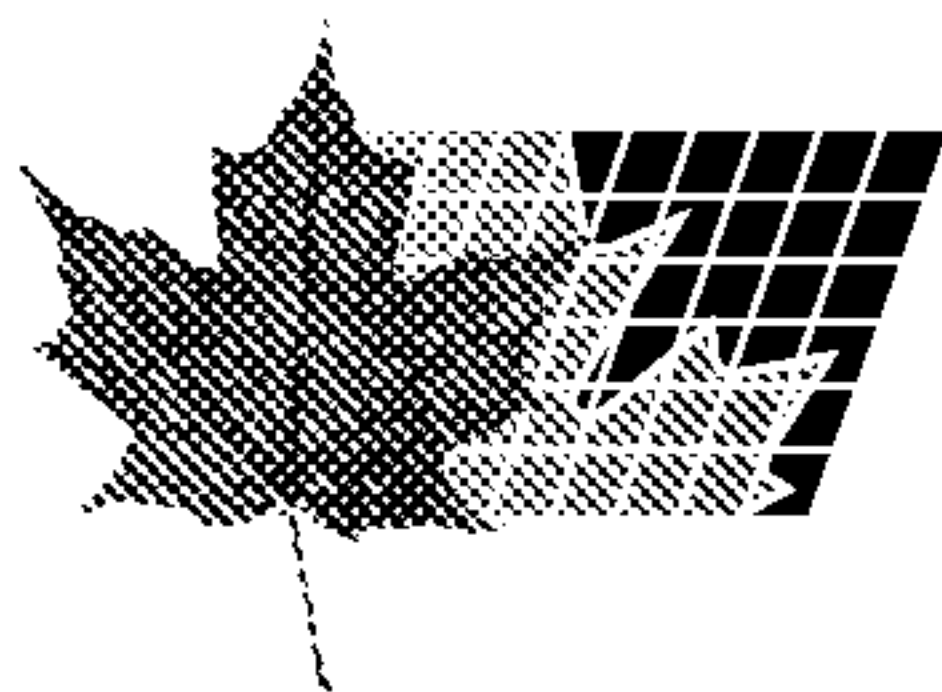




(11) (21) (C) **2,010,009**
(22) 1990/02/14
(43) 1990/08/15
(45) 2000/08/08

(72) Naka, Takehiko, JP
(72) Nagaoka, Akinobu, JP
(73) TAKEDA CHEMICAL INDUSTRIES, LTD., JP

(51) Int.Cl.⁵ C07D 487/14, A61K 31/505

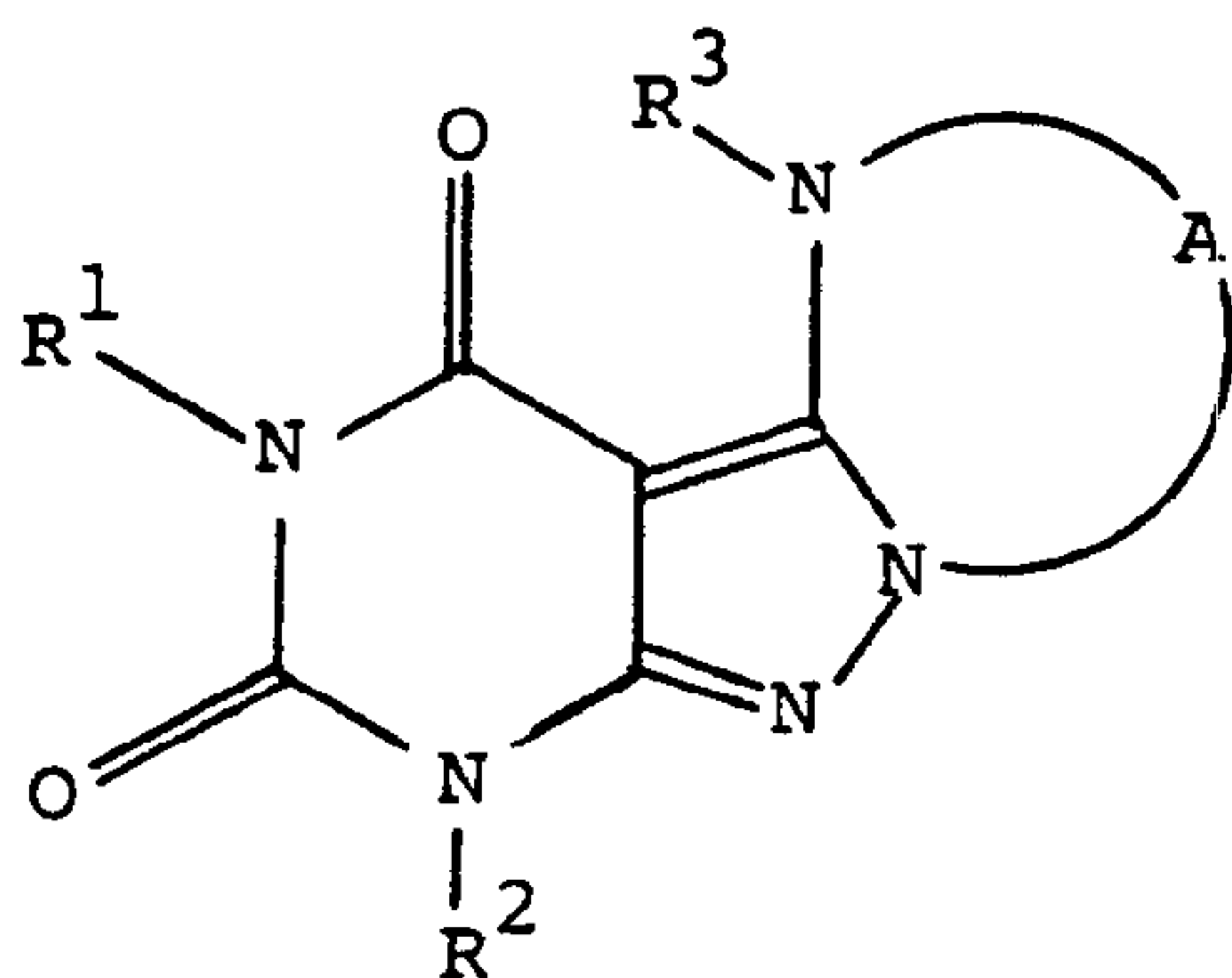
(30) 1989/02/15 (037126-1989) JP

(30) 1989/10/24 (277386-1989) JP

(30) 1990/01/08 (2215/1990) JP

(54) **DERIVES TRICYCLIQUES DE PYRIMIDINE FUSIONNEE,
LEUR PRODUCTION ET LEUR UTILISATION**

(54) **TRICYCLIC FUSED PYRIMIDINE DERIVATIVES, THEIR
PRODUCTION AND USE**



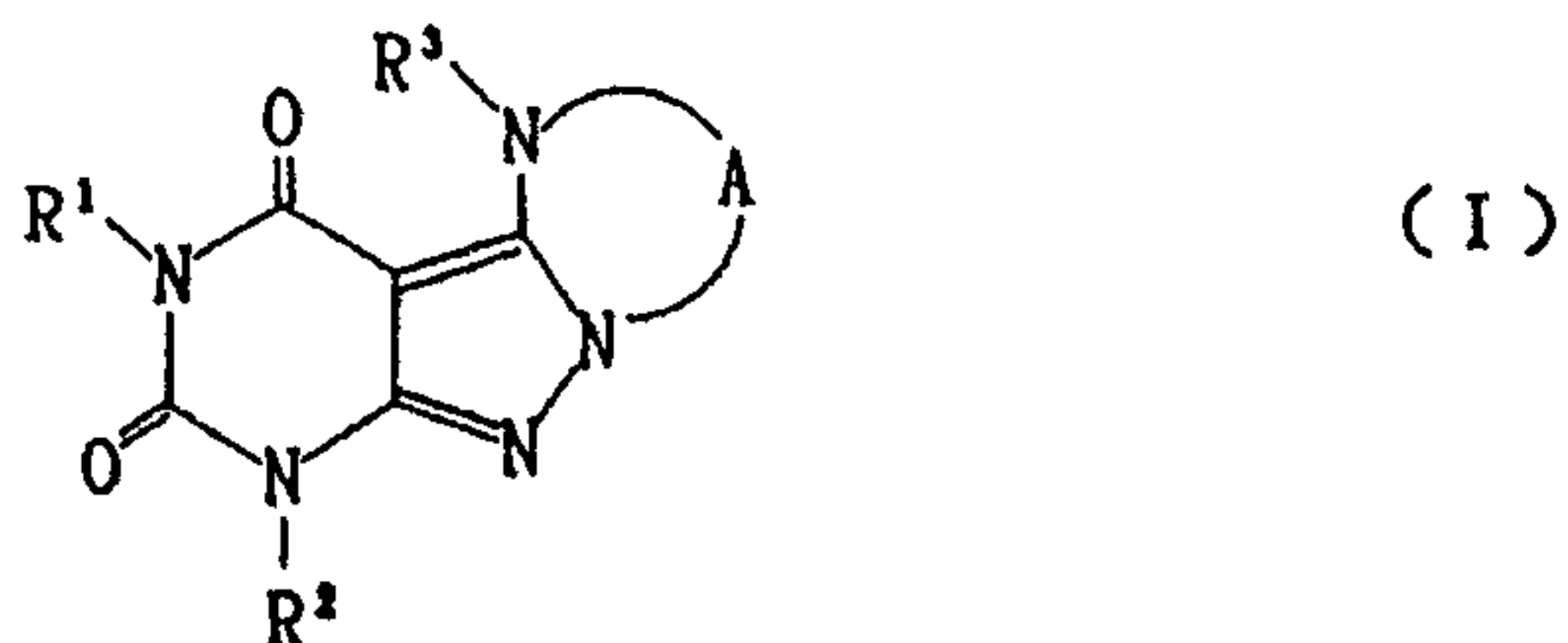
(I)

(57) Novel tricyclic fused pyrimidine derivatives of the formula (I): (see formula I) wherein either one of R¹ and R² is hydrogen or an optionally substituted aralkyl group and the other is hydrogen, an optionally substituted aralkyl group or an aliphatic hydrocarbon group; R³ is hydrogen, an aliphatic hydrocarbon group or acyl group; and A is an optionally substituted divalent hydrocarbon chain having 2 to 4 carbon atoms and salts thereof are strong adenosine antagonists and activate cerebral functions and metabolisms, thus being useful as therapeutic or prophylactic agents for neurological or psychic changes caused by cerebral apoplexy, brain injury or cerebral atrophy.



Abstract of the Disclosure

Novel tricyclic fused pyrimidine derivatives of the formula (I):



wherein either one of R^1 and R^2 is hydrogen or an optionally substituted aralkyl group and the other is hydrogen, an optionally substituted aralkyl group or an aliphatic hydrocarbon group; R^3 is hydrogen, an aliphatic hydrocarbon group or acyl group; and A is an optionally substituted divalent hydrocarbon chain having 2 to 4 carbon atoms and salts thereof are strong adenosine antagonists and activate cerebral functions and metabolisms, thus being useful as therapeutic or prophylactic agents for neurological or psychic changes caused by cerebral apoplexy, brain injury or cerebral atrophy.

Tricyclic Fused Pyrimidine Derivatives,
Their Production and Use

Background of the Invention

5 This invention relates to novel tricyclic fused pyrimidine derivatives useful as medicines.

 Pyrazolo[3,4-d]pyrimidine derivatives having, among others, analgesic, antiinflammatory and diuretic actions are disclosed in Japanese Unexamined Patent Publication No. 31694/1978, Japanese Unexamined Patent Publication No. 5082/1986 corresponding to EP166054, etc., and those having, among others, an action of ameliorating cerebral dysfunction are disclosed in Jaapanese Unexamined Patent Publication No. 10788/1988
10 corresponding to EP237289. While tricyclic fused pyrimidine derivatives, the fused ring formed at 2- and 3-positions of 3-aminopyrazolo[3,4-d]pyrimidine ring, have been synthesized [cf. EP306185], tricyclic fused pyrimidine derivatives, at least one of the 1- and 3-
15 positions being hydrogen or an optionally substituted aralkyl group, are novel compounds which have not been known at all.

 On the other hand, adenosine, as one of the important constituents of a living body, plays an
20 important role for appearance, maintenance and control of various physiological functions intra- and extra-cellularly. More specifically, adenosine displays a variety of physiological actions in most of the organs and tissues, for example inhibition of cerebral
25 function, vasodilation, cardiac depression, renal vasoconstriction, inhibition of platelet aggregation, modulation of insulin secretion, dysfunction of lymphocyte and modulation of renin-release. These actions appear via adenosine receptors which are
30 widespread on the surface of cells in a living body [J. W. Daly, J. Med. Chem., 25, (1982), M. Williams et al.,
35

5 Annu. Rep. Med. Chem., 22, 1 (1987), A. J. Bridges et
al., Annu. Rep. Med. Chem., 23, 41 (1988)]. Therefore,
diseases caused by physiological abnormality due to
changes of interaction between adenosine and its
receptors occur generally in neurosecretion system,
cardiovasculature and gastro-intestinal tract system.
Use of an adenosine antagonist inhibiting the
interaction between adenosine and its receptors is
considered useful for the therapy and prophylaxis of
these diseases [M. Williams et al., Pharm. Biochem. &
10 Behavior, 29, 433 (1988)]. Theophylline having an
adenosine antagonist activity, for example, has various
pharmacological activities including stimulation of
central nervous system and heart muscle, diuretic
15 action and relaxation of smooth muscle, especially
bronchial smooth muscle, and has been widely used
clinically. In the cerebral tissue, it is considered
that, under conditions of hypoxia or when cerebral
blood circulation is blocked, adenosine triphosphate
20 (ATP) of a high-energy compound is decreased to
increase the adenosine concentration, and the adenosine
acts on the adenosine receptor (A_1) on nerve terminals
to cause decrease of intracellular cyclic AMP
concentration, opening of K^+ channels and reduction of
25 the Ca^{2+} influx, resulting in inhibiting the release of
cerebral neuro-transmitters such as acetylcholine,
noradrenaline, dopamine and serotonin, thus abnormality
occurring in cerebral function and metabolism [B. B.
Fredholm et al., Trends in Pharm. Sci. 9, 130 (1988)].

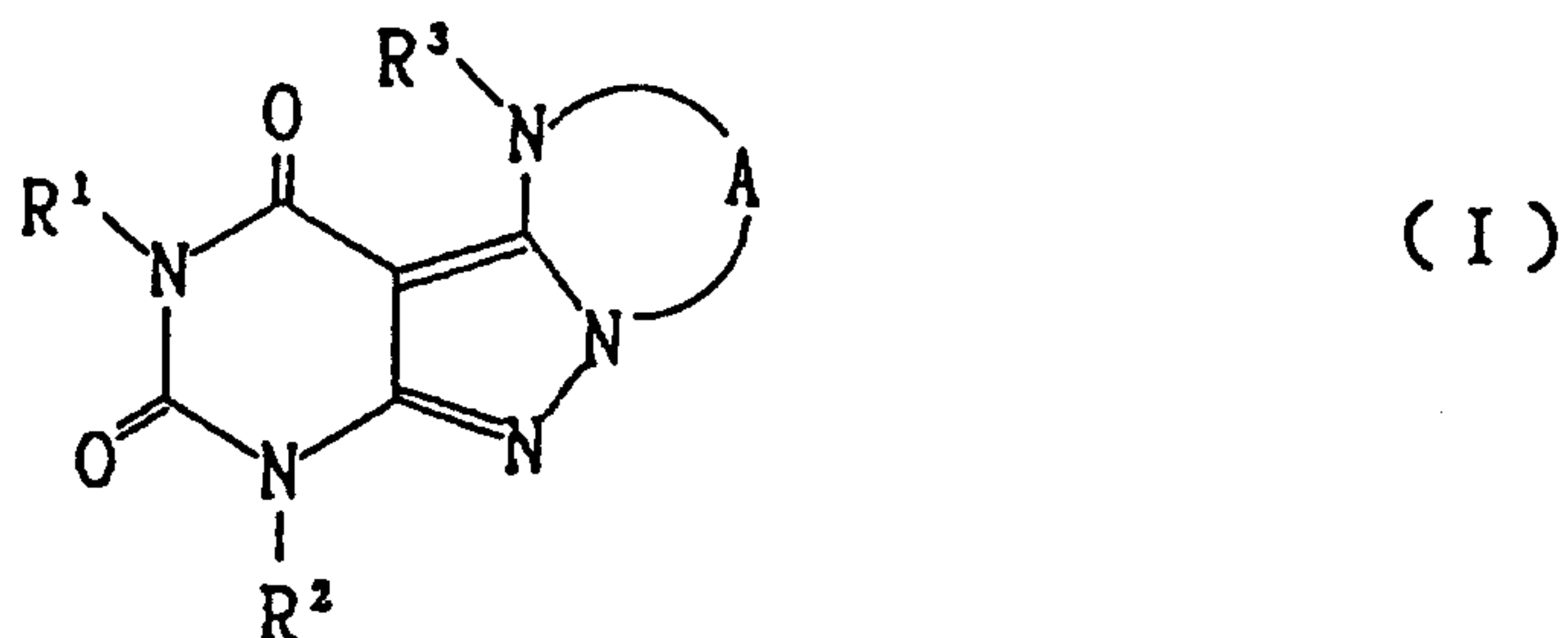
30 Detailed Description

The present invention is to provide novel
tricyclic pyrimidine derivatives which are useful for
the therapy and prophylaxis, by the action of
ameliorating cerebral function based on a strong
35 adenosine-antagonism, of mental disorders, neurological
symptoms, etc. including symptoms of dementia, caused

- 3 -

by cerebral apoplexy, brain injury or cerebral atrophy.

The present invention relates to a compound represented by the general formula (I)



wherein either one of R^1 and R^2 stands for hydrogen or an optionally substituted aralkyl group and the other stands for hydrogen, an optionally substituted aralkyl group or an aliphatic hydrocarbon group; R^3 stands for hydrogen, an aliphatic hydrocarbon group or acyl group; and A stands for an optionally substituted divalent hydrocarbon chain having 2 to 4 carbon atoms or a salt thereof.

15

Referring to the above-mentioned general formula (I), as the optionally substituted aralkyl group shown by R^1 or R^2 , mention is made of an alkyl group having 1 to about 4 carbon atoms (e.g. methyl, ethyl, propyl, butyl, etc.) substituted with an aromatic hydrocarbon group (e.g. phenyl, naphthyl, etc.), and the aromatic hydrocarbon group may be substituted with 1 to 3 substituents such as halogen (e.g. fluorine, chlorine, bromine), a lower(C_{1-4}) alkyl (e.g. methyl, ethyl), a lower(C_{1-4}) alkoxy (e.g. methoxy, ethoxy), nitro, amino, N-lower(C_{1-4}) alkylamino (e.g. methylamino), N,N-dilower (C_{1-4}) alkylamino (e.g. dimethylamino), hydroxy, trifluoromethyl, carbamoyl, N-lower(C_{1-4}) alkylcarbamoyl (e.g. N-methylcarbamoyl), N,N-dilower(C_{1-4}) alkylcarbamoyl (e.g. N,N-dimethylcarbamoyl), etc. Among these substituents, halogen, lower alkyl, lower alkoxy, nitro, amino, etc. are preferable, more preferably halogen. The

20

25

30

35

substitution position is not specifically limited, and it may be any of ortho-, meta- and para-positions. When the substituent is halogen, meta-position is preferable. As the aliphatic hydrocarbon group shown by R^1 or R^2 , mention is made of, for example, an alkyl group having 1 to about 8 carbon atoms (e.g. methyl, ethyl, propyl, 1-propyl, butyl, 1-butyl, pentyl, 1-pentyl, hexyl, heptyl, octyl, etc.), an alkenyl group having about 2 to about 8 carbon atoms (e.g. vinyl, allyl, 1-propenyl, isopropenyl, 2-butenyl, 1,3-butadienyl, 2-pentenyl, 1-hexenyl, 1-heptenyl, 1-octenyl, etc.), etc. Among them, aliphatic hydrocarbon groups having about 2 to about 5 carbon atoms are preferable, especially alkyl groups having about 2 to about 5 carbon atoms are preferable.

Among the compounds represented by the above-mentioned general formula (I), compounds wherein either one of R^1 and R^2 stands for an optionally substituted aralkyl group and the other stands for an optionally substituted aralkyl group or an aliphatic hydrocarbon group are preferable, especially compounds wherein R^1 is an aliphatic hydrocarbon group and R^2 is an optionally substituted aralkyl group are preferable.

As the aliphatic hydrocarbon group shown by R^3 , mention is made of, for example, an alkyl group having 1 to about 3 carbon atoms (e.g. methyl, ethyl, propyl, 1-propyl), an alkenyl group having about 2 to about 3 carbon atoms (e.g. vinyl, allyl, 1-propenyl, isopropenyl), and, among them, alkyl groups having 1 to about 3 carbon atoms are preferable.

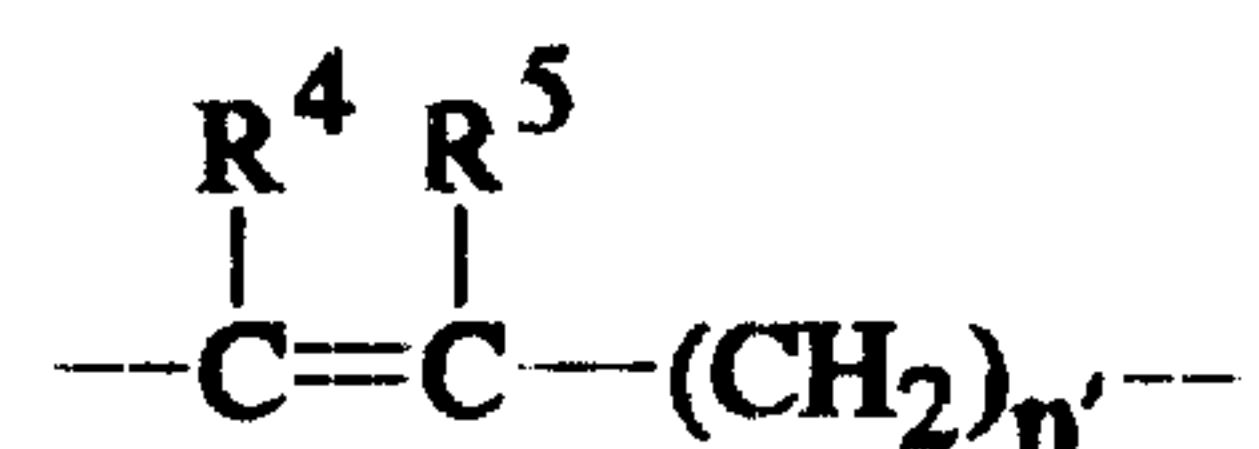
As the acyl group shown by R^3 , mention is made of that derived from an organic acid, for example, alkanoyl

groups which may be substituted by halogen, preferably having not more than 7 carbon atoms (e.g., acetyl, trifluoroacetyl, propionyl, butyryl, valeryl, etc.), cycloalkylcarbonyl groups having 3 to 8 carbon atoms in the cycloalkyl moiety (e.g. cyclohexylcarbonyl), aromatic carbonyl group (e.g. optionally substituted benzoyl, etc.), alkoxycarbonyl groups preferably those whose carbon number of the alkyl moiety is 1 to about 4 (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl etc.) carbamoyl, formyl, etc. Among them, alkanoyl groups whose carbon number is not more than 7 or alkoxycarbonyl groups whose carbon number at the alkyl moiety is 1 to about 4 are preferable, especially acetyl, propionyl and methoxycarbonyl are preferable.

As the divalent hydrocarbon chain having 2 to 4 carbon atoms shown by A, mention is made of C_{2-4} alkylene (e.g. ethylene, trimethylene, tetramethylene), C_{2-4} alkenylene (e.g. vinylene, propenylene, etc.), etc. The hydrocarbon chain may have a substituent, and, as the substituent, mention is made of, for example, an optionally substituted aliphatic or aromatic hydrocarbon group (e.g. aliphatic hydrocarbon group which may be substituted with an optionally substituted amino (e.g. amino; mono- or di- C_{1-4} alkylamino such as dimethylamino; cyclic amino such as morpholino), halogen, nitro, hydroxy, alkoxy having 1 to about 4 carbon atoms, alkylthio having 1 to about 4 carbon atoms). Among them, preferred are an alkyl group having 1 to about 8 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, octyl, etc.), a cycloalkyl group having 3 to 8 carbon atoms (e.g.

cyclopropyl), an optionally substituted aromatic hydrocarbon group (e.g. phenyl optionally substituted at ortho-, meta- or para-position, with 1 to 2 substituents such as an optionally substituted amino, nitro, hydroxy, C₁-C₄ alkoxy such as methoxy, C₁-C₄ alkyl such as methyl, halogen, phenyl, etc.), etc. halogen (e.g. F, Cl, Br etc.), nitro, amino, oxo, etc., such as a divalent linear aliphatic hydrocarbon group (preferably having 3 to 6 carbon atoms) that the hydrocarbon group together with two adjacent carbon atoms of the hydrocarbon chain as A forms a cyclic group (e.g. cyclic aliphatic hydrocarbon groups having about 5 to about 8 carbon atoms, etc.).

As the above-mentioned optionally substituted divalent hydrocarbon chain having about 2 to about 4 carbon atoms shown by A, mention is made of, preferably, alkylene having 2 to 4 carbon atoms, hydrocarbon chain represented by the formula:



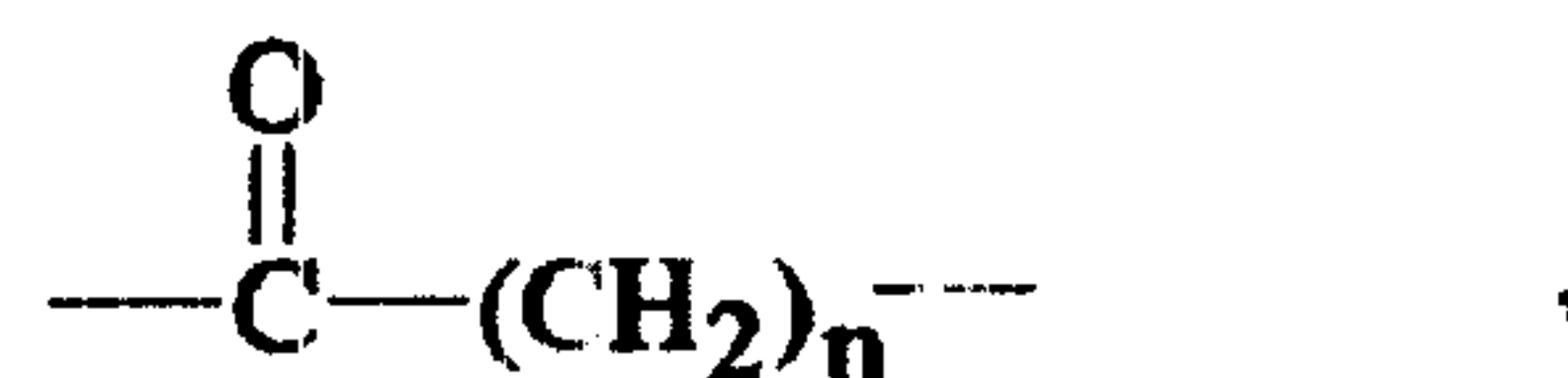
wherein R⁴ and R⁵ each stand for hydrogen, a cycloalkyl group having 3 to 8 carbon atoms, an optionally substituted aliphatic hydrocarbon group (such as an alkyl having 1 to 8 carbon atoms and optionally substituted by amino, morpholino or mono- or di-C₁₋₄alkylamino), an optionally substituted aromatic hydrocarbon group (such as phenyl optionally substituted by C₁₋₄alkyl, phenyl, C₁₋₄alkoxy or halogen) or halogen, or R⁴ and R⁵ together form a cyclic aliphatic hydrocarbon group having about 5 to about 8 carbon atoms

-6a-

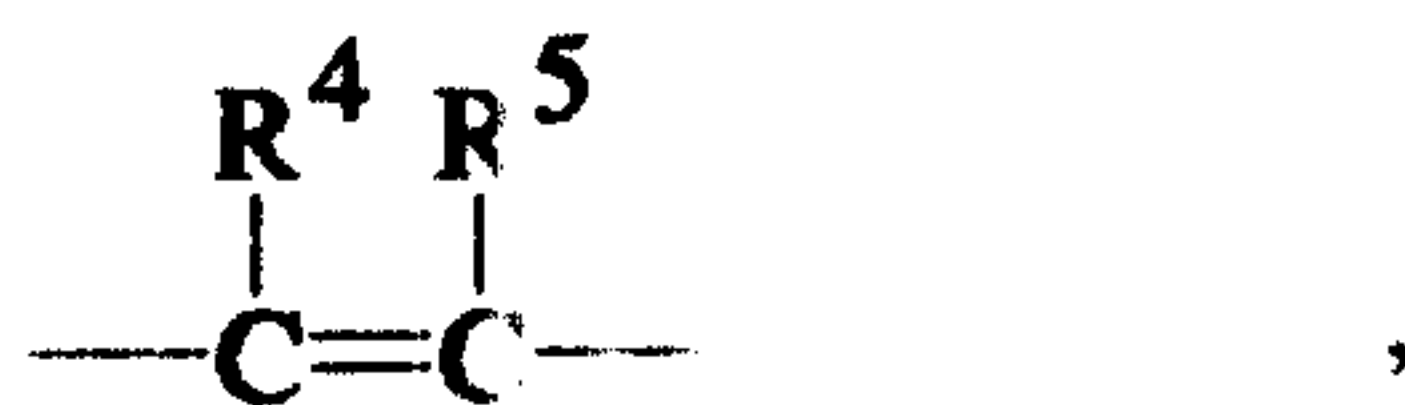
represented by the formula:



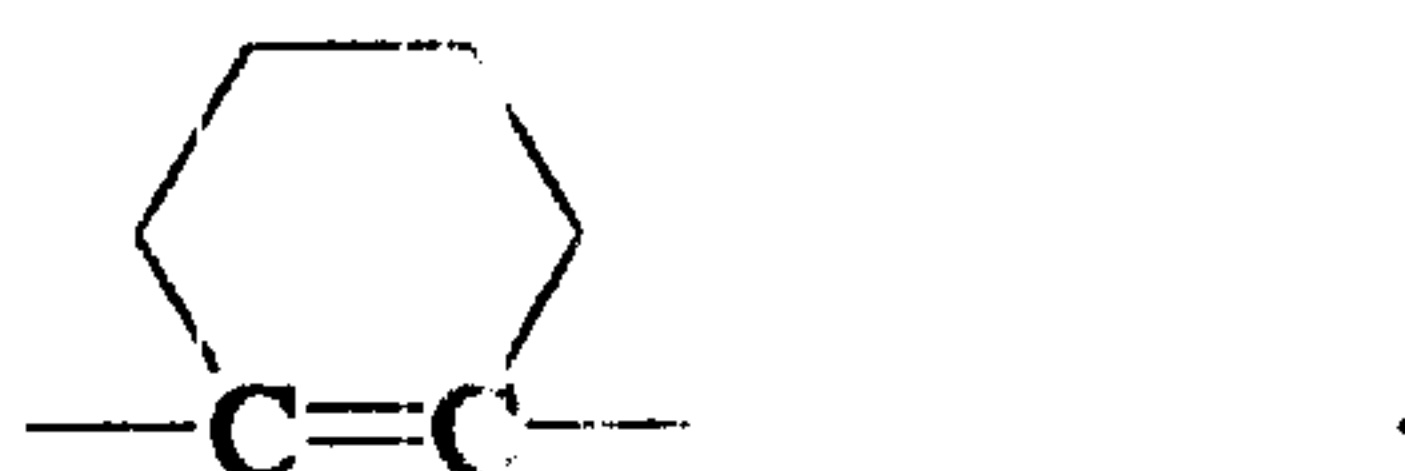
and N' denotes an integer of 0 to 2 or a hydrocarbon chain represented by the formula:



wherein n denotes an integer of 1 to 3. Among them, preferred are ethylene and a group represented by the formula:



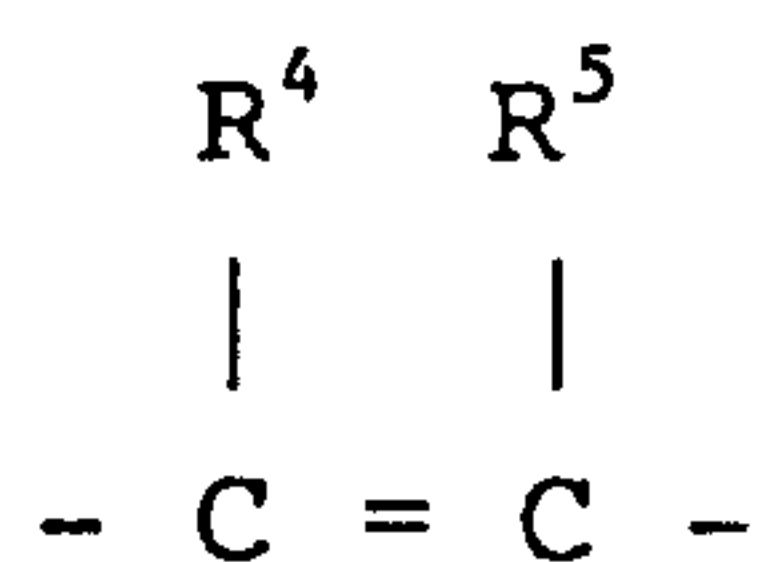
wherein R⁴ and R⁵ each stand for (1) hydrogen, (2) phenyl which may have a substituent such as halogen, lower (C₁₋₄) alkoxy, phenyl, etc., (3) cyclopropyl or (4) alkyl having 1 to about 4 carbon atoms which may have a substituent such as an optionally substituted amino (e.g. dimethylamino, etc.), provided that at least one of R⁴ and R⁵ is other than hydrogen or R⁴ and R⁵ together with the carbon atoms to which they are attached form a cyclic group of the formula:



--6b--

Among the compounds represented by the above-mentioned formula (I), compounds (I) wherein R^1 stands for an aliphatic hydrocarbon group having 2 to 5 carbon atoms (especially an alkyl group having 3 to 5 carbon atoms), R^2 stands for hydrogen or an

optionally substituted phenyl- lower (C₁₋₄) alkyl
group (especially benzyl group which may be substituted
with halogen), R³ stands for hydrogen, methyl, acetyl
or methoxycarbonyl (especially hydrogen), and A stands
for ethylene or a hydrocarbon chain represented by the
formula:



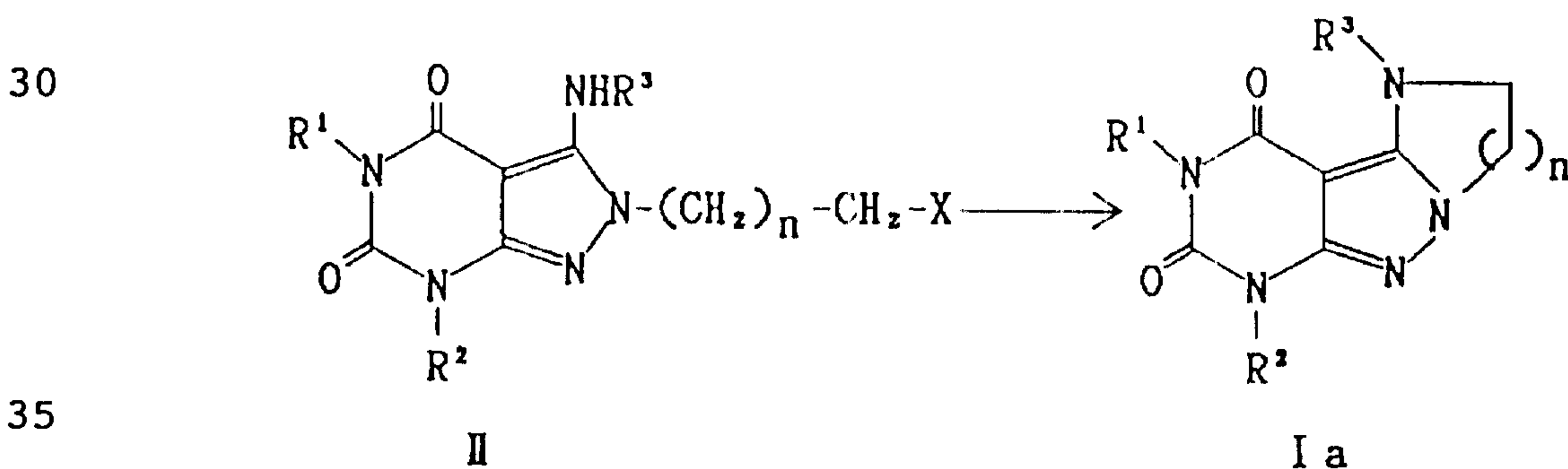
wherein R⁴ and R⁵ each stand for hydrogen, a C₁₋₈ lower
alkyl group or an optionally substituted aromatic
hydrocarbon group (especially hydrogen, C₁₋₄ alkyl,
phenyl which may be substituted with lower (C₁₋₄)
alkoxy) are further preferable.

Examples of the salts of compound (I) include
pharmacologically acceptable ones, i.e. acid addition
salts such as inorganic acid salts e.g. hydrochloride,
hydrobromide, sulfate, nitrate, phosphate, etc.,
organic acid salts such as acetate, tartrate, citrate,
fumarate, maleate, etc.

Production Method :

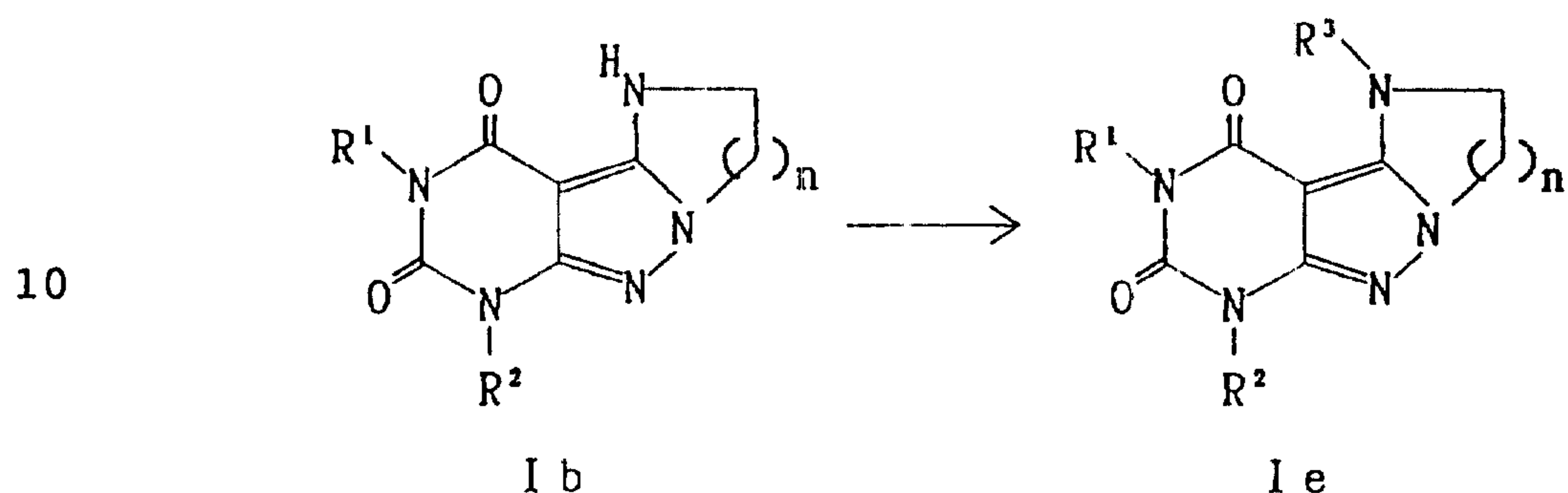
The above-mentioned compounds of the general
formula (I) can be produced by, for example, methods
shown below.

Process (a)



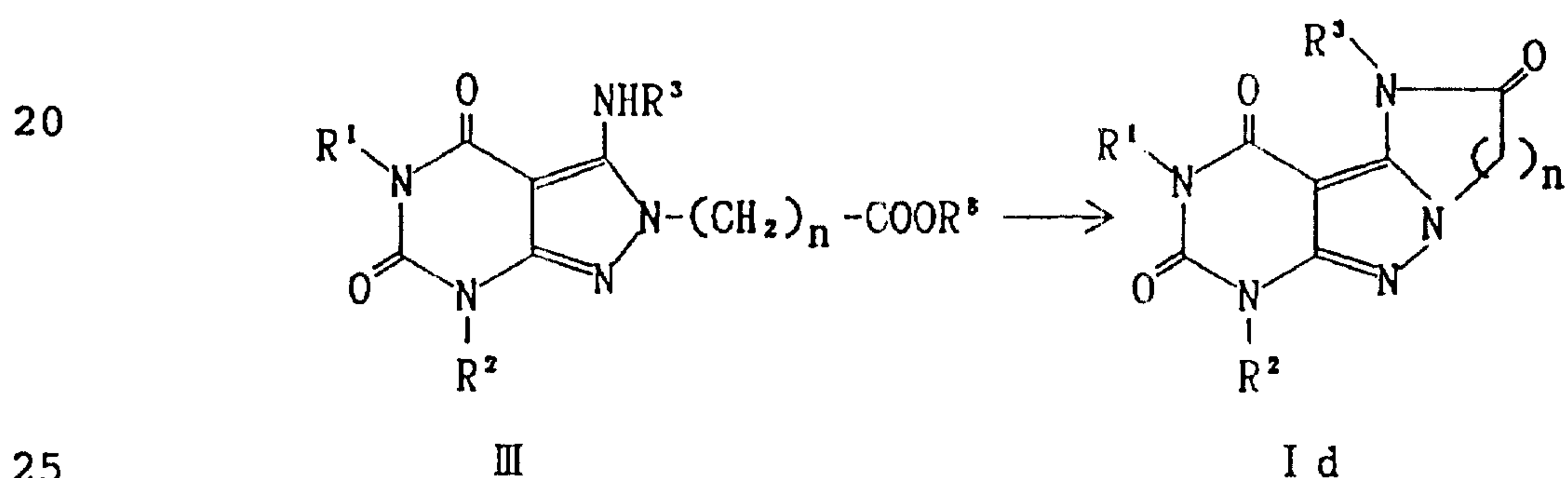
wherein R^1 , R^2 and R^3 are of the same meaning as defined above, X stands for halogen, and n denotes an integer of 1 to 3.

5 Process (b)



15 wherein R^1 , R^2 , R^3 and n are of the same meaning as defined above, provided that R^3 is not hydrogen.

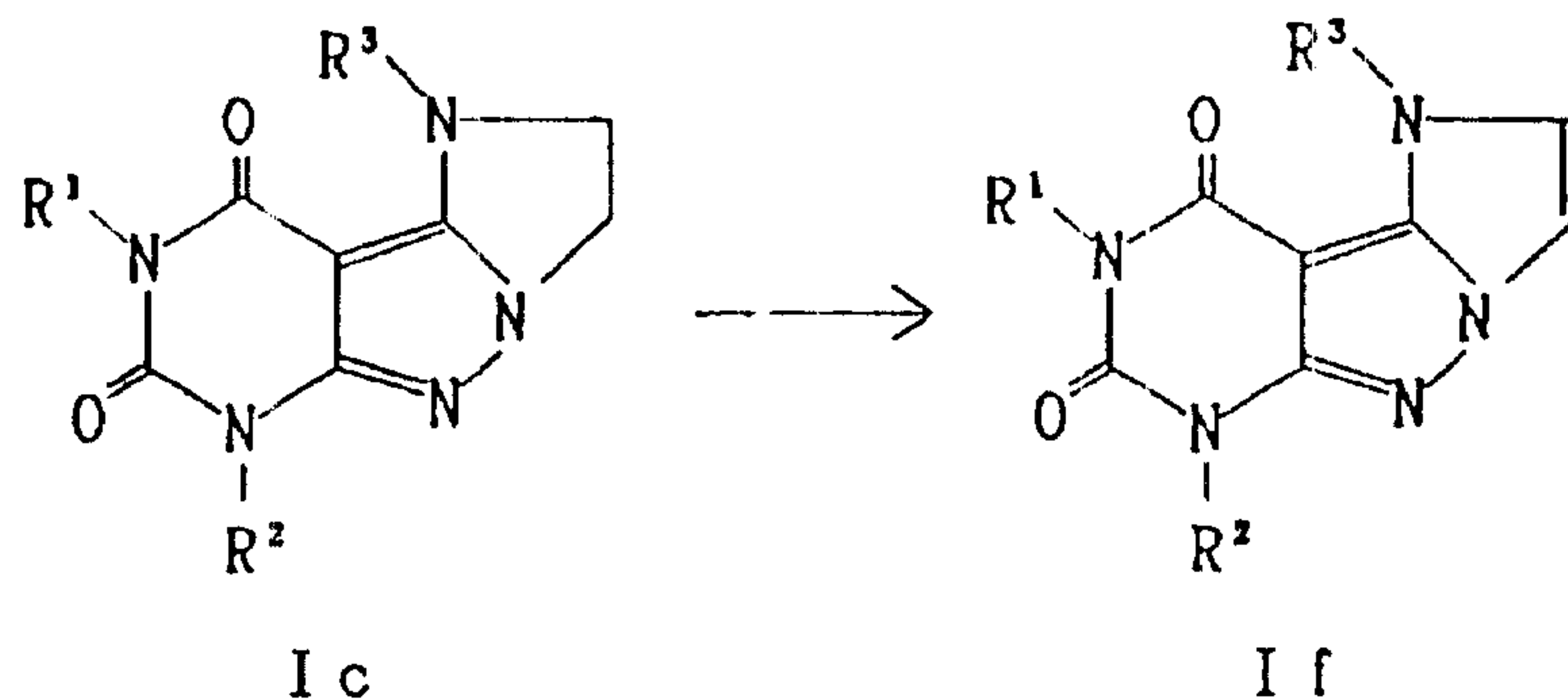
Process (c)



wherein R^1 , R^2 , R^3 and n are of the same meaning as defined above, and R^6 stands for a lower alkyl group.

Process (d)

5

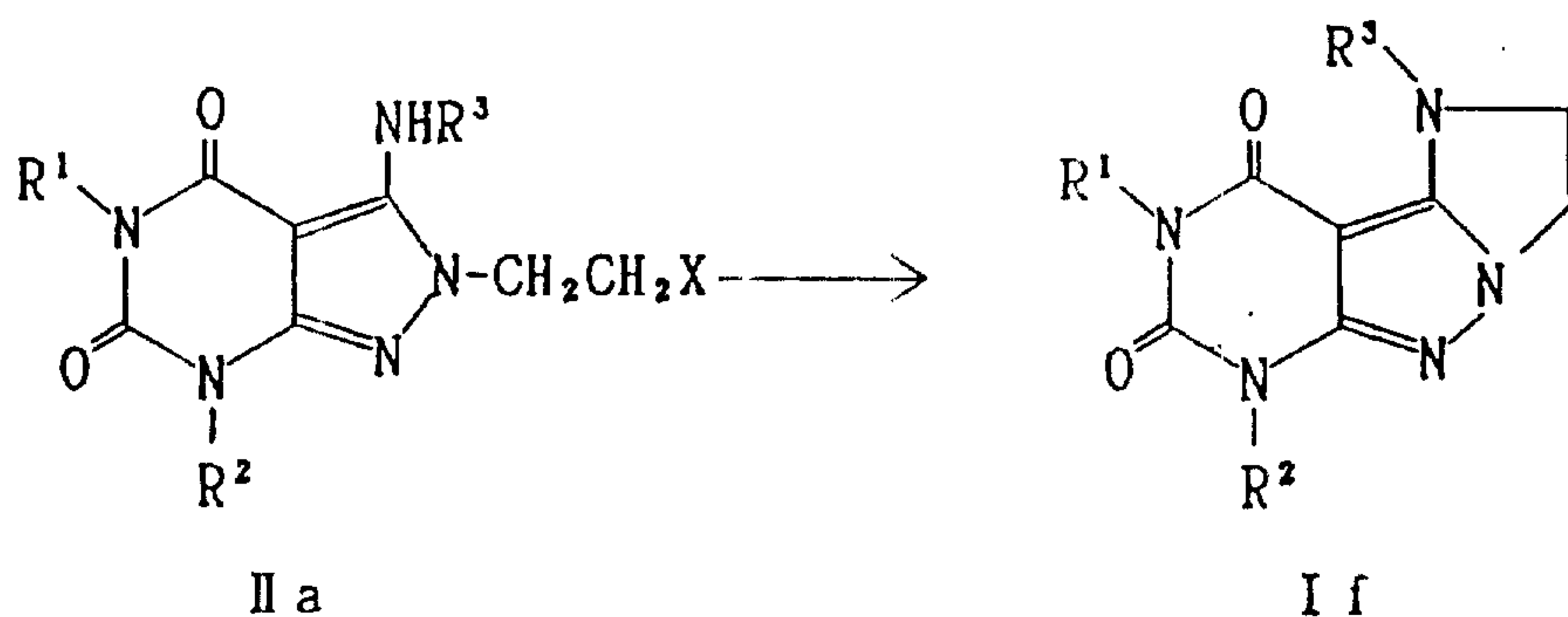


10

wherein R^1 , R^2 and R^3 are of the same meaning as defined above.

Process (e)

15

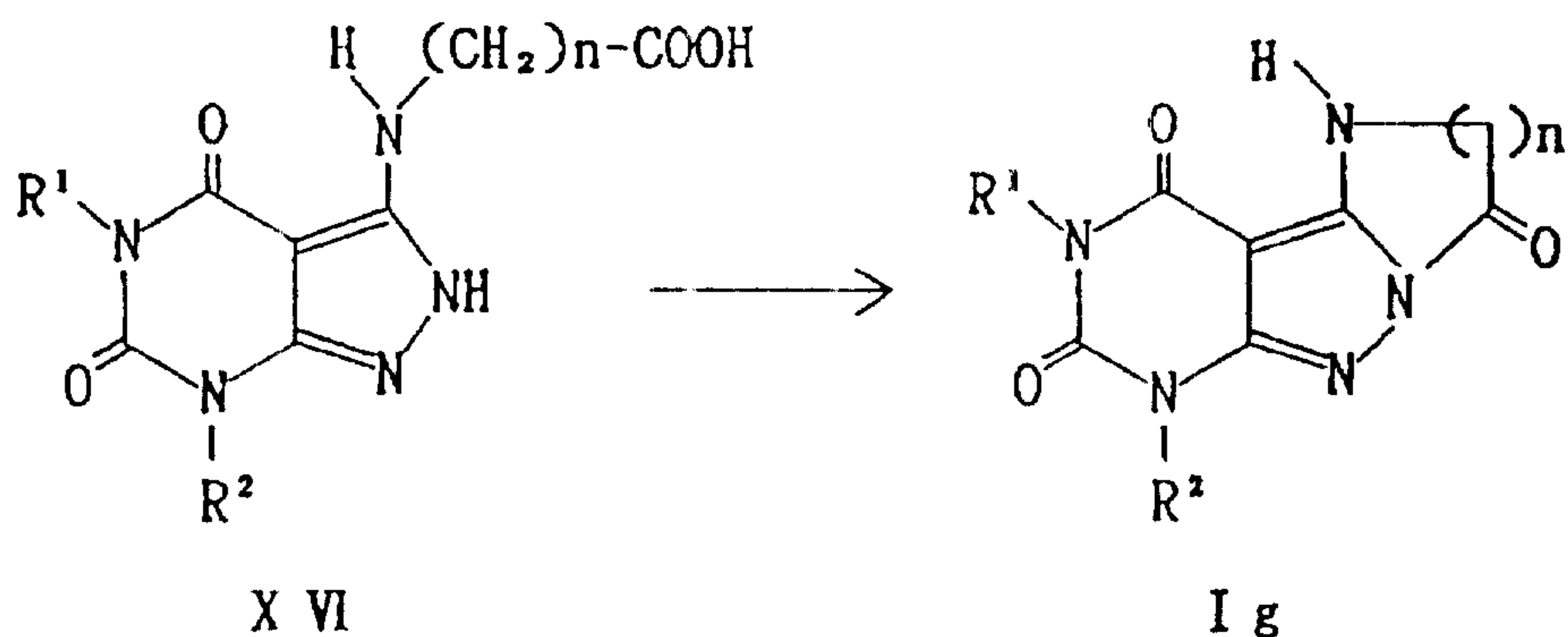


20

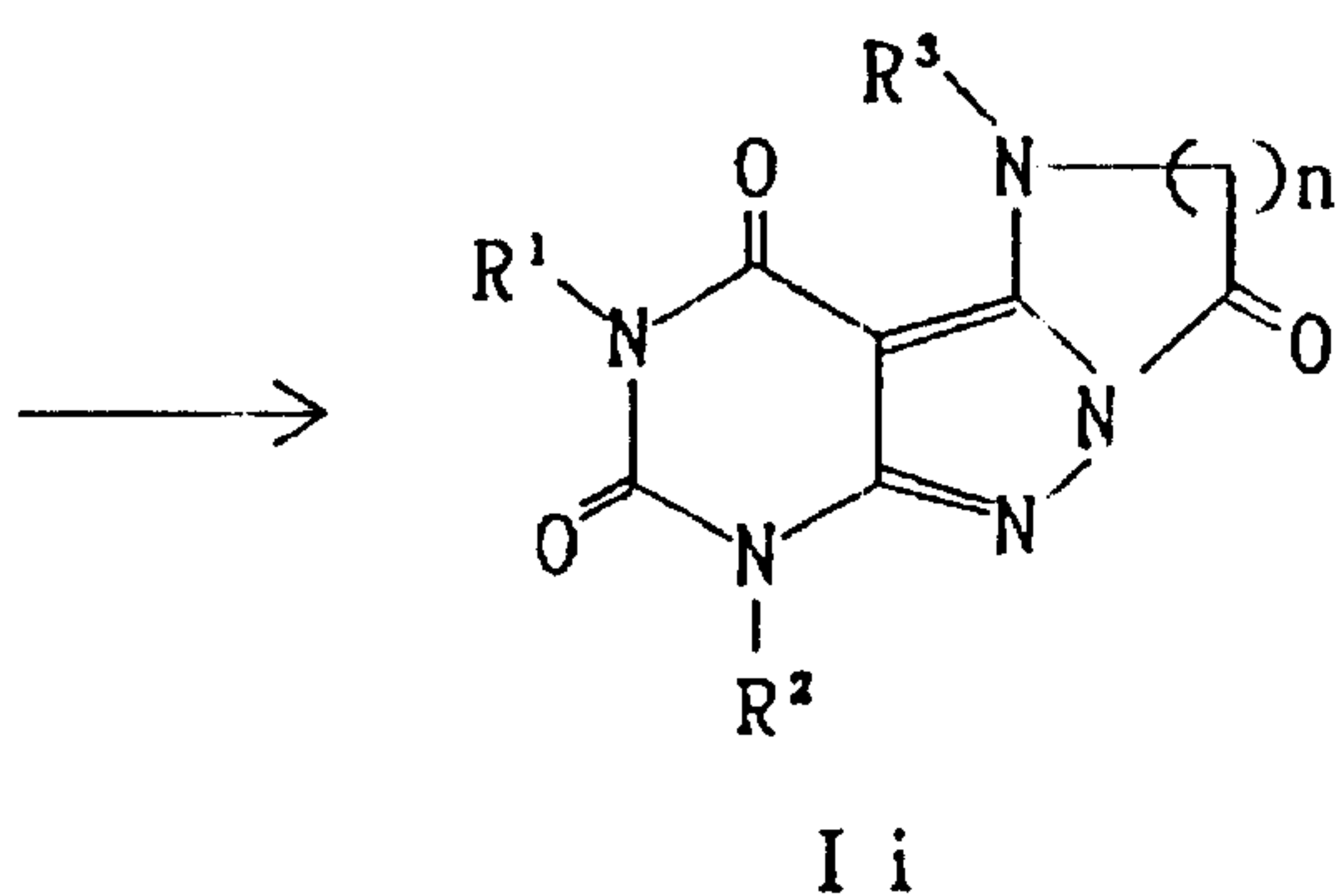
wherein R^1 , R^2 , R^3 and X are of the same meaning as defined above.

Process (f)

5



10

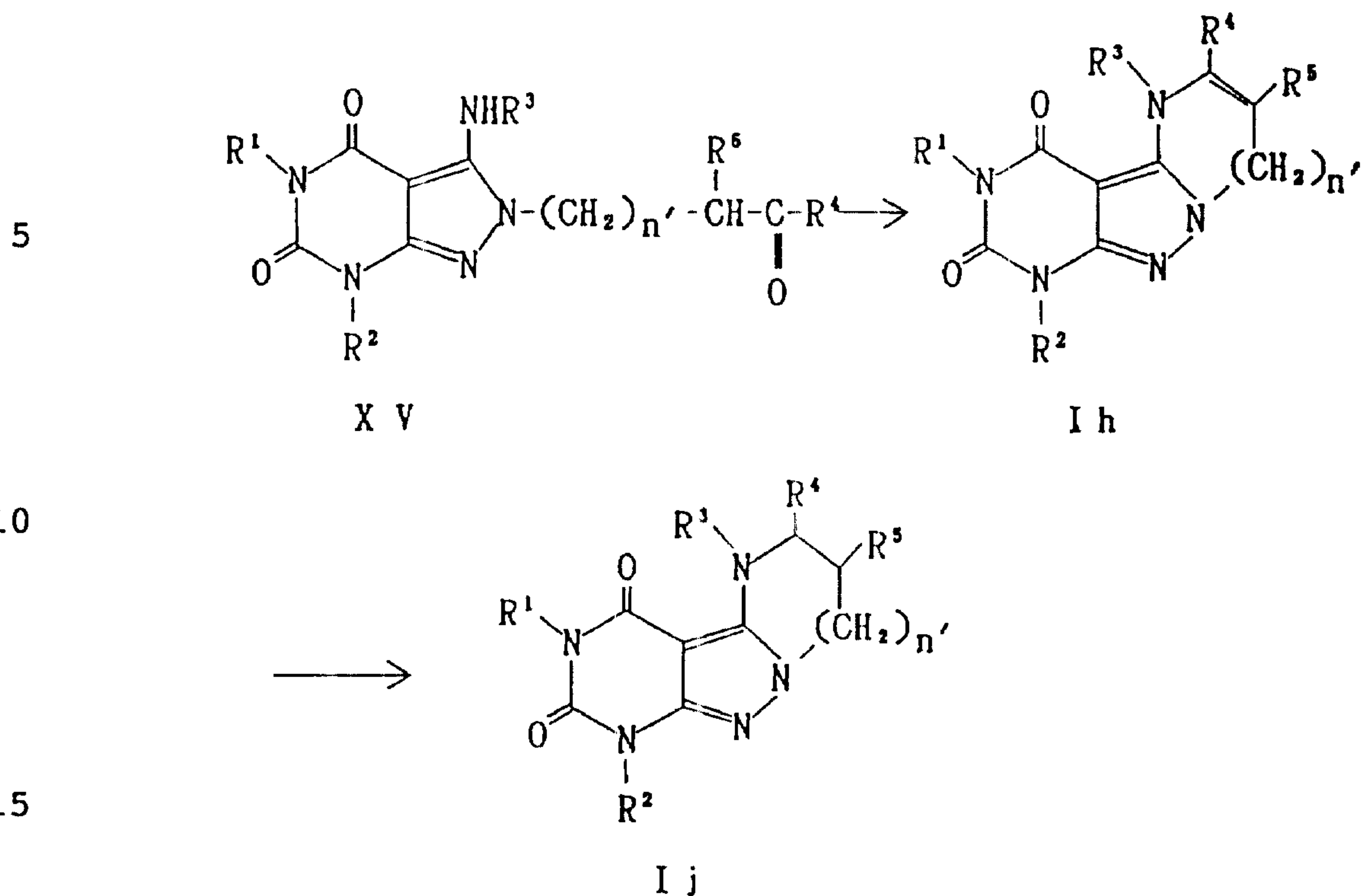


15

wherein R^1 , R^2 , R^3 and n are of the same meaning as defined above, provided that R^3 is not hydrogen.

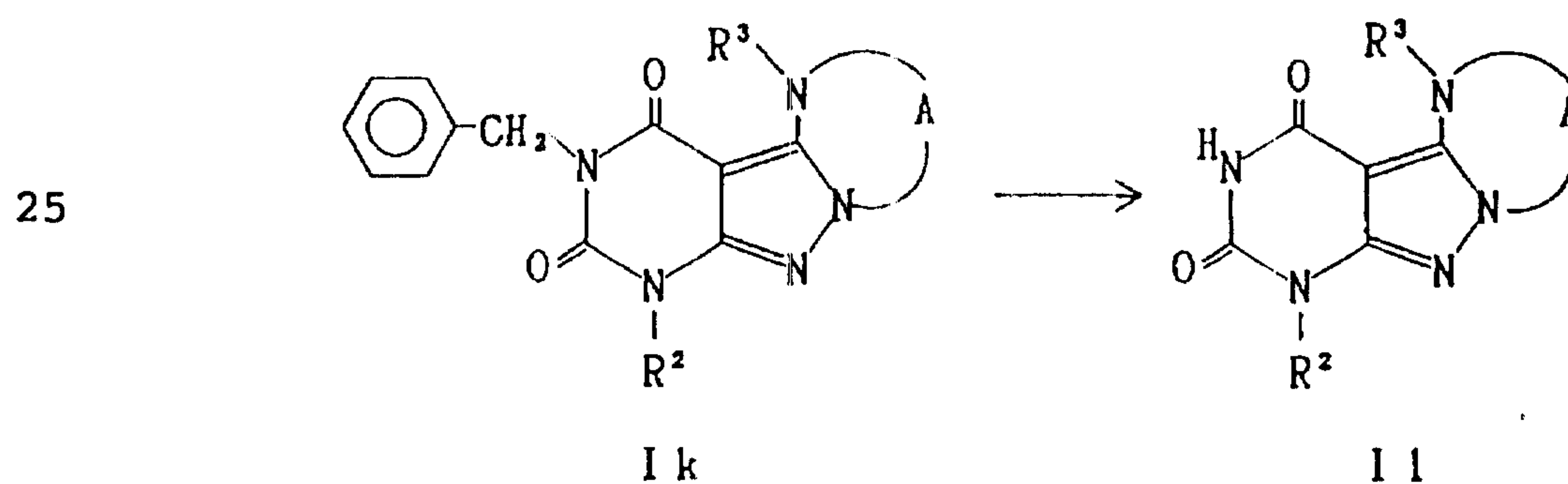
20

Process (g)



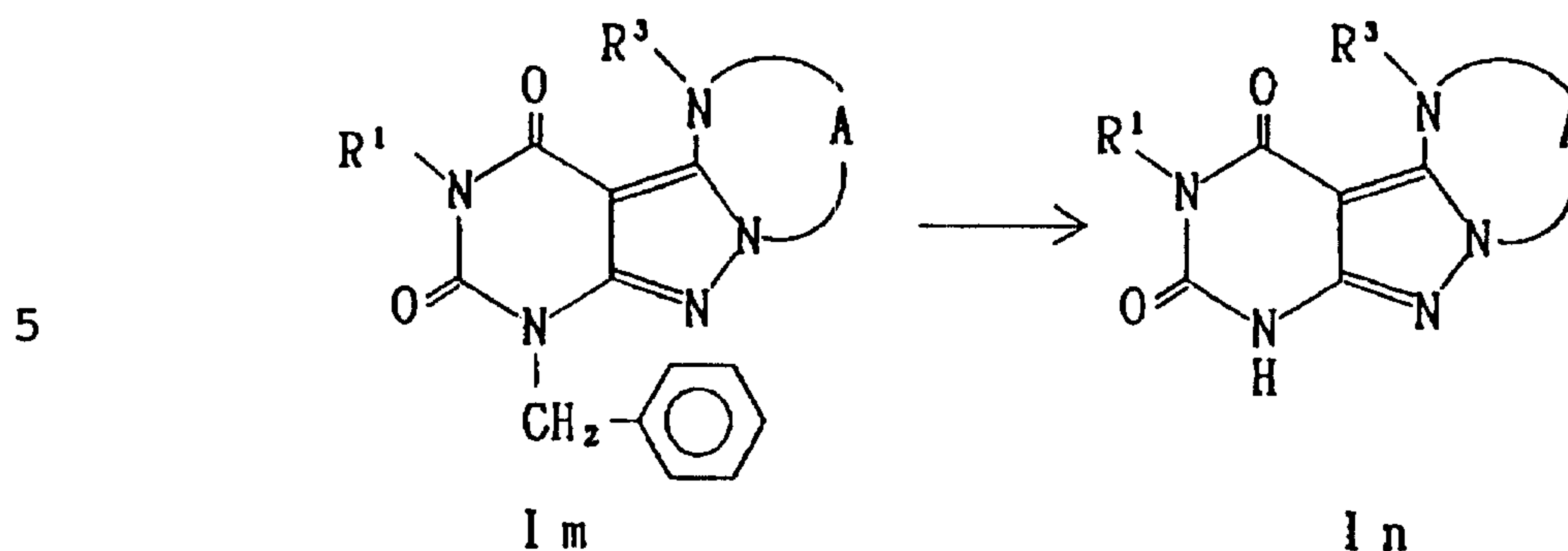
wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are of the same meaning as defined above, and n' denotes an integer of 0 to 2.

Process (h)



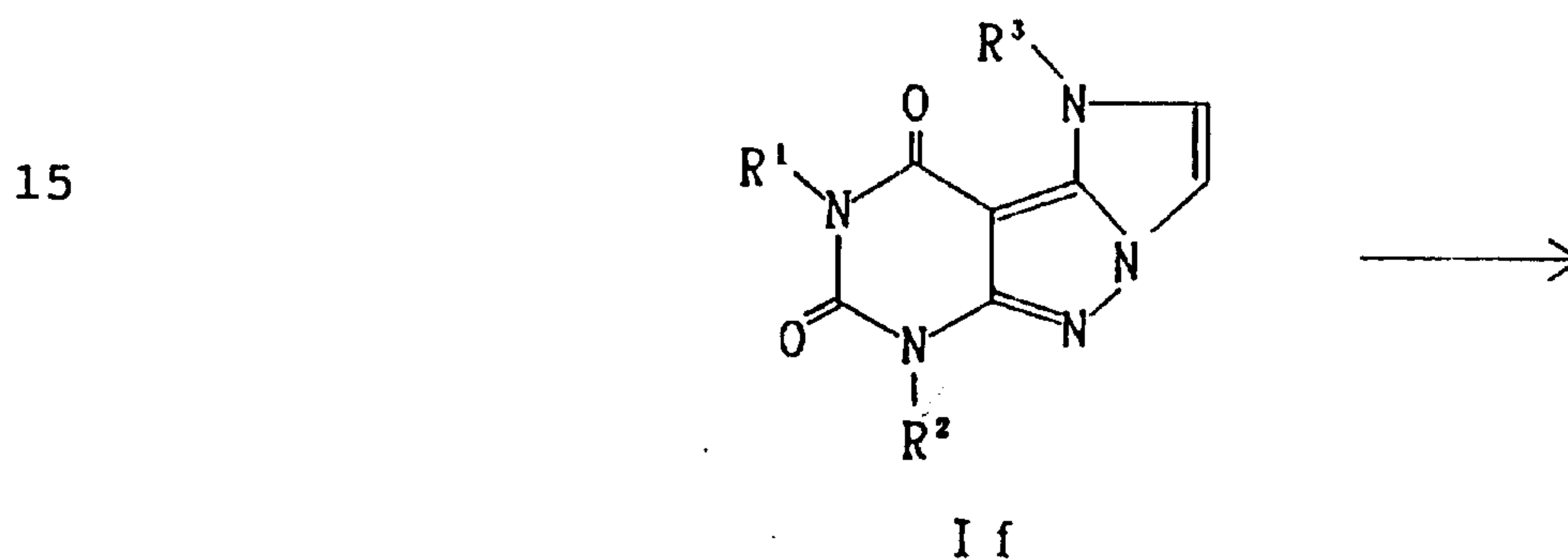
30 wherein R^2 , R^3 and A are of the same meaning as defined above, provided that R^2 is not an optionally substituted benzyl group.

Process (i)

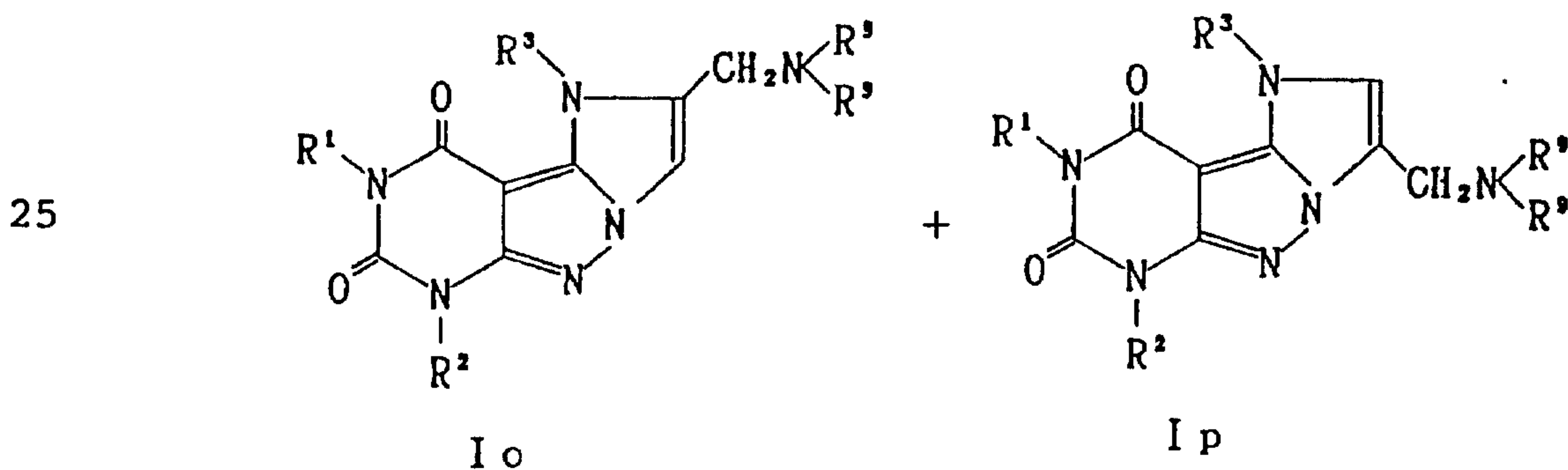


10 wherein R^1 , R^3 and A are of the same meaning as defined above, provided that R^1 is not an optionally substituted benzyl group.

Process (j)

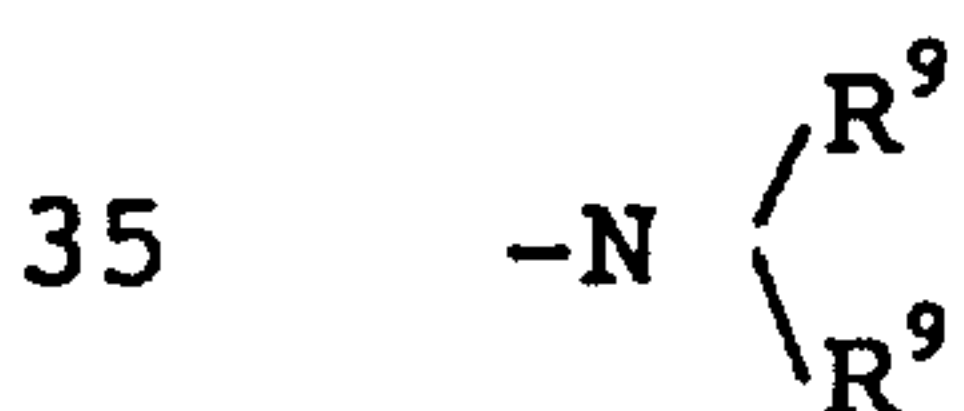


20



30

wherein R^1 , R^2 and R^3 are of the same meaning as defined above, and R^9 is a lower alkyl group or



is a cyclic amino group.

40

The above-mentioned process (a) is to conduct a

ring-closure reaction in the presence of a base, and the amount of the base is in the range of 1 to about 3 mol. relative to 1 mol. of compound (II). As the base, use is made of, among others, sodium hydride, potassium t-butoxide, potassium carbonate and sodium carbonate. As the solvent, use is made of a polar aprotic solvent such as dimethylformamide, dimethylacetamide, dimethyl sulfoxide, acetonitrile, etc. The reaction is carried out preferably under ice-cooling or at temperatures not higher than about 100°C for about 0.5 to about 30 hours. When a strong base such as sodium hydride or potassium t-butoxide is employed, the reaction is carried out preferably by dissolving compound (II) in a solvent then by adding portionwise such a base as above to the solution under ice-cooling. The reaction can be conducted advantageously by suspending a strong base such as sodium hydride in a solvent such as dimethylformamide then by adding to the suspension portionwise under ice-cooling a solution of compound (II) in the same solvent. After the addition of a base in such a manner as above, the reaction is preferably conducted by raising the reaction temperature to about room temperature and allowing the reaction to proceed for further 1 to 2 hours. On the other hand, when the reaction is conducted in the presence of a weak base such as potassium carbonate or sodium carbonate, it is preferable to allow the compound (II) to react with such a base as mentioned above in a solvent such as dimethylformamide (DMF) at about 50°C to about 130°C for about 10 hours to about 30 hours. After completion of the reaction, the solvent is distilled off, then the residue is poured into ice-water, and resulting crystals are recrystallized from e.g. aqueous alcohol, thereby the desired reaction product can be easily obtained. Depending on cases, a conventional isolation and purification step such as column chromatography can

be resorted to.

The process (b) is to obtain compound (Ie) by
subjecting compound (Ib) to alkylation or acylation.
5 As an alkylation agent, mention is made of an alkyl
halogenide (e.g. methyl iodide, ethyl iodide, propyl
iodide, benzyl bromide, etc.), and, as an acylating
agent, mention is made of an acid anhydride (e.g.
acetic anhydride, propionic anhydride, butyric
10 anhydride, etc.) or an acid halogenide (e.g. acetyl
chloride, propionyl chloride, butyryl chloride, etc.).
And, when alkoxycarbonylation is conducted, use is made
of an alkyl halogenocarbonate (e.g. methyl ester of
chlorocarbonic acid, ethyl ester of chlorocarbonic
15 acid, etc.). These reagents are used in an excess
amount of about 1 to about 5 mol. relative to 1 mol. of
the compound (Ib), and the reaction is allowed to
proceed in the presence of a suitable base. As the
base, use is made of potassium carbonate, sodium
20 carbonate, triethylamine, pyridine, etc., and,
depending on cases, the reaction is conducted by the
addition of a catalytic amount of dimethyl
aminopyridine. As the solvent, use is made of
pyridine, dimethylformamide, dimethylacetamide,
25 acetonitrile, dioxane, etc., and the reaction is
allowed to proceed preferably under ice-cooling or at
temperatures not higher than about 100°C for about 1 to
about 50 hours. The alkylation is conducted preferably
using about 1 to about 2 mol. of an alkyl halogenide in
30 dimethylformamide at temperatures ranging from room
temperature to about 50°C for about 5 to about 20
hours. And the acylation is conducted preferably
using about 1 to about 3 mol. of an acid anhydride in
pyridine at temperatures ranging from about 50°C to
35 about 100°C for about 5 to about 20 hours. Depending
on cases, the reaction can be conducted more

advantageously by adding a catalytic amount of dimethylaminopyridine.

5 The alkoxy carbonylation is desirably carried out in a solvent such as dioxane, etc. in the presence of a base such as triethylamine by adding alkyl halogenocarbonate under ice cooling or at temperatures up to room temperatures, then the reaction being allowed to proceed at temperatures ranging from temperatures to about 60°C for about 5 to about 20 hours. The reaction product can be isolated as crystals easily by evaporating the reaction solvent, and then by pouring the residue to ice-water, or by employing a conventional isolation and purification means.

15

The process (c) is a lactam-ring formation reaction in the presence of a base in an amount of 1 to about 3 mol. relative to 1 mol. of compound (III). As preferable bases, there may be used sodium methoxide, sodium ethoxide, etc. As preferable solvents, there may be used alcohol solvents such as methanol, ethanol, etc. The reaction is conducted preferably under ice-cooling or temperatures not higher than about 50°C for about 30 minutes to about 2 hours. After completion of the reaction, the solvent is distilled off, and the residue is dissolved in water, followed by neutralization with about 1N to about 2N hydrochloric acid to obtain the desired product as crystals.

30 The process (d) is to obtain compound (If) by dehydrogenation, and the reaction is carried out in a conventional organic solvent such as dimethylformamide, dimethylacetamide, acetonitrile, dioxane, toluene, benzene, chloroform, methylene chloride, etc. at temperatures ranging from about 50°C to about 150°C for a period ranging from about 5 hours to about 60 hours. The reaction can also be conducted in the presence of

35

benzoyl peroxide, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), selenium dioxide, manganese dioxide, etc., or in the presence of of a base such as potassium carbonate or sodium carbonate, and it is especially preferable to conduct the reaction, using, as an oxidant, about 1 to about 2 mol. of benzoyl peroxide, in an aprotic solvent such as chloroform by heating under reflux for about 5 to about 15 hours.

The process (e) is to obtain the compound (If) from compound (IIa) directly. The reaction conditions are analogous to those in the case of process (a). In the case of process (e), as the base, use is made of potassium carbonate or sodium carbonate, and the reaction is preferably conducted in a solvent such as dimethylformamide, dimethylacetamide, etc. The reaction is conducted more preferably at temperatures ranging from about 80°C to about 120°C for about 20 to about 40 hours. The products obtained by process (d) and process (e) can be isolated as crystals easily by, after distilling off the reaction solvent, pouring the residue to water, or by subjecting the residue conventional isolation and purification means such as column chromatography, etc.

The process (f) is to obtain the compound (Ii) by subjecting the compound (XVI) to a ring-closure reaction in the presence of a dehydrating agent to give compound (Ig), then by subjecting, when desired, to acylation or alkylation like in the case of process (b) to give compound (Ii). As the dehydrating agent employable for the reaction from compound (XVI) to compound (Ig), use is made of dicyclohexyl carbodiimide (DCC), carbonyl diimidazole (CDI), etc. or a chlorinating agent such as thionyl chloride, phosphorus oxychloride, etc. It is preferable to use about 1 to

about 10 equivalents of a dehydrating agent relative to the compound (XVI) in such a solvent as methylene chloride, chloroform, benzene, etc. and to allow the reaction to proceed at temperatures ranging from room temperature to about 100°C for about 1 to about 10 hours. It is especially preferable to conduct the reaction in a solvent such as chloroform or methylene chloride, using about 5 to about 10 equivalents of thionyl chloride, for about 1 to about 5 hours by heating under reflux.

The process (g) comprises dehydration of compound (XV) under acid or basic conditions to give the desired compound (Ih), and, when desired, subjecting the compound (Ih) to reduction to yield compound (Ij). In the reaction of leading compound (XV) to compound (Ih), as an acid, use is made of an organic or inorganic acid such as p-toluenesulfonic acid, hydrochloric acid, sulfuric acid, etc., and, as a base, use is made of tri-ethylamine, potassium carbonate, sodium carbonate, sodium hydroxide, etc. in an amount ranging from catalytic amount to about 2 equivalents relative to the compound (XV), and, as a solvent, use is made of benzene, toluene, xylene, methyl ethyl ketone, etc., and the reaction is allowed to proceed at temperatures ranging from room temperature to about 150°C for about 5 hours to about 3 days. Especially, it is preferable to conduct the reaction in a solvent such as benzene or toluene, etc., using a catalytic amount of p-toluenesulfonic acid, by heating under reflux for about 10 to about 20 hours. The hydrogenation of compound (Ih) to compound (Ij) is carried out preferably in a conventional organic solvent such as methanol, ethanol, chloroform, dichloromethane, benzene, acetic acid, etc., in hydrogen streams of normal to about 5 atmospheric pressure in the presence of a suitable

catalyst, at temperatures ranging from room temperature to about 50°C for about 1 to about 10 hours. As the catalyst, Raney nickel, palladium-carbon, platinum-carbon, platinum oxide or rhodium catalyst, etc. are exemplified.

The products obtained by process (f) and process (g) can be isolated easily as crystals, after distilling off the reaction solvent, by a conventional isolation and purification means.

The process (h) is to obtain compound (Il) by subjecting compound (Ik) to debenzylation, and the process (i) is to obtain compound (In) by subjecting compound (Im) to debenzylation..

The process (j) is to obtain the compounds (Io) and (Ip) by subjecting the compound (If) to aminomethylation with Mannich reaction.

The reaction is conducted using about 2 to about 5 mol. of paraformaldehyde and amine relative to 1 mol. of the compound (If). As the amine, use is made of ammonia, primary amine, secondary amine, etc. Usually, secondary amine (e.g. dimethylamine, morpholine, etc.) is employed. Amines can also be used as salts thereof (e.g. hydrochloride, acetate, etc.) in the reaction. As the solvent, use is made of a protic solvent such as acetic acid, alcohols (e.g. methanol, ethanol, etc.) and mixtures thereof can also be used. The reaction condition varies with an amine or a solvent. It is preferable to carry out the reaction at temperatures ranging from room temperatures to about 100°C for 1 to about 10 hours. More preferably, the reaction is carried out in acetic acid in the presence of paraformaldehyde and an aqueous solution of dimethylamine at temperatures ranging from about 50°C to about 80°C for 1 to about 3 hours. When the compound (If) is used, the product is obtained as a

5 mixture of compounds substituted at 6- and 7-positions (Io and Ip), which can easily be obtained as respective crystals by a conventional isolation and purification means (recrystallization or silica gel column chromatography).

10 Among these compounds, the starting compounds (II), (III), (XV) and (XVI) are novel ones, which can be synthesized by the following methods. Starting with compounds (IV) and (XI) synthesized by a method analogous to that described in Chem. Ber., 95, 1597 (1962) and Ann. Chem., 691, 142 (1966), the compound (II) can be obtained by methods described in Chem. Pharm. Bull., 27, 1328 (1978) and Chem. Pharm. Bull., 15 27, 1965 (1978) or in Japanese Unexamined Patent Publication No. 31694/1978, Japanese Unexamined Patent Publication No. 5082/1986 corresponding to EP 166054. More specifically, the 3-amino derivative (IX) obtained by four processes shown by the process (k), (l), (m) or 20 (n) is allowed to react with one of the various alkyl dihalides (e.g. 1-bromo-2-chloroethane, 1-bromo-3-chloropropane, 1-bromo-4-chlorobutane, etc.) as shown by process (o) in an aprotic solvent such as dimethylformamide, etc. in the presence of potassium 25 carbonate, sodium carbonate, etc. at temperatures ranging from 50 C to 120 C for about 10 to about 20 hours to obtain the starting compound (II). On the other hand, the starting compound (III) can be obtained, as shown by process (p), by allowing compound 30 (IX) to react with a halogenated aliphatic alkyl ester (e.g. bromoacetic acid methyl ester, bromoacetic ethyl ester, etc.), in the presence of potassium carbonate or sodium carbonate, in an aprotic solvent such as dimethylformamide, etc. at temperatures ranging from 35 room temperature to about 80°C for about 1 to about 5 hours.

The starting compound (XVI) can be obtained by subjecting the compound (VIIIb) prepared by the method shown in process (l) to alkaline hydrolysis as shown in process (r).

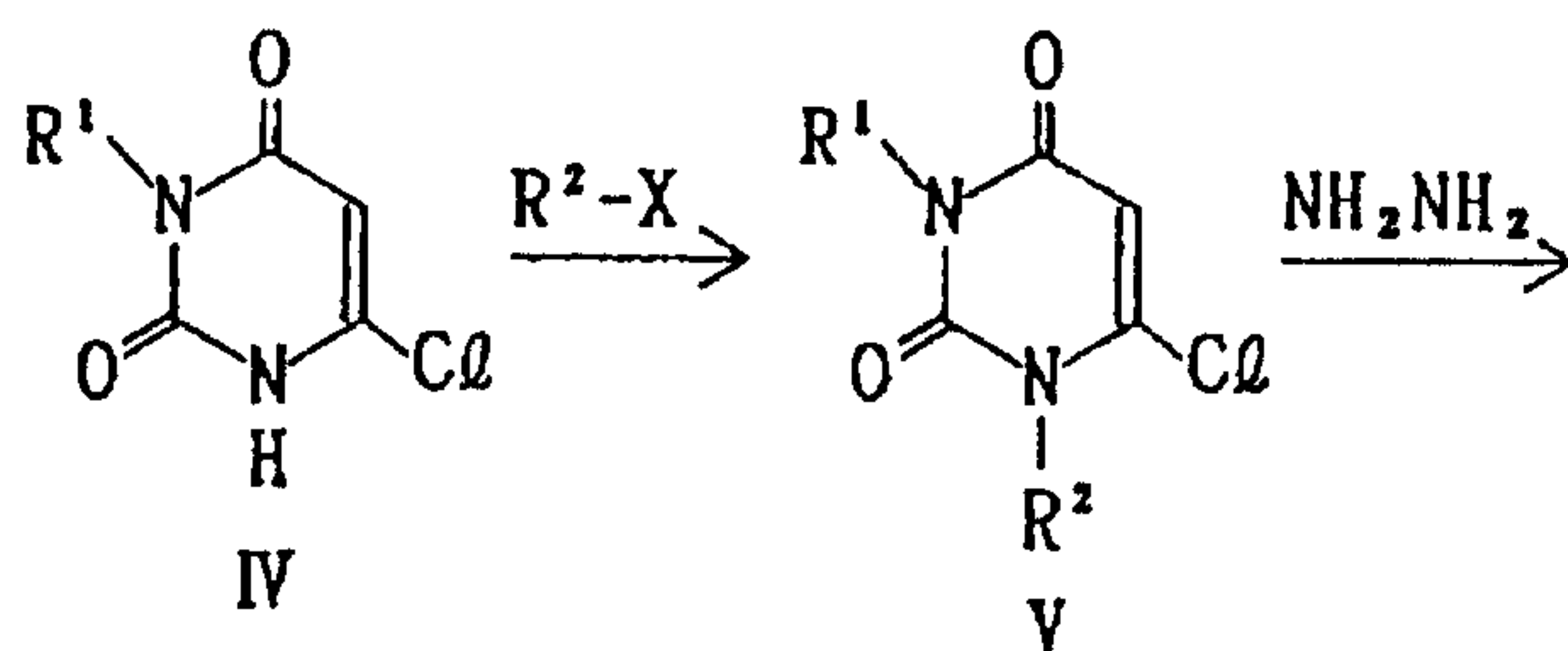
5 The starting compound (XV) can be prepared, as shown in process (q), by allowing the above-mentioned 3-amino derivatives (IX) to react with a haloketone (e.g. bromoacetone, chloroacetone, 3-chloro-2-butanone, phenacyl chloride, phenacyl bromide, 2-
10 chlorocyclohexanone, 1-chlorohexane-2-one, etc.) in the presence of a base such as potassium carbonate, sodium carbonate, triethylamine, etc., and in the presence of potassium iodide as a reaction promoter, at
15 temperatures ranging from room temperature to about 50°C for about 1 to about 4 days.

20

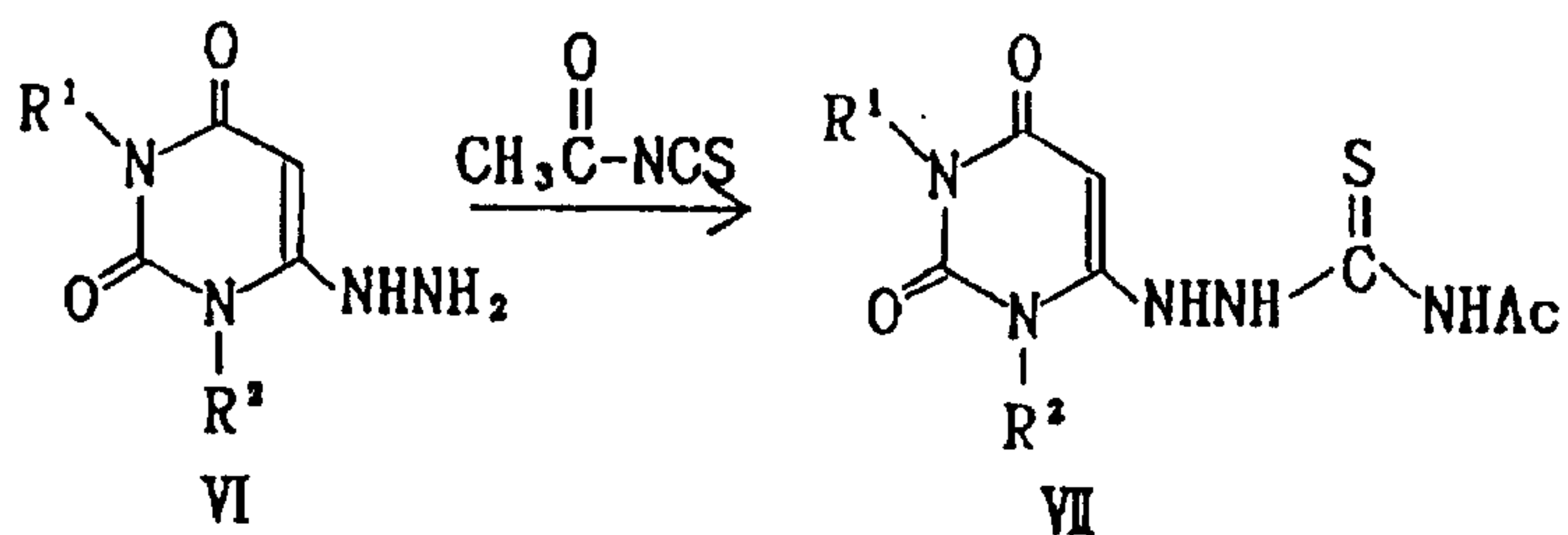
25

Process (k)

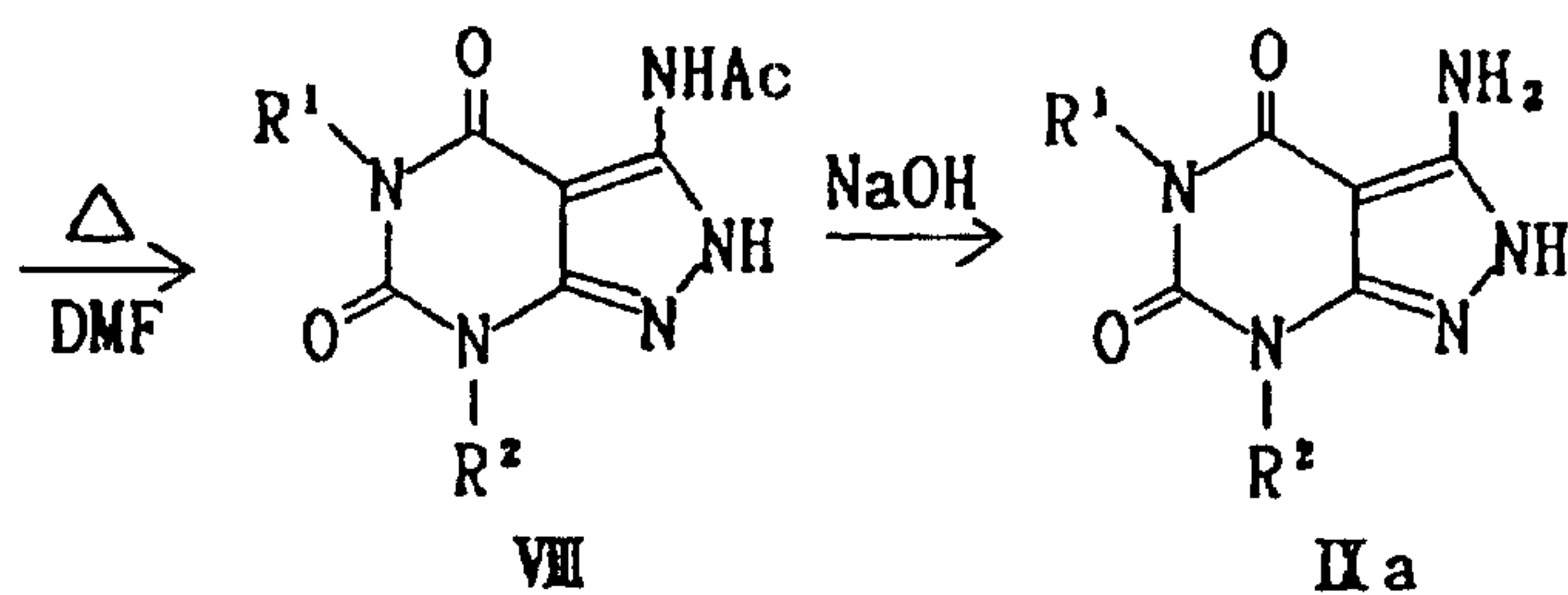
5



10



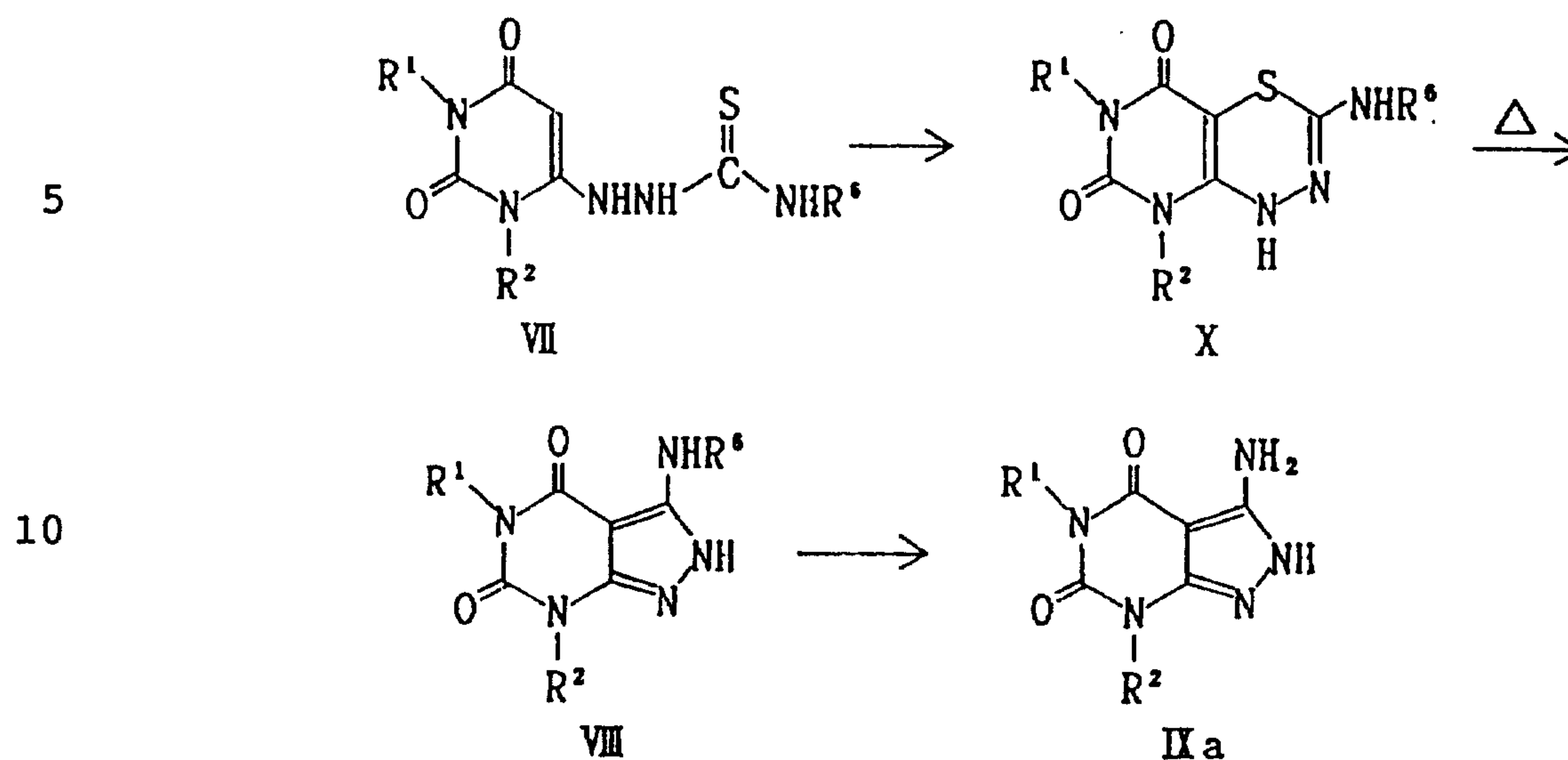
15



20

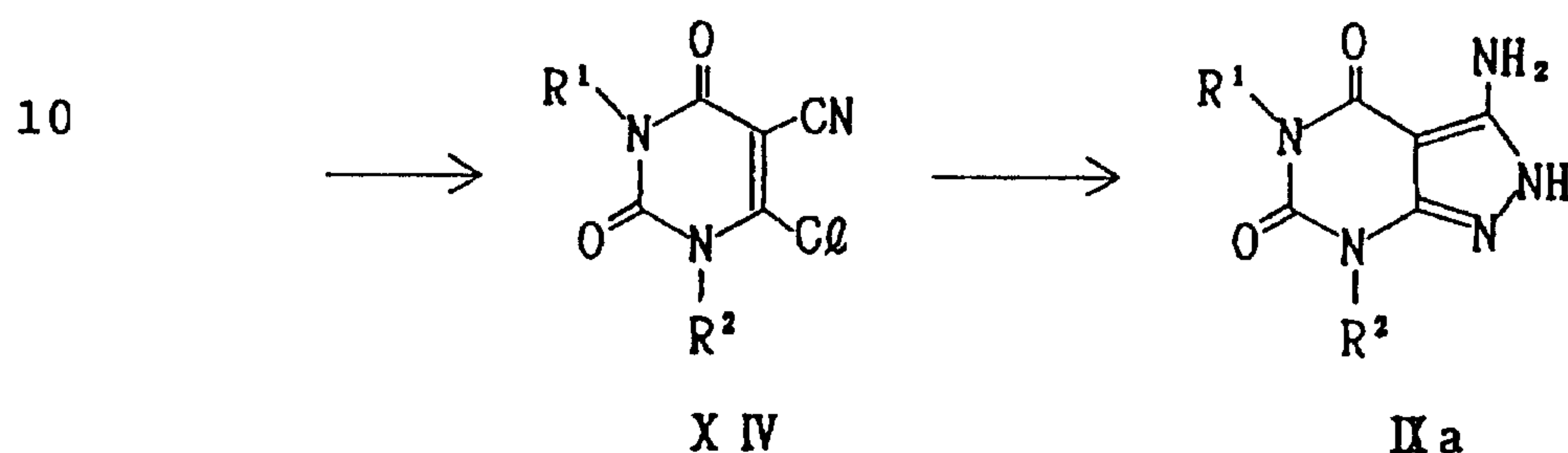
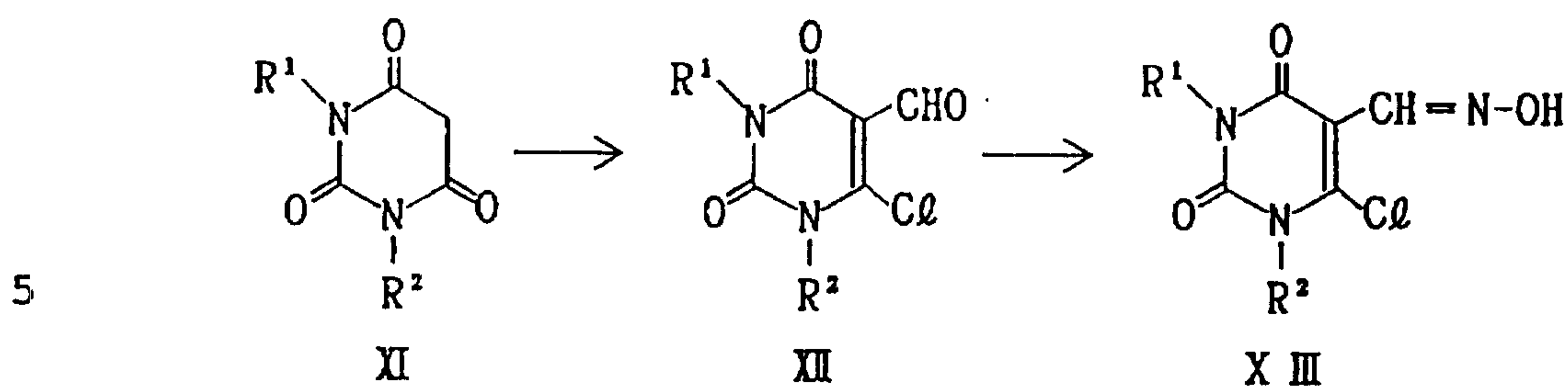
wherein R^1 , R^2 and X are of the same meaning as defined above.

Process (1)



wherein R^1 , R^2 and R^3 are of the same meaning as defined above, provided that R^3 is not hydrogen.

Process (n)

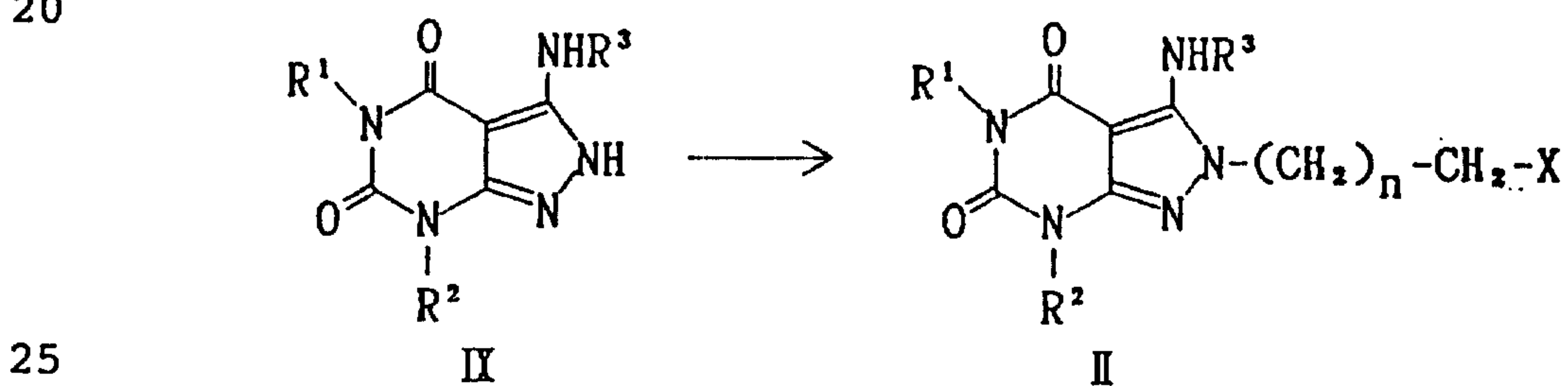


15

wherein R^1 and R^2 are of the same meaning as defined above, provided that $R^1 = R^2$.

Process (o)

20

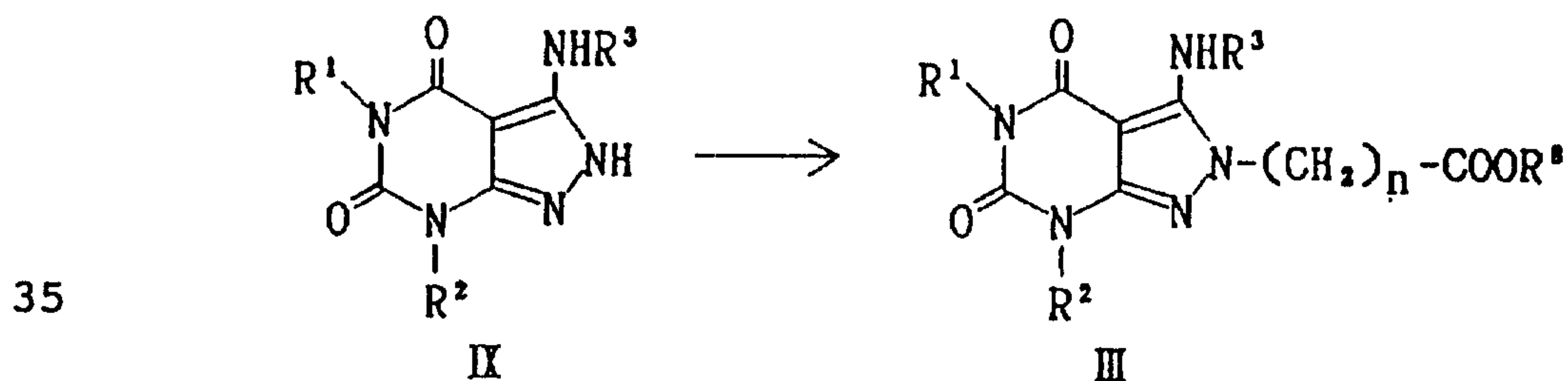


25

wherein R^1 , R^2 , R^3 , X and n are of the same meaning as defined above.

30

Process (p)



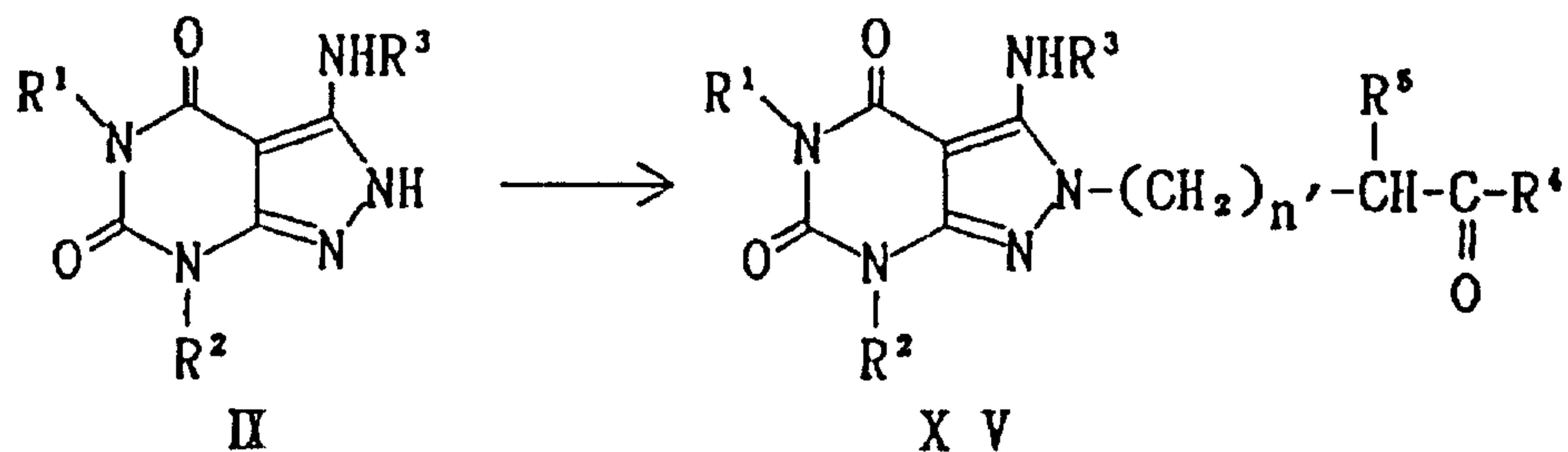
35

wherein R^1 , R^2 , R^3 , R^8 and n are of the same meaning as defined anove.

Process (q)

5

10

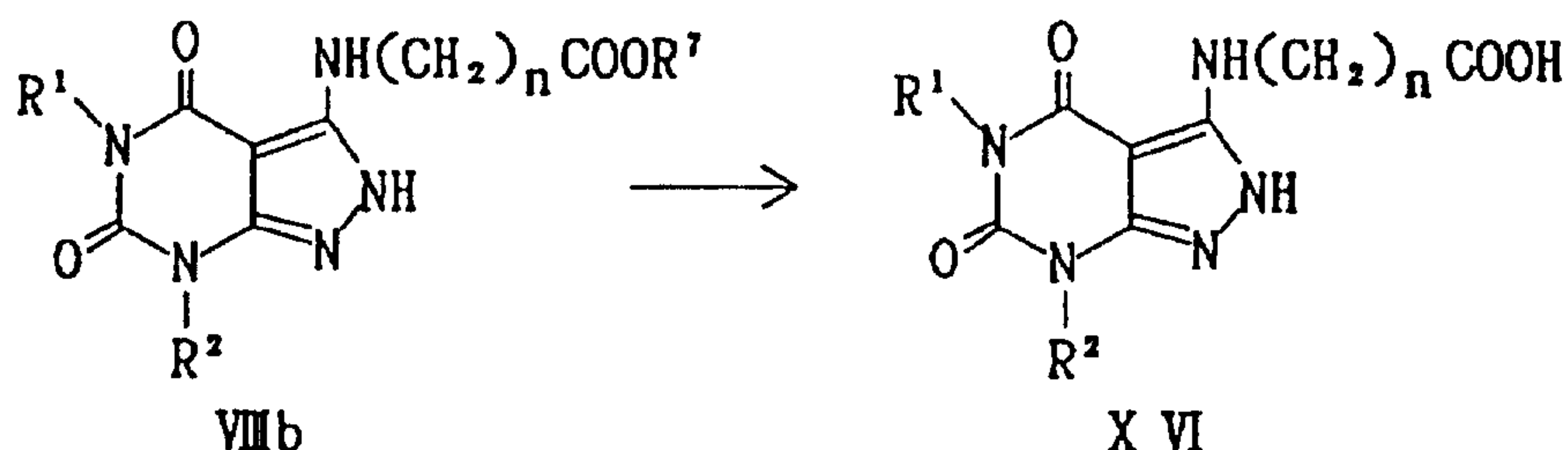


wherein R^1 , R^2 , R^3 , R^4 , R^5 and n' are of the same meaning as defined above.

15

Process (r)

20



25

wherein R^1 , R^2 , R^7 and n are of the same meaning as defined above.

Action

30

35

The compounds (I) of the present invention have a strong antagonistic action in the adenosine-receptor derived from rat's cerebral cortex, cause acceleration of release of various neurotransmitters in brain and increase of the concentration thereof in brain to perform activation of cerebral functions and metabolisms. Namely, the compounds (I) are useful, owing to their properties of activating cerebral functions and metabolisms which are decreased by the

occurrence of cerebrovascular disease, brain injury or aging, for the therapy and prophylaxis, to mammals, of neurological or psychic changes (neurological deficits or psychic disturbances) including dementia symptom
5 caused by cerebral apoplexy, brain injury or cerebral atrophy (Alzheimer's diseases, etc.), and they can be used for the prophylaxis and therapy of, for example, memory impairment (e.g. amnesia, retention disturbance, etc.), disorientation for place and time, emotional
10 disturbances, decreased spontaneity and dystropy. And, the compounds (I) are of low toxicity [$LD_{50}(p.o.)$: not less than 1000 mg/kg body weight (mouse)]. When the compounds (I) are used as medicines mentioned above, they can be safely administered to mammals including
15 man orally or non-orally as such or an admixture with suitable, pharmaceutically acceptable carriers, excipients or diluents in such dosage forms as powder, granules, tablets, capsules, injections, suppositories, ointments and so forth.

20 Additives employable for such medicinal preparations as mentioned above include excipients e.g. sucrose, lactose, glucose, starch, mannitol, sorbitol, micro-crystalline cellulose, talc, cryclodextrin, etc., binders e.g. hydroxypropylcellulose, hydroxypropyl
25 methylcellulose, carboxymethylcellulose, pullulan, methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, polyethylene glycol, sucrose, starch, etc., disintegrants e.g. starch, carboxymethylcellulose, calcium salt of carboxymethylcellulose,
30 hydroxypropylcellulose of low substitution degree, etc., lubricants e.g. talc, magnesium stearate, etc., coloring agents e.g. hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose phthalate, Eudragit [Rohm
35 Pharma GmbH (W. Germany); methacrylic acid.acrylic acid copolymer], titanium oxide, red iron oxide, etc.,

preservatives e.g. sodium benzoate, sodium
hydrogensulfite, etc., suspending agents e.g. methyl
cellulose, aluminum stearate, etc., dispersants e.g.
Polysorbate 80, Emal Gel 408, Emasol 310, etc. solvents
5 e.g. water, base materials e.g. cacao butter,
polyethylene glycol, Wittep Sol, white petrolatum,
etc., and these adjuvants may be suitably selected in
accordance with the types of preparations.

Although the dosage should vary with such factor
10 as the subject diseases, symptoms, subject patients,
the routes of administration, etc., when orally
administered to an adult human patient with including
dementia symptom caused by cerebral apoplexy, brain
injury or cerebral atrophy, preferable dosage is in the
15 range of from about 1 to about 50 mg/kg (body weight) 1
to about 3 times a day, more preferably about 1 to
about 20 mg/kg (body weight) 1 to about 3 times a day.

Working Examples

20 The following reference examples, working
examples, formulation examples and experimental
examples are intended to illustrate the present
invention in further detail and should by no means be
construed as limiting the scope of the present
25 invention.

Abbreviations employed in the present
specification are exemplified below.

Me : methyl	Hex : hexyl	
Et : ethyl	Hep : heptyl	
30 Pr : propyl	All : allyl	
Bu : butyl	Ac : acetyl	
Pen: pentyl	Ph : phenyl	
s : singlet	d : doublet	t : triplet
m : multiplet	br s : broad singlet	

35

Reference Example 1

2010009

6-(4-Acetylthiosemicarbazido)-1-benzyl-3-propylpyrimidine-2,4(1H,3H)-dione

Acetyl chloride (11g) was added to a suspension of potassium thiocyanate (20 g) in dioxane (300 ml) and the mixture was stirred for 5 hours at room temperature. After removal of an insoluble material by filtration, the filtrate was stirred at room temperature and 1-benzyl-6-hydrazino-3-propylpyrimidine-2,4(1H,3H)-dione (18.2 g) was added in portions to the filtrate at room temperature. The reaction mixture was allowed to stir for one hour at room temperature and was concentrated to dryness. The resulting product was triturated with isopropyl ether to give crystals (24 g, 96%), m.p. 184 to 185°C.

Elemental Analysis for $C_{17}H_{21}N_5O_3S$:

Calcd.(%) : C, 54.38; H, 5.64; N, 18.65

Found (%) : C, 54.21; H, 5.87; N, 18.59

The following compounds (Reference Examples 2 to 5) were synthesized by the same procedure.

Reference Example 2

6-(4-acetylthiosemicarbazido)-1-(4-chlorobenzyl)-3-propylpyrimidine-2,4(1H,3H)-dione, m.p. 195 - 196°C

Reference Example 3

6-(4-Acetylthiosemicarbazido)-1-(3-chlorobenzyl)-3-propylpyrimidine-2,4(1H,3H)-dione, m.p. 189 - 190°C

Reference Example 4

6-(4-Acetylthiosemicarbazido)-1-(2-chlorobenzyl)-3-propylpyrimidine-2,4(1H,3H)-dione, m.p. 126 - 127°C

Reference Example 5

6-(4-Acetylthiosemicarbazide)-3-benzyl-1-butylpyrimidine-2,4(1H,3H)-dione, m.p. 124 - 125°C

Reference Example 6

3-Acetylamino-8-benzyl-6-propyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-5,7(6H,8H)-dione

5 6-(4-Acetylthiosemicarbazido)-1-benzyl-3-propylpyrimidine-2,4(1H,3H)-dione (7 g) was added in portions to a mixture of N-chlorosuccinimide (3 g) at room temperature and the reaction mixture was stirred further 3 hours, to which was added hexane (200 ml).
10 Resulting crystals were collected by filtration and washed with water to give yellowish brown crystals (9.3 g), m.p. 135 - 140°C. This product was used for the subsequent reaction without further purification. In a manner analogous to the above, the following compounds
15 (Reference Examples 7 to 10) were synthesized.

Reference Example 7

3-Acetylamino-8-(4-chlorobenzyl)-6-propyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-5,7(6H,8H)-dione,
20 m.p. 137 - 139°C

Reference Example 8

3-Acetylamino-8-(3-chlorobenzyl)-6-propyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-5,7(6H,8H)-dione,
25 m.p. 135 - 140°C

Reference Example 9

3-Acetylamino-8-(2-chlorobenzyl)-6-propyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-5,7(6H,8H)-dione,
30 m.p. 135 - 136°C

Reference Example 10

3-Acetylamino-6-benzyl-8-butyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-5,7(6H,8H)dione, m.p. 136 - 137°C
35

Reference Example 11

3-Acetylamino-7-benzyl-5-propylpyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

A solution of 3-acetylamino-8-benzyl-6-propylpyrimido[4,5-e][1,3,4]thiadiazine-5,7(6H,8H)-dione (4.0 g) in dioxane (50 ml) was refluxed for one hour. The reaction mixture was concentrated to dryness, and the concentrate was dissolved in methanol. Insoluble sulfur was filtered off. To the filtrate was added a small volume of water, which was left standing for cooling, then colorless crystals (3.4 g), m.p. 108 - 110°C, were obtained.

Elemental Analysis for $C_{17}H_{19}N_5O_3$:

	C(%)	H(%)	N(%)
Calcd.:	59.81;	5.61;	20.52
Found :	59.73;	5.68;	20.59

By a manner analogous to Reference Example 11, the following compound was synthesized.

Reference Example 12

3-Acetylamino-7-(m-chlorobenzyl)-5-propylpyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, m.p. 204 - 205°C

Reference Example 13

3-Acetylamino-7-benzyl-5-propylpyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

A solution of 6-(4-acetylthiosemicarbazido)-1-benzyl-3-propylpyrimidine-2,4(1H,3H)-dione (3.0 g) in dimethylformamide (50 ml) was heated at 100 to 110°C for 60 hours. The reaction mixture was concentrated, which was dissolved in 90% methanol. The solution was left standing for cooling to give pale brown crystals, followed by recrystallization from ethanol to obtain colorless crystals, m.p. 108 to 110°C.

	C(%)	H(%)	N(%)
Calcd.:	59.81;	5.61;	20.52
Found :	59.64;	5.75;	20.44

5 Reference Example 14

3-Amino-7-benzyl-5-propylpyrazolo[3,4-
d]pyrimidine-4,6(5H,7H)-dione

3-Acetylamino-7-benzyl-5-propylpyrazolo[3,4-
10 d]pyrimidine-4,6(5H,7H)-dione (18 g) was refluxed for 5
hours in 80% ethanol (200 ml) dissolving sodium
hydroxide (6 g). The reaction mixture was
concentrated, and the resulting crystals were suspended
in water. To the suspension was added 6N-HCl to obtain
15 colorless crystals (11 g, 70%), m.p. 214 - 215°C.
Elemental Analysis for C₁₅H₁₇N₅O₂ :

	C(%)	H(%)	N(%)
Calcd.:	60.19;	5.72;	23.40
Found :	60.35;	5.65;	23.24

20

By a manner analogous to the above, the following
compounds (Reference Examples 15 to 18) were
synthesized.

25 Reference Example 15

3-Amino-7-(4-chlorobenzyl)-5-propylpyrazolo[3,4-
d]pyrimidine-4,6(5H,7H)-dione, m.p. 208 - 210°C

Reference Example 16

30 3-Amino-7-(3-chlorobenzyl)-5-propylpyrazolo[3,4-
d]pyrimidine-4,6(5H,7H)-dione, m.p. 141 - 142°C

Reference Example 17

35 3-Amino-7-(2-chlorobenzyl)-5-propylpyrazolo[3,4-
d]pyrimidine-4,6[5H,7H)-dione, m.p. 263 - 265°C

Reference Example 18

3-Amino-5-benzyl-7-butylpyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, m.p. 197 - 198°C

5 Reference Example 19

3-Amino-7-benzyl-2-(2-chloroethyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

10 A mixture of 3-amino-7-benzyl-5-propylpyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (11 g), 1-bromo-2-chloroethane (8.0 g) and potassium carbonate (7.0 g) was stirred in DMF (120 ml) at 50 - 60°C for 12 hours. The reaction mixture was concentrated to dryness, then the concentrate was extracted with chloroform/water. 15 The chloroform layer was washed with water, dried and concentrated. The resultant brown syrup was purified by flash chromatography (silica gel 100 g, chloroform). The resultant syrup was crystallized from isopropylether to afford colorless needles (8.0 g, 20 60%), m.p. 126 to 128°C.

Elemental Analysis for $C_{17}H_{20}N_5O_2Cl$:

	C(%)	H(%)	N(%)
Calcd.:	56.43;	5.57;	19.36
Found :	56.61;	5.49;	19.18

25

By a manner analogous to Reference Example 19, the following compounds (Reference Examples 20 to 25) were synthesized.

30 Reference Example 20

3-Amino-7-(4-chlorobenzyl)-2-(2-chloroethyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, m.p. 161 - 163°C

35 Reference Example 21

3-Amino-7-(3-chlorobenzyl)-2-(2-chloroethyl)-5-propyl-

2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, m.p. 128
- 130°C

Reference Example 22

- 5 3-Amino-7-(2-chlorobenzyl)-2-(2-chloroethyl)-5-propyl-
2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, m.p. 162
- 165°C

Reference Example 23

- 10 3-Amino-5-benzyl-7-butyl-2-(2-chloroethyl)-2H-
pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, m.p. 172 -
173°C

Reference Example 24

- 15 3-Amino-2-(2-chloroethyl)-7-phenethyl-5-propyl-2H-
pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, m.p. 276 -
277°C

Reference Example 25

- 20 3-Amino-2-(2-chloroethyl)-7-(3-phenylpropyl)-5-propyl-
2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione, m.p. 219
- 220°C

Reference Example 26

- 25 3-Amino-7-benzyl-2-(hexan-2-on-1-yl)-5-propyl-2H-
pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione
A mixture of 3-amino-7-benzyl-5-propylpyrazolo[3,4-
d]pyrimidine- 4,6(5H,7H)-dione (1g), 1-chloro-2-
hexanone (2g) and potassium carbonate (2g) in
30 acetonitrile (50 ml) was stirred at room temperatures
for 4 days. Insoluble material was filtered off. The
filtrate was concentrated and the concentrate was
washed with water and subsequently hexane to obtain
pale brown powder (1.3 g, 98%). This product was used
35 for the subsequent reaction without further
purification.

¹H-NMR (CDCl₃) δ: 0.75-1.05 (6H,m), 1.05-2.20 (6H,m), 2.43 (2H,t), 3.85 (2H,t), 4.65 (2H,s), 5.05 (2H,s), 5.10 (2H,s), 7.20-7.50 (5H,m)

5 Reference Example 27

3-Amino-7-benzyl-2-(3-methoxyphenacyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione

A mixture of 3-amino-7-benzyl-5-propylpyrazolo[3,4-d]pyrimidine (1.0 g), p-methoxyphenacylbromide (2 g)
10 and potassium carbonate (1 g) in acetonitrile (50 ml) was stirred for 3-4 days. Precipitating crystals in the mixture were collected by filtration and washed with water to obtain colorless crystals (1.16 g, 78%), m.p. 184 - 185°C.

15 ¹H-NMR (CDCl₃) δ: 0.90 (3H,t), 1.35-1.90 (2H,m), 3.80 (2H,t), 3.81 (3H,s), 5.05 (2H,s), 5.17 (2H,s), 5.27 (2H,s), 7.05-7.65 (9H,m)

By a manner analogous to Reference Example 27, the following compounds (Reference Examples 28 to 32) were
20 synthesized.

Reference Example 28

3-Amino-7-benzyl-2-(2-methoxyphenacyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (m.p. 173 -
25 174°C, 100%)

Reference Example 29

3-Amino-7-benzyl-2-(4-methoxyphenacyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (m.p. 205 -
30 206°C, 89%)

Reference Example 30

3-Amino-7-benzyl-2-(4-chlorophenacyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (69%)
35

Reference Example 31

3-Amino-7-benzyl-2-(3-chlorophenacyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (61%)

Reference Example 32

5 3-Amino-7-benzyl-2-(4-butoxyphenacyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine- 4,6(5H,7H)-dione (m.p. 148 - 149°C, 56%)

10 Working Example 1

1-benzyl-3-propyl-1,2,3,4,6,7-hexahydro-5H-imidazo[2',1': 5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione

15 Sodium hydride (60% oil, 0.8 g) was added in portions to a stirring solution of 3-amino-7-benzyl-2-(2-chloroethyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (4.9 g) under cooling with ice bath. The mixture was stirred for 17 hours and was concentrated to dryness. The residue was triturated with water and the resulting crystals were collected by filtration, washed with water and dried.

Recrystallization from DMF-methylene chloride gave colorless crystals (2.5 g, 57%), m.p. 215 - 216°C.

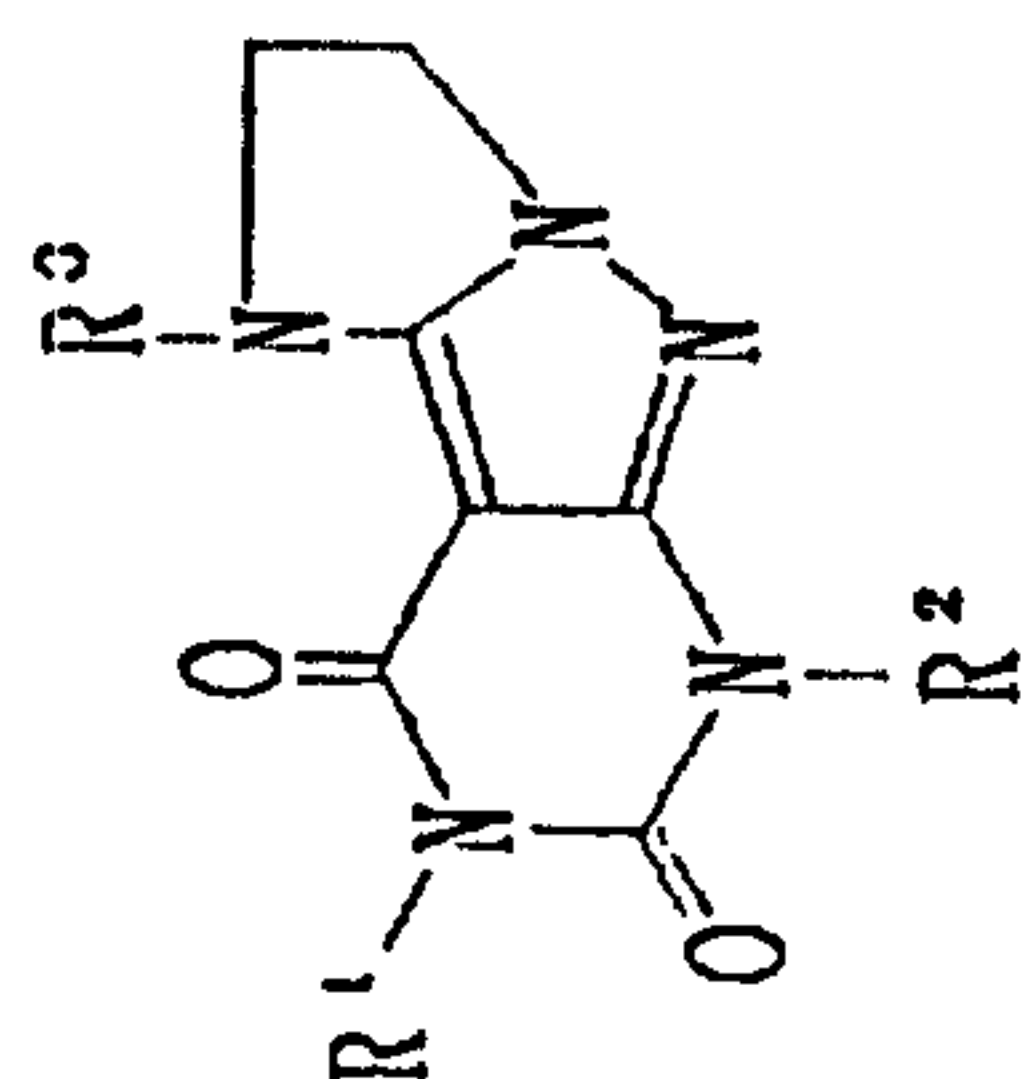
Elemental Analysis for C₁₇H₁₉N₅O₂ :

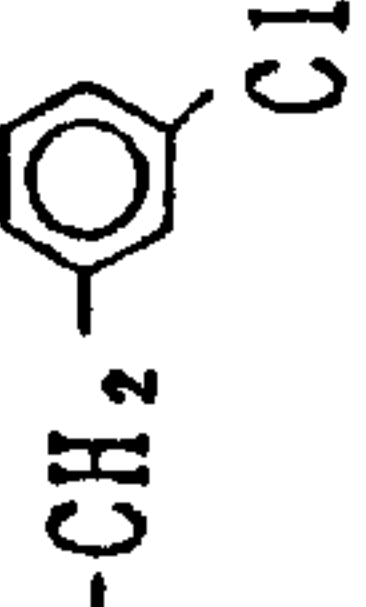
25	C(%)	H(%)	N(%)
	Calcd.: 62.76;	5.89;	21.52
	Found : 62.59;	5.87;	21.42

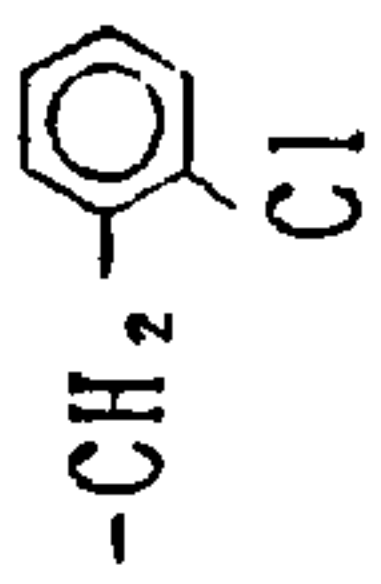
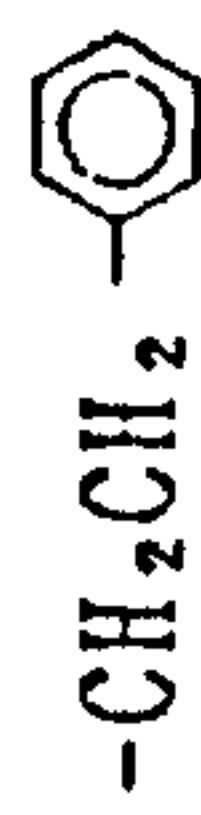
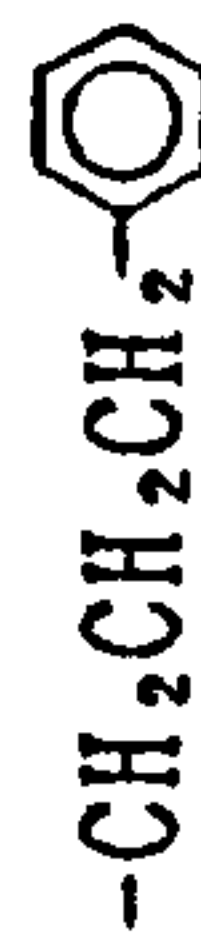
30 NMR(d₆-DMSO) δ: 0.90 (3H,t), 1.40-1.85 (2H,m), 3.87 (2H,t), 4.05 (4H,s), 5.07 (2H,s), 6.73 (1H,s), 7.20-7.55(5H,m)

The following compounds were synthesized by the same procedure as Working Example 1.

Table-1



W. Ex. No.	R ¹	R ²	R ³	Yield (%)	m.p. (°C)	¹ H - NMR Spectrum (Solvent)
2	Pr	-CH ₂ - 	H	51	236-238	(d ₆ -DMSO) 0.90(3H, t), 1.40-1.85(2H, m), 3.87(2H, t), 4.05(4H, s), 5.07(2H, s), 6.73(1H, s), 7.20-7.55(5H, m)
3	Pr	-CH ₂ - 	H	73	205-207	(CDCl ₃) 0.90(3H, t), 1.40-1.85(2H, m), 3.87(2H, t), 4.10(4H, s), 5.05(2H, s), 5.40-5.90(1H, br s), 7.10-7.35(3H, m), 7.40(1H, s)

4	Pr		H	55	262-263	(d ₆ -DMSO) 0.90(3H, t), 1.35-1.80(2H, m), 3.87(2H, t), 4.03(4H, s), 5.17(2H, s), 6.85-7.45(5H, m)
5	 -CH ₂ -Bu	Bu	H	72	156-157	(CDCl ₃) 0.93(3H, t), 1.15-1.93(4H, m), 3.80-4.25(6H, m), 5.10(2H, s), 5.80(1H, s), 7.20-7.50(5H, m)
6	Pr		H	94	209-210	
7	Pr		H	99	138-139	

Working Example 8

1-Benzyl-3-propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione

5 A solution of 1-benzyl-3-propyl-1,2,3,4,6,7-hexahydro-5H-imidazo[2',1':5,1]-pyrazolo[3,4-d]pyrimidine-2,4-dione (4.5 g) and benzoyl peroxide (5.0 g) in chloroform (100 ml) was refluxed for 18 hours. The reaction mixture was concentrated to dryness, and the residue was dissolved in chloroform. The solution was washed with an aqueous solution of sodium carbonate and water, followed by drying and concentration to dryness. The residue was purified by flash chromatography. Recrystallization of thus
10 obtained crystals from methylene chloride/hexane afforded colorless crystals (2.3 g, 52%), m.p. 290 - 292°C.

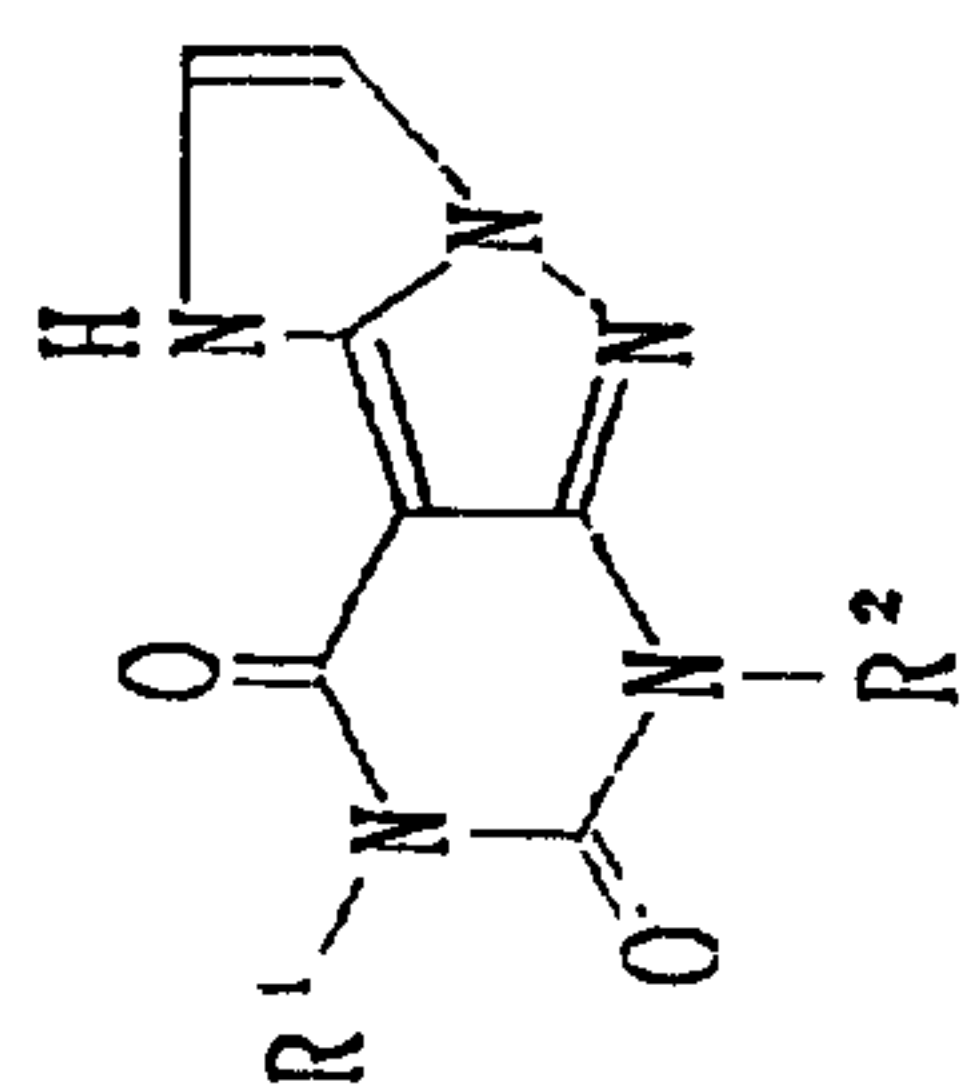
Elemental Analysis for $C_{17}H_{17}N_5O_2$:

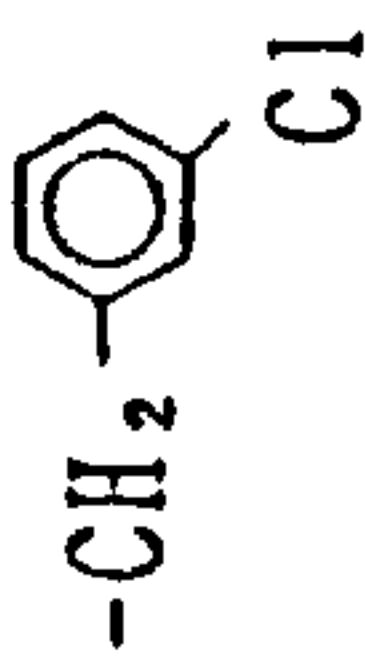
	C(%)	H(%)	N(%)
20 Calcd.:	63.15;	5.30;	21.66
Found :	63.38;	5.19;	21.50

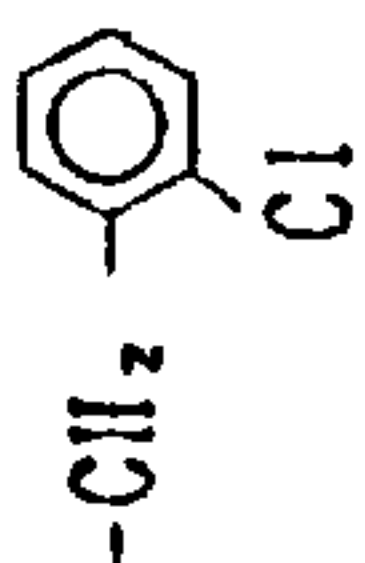
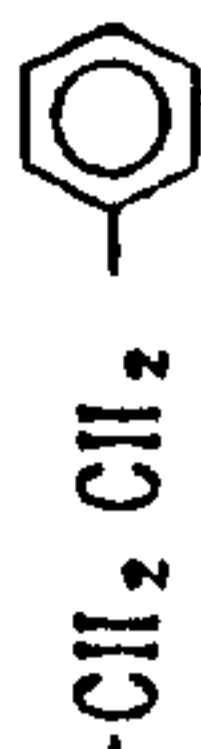
$^1\text{H-NMR}$ (d_6 -DMSO) δ : 0.91(3H,t), 1.45-1.90(2H,m),
3.93(2H,t), 5.20(2H,s), 6.93(1H,s), 7.20-7.60(6H,m),
25 12.45(1H,s)

The following compounds were synthesized by the same procedure as Working Example 8.

Table -2



W. Ex No.	R ¹	R ²	Yield (%)	m.p. (°C)	¹ H - NMR Spectrum (Solvent)
9	Pr	-CH ₂ - 	51	288-290	(d ₈ -DMSO) 0.87(3H, t), 1.30-1.80(2H, m), 3.87(2H, t), 5.10(2H, s), 7.10-7.50(5H, m), 7.70(1H, d)
10	Pr	-CH ₂ - 	50	278-280	(d ₈ -DMSO) 0.87(3H, t), 1.35-1.85(2H, m), 3.87(2H, t), 5.15(2H, s), 7.37(4H, s), 7.43(1H, s), 7.79 (1H, d)

11	Pr		47	>300	(d ₈ -DMSO) 0.87(3H, t), 1.35-1.85(2H, m), 3.87(2H, t), 5.20(2H, s), 6.90-7.10(1H, m), 7.10-7.40(3H, m), 7.40-7.60(1H, m), 7.70(1H, d)
12	 -CH ₂ -Bu	Bu	60	250-251	(d ₈ -DMSO) 0.90(3H, t), 1.10-1.50(2H, m), 1.50-1.90(2H, m), 3.93(2H, t), 5.07(2H, s), 7.27(6H, s), 7.77(1H, d), 12.83(1H, s)
13	Pr		60	276-277	(d ₈ -DMSO) 0.90(3H, t), 1.40-1.90(2H, m), 3.00-3.25(2H, m), 3.95(2H, t), 4.17-4.40(2H, m), 6.97(1H, d) 7.30(5H, s), 7.39(1H, d), 12.45(1H, s)
14	Pr		59	219-220	(CDCl ₃) 1.00(3H, t), 1.50-2.00(2H, m), 2.0-2.4(2H, m) 2.6-2.9(2H, m), 4.03(2H, t), 4.17(2H, t), 6.90 (1H, t), 7.20(5H, s), 7.37(1H, d), 12.03(1H, s)

Working Example 15

1-Benzyl-3-propyl-6-phenyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione

5 A suspension of 3-amino-7-benzyl-5-propylpyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (2.0 g), phenacyl chloride (4.4 g), K₂CO₃ (2.5 g) and potassium iodide (1.4 g) in acetonitrile (150 ml) was stirred for 3 days at room temperature. Precipitating
10 crystals were collected by filtration and washed with water. The filtrate was concentrated to give a syrup. The syrup was crystallized by the addition of isopropyl ether. The crystals were combined and dissolved in toluene (200 ml). To the solution was added p-
15 toluenesulfonic acid (0.1 g), followed by heating for 3 hours under reflux. The reaction mixture was concentrated to dryness, to which was added isopropyl ether to give crude crystals, followed by recrystallization from methanol to afford colorless
20 crystals (1.1 g, 43%), m.p. 261-262°C.

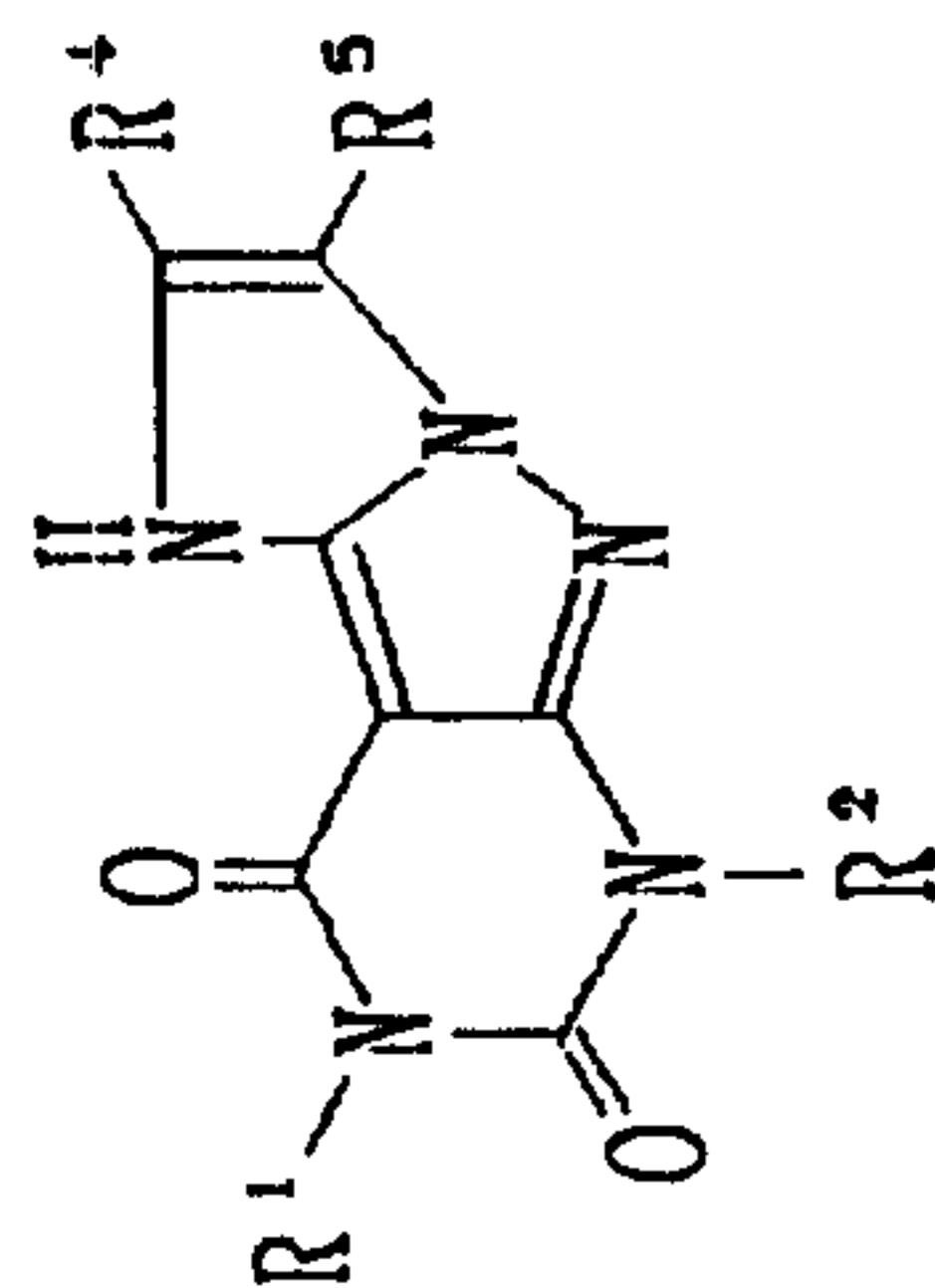
Elemental Analysis for C₂₃H₂₁N₅O₂ :

	C(%)	H(%)	N(%)
Calcd.:	69.15;	5.30;	17.53
Found :	69.04;	5.44;	17.69

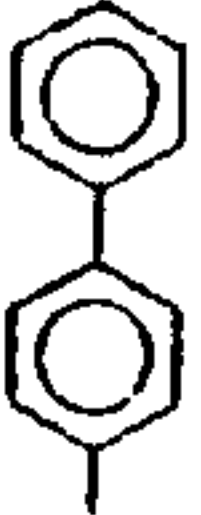
25 ¹H-NMR(d₆-DMSO) δ : 0.91(3H,t), 1.40-1.90(2H,m), 3.95(2H,t), 5.21(2H,s), 7.10-7.85(11H,m)

30 The following compounds were synthesized by the same procedure as Working Example 15.

Table-3



W. Ex. No.	R ¹	R ²	R ⁴	R ⁵	Yield (%)	m.p. (°C)	¹ H - NMR Spectrum (Solvent)
16	Pr	-CH ₂ -	Me	Me	63	>300	(d ₆ -DMSO) 0.90(3H, t), 1.40-1.90(2H, m), 2.27(3H, s), 2.31(3H, s), 3.90(2H, t), 5.20(2H, s), 7.15-7.40(3H, m), 7.40-7.57(2H, m), 12.17(1H, s)
17	Pr	-CH ₂ -	Bu	H	71	208-209	(CDCl ₃) 0.85(3H, t), 0.93(3H, t), 1.10-2.00(6H, m), 2.67(2H, t), 4.00(2H, t), 5.27(2H, s), 7.07(1H, s), 7.20-7.40(3H, m), 7.40-7.65(2H, m), 11.30(1H, s)

18	Pr			H	25	265-266	
19	Pr				6	300-302	(CDCl ₃) 0.90(3H, t), 1.30-2.10(6H, m), 2.45-2.85(4H, m), 3.90(2H, t), 5.20(2H, s) 7.15-7.70(5H, m), 12.07(1H, s)
20	Pr			H	52	307-309	(d ₆ -DMSO) 0.93(3H, t), 1.40-1.90(2H, m), 3.95(2H, t), 5.20(2H, s), 7.15-7.80(9H, m) 7.63(1H, s), 12.95(1H, s)

Working Example 21

1-Benzyl-6-(3-methoxyphenyl)-3-propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione

5

3-Amino-7-benzyl-2-(3-methoxyphenacyl)-5-propyl-2H-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (1.16 g) and p-toluenesulfonic acid (0.1 g) were dissolved in toluene (50 ml) and the solution was refluxed for 3 hours. The reaction solution was concentrated and to the concentrate was added methanol. Precipitating crystals were collected by filtration to obtain pale yellow crystals (0.83 g, 75%), m.p. 249 - 250°C.

10

Elemental Analysis for $C_{24}H_{23}N_5O_3$:

15

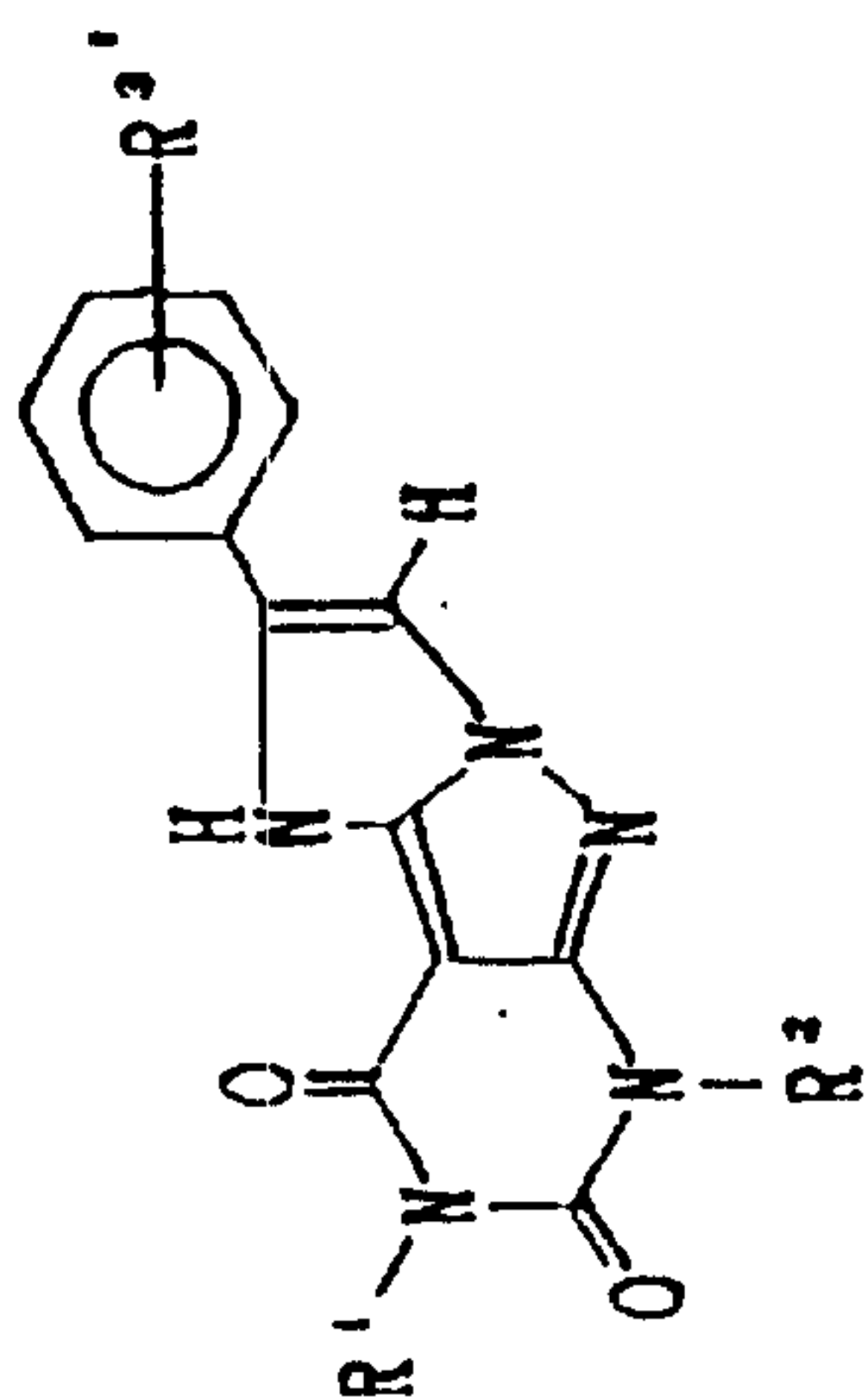
	C(%)	H(%)	N(%)
Calcd.:	67.12;	5.40;	16.31
Found :	67.43;	5.24;	16.05

20

$^1\text{H-NMR}(\text{CDCl}_3+\text{d}_6\text{-DMSO})$ δ : 0.90(3H,t), 1.40-1.90(2H,m), 3.80(3H,s), 3.93(2H,t), 5.17(2H,s), 6.70-7.65(10H,m), 12.90(1H,s)

The following compounds were synthesized by the same procedure as Working Example 21.

25



W. Ex. No.	R¹	R²	R³	Yield (%)	m.p. (°C)	¹H-NMR spectrum (solvent)
22	Pr	-CH₂-	p-MeO	69	275-276	(d₆-DMSO) 0.90(3H, t), 1.40-1.90(2H, m), 3.77(3H, s), 3.93(2H, t), 5.19(2H, s), 6.90(2H, d), 7.60 (2H, d), 7.43(1H, s), 7.20-7.35(3H, m), 7.35 -7.50(2H, m), 12.70(1H, s)
23	Pr	-CH₂-	o-MeO	88	112-113	(CDCl₃) 0.87(3H, t), 1.40-1.90(2H, m), 3.90(2H, t), 3.90(3H, s), 5.20(2H, s), 6.80-7.70(10H, m), 11.07(1H, s)

24	Pr	-CH ₂ 	p-BuO	81	108-109	(CDCl ₃) 0.80(3H, t), 0.95(3H, t), 1.20-1.95(6H, m), 2.33(3H, s), 3.87(2H, t), 3.93(2H, t), 5.20(2H, s), 6.85(2H, d), 7.20-7.60(8H, m), 11.75(1H, s),
25	Pr	-CH ₂ 	p-Me	48	261-262	(CDCl ₃) 0.78(3H, t), 1.30-1.80(2H, m), 2.33(3H, s), 3.80(2H, t), 5.20(2H, s), 7.00-7.60(10H, m), 11.50(1H, s)
26	Pr	-CH ₂ 	m-Cl	52	247-248	(d ₈ -DMSO) 0.93(3H, t), 1.40-1.90(2H, m), 3.93(2H, s), 5.20(2H, s), 7.17-7.90(10H, m), 13.07(1H, s)
27	Pr	-CH ₂ 	o-Cl	60	164-165	(CDCl ₃ -CD ₃ OD) 0.97(3H, t), 1.40-1.90(2H, m), 4.00(2H, s), 5.27(2H, s), 7.30-7.87(10H, m)
28	Pr	-CH ₂ 	p-Cl	70	307-309	(d ₈ -DMSO) 0.93(3H, t), 1.40-1.90(2H, m), 3.95(2H, t), 5.20(2H, s), 7.15-7.80(9H, m), 7.63(1H, s), 12.95(1H, s)

2010009

Working Example 29

1-Butyl-1,2,3,4,6,7-hexahydro-5H-
imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione

5

Boron tribromide (0.35 ml) was added to a stirred suspension of 3-benzyl-1-butyl-1,2,3,4,6,7-hexahydroimidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione (0.5 g) at room temperature. The reaction mixture was refluxed for 19 hours, which was cooled to room temperature, followed by addition of methanol (5 ml). The mixture was stirred for a while, then concentrated to dryness. The residue was dissolved in ethyl acetate, washed with water, dried and concentrated to give crude crystals, followed by recrystallization from ethyl acetate/hexane to afford colorless crystals (0.1 g, 27%), m.p. 239-240°C.

10

Elemental Analysis for C₁₁H₁₅N₅O₂ :

	C(%)	H(%)	N(%)
20 Calcd.:	53.00;	6.07;	28.10
Found :	53.24;	6.11;	27.86

¹H-NMR(d₆-DMSO) δ : 0.93(3H,t), 1.10-1.90(4H,m), 3.87(2H,t), 4.10(4H,s), 6.90(1H,s), 9.73(1H,s)

25

Working Example 30

3-Propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione

30

Boron tribromide (0.35 ml) was added to a stirred suspension of 1-benzyl-3-propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione (0.5 g) at room temperature. The reaction mixture was refluxed for 22 hours, which was then cooled to room temperature, followed by addition of methanol (10 ml). The mixture was stirred for a

35

while and was concentrated to dryness. After addition of ethyl acetate, resulting crystals were collected by filtration and washed with water to give crude crystals. Recrystallization from ethyl acetate gave
5 colorless crystals (0.16 g, 44%), m.p. 326 - 328°C (decomp.).

Elemental Analysis for $C_{10}H_{11}N_5O_2$:

	C(%)	H(%)	N(%)
Calcd.:	51.49;	4.75;	30.03
10 Found :	51.10;	4.83;	29.84

^1H -NMR(d_6 -DMSO) δ : 0.87(3H,t), 1.30-1.80(2H,m),
3.83(2H,t), 7.20(1H,s), 7.60(1H,s), 11.40(1H,s),
12.67(1Hs)

15 Working Example 31

1-Benzyl-6-butyl-5-methyl-3-propyl-1,2,3,4-tetrahydro-
5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-
dione

20

In DMF (20 ml) was dissolved 1-benzyl-6-butyl-3-propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]-pyrazolo[3,4-d]pyrimidine-2,4-dione (0.5 g). To the solution were added, at room temperature, K_2CO_3 (0.5 g)
25 and methyl iodide (0.5 g). The mixture was stirred for 8 hours and concentrated to dryness. To the residue was added water, then precipitating crystals were recrystallized from aqueous methanol to give colorless crystals (0.51 g, 98%), m.p. 139 - 140°C.

30 Elemental Analysis for $C_{22}H_{27}N_5O_2$:

	C(%)	H(%)	N(%)
Calcd.:	67.15;	6.92;	17.80
Found :	66.92;	6.78;	17.65

35 ^1H -NMR($CDCl_3$) δ : 0.93(6H,t), 1.20-1.90(6H,m),
2.60(2H,t), 3.95(2H,t), 4.00(3H,s), 5.20(2H,s),

7.05(1H,s), 7.20-7.40(3H,m), 7.40-7.60(2H,m)

Working Example 32

5 1-Benzyl-6-cyclopropyl-3-propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione

3-Amino-7-benzyl-2-(5-chloro-2-oxopentyl)-5-propylpyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (0.8
10 g) was suspended in methanol (20 ml). To the suspension was added a solution of 28% NaOMe in methanol (4 ml). The mixture was stirred at room temperature for 30 minutes and then at 60°C for 3 hours. The reaction solution was concentrated to
15 dryness. The residue was dissolved in methylene chloride, washed with water and concentrated to dryness to obtain crude crystals. Recrystallization from isopropyl ether gave colorless crystals (0.52 g), m.p. 264 - 265°C.

20 Elemental Analysis for C₂₀H₂₁N₅O₂ :

	C(%)	H(%)	N(%)
Calcd.:	66.10;	5.82;	19.27
Found :	66.48;	5.84;	19.07

25 Working Example 33

1-Benzyl-6-dimethylaminomethyl-3-propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione

30

1-Benzyl-3-propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione (1.6 g) was dissolved in 80% acetic acid (18 ml). To the solution were added paraformaldehyde (0.57 g) and
35 dimethylamine (50% aqueous solution, 1.73 g). The mixture was stirred at 70°C for 2 hours. The reaction

5 solution was concentrated to dryness. To the residue
were added methylene chloride (50 ml), water (50 ml),
2N-hydrochloric acid (5 ml) and acidic sodium bisulfite
(2 g) and the mixture was stirred at room temperature
for 15 hours. To the mixture was added sodium hydrogen
carbonate to render it to weak alkali. The organic
layer was washed with water, dried and concentrated to
obtain a mixture of 6-dimethylamino compound and 7-
dimethylamino compound. Recrystallization from ethanol
10 gave 6-dimethylamino compound.

Working Example 34

15 1-Benzyl-7-dimethylaminomethyl-3-propyl-1,2,3,4-
tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-
d]pyrimidine-2,4-dione

A mixture of 6-dimethylaminomethyl compound and 7-
dimethylaminomethyl compound was obtained by the same
20 procedure as Working Example 33. Recrystallization
from ethanol gave 7-dimethylaminomethyl compound.

Examples of Pharmaceutical Preparations

25 When a compound (I) of the present invention is
intended to use as a therapeutic and prophylactic
agent, owing to its properties of ameliorating cerebral
functions and activating cerebral metabolisms which are
decreased by the occurrence of cerebrovascular disease,
brain injury or aging, of, for example, dementia caused
30 by cerebral apoplexy, brain injury or cerebral atrophy,
the compound can be used in forms of, for example, the
following prescriptions.

1. Tablet

	(1) 1-Benzyl-3-propyl-1,2,3,4-tetrahydro-5H-imidazo- [2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4- dione	10 mg
5	(2) Lactose	35 mg
	(3) Corn starch	150 mg
	(4) Microcrystalline cellulose	30 mg
	(5) Magnesium stearate	5 mg

10 230 mg

The whole amount each of (1), (2) and (3),
together with two thirds of the amount of (4) and a
half of the amount of (5), are mixed and then
granulated. The residual amounts of (4) and (5) are
15 added to the granules and compressed into a tablet.

2. Capsule

20	(1) 1-Benzyl-6-phenyl-3-propyl-1,2,3,4-tetrahydro- 5H-imidazo[2',1':5,1]pyrazolo[3,4- d]pyrimidine-2,4-dione	10 mg
	(2) Lactose	100 mg
	(3) Microcrystalline cellulose	70 mg
25	(4) Magnesium stearate	10 mg

190 mg

The whole amount each of (1), (2) and (3),
30 together with a half of the amount of (4), are mixed
and then granulated. The residual amount of (4) is
added to the granules, and the mixture is filled into a
gelatine capsule.

35 Experimental Example 1

Adenosine Antagonism

Preparation of membranes was performed in accordance with the method of Burns et al. described in Proc. Natl. Acad. Sci., 77, 5547 (1980). More specifically, a rat was decapitated, and the cerebral cortex (A_1 receptor) or corpus striatum (A_2 receptor), which was suspended using Polyton in a Tris-HCl buffer solution of pH 7.7 (50 mM, 20 ml). This suspension was centrifuged at 48,000 g for 10 minutes, and the pellet was resuspended and centrifuged in a similar manner. The pellet was resuspended in a Tris-HCl buffer solution (50 mM), to which was added adenosine deaminase (2U/ml). The mixture was incubated at 37°C for 30 minutes. This suspension was centrifuged and the pellet was stored at -20°C.

Using the above-mentioned pellet, adenosine antagonism (A_1 and A_2) was examined.

1) A_1 receptor antagonism

The above-mentioned pellet was thawed at room temperature and suspended in a Tris-HCl buffer solution. To the suspension (0.9 ml) were added ^3H -cyclohexyladenosine (^3H -CHA)(ca. 0.05 μCi , 0.1 ml) and the test drug (10 μl), and the mixture was incubated at 25 C for 60 minutes. The reaction mixture was subjected to filtration with GF/B filter. The filter was washed four times with a Tris-HCl buffer solution. The radioactivity on the filter was measured by liquid scintillation. The nonspecific binding amount was measured in the presence of 10^{-5}M of L-phenyl isopropyladenosine.

2) A_2 receptor antagonism

The experiment was performed analogously to that for A_1 receptor antagonism. Using ^3H -adenosine-5'-ethylcarboxamide (^3H -NECA; about 0.1 μCi) as ligand, the experiment was conducted in the presence of 50 nM of cyclopentyladenosine. The nonspecific binding amount was measured in the presence of 10^{-4}M of

cyclopentyladenosine.

The results of these A₁ and A₂ receptor antagonism are shown in Table 4.

Table 4 Inhibitory Action of Adenosine Receptor Binding

The action was shown in terms of binding-inhibition constants (K_i, μM).

	Working Example	A ₁ receptor (K _i , μM)	A ₂ receptor (K _i , μM)
10	1	0.12	3.3
	2	0.14	2.9
	3	0.19	4.2
	4	0.27	6.5
15	5	0.67	4.5
	8	0.034	0.26
	9	0.050	0.37
	10	0.098	0.46
	11	0.092	1.0
20	12	0.20	1.1
	13	0.53	16.0
	14	0.11	2.5
	15	0.01	0.28
	16	0.024	0.43
25	17	0.0051	0.35
	19	0.027	0.19
	20	0.013	1.1
	21	0.0069	0.12
	22	0.0047	0.21
30	23	0.53	0.50
	24	0.053	>0.5
	25	0.58	>0.5
	26	0.037	>0.5
	27	0.58	>0.5
35	29	18.0	39.0
	30	0.42	0.42

Experimental Example 2

Action of ameliorating retention deficit induced
by an anticholinergic, scopolamine

5

Actions of the compound (8) obtained in Working
Example 8 and the compound (9) obtained in Working
Example 9 on amelioration of memory impairment was
studied using the passive avoidance task shown below.
10 Five-week old male mice were placed first in the light
chamber of a passive avoidance learning apparatus
consisting of light and dark chambers. The mice
immediately moved into the dark chamber, then an
unescapable electric shock (0.5 mA, 3 sec.) was
15 applied to the animals. These animals retained for
several weeks the memory that they received the
electric shock. This memory retention was disrupted by
the following procedure, and the effect of the
compounds (8) and (9) was tested. Thirty minutes prior
20 to the application of electric shock, these animals
were each administered with scopolamine (1 mg/kg, i.p),
then these mice lost the memory of this experience of
an electric shock.

On the following day, a retention recovery test
25 was conducted. These mice were again placed in the
light chamber of the passive avoidance apparatus and
the time until the animals moved into the dark chamber
(avoidance time) was measured. These mice which lost
the memory of the experience of an electric shock moved
30 again into the dark chamber in 10 to 20 seconds. On
the other hand, the mice orally administered with a 5%
gum arabic suspension of the compound (8) or (9)
recovered the memory, and they would not move into the
dark chamber or took a long time before they moved
35 there. The effects of these test compounds were
examined by comparing the average value (11-15

animals/group) of the period of time during which the mice stayed in the light chamber with that of the control group (administered with only a suspension of 5% gum arabic containing no test compound). The results were expressed by the percent change rate relative to the mean value (100) in the control group (Table 5).

Table 5 shows ameliorating effects of the compounds (8) and (9) on retention deficit induced by scopolamine.

Table 5 Ameliorating Effects on Retention Deficit Induced by Scopolamine (1 mg/kg, i.p.)

Working Example No.	Administration Route	Dosage (mg/kg)	Avoidance Time (%)
Control Group	p.o.	-	100
8	p.o.	3	243*
9	p.o.	3	262*

* $P < 0.05$ (comparison with the control group)

Experimental Example 3

Action on depression of cerebral functions induced by experimental ischemia

25

3-1 Action of accelerating recovery of motility

Experimental cerebral ischemia was produced in accordance with the method of Pulsinelli et al. (Stroke 10, 267-272, 1979), using Wistar rats of 8-week old. On the first day of the experiment, the rats were anesthetized with pentobarbital, and their occipital skin and muscle were incised along the median line, then their vertebral arteries were cauterized bilaterally, and their ventral necks were incised, the bilateral common carotid arteries were separated from the surrounding tissue, to which a thread was applied.

35

On the next day, the common carotid arteries were drawn out by the use of this thread under unaesthetic conditions, and occluded with clips for 30 minutes. By this treatment, serious cerebral ischemia was induced.

5 After 30 minutes' occlusion, the clip was removed to allow the cerebral circulation to resume. Time to recovery of righting reflex and time to reappearance of spontaneous motor activity were measured on individual test animals. The test compound was orally

10 administered to the animals as a 5% suspension in gum arabic one hour before causing the cerebral ischemia and immediately after the resumption of cerebral circulation. And, the control group was orally administered with only a 5% gum arabic suspension.

15 As shown in Table 6, the compound (8) tended to shorten the time to recovery of righting reflex dose-dependently and shortened the time to reappearance of spontaneous motor activity. In the latter's index, the high dose of the compound (8) showed statistically

20 significant action. Incidentally, this motility depression has a close relation with the depression of consciousness level. From these data, it was revealed that the compound (8) accelerated the recovery from disorders of cerebral functions caused by cerebral

25 ischemia.

Table 6 Action of recovering from motility depression
(depression of consciousness level)
associated with cerebral ischemia

5	Working Example No.	Number of animals	Time to recovery of righting reflex (min.)	Time to reappearance of spontaneous motility (min.)
10	Control group	15	29.8±5.9	81.5±13.3
	Compound (8)			
	3mg/kg	20	21.0±3.2	55.2±6.5
	10mg/kg	23	16.7±2.6	43.8±4.7*

15 The data are shown in terms of average values and standard errors. * $P < 0.05$ (comparison with the control group)

3-2 Action of ameliorating impaired learning

20 As in the case of the above test (3-1), Wistar rats were used to produce an experimental model for cerebral ischemia. In this experiment, the time during which cerebral ischemia was caused in the animals was 5 minutes. By this treatment, a passive avoidance

25 learning impairments was induced. The passive avoidance learning was tested in accordance with the method in Experiment 1. The test compound was suspended in a 5% gum arabic vehicle. Test animals were administered with this suspension three times,

30 i.e. one hour prior to causing cerebral ischemia, two hours prior to a passive avoidance learning and two hours prior to the test. The control group was administered with only a 5% gum arabic suspension. As shown in Table 7, the compound (8) prolonged the

35 avoidance time, in the doses of 3 mg/kg and 10 mg/kg, dose-dependently. These data suggest that the

compounds of the present invention show an action of ameliorating depression of cerebral functions associated with cerebral ischemia.

5 Table 7 Ameliorating action on impaired learning after cerebral ischemia

	Number of animals	Avoidance time
Control group	9	17.5 (sec.)
10 Compound (8)		
3 mg/kg	7	152.8
10 mg/kg	10	285.9*

15 Data are shown in terms of median value. * P<0.05 (comparison with the control group)

Experimental Example 4

Acute toxicity

20 A group of 5 male Jcl:Wistar rats (9 week old, Japan Clea) and a group of 5 male Jcl:ICR mice (5 week old, Japan Clea) were used. These rats were each administered orally with 500 mg and 1000 mg/kg/3 ml of the test compound, while these mice were each administered orally with 600 mg and 2000 mg/kg/2 ml of the test compound. These oral administrations were made in the form of a suspension in 5% gum arabic vehicle. Twenty four hours later, the number of dead animals were counted. The results are shown in Table 8.

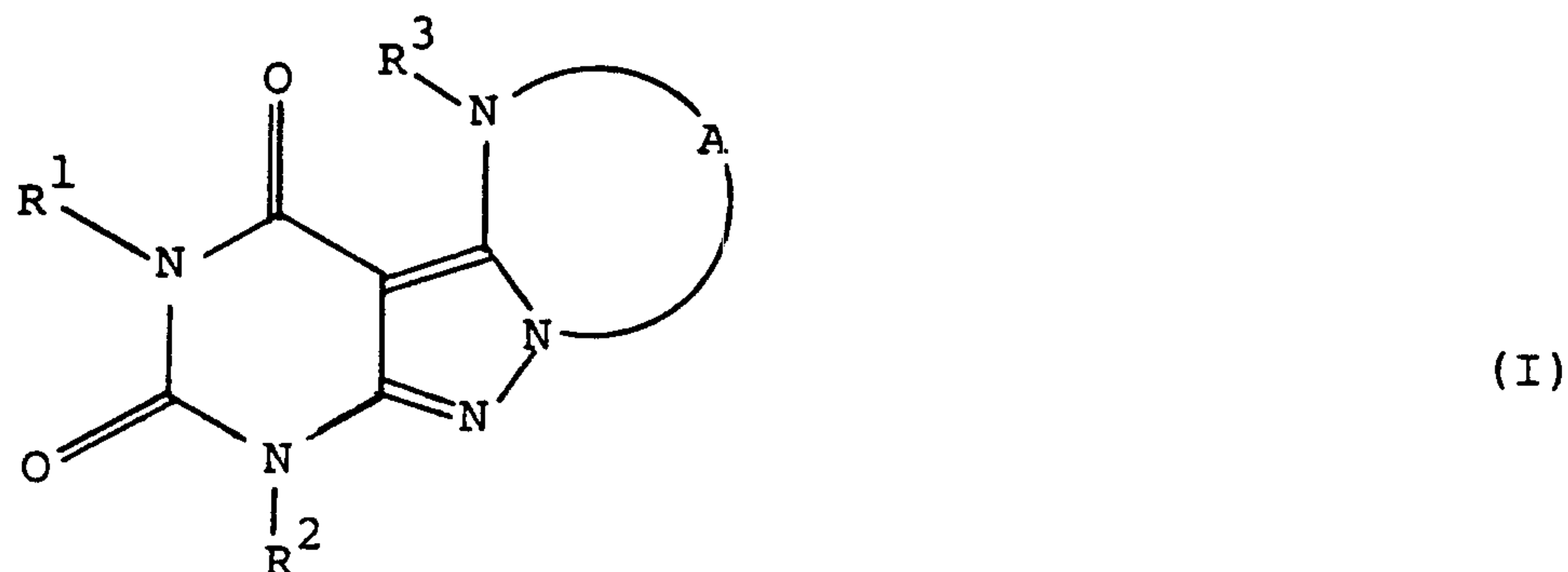
Table 8

	Animals	Dosage	Number of dead animals
		(mg/kg, p.o.)	
5	Rats	500	0
		1000	0
	Mice	600	0
		2000	0

- 59 -

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A tricyclic fused pyrimidine compound of the formula:



[in which one of R^1 and R^2 is hydrogen or an optionally substituted aralkyl group and the other is hydrogen, an optionally substituted aralkyl group or an aliphatic hydrocarbon group;

R^3 is hydrogen, an aliphatic hydrocarbon group or an acyl group; and

A is an optionally substituted divalent hydrocarbon chain having 2 to 4 carbon atoms,

wherein:

the optionally substituted aralkyl group for R^1 and R^2 is an aromatic hydrocarbon- C_{1-4} alkyl group in which the aromatic hydrocarbon is selected from the class consisting of phenyl and naphthyl and may be substituted with 1 to 3 substituents each independently selected from the class consisting of halogen, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, amino, $N-C_{1-4}$ alkyl-amino, N,N -di- C_{1-4} alkylamino, hydroxy, trifluoromethyl, carbamoyl, $N-C_{1-4}$ alkylcarbamoyl, and N,N -di- C_{1-4} alkylcarbamoyl;

the aliphatic hydrocarbon group for R^1 and R^2 is selected from the class consisting of C_{1-8} alkyl and C_{2-8} alkenyl;

the aliphatic hydrocarbon group for R^3 is selected from the class consisting of C_{1-3} alkyl and C_{2-3} alkenyl;

the acyl group for R^3 is selected from the class consisting of C_{2-7} alkanoyl (which may be substituted by halogen), C_{3-8} cycloalkylcarbonyl, benzoyl, C_{2-5} alkoxy-carbonyl, carbamoyl and formyl;

the optionally substituted divalent hydrocarbon chain having 2 to 4 carbon atoms for A is selected from the class consisting of C_{2-4} alkylene and C_{2-4} alkenylene and may have at least one substituent each independently selected from the class consisting of:

(i) C_{1-8} alkyl which may be substituted by amino, mono- or di- C_{1-4} alkylamino or morpholino,

(ii) phenyl which may be substituted by up to 2 substituents each independently selected from the class consisting of amino, mono- or di- C_{1-4} alkylamino, morpholino, nitro, hydroxy, C_{1-4} alkoxy, C_{1-4} alkyl, halogen and phenyl,

(iii) a divalent linear C_{3-6} aliphatic hydrocarbon group,

(iv) halogen,

(v) C_{3-8} cycloalkyl,

(vi) nitro,

(vii) hydroxy,

(viii) C_{1-4} alkoxy,

(ix) C_{1-4} alkylthio,

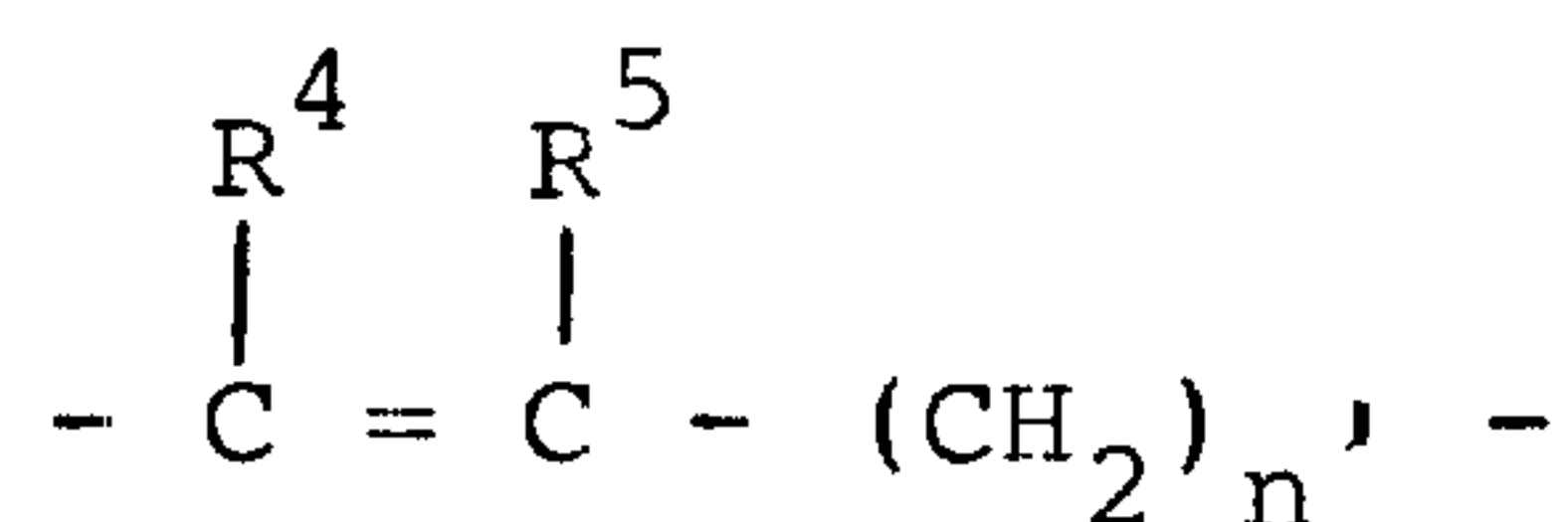
(x) amino, and

(xi) oxo]

or a pharmaceutically acceptable salt thereof.

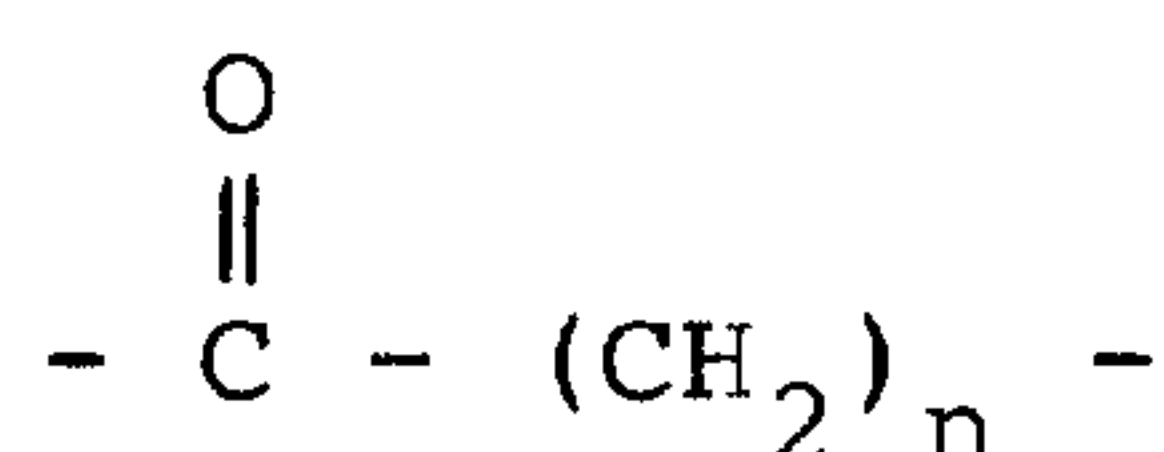
2. The compound or salt according to claim 1, wherein A is selected from the class consisting of:

- (a) C₂₋₄ alkylene;
- (b) alkenylene of the formula:



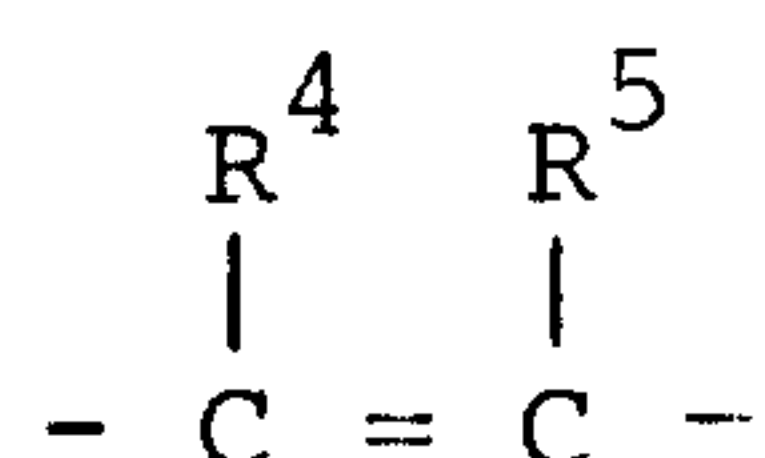
[wherein R^4 and R^5 are each hydrogen, halogen, C_{3-8} cycloalkyl, C_{1-8} alkyl (which may be substituted by amino, morpholino or mono- or di- C_{1-4} alkylamino), or phenyl (which may be substituted by C_{1-4} alkyl, phenyl, C_{1-4} alkoxy or halogen), or R^4 and R^5 together form C_{3-6} alkylene, and n' is an integer of 0, 1 or 2]; and

(c) a chain of the formula:



[wherein n is an integer of 1, 2 or 3].

3. The compound or salt according to claim 1, wherein A is selected from the class consisting of ethylene and alkenylene of the formula:



[wherein R^4 and R^5 are each hydrogen, C_{1-4} alkyl (which may be substituted by amino or mono- or di- C_{1-4} alkylamino) or phenyl (which may be substituted by halogen or C_{1-4} alkoxy)].

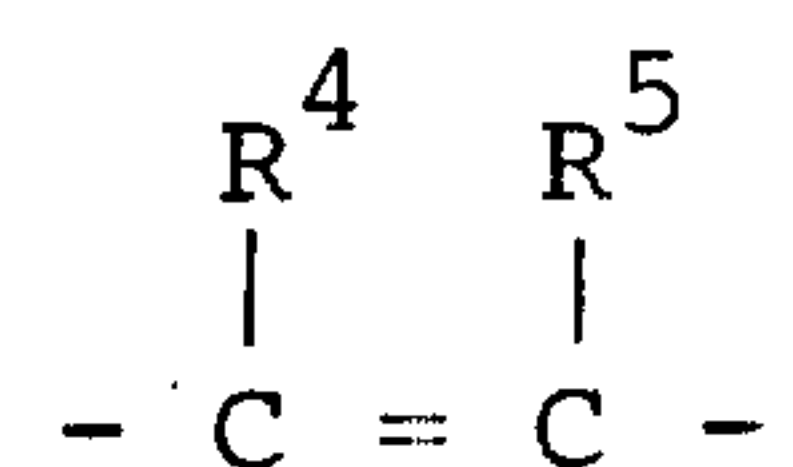
4. The compound or salt according to claim 1, wherein:

R^1 is C_{1-8} alkyl or C_{2-8} alkenyl;

R^2 is hydrogen or phenyl- C_{1-4} alkyl [in which the phenyl may be substituted by halogen];

R^3 is hydrogen, C_{1-3} alkyl, C_{2-7} alkanoyl or C_{1-4} alkoxy carbonyl;

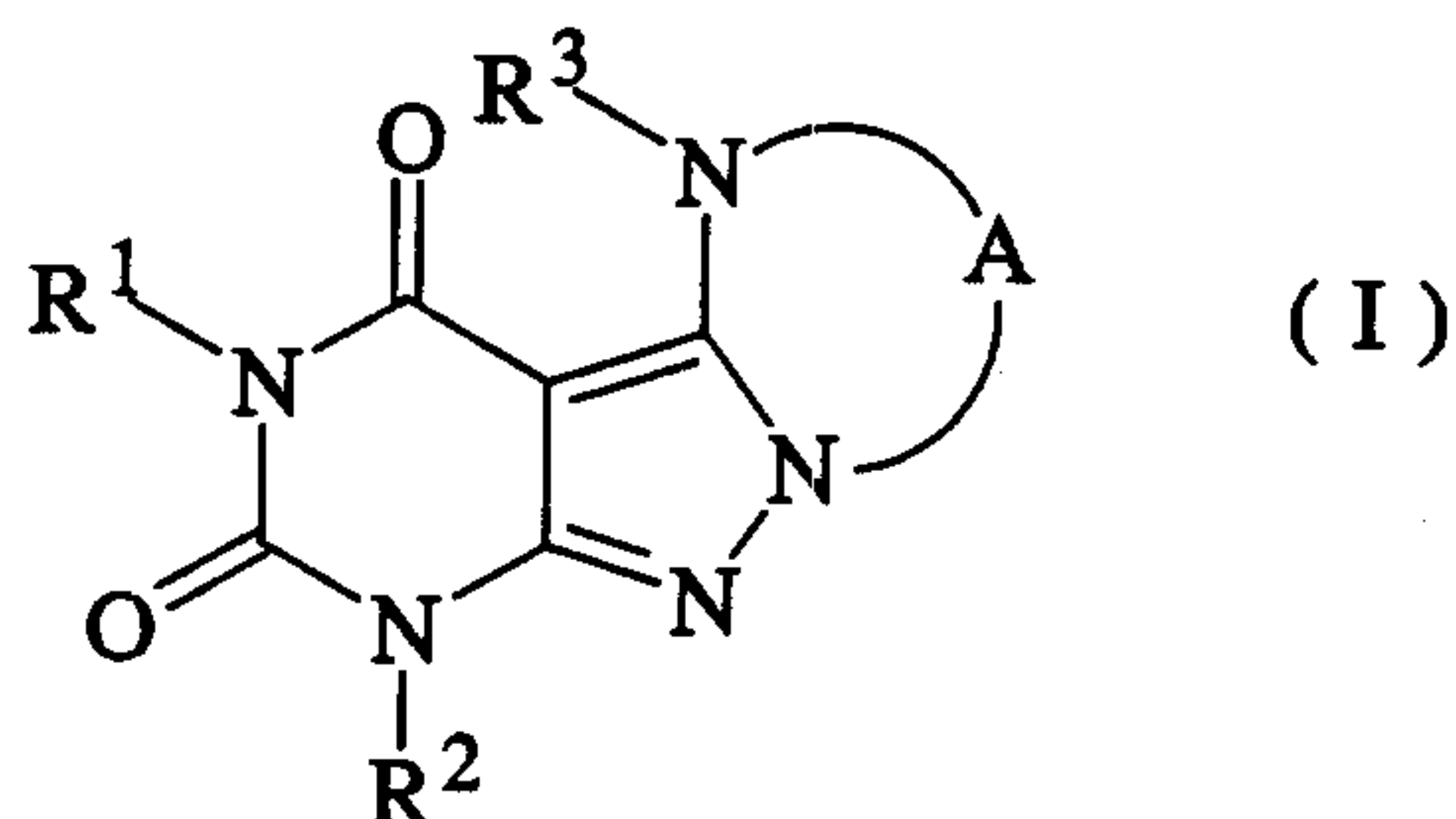
A is ethylene or alkenylene of the formula:



[wherein R^4 and R^5 are each hydrogen, C_{1-8} alkyl (which may be substituted by di- C_{1-4} alkylamino) or phenyl (which may be substituted by C_{1-4} alkoxy)].

- 63 -

5. A compound of the formula:



[wherein:

one of R^1 and R^2 is hydrogen or an optionally substituted aralkyl group and the other is hydrogen, an optionally substituted aralkyl group or an aliphatic hydrocarbon group;

R_3 is hydrogen, an aliphatic hydrocarbon group or acyl group; and

A is an optionally substituted divalent hydrocarbon chain having 2 to 4 carbon atoms,

wherein the aralkyl group for R^1 and R^2 is an aromatic hydrocarbon- C_{1-4} alkyl group in which the aromatic hydrocarbon is phenyl or naphthyl,

the aliphatic hydrocarbon group for R^1 and R^2 is a C_{1-8} alkyl or C_{2-8} alkenyl group,

the aliphatic hydrocarbon group for R^3 is a C_{1-3} alkyl or C_{2-3} alkenyl group, and

the acyl group for R^3 is an alkanoyl group which may be substituted by halogen, a cycloalkylcarbonyl group, a benzoyl group, an alkoxycarbonyl group, a carbamoyl group or a formyl group]

or a salt thereof.

- 63a -

6. A compound according to claim 5, wherein the optionally substituted aralkyl group shown by R¹ or R² is an aromatic hydrocarbon-C₁₋₄alkyl group in which the aromatic hydrocarbon is phenyl or naphthyl and is unsubstituted or substituted with 1 to 3 substituents selected from the class consisting of halogen, a lower (C₁₋₄)alkyl, a lower (C₁₋₄)alkoxy, nitro, amino N-lower (C₁₋₄)alkylamino, N,N-dilower (C₁₋₄)alkylamino, hydroxyl, trifluoromethyl, carbamoyl, N-lower, (C₁₋₄)alkylcarbamoyl and N,N-dilower (C₁₋₄)alkylcarbamoyl.

7. A compound according to claim 6, wherein the aromatic hydrocarbon group is unsubstituted.

8. A compound according to claim 6, wherein the aromatic hydrocarbon group is phenyl.

9. A compound according to claim 8, wherein the substituents are those selected from the class consisting of halogen, lower (C₁₋₄)alkyl, lower (C₁₋₄)alkoxy, nitro and amino.

10. A compound according to claim 1, wherein the aliphatic hydrocarbon group shown by R^1 or R^2 is C_{1-8} alkyl group or C_{2-8} alkenyl group.
11. A compound according to claim 1, wherein the aliphatic hydrocarbon group shown by R^1 or R^2 is C_{2-5} aliphatic hydrocarbon group.
12. A compound according to claim 1, wherein the aliphatic hydrocarbon group shown by R^1 or R^2 is C_{2-5} alkyl group.
13. A compound according to claim 1, wherein one of R^1 and R^2 is the optionally substituted aralkyl group and the other is the optionally substituted aralkyl group or the aliphatic hydrocarbon group.
14. A compound according to claim 1, wherein R^1 is the aliphatic hydrocarbon group and R^2 is the optionally substituted aralkyl group.
15. A compound according to claim 1, wherein the aliphatic hydrocarbon group shown by R^3 is C_{1-3} alkyl group or C_{2-3} alkenyl group.
16. A compound according to claim 1, wherein the aliphatic hydrocarbon group shown by R^3 is C_{1-3} alkyl group.
17. A compound according to claim 1, wherein the acyl group is C_{2-7} alkanoyl group, benzoyl group, C_{2-5} alkoxy carbonyl group, carbamoyl or formyl.
18. A compound according to claim 1, wherein the acyl group is C_{2-7} alkanoyl group or C_{2-5} alkoxy carbonyl

- 65 -

group.

19. A compound according to claim 1, wherein the acyl group is acetyl, propionyl or methoxycarbonyl.

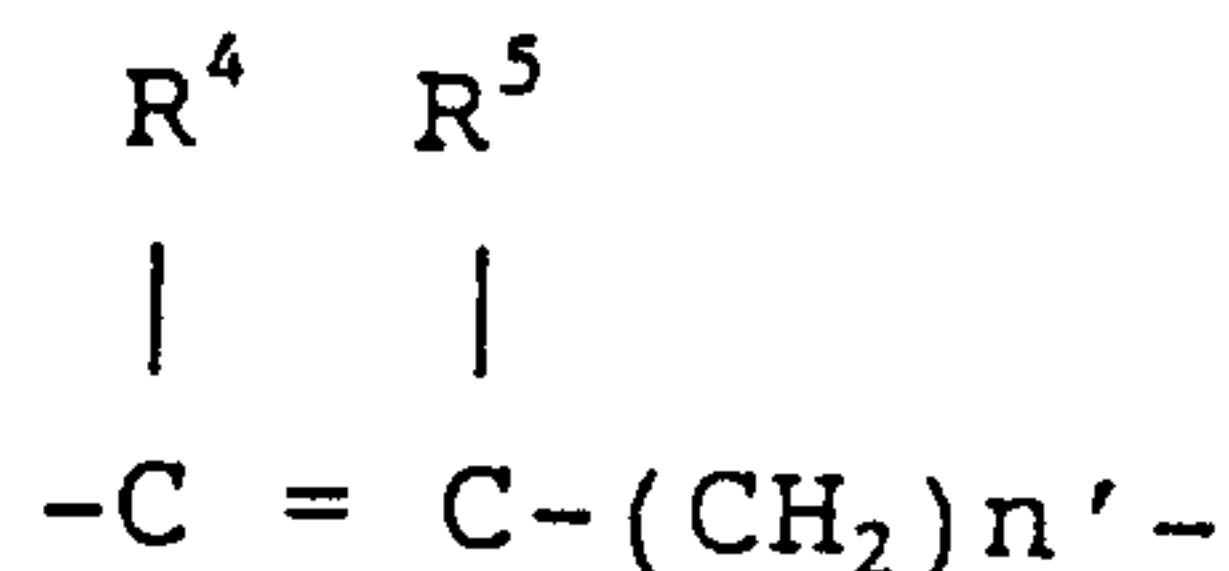
20. A compound according to claim 1, wherein the divalent hydrocarbon chain having 2 to 4 carbon atoms is C₂₋₄ alkylene.

21. A compound according to claim 5, wherein A is a divalent straight hydrocarbon chain having 2 to 4 carbon atoms unsubstituted or substituted with 1 to 2 substituents selected from the class consisting of an optionally substituted aliphatic hydrocarbon group, an optionally substituted aromatic hydrocarbon group, halogen, nitro, amino and oxo.

22. A compound according to claim 21, wherein the optionally substituted aliphatic hydrocarbon group is C₁₋₈ alkyl group unsubstituted or substituted with a member of selected from the class consisting of an optionally substituted amino, nitro, hydroxy, C₁₋₄ alkoxy and C₁₋₄ alkylthio.

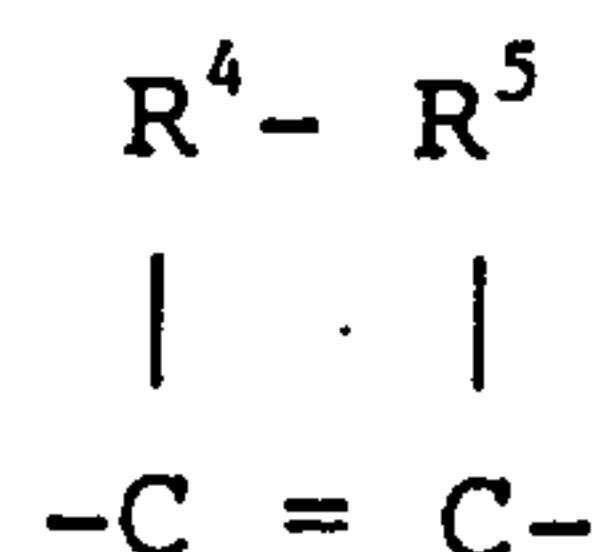
23. A compound according to claim 21, wherein the optionally substituted aromatic hydrocarbon group is phenyl unsubstituted or substituted with 1 to 2 substituents selected from the class consisting of an optionally substituted amino, nitro, hydroxy, methoxy, methyl and phenyl.

24. A compound according to claim 5, wherein A is C₂₋₄ alkylene; a hydrocarbon chain of the formula:

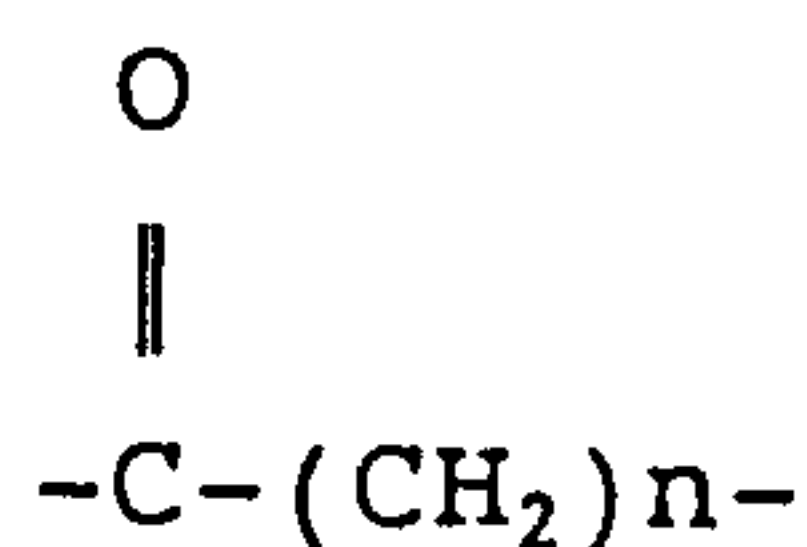


- 66 -

wherein R^4 and R^5 are independently hydrogen, an optionally substituted aliphatic hydrocarbon group, an optionally substituted aromatic hydrocarbon group or halogen, or R^4 and R^5 are combined to form a cyclic aliphatic hydrocarbon group having 5 to 8 carbon atoms of the formula:

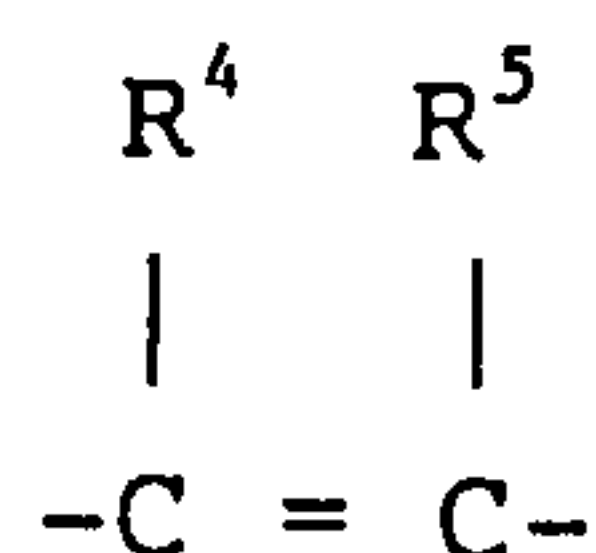


and n' is an integer of 0 to 2; or a hydrocarbon chain of the formula:



wherein n is an integer of 1 to 3.

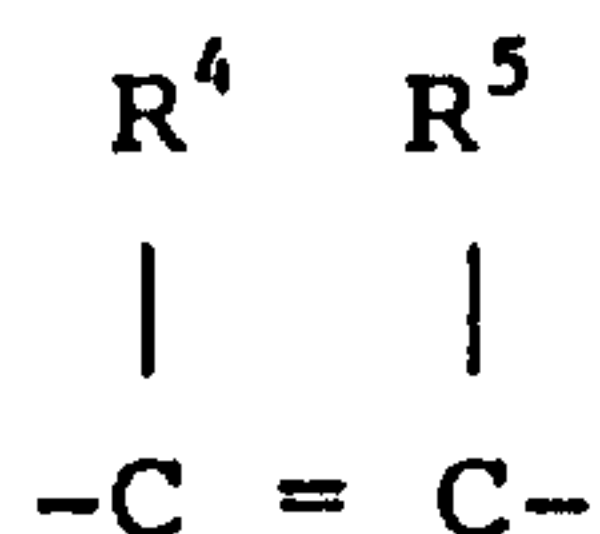
25. A compound according to claim 5, wherein A is ethylene or a group of the formula:



wherein R^4 and R^5 are independently hydrogen, phenyl unsubstituted or substituted with halogen or lower (C_{1-4}) alkoxy, or C_{1-4} alkyl unsubstituted or substituted with amino, dimethylamino or morpholino.

26. A compound according to claim 5, wherein R^1 is C_{2-5} aliphatic hydrocarbon group; R^2 is hydrogen or phenyl-lower (C_{1-4}) alkyl group, said phenyl group being unsubstituted or substituted with 1 to 3 substituents selected from the class consisting of halogen, a lower (C_{1-4}) alkyl, a lower (C_{1-4}) alkoxy, nitro, amino, N-lower (C_{1-4}) alkylamino, N,N-dilower (C_{1-4}) alkylamino, hydroxyl, trifluoromethyl, carbamoyl, N-lower (C_{1-4}) alkylcarbamoyl and N,N-dilower (C_{1-4}) alkylcarbamoyl; R^3 is hydrogen, methyl, acetyl or methoxycarbonyl; and

A is ethylene or a hydrocarbon chain of the formula:



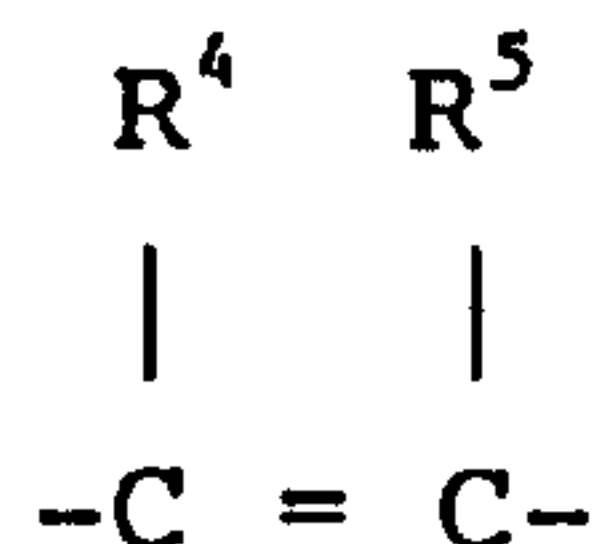
wherein R^4 and R^5 are independently hydrogen, C_{1-8} alkyl group, or phenyl unsubstituted or substituted with halogen or lower (C_{1-4}) alkoxy.

27. A compound according to claim 26, wherein R^1 is C_{3-5} alkyl group.

28. A compound according to claim 26, wherein R^2 is benzyl group unsubstituted or substituted with halogen.

29. A compound according to claim 26, wherein R^3 is hydrogen.

30. A compound according to claim 26, wherein A is ethylene or a hydrocarbon chain of the formula:



wherein R^4 and R^5 are independently hydrogen, C_{1-4} alkyl or phenyl unsubstituted or substituted with lower (C_{1-4}) alkoxy.

31. The compound 1-
benzyl-6-(4-methoxyphenyl)-3-propyl-1,2,3,4-tetrahydro-
5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-
dione or a pharmaceutically acceptable salt thereof.

32. The compound 1-
benzyl-6-(4-chlorophenyl)-3-propyl-1,2,3,4-tetrahydro-
5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-
dione or a pharmaceutically acceptable salt thereof.

33. The compound
1-benzyl-6-butyl-3-propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione
or a pharmaceutically acceptable salt thereof.
34. The compound
1-benzyl-3-propyl-6-phenyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione
or a pharmaceutically acceptable salt thereof.
35. The compound
1-benzyl-7-dimethylaminomethyl-3-propyl-1,2,3,4-tetrahydro-5H-imidazo[2',1':5,1]pyrazolo[3,4-d]pyrimidine-2,4-dione or a pharmaceutically acceptable salt thereof.
36. A pharmaceutical composition for
antagonizing adenosine which comprises (a) as the active ingredient, an amount effective to antagonize adenosine of the compound or salt according to any one of claims 1 to 35 and (b) a pharmaceutically acceptable carrier, excipient or diluent therefor.
37. A pharmaceutical composition for
activating cerebral functions and metabolisms which are decreased by the occurrence of cerebrovascular disease, brain injury or aging, which comprises (a) as the active ingredient, an effective amount of the compound or salt according to any one of claims 1 to 35 and (b) a pharmaceutically acceptable carrier, excipient or diluent therefor.
38. A pharmaceutical composition for the
therapy or prophylaxis of neurological or psychic changes caused by cerebral apoplexy, brain injury or cerebral atrophy which comprises (a) as the active

- 69 -

ingredient, an effective amount of the compound or salt according to any one of claims 1 to 35 and (b) a pharmaceutically acceptable carrier, excipient or diluent therefor.

39. A use for antagonising adenosine in a mammal, of the compound or salt according to any one of claims 1 to 35.

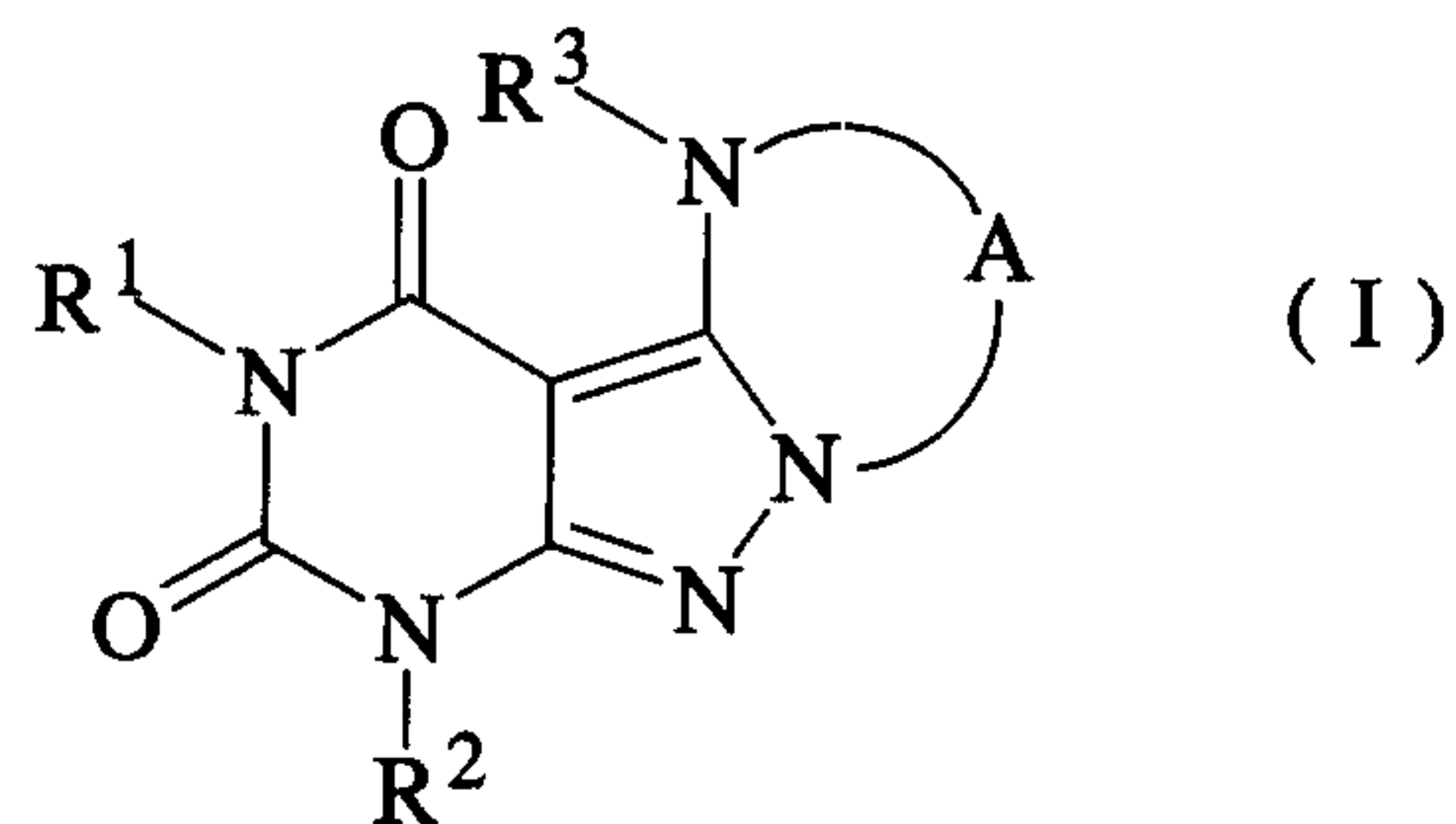
40. A use for activating cerebral functions or metabolisms which are decreased by the occurrence of cerebrovascular disease, brain injury or aging in a mammal, of the compound or salt according to any one of claims 1 to 35.

41. A use for the therapy or prophylaxis of neurological or psychic changes caused by cerebral apoplexy, brain injury or cerebral atrophy in a mammal, of the compound or salt according to any one of claims 1 to 35.

42. A use of the compound or salt according to any one of claims 1 to 35 for therapeutical treatment of a mammal.

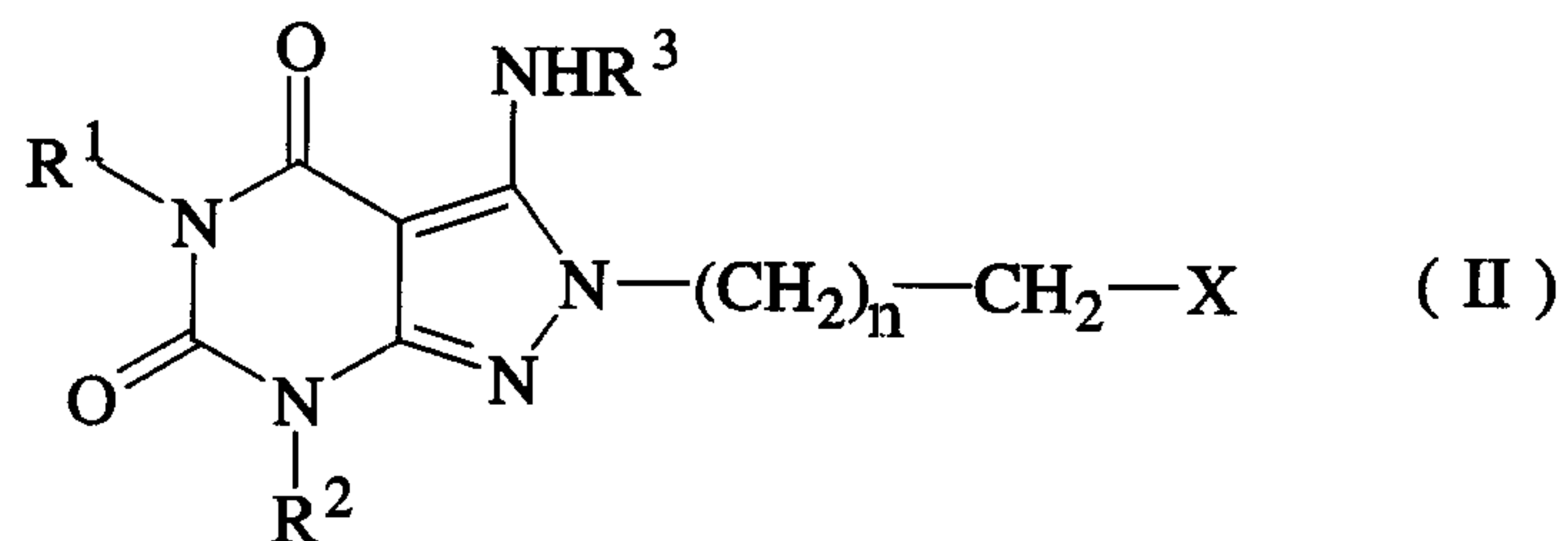
43. A method for producing a compound of the formula (I):

- 70 -

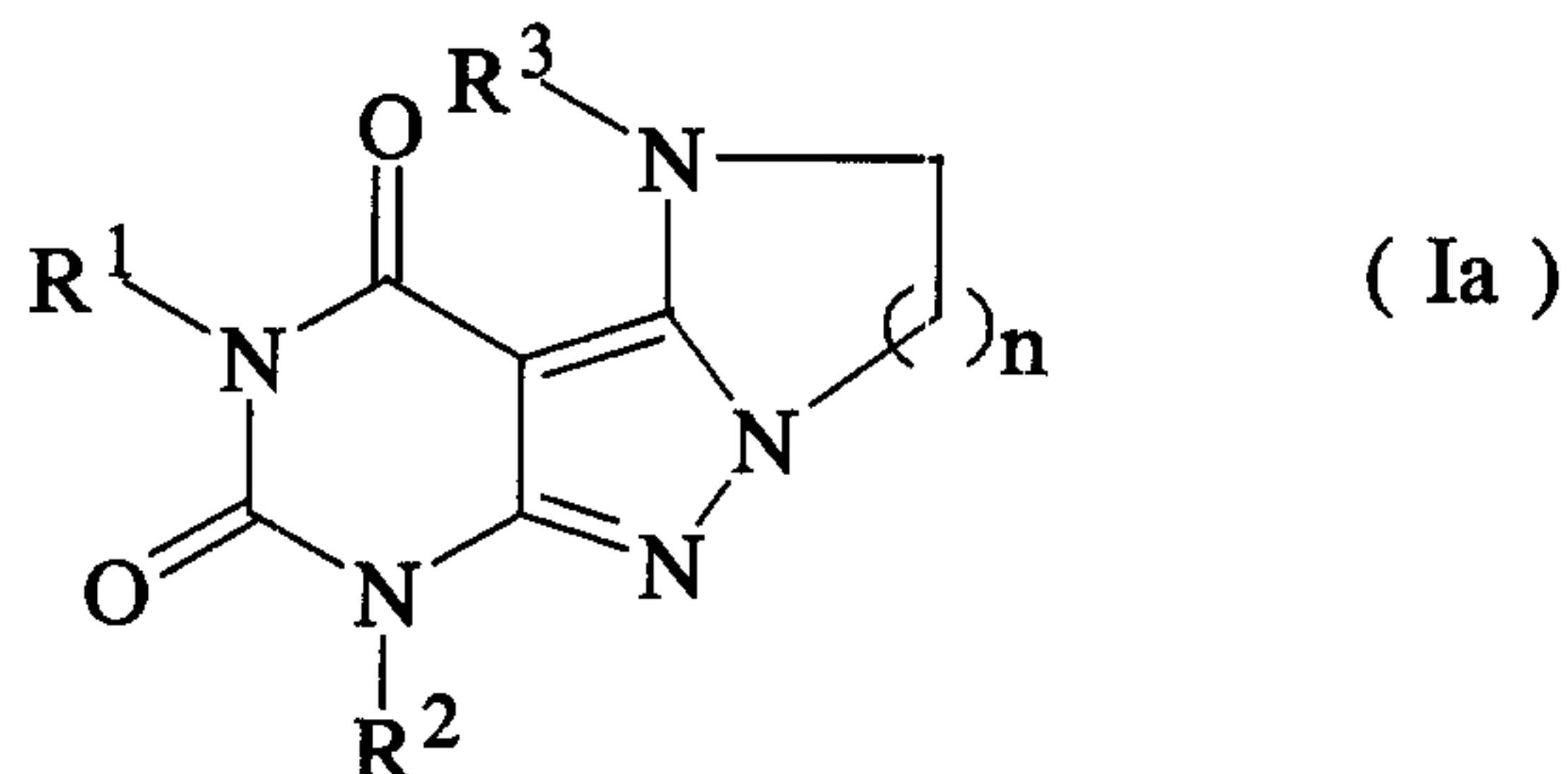


[wherein R^1 , R^2 , R^3 and A are of the same meaning as claim 1] or a salt thereof, which comprises:

(a) subjecting a compound of the formula (II):



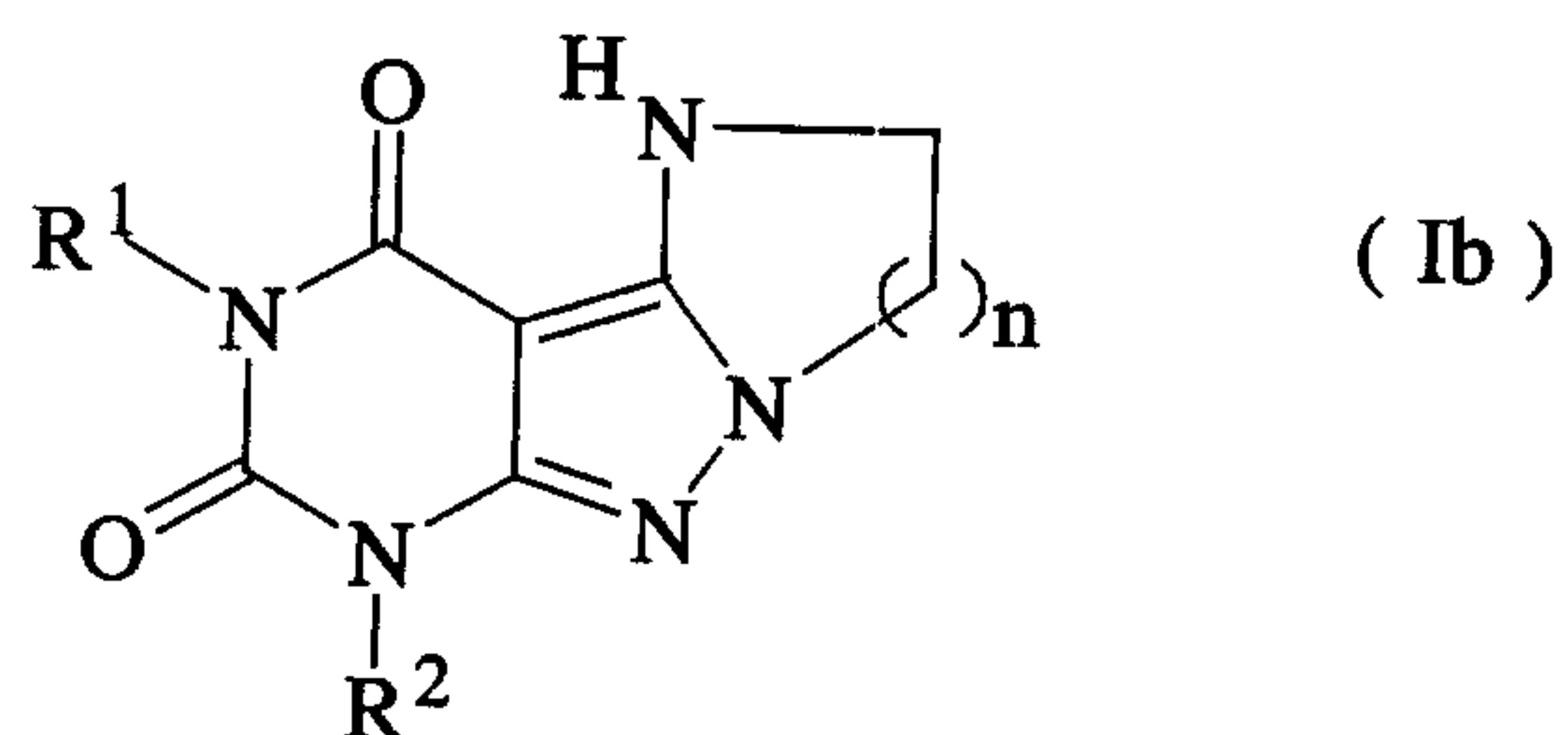
[wherein R^1 , R^2 and R^3 are of the same meaning as defined above, X is halogen and n is an integer of 1 to 3] to a ring-closure reaction to produce a compound of the formula (Ia):



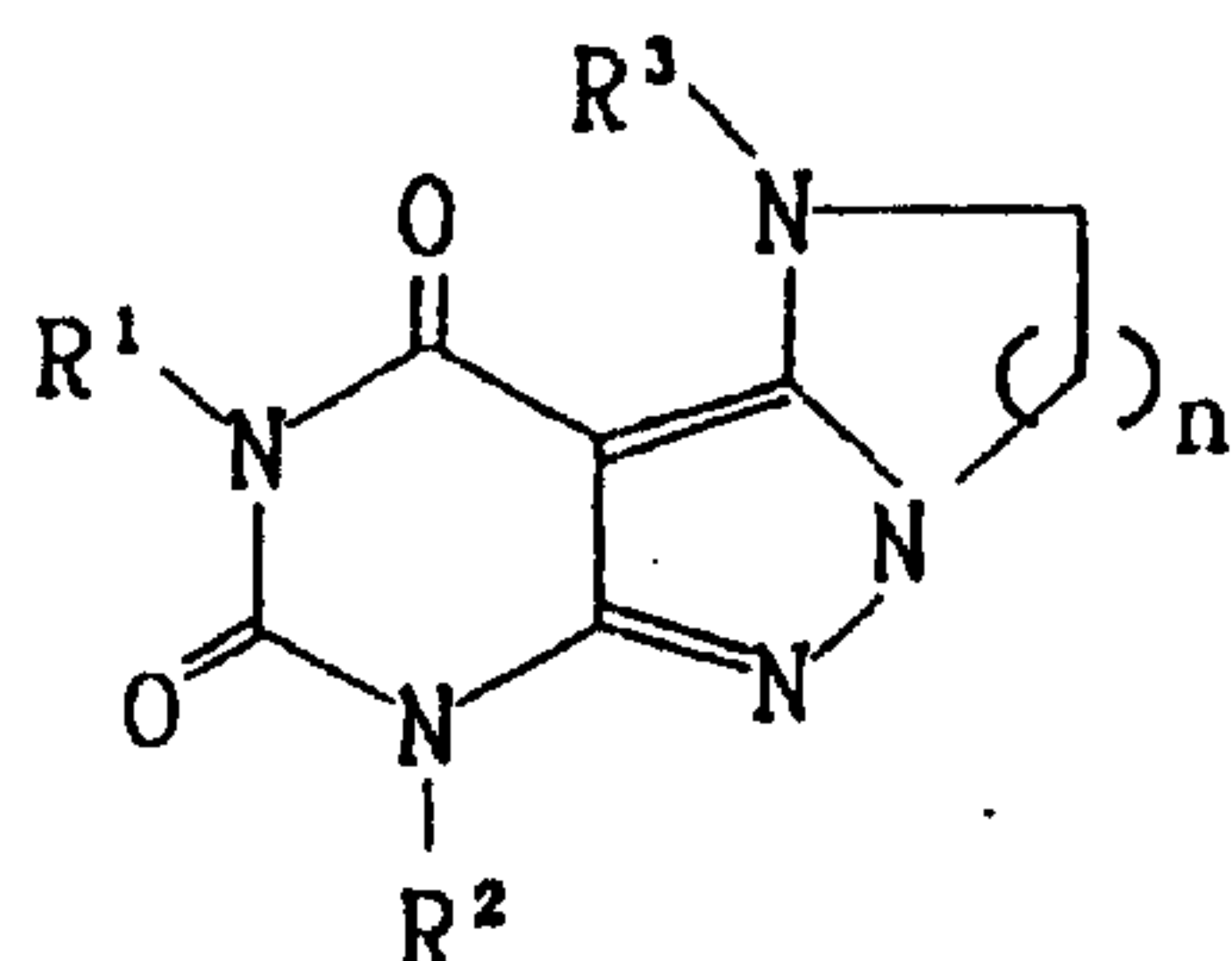
[wherein R^1 , R^2 , R^3 and n are as defined above],

(b) subjecting a compound of the formula (Ib):

- 70a -

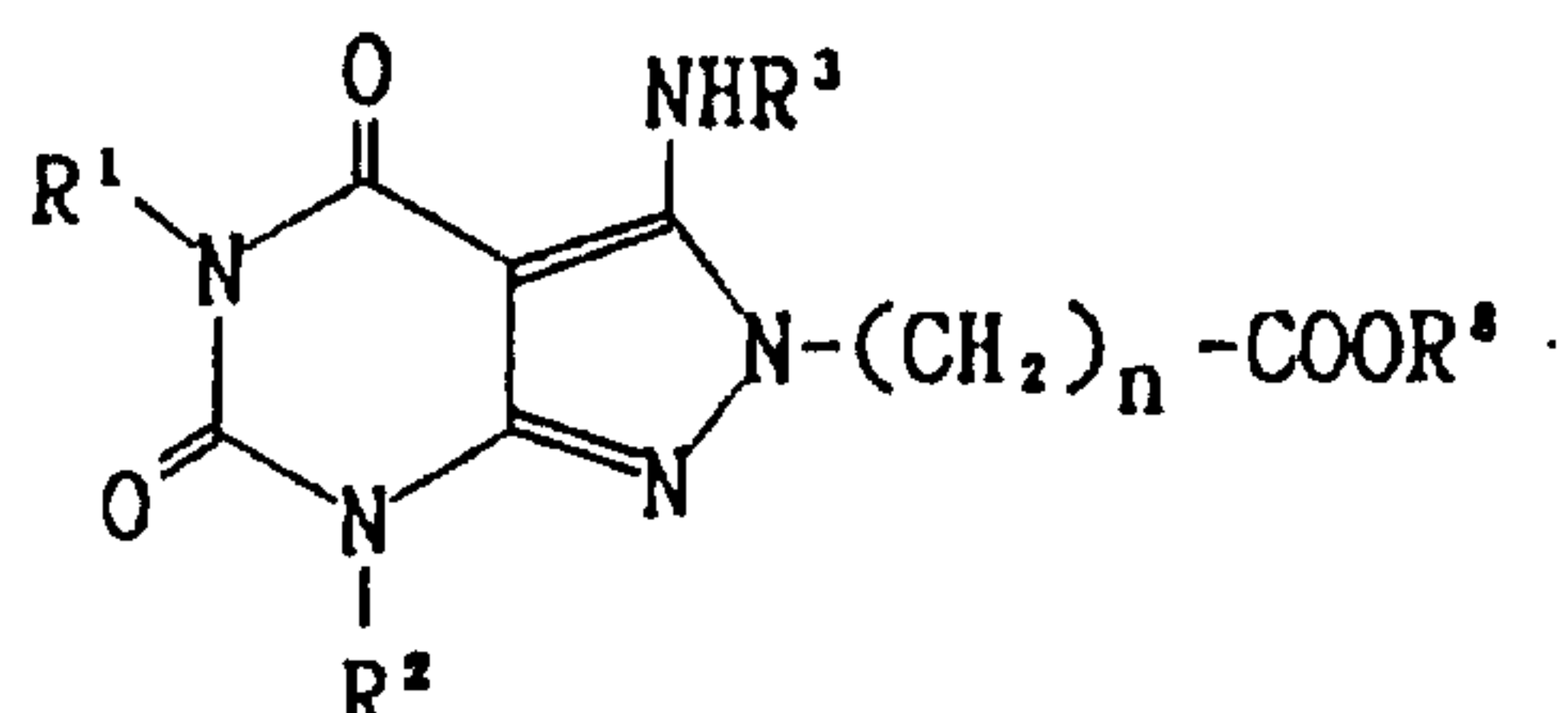


[wherein R^1 , R^2 and n are of the same meaning as defined above] to alkylation or acylation to produce a compound of the formula (Ie):



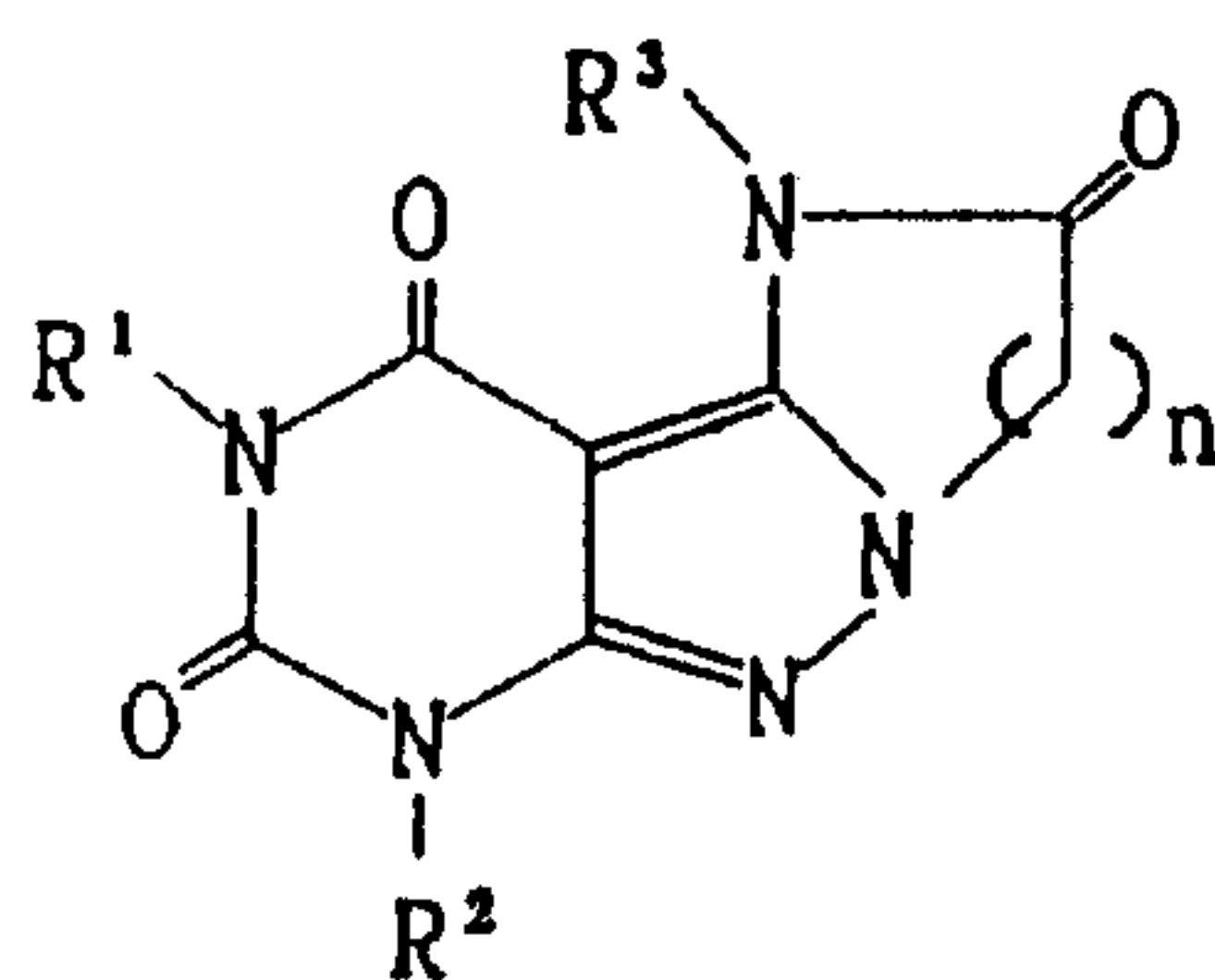
(Ie)

[wherein R^1 , R^2 , R^3 and n are of the same meaning as defined above, provided that R^3 is not hydrogen],
 (c) subjecting a compound of the formula (III):



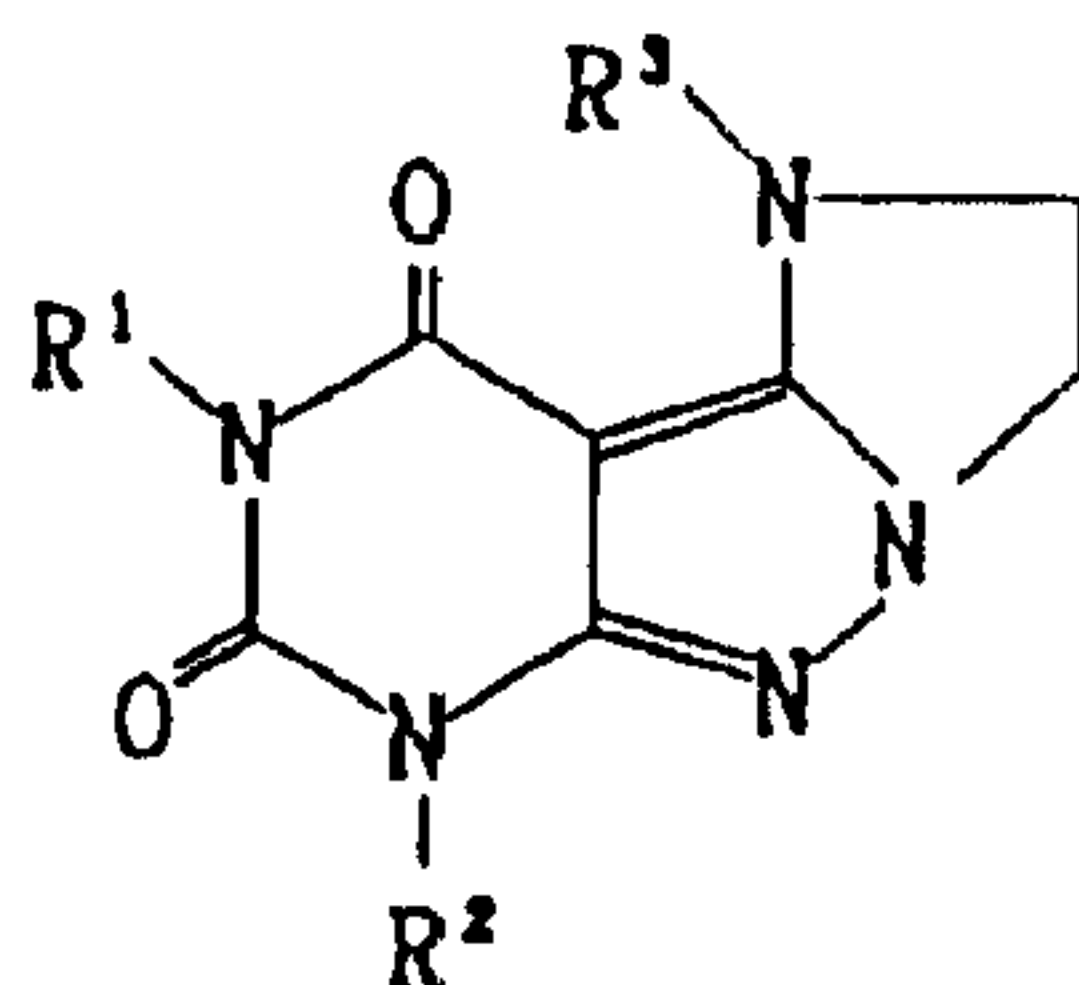
(III)

[wherein R^1 , R^2 , R^3 and n are of the same meaning as defined above, and R^8 is a lower alkyl group]
 to a lactam-ring formation reaction to produce a compound of the formula (Id):



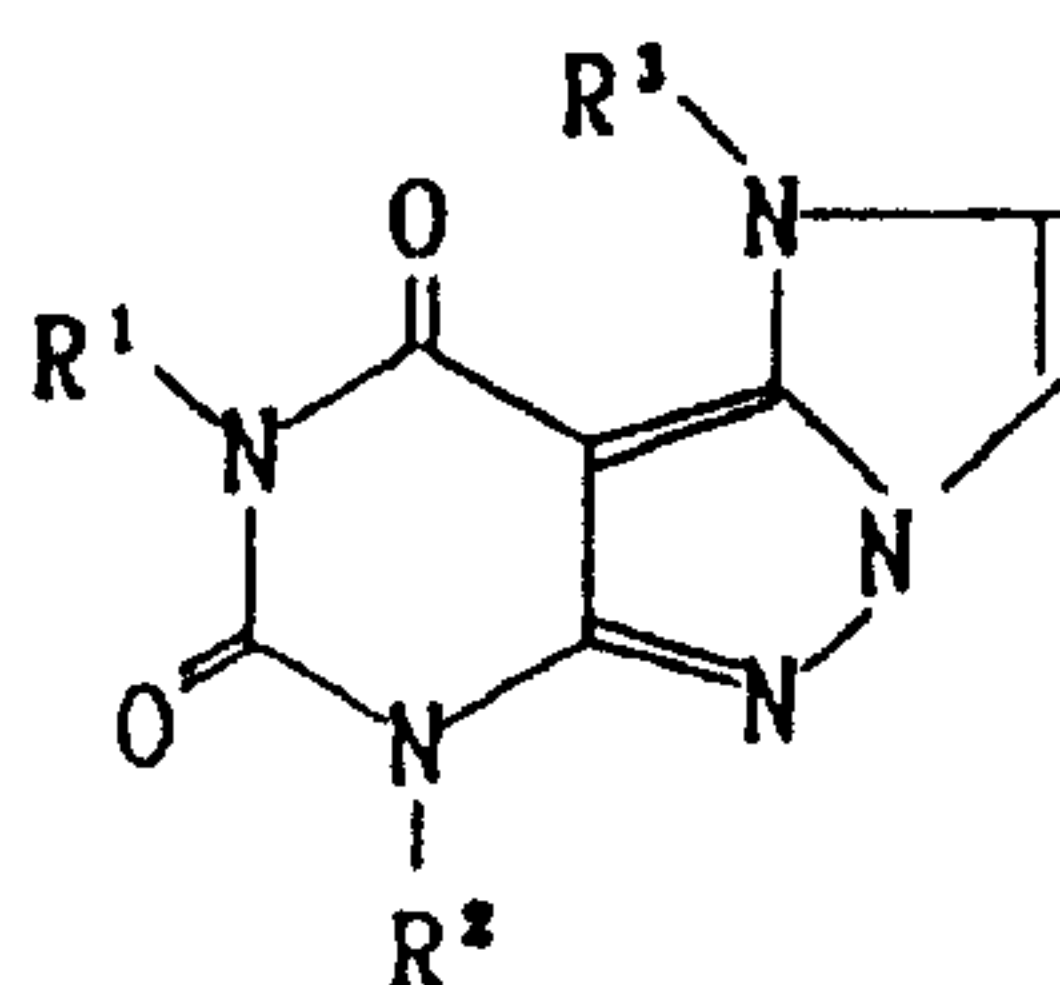
(Id)

[wherein R^1 , R^2 , R^3 and n are of the same meaning as defined above],
 (d) subjecting a compound of the formula (Ic):



(Ic)

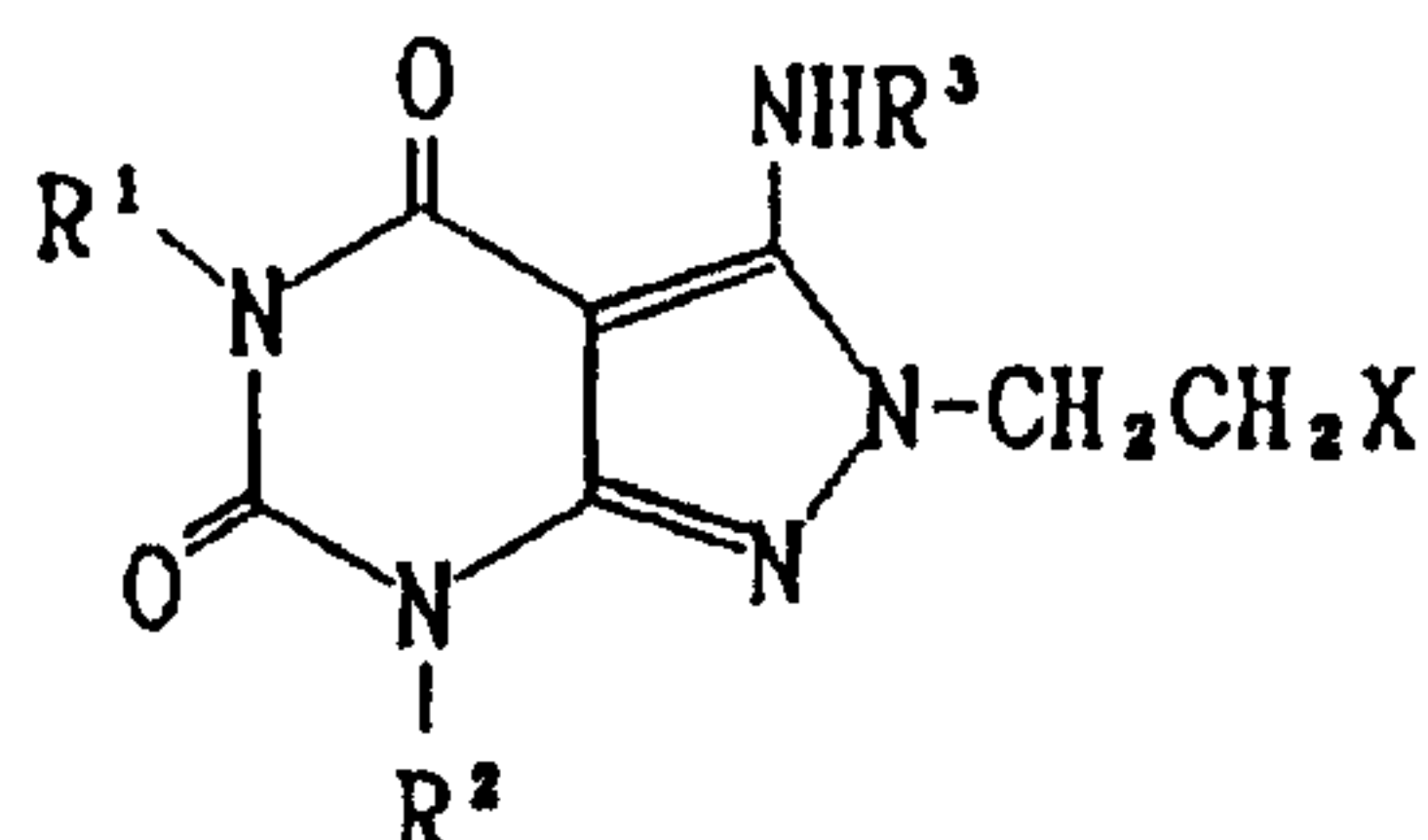
[wherein R¹, R² and R³ are of the same meaning as defined above] to dehydrogenation to produce a compound of the formula (If):



(If)

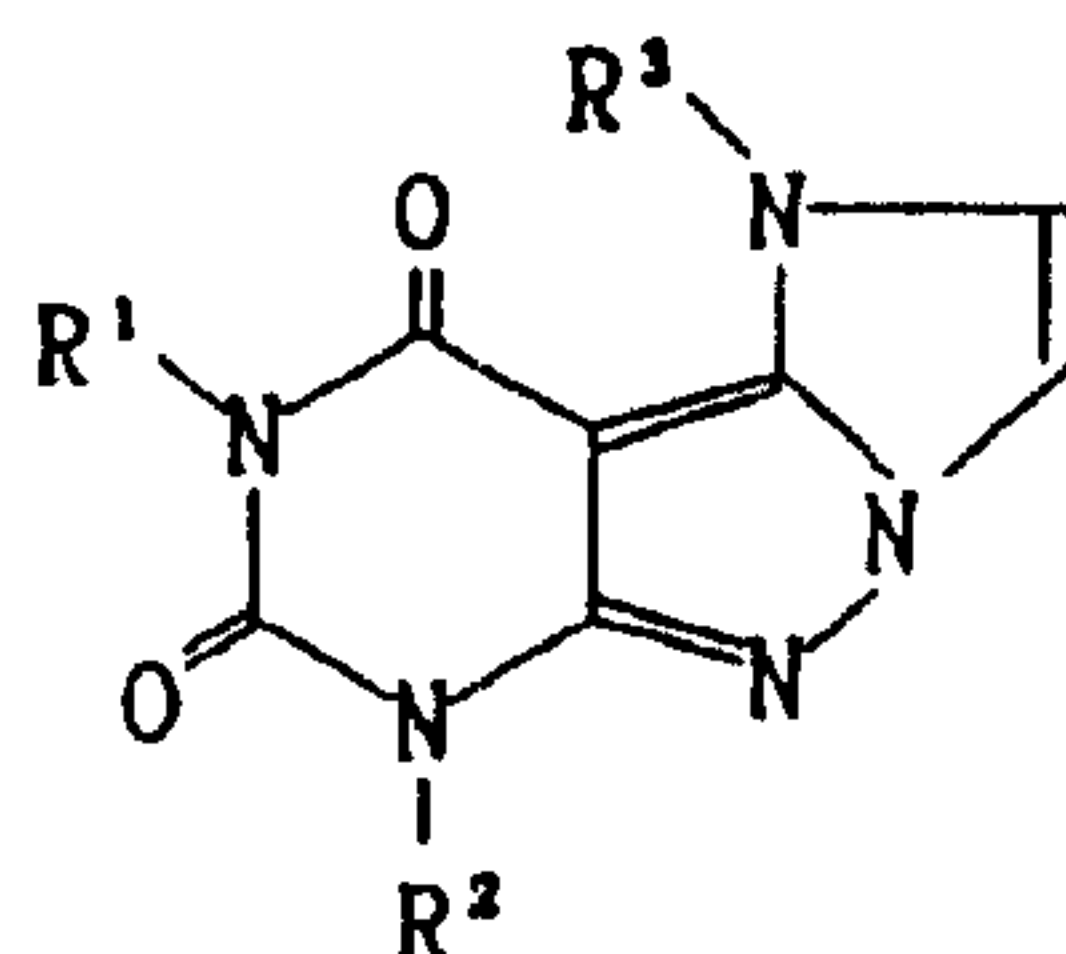
[wherein R¹, R² and R³ are of the same meaning as defined above],

(e) subjecting a compound of the formula (IIa):



(IIa)

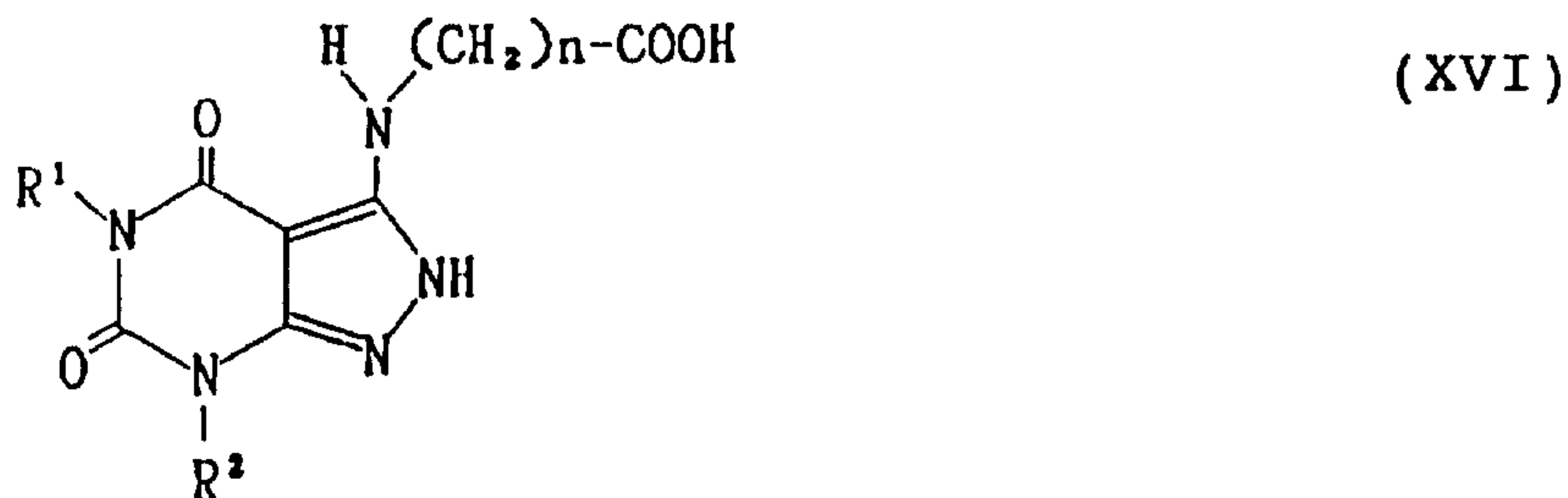
[wherein R¹, R², R³ and X are of the same meaning as defined above] to ring-closure reaction to produce a compound of the formula (If):



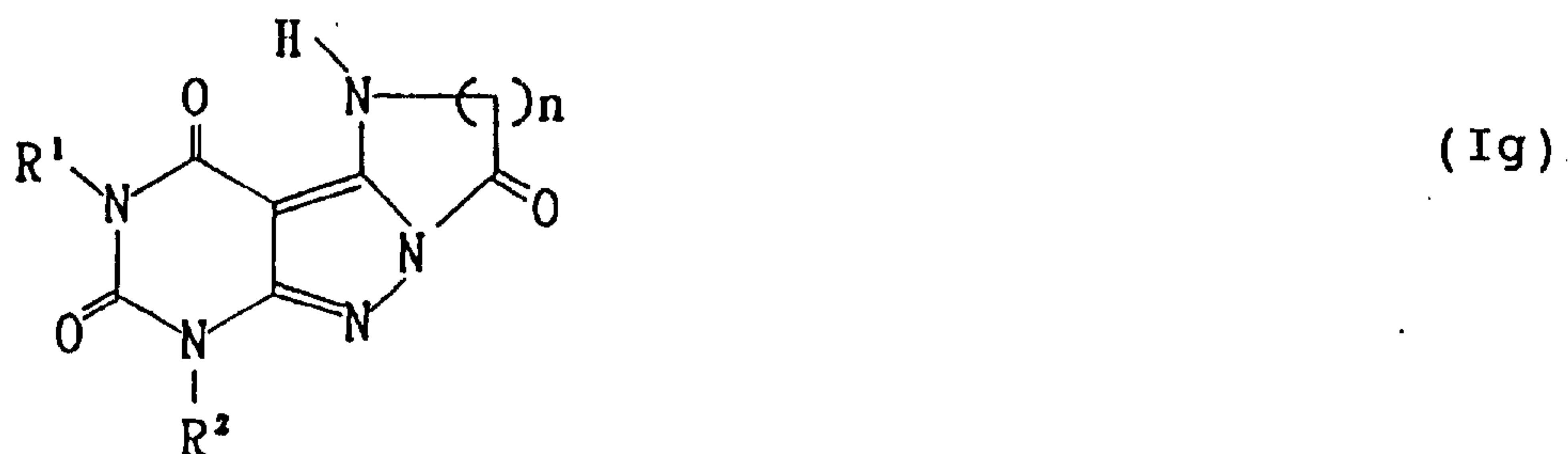
(If)

[wherein R¹, R² and R³ are of the same meaning as defined above],

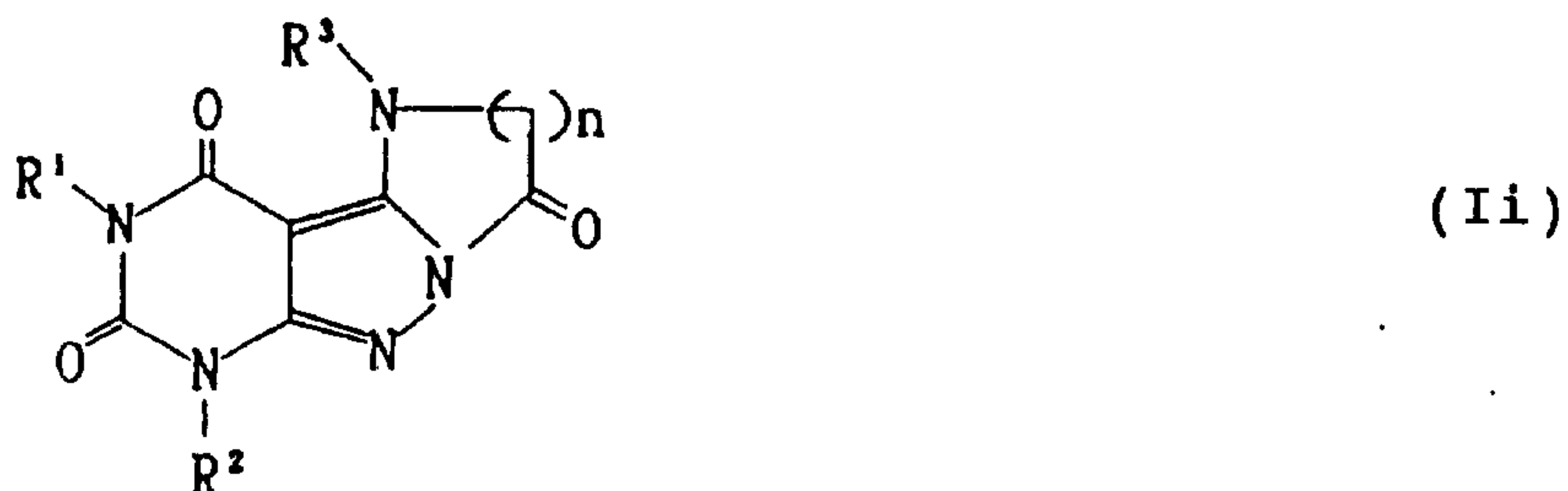
(f) subjecting a compound of the formula (XVI):



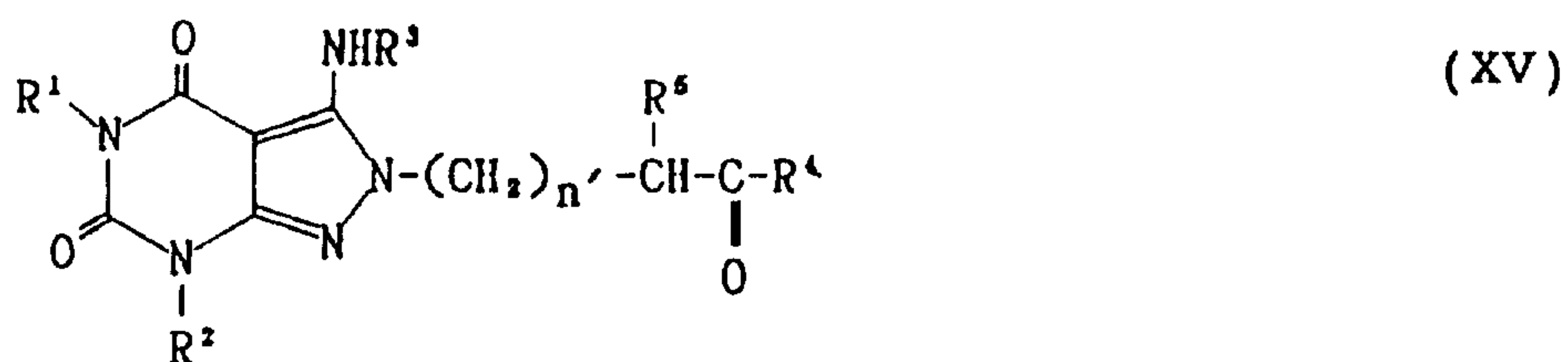
[wherein R¹, R² and n are of the same meaning as defined above] to ring-closure reaction to produce a compound of the formula (Ig):



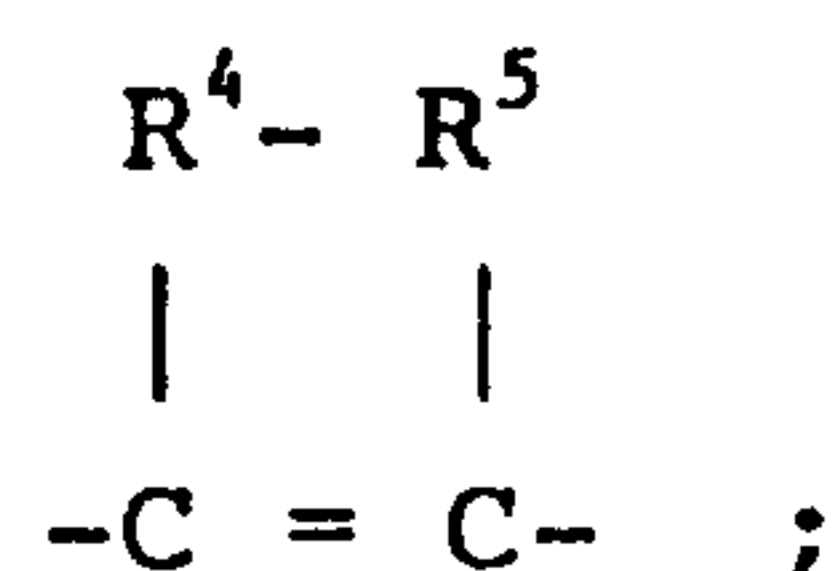
[wherein R¹, R² and n are of the same meaning as defined above], and, if necessary, subjecting the compound of the formula (Ig) to alkylation or acylation to produce a compound of the formula (Ii):



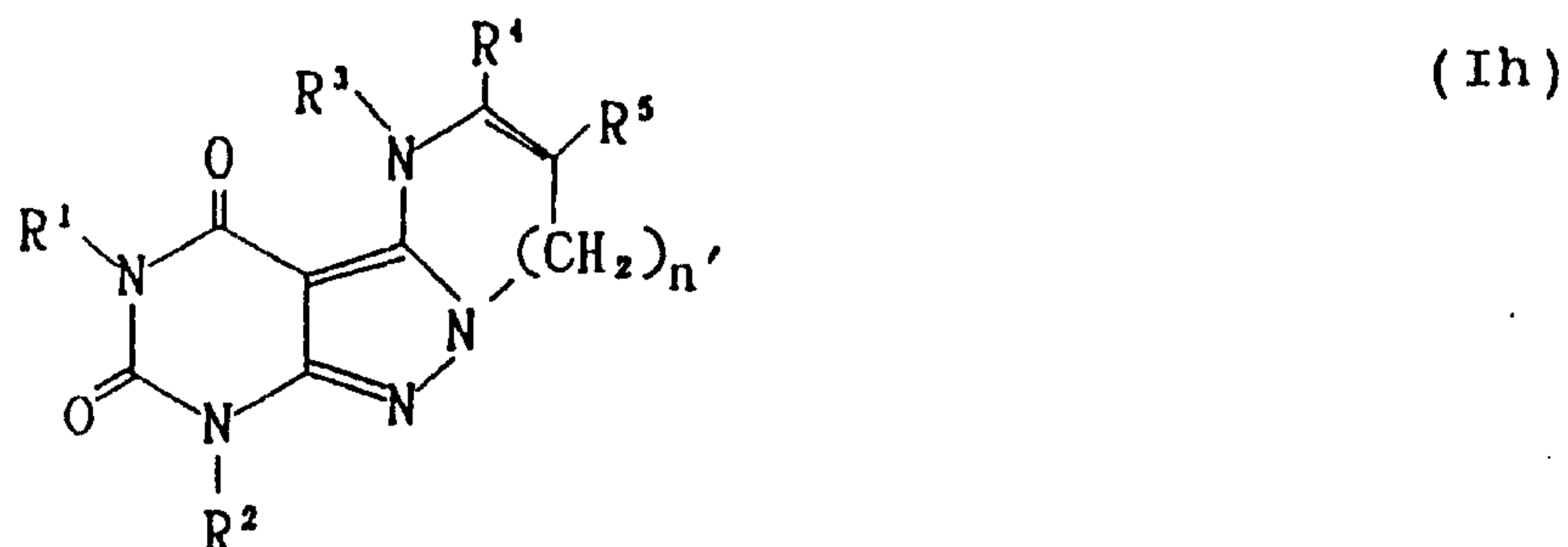
[wherein R¹, R², R³ and n are of the same meaning as defined above, provided that R³ is not hydrogen],
(g) subjecting a compound of the formula (XV):



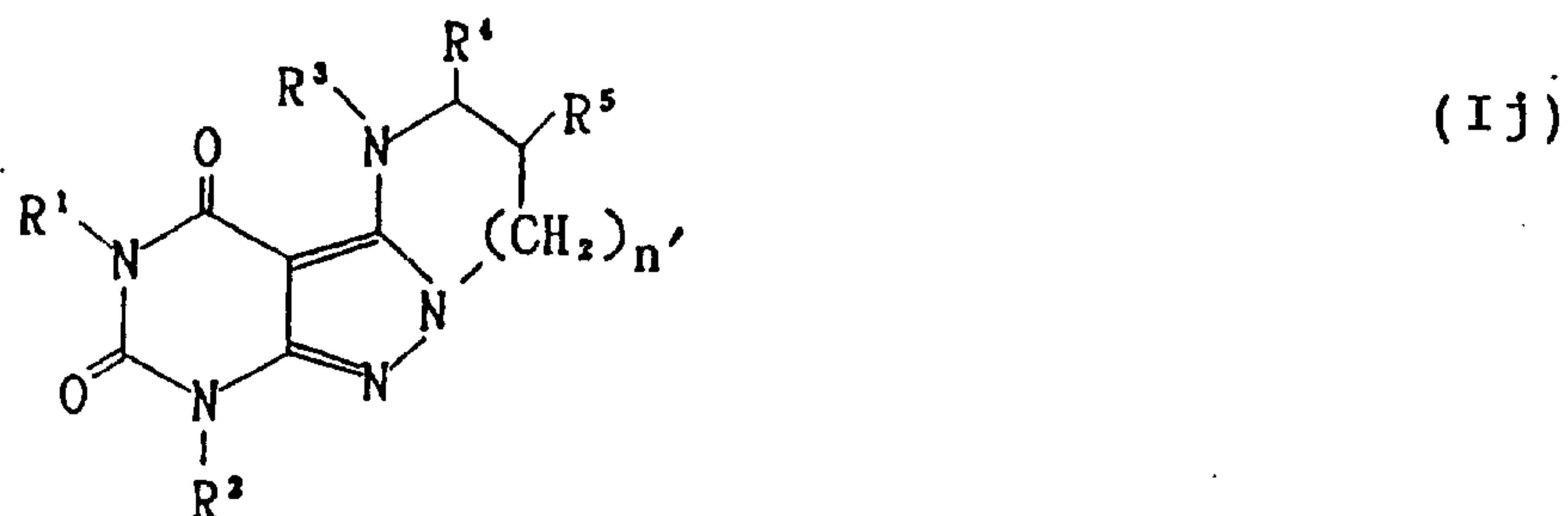
[wherein R^1 , R^2 and R^3 are of the same meaning as defined above; R^4 and R^5 are independently hydrogen, an optionally substituted aliphatic hydrocarbon group, an optionally substituted aromatic hydrocarbon group or halogen, or R^4 and R^5 are combined to form a cyclic aliphatic hydrocarbon group having 5 to 8 carbon atoms of the formula:



and n' is an integer of 0 to 2] to dehydration to produce a compound of the formula (Ih):

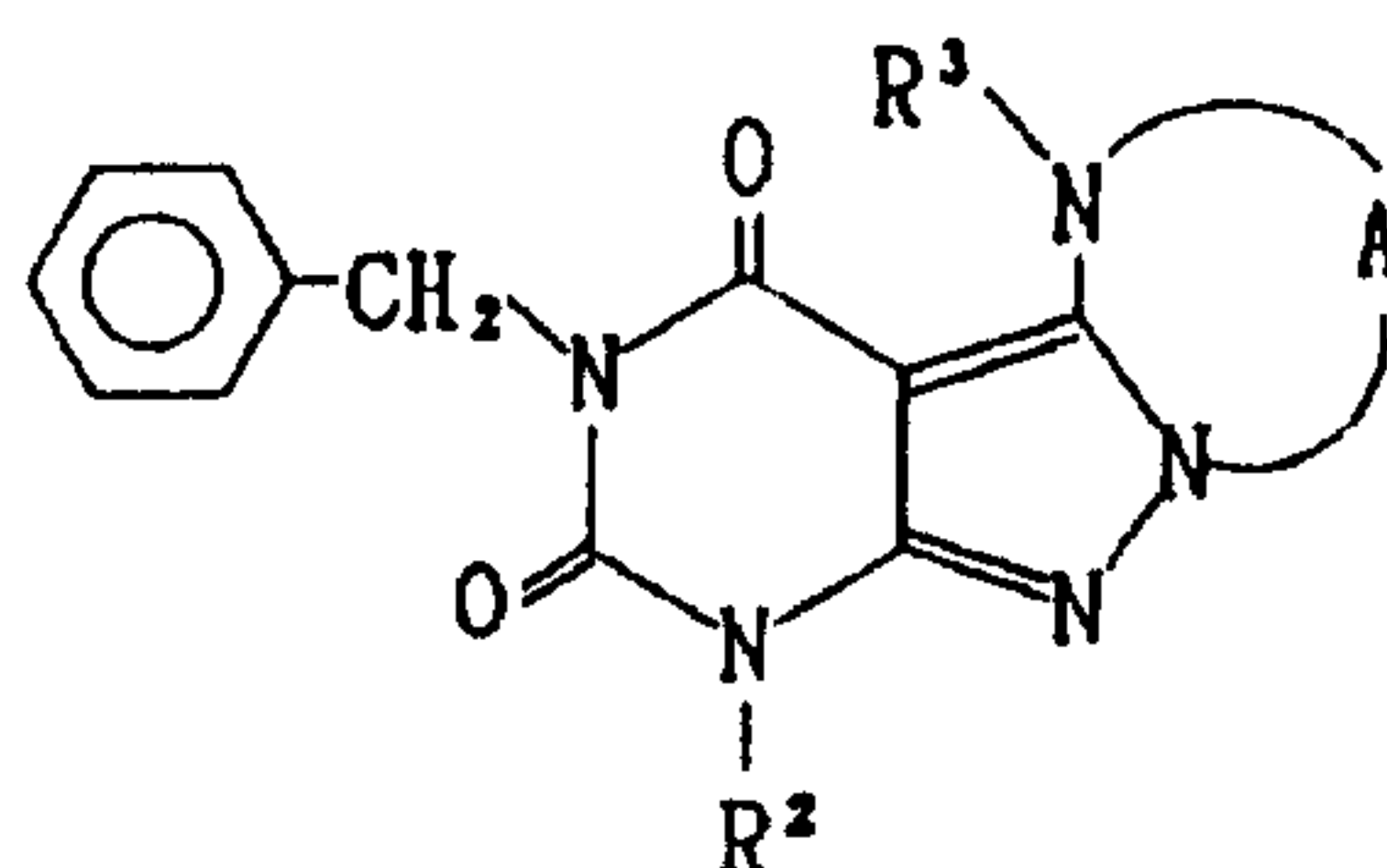


[wherein R^1 , R^2 , R^3 , R^4 , R^5 and n' are of the same meaning as defined above], and, if necessary, subjecting the compound of the formula (Ih) to reduction to produce a compound of the formula (Ij):



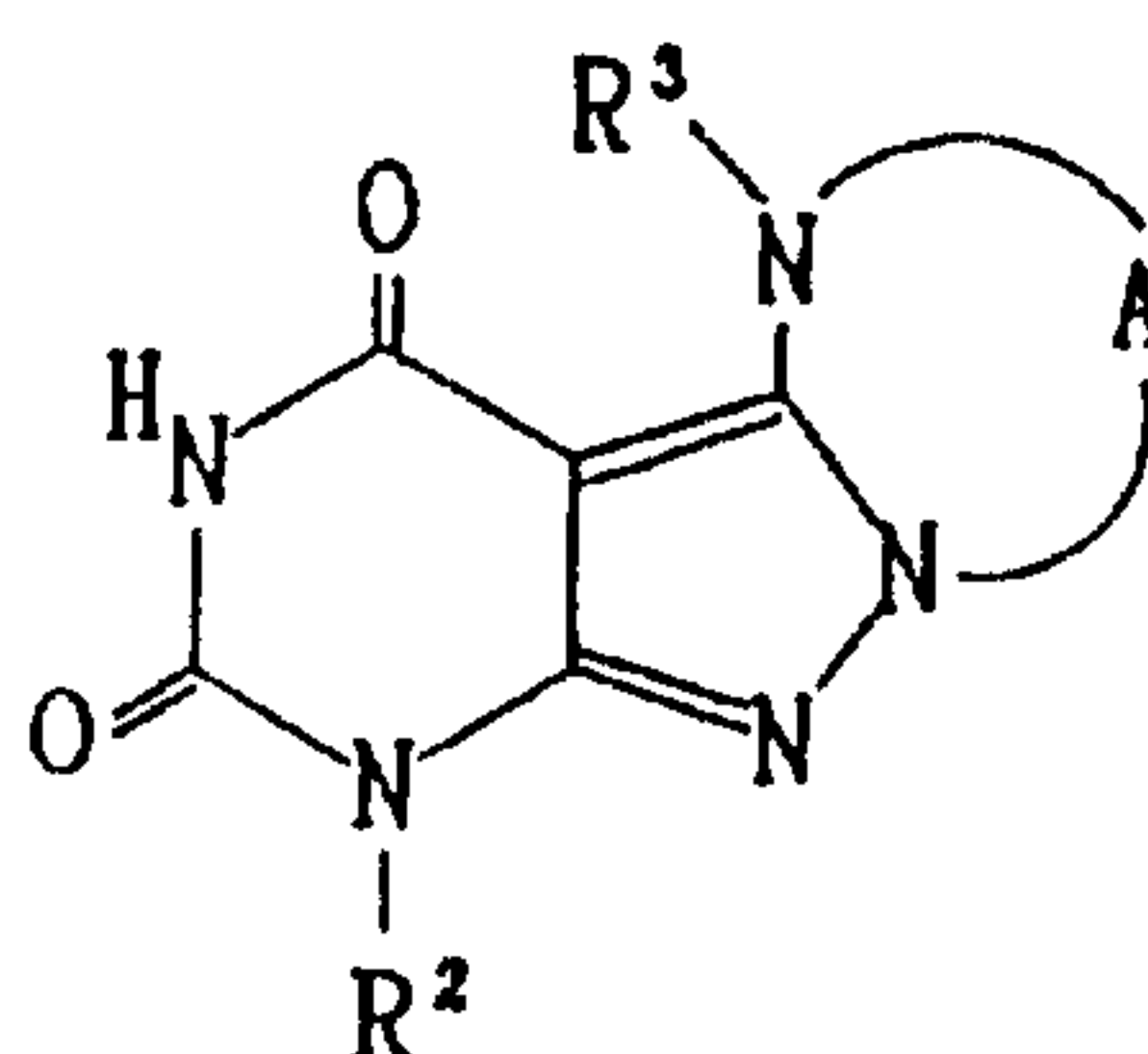
[wherein R^1 , R^2 , R^3 , R^4 , R^5 and n' are of the same meaning as defined above],

(h) subjecting a compound of the formula (Ik):



(Ik)

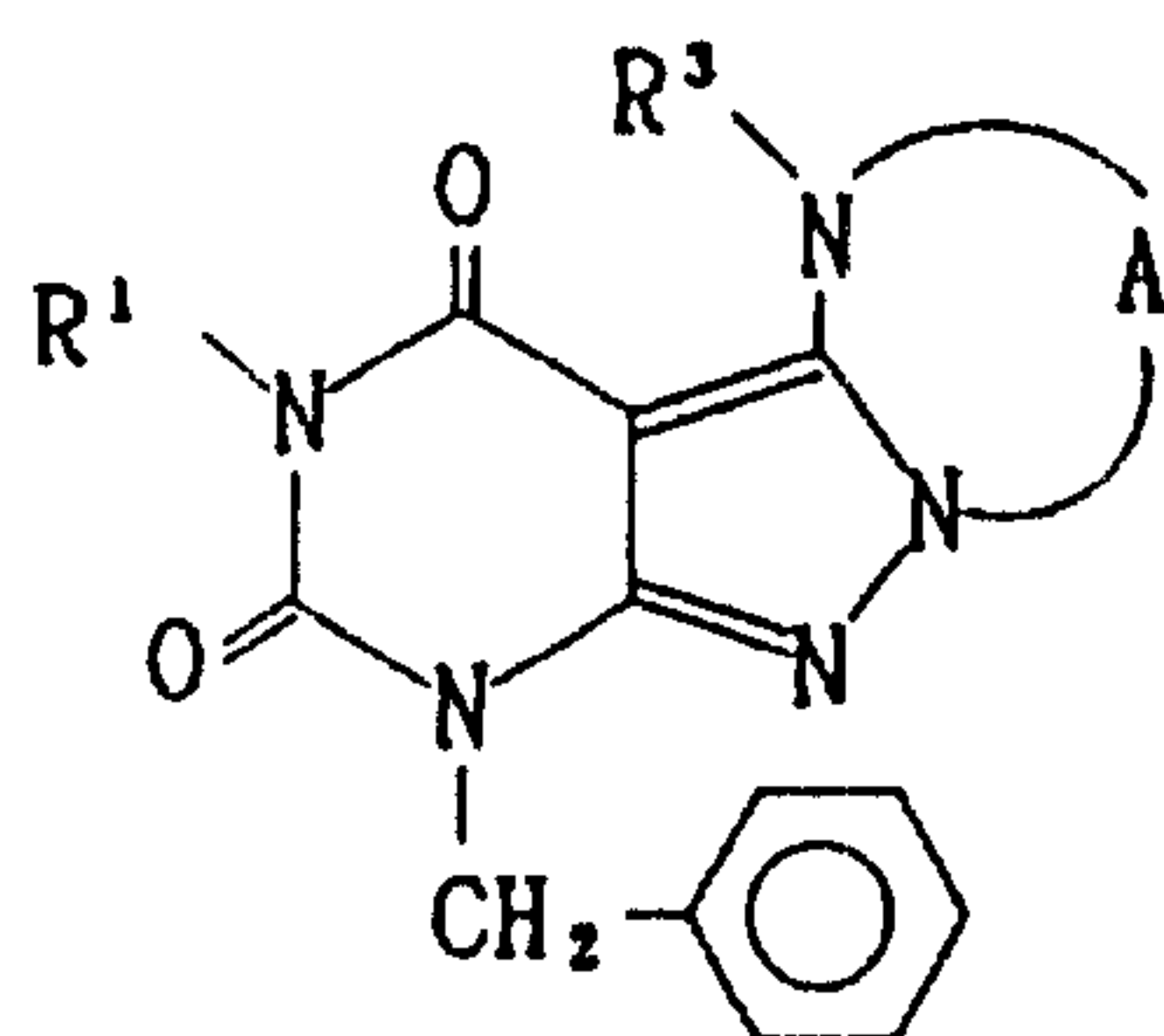
[wherein R^2 , R^3 and A are of the same meaning as defined above, provided that R^2 is not an optionally substituted benzyl group] to debenylation to produce a compound of the formula (Il):



(Il)

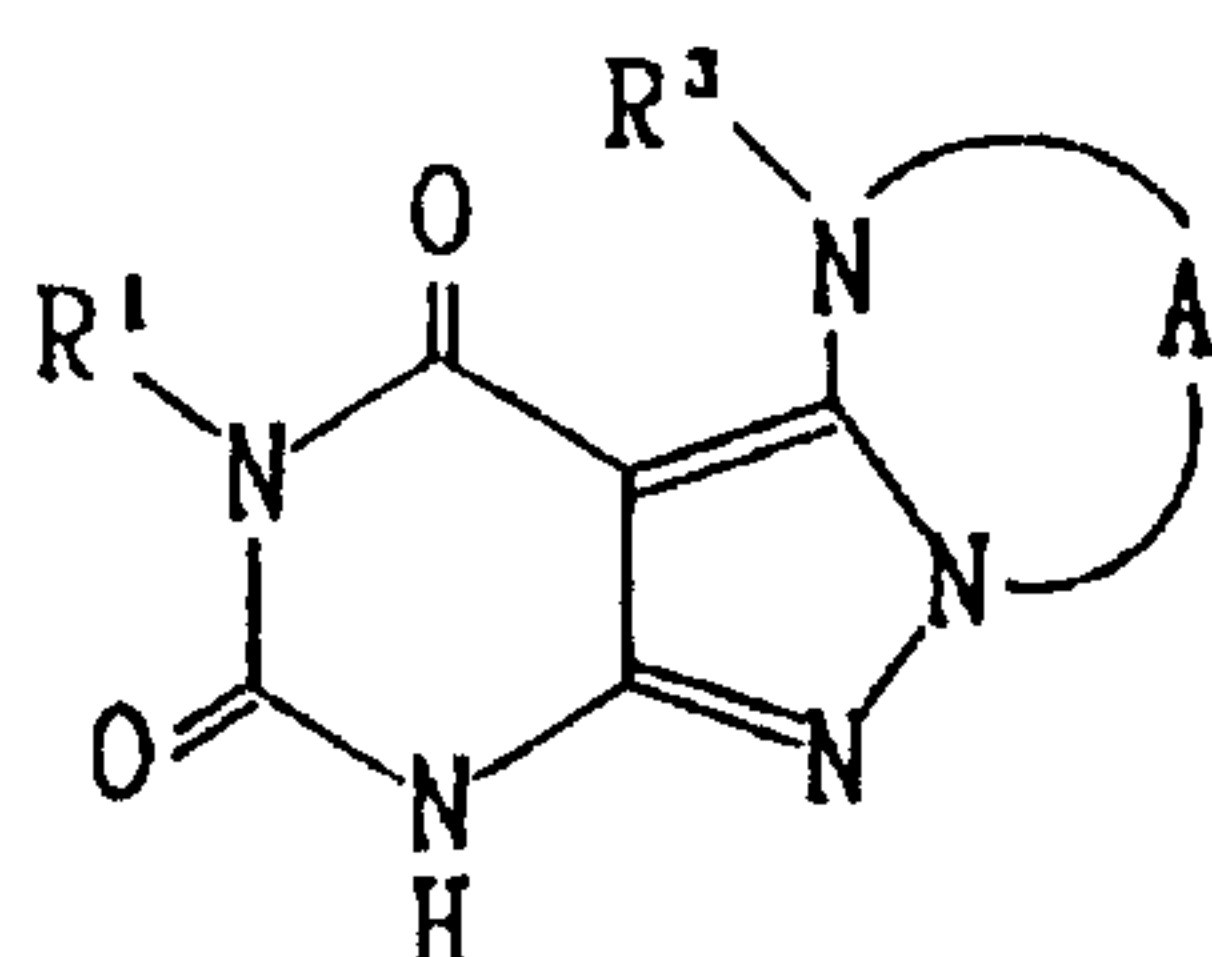
[wherein R^2 , R^3 and A are of the same meaning as defined above, provided that R_2 is not an optionally substituted benzyl group],

(i) subjecting a compound of the formula (Im):



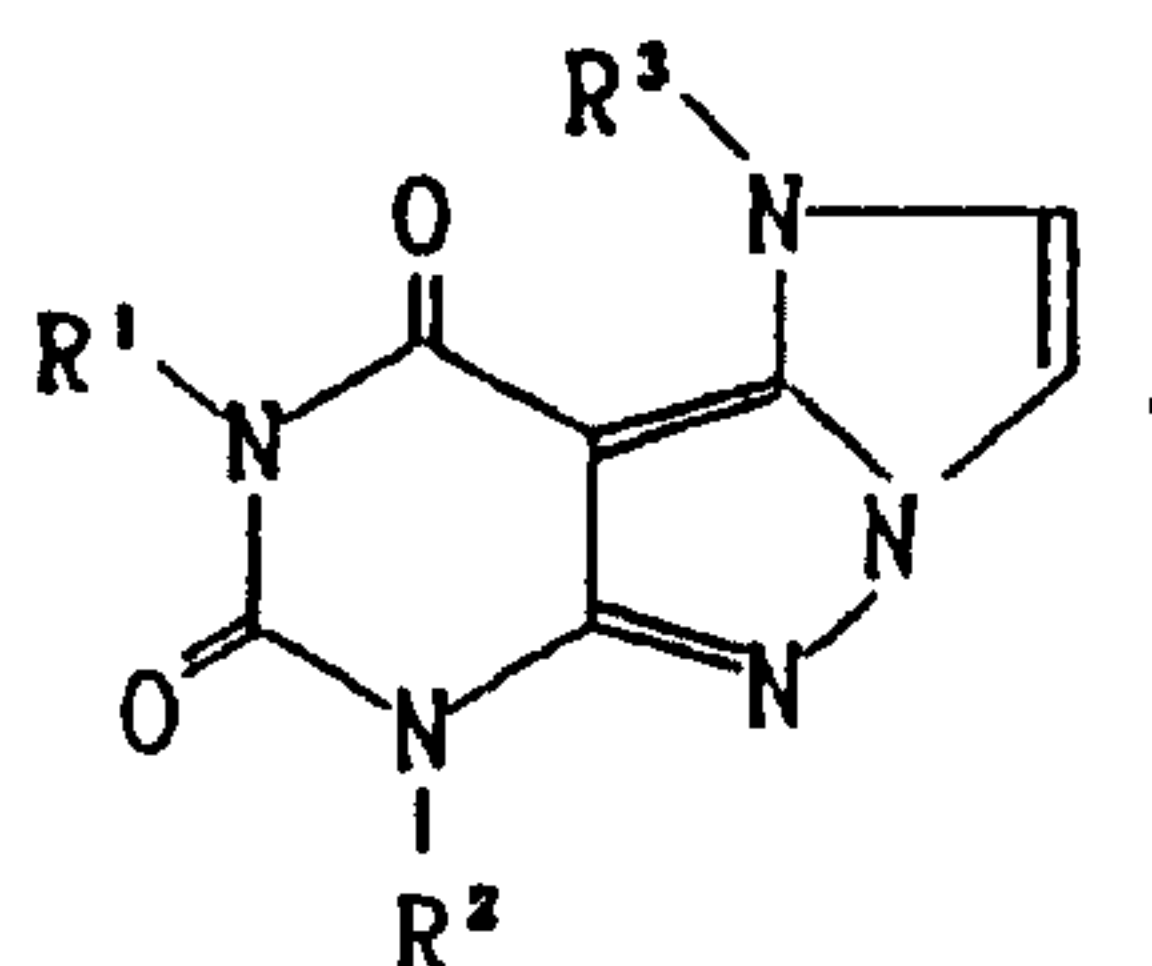
(Im)

[wherein R^1 , R^3 and A are of the same meaning as defined above, provided that R^1 is not an optionally substituted benzyl group] to debenylation to produce a compound of the formula (In):



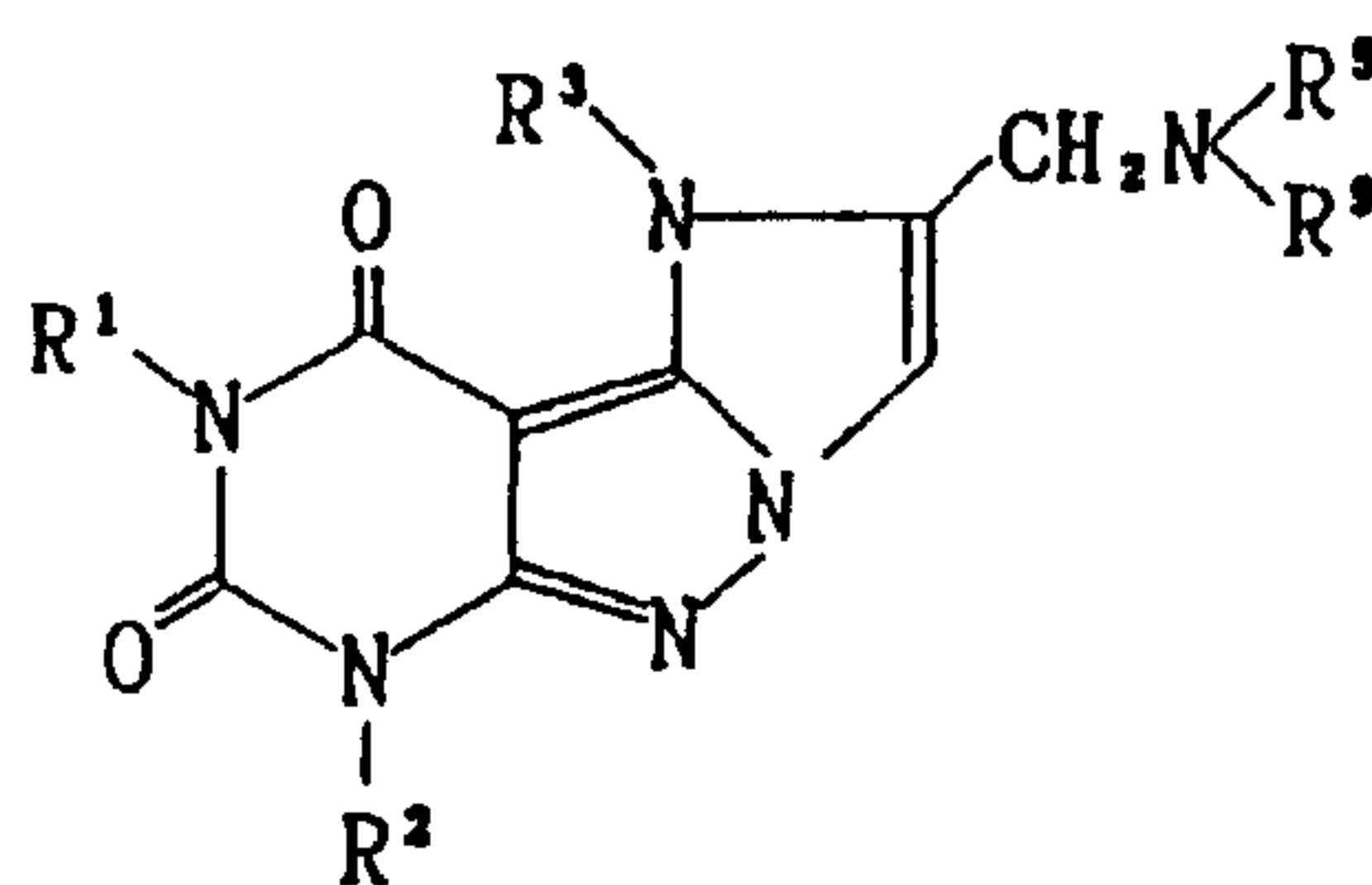
(In)

[wherein R¹, R³ and A are of the same meaning as defined above, provided that R¹ is not an optionally substituted benzyl group], or
 (j) subjecting a compound of the formula (If):



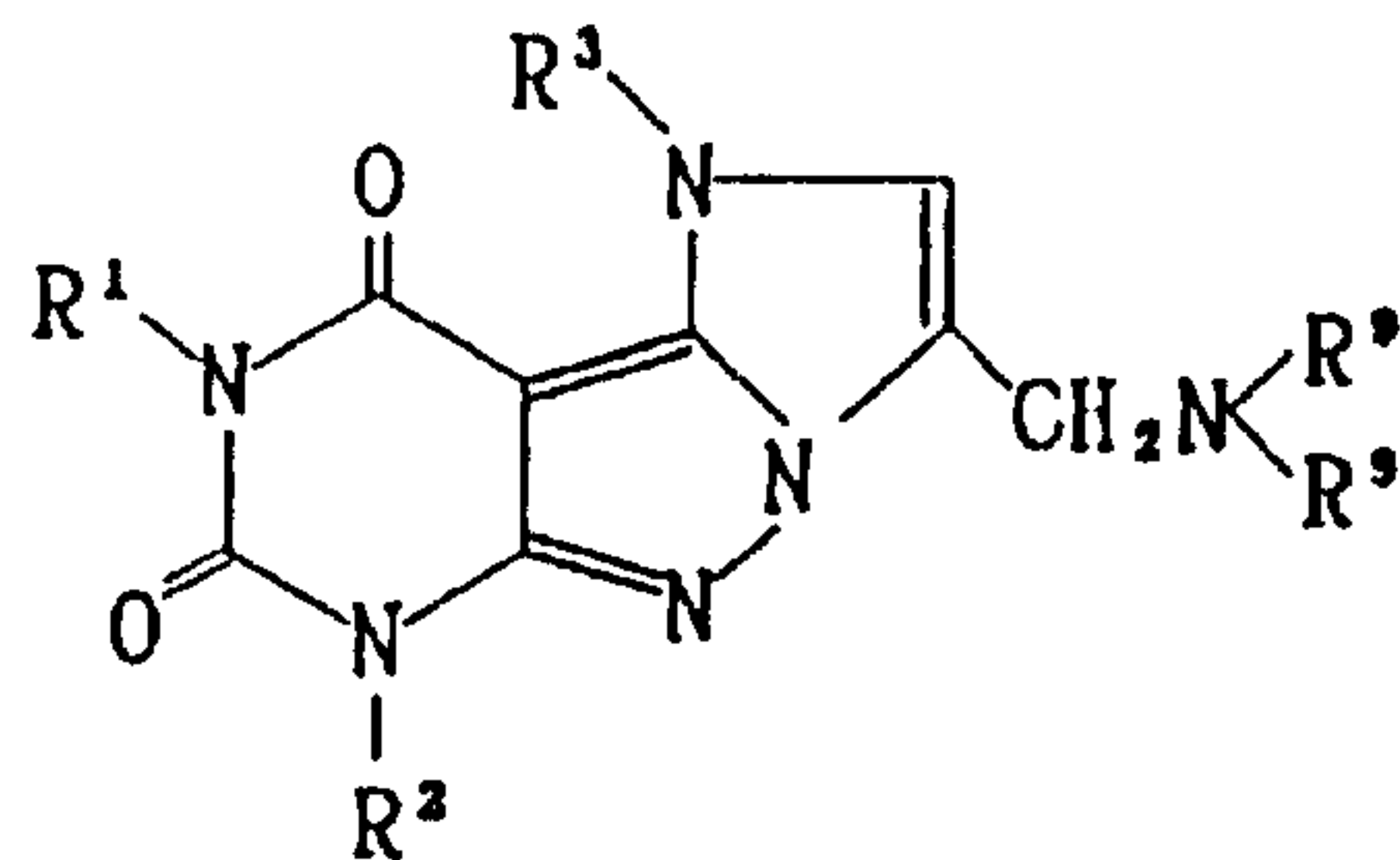
(If)

[wherein R¹, R², and R³ are of the same meaning as defined above] to aminomethylation to produce a compound of the formula (Io):



(Io)

and a compound of the formula (Ip):



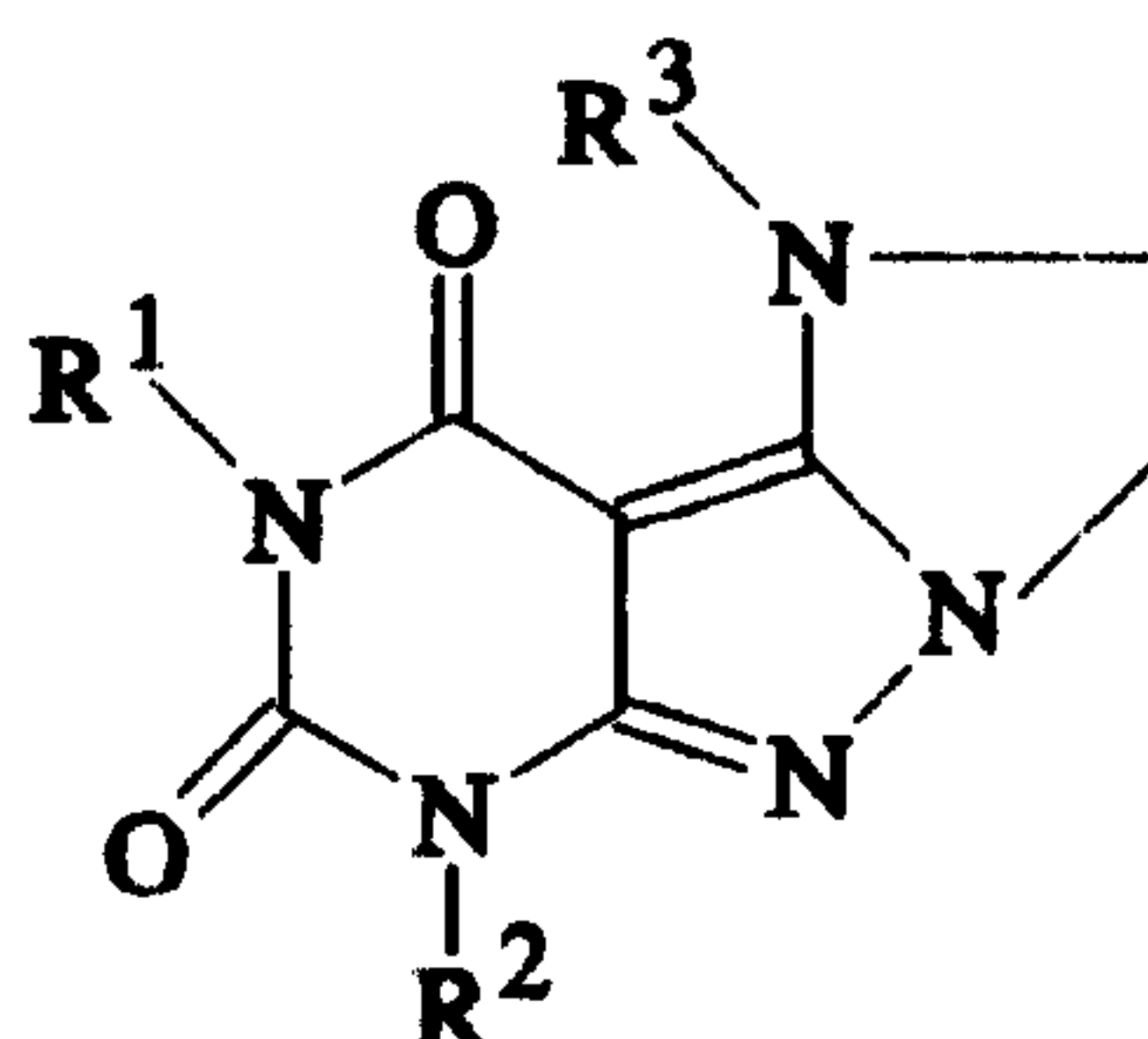
(Ip)

[wherein R^1 , R^2 , and R^3 are of the same meaning as defined above and R^9 is lower alkyl group or $-N \begin{smallmatrix} R' \\ R' \end{smallmatrix}$ is a cyclic amino group], and, if necessary,
(k) converting a product obtained by the above processes (a) to (j) into a salt thereof.

~~FETHERSTONHAUGH & CO.~~
~~OTTAWA, CANADA~~

~~PATENT AGENTS~~

44. The compound or salt according to claim 1, wherein the compound is represented by the formula:



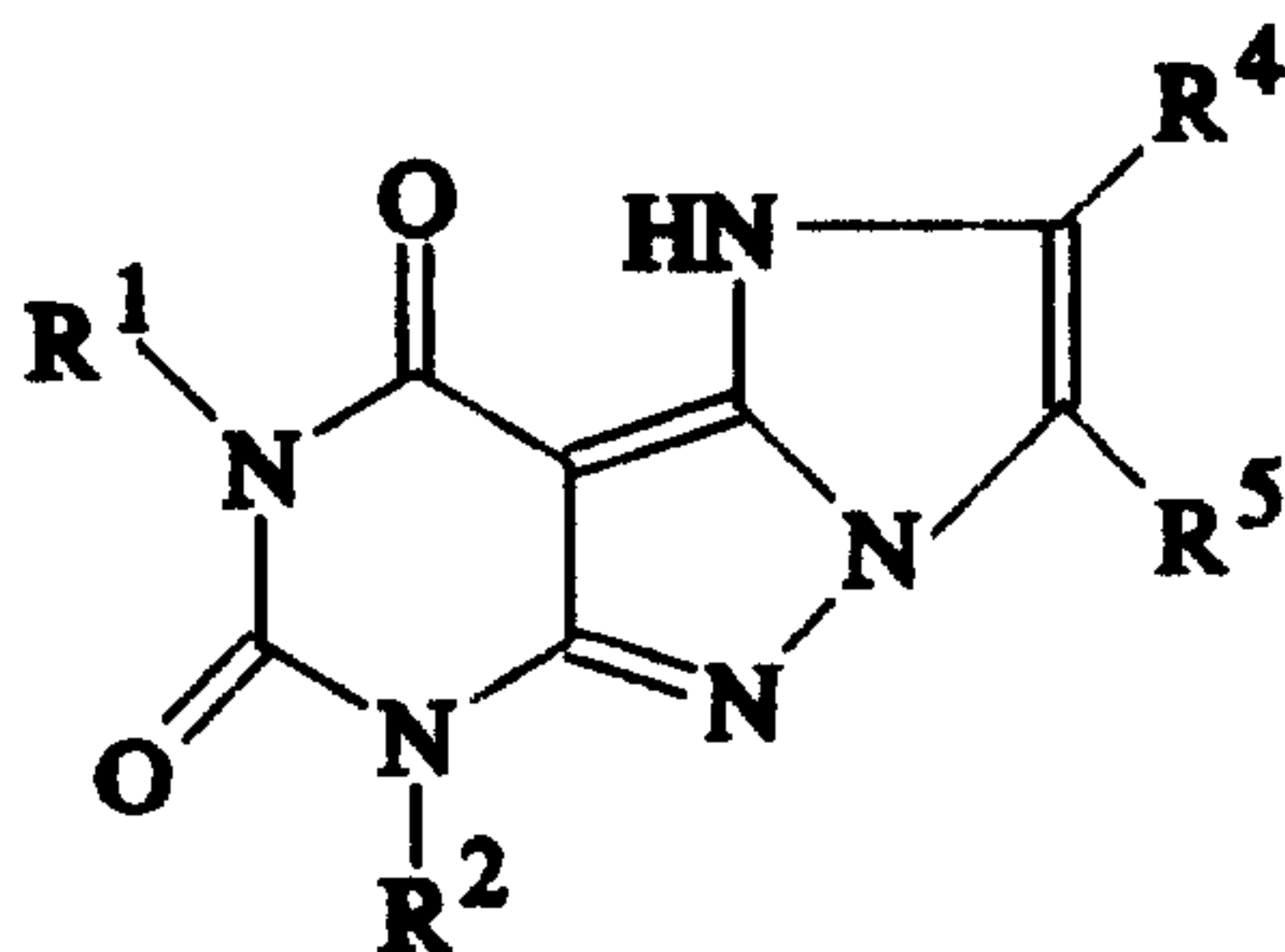
(wherein R^1 , R^2 and R^3 are as defined in claim 1).

45. The compound or salt according to claim 44, in which:

one of R^1 and R^2 is hydrogen or an optionally substituted aralkyl group and the other is hydrogen, an optionally substituted aralkyl group or an aliphatic hydrogen group, wherein the optionally substituted aralkyl group is selected from benzyl, 4-chlorobenzyl, 3-chlorobenzyl, 2-chlorobenzyl, 2-phenethyl, and 3-phenylpropyl and the aliphatic hydrocarbon is selected from propyl and butyl; and

R^3 is hydrogen.

46. The compound or salt according to claim 2, wherein the compound is represented by the formula:



(wherein R^1 and R^2 are as defined in claim 1 and R^4 and R^5 are as defined in claim 2).

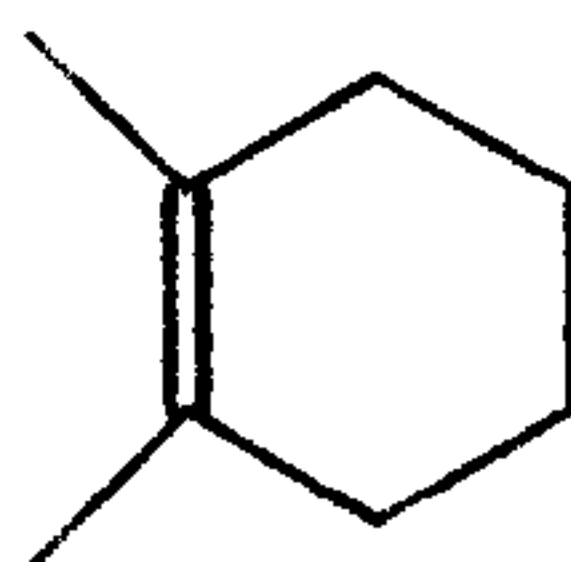
47. The compound or salt according to claim 46, in which:

R^1 is propyl;

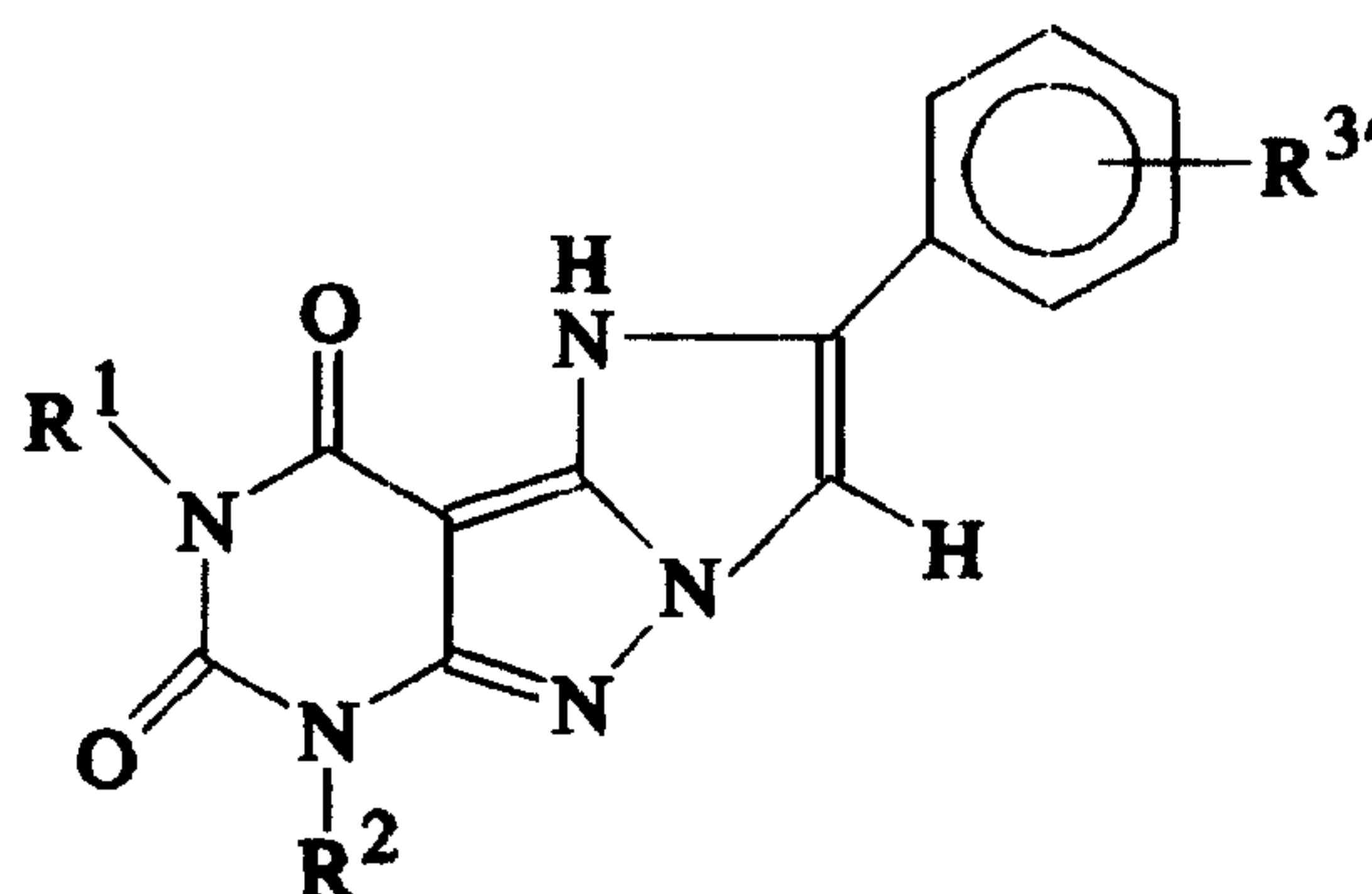
R^2 is benzyl;

R^4 and R^5 are each (1) hydrogen, (2) phenyl which may be substituted by halogen, C_{1-4} alkoxy, C_{1-4} alkyl or phenyl, (3) cyclopropyl, (4) C_{1-4} alkyl which may be substituted by dimethylamino, provided that at least one of R^4 and R^5 is other than hydrogen, or

R^4 and R^5 together with the carbon atoms to which they are attached form a cyclic group of the formula:



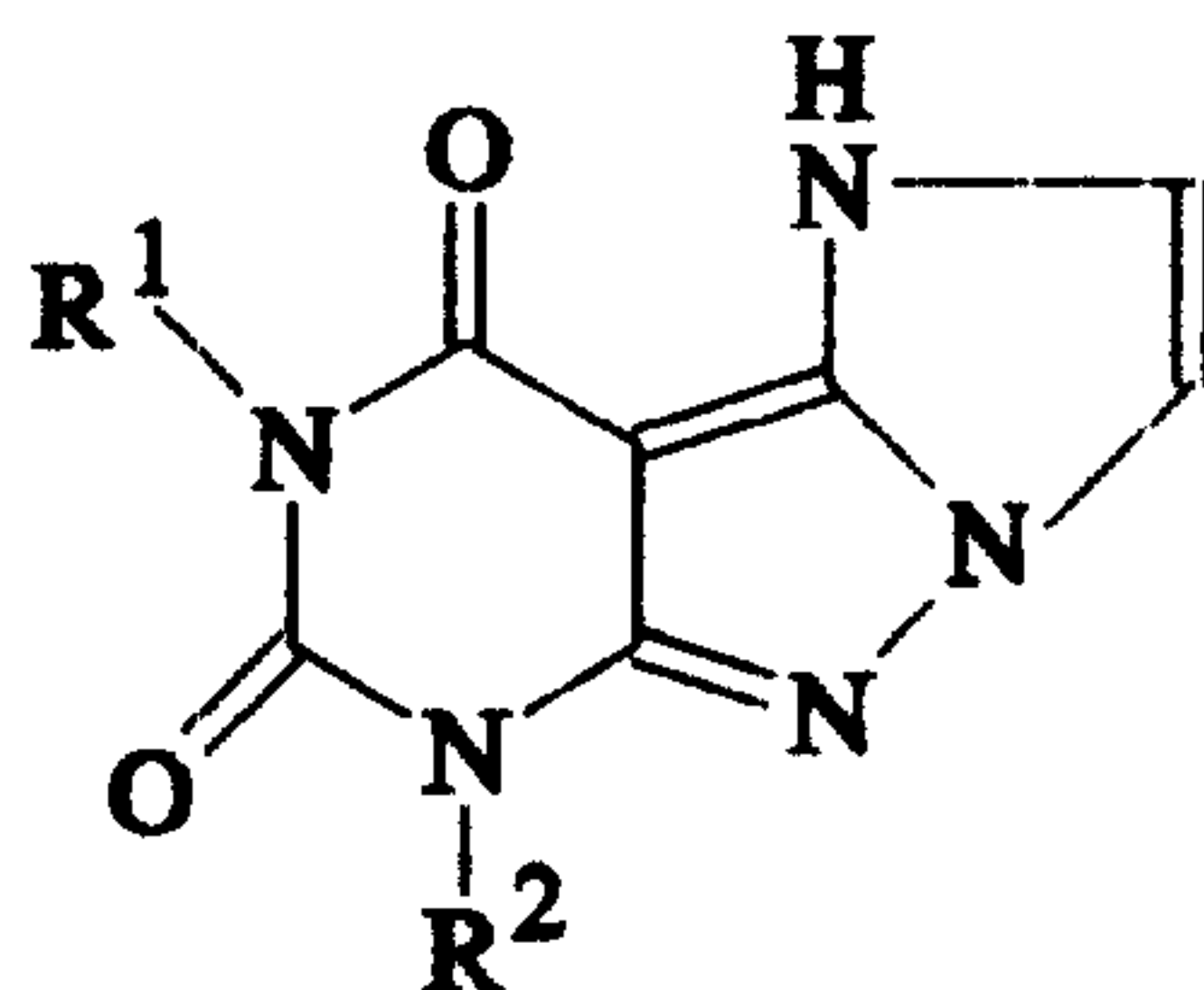
48. The compound or salt according to claim 47, in which the compound is represented by the formula:



(wherein R^1 and R^2 are as defined in claim 47, and $R^{3'}$ is halogen or C_{1-4} alkoxy).

49. The compound or salt according to claim 48, wherein $R^{3'}$ is m-MeO, p-MeO, o-MeO, p-BuO, p-Me, m-Cl, o-Cl or p-Cl.

50. The compound or salt according to claim 1, in which the compound is represented by the formula:



(wherein R^1 and R^2 are as defined in claim 1).

51. The compound or salt according to claim 50, in which one of R^1 and R^2 is hydrogen or an optionally substituted aralkyl group and the other is hydrogen, an optionally substituted aralkyl group or an aliphatic hydrogen group, wherein

the optionally substituted aralkyl group is selected from benzyl, 4-chlorobenzyl, 3-chlorobenzyl, 2-chlorobenzyl, 2-phenethyl, and 3-phenylpropyl and the aliphatic hydrocarbon is selected from propyl and butyl.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS