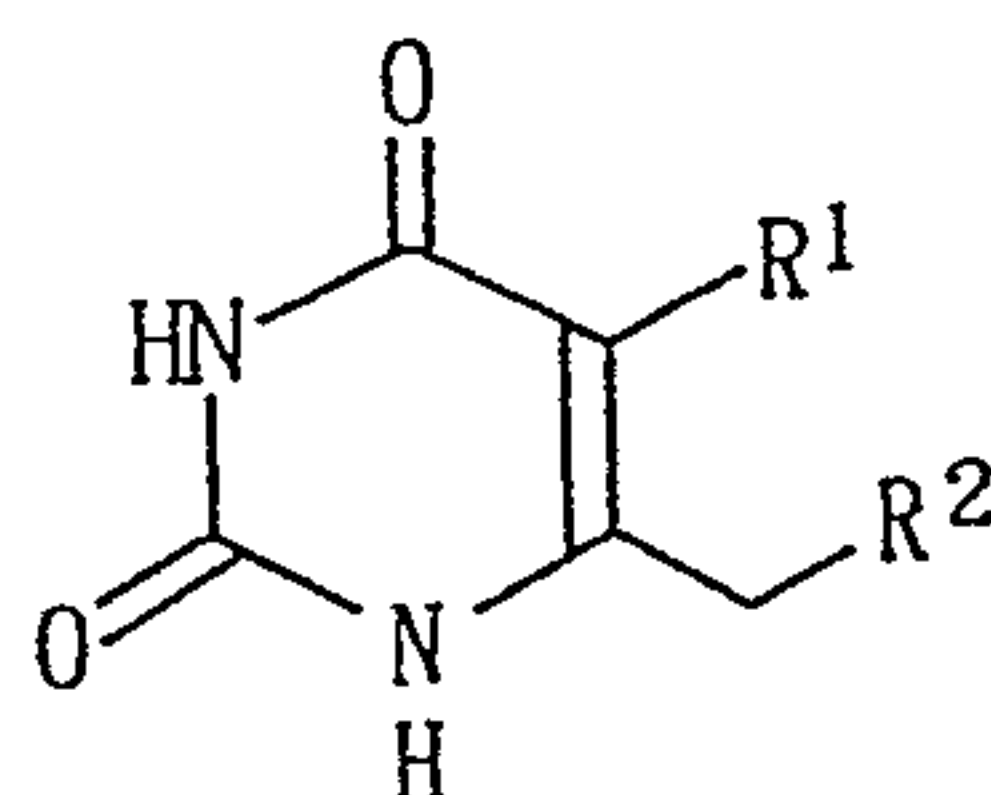
Compound No.	R ¹	R ²	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%) Calculated (Found) C H N
28	Cl		≥235 (decomp'd) C ₇ H ₆ N ₅ O ₂ Cl 1/5H ₂ O	14	36.36 2.79 30.29 (36.74 2.71 29.96)
29	Cl		≥255 (decomp'd) C ₉ H ₁₁ N ₄ O ₂ Cl HCl 1/10H ₂ O	38	38.48 4.38 19.94 (38.32 4.35 19.68)
30	Cl		≥210 (decomp'd) C ₉ H ₁₁ N ₄ O ₂ Cl TsOH 1/10H ₂ O	26	46.12 4.64 13.45 (45.71 4.59 13.89)
31	Br		≥180 (decomp'd) C ₉ H ₁₁ N ₄ O ₂ Br HCl 5/4H ₂ O	13	31.23 4.22 16.19 (31.23 4.31 16.16)
32	CH ₃		≥250 (decomp'd) C ₁₀ H ₁₄ N ₄ O ₂ HCl 1/2H ₂ O	45	44.86 6.02 20.93 (44.55 6.14 20.72)
33	CN		≥263 (decomp'd) C ₁₀ H ₁₁ N ₅ O ₂ 1/4H ₂ O	29	50.52 4.88 29.46 (50.56 4.70 29.25)
34	Cl		≥215 (decomp'd) C ₉ H ₁₂ N ₅ O ₂ Cl	22	41.95 4.69 27.18 (41.64 4.75 26.80)
35	Cl		≥205 (decomp'd) C ₁₀ H ₁₄ N ₅ O ₂ Cl 1/6H ₂ O	11	43.72 5.26 25.49 (43.69 5.23 25.51)
36	Cl		≥220 (decomp'd) C ₁₁ H ₁₆ N ₅ O ₂ Cl 4/5H ₂ O	15	44.02 5.91 23.33 (44.07 5.90 23.37)

Table 13



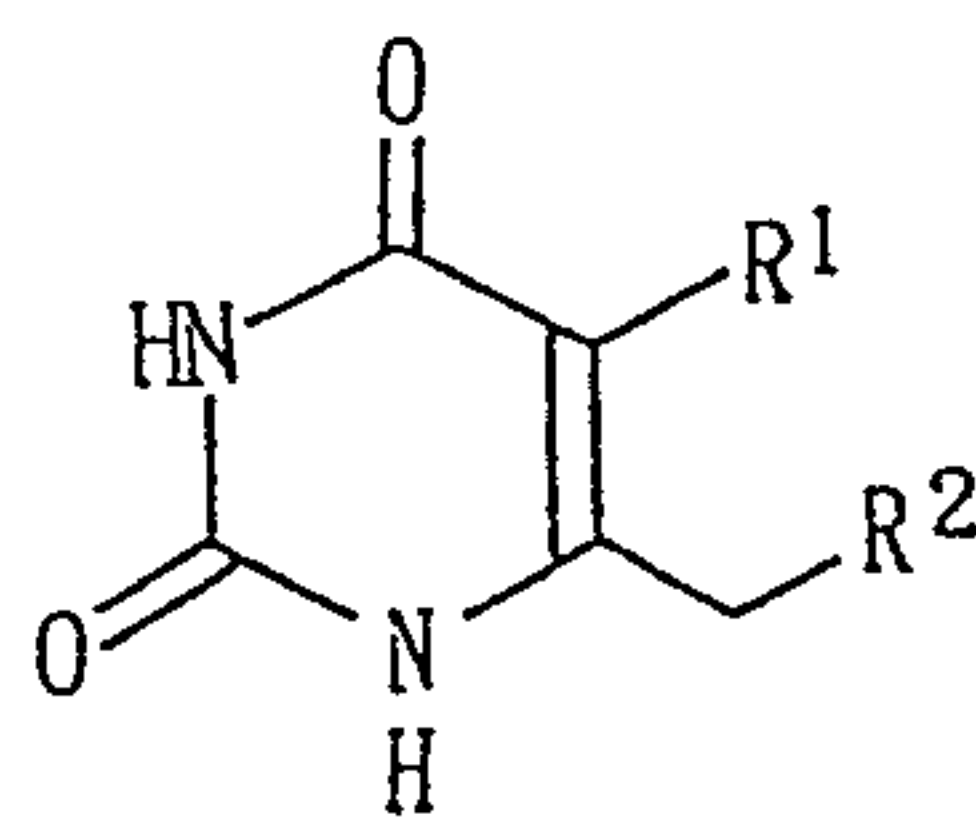
Compound No.	R 1	R 2	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%)		
					Calculated	(Found)	
					C	H	N
37	Cℓ	-NH(CH ₂) ₂ NH ₂	≥140 (decomp'd) C ₇ H ₁₁ N ₄ O ₂ Cℓ 1/3H ₂ O	70	37.43 (37.44)	5.23 5.47	24.94 24.94
38	Br	-NH(CH ₂) ₂ NH ₂	≥168 (decomp'd) C ₇ H ₁₁ N ₄ O ₂ Br	46	31.96 (31.73)	4.21 4.31	21.30 21.32
39	I	-NH(CH ₂) ₂ NH ₂	≥145 (decomp'd) C ₇ H ₁₁ N ₄ O ₂ I	69	27.11 (27.01)	3.58 3.70	18.07 17.91
40	Cℓ	-NH-N(CH ₃) ₂ · HCℓ	≥160 (decomp'd) C ₇ H ₁₂ N ₄ O ₂ Cℓ ₂	94	32.96 (32.83)	4.74 4.92	21.96 21.93
41	Cℓ	-NH(CH ₂) ₂ N(CH ₃) ₂	≥160 (decomp'd) C ₉ H ₁₅ N ₄ O ₂ Cℓ 3/2HCℓ 3/2H ₂ O	23	32.92 (32.90)	5.98 6.05	17.06 17.14
42	Cℓ	-NH(CH ₂) ₃ NH ₂	≥135 (decomp'd) C ₈ H ₁₃ N ₄ O ₂ Cℓ 1/10H ₂ O	6	40.98 (40.99)	5.67 5.89	23.89 23.56
43	Cℓ	-NH(CH ₂) ₂ CN	≥205 (decomp'd) C ₈ H ₉ N ₄ O ₂ Cℓ	89	42.03 (42.05)	3.97 3.89	24.50 24.35
44	Cℓ	-NH(CH ₂) ₃ OH	167-169 C ₈ H ₁₂ N ₃ O ₃ Cℓ	12	41.12 (41.12)	5.18 5.43	17.98 18.05
45	Cℓ	CH ₃ -N(CH ₂) ₂ OH	159-160 C ₈ H ₁₂ N ₃ O ₃ Cℓ	38	41.12 (41.17)	5.19 5.35	17.98 17.93

Table 14



Compound No.	R 1	R 2	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%) Calculated (Found) C H N
46	Cℓ	-NH(CH ₂) ₄ OH	164-166 C ₉ H ₁₄ N ₃ O ₃ Cℓ	2	43.64 5.70 16.97 (43.57 5.92 16.72)
47	Cℓ		≥228 (decomp'd) C ₈ H ₁₀ N ₅ O ₂ Cℓ 5/4H ₂ O	34	36.10 4.73 26.31 (36.10 4.67 26.24)
48	Br		≥235 (decomp'd) C ₈ H ₁₀ N ₅ O ₂ Br 5/4H ₂ O	25	30.93 4.06 22.55 (31.05 3.96 22.70)
49	I		≥207 (decomp'd) C ₈ H ₁₀ N ₅ O ₂ I 4/5H ₂ O	4	27.49 3.35 20.04 (27.87 3.15 19.54)
50	Cℓ		≥260 (decomp'd) C ₈ H ₉ N ₄ O ₂ Cℓ HCℓ	18	36.38 3.82 21.21 (36.34 3.83 20.87)
51	Cℓ		244-246 C ₈ H ₇ N ₄ O ₂ Cℓ HCℓ 2/3H ₂ O	64	34.93 3.42 20.37 (35.14 3.36 20.07)
52	Cℓ		≥195 (decomp'd) C ₇ H ₆ N ₅ O ₂ Cℓ 1/5H ₂ O	58	36.36 2.79 30.29 (35.98 2.56 30.63)
53	Cℓ		≥220 (decomp'd) C ₆ H ₇ N ₄ O ₂ Cℓ S HCℓ	81	26.58 2.97 20.66 (26.93 3.05 20.31)
54	Br		≥235 (decomp'd) C ₆ H ₇ N ₄ O ₂ BrS HCℓ	23	22.84 2.56 17.75 (22.97 2.68 17.54)

Table 15



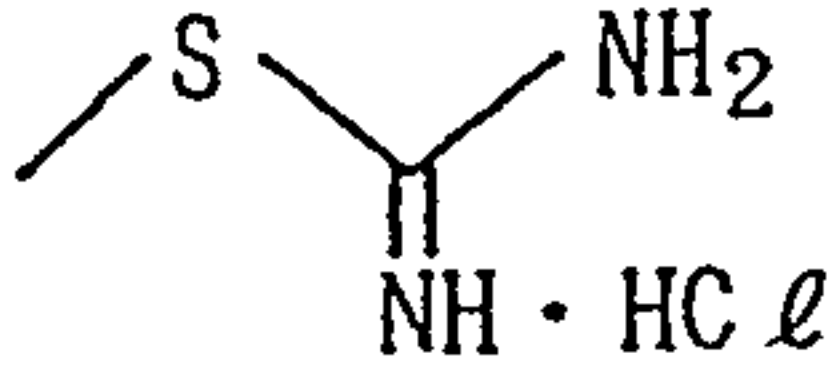
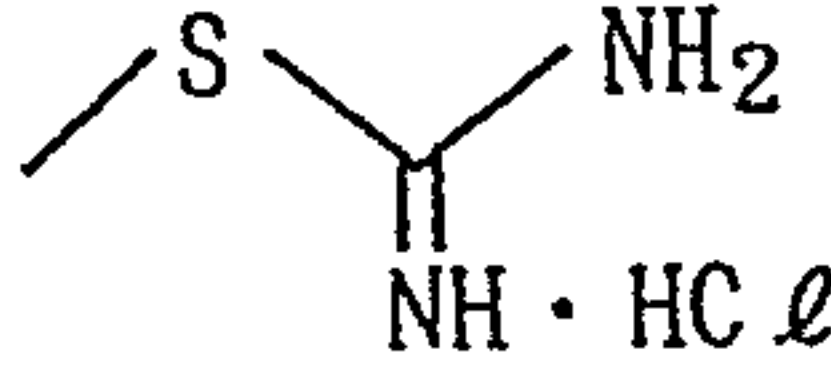
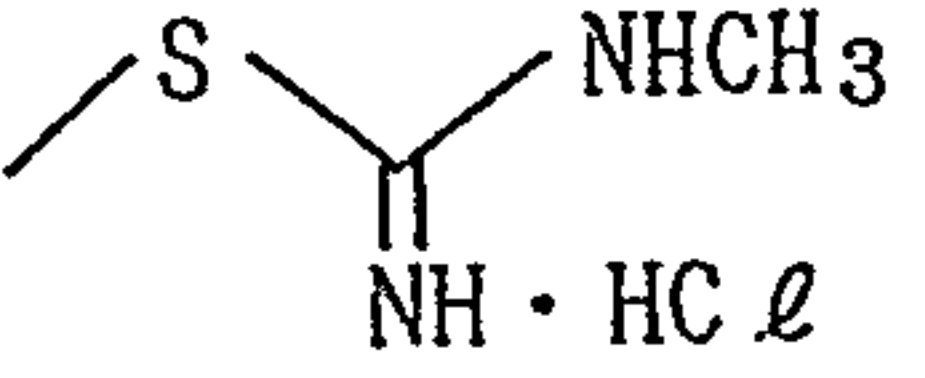
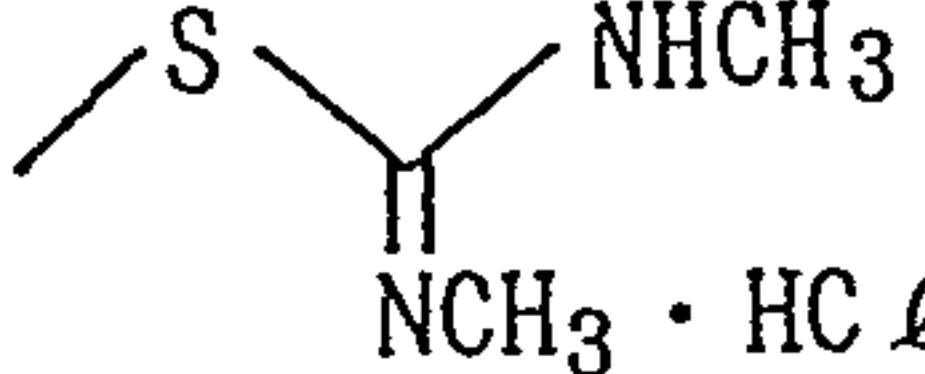
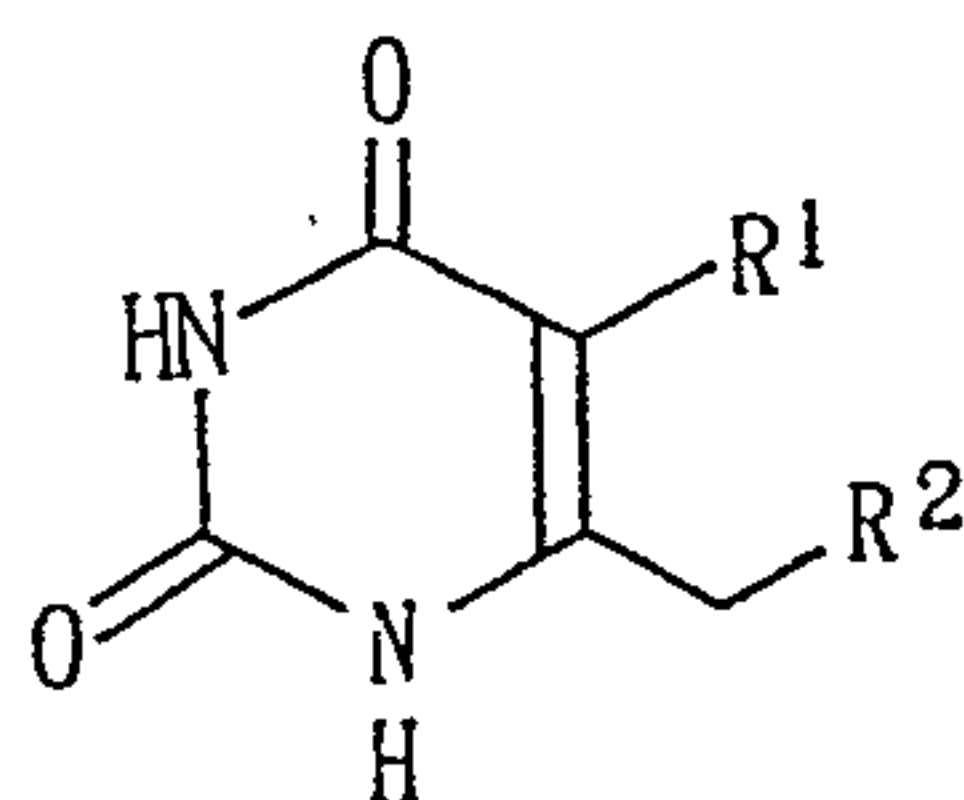
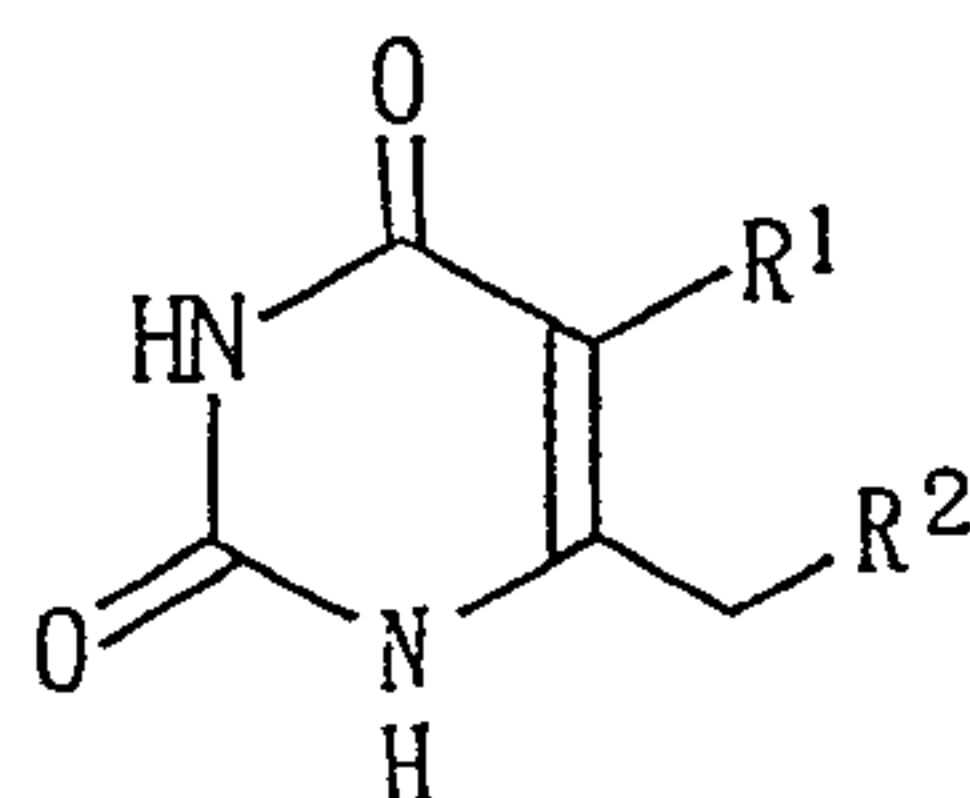
Compound No.	R ¹	R ²	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%)		
					Calculated	Found	
					C	H	N
55	CH ₃		≥160 (decomp'd) C ₇ H ₁₀ N ₄ O ₂ S HCℓ H ₂ O	23	31.29 (31.34)	4.88 (5.06)	20.85 (20.90)
56	CN		≥178 (decomp'd) C ₇ H ₇ N ₅ O ₂ S HCℓ	59	32.13 (32.33)	3.08 (2.97)	26.76 (26.50)
57	Cℓ		≥205 (decomp'd) C ₇ H ₉ N ₄ O ₂ CℓS HCℓ	93	29.49 (29.61)	3.53 (3.60)	19.65 (19.70)
58	Cℓ		≥200 (decomp'd) C ₈ H ₁₁ N ₄ O ₂ CℓS HCℓ	61	32.12 (32.04)	4.04 (4.15)	18.73 (18.54)
59	Cℓ	-NH ₂	210 C ₅ H ₆ N ₃ O ₂ 1/10H ₂ O	81	33.86 (34.28)	3.52 (3.36)	23.69 (23.20)
60	Cℓ	-NHCH ₃	197-199 C ₆ H ₈ N ₃ O ₂ Cℓ	92	38.01 (37.62)	4.25 (4.26)	22.16 (21.94)
61	Cℓ	-N(CH ₃) ₂	≥130 (decomp'd) C ₇ H ₁₀ N ₃ O ₂ Cℓ	22	41.29 (41.25)	4.95 (5.01)	20.64 (20.42)
62	Cℓ	-NHC ₂ H ₅	189-191 C ₇ H ₁₀ N ₃ O ₂ Cℓ 1/5H ₂ O	52	40.57 (40.60)	5.06 (5.11)	20.28 (20.05)
63	Cℓ	-N(C ₂ H ₅) ₂	≥155 (decomp'd) C ₉ H ₁₄ N ₃ O ₂ Cℓ	33	46.66 (46.39)	6.09 (6.28)	18.14 (17.95)

Table 16



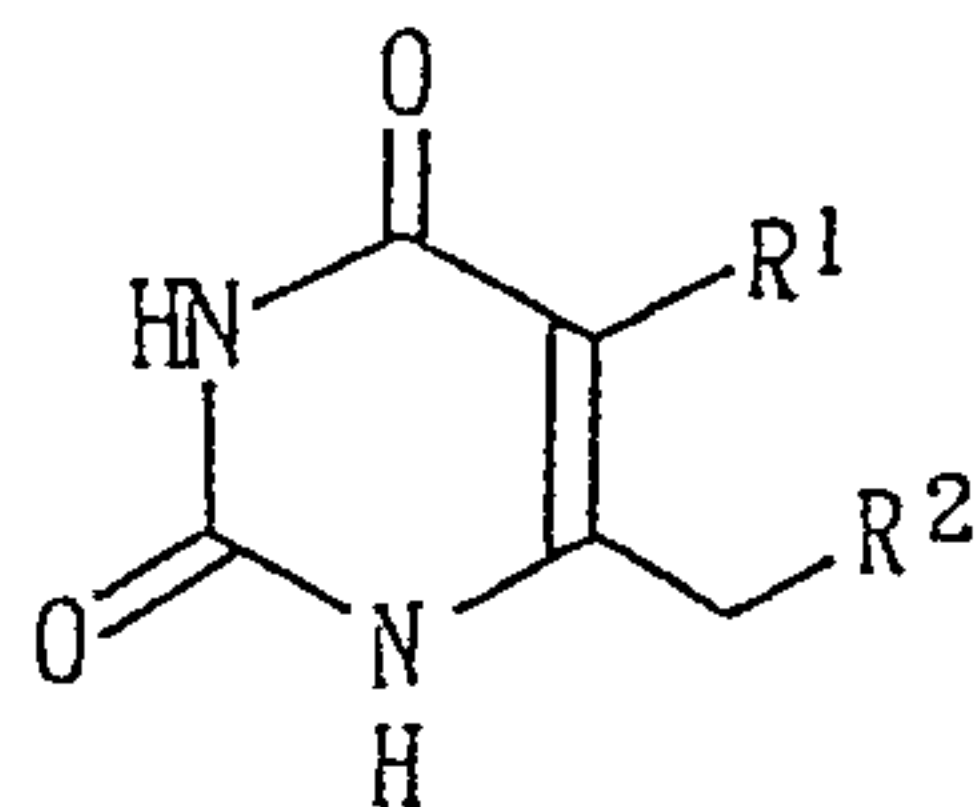
Compound No.	R ¹	R ²	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%)		
					Calculated	Found	
					C	H	N
64	Cℓ	-NH(CH ₂) ₂ CH ₃	193-195 C ₈ H ₁₂ N ₃ O ₂ Cℓ 1/5H ₂ O	75	43.43 (43.60)	5.65 (5.85)	18.99 (18.98)
65	Cℓ	-NHCH(CH ₃) ₂	≥185 (decomp'd) C ₈ H ₁₂ N ₃ O ₂ Cℓ 1/4H ₂ O	6	43.25 (43.31)	5.67 (5.80)	18.91 (18.86)
66	Cℓ	-CH ₂ NHCH ₃	≥256 (decomp'd) C ₇ H ₁₀ N ₃ O ₂ Cℓ 1/2H ₂ O	21	39.54 (39.67)	5.21 (5.21)	19.76 (19.42)
67	Cℓ	-CH ₂ N(CH ₃) ₂	≥263 (decomp'd) C ₈ H ₁₂ N ₃ O ₂ Cℓ	67	44.15 (43.83)	5.56 (5.79)	19.31 (18.84)
68	Cℓ		≥255 (decomp'd) C ₆ H ₈ N ₅ O ₂ Cℓ HCl 1/10H ₂ O	33	28.16 (28.37)	3.62 (3.67)	27.37 (27.13)
69	Cℓ		≥200 (decomp'd) C ₇ H ₁₀ N ₅ O ₂ Cℓ H ₂ O	22	33.68 (33.96)	4.84 (4.97)	28.05 (27.92)
70	Cℓ		≥172 (decomp'd) C ₇ H ₁₀ N ₅ O ₂ Cℓ HCl H ₂ O	42	29.65 (29.39)	4.23 (4.58)	24.17 (24.48)
71	Cℓ		≥189 (decomp'd) C ₈ H ₁₂ N ₅ O ₂ Cℓ HCl H ₂ O	12	32.01 (32.37)	5.04 (5.26)	23.33 (23.14)
72	Cℓ		≥235 (decomp'd) C ₈ H ₁₀ N ₅ O ₂ Cℓ HCl 1/2H ₂ O	25	33.23 (33.26)	4.18 (4.09)	24.22 (24.13)

Table 17



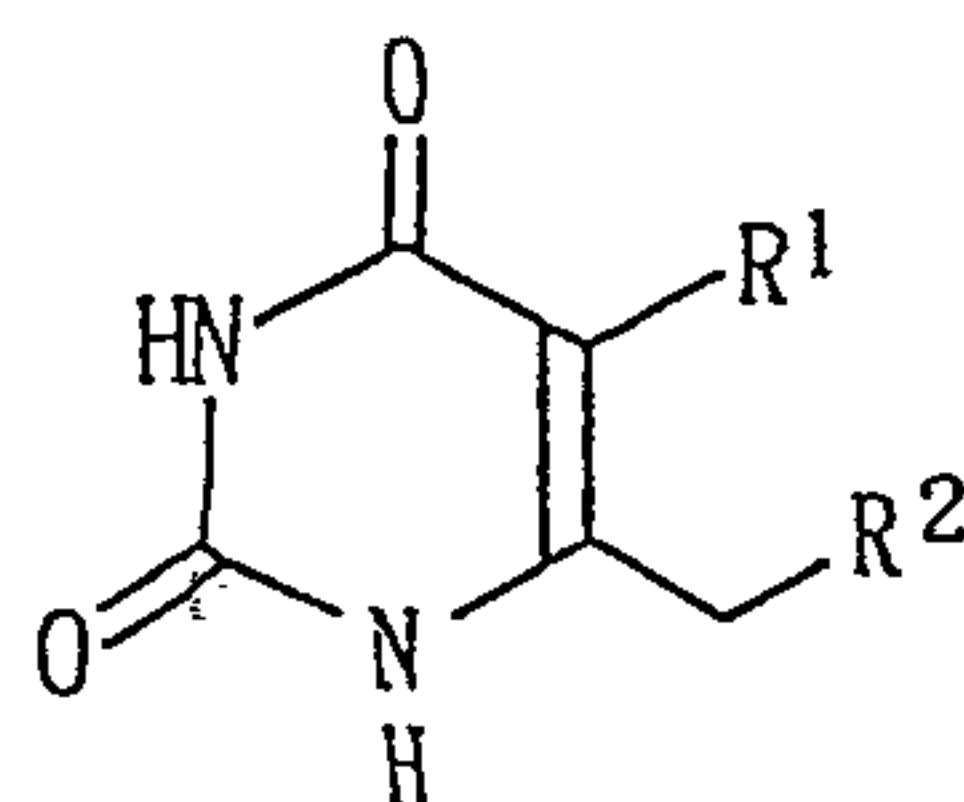
Compound No.	R ¹	R ²	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%)		
					Calculated	(Found)	
					C	H	N
73	Cℓ		≥220 (decomp'd) C ₇ H ₉ N ₄ O ₂ Cℓ HCℓ 3/5H ₂ O	26	31.86 (31.68)	4.28 4.13	21.23 21.49
74	Cℓ		≥210 (decomp'd) C ₉ H ₈ N ₃ O ₂ Cℓ 1/5H ₂ O	24	47.16 (47.63)	3.69 3.70	18.33 17.92
75	Cℓ		≥195 (decomp'd) C ₈ H ₇ N ₄ O ₂ SCℓ HCℓ 2/5C ₂ H ₅ OH	77	33.71 (33.85)	3.34 3.45	17.87 17.71
76	Cℓ		≥220 (decomp'd) C ₈ H ₉ N ₄ O ₂ SCℓ HCℓ	80	32.34 (32.46)	3.39 3.40	18.85 18.98
77	Cℓ		≥210 (decomp'd) C ₉ H ₉ N ₄ O ₂ SCℓ HCℓ	87	34.96 (34.90)	3.26 3.31	18.12 17.98
78	Cℓ		≥215 (decomp'd) C ₇ H ₆ N ₅ O ₂ SCℓ HCℓ	74	28.39 (28.58)	2.38 2.40	23.65 23.49
79	Cℓ		≥223 (decomp'd) C ₁₂ H ₉ N ₄ O ₂ SCℓ HCℓ	81	41.75 (41.82)	2.92 2.83	16.23 16.20

Table 18



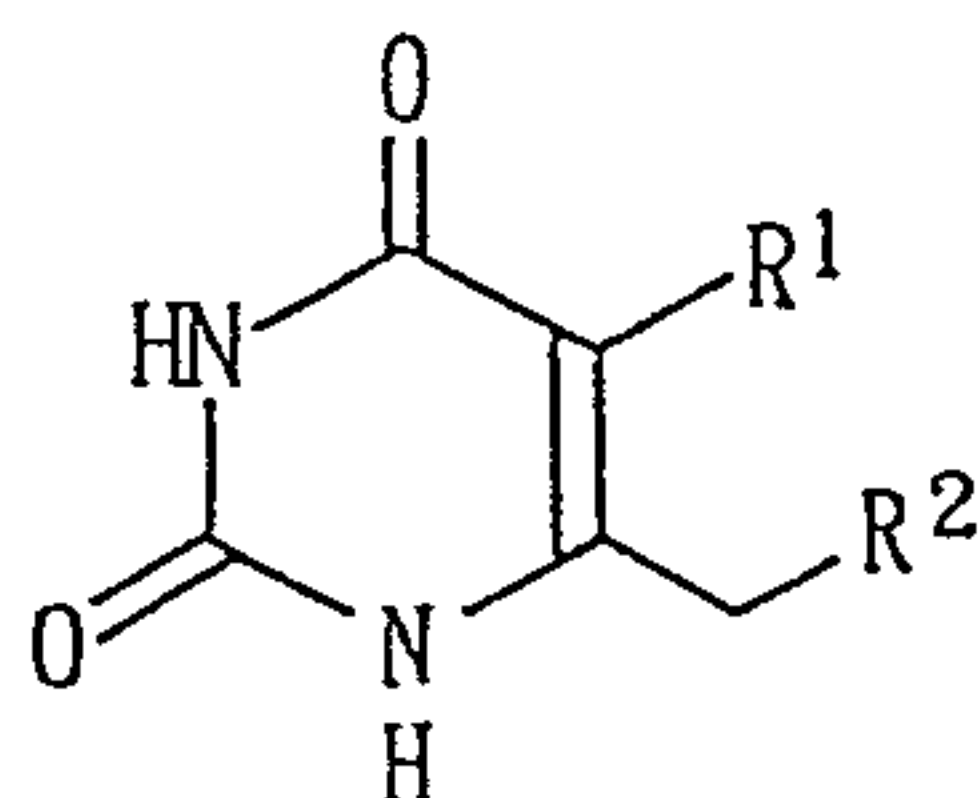
Compound No.	R 1	R 2	Melting point (°C) Molecular formula	Yield (%)	Elemental analysis data (%)		
					Calculated	(Found)	
					C	H	N
80	Cℓ		≥243 (decomp'd) C ₉ H ₇ N ₄ O ₂ SCℓ	96	39.93 (40.01)	2.61 (3.11)	20.70 (20.47)
81	Cℓ		≥195 (decomp'd) C ₇ H ₉ N ₄ O ₂ SCℓ 2/5H ₂ O	61	32.86 (32.81)	3.86 (3.58)	21.89 (21.83)
82	Cℓ		≥145 (decomp'd) C ₈ H ₉ N ₆ O ₂ Cℓ	9	37.44 (37.27)	3.53 (3.50)	32.74 (33.03)
83	Cℓ		≥225 (decomp'd) C ₆ H ₇ N ₄ O ₃ Cℓ H ₂ O	9	30.46 (30.31)	3.83 (3.71)	23.68 (23.04)

Table 19



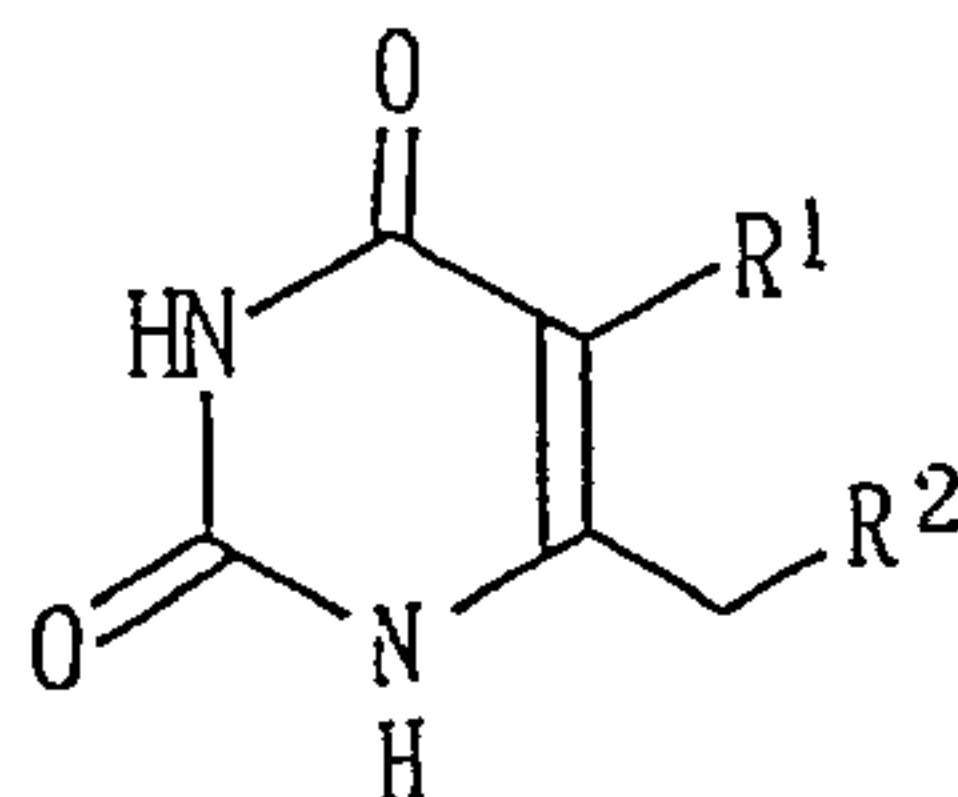
Compound No.	R 1	R 2	NMR spectrum (DMSO-d ₆) δ
1	Cl		1.66-1.76(4H, m), 2.48-2.60(4H, m), 3.52(2H, s)
2	Br		1.64-1.79(4H, m), 2.52-2.63(4H, m), 3.55(2H, s)
3	I		1.64-1.79(4H, m), 2.49-2.57(4H, m), 3.57(2H, s), 11.36(1H, br-s)
4	CN		1.75-1.85(4H, m), 2.80-2.88(4H, m), 3.82(2H, s)
5	CH ₃		1.67-1.75(4H, m), 1.78(3H, s), 2.45-2.55(4H, m), 3.38(2H, s)
6	Cl		1.98(2H, quintet, J=7.0Hz), 3.27(4H, t, J=7.0Hz), 3.46(2H, s), 11.23(1H, br-s)
7	Cl		1.00(6H, d, J=5.9Hz), 1.38(2H, m), 1.83(2H, m), 2.67(2H, m), 3.59(2H, s)
8	Cl		1.56(1H, m), 2.01(1H, m), 2.40-2.50(2H, m), 2.68-2.78(2H, m), 3.55(2H, s), 4.16(1H, m), 4.82(1H, br. s)
9	Cl		1.57-1.82(4H, m), 2.30(1H, q, J=8.0Hz), 2.65(1H, m), 2.92(1H, m), 3.30(1H, dd, J=11.3, 4.6Hz), 3.44(1H, dd, J=11.3, 3.8Hz), 3.55(1H, d, J=5.3Hz), 3.81(1H, d, J=5.3Hz), 4.72(1H, br. s), 11.46(1H, br. s)

Table 20



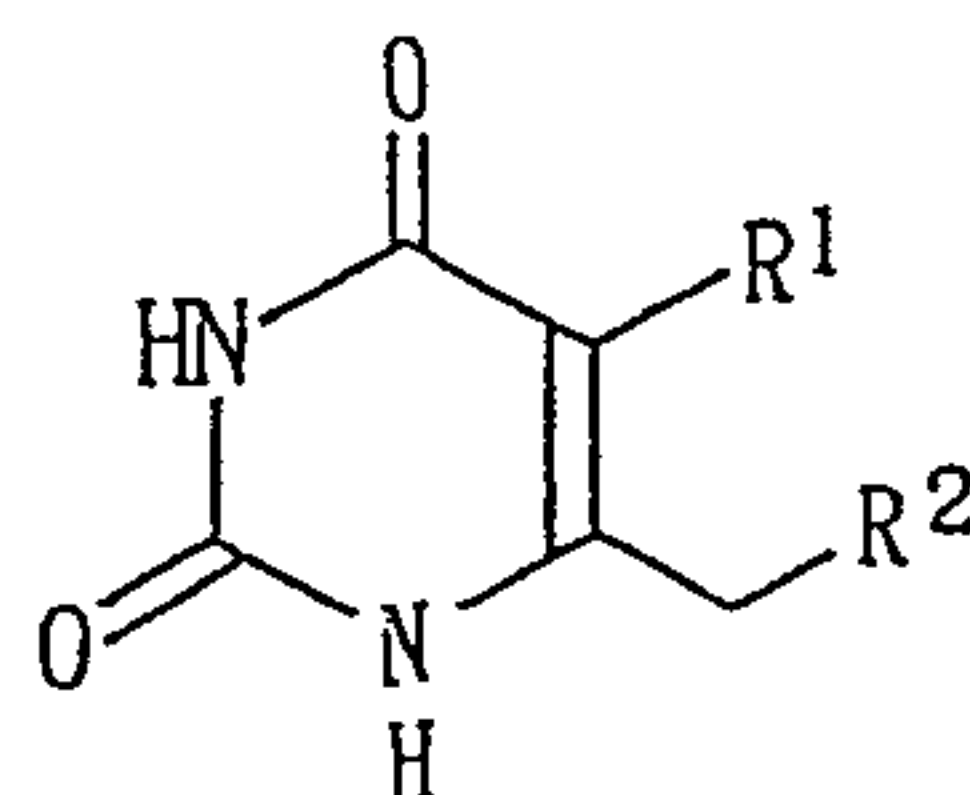
Compound No.	R ¹	R ²	NMR spectrum (DMSO-d ₆) δ
10	Cℓ		1.55-1.85(4H, m), 2.30(1H, q, J=7.8Hz), 2.65(1H, m), 2.92(1H, m), 3.25-3.37(1H, m), 3.44(1H, dd, J=11.2, 3.6Hz), 3.55(1H, d, J=5.3Hz), 3.81(1H, d, J=5.3Hz), 4.67(1H, br. s), 10.60(1H, br. s), 11.51(1H, br. s)
11	Cℓ		(in D ₂ O) 2.14(1H, m), 2.56(1H, m), 3.43-3.68(3H, m), 3.84(1H, dd, J=8.1, 12.7Hz), 4.13(1H, m), 4.37(2H, s)
12	Cℓ		2.61(2H, d, J=9.2Hz), 3.01(2H, d, J=9.2Hz), 3.94(2H, s), 6.92(1H, s), 11.49(1H, s), 11.57(1H, s)
13	Cℓ		1.32-1.56(6H, m), 2.34-2.46(4H, m), 3.36(2H, s), 11.11(1H, br. s)
14	Br		1.31-1.58(6H, m), 2.36-2.53(4H, m), 3.37(2H, s), 11.39(1H, br. s)
15	Cℓ		2.14(3H, s), 2.25-2.45(4H, br. s), 2.45-2.55(4H, br. s), 3.33(2H, s)
16	Cℓ		2.44-2.47(4H, m), 3.40(2H, s), 3.56-3.60(4H, m), 10.84(1H, br. s), 11.53(1H, br. s)
17	Cℓ		1.51-1.66(8H, m), 2.62-2.70(4H, m), 3.54(2H, s)
18	Cℓ		1.45-1.63(10H, m), 2.55-2.65(4H, m), 3.49(2H, s)

Table 21



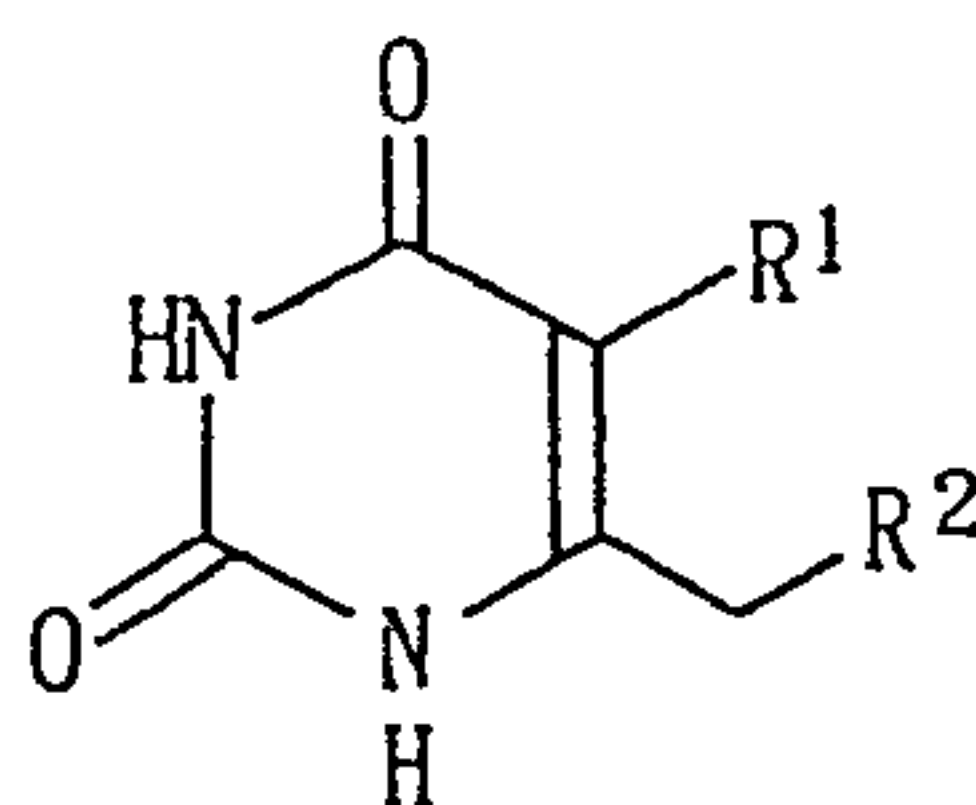
Compound No.	R 1	R 2	NMR spectrum (DMSO-d ₆) δ
19	C _ℓ	-CH ₂ -N	(in CDCl ₃) 1. 89(4H, quintet, J=3.3Hz), 2. 68(4H, t, J=3.3Hz), 2. 82(2H, m), 2. 93(2H, m), 3. 64(2H, s)
20	C _ℓ	NCH ₃ HN · HC _ℓ	3. 46(3H, s), 5. 04(2H, s), 7. 06(1H, d, J=11. 4Hz), 7. 07(1H, d, J=11. 4Hz), 8. 11(2H, br-s), 11. 38(1H, br-s), 11. 70(1H, s)
21	C _ℓ	NC ₂ H ₅ HN · HC _ℓ	1. 26(3H, J=7. 2Hz), 3. 89(2H, q, J=7. 2Hz), 5. 06(2H, s), 7. 07(1H, d, J=2. 6Hz), 7. 15(1H, d, J=2. 6Hz), 8. 19(1H, s), 11. 47(1H, s), 11. 72(1H, s)
22	C _ℓ	O O-S-CH ₃ O	1. 92(1H, m), 2. 26(1H, m), 2. 51(1H, m), 2. 79-2. 94(3H, m), 3. 18(3H, s), 3. 56(2H, s), 5. 15(1H, m), 10. 94(1H, br. s), 11. 54(1H, br. s)
23	C _ℓ	N N-NO ₂ N	5. 44(2H, s), 8. 99(1H, s), 11. 55-11. 65(1H, br. s), 11. 79(1H, br. s)
24	C _ℓ	N	5. 17(2H, s), 6. 29(1H, dd, J=2. 3, 1. 5Hz), 7. 50(1H, d, J=1. 5Hz), 7. 86(1H, d, J=2. 3Hz), 11. 53(1H, s), 11. 68(1H, s)
25	C _ℓ	N · HC _ℓ CH ₃	2. 60(3H, s), 5. 22(2H, s), 7. 54(1H, d, J=2. 0Hz), 7. 61(1H, d, J=2. 0Hz), 11. 77(1H, s)
26	C _ℓ	N NO ₂	5. 54(2H, s), 7. 23(1H, d, J=1. 2Hz), 7. 68(1H, d, J=1. 2Hz), 11. 20-11. 60(1H, br. s), 11. 70(1H, s)
27	C _ℓ	N NO ₂	5. 18(2H, s), 7. 95(1H, d, J=1. 3Hz), 8. 43(1H, d, J=1. 3Hz), 11. 50(1H, s), 11. 70(1H, s)

Table 22



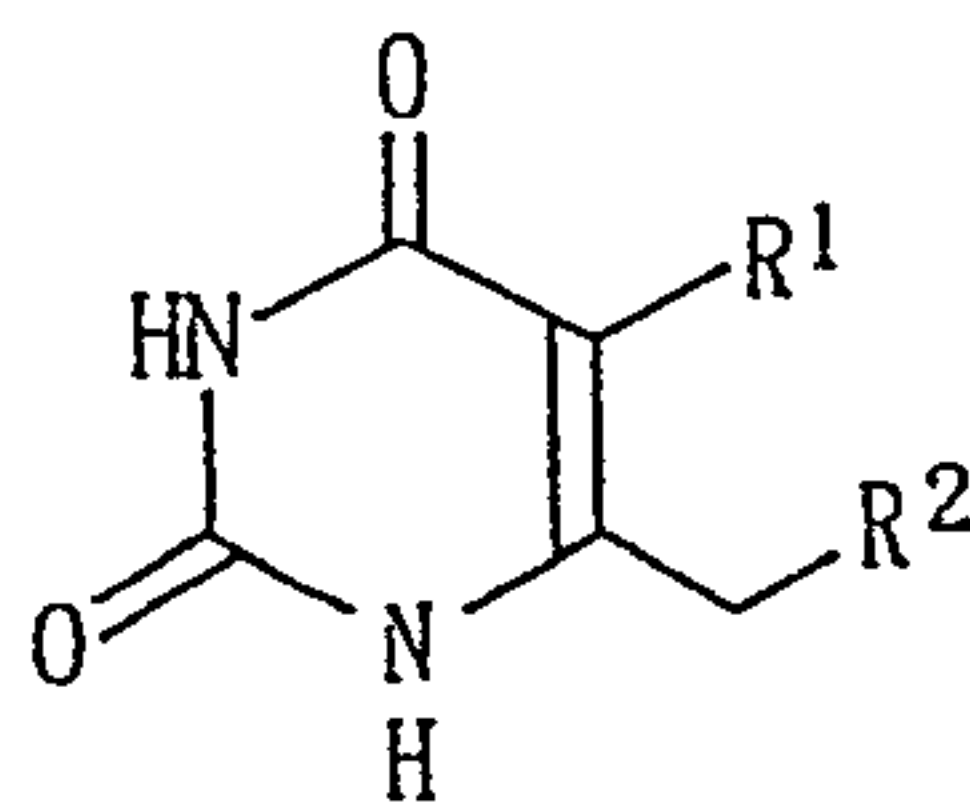
Compound No.	R 1	R 2	NMR spectrum (DMSO-d ₆) δ
28	Cℓ		5.26(2H, s), 8.03(1H, s), 8.64(1H, s), 11.57(1H, s), 11.70(1H, s)
29	Cℓ		2.04(2H, quintet, J=7.6Hz), 2.87(2H, t, J=7.6Hz), 3.59(2H, t, J=7.6Hz), 4.69(2H, s), 9.40(1H, s), 9.75(1H, s), 11.46(1H, s), 11.73(1H, s)
30	Cℓ		2.05(2H, quintet, J=7.7Hz), 2.29(3H, s), 2.87(2H, t, J=7.7Hz), 3.60(2H, t, J=7.7Hz), 4.56(2H, s), 7.11(2H, d, J=7.3Hz), 7.47(2H, d, J=7.3Hz), 9.51(1H, br-s), 11.0-11.8(2H, very br)
31	Br		2.05(2H, quintet, J=7.4Hz), 2.86(2H, t, J=7.4Hz), 3.59(2H, t, J=7.4Hz), 4.63(2H, s), 9.29(1H, br-s), 9.68(1H, br-s), 11.44(1H, s), 11.69(1H, s)
32	CH ₃		1.76(3H, s), 2.02(2H, quintet, J=7.6Hz), 2.84(2H, t, J=7.6Hz), 3.51(2H, t, J=7.6Hz), 4.55(2H, s)
33	CN		2.07(2H, quintet, J=7.6Hz), 2.89(2H, t, J=7.6Hz), 3.65(2H, t, J=7.6Hz), 4.50(2H, s)
34	Cℓ		2.92(3H, s), 3.57(4H, s), 4.27(2H, s)
35	Cℓ		1.11(3H, t, J=7.3Hz), 3.35(2H, q, J=7.3Hz), 3.59(4H, s), 4.26(2H, s), 9.76(1H, s)
36	Cℓ		1.15(6H, d, J=6.3Hz), 3.48-3.62(4H, m), 4.04(1H, septet, J=6.3Hz), 4.26(2H, s)

Table 23



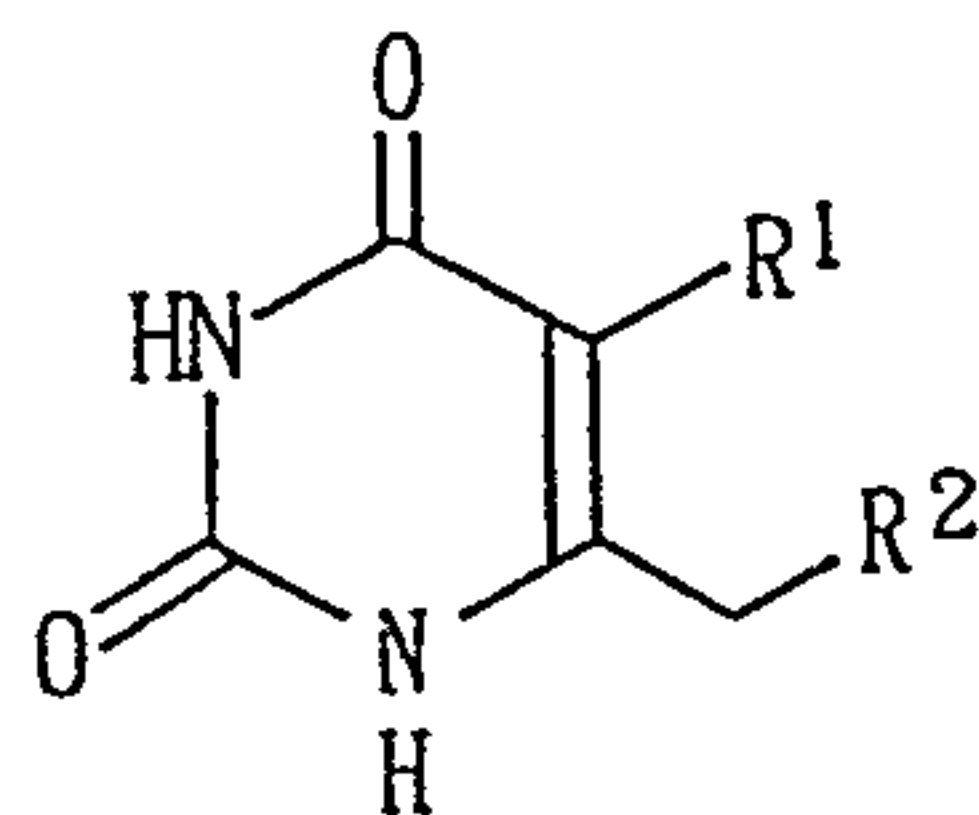
Compound No.	R ¹	R ²	NMR spectrum (DMSO-d ₆) δ
37	Cl	-NH(CH ₂) ₂ NH ₂	2.57-2.72(4H, m), 3.59(2H, s)
38	Br	-NH(CH ₂) ₂ NH ₂	2.63-2.75(4H, m), 3.58(2H, s)
39	I	-NH(CH ₂) ₂ NH ₂	2.58-2.72(4H, m), 3.58(2H, s)
40	Cl	-NH-N(CH ₃) ₂ · HCl	3.39(6H, s), 4.67(2H, s), 6.48(2H, s), 11.49(1H, s), 11.84(1H, s)
41	Cl	-NH(CH ₂) ₂ N(CH ₃) ₂	2.83(6H, s), 3.42(4H, s), 4.12(2H, s), 8.42(1H, br. s), 11.76(1H, br. s)
42	Cl	-NH(CH ₂) ₃ NH ₂	1.59(2H, quintet, J=6.1Hz), 2.58(2H, t, J=6.1Hz), 2.83(2H, t, J=6.1Hz), 3.55(2H, s)
43	Cl	-NH(CH ₂) ₂ CN	2.61(2H, t, J=6.4Hz), 2.74(2H, t, J=6.4Hz), 3.66(2H, s), 6.66(1H, br. s)
44	Cl	-NH(CH ₂) ₃ OH	1.55(2H, quintet, J=6.6Hz), 2.54(2H, t, J=6.6Hz), 3.44(2H, t, J=6.6Hz), 3.63(2H, s)
45	Cl	CH ₃ -N(CH ₂) ₂ OH	2.21(3H, s), 2.49-2.53(2H, m), 3.48(2H, t, J=5.4Hz), 3.52(2H, s), 4.73(1H, br. s), 10.60(1H, br. s), 11.52(1H, br. s)

Table 24



Compound No.	R 1	R 2	NMR spectrum (DMSO-d ₆) δ
46	Cℓ	-NH(CH ₂) ₄ OH	1.38-1.48(4H, m), 2.46-2.51(2H, m), 3.38(2H, t, J=5.6Hz), 3.63(2H, s)
47	Cℓ		3.45-3.70(4H, s), 4.26(2H, s)
48	Br		3.48-3.68(4H, s), 4.25(2H, s)
49	I		3.45-3.68(4H, m), 4.22(2H, s)
50	Cℓ		3.78-3.98(4H, m), 4.60(2H, s), 8.59(1H, s), 10.90(1H, br-s), 11.71(1H, s)
51	Cℓ		5.40(2H, s), 7.74(1H, d, J=1.3Hz), 7.82(1H, d, J=1.3Hz), 9.29(1H, s), 11.74(1H, s), 11.78(1H, br-s)
52	Cℓ		5.45(2H, s), 7.79(1H, s), 8.26(1H, s), 11.69(1H, s), 11.74(1H, s)
53	Cℓ		4.35(2H, s), 9.46(4H, br-s), 11.57(1H, br-s), 11.70(1H, br-s)
54	Br		4.33(2H, s), 9.42(4H, br-s), 11.60(1H, br-s), 11.66(1H, br-s)

Table 25



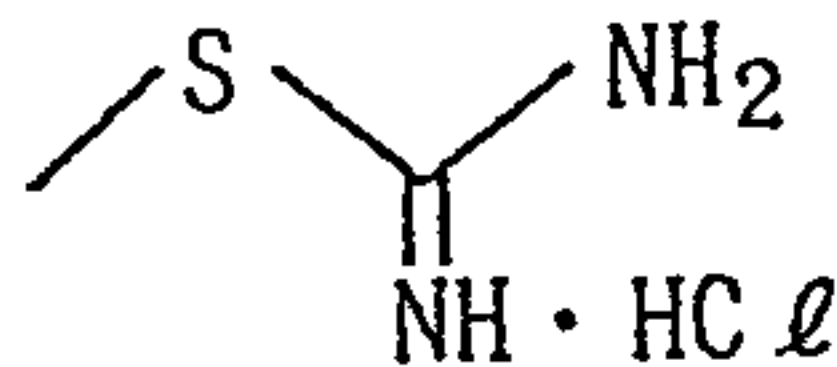
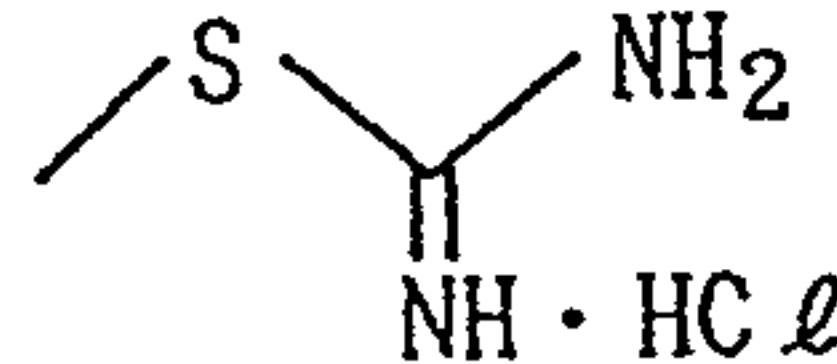
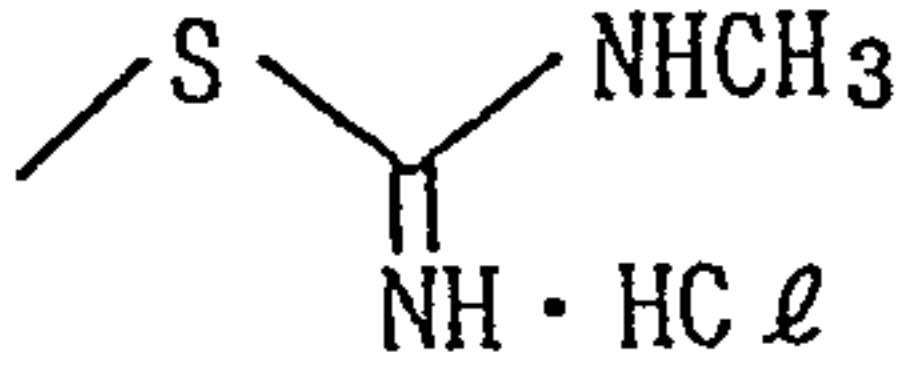
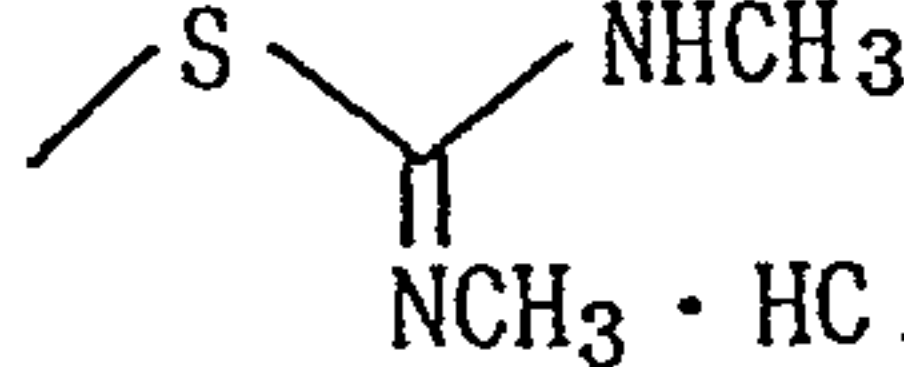
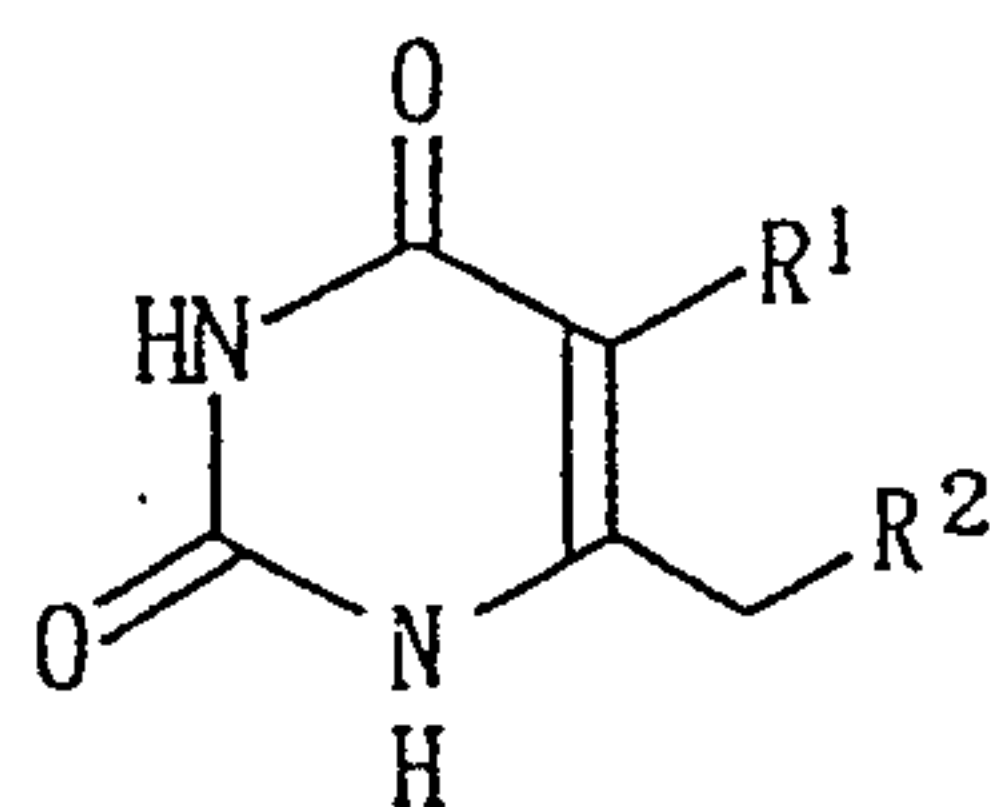
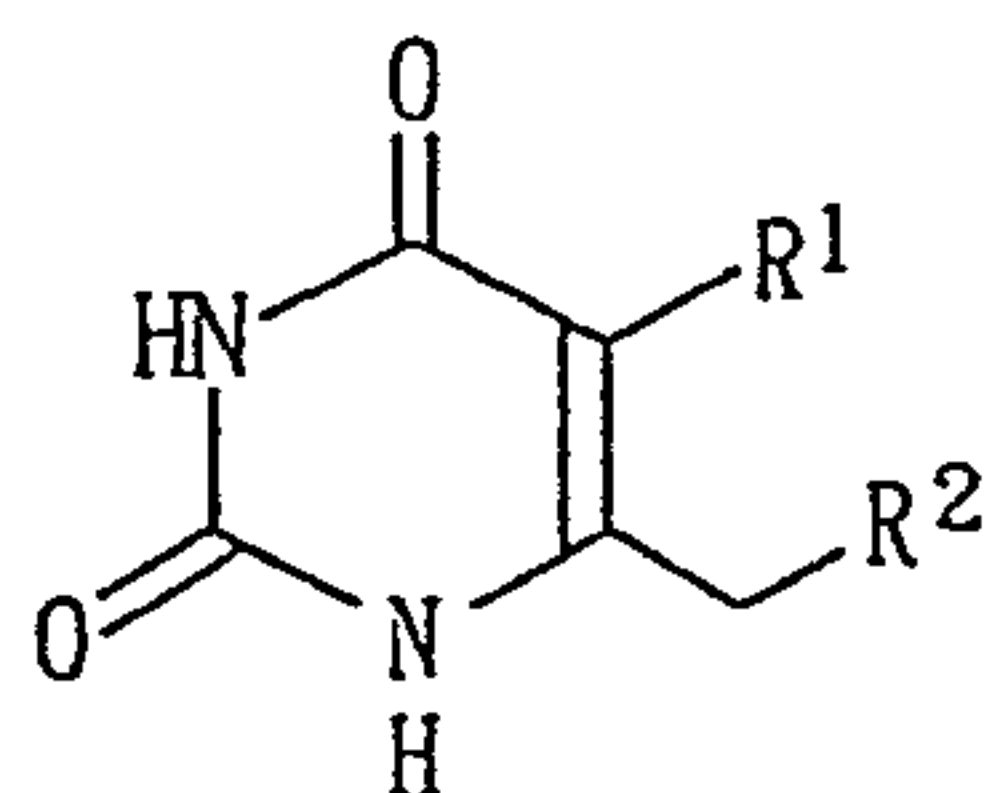
Compound No.	R 1	R 2	NMR spectrum (DMSO-d ₆) δ
55	CH ₃		1. 81(3H, s), 4. 26(2H, s), 9. 39(4H, br-s), 10. 83(1H, br-s), 11. 18(1H, br-s)
56	CN		4. 33(2H, s)
57	Cℓ		2. 90(3H, s), 4. 32(2H, s), 9. 40(1H, br-s), 9. 77(1H, br-s), 10. 20(1H, br-s), 11. 51(1H, br-s), 11. 67(1H, br-s)
58	Cℓ		2. 93(3H, s), 3. 03(3H, s), 4. 27(2H, s), 9. 60(1H, br-s), 9. 94(1H, br-s), 11. 53(1H, br-s), 11. 67(1H, br-s)
59	Cℓ	-NH ₂	3. 60(2H, s)
60	Cℓ	-NHCH ₃	2. 27(3H, s), 3. 61(2H, s)
61	Cℓ	-N(CH ₃) ₂	2. 22(6H, s), 3. 33(2H, s), 11. 41(1H, br. s)
62	Cℓ	-NHC ₂ H ₅	1. 02(3H, t, J=7. 1Hz), 2. 53(2H, q, J=7. 1Hz), 3. 64(2H, s)
63	Cℓ	-N(C ₂ H ₅) ₂	0. 97(6H, t, J=7. 1Hz), 2. 55(4H, q, J=7. 1Hz), 3. 49(2H, s)

Table 26



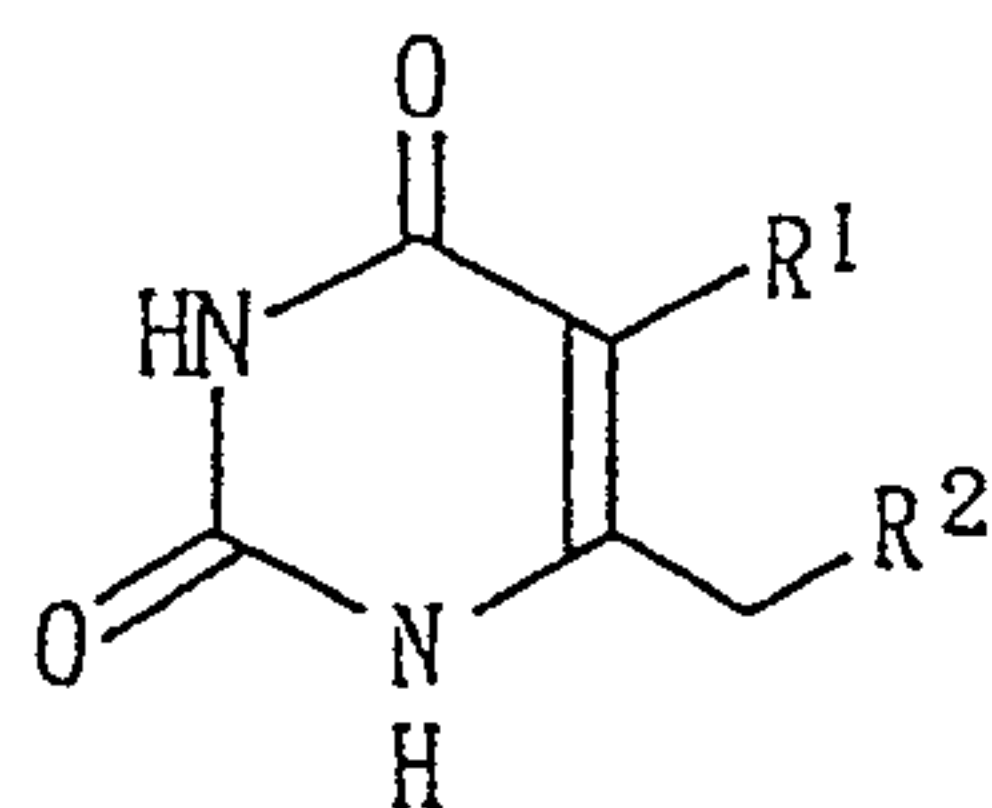
Compound No.	R ¹	R ²	NMR spectrum (DMSO-d ₆) δ
64	Cℓ	-NH(CH ₂) ₂ CH ₃	0.86(3H, t, J=7.3Hz), 1.41(2H, tq, J=7.3, 7.3Hz), 2.44(2H, t, J=7.3Hz), 3.63(2H, s), 8.05(1H, br. s)
65	Cℓ	-NHCH(CH ₃) ₂	0.99(6H, d, J=6.1Hz), 2.70(1H, sept, J=6.1Hz), 3.64(2H, s)
66	Cℓ	-CH ₂ NHCH ₃	2.32(3H, s), 2.67(2H, d, J=6.4Hz), 2.79(2H, d, J=6.4Hz)
67	Cℓ	-CH ₂ N(CH ₃) ₂	(in CDCl ₃) 2.36(6H, s), 2.71-2.82(4H, m)
68	Cℓ		4.29(2H, d, J=5.0Hz), 7.45(3H, br-s), 7.99(1H, t, J=5.0Hz), 11.45(1H, br-s), 11.64(1H, br-s)
69	Cℓ		2.88(3H, s), 4.48(2H, s), 7.65(4H, s), 11.39(1H, br-s), 11.63(1H, br-s)
70	Cℓ		2.54(3H, d, J=4.6Hz), 4.28(2H, d, J=5.5Hz), 7.57(1H, br-s), 7.74-7.82(2H, m), 11.37(1H, br-s), 11.66(1H, s)
71	Cℓ		2.77(6H, d, J=4.6Hz), 4.32(2H, d, J=5.6Hz), 7.66-7.80(3H, m), 11.29(1H, s), 11.67(1H, s)
72	Cℓ		3.62(4H, s), 4.38(2H, d, J=5.6Hz), 8.45(1H, br. s), 8.69(1H, t, J=5.6Hz), 11.44(1H, s), 11.67(1H, s)

Table 27



Compound No.	R ¹	R ²	NMR spectrum (DMSO-d ₆) δ
73	Cℓ		2.19(3H, s), 4.40(2H, d, J=5.0Hz), 9.13(1H, s), 9.63(1H, s), 9.86(1H, d, J=5.0Hz), 11.53(1H, s), 11.73(1H, s)
74	Cℓ		4.92(2H, s), 6.04(2H, d, J=1.8Hz), 6.87(2H, d, J=1.8Hz), 11.61(2H, br. s)
75	Cℓ		4.03(2H, s), 7.81(2H, s), 11.30-11.50(1H, br. s), 11.60(1H, s)
76	Cℓ		3.34(4H, s), 4.41(2H, s), 10.50-10.70(1H, br. s), 11.70(1H, s)
77	Cℓ		3.88(3H, s), 3.99(2H, s), 7.77(1H, d, J=1.7Hz), 7.90(1H, d, J=1.7Hz), 11.41(1H, s), 11.60(1H, s)
78	Cℓ		4.11(2H, s), 8.55(1H, s), 11.33(1H, s), 11.58(1H, s)
79	Cℓ		4.35(2H, s), 7.33-7.63(4H, m), 11.63(1H, s)

Table 28



Compound No.	R ¹	R ²	NMR spectrum (DMSO-d ₆) δ
80	Cℓ		4.31(2H, s), 7.30(1H, t, J=5.0Hz), 8.69(2H, d, J=5.0Hz), 11.36(1H, s), 11.61(1H, s)
81	Cℓ		2.77-2.87(3H, br. s), 4.49-4.54(2H, br. s), 7.55-8.20(2H, br. s), 10.80-11.00(1H, br. s), 11.55-11.65(1H, br. s)
82	Cℓ		2.72(3H, d, J=3.6Hz), 4.21(2H, d, J=4.6Hz), 7.17-7.35(2H, m), 11.03(1H, s), 11.58(1H, s)
83	Cℓ		4.09(2H, d, J=5.9Hz), 5.86(2H, s), 6.40(1H, t, J=5.9Hz), 10.70-10.95(1H, br. s), 11.54(1H, s)

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Preparation Example 1 (Tablets)

Table 29

	Compound 29	25.0 mg
	Lactose	8.0
5	Crystalline cellulose	4.0
	Magnesium stearate	1.0
	Talc	1.0
	Corn starch	3.5
	Hydroxypropyl methylcellulose	2.5
10	Tablet	45.0 mg

In accordance with the above formula, tablets were prepared in a manner known *per se* in the art.

Preparation Example 2 (Granules)

Table 30

15	Compound 29	50.0 mg
	Lactose	85.0
	Corn starch	100.0
	Hydroxypropyl cellulose	3.0
	Granules	238.0 mg

20 In accordance with the above formula, granules were prepared in a manner known *per se* in the art.

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Preparation Example 3 (Capsules)

Table 31

	Compound 29	50.0 mg
	Lactose	24.0
5	Crystalline cellulose	13.0
	Magnesium stearate	1.0
	Capsule	88.0 mg

In accordance with the above formula, capsules were prepared in a manner known *per se* in the art.

10 Test 1 (Thymidine Phosphorylase Inhibiting Effects)

Inhibitory effects of some uracil derivatives (I) or salts thereof on thymidine phosphorylase were each determined by measuring the formation of [6-³H]thymine from [6-³H]thymidine in the below-described manner.

15 Namely, reacted at 37°C for 5 minutes were 0.05 ml of a 3 mM aqueous solution of thymidine (which contained 74 Bq/ml of [6-³H]thymidine), 0.05 ml of a 0.5 M potassium phosphate buffer (pH 7.4), 0.05 ml of a solution of one of the test compounds at one of vari-
20 ous concentrations or purified water as a control, and 0.1 ml of a solution of thymidine phosphorylase obtained from human placenta in a highly purified form, 0.25 ml in total. Immediately after the reaction, the
25 reaction mixture was heated for 2 minutes in a boiling water bath of 100°C to terminate the reaction, followed

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by centrifugation at 3000 rpm for 10 minutes. Subsequent to the centrifugation, a portion (10 μ l) of the resultant supernatant was spotted on a silica gel 60F₂₅₄ plate of 2.0 x 10 cm and was then dried in air.

5 The plate was placed in a developer bath which was filled with chloroform-methanol-acetic acid (v/v/v, 17:3:1), so that the spot was developed to a position of about 8 cm. The silica gel plate was pulled out and then dried in air. Under a UV lamp, a position (R_f

10 0.46) of [6-³H]thymine was marked. Silica gel was scraped off from the position by a stainless steel spatula and then placed in a vial for liquid scintillation. One hundred microliters of 2 N HCl were added to moisten the silica gel, whereby [6-³H]thymine was

15 liberated from the gel. Thereafter, 10 ml of scintillator ("AQUASOL-II", product of Amersham International plc) were added, followed by thorough agitation with a stirrer. Radioactivity was then measured by a scintillation counter ("WALLAC SYSTEM 1410", manufactured by

20 Pharmacia AB).

Inhibitory activities of the test compound were determined by the following formula:

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Inhibition rate (%) =

$$\left(1 - \frac{\text{Amount of [6-}^3\text{H]thymine in the presence of the test solution (dpm)} - \text{Blank (dpm)}}{\text{Amount of [6-}^3\text{H]thymine in the control (dpm)} - \text{Blank (dpm)}} \right) \times 100$$

The concentration of each test solution which inhibited 50% of the amount of [6-³H]thymine formed by thymidine phosphorylase is shown as IC₅₀ (μM) in Table 32.

To compare inhibitory activities, IC₅₀s of 6-amino-5-chlorouracil, 6-amino-5-bromouracil, 6-amino-thymine, acyclothyridine and 3-cyano-2,6-dihydroxypyrimidine were also measured and calculated.

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Table 32

Compound No. or Compound Name	IC ₅₀ (μM)
1	2.2
2	0.51
3	1.3
6	2.6
20	0.24
29	0.035
32	0.12
33	0.017
34	0.046
47	0.013
48	0.030
50	1.2
51	1.0
53	0.35
56	0.10
57	0.15
68	0.27
73	1.5
6-Amino-5-chlorouracil	12
6-Amino-5-bromouracil	19
6-Aminothymine	100
Acyclothymidine	>1000
3-Cyano-2,6-dihydroxypyridine	130

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Test 2 (Effects of Life Prolongation on Liver
Metastasis Model)

Effects of life prolongation were assessed using
a liver metastasis model system consisting of BALB/c-
5 nu/nu male mice (seven weeks old) each of which had
been transplanted in the spleen thereof with 1×10^6
cells/mouse of TMK-1 (human gastric cancer) cells.

Specific experimental procedures were carried out
by modifying the method proposed by Morikawa et al. in
10 Cancer Research, 48, 1943-1948 (1988). Described spe-
cifically, cells which had been cultured *in vitro* were
collected with 0.25%(w/v) trypsin-0.2%(w/v) EDTA and
were then washed with a physiological phosphate buffer.
The cells were next counted, followed by dilution to 1
15 $\times 10^6$ cells/50 μ l. Under anesthetization with 30 mg/kg
of "Nembutal", each of the mice was incised at its left
abdominal region and the spleen was then pulled out.
The cell suspension of 10^6 cells/50 μ l which had been
prepared above was injected in an amount of 50 μ l into
20 the spleen by a syringe fitted with a 28-gauge injec-
tion needle. After the mouse was left over for 2
minutes, the blood vessel to the spleen was tied at two
positions by ligating clips, respectively, and the
spleen was cut off. The excised abdominal region was
25 closed with a suturing stapler. Compound No. 29 of the

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present invention, in a form dissolved in distilled water, was orally administered everyday for 42 days from the day following the transplant. Using the increase of life span (ILS%) of a control as a reference, an assessment was conducted by observing the mouse for 120 days after the transplant of the cells to confirm its survival. The increase of life span (ILS%) was calculated in accordance with the following formula. The results are presented in Table 33.

10 Increase of life span (ILS%) =

$$\left(\frac{\text{Average number of survival time in the drug-administered group}}{\text{Average number of survival time in control}} - 1 \right) \times 100$$

Compound No. 29 was found to significantly prolong the period of survival and, compared with the control, prolonged the period of survival by 39.6% in a 50 mg/kg/day administration group and by 43.2% in a 100 mg/kg/day administration group.

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Table 33

Group	N	Daily dose (mg/kg/day)	Average # of survival time (days)	ILS (%)
Control	9	-	63.4	-
Drug- administered	8	50	88.5	39.6
Drug- administered	9	100	90.8	43.2

Test 3 (Metastasis Inhibiting Effects on Liver
Metastasis Model)

About 100 mm³ of human colon cancer strain Co-3
were transplanted to the cecum of each SPF KSN-nu/nu
male mouse (seven weeks old). Two weeks after the
transplant, a primary carcinoma lesion was removed by
surgically cutting off the cecum. On the fourth day
after the removal, Compound No. 29 was suspended in a
0.5% (w/v) hydroxypropyl methylcellulose solution (0.5%
HPMC solution), and the thus-prepared suspension was
orally administered. The administration was conducted
for 6 courses, each consisting of administration of 5
straight days followed by a suspension of administra-
tion for 2 days. To mice in a control, only 0.5% (w/v)
hydroxypropyl methylcellulose solution was orally ad-
ministered. On the day following the completion of the
administration, each mouse was sacrificed and

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metastasis to the liver was determined based on autopsy. The results are presented in Table 34.

Compared with the control, Compound No. 29 inhibited liver metastasis by 50% in an 18.4 mg/kg/day administration group and by 75% in a 36.9 mg/kg/day administration group.

Table 34

Group	N	Daily dose (mg/kg/day)	Number of metastasized mice	Metastasis inhibition rate(%)
Control	6	-	4/6	-
Drug-administered	6	18.4	2/6	50
Drug-administered	6	36.9	1/6	75

Capability of Exploitation in Industry

The uracil derivatives (1) and their salts have the merits that they have extremely great thymidine phosphorylase inhibiting activities compared with conventionally-known thymidine phosphorylase inhibitors and inhibit cancerous metastases extremely well. Accordingly, the cancerous metastasis inhibitors according to the present invention have extremely high utility.

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CLAIMS

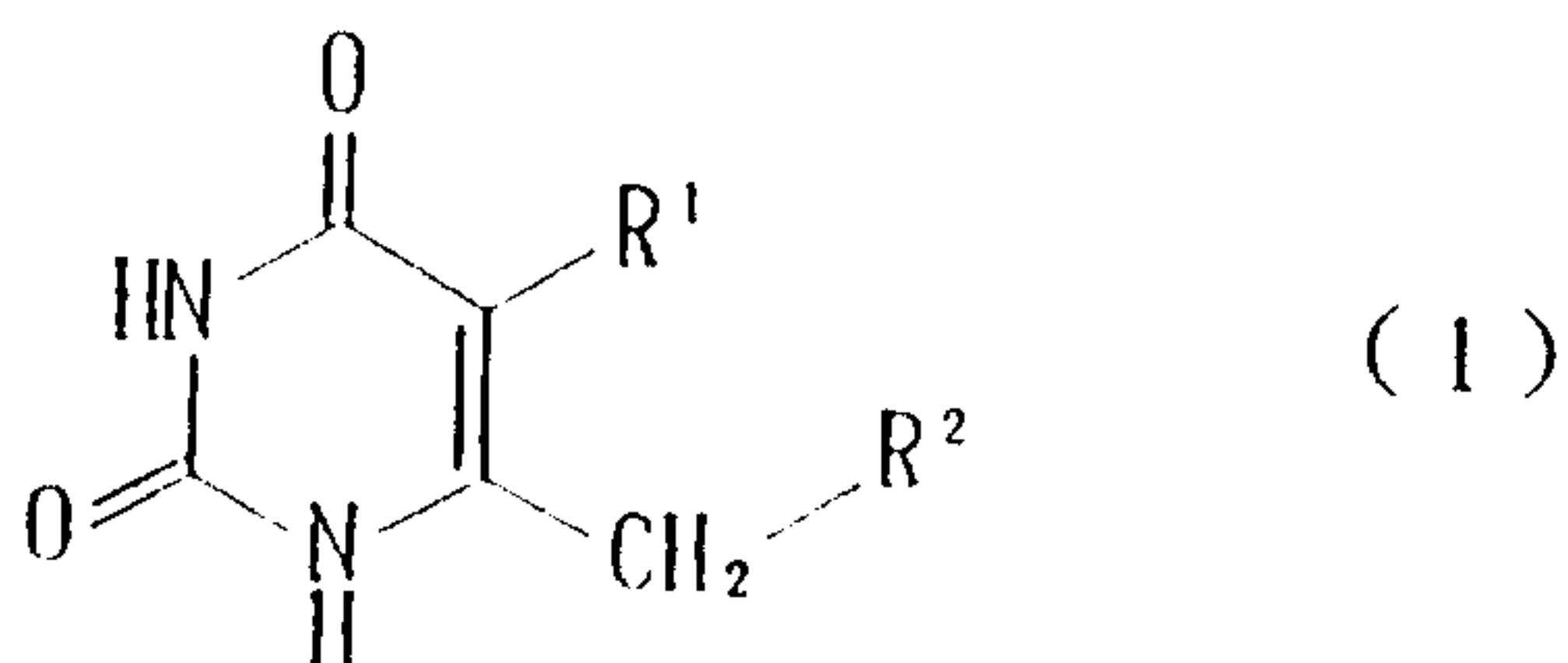
1

2

3

1. The use of a uracil derivative
represented by the following formula (1):

4



5 wherein R^1 represents a chlorine, bromine or iodine
6 atom or a cyano or lower alkyl group; and R^2 represents
7 a 4-8 membered heterocyclic group having 1-3 nitrogen
8 atoms, which may be substituted by one or more lower
9 alkyl, imino, hydroxyl, hydroxymethyl, methanesul-
10 fonyloxy, amino or nitro groups; an amidinothio group,
11 one or more of the hydrogen atom(s) on one or both of
12 the nitrogen atoms of which may each be substituted by
13 a lower alkyl group; a guanidino group, one or more of
14 the hydrogen atom(s) on one, two or all of the nitrogen
15 atoms of which may each be substituted by a lower alkyl
16 or cyano group; a (lower alkyl)amidino group; an amino
17 group, one or both of the hydrogen atoms on the
18 nitrogen atom of which may each be substituted by a
19 lower alkyl group; a group $-CH_2N(R^a)R^b$ in which R^a and
20 R^b may be the same or different and each represents a
21 hydrogen atom or a lower alkyl group or R^a and R^b may

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22 form a pyrrolidine ring together with the nitrogen atom
23 to which R^a and R^b are bonded; a group $-NH-(CH_2)_m-Z$ in
24 which Z represents an amino group, one or both of the
25 hydrogen atoms on the nitrogen atom of which may each
26 be substituted by a lower alkyl group, or a cyano
27 group, and m stands for an integer of from 0 to 3; a
28 group $NR^c(CH_2)_n-OH$ in which R^c represents a hydrogen
29 atom or a lower alkyl group, and n stands for a natural
30 number of from 1 to 4; a group $-X-Y$ in which X
31 represents S or NH, and Y represents a 2-imidazolin-2-
32 yl, 2-imidazolyl, 1-methylimidazol-2-yl, 1,2,4-triazol-
33 3-yl, 2-pyrimidyl or 2-benzimidazolyl group which may
34 be substituted by one or more lower alkyl groups; or a
35 ureido or thioureido group, one or more of the hydrogen
36 atom(s) on one or both of the nitrogen atoms of which
37 may each be substituted by a lower alkyl group; or a
38 salt thereof, as a cancerous metastasis inhibitor.

1 2. The use according to claim 1,
2 wherein in formula (1), the group
3 represented by R^2 is a 4-8 membered heterocyclic group
4 having 1-3 nitrogen atoms, which may be substituted by
5 one or more lower alkyl, imino, hydroxyl, hydroxy-
6 methyl, methanesulfonyloxy, amino or nitro groups; an
7 amidinothio group, one or more of the hydrogen atom(s)
8 on one or both of the nitrogen atoms of which may each

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9 be substituted by a lower alkyl group; a guanidino
10 group, one or more of the hydrogen atom(s) on one, two
11 or all of the nitrogen atoms of which may each be sub-
12 stituted by a lower alkyl or cyano group; or a (lower
13 alkyl)amidino group.

1 3. The use according to claim 1
2 or 2, wherein in formula (1), the 4-8
3 membered heterocyclic group represented by R^2 and hav-
4 ing 1-3 nitrogen atoms is a 1-azetidiny1, 1-
5 pyrrolidinyl, 2-pyrrolin-1-yl, 3-pyrrolin-1-yl, 1-
6 pyrrolyl, 1-pyrazolidinyl, 2-pyrazolin-1-yl, 3-
7 pyrazolin-1-yl, 4-pyrazolin-1-yl, 1-pyrazolyl, 1-
8 imidazolidinyl, 2-imidazolin-1-yl, 3-imidazolin-1-yl,
9 4-imidazolin-1-yl, 1-imidazolyl, 1,2,3-triazol-1-yl,
10 1,2,4-triazol-1-yl, piperidino, 1-piperazyl, mor-
11 pholino, 1-perhydroazepinyl or 1-perhydroazocinyl
12 group.

1 4. The use according to claim 1
2 or 2, wherein in formula (1), the 4-8
3 membered heterocyclic group having 1-3 nitrogen atoms,
4 which is represented by R^2 and may be substituted by
5 one or more lower alkyl, imino, hydroxyl, hydroxy-
6 methyl, methanesulfonyloxy, amino or nitro groups, is a
7 1-azetidiny1, 1-pyrrolidinyl, 2,5-dimethylpyrrolidin-1-
8 yl, 2-iminopyrrolidin-1-yl, 3-hydroxypyrrolidin-1-yl,

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9 2-hydroxymethylpyrrolidin-1-yl, 3-methanesulfonyloxy-
 10 pyrrolidin-1-yl, 3-aminopyrrolidin-1-yl, 1-pyrrolyl, 2-
 11 pyrazolin-1-yl, 1-pyrazolyl, 2-iminoimidazolidin-1-yl,
 12 2-imino-3-methylimidazolidin-1-yl, 2-imino-3-ethyl-
 13 imidazolidin-1-yl, 2-imino-3-isopropylimidazolidin-1-
 14 yl, 2-imidazolin-1-yl, 2-imino-3-methyl-4-imidazolin-1-
 15 yl, 2-imino-3-ethyl-4-imidazolin-1-yl, 1-imidazolyl, 2-
 16 methylimidazol-1-yl, 2-nitroimidazol-1-yl, 4-nitro-
 17 imidazol-1-yl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl,
 18 3-nitro-1,2,4-triazol-1-yl, piperidino, 4-methyl-
 19 piperazin-1-yl, morpholino, 1-perhydroazepinyl or 1-
 20 perhydroazocinyl group.

1 5. The use according to claim 1
 2 or 2, wherein in formula (1), the group
 3 represented by R^2 is a 1-azetidiny1, 1-pyrrolidinyl, 2-
 4 iminopyrrolidin-1-yl, 2-iminoimidazolidin-1-yl, 2-
 5 imino-3-methylimidazolidin-1-yl, 2-imino-3-ethyl-
 6 imidazolidin-1-yl, 2-imino-3-isopropylimidazolidin-1-
 7 yl, 2-imidazolin-1-yl, 2-imino-3-methyl-4-imidazolin-1-
 8 yl, 2-imino-3-ethyl-4-imidazolin-1-yl, 1-imidazolyl,
 9 amidinothio, N^1 -methylamidinothio, N^1, N^2 -dimethyl-
 10 amidinothio, 1-guanidino, 1-methylguanidino, 3-methyl-
 11 guanidino, 2,3-dimethylguanidino or acetoamidino group.

1 6. The use according to claim 1,
 2 wherein in formula (1), the group

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3 represented by R^1 is a chlorine or bromine atom or a
 4 cyano group, and the group represented by R^2 is a 1-
 5 pyrrolidinyl, 1-azetidiny, 2-iminopyrrolidin-1-yl, 2-
 6 iminoimidazolidin-1-yl, 1-imidazolyl, amidinothio or 1-
 7 guanidino group.

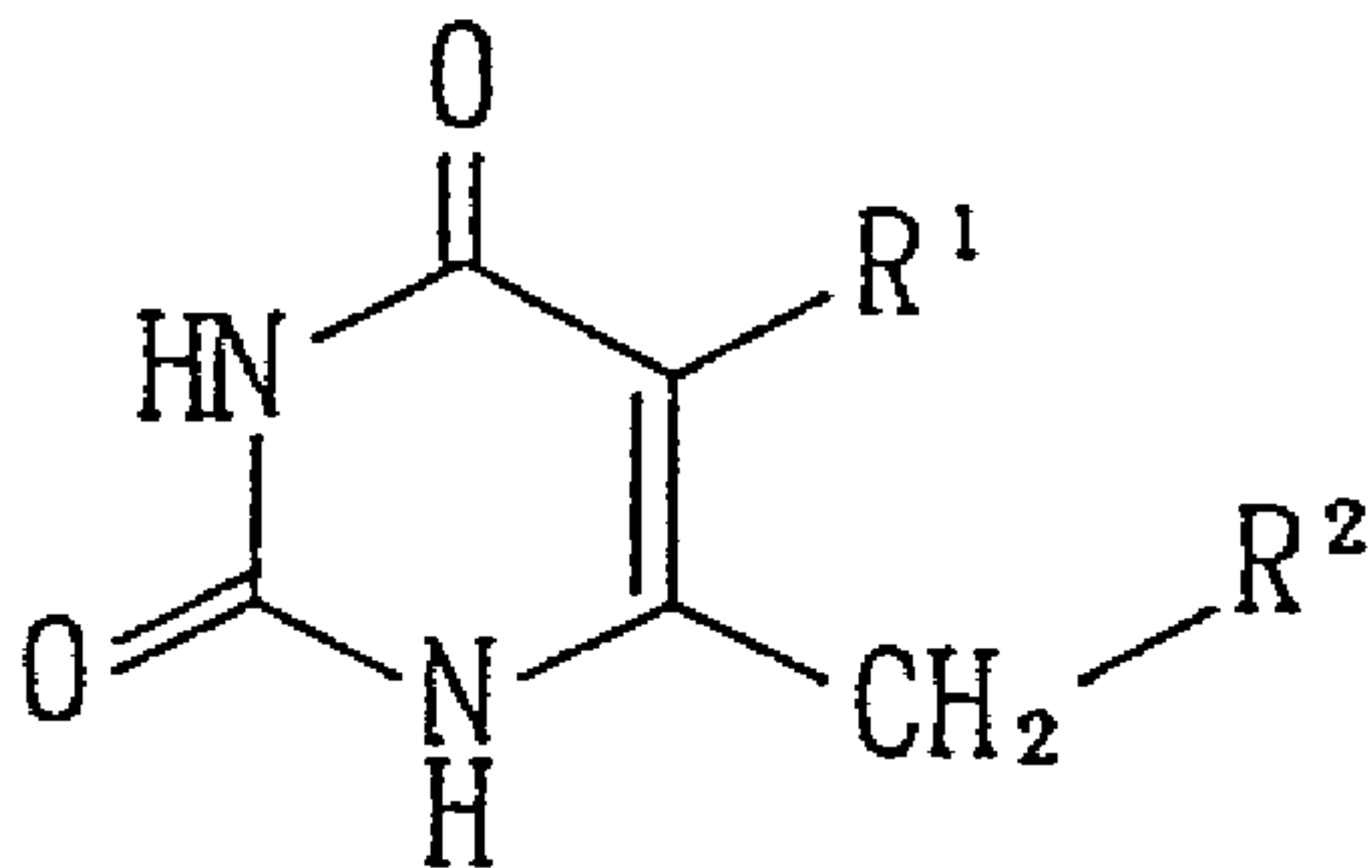
1 7. The use according to claim 1,
 2 wherein the compound represented by the
 3 formula (1) is selected from 5-chloro-6-(1-
 4 pyrrolidinylmethyl)uracil, 5-bromo-6-(1-pyrrolidinyl-
 5 methyl)uracil, 5-chloro-6-(1-azetidinylmethyl)uracil,
 6 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydro-
 7 chloride, 5-bromo-6-(1-(2-iminopyrrolidinyl)methyl)-
 8 uracil hydrochloride, 5-cyano-6-(1-(2-imino-
 9 pyrrolidinyl)methyl)uracil, 5-chloro-6-(1-(2-
 10 iminoimidazolidinyl)methyl)uracil, 5-bromo-6-(1-(2-
 11 iminoimidazolidinyl)methyl)uracil, 5-chloro-6-(1-
 12 imidazolylmethyl)uracil hydrochloride, 2-(5-chloro-
 13 uracil-6-ylmethyl)isothiourea hydrochloride, 2-(5-
 14 cyanouracil-6-ylmethyl)isothiourea hydrochloride or 5-
 15 chloro-6-(1-guanidino)methyluracil hydrochloride.

1 8. A composition comprising the uracil
 2 derivative of formula (1) or the salt thereof as defined
 3 in any one of claims 1-7 and a pharmaceutically
 4 acceptable carrier, for use as a cancerous metastasis
 inhibitor.

1 9. Use of the uracil derivative
 of formula (1) or the salt

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2 thereof as defined in any one of claims 1-7 for the pro-
3 duction of a cancerous metastasis inhibitor.



(1)