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CONVENTION

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

We, **SUNTORY LIMITED** of 1140, Dojimahama 2-chome, Kita-ku, Osaka-shi, Osaka 530 Japan state the following in connection with Australian Application No. 24030/92:

1. We are the nominated person.
2. The nominated person is the assignee of the actual inventors.
3. The nominated person is the applicant of the basic application listed in the declaration under Article 8 of the PCT.
4. The basic application is the application first made in a Convention country in respect of the invention.

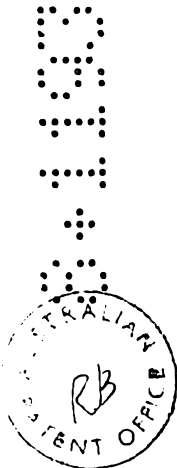
Dated: 4 November 1993

By PHILLIPS ORMONDE & FITZPATRICK
Patent Attorneys for the Applicant

By:

David B Fitzpatrick

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To: The Commissioner of Patents

Our Ref: 324274

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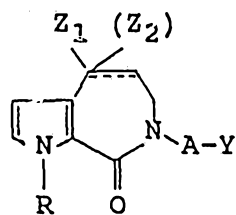


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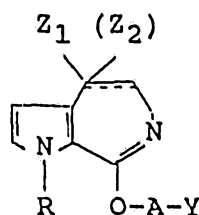
(12) PATENT ABRIDGMENT (11) Document No. AU-B-24030/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 645441

- (54) Title
 PYRROLO {2,3-C} AZEPIN-4-ONE DERIVATIVES
- (51)⁵ International Patent Classification(s)
 C07D 487/04 A61K 031/55
- (21) Application No. : 24030/92 (22) Application Date : 06.08.92
- (87) PCT Publication Number : WO93/03032
- (30) Priority Data
- (31) Number (32) Date (33) Country
 3-221192 07.08.91 JP JAPAN
- (43) Publication Date : 02.03.93
- (44) Publication Date of Accepted Application : 13.01.94
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- (57) Claim

1. A pyrroloazepine compound represented by the following formula (I) or (II):



(I)



(II)

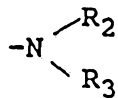
wherein the dashed line indicates the presence or absence of a bond and when the bond indicated by the dashed line is present, Z₁ represents a hydrogen atom but, when the bond indicated by the dashed line is absent, Z₁ represents a hydrogen atom and Z₂ represents a hydroxyl group or Z₁ and Z₂ are taken together to form an oxygen atom or a group NOR₁, in which R₁ represents a hydrogen atom, an alkyl group, a substituted or un-

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substituted aryl group or a substituted or unsubstituted aralkyl group; R represents an alkyl group, a cycloalkyl group, a cycloalkyl-alkyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted aralkyl group; A represents an alkylene, alkenylene or alkynylene group; and Y represents a substituted or unsubstituted heterocyclic group or a group:



in which R₂ and R₃ may be the same or different and individually represent a hydrogen atom, an alkyl group which may be substituted by a lower alkoxy group or a substituted or unsubstituted aryloxy group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group; or a salt thereof.



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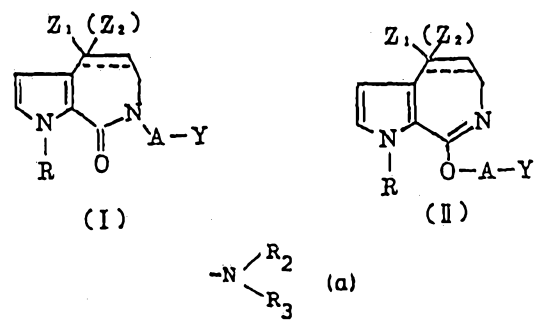
(51) 国際特許分類 5 C07D 487/04, A61K 31/55	A1	(11) 国際公開番号 WO 93/03032 (43) 国際公開日 1993年2月18日 (18.02.1993)
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<p>(21) 国際出願番号 PCT/JP92/01009 (22) 国際出願日 1992年8月6日 (06. 08. 92) (30) 優先権データ 特願平3/221192 1991年8月7日 (07. 08. 91) JP (71) 出願人 (米国を除くすべての指定国について) サントリー株式会社 (SUNTORY LIMITED) [JP/JP] 〒530 大阪府大阪市北区堂島浜二丁目1番40号 Osaka, (JP) (72) 発明者: および (75) 発明者/出願人 (米国についてのみ) 水野 章 (MIZUNO, Akira) [JP/JP] 〒610-11 京都府京都市西京区大枝東新林町3丁目7-28-306 Kyoto, (JP) 味谷美樹子 (MIYA, Mikiko) [JP/JP] 〒305 茨城県つくば市春日1丁目7-9-701 Ibaragi, (JP) 猪俣剛夫 (INOMATA, Norio) [JP/JP] 〒562 大阪府箕面市牧落5丁目8-1-508 Osaka, (JP) 立岡敏雄 (TATSUOKA, Toshio) [JP/JP] 〒662 兵庫県西宮市上甲東園1丁目2-3-101 Hyogo, (JP) 石原高文 (ISHIHARA, Takafumi) [JP/JP] 〒569 大阪府高槻市宮田町3丁目15-1-604 Osaka, (JP) (74) 代理人 弁理士 小野信夫, 外 (ONO, Nobuo et al.) 〒101 東京都千代田区神田佐久間町3-15 藤井ビル7階 Tokyo, (JP)</p>	<p>(81) 指定国 AT (欧州特許), AU, BE (欧州特許), CA, CH (欧州特許), DE (欧州特許), DK (欧州特許), ES (欧州特許), FR (欧州特許), GB (欧州特許), GR (欧州特許), IE (欧州特許), IT (欧州特許), JP, KR, LU (欧州特許), MC (欧州特許), NL (欧州特許), SE (欧州特許), US. 添付公開書類 国際調査報告書</p>
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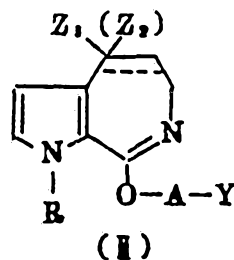
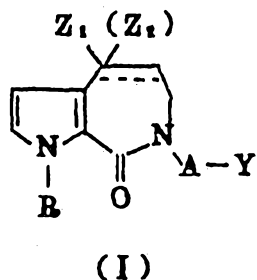
(54) Title : PYRROLOAZEPINE COMPOUND

(54) 発明の名称 ピロロアゼピン化合物

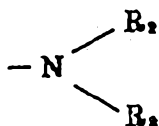


(57) Abstract
 A pyrroloazepine compound represented by general formula (I) or (II), a salt thereof, a process for the production thereof, and a remedy for the diseases of circulatory organs containing the same as the active ingredient. In general formula (I) or (II) Z₁ represents H when there is a bond represented by the broken line, whereas when there is no such a bond, Z₁ represents H and Z₂ represents OH, or alternatively Z₁ and Z₂ are combined together to represent O or NOR₁ (wherein R₁ represents H, alkyl, aryl or aralkyl); R represents alkyl, cycloalkyl, cyclalkyl-alkyl, aryl or aralkyl; A represents alkylene, alkenylene or alkynylene; and Y represents optionally substituted heterocycle or (α) wherein R₂ and R₃ represent each H, alkyl, lower alkoxy, aryloxy-substituted alkyl, aryl or aralkyl.

(57) 要約 本発明は、次の一般式 (I) または (II)



[点線結合が存在する場合、 Z_1 はHを、点線結合が存在しない場合、 Z_1 がHで Z_2 がOHであるか、 Z_1 と Z_2 が一緒になって、Oまたは基NO R_1 (R_1 はH、アルキル、アリアルまたはアラルキルを示す)を示し、Rはアルキル、シクロアルキル、シクロアルキル-アルキル、アリアルもしくはアラルキルを示し、Aはアルキレン、アルケニレンまたはアルキニレンを示し、Yは置換されていても良い複素環または基



(R_2 、 R_3 は、H、アルキル、低級アルコキシ、アリアルオキシ置換アルキル、アリアルまたはアラルキルを示す)を示す]

で表されるピロロアゼピン化合物およびその塩、それらの製造法並びにそれらを有効成分とする循環器系疾患治療剤を提供するものである。

情報としての用途のみ

PCTに基づいて公開される国際出願のパンフレット第1頁にPCT加盟国を同定するために使用されるコード

AT オーストリア
 AU オーストラリア
 BB パルバードス
 BE ハルギー
 BF ブルキナ・ファソ
 BG ブルガリア
 BJ ハナン
 BR ブラジル
 CA カナダ
 CF 中央アフリカ共和国
 CG コンゴ
 CH スイス
 CI コート・ジボアール
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 CS チェコスロヴァキア
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 LI リヒテンシュタイン
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DESCRIPTION

PYRROLOAZEPINE COMPOUND

5 **Technical Field**

 The present invention relates to novel pyr-
 roloazepine compounds, and more specifically to novel
 pyrroloazepine compounds and salts thereof, said com-
 pounds and salts being useful as therapeutics for cir-
10 culatory diseases such as ischemic heart diseases and
 hypertension, their preparation processes and thera-
 peutics for circulatory diseases, said therapeutics
 containing them as active ingredients.

15 **Background Art**

 It is known that serotonin is contained abundant-
 ly in platelets, a blood component, and that upon
 stimulation by thromboxane A₂, ADP, collagen or the
 like, it is released to synergistically act on the
20 release of various platelet aggregation factors through
 activation of the serotonin-2 receptor in platelets and
 vascular smooth muscle cells and on vasoconstriction by
 norepinephrine through the α_1 receptor, thereby induc-
 ing strong platelet aggregation and vasoconstriction
25 [P.M. Vanhoutte, "Journal of Cardiovascular Pharmacol-

ogy", Vol. 17 (Supple. 5), S6-S12 (1991)].

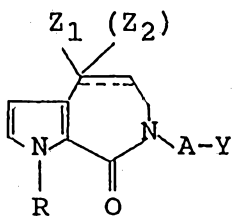
With the foregoing in view, there is hence an outstanding desire for the development of a serotonin-2 receptor antagonist as a circulatory disease
5 therapeutic for preventing thrombus formation and vasoconstriction so that the serotonin-2-receptor antagonist can be used for hypertension and ischemic heart diseases such as angina pectoris, myocardial infarction, heart failure and post-PTCA restenosis. It
10 is however the present situation that no drug has been obtained yet with sufficient antagonism and selectivity. Pharmaceuticals having α_1 -blocking action in combination with anti-serotonin action are expected to reduce side effects caused by hypotensive action based
15 on α_1 -blocking action, such as orthostatic disorder and reflex tachycardia, so that some drugs having both actions have been developed. However, none of them have been provided with sufficient hypotensive action.

20 **Disclosure of the Invention**

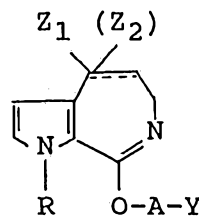
In view of the foregoing circumstances, the present inventors have carried out an extensive investigation, resulting in the finding of certain pyrrolo-azepine compounds which have strong anti-serotonin
25 action without significant side effects and toxicity and

are useful as therapeutics for ischemic heart diseases based on their antagonism against serotonin receptors. Some of the compounds according to the present invention have also been found to have α_1 -blocking action too, whereby they are useful as hypotensive drugs with reduced side effects and can be used in a wide variety of therapeutics for circulatory diseases.

The present invention has been completed based on the above described findings and provides a pyrrolo-azepine compound represented by the following formula (I) or (II):



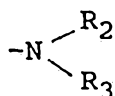
(I)



(II)

wherein the dashed line indicates the presence or absence of a bond and when the bond indicated by the dashed line is present, Z₁ represents a hydrogen atom but, when the bond indicated by the dashed line is absent, Z₁ represents a hydrogen atom and Z₂ represents a hydroxyl group or Z₁ and Z₂ are taken together to form an oxygen atom or a group NOR₁, in which R₁ represents a hydrogen atom, an alkyl group, a substituted or un-

substituted aryl group or a substituted or unsubstituted aralkyl group; R represents an alkyl group, a cycloalkyl group, a cycloalkyl-alkyl group, a substituted or unsubstituted aryl group, or a substituted or unsubstituted aralkyl group; A represents an alkylene, alkenylene or alkynylene group; and Y represents a substituted or unsubstituted heterocyclic group or a group:



in which R₂ and R₃ may be the same or different and individually represent a hydrogen atom, an alkyl group which may be substituted by a lower alkoxy group or a substituted or unsubstituted aryloxy group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group; or a salt thereof; a preparation process thereof; and a therapeutic for circulatory diseases, said therapeutic containing as an active ingredient the pyrroloazepine compound or the salt thereof.

20

Best Modes for Carrying Out the Invention

In the pyrroloazepine compounds (I) and (II) of the present invention, preferred examples of group R include branched or linear C₁₋₈ alkyl groups such as

methyl, ethyl, n-propyl, isopropyl and n-pentyl; C₃₋₈ cycloalkyl groups such as cyclopropyl, cyclopentyl and cyclohexyl; C₃₋₈ cycloalkyl-alkyl groups such as cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl; aryl groups such as phenyl, phenyl substituted by one or more halogen atoms such as fluorine, chlorine and bromine, C₁₋₄ alkyl groups such as methyl and ethyl and/or C₁₋₄ alkoxy groups such as methoxy and ethoxy, and naphthyl; and aralkyl groups such as diphenylmethyl, benzyl and phenethyl. In this case, each aromatic ring may be substituted by one or more of the halogen atoms, alkyl groups and/or alkoxy groups referred to above. Among them, methyl, ethyl and benzyl groups are particularly preferred.

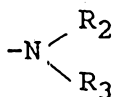
In addition, preferred examples of group A include branched or linear C₂₋₁₀ alkylene groups such as ethylene, trimethylene, tetramethylene, pentamethylene, 3,3-dimethylpentamethylene and octamethylene; branched or linear C₄₋₁₀ alkenylene groups such as 2-hutenylene and 3-pentenylene; and branched or linear C₄₋₁₀ alkynylene groups such as 2-butynylene and 3-pentynylene. Among them trimethylene, tetramethylene and pentamethylene groups are particularly preferred.

Further, preferred examples concerning groups Z₁ and Z₂ include that inducing no bond indicated by the

dashed line and containing a hydrogen atom as Z_1 and a hydroxyl group as Z_2 and those where Z_1 and Z_2 are taken together to form an oxygen atom or a group $-NOR_1$.

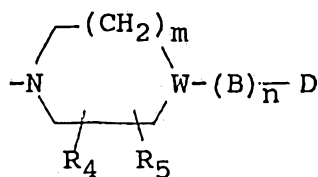
5 Preferred examples of R_1 in the group $-NOR_1$ include a hydrogen atom; branched or linear C_{1-4} alkyl groups such as methyl, ethyl and isopropyl; aryl groups such as phenyl and phenyl substituted by one or more of the halogen atoms, alkyl groups and/or alkoxy groups referred to above; and aralkyl groups such as benzyl
10 and diphenylmethyl. In this case, each aromatic ring may be substituted by one or more of the halogen atoms, alkyl groups and/or alkoxy groups referred to above. Among these, a hydrogen atom and a methyl group are particularly preferred.

15 Furthermore, preferred examples of group $-Y$ include groups represented by the following formula:



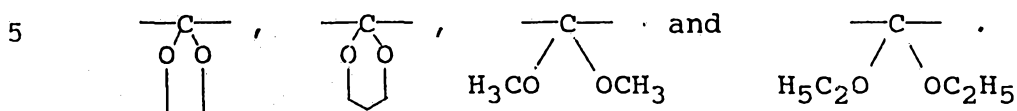
in which R_2 and R_3 may be the same or different and individually represent a hydrogen atom, a lower alkyl group such as methyl, ethyl and n-propyl, an alkyl
20 group which is substituted by a lower alkoxy group or a substituted or unsubstituted aryloxy group such as 3-methoxypropyl, 2-phenoxyethyl and 2-(2-methoxyphenyloxy)ethyl, a substituted or unsubstituted aryl group

such as phenyl and 2-methoxyphenyl and a substituted or unsubstituted aralkyl group such as 2-(3,4-dimethoxyphenyl)ethyl; and a heterocyclic group led by a monovalent group derived from piperazine, homopiperazine, piperidine or imidazole. These heterocyclic groups may be substituted. The following heterocyclic groups can be given as more preferred examples.



wherein R_4 and R_5 individually represent a hydrogen atom or a branched or linear alkyl group, preferably a hydrogen atom or a lower alkyl group such as a methyl or ethyl group, when W represents C- R_6 (R_6 is preferably a hydrogen atom or a C_{1-4} alkyl group such as a methyl and ethyl group with a hydrogen atom being particularly preferred), m stands for 0, 1 or 2 with 1 being preferred, B represents an oxygen atom, a sulfur atom, a carbonyl group, a sulfinyl group, a sulfonyl group, an alkylene group (preferably a methylene group), alkenylene group (preferably 2-propenylene group), a substituted or unsubstituted phenylmethylene group, a substituted or unsubstituted hydroxymethylene group, a substituted or unsubstituted, cyclic or non-

cyclic acetal group, with a carbonyl group being particularly preferred. Examples of the cyclic and non-cyclic acetal, which may be substituted or unsubstituted, include:



When W represents a nitrogen atom, m stands for 1 or 2, with 1 being more preferred, and B represents a carbonyl group, a sulfonyl group, an alkylene group (preferably, a methylene group), an alkenylene group (preferably a 2-propenylene group) and a substituted or
10 unsubstituted phenylmethylene group.

In addition, n stands for 0 or 1 and D represents a substituted or unsubstituted aryl group or a substituted or unsubstituted aromatic heterocyclic group, preferably a phenyl group, a phenyl group substituted
15 by one or more of the halogen atoms, alkyl groups and/or alkoxy groups referred to above, a pyrimidinyl group, a pyridyl group, a benzisothiazolyl group, a benzisoxazolyl group or a furyl group, with a phenyl group or a halogen- or alkoxy-substituted phenyl group
20 being preferred.

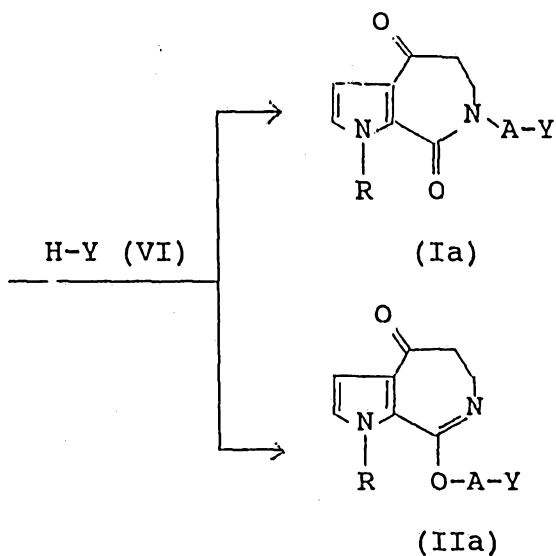
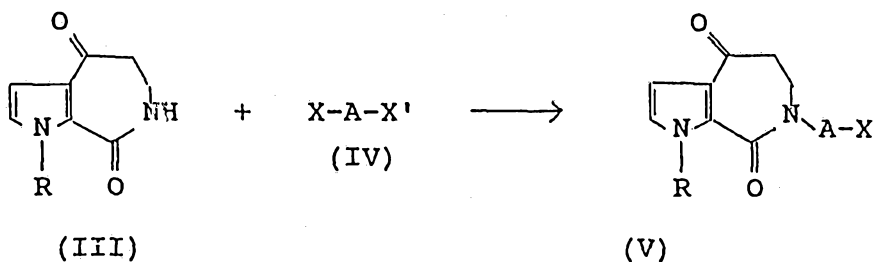
Many of the compounds (I) and (II) according to

the present invention have isomers. It is to be noted that these isomers are all embraced by the present invention. For example, when there is a hydroxyimino group or an O-substituted hydroxyimino group at 4-
5 position of the pyrroloazepine ring, there are both an (E)-isomer and a (Z)-isomer with respect to the group. The compounds of the present invention also include these individual isomers and their mixtures.

Various processes can be employed for the preparation of the pyrroloazepine compounds (I) and (II) according to the present invention. It is however preferable to prepare the pyrroloazepine compounds (I) and (II), for example, by any of the following processes.

15 Process 1:

Among the pyrroloazepine compounds (I) and (II), each of compounds (Ia) and (IIa) in which Z_1 and Z_2 are taken together to form an oxygen atom can be obtained in accordance with the following reaction scheme, namely, by converting the compound represented by formula
20 (III) to the compound represented by formula (V) and then reacting the compound (V) with the nitrogen-containing compound represented by formula (VI) or a salt thereof.



5 wherein A, R and Y have the same meanings as defined above, X and X' may be the same or different and individually represents a substituent easily replaceable with an amino group.

10 The conversion from the compound (III) to the compound (V) can be effected by treating the compound (III) with an organic or inorganic base and then reacting with the compound (IV) or by causing the compound (IV) to act on the compound (III) in the presence of

such a base.

Examples of the substituent, which is easily replaceable with an amino group, as each of the groups X and X' in the compound (IV) include halogen atoms such as chlorine and bromine, alkylsulfonyloxy groups such as methanesulfonyloxy, and arylsulfonyloxy groups such as p-toluenesulfonyloxy. Further, exemplary organic or inorganic bases include sodium hydride, potassium hydride, n-butyl lithium, potassium t-butoxide and the like. Illustrative solvents usable in the present reaction include ether, tetrahydrofuran, dioxane, dimethylformamide, N-methylpyrrolidone, dimethyl sulfoxide and the like. The reaction may be conducted at -20°C to reflux temperature.

To prepare the compound (Ia) and (IIa) by reacting the compound (V) with the nitrogen-containing compound (VI), it is only necessary to react the nitrogen-containing compound (VI) or an organic acid or inorganic acid salt thereof with the compound (V), optionally together with an organic base such as triethylamine, pyridine, collidine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or potassium t-butoxide or an inorganic base such as potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide or sodium hydride, optionally after addition of an iodide such as

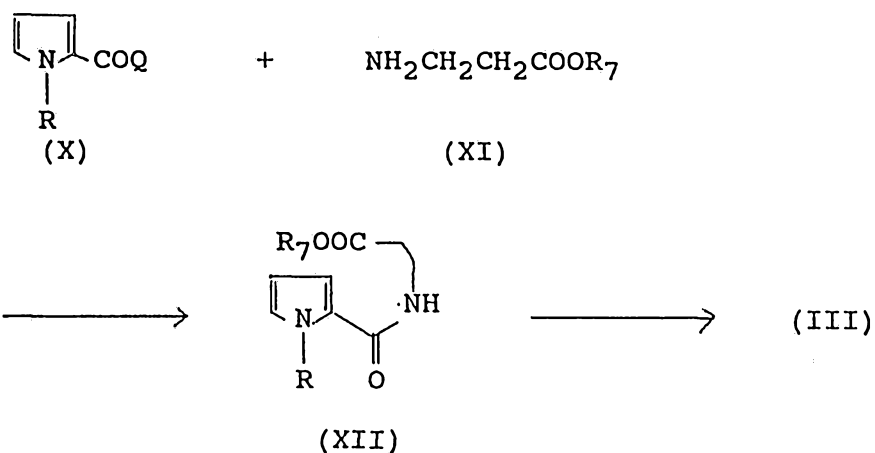
sodium iodide or potassium iodide at 0-150°C in the above solvent or in a solvent such as methanol, ethanol, propanol or butanol.

5 In the above reaction, it is possible to change the respective production ratios of the compound (Ia) and (IIa) by altering their reaction conditions. The ratio of the compound (Ia) can be raised substantially, for example, by the addition of sodium iodide upon reaction.

10 Examples of the nitrogen-containing compound (VI) include dimethylamine, isopropylamine, t-butylamine, 3-phenylpropylamine, 2-phenoxyethylamine, N-methyl-3,4-dimethoxyphenethylamine, N-propyl-2-(8-hydroxy-1,2,3,4-tetrahydronaphthyl)amine, 1-ethoxycarbonylpiperazine,
15 1-phenylpiperazine, 1-(2-methoxyphenyl)piperazine, 1-(3-methoxyphenyl)piperazine, 1-(4-methoxyphenyl)-piperazine, 1-(2-chlorophenyl)piperazine, 1-(3-chlorophenyl)piperazine, 1-(4-chlorophenyl)piperazine, 1-(4-fluorophenyl)piperazine, 1-(2-pyridyl)piperazine, 1-(2-pyrimidyl)piperazine, 1-benzylpiperazine, 1-diphenylmethylpiperazine, 1-cinnamylpiperazine, 1-(1,4-benzodioxan-2-ylmethyl)piperazine, 1-benzoylpiperazine, 1-(4-benzyloxybenzoyl)piperazine, 1-(4-hydroxybenzoyl)-
20 piperazine, 2-furoylpiperazine, 4-phenylpiperidine, 4-benzylpiperidine, α,α -bis(4-fluorophenyl)-4-

piperidinemethanol, 4-(diphenylmethoxy)piperidine, 4-(4-fluorobenzoyl)piperidine, 4-benzoylpiperidine, 4-(4-methoxybenzoyl)piperidine, 4-(4-chlorobenzoyl)-piperidine, 3-(4-fluorobenzoyl)piperidine, 3-benzoyl-
5 pyrrolidine, 3-(4-fluorobenzoyl)pyrrolidine, 4-(4-fluorophenoxy)piperidine, 4-[(4-fluorophenyl)thio]-piperidine, 4-[(4-fluorophenyl)sulfinyl]piperidine, 4-[(4-fluorophenyl)sulfonyl]piperidine, 4-(4-fluorobenzoyl)piperidine ethylene acetal, imidazole and the
10 like. They are all either known compounds or compounds which can be readily prepared by a known process or a process similar to the known process.

Incidentally, the compounds (III) employed as starting materials in the above reaction are novel com-
15 pounds. They can each be prepared, for example, in accordance with the following reaction scheme, namely, by reacting a 1-substituted pyrrole-2-carboxylic acid or a derivative thereof represented by the formula (X) with β -alanine or a derivative thereof represented by the
20 formula (XI) or with an organic or inorganic salt of the β -alanine or the derivative thereof and optionally removing any protecting group, thereby obtaining a compound represented by the formula (XII) and then subjecting this compound to ring closure.



wherein R has the same meaning as defined above, R₇ represents a hydrogen atom or a carboxyl-protecting group, and Q represents a hydroxyl group or a substituent easily replaceable with an amino group.

Examples of the substituent easily replaceable with an amino group as represented by Q in the compound (X) include halogen atoms, carboxylic acid residue and the like. On the other hand, as the carboxyl-protecting group of the group R₇ in the compound (XI), it is possible to use, in addition to lower alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl and C₇₋₂₀ aralkyl groups such as benzyl and 9-anthrylmethyl, the conventional protecting groups described by T.W. Greene in "Protective Groups in Organic Synthesis" (John Wiley & Sons, Inc.) and the like.

For the synthesis of the compounds (XII), it is

possible to use any one of the various processes described in "Compendium of Organic Synthetic Methods" (WILEY-INTERSCIENCE; A Division of John Wiley & Sons, Inc.) and the like.

5 Illustrative processes include the process in which the 1-substituted pyrrole-2-carboxylic acid (the compound (X) in which Q is OH) and the compound (XI), which is β -alanine or a derivative thereof, or an organic or inorganic salt thereof, are treated with an
10 organic compound such as diethyl phosphoryl cyanide (DEPC), diphenylphosphoryl azide (DPPA), dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride or 2-iodo-1-methylpyridinium iodide or an inorganic compound such as silicon tetra-
15 chloride or tin tetrachloride, if necessary, in the presence of an organic or inorganic base; and the process in which the 1-substituted pyrrole-2-carboxylic acid is converted to an acid halide, a symmetric acid anhydride, a mixed acid anhydride, an active ester such
20 as the p-nitrophenyl ester, or the like by a method known *per se* in the art and the compound so converted is then reacted with the compound (XI), if necessary, in the presence of an organic or inorganic base.

 Each compound (XII) thus obtained is subjected to
25 a cyclization reaction, optionally after removing the

protecting group by virtue of a suitable method such as the action of an acid or a base, or catalytic reduction.

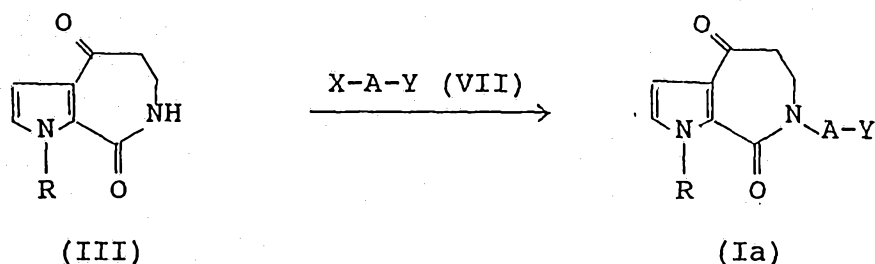
This cyclization reaction is conducted by treating the compound (XII) together with an organic acid such as methanesulfonic acid, an inorganic acid such as sulfuric acid or polyphosphoric acid or a mixture of such an organic or inorganic acid and phosphorus pentoxide at room temperature to 170°C, preferably at 80-120°C.

In this case, a solvent which does not take part in the reaction may be added as needed. As an alternative, the cyclization reaction can also be practiced by, optionally after addition of a catalyst, treating the compound (XII) with oxalyl chloride, thionyl chloride, thionyl bromide, oxalyl bromide, phosgene, phosphorus trichloride, phosphorus tribromide, phosphoryl chloride, phosphoryl bromide or the like to convert the compound (XII) to its corresponding acid halide and then treating the acid halide at -20°C to reflux temperature in the presence of a Lewis acid such as aluminum chloride, aluminum bromide, boron trifluoride-ether complex or tin tetrachloride in a solvent such as dichloromethane, 1,2-dichloroethane or nitromethane or heating the acid halide in acetic acid.

The compounds (III) obtained in the above manner can be used directly as starting materials for the preparation of the compounds (I) or compound (II) of the present invention. They can also be used after purification by a conventional purification method, for example, by recrystallization or column chromatography if necessary.

Process 2:

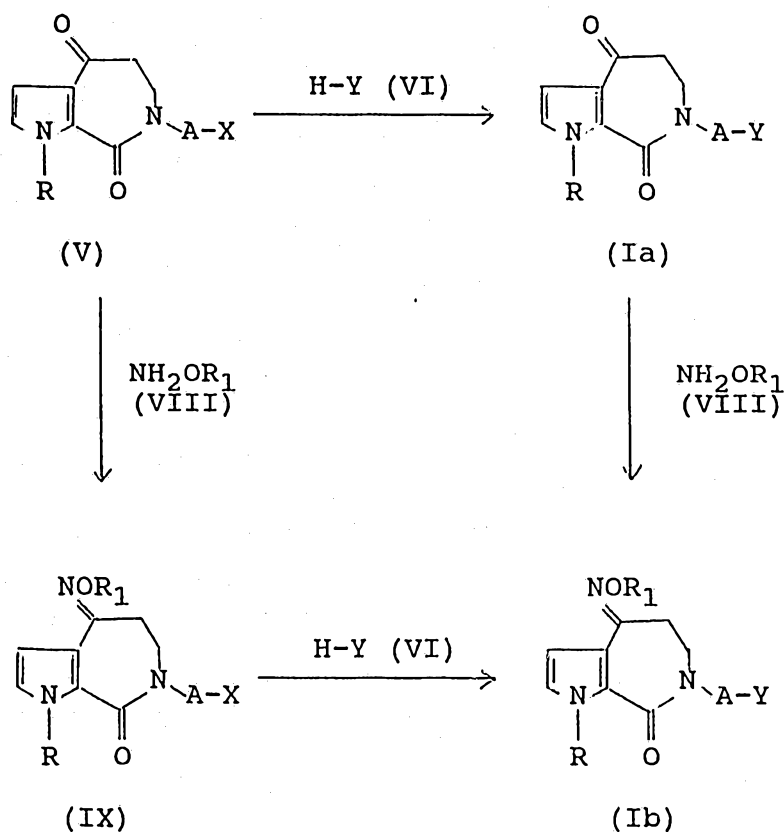
Among the pyrroloazepine compounds (I), each compound (Ia) in which Z_1 and Z_2 are taken together to form an oxygen atom can be obtained by reacting the compound represented by the formula (III) with a nitrogen-containing compound represented by formula (VII) or a salt thereof in accordance with the following reaction scheme.



wherein A, R, X and Y have the same meanings as defined above. The conversion from the compound (III) to the compound (Ia) can be effected under the conditions similar to those shown in the conversion from the compound (III) to the compound (V) in Process 1.

Process 3:

Among the pyrroloazepine compounds (I), each compound (Ib) in which Z_1 and Z_2 are taken together to form a group NOR_1 can be prepared in accordance with the following reaction scheme, namely, (i) by causing a hydroxylamine or a derivative thereof represented by the formula (VIII) or a salt thereof to act on the compound (Ia) obtained by the above-described reaction or (ii) by causing the hydroxylamine or its derivative (VIII) or a salt thereof to act on the compound (V) and then causing a nitrogen-containing compound (VI) or a salt thereof to act further.



wherein A, R, R₁, X and Y have the same meanings as
5 defined above.

The reaction between the above compound (Ia) or
(V) and either the hydroxylamine or its derivative
(VIII) can be practiced, if necessary, in the presence
of an organic base such as pyridine, triethylamine,
10 collidine, DBU or sodium acetate or an inorganic base
such as potassium carbonate or sodium hydroxide. The
hydroxylamine or its derivative (VIII) may also be used

in the form of an organic acid salt or an inorganic acid salt.

The reaction can be conducted at 0°C to reflux temperature, preferably 0°C-100°C, optionally in a
5 suitable solvent such as methanol, ethanol, propanol, tetrahydrofuran, dimethylformamide or dimethylsulfoxide.

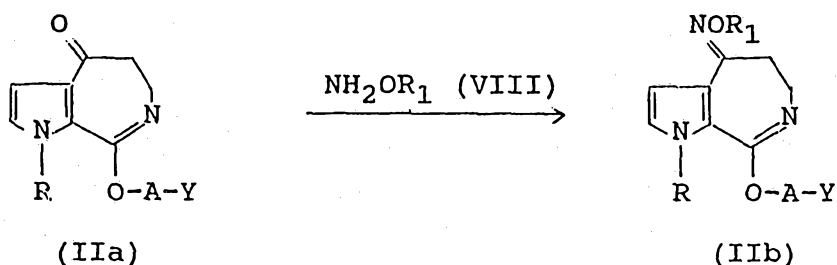
The compound (IX) obtained by the reaction of the compound (V) with the compound (VIII) can be reacted
10 further with the nitrogen-containing compound (VI) by the method described in Process 1, whereby the compound (V) can be converted to the compound (Ib).

Upon preparation of the compound (Ib), it is determined depending on the structure and properties of
15 the nitrogen-containing compound (VI) whether the hydroxylamine or its derivative (VIII) should be reacted to the compound (V) or to the compound (Ia).

Where there is a group reactive to the hydroxylamine or its derivative (VIII), such as a carbonyl
20 group, in the nitrogen-containing compound (VI), it is desirable to choose the process that the hydroxylamine or its derivative (VIII) is reacted to the compound (V).

Among the pyrroloazepine compounds (II), each
25 compound (IIb) in which Z₁ and Z₂ are taken together to

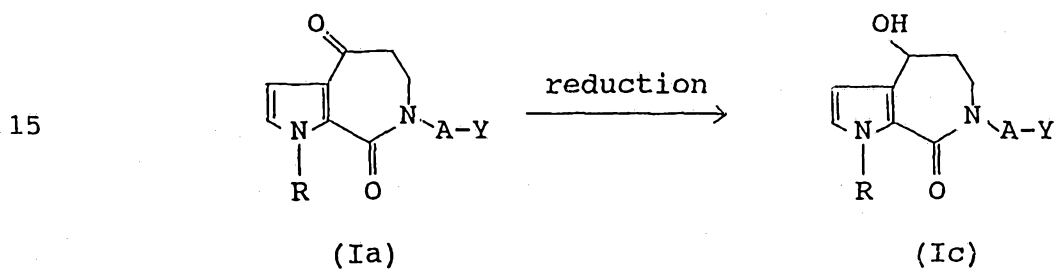
form a group NOR_1 can be prepared following the following reaction formula in exactly the same manner as that described above.

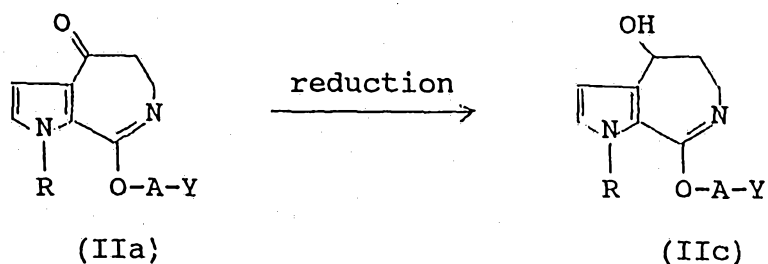


5 wherein A, R, R_1 and Y have the same meanings as defined above.

Process 4:

Among the pyrroloazepine compounds (I) and (II), compounds (Ic) and (IIc) in which Z_1 represents a
10 hydrogen atom and Z_2 represents a hydroxyl group can be prepared by reducing the compounds (Ia) and (IIa), which have been obtained following the above reaction formula, respectively, in accordance with the following reaction formula.





wherein A, R and Y have the same meanings as defined above.

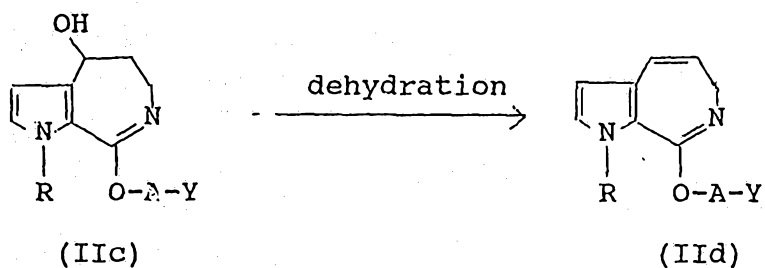
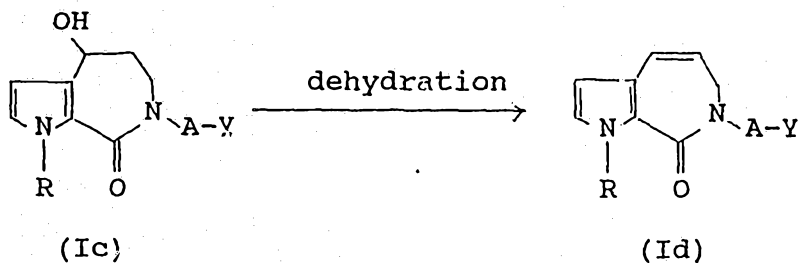
5 The above reaction can be effected by reducing the compound represented by formula (Ia) or (IIa) with a reducing agent such as sodium borohydride, potassium borohydride, sodium cyanoborohydride or tri-n-butyltin hydride, in a solvent used commonly, at -78°C to reflux temperature, preferably at -20°C to room temperature.

10 The conversion from the compounds (Ia) and (IIa) to the compounds (Ic) and (IIc), respectively, can also be effected by catalytic reduction which uses Raney nickel or the like.

Process 5:

15 Among the pyrroloazepine compounds (I) and (II), compounds (Id) and (IIId) in which the bond indicated by a dashed line exists, namely, a double bond exists and Z₁ represents a hydrogen atom can be prepared by subjecting the compounds (Ic) and (IIc), which have been
20 obtained by the above reaction, respectively, to

dehydration in accordance with the following reaction formula.



5 wherein A, R and Y have the same meanings as defined above.

10 The above reaction can be conducted by treating the compound (Ic) or (IIc) together with an acid such as hydrogen chloride, hydrogen bromide, sulfuric acid, methanesulfonic acid or p-toluenesulfonic acid optionally in a solvent such as water, methanol, ethanol, chloroform, toluene or ethyl acetate, at -20°C to 100°C, preferably at -20°C to room temperature.

As an alternative, the conversion from the com-

pound represented by the formula (Ic) or (IIc) to the compound (Id) or (IID) can be effected by causing methanesulfonyl chloride, p-toluenesulfonyl chloride, phosphorus trichloride, phosphorus oxychloride, thionyl chloride or the like and a base such as triethylamine, collidine or pyridine to act on the compound (Ic) or (IIc), if necessary in a solvent such as dichloromethane, chloroform or toluene.

If necessary, the compounds (I) and (II) of the present invention obtained as described above can be reacted with various acids to convert the compounds (I) and (II) to their salts, followed by purification by a method such as recrystallization or column chromatography.

Exemplary acids usable to convert the pyrroloazepine compounds (I) and (II) to their salts include inorganic acids such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid and hydrobromic acid; and organic acids such as maleic acid, fumaric acid, tartaric acid, lactic acid, citric acid, acetic acid, methanesulfonic acid, p-toluenesulfonic acid, adipic acid, palmitic acid and tannic acid.

The pyrroloazepine compounds (I) and (II) and their salts according to the present invention, which are obtained as described above, have anti-serotonin

action and anti- α_1 action as will be demonstrated later by tests. Further, as a result of a toxicity test, they have been found to feature high safety. The compounds according to the present invention can therefore
5 be used as therapeutics for circulatory diseases such as ischemic heart diseases and hypertension.

When the pyrroloazepine compounds (I) or (II) according to this invention are used as drugs, they can be administered in an effective dose as they are. As
10 an alternative, they can also be formulated into various preparation forms by known methods and then administered.

Exemplary preparation forms as drugs include orally administrable preparation forms such as tablets,
15 powders, granules, capsules and syrups as well as parenterally administrable preparation forms such as injections and suppositories. Whichever preparation form is used, a known liquid or solid extender or carrier usable for the formulation of the preparation form
20 can be employed.

Examples of such extender or carrier include polyvinylpyrrolidone, arabic gum, gelatin, sorbit, cyclodextrin, tragacanth gum, magnesium stearate, talc, polyethylene glycol, polyvinyl alcohol, silica, lac-
25 tose, crystalline cellulose, sugar, starch, calcium

phosphate, vegetable oil, carboxymethylcellulose, sodium laurylsulfate, water, ethanol, glycerin, mannitol syrup, and the like.

5 When the compounds according to the present invention are used as drugs, their dose varies depending on the administration purpose, the age, body weight and conditions of the patient to be administered, etc. In oral administration, the daily dose may generally be about 0.1-1,000 mg.

10 The present invention will next be described in further detail by the following examples and tests. But the present invention is not limited to the following examples and tests.

Example 1

15 Synthesis of benzyl 3-[2-(1-methylpyrrole)-carboxamido]propionate (Compound No. 1)

A solution of 72.86 g (720 mmol) of triethylamine in 100 ml of dimethylformamide (DMF) was gradually added under cooling and stirring to a solution of 37.54 g (300 mmol) of 1-methyl-2-pyrrole-20 carboxylic acid, 126.51 g (360 mmol) of β -alanine benzyl ester tosylate and 58.76 g (360 mmol) of diethyl cyanophosphate in 400 ml of DMF. The resulting solution was stirred at room temperature for 15 hours. The
25 reaction mixture was concentrated under reduced pres-

sure, followed by the addition of 1 l of a 3:1 v/v
mixed solvent of ethyl acetate and benzene. The
organic layer was washed successively with a saturated
aqueous solution of potassium carbonate, water, 5%
5 hydrochloric acid, water and saturated saline, followed
by drying over anhydrous sodium sulfate. The solvent
was concentrated under reduced pressure and the
resultant oil was crystallized from hexane. The crys-
tals so obtained were washed with hexane and then
10 recrystallized from ethyl acetate-isopropyl ether,
whereby 68.60 g of the title compound were obtained
(yield: 80%).

Appearance: Colorless needle crystals.

Melting point: 61.0-62.0°C.

15 Example 2

Compound Nos. 2 and 3 were obtained using 1-
ethyl-2-pyrrolicarboxylic acid and 1-benzyl-2-pyrrolic-
carboxylic acid, respectively, in place of 1-methyl-2-
pyrrolicarboxylic acid in the procedure of Example 1.

20 (Compound No. 2)

Benzyl 3-[2-(1-ethylpyrrole)carboxamido]-
propionate

(Compound No. 3)

25 Benzyl 3-[2-(1-benzylpyrrole)carboxamido]-
propionate

Example 3

Synthesis of 3-[2-(1-methylpyrrole)carboxamido]-
propionic acid (Compound 4)

A suspension of 27.78 g (97 mmol) of Compound
5 No. 1 obtained in Example 1 and 2.78 g of 5% palladium-
carbon in 350 ml of tetrahydrofuran (THF) was
vigorously stirred under a hydrogen stream (at atmo-
spheric pressure). After the full consumption of the
starting material was confirmed by thin layer
10 chromatography on silica gel, the reaction mixture was
filtered and an insoluble matter was washed with THF.
The filtrate and the washing were combined and then
concentrated under reduced pressure, whereby 18.96 g of
the title compound were obtained (yield: 99%).

15 Although this compound was sufficiently pure, it
can be recrystallized from chloroform-hexane as needed.

Appearance: Colorless needle crystals.

Melting point: 135.0-137.0°C.

Example 4

20 Compound Nos. 5 and 6 were obtained using Com-
pound Nos. 2 and 3, respectively, in place of Compound
1 in the procedure of Example 3.

(Compound No. 5)

3-[2-(1-Ethylpyrrole)carboxamido]propionic acid

25 (Compound No. 6)

3-[2-(1-Benzylpyrrole)carboxamido]propionic acid

Example 5

Synthesis of 1-methyl-6,7-dihydropyrrolo[2,3-c]-
azepine-4,8(1H,5H)-dione (Compound No. 7)

5 A mixture of 28.0 g (143 mmol) of Compound No. 4
obtained in Example 3 and 1,000 g of polyphosphoric
acid (80%) was vigorously stirred for 30 minutes at
100°C. The reaction mixture was poured into 2 l of ice
water. The water layer was saturated with sodium
10 chloride, followed by extraction with chloroform. The
chloroform layer was washed with a saturated aqueous
solution of sodium chloride, dried over anhydrous
sodium sulfate, and then concentrated under reduced
pressure.

15 Crude crystals so obtained were purified by
chromatography on an alumina column in which "Art.
1097" (product of Merck & Co.) was used as active
alumina (eluent: 3% methanol-chloroform), whereby
17.1 g of the title compound were obtained (yield:
20 67%).

Although this compound was sufficiently pure, it
can be recrystallized from acetonitrile as needed.

Example 6

25 Compound Nos. 8 and 9 were obtained using Com-
pound Nos. 5 and 6, respectively, in place of Compound

No. 4 in the procedure of Example 5.

(Compound No. 8)

1-Ethyl-6,7-dihydropyrrolo[2,3-c]azepine-
4,8(1H,5H)-dione

5 (Compound No. 9)

1-Benzyl-6,7-dihydropyrrolo[2,3-c]azepine-
4,8(1H,5H)-dione

Example 7

10 Synthesis of 7-(3-chloropropyl)-1-methyl-6,7-
dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione
(Compound No. 10)

In 110 ml of DMF, 0.80 g (20 mmol) of 60% sodium
hydride was suspended. A solution of 3.56 g (20 mmol)
of Compound No. 7 obtained in Example 5 in 10 ml of
15 DMF was added to the above suspension under a nitrogen
stream, ice cooling and stirring, followed by stirring
at 60°C for 10 minutes. The reaction mixture was
thereafter ice-cooled, to which 9.04 g (80 mmol) of
1,3-dichloropropane were added under stirring. The
20 resulting mixture was stirred at 0°C for one hour and
then at room temperature for 30 minutes. The reaction
mixture was concentrated under reduced pressure. The
oil so obtained was added with 500 ml of a 3:1 v/v
mixed solvent of ethyl acetate and benzene. The
25 organic layer was washed successively with a 10%

aqueous solution of citric acid, water and saturated saline, followed by drying over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The resultant oil was purified by chromatography on a silica gel column in which silica gel "Art. 9385" (product of Merck & Co.; the same silica gel was also used in the subsequent examples) was used as silica gel (eluent: 1:1 mixed solvent of ethyl acetate and hexane), whereby 1.84 g of the title compound were obtained (yield: 36%).

Although this compound was sufficiently pure, it can be recrystallized from isopropyl ether as needed.

Example 8

Compound Nos. 11 and 12 were obtained using 1,4-dibromobutane and 1,5-dichloropentane, respectively, in place of 1,3-dichloropropane in the procedure of Example 7.

(Compound No. 11)

7-(4-bromobutyl)-1-methyl-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

(Compound No. 12)

7-(5-chloropentyl)-1-methyl-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

Example 9

Compound Nos. 13 and 14 were obtained using Com-

pound Nos. 8 and 9, respectively, in place of Compound No. 7 in the procedure of Example 7.

(Compound No. 13)

5 7-(3-Chloropropyl)-1-ethyl-6,7-dihydropyrrolo-
[2,3-c]azepine-4,8(1H,5H)-dione

(Compound No. 14)

1-Benzyl-7-(3-chloropropyl)-6,7-dihydropyrrolo-
[2,3-c]azepine-4,8(1H,5H)-dione

Example 10

10 Synthesis of 7-(3-chloropropyl)-4-hydroxyimino-1-
methyl-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-
8(1H)-one (Compound No. 15)

A solution of 371 mg (1.45 mmol) of Compound No. 10 obtained in Example 7 and 121 mg (1.74 mmol) of hydroxylamine hydrochloride in 25 ml of pyridine was stirred at 70°C for 8 hours. The reaction mixture was concentrated under reduced pressure. The residue was added with chloroform and washed successively with a half-saturated aqueous solution of potassium carbonate, water and saturated saline, followed by drying over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting oil was purified by chromatography on a silica gel column (eluent: 1:1 mixed solvent of ethyl acetate and hexane), whereby 190 mg of the title compound were ob-

15

20

25

tained (yield 49%).

Example 11

Compound No. 16 was obtained using Compound No. 13 in place of Compound No. 10 in the procedure of Example 10.

(Compound No. 16)

7-(3-Chloropropyl)-1-ethyl-4-hydroxyimino-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8(1H)-one

Example 12

Synthesis of 1-methyl-7-[4-(4-phenylpiperazin-1-yl)butyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione (Compound No. 17)

A suspension of 157 mg (0.5 mmol) of Compound No. 11 obtained in Example 8, 243 mg (1.5 mmol) of 1-phenylpiperazine and 75 mg (0.5 mmol) of sodium iodide in 15 ml of DMF was stirred at room temperature for 3 hours. The solvent was thereafter distilled off under reduced pressure. The residue was added with a 3:1 v/v mixed solvent of ethyl acetate and benzene and water. The resulting mixture was allowed to separate into layers. The organic layer was successively washed with a saturated aqueous solution of sodium hydrogen-carbonate and saturated saline, followed by drying over anhydrous sodium sulfate.

The solvent was distilled off under reduced pres-

sure and the resulting oil was purified by chromatography on a silica gel column (eluent: 3% methanol in chloroform), whereby 190 mg of the title compound were obtained (yield: 96%).

5 Although this compound was sufficiently pure, it can be recrystallized from ethyl acetate-ethyl ether as needed.

Example 13

10 Compound Nos. 18, 19 and 20 were obtained by conducting the reaction using Compound Nos. 10, 13 and 14, respectively at temperatures of 80-100°C, in place of Compound No. 11 in the procedure of Example 12.

(Compound No. 18)

15 1-Methyl-7-[3-(4-phenylpiperazin-1-yl)propyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

(Compound No. 19)

1-Ethyl-7-[3-(4-phenylpiperazin-1-yl)propyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

(Compound No. 20)

20 1-Benzyl-7-[3-(4-phenylpiperazin-1-yl)propyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

Example 14

25 Compound No. 21 was obtained using 4-phenylpiperidine in place of 1-phenylpiperazine in the procedure of Example 12.

(Compound No. 21)

1-Methyl-7-[4-(4-phenylpiperidin-1-yl)butyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

Example 15

5 Compound No. 22 was obtained by conducting the reaction using Compound No. 10 and 1-(3-methoxyphenyl)-piperazine at the temperature of 80°C in place of Compound No. 11 and 1-phenylpiperazine.

(Compound No. 22)

10 7-[3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl]-1-methyl-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

Example 16

15 Synthesis of 7-[3-[4-(4-methoxyphenyl)piperazin-1-yl]propyl]-1-methyl-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione (Compound No. 23)

20 A suspension of 200 mg (0.79 mmol) of Compound No. 10 obtained in Example 7, 623 mg (2.36 mmol) of 1-(4-methoxyphenyl)piperazine dihydrochloride, 652 mg (4.72 mmol) of potassium carbonate and 118 mg (0.79 mmol) of sodium iodide in 20 ml of DMF was stirred at 80°C for 6 hours. The reaction mixture was then treated as in Example 12, whereby 155 mg of the title compound were obtained (yield: 48%).

25 Example 17

Compound Nos. 24, 25, 26 and 27 were obtained using 1-(2-pyrimidinyl)piperazine dihydrochloride, 4-(4-fluorophenoxy)piperidine hydrochloride, 4-(4-fluorophenylthio)piperidine hydrochloride and 2-phenoxyethylamine, respectively, in place of 1-(4-methoxyphenyl)piperazine dihydrochloride in the procedure of Example 16.

(Compound No. 24)

1-Methyl-7-[3-[4-(2-pyrimidinyl)piperazin-1-yl]propyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

(Compound No. 25)

7-[3-[4-(4-fluorophenoxy)piperidin-1-yl]propyl]-1-methyl-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

(Compound No. 26)

7-[3-[4-(4-fluorophenylthio)piperidin-1-yl]propyl]-1-methyl-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

(Compound No. 27)

1-Methyl-7-[3-(2-phenoxyethylamino)propyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

Example 18

Compound Nos. 28 and 29 were obtained by conducting reactions in a similar manner to Example 16 except

that triethylamine was used in place of potassium carbonate and in addition, N-methyl-3,4-dimethoxyphenethylamine hydrochloride and 4-(4-fluorobenzoyl)piperidine hydrochloride were used respectively in place of 1-(4-methoxyphenyl)piperazine dihydrochloride.

(Compound No. 28)

1-Methyl-7-[3-[N-methyl-N-[2-(3,4-dimethoxyphenyl)ethyl]amino]propyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

10 (Compound No. 29)

7-[3-[4-(4-fluorobenzoyl)piperidin-1-yl]propyl]-1-methyl-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

Example 19

15 Compound No. 30 was obtained by conducting reaction in a similar manner to Example 16 except that Compound No. 13 and 4-(4-fluorobenzoyl)piperidine hydrochloride were used in place of Compound No. 10 and 1-(4-methoxyphenyl)piperazine dihydrochloride.

20 (Compound No. 30)

1-Ethyl-7-[3-[4-(4-fluorobenzoyl)piperidin-1-yl]propyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

Example 20

25 Synthesis of 7-[3-[4-(4-fluorophenyl)piperazin-1-

yl]propyl]-1-methyl-6,7-dihydropyrrolo[2,3-
c]azepine-4,8(1H,5H)-dione (Compound No. 31)

To a suspension of 480 mg (12 mmol) of 60% sodium
hydride in 60 ml of DMF, a solution of 1.78 g
5 (10 mmol) of Compound 7 obtained in Example 5 in 20 ml
of DMF was gradually added under cooling and stirring.
The reaction mixture was stirred at room temperature
for one hour and then at 40°C for 10 minutes, followed
by the addition of a solution of 3.85 g (15 mmol) of 1-
10 (3-chloropropyl)-4-(4-fluorophenyl)piperazine in 20 ml
of DMF at room temperature. The resulting solution was
stirred at room temperature for 16 hours.

The reaction mixture was added with a 2:1 v/v
mixed solvent of ethyl acetate and benzene and the
15 organic layer was washed successively with a half-
saturated aqueous solution of potassium carbonate,
water (thrice) and saturated saline, followed by drying
over anhydrous sodium sulfate. The solvent was dis-
tilled off under reduced pressure and the resultant oil
20 was purified by chromatography on a silica gel column
(eluent: ethyl acetate → 5% methanol in chloroform),
whereby 1.71 g of the title compound were obtained
(yield: 43%).

Example 21

25 Compound No. 32 was obtained by conducting a

reaction in a similar manner to Example 20 except that Compound No. 8 was used in place of Compound No. 7.

(Compound No. 32)

5 1-Ethyl-7-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

Example 22

 Synthesis of 7-[5-(1-imidazolyl)pentyl]-1-methyl-6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione
10 (Compound No. 33)

 A suspension of 68 mg (1 mmol) of imidazole and 40 mg (1 mmol) of 60% sodium hydride in 15 ml of DMF was stirred at room temperature for one hour under a nitrogen stream, followed by the gradual addition of a
15 solution of 283 mg (1 mmol) of Compound No. 12 obtained in Example 8 in 5 ml of DMF. The resulting solution was stirred at 80°C for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column
20 (eluent: ethyl acetate → 10% methanol in chloroform), whereby 84 mg of the title compound were obtained (yield: 27%).

Example 23

 Synthesis of 1-methyl-8-[3-(4-phenylpiperidin-1-yl)propoxy]-5,6-dihydropyrrolo[2,3-c]azepin-
25

4(1H)-one (Compound No. 34)

A suspension of 300 mg (1.18 mmol) of Compound No. 10 obtained in Example 7, 570 mg (3.53 mmol) of 4-phenylpiperidine and 488 mg (3.53 mmol) of potassium carbonate in 30 ml of DMF was stirred at 80°C for 15 hours. The reaction mixture was added with 400 ml of a 3:1 v/v mixed solvent of ethyl acetate and benzene and washed successively with water and saturated saline, followed by drying over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was purified by chromatography on a silica gel column (eluent: 2:1 mixed solvent of ethyl acetate and hexane), whereby 270 mg of the title compound were obtained (yield: 60%) from a first fraction.

In addition, Compound No. 35 was obtained from the next fraction.

(Compound No. 35)

1-Methyl-7-[3-(4-phenylpiperidin-1-yl)propyl]-6,7-dihydro-1H-indolo[2,3-c]azepine-4,8(1H,5H)-dione
Example 24

Compound Nos. 36 and 37 and Compound Nos. 38 and 18 were obtained successively using 1-(2-methoxyphenyl)piperazine and 1-phenylpiperazine, respectively, in place of 4-phenylpiperidine in the procedure of Ex-

ample 23.

(Compound No. 36)

8-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy]-
1-methyl-5,6-dihydropyrrolo[2,3-c]azepin-4(1H)-
5 one

(Compound No. 37)

7-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl]-
1-methyl-6,7-dihydropyrrolo[2,3-c]azepine-
4,8(1H,5H)-dione

10 (Compound No. 38)

1-Methyl-8-[3-(4-phenylpiperazin-1-yl)propoxy]-
5,6-dihydropyrrolo[2,3-c]azepin-4(1H)-one

(Compound No. 18)

1-Methyl-7-[3-(4-phenylpiperazin-1-yl)propyl]-
15 6,7-dihydropyrrolo[2,3-c]azepine-4,8(1H,5H)-dione

Example 25

Synthesis of 4-hydroxy-1-methyl-7-[3-(4-
phenylpiperazin-1-yl)propyl]-4,5,6,7-
tetrahydropyrrolo[2,3-c]azepin-8(1H)-one (Com-
20 pound No. 39)

In 15 ml of methanol, 158 mg (0.41 mmol) of Com-
pound No. 18 obtained in Example 13 were dissolved.
The resulting solution was gradually added with 31 mg
(0.83 mmol) of sodium borohydride under cooling and
25 stirring, followed by stirring at 0°C for 30 minutes

and then at room temperature for 2 hours. The solvent was distilled off under reduced pressure. The residue was added with saturated saline and then extracted with chloroform three times. The organic layer was dried
5 over anhydrous sodium sulfate, followed by concentration under reduced pressure. The resultant crude product was purified by chromatography on a silica gel column (eluent: 5% methanol in chloroform), whereby 140 mg of the title compound were obtained (yield: 89%).

10 Although this compound was sufficiently pure, it can be recrystallized from ethyl acetate as needed.

Example 26

Compound Nos. 40 and 41 were obtained by conducting reactions in a similar manner to Example 25 except
15 that Compound Nos. 31 and 36 were used, respectively, in place of Compound No. 18.

(Compound No. 40)

7-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-4-hydroxy-1-methyl-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8(1H)-one
20

(Compound No. 41)

4-Hydroxy-1-methyl-8-[3-[4-(2-methoxyphenyl)-piperazin-1-yl]propoxy]-1,4,5,6-tetrahydropyrrolo[2,3-c]azepine

25 Example 27

Synthesis of 1-methyl-7-[3-(4-phenylpiperazin-1-yl)propyl]-6,7-dihydropyrrolo[2,3-c]azepin-8(1H)-one (Compound No. 42)

5 In 10 ml of chloroform, 100 mg (0.26 mmol) of Compound No. 39 obtained in Example 25 were dissolved. The resulting solution was added with 6 ml of a chloroform solution which was saturated with HCl, followed by stirring at room temperature for one hour. The reaction mixture was concentrated under reduced pressure and then added with a saturated aqueous solution of potassium carbonate and chloroform. The resulting mixture was allowed to separate into layers. The organic layer was washed with saturated saline, followed by drying over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting oil was purified by chromatography on a silica gel column (eluent: 5% methanol in chloroform), whereby 50 mg of the title compound were obtained (yield: 53%).

15
20 Example 28

Compound Nos. 43 and 44 were obtained using Compound No. 15 and 4-(4-fluorobenzoyl)piperidine hydrochloride in combination and Compound No. 16 and 4-(4-fluorobenzoyl)piperidine p-toluenesulfonate in combination, respectively, in place of the combination of

25

Compound No. 10 and 1-(4-methoxyphenyl)piperazine dihydrochloride in the procedure of Example 16.

(Compound No. 43)

5 7-[3-[4-(4-Fluorobenzoyl)piperidin-1-yl]propyl]-
4-hydroxyimino-1-methyl-4,5,6,7-tetrahydro-
pyrrolo[2,3-c]azepin-8(1H)-one

(Compound No. 44)

10 1-Ethyl-7-[3-[4-(4-fluorobenzoyl)piperidin-1-
yl]propyl]-4-hydroxyimino-4,5,6,7-tetrahydro-
pyrrolo[2,3-c]azepin-8(1H)-one

Example 29

15 Synthesis of 4-hydroxyimino-1-methyl-7-[3-(4-
phenylpiperazin-1-yl)propyl]-4,5,6,7-tetra-
hydropyrrolo[2,3-c]azepin-8(1H)-one (Compound
No. 45)

20 A solution of 1.073 g (2.82 mmol) of compound
No. 18 obtained in Example 13 and 0.275 g (3.38 mmol)
of hydroxylamine hydrochloride in 50 ml of pyridine
was stirred at 70°C for 14 hours. The solvent was dis-
tilled off under reduced pressure. The residue was
added with a half-saturated aqueous solution of potas-
sium carbonate and extracted with chloroform three
times. The chloroform layer was washed with saturated
saline, followed by drying over anhydrous sodium sul-
25 fate. The solvent was distilled off under reduced

pressure and the residue was purified by chromatography on a silica gel column (eluent: ethyl acetate), whereby 1.074 g of the title compound were obtained (yield: 96%).

5 Although this compound was sufficiently pure, it can be recrystallized from methanol-isopropyl ether as needed.

Example 30

10 Compound No. 46 was obtained using O-methyl-hydroxylamine hydrochloride in place of hydroxylamine hydrochloride in the procedure of Example 29.

(Compound No. 46)

15 4-Methoxyimino-1-methyl-7-[3-(4-phenylpiperazin-1-yl)propyl]-4,5,6,7-tetrahydropyrrolo[2,3-c]-azepin-8(1H)-one

Example 31

20 Compound Nos. 47, 48, 49, 50, 51, 52, 53 and 54 were obtained using Compound Nos. 19, 20, 37, 22, 23, 35, 21 and 17, respectively, in place of Compound No. 18 in the procedure of Example 29.

(Compound No. 47)

25 1-Ethyl-4-hydroxyimino-7-[3-(4-phenylpiperazin-1-yl)propyl]-4,5,6,7-tetrahydropyrrolo[2,3-c]-azepin-8(1H)-one

(Compound No. 48)

1-Benzyl-4-hydroxyimino-7-[3-(4-phenylpiperazin-1-yl)propyl]-4,5,6,7-tetrahydropyrrolo[2,3-c]-azepin-8(1H)-one

(Compound No. 49)

5 4-Hydroxyimino-7-[3-[4-(2-methoxyphenyl)-piperazin-1-yl]propyl]-1-methyl-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8(1H)-one

(Compound No. 50)

10 4-Hydroxyimino-7-[3-[4-(3-methoxyphenyl)-piperazin-1-yl]propyl]-1-methyl-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8(1H)-one

(Compound No. 51)

15 4-Hydroxyimino-7-[3-[4-(4-methoxyphenyl)-piperazin-1-yl]propyl]-1-methyl-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8(1H)-one

(Compound No. 52)

20 4-Hydroxyimino-1-methyl-7-[3-(4-phenylpiperidin-1-yl)propyl]-4,5,6,7-tetrahydropyrrolo[2,3-c]-azepin-8(1H)-one

(Compound No. 53)

4-Hydroxyimino-1-methyl-7-[4-(4-phenylpiperidin-1-yl)butyl]-4,5,6,7-tetrahydropyrrolo[2,3-c]-azepin-8(1H)-one

(Compound No. 54)

25 4-Hydroxyimino-1-methyl-7-[4-(4-phenylpiperazin-

1-yl)butyl]-4,5,6,7-tetrahydropyrrolo[2,3-c]-
azepin-8(1H)-one

Example 32

5 Synthesis of 4-hydroxyimino-1-methyl-7-[3-[4-(2-
pyrimidinyl)piperazin-1-yl]propyl]-4,5,6,7-
tetrahydropyrrolo[2,3-c]azepin-8(1H)-one (Com-
pound No. 55)

10 A suspension of 180 mg (0.47 mmol) of Compound
No. 24 obtained in Example 17, 65 mg (0.94 mmol) of
hydroxylamine hydrochloride and 77 mg (0.94 mmol) of
sodium acetate in 30 ml of methanol was refluxed for
19 hours. The reaction mixture was concentrated under
reduced pressure. The residue was added with a half-
saturated aqueous solution of potassium carbonate and
15 then extracted with chloroform (three times). The
organic layer was washed successively with water and
saturated saline, followed by drying over anhydrous
sodium sulfate. The solvent was thereafter distilled
off under reduced pressure. The resultant oil was
20 purified by chromatography on a silica gel column
(eluent: 5% methanol in chloroform), whereby 179 mg of
the title compound were obtained (yield: 96%).

Example 33

25 Compound Nos. 56, 57, 58 and 59 were obtained
using Compound Nos. 31, 32, 25 and 26, respectively, in

place of Compound No. 24 in the procedure of Example 32.

(Compound No. 56)

5 7-[3-[4-(4-Fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-1-methyl-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8(1H)-one

(Compound No. 57)

10 1-Ethyl-7-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8(1H)-one

(Compound No. 58)

15 7-[3-[4-(4-Fluorophenoxy)piperidin-1-yl]propyl]-4-hydroxyimino-1-methyl-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8(1H)-one

(Compound No. 59)

7-[3-[4-(4-Fluorophenylthio)piperidin-1-yl]propyl]-4-hydroxyimino-1-methyl-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8(1H)-one

Example 34

20 Compound Nos. 60, 61 and 62 were obtained using Compound Nos. 34, 36 and 38, respectively, in place of Compound No. 18 in the procedure of Example 29.

(Compound No. 60)

25 1-Methyl-8-[3-(4-phenylpiperidin-1-yl)propoxy]-5,6-dihydropyrrolo[2,3-c]azepin-4(1H)-one oxime

(Compound No. 61)

8-[3-[4-(2-Methoxyphenyl)piperazin-1-yl]propoxy]-
1-methyl-5,6-dihydropyrrolo[2,3-c]azepin-4(1H)-
one oxime

5 (Compound No. 62)

1-Methyl-8-[3-(4-phenylpiperazin-1-yl)propoxy]-
5,6-dihydropyrrolo[2,3-c]azepin-4(1H)-one oxime

Data of the physical properties of the compounds
obtained in the above examples are summarized in

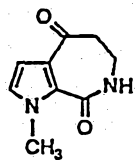
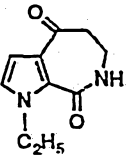
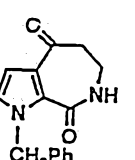
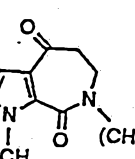
10 Table 1.

15

20

25

Table 1

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
7	Colorless prism crystals 196.0-198.0°C (acetonitrile)	2.82(2H,m), 3.52(2H,m), 3.97(3H,s), 6.72(1H,d,J=2.6Hz), 6.79(1H,d,J=2.6Hz), 6.96(1H,br.)	3410, 1645, 1485, 1460, 1355, 1315, 1100	67	
8	Colorless prism crystals 157.0-158.5°C (ethyl acetate)	1.45(3H,t,J=7.3Hz), 2.83(2H,m), 3.53(2H,m), 4.41(2H,q,J=7.3Hz), 6.35(1H,br.), 6.74(1H,d,J=2.6Hz), 6.86(1H,d,J=2.6Hz)	3420, 1655, 1485, 1465, 1375, 1320, 1120, 895	73	
9	Colorless needle crystals 148.0-149.0°C (ethyl acetate-hexane)	2.80(2H,m), 3.46(2H,m), 5.63(2H,s), 6.76(1H,d,J=2.6Hz), 6.85(1H,d,J=2.6Hz), 7.05(1H, br.t), 7.13(2H,dd,J=7.3Hz, 2.1Hz), 7.21-7.39(3H,m)	3420, 1655, 1485, 1470, 1375, 1320, 1115, 895	60	
10	Colorless prism crystals 80.0-81.0°C (isopropyl ether)	2.15(2H,m), 2.79(2H,m), 3.63(2H,t,J=6.3Hz), 3.66-3.85(4H,m), 3.93(3H,s), 6.64(1H,d, J=3.0Hz), 6.75(1H,d,J=3.0Hz)	2940, 1655, 1630, 1485, 1425, 1375, 1290, 1105	36	

*1: Measured in CDCl_3 with TMS as an internal standard.

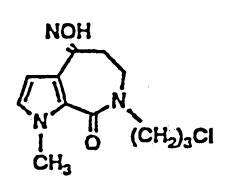
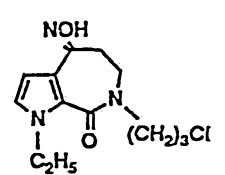
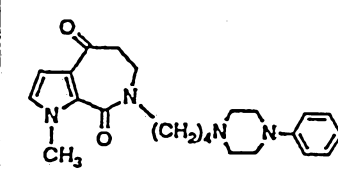
*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR* ¹ (δ ppm/270MHz)	IR* ² (cm^{-1})	Yield (%)	Structural formula
11	Colorless plate crystals 77.0-78.0°C (isopropyl ether)	1.82(2H,m), 1.92(2H,m), 2.80(2H,m), 3.48(2H,t,J=6.3Hz), 3.56-3.77(4H,m), 3.93(3H,s), 6.64(1H,d,J=3.3Hz), 6.74(1H,d,J=3.3Hz)	2950, 1640, 1480, 1430, 1380, 1315, 1220, 1045	53	
12	Colorless oil	1.53(2H,m), 1.68(2H,m), 1.83(2H,m), 2.78(2H,m), 3.48-3.63(4H,m), 3.68(2H,m), 3.93(3H,s), 6.63(1H,d,J=2.6Hz), 6.74(1H,d,J=2.6Hz)	2930, 1655, 1630, 1485, 1475, 1425, 1375, 1305, 1105	43	
13	Colorless oil	1.26(3H,t,J=7.3Hz), 2.14(2H,m), 2.79(2H,m), 3.63(2H,t,J=6.3Hz), 3.66-3.83(4H,m), 4.35(2H,q,J=7.3Hz), 6.66(1H,d,J=3.0Hz), 6.83(1H,d,J=3.0Hz)	2950, 1640, 1480, 1435, 1380, 1285, 1050	72	
14	Colorless powdery crystals	1.99(2H,m), 2.79(2H,dd, J=5.9Hz,4.0Hz), 3.40(2H,t, J=6.6Hz), 3.52-3.80(4H,m), 5.56(2H,s), 6.67(1H,d,J=2.6Hz), 6.86(1H,d,J=2.6Hz), 7.12(2H,m), 7.20-7.45(3H,m)	(KBr) 1663, 1634, 1482, 1454, 1431, 1378, 1309, 1250, 1186, 1136, 927	46	

*1: Measured in CDCl_3 with TMS as an internal standard.*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

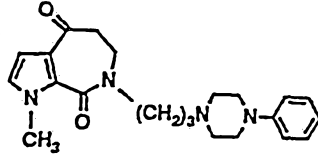
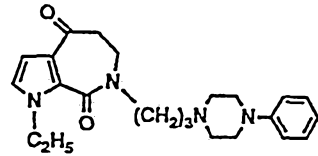
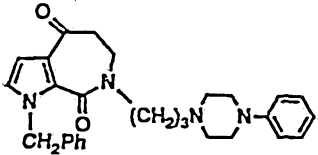
Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR ^{*1} (δ ppm/270MHz)	IR ^{*2} (cm ⁻¹)	Yield (%)	Structural formula
15	Colorless powdery crystals	2.12(2H,m), 3.01(2H,m), 3.50-3.73(6H,m), 3.88 (3H,s), 6.46(1H,d,J= 2.7Hz), 6.71(1H,d,J= 2.7Hz), 7.70(1H,br.s)	1625, 1485, 1420, 1375, 1100	49	
16	Colorless needle crystals 142.0-145.0°C (ethanol)	1.40(3H,t,J=7.3Hz), 2.13(2H,m), 2.97(2H,m), 3.48-3.77(6H,m), 4.29(2H,q,J=7.3Hz), 6.39(1H,d,J=2.6Hz), 6.79(1H,d,J=2.6Hz), 7.41(1H,br.s)	(KBr) 2980, 1626, 1476, 1437, 1376, 1303, 1244, 1019, 914	41	
17	Colorless prism crystals 126.0-127.0°C (ethyl acetate -ethyl ether)	1.55-1.80(4H,m), 2.49 (2H,t,J=7.2Hz), 2.60- 2.70(4H,m), 2.79(2H,t, J=5.3Hz), 3.15-3.30 (4H,m), 3.62(2H,t,J= 7.2Hz), 3.66(2H,m), 3.93(3H,s), 6.64(1H,d, J=2.6Hz), 6.74(1H,d,J= 2.6Hz), 6.86(1H,t,J= 7.2Hz), 6.93(2H,d,J=7.2Hz), 7.26(2H,t,J=7.2Hz)	2950, 2820, 1660, 1630, 1600, 1490, 1480, 1380, 1300, 990, 905	96	

*1: Measured in CDCl₃ with TMS as an internal standard.

*2: Measured as a CHCl₃ solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR ^{*1} (δ ppm/270MHz)	IR ^{*2} (cm^{-1})	Yield (%)	Structural formula
18	Yellow oil	1.90(2H,m), 2.45(2H,t,J=7.3Hz), 2.54-2.70(4H,m), 2.79(2H,m), 3.10-3.30(4H,m), 3.58-3.78(4H,m), 3.92(3H,s), 6.63(1H,d,J=3.3Hz), 6.73(1H,d,J=3.3Hz), 6.84(1H,t,J=7.3Hz), 6.92(2H,d,J=7.3Hz), 7.25(2H,d,J=7.3Hz)	2940, 2820, 1660, 1630, 1595, 1490, 1380, 1145, 910	97	
19	Colorless oil	1.44(3H,t,J=7.2Hz), 1.91(2H,m), 2.50(2H,t,J=7.2Hz), 2.55-2.70(4H,m), 2.78(2H,m), 3.15-3.30(4H,m), 3.65(2H,t,J=7.2Hz), 3.69(2H,m), 4.35(2H,q,J=7.2Hz), 6.65(1H,d,J=3.0Hz), 6.82(1H,d,J=3.0Hz), 6.86(1H,t,J=7.3Hz), 6.93(2H,d,J=7.3Hz), 7.27(2H,t,J=7.3Hz)	2950, 2830, 1665, 1640, 1600, 1490, 1380, 1150, 995	88	
20	Colorless oil	1.79(2H,m), 2.36(2H,t,J=7.3Hz), 2.56(4H,m), 2.79(2H,m), 3.19(4H,m), 3.50-3.77(4H,m), 5.58(2H,s), 6.67(1H,d,J=2.7Hz), 6.79-6.90(2H,m), 6.92(2H,d,J=7.9Hz), 7.13(2H,d,J=7.9Hz), 7.20-7.39(5H,m)	2935, 2810, 1655, 1630, 1600, 1485, 1375, 1140	quant	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
21	Yellow oil	1.55-1.80(4H,m), 1.80-1.98(4H,m), 2.12(2H,m), 2.40-2.60(3H,m), 2.79(2H,t,J=5.3Hz), 3.10(2H,m), 3.62(2H,t,J=7.2Hz), 3.67(2H,m), 3.93(3H,s), 6.63(1H,d,J=2.6Hz), 6.74(1H,d,J=2.6Hz), 7.10-7.40(5H,m)	2950, 2820, 2780, 1660, 1635, 1490, 1440, 1380, 1310, 1150, 1120, 910	96	
22	Colorless oil	1.90(2H,m), 2.49(2H,t,J=7.3Hz), 2.55-2.70(4H,m), 2.79(2H,m), 3.15-3.25(4H,m), 3.65(2H,t,J=7.3Hz), 3.70(2H,m), 3.79(5H,s), 3.93(3H,s), 6.42(1H,dd,J=7.9Hz, 1.9Hz), 6.46(1H,t,J=1.9Hz), 6.53(1H,dd,J=7.9Hz,1.9Hz), 6.64(1H,d,J=2.7Hz), 6.74(1H,d,J=2.7Hz), 7.17(1H,t,J=7.9Hz)	2950, 2830, 1660, 1635, 1490, 1380, 1165, 995	84	
23	Colorless powdery crystals	1.98(2H,m), 2.59(2H,m), 2.65-2.80(m), 2.79(m) (6H in total), 3.10-3.25(4H,m), 3.66(2H,t,J=7.3Hz), 3.70(2H,m), 3.77(3H,s), 3.93(3H,s), 6.64(1H,d,J=2.6Hz), 6.74(1H,d,J=2.6Hz), 6.84(2H,d,J=9.2Hz), 6.90(2H,d,J=9.2Hz)	2820, 1660, 1630, 1600, 1490, 1370, 1140	48	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
24	Yellow oil	1.90(2H,m), 2.42-2.57(6H,m), 2.80(2H,m), 3.66(2H,t,J=7.3Hz), 3.71(2H,m), 3.83(4H,m), 3.93(3H,s), 6.48(1H,t,J=4.6Hz), 6.63(1H,d,J=3.0Hz), 6.75(1H,d,J=3.0Hz), 8.30(2H,d,J=4.6Hz)	(film) 1658, 1629, 1585, 1546, 1491, 1444, 1359, 1308, 1256, 983, 780	55	
25	Yellow oil	1.69-2.05(6H,m), 2.28(2H,m), 2.43(2H,t,J=7.3Hz), 2.65-2.84(4H,m), 3.62(2H,t,J=7.3Hz), 3.70(2H,m), 3.92(3H,s), 4.21(1H,m), 6.61(1H,d,J=3.3Hz), 6.74(1H,d,J=3.3Hz), 6.78-6.90(2H,m), 6.94(2H,t,J=8.6Hz)	(film) 1661, 1633, 1504, 1493, 1246, 1206, 1045, 778, 764	66	
26	Yellow oil	1.53-1.98(6H,m), 2.04(2H,m), 2.38(2H,m), 2.77(2H,dd,J=4.0Hz,6.6Hz), 2.86(2H,m), 2.95(1H,m), 3.50(2H,t,J=7.3Hz), 3.68(2H,m), 3.92(3H,s), 6.63(1H,d,J=3.3Hz), 6.73(1H,d,J=3.3Hz), 6.99(2H,t,J=8.6Hz), 7.41(2H,m)	(film) 2943, 1662, 1632, 1490, 1433, 1377, 1245, 1220, 779	85	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
27	Pale yellow oil	1.89(2H,m), 2.27(1H,br.s), 2.72-2.82(4H,m), 3.03(2H,t, J=5.3Hz), 3.62-3.72(4H,m), 3.90(3H,s), 4.09(2H,t, J=5.3Hz), 6.63(1H,d, J=2.6Hz), 6.72(1H,d, J=2.6Hz), 6.86-6.99(3H,m), 7.22-7.32(2H,m)	(film) 1628, 1491, 1245, 758	10	
28	Brown oil	1.82(2H,m), 2.31(3H,s), 2.47(2H,t,J=7.3Hz), 2.60(2H,m), 2.66-2.82(4H,m), 3.58(2H,t, J=7.3Hz), 3.63(2H,m), 3.85(3H,s), 3.87(3H,s), 3.92(3H,s), 6.63(1H,d, J=2.7Hz), 6.67-6.85(4H,m)	2940, 1660, 1635, 1595, 1375, 1230, 1140, 1025,	51	
29	Pale brown oil (hydrochloride) Colorless needle crystals 195.0-201.0°C (methanol-isopropyl ether)	1.75-1.99(6H,m), 2.11(2H,m), 2.44(2H,t,J=7.3Hz), 2.81(2H,m), 3.03(2H,m), 3.21(1H,m), 3.63(2H,t, J=7.3Hz), 3.70(2H,m), 3.93(3H,s), 6.64(1H,d,J=3.0Hz), 6.74(1H,d, J=3.0Hz), 7.14(2H,t,J=8.6Hz), 7.99(2H,m)	2930, 1655, 1625, 1595, 1485, 1265, 1150, 970	77	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
30	Pale brown oil	1.44(3H,t,J=7.3Hz), 1.50-2.50(8H,m), 2.58(2H,m), 2.79(2H,m), 3.07(2H,m), 3.30(1H,m), 3.65(2H,t,J=7.3Hz), 3.72(2H,m), 4.34(2H,q,J=7.3Hz), 6.65(1H,d,J=3.0Hz), 6.82(1H,d,J=3.0Hz), 7.15(2H,t,J=8.6Hz), 7.96(2H,dd,J=8.6Hz,5.3Hz)	2940, 1660, 1635, 1600, 1485, 1380, 1280, 1160, 975, 910	58	
31	Yellow oil (monomaleate) Pale brown prism crystals 168.0-171.0°C (decomposed) (ethanol)	1.87(2H,quint,J=7.3Hz), 2.47(2H,t,J=7.3Hz), 2.60(4H,m), 2.78(2H,m), 3.11(4H,m), 3.57-3.77(4H,m), 3.92(3H,s), 6.62(1H,d,J=3.3Hz), 6.73(1H,d,J=3.3Hz), 6.80-7.00(4H,m)	(film) 1662, 1631, 1509, 1491, 1378, 1244, 1149, 816, 779	43	
32	Pale yellow oil	1.44(3H,t,J=7.3Hz), 1.89(2H,quint,J=7.3Hz), 2.48(2H,t,J=7.3Hz), 2.62(4H,m), 2.79(2H,dd,J=6.6Hz,4.0Hz), 3.13(4H,m), 3.65(2H,t,J=7.3Hz), 3.71(2H,m), 4.36(2H,q,J=7.3Hz), 6.65(1H,d,J=2.6Hz), 6.81(1H,d,J=2.6Hz), 6.83-7.01(4H,m)	(film) 2940, 2820, 1660, 1635, 1510, 1485, 1375, 1235, 1150, 925.	25	

*1: Measured in CDCl_3 with TMS as an internal standard.*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
33	Pale yellow oil	1.36(2H,m), 1.66(2H,m), 1.88(2H,m), 2.77(2H,dd,J=6.3Hz,4.3Hz), 3.56(2H,t,J=7.3Hz), 3.65(2H,m), 3.92(s), 3.95(m), (5H in total), 6.63(1H,d,J=3.0Hz), 6.74(1H,d,J=3.0Hz), 6.91(1H,s), 7.06(1H,s), 7.50(1H,s)	(film) 2938, 1628, 1493, 1436, 1378, 1247, 1149, 1082, 918	27	
34	Colorless oil	1.55-1.90(4H,m), 2.03(2H,m), 2.66(1H,m), 2.75-2.95(4H,m), 3.60-3.80(4H,m), 3.92(3H,s), 4.20(2H,t,J=7.2Hz), 4.20-4.35(2H,m), 6.64(1H,d,J=2.6Hz), 6.74(1H,d,J=2.6Hz), 7.15-7.35(5H,m)	2940, 2860, 1680, 1630, 1480, 1430, 1380, 1280, 1120, 1010, 900	60	
35	Colorless oil	1.75-2.00(6H,m), 2.10(2H,m), 2.48(2H,t,J=7.2Hz), 2.65(1H,m), 2.80(2H,m), 3.00-3.15(2H,m), 3.65(2H,t,J=7.2Hz), 3.70(2H,m), 3.93(3H,s), 6.64(1H,d,J=2.7Hz), 6.74(1H,d,J=2.7Hz), 7.15-7.35(5H,m)	2930, 2800, 1650, 1630, 1485, 1470, 1430, 1375, 1140, 1110,	34	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR ^{*1} (δ ppm/270MHz)	IR ^{*2} (cm^{-1})	Yield (%)	Structural formula
36	Colorless oil	2.03(2H,m), 2.81(2H,t, J=5.6Hz), 2.90-3.15(4H,m), 3.55-3.80(8H,m), 3.88(3H,s), 3.93(3H,s), 4.21(2H,t, J=7.3Hz), 6.64(1H,d,J=2.7Hz), 6.74(1H,d,J=2.7Hz), 6.80-7.10(4H,m)	2950, 2830, 1690, 1640, 1490, 1430, 1380, 1150, 1120, 1020, 910	50	
37	Pale yellow oil	1.92(2H,m), 2.53(2H,t, J=7.2Hz), 2.60-2.78(m), 2.80(m), (6H in total), 3.00-3.20(4H,m), 3.65(2H,t, J=7.2Hz), 3.70(2H,m), 3.86(3H,s), 3.93(3H,s), 6.64(1H,d, J=2.6Hz), 6.74(1H,d, J=2.6Hz), 6.80-7.05(4H,m)	2950, 2830, 1660, 1630, 1490, 1380, 1150, 1110, 1020, 910	29	
38	Colorless needle crystals 107.0-110.0°C (ethyl acetate)	2.03(2H,m), 2.80(2H,m), 3.05-3.25(4H,m), 3.55-3.80(8H,m), 3.92(3H,s), 4.21(2H,t, J=6.6Hz), 6.64(1H,d, J=2.7Hz), 6.74(1H,d, J=2.7Hz), 6.85-7.00(3H,m), 7.29(2H,t, J=7.9Hz)	3650, 2950, 2820, 1690, 1630, 1600, 1480, 1430, 1380, 1120, 930	26	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

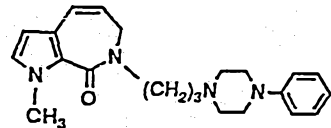
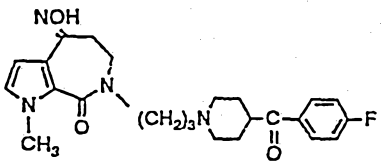
Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm ⁻¹)	Yield (%)	Structural formula
39	Colorless prism crystals 128.0-131.0°C (ethyl acetate)	1.87(2H,m), 2.05-2.30(3H,m), 2.48(2H,t,J=7.3Hz), 2.55-2.70 (4H,m), 3.15-3.25(4H,m), 3.30- 3.65(m), 3.58(t,J=7.3Hz) (4H in total), 3.87(3H,s), 4.91(1H,m), 6.16(1H,d,J=2.6Hz), 6.71(1H,d,J= 2.6Hz), 6.85(1H,t,J=7.3Hz), 6.92 (2H,d,J=7.3Hz), 7.26(2H,t,J=7.3Hz)	3650, 3580, 3400, 2930, 2820, 1600, 1470, 1420, 1300, 970, 900	85	
40	Colorless needle crystals 133.5-134.5°C (ethyl acetate)	1.85(2H,quint,J=7.3Hz), 2.03-2.31(3H,m), 2.47(2H,dt, J=2.0Hz,7.3Hz), 2.63(4H,m), 3.12(4H,m), 3.35(1H,ddd,J=3.3Hz, 7.3Hz,14.9Hz), 3.48-3.63(3H,m), 3.87(3H,s), 4.91(1H,t,J=5.3Hz), 6.16(1H,d,J=2.6Hz), 6.71(1H,d,J= 2.6Hz), 6.82-7.03(4H,m)	(KBr) 3378, 1601, 1508, 1443, 1237, 1132, 1049, 1002, 979, 822, 776	67	
41	Colorless oil	1.99(2H,m), 2.07-2.30(3H,m), 3.00(4H,m), 3.33(1H,ddd,J=3.3Hz, 6.4Hz,14.8Hz), 3.47-3.75(7H,m), 3.86(3H,s), 3.87(3H,s), 4.20 (2H,t,J=6.3Hz), 4.91(1H,m), 6.16(1H,d,J=2.6Hz), 6.70(1H,d, J=2.6Hz), 6.85-7.10(4H,m)	(film) 3448, 1698, 1616, 1500, 1435, 1241.	99	

*1: Measured in CDCl₃ with TMS as an internal standard.

*2: Measured as a CHCl₃ solution unless otherwise specifically indicated.

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Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
42	Brown oil	1.84(2H,m), 2.44(2H,t, J=7.3Hz), 2.50-2.70(4H,m), 3.15-3.30(4H,m), 3.60(2H,t, J=7.3Hz), 3.69(2H,d, J=6.6Hz), 3.96(3H,s), 5.96(1H, dt, J=9.3Hz, 6.6Hz), 6.09(1H,d, J=2.6Hz), 6.74(1H,d, J=2.6Hz), 6.75(1H,d, J=9.3Hz), 6.85(1H,t, J=7.3Hz), 6.92(2H,d, J=7.3Hz), 7.26(2H,t, J=7.3Hz)	2930, 2820, 1595, 1490, 1460, 1420, 1370, 1305, 1100, 995	53	
43	Pale yellow crystals 103.0-105.0°C (methanol-ethyl ether)	1.80-2.60(10H,m), 2.98(2H,t, J=5.6Hz), 3.05-3.15(2H,m), 3.29(1H,m), 3.50-3.65(4H,m), 3.60(3H,s), 6.40(1H,d, J=2.6Hz), 6.70(1H,d, J=2.6Hz), 7.14(2H,t, J=8.6Hz), 7.96(2H,dd, J=8.6Hz, 5.3Hz), 9.50(1H,br.s)	3560, 2920, 1680, 1620, 1600, 1370, 1100, 970	41	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
46	Colorless oil	1.89(2H,m), 2.49(2H,t,J=7.2Hz), 2.55-2.75(4H,m), 2.90(2H,t,J= 5.3Hz), 3.10-3.35(4H,m), 3.45- 3.65(4H,m), 3.87(3H,s), 3.94 (3H,s), 6.42(1H,d,J=2.6Hz), 6.69(1H,d,J=2.6Hz), 6.86(1H, t,J=7.3Hz), 6.92(2H,d,J=7.3Hz), 7.26(2H,t,J=7.3Hz)	2940, 2810, 1620, 1600, 1470, 1430, 1375, 1100, 1040	63	
47	Colorless needle crystals 160.0-163.0°C (methanol)	1.37(3H,t,J=7.3Hz), 1.90(2H,m), 2.48(2H,t,J=7.3Hz), 2.50-2.75 (4H,m), 2.93(2H,m), 3.05-3.35 (4H,m), 3.40-3.60(4H,m), 4.26 (2H,q,J=7.3Hz), 6.35(1H,d,J=2.6Hz), 6.72(1H,d,J=2.6Hz), 6.84(1H,t, J=7.3Hz), 6.92(2H,d,J=7.3Hz), 7.25(2H,m), 10.50(1H,br.s)	3570, 2940, 2820, 1625, 1600, 1470, 1155, 1000, 900	96	
48	Colorless prism crystals 180.0-181.0°C (ethanol -isopropyl ether)	1.80(2H,m), 2.37(2H,m), 2.50-2.68 (4H,m), 2.93(2H,m), 3.15-3.30 (4H,m), 3.40-3.60(4H,m), 5.51 (2H,s), 6.38(1H,d,J=3.0Hz), 6.76 (1H,d,J=3.0Hz), 6.85(1H,t,J=7.3Hz), 6.92(1H,d,J=7.9Hz), 7.08(2H,m), 7.17-7.35(6H,m), 9.84(1H,br.s)	(Nujol) 1615, 1600, 1500, 1470, 1245, 1230, 1000	quant	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

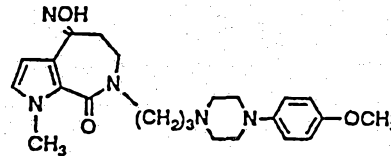
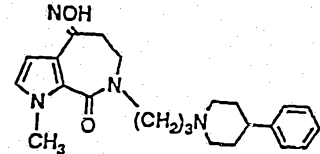
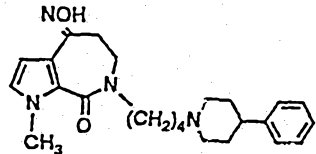
Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR ^{*1} (δ ppm/270MHz)	IR ^{*2} (cm ⁻¹)	Yield (%)	Structural formula
49	Colorless needle crystals 119.0-121.0°C (methanol-ethyl ether)	1.95(2H,m), 2.57(2H,t, J=7.3Hz), 2.65-2.85(4H,m), 2.98(2H,t, J=5.3 Hz), 3.05-3.25(4H,m), 3.50-3.65(4H,m), 3.86(3H,s), 3.87(3H,s), 6.38(1H,d, J=2.6Hz), 6.69(1H,d, J=2.6Hz), 6.80-7.05(4H,m), 8.65(1H,br.s)	3560, 2930, 2820, 1620, 1495, 1465, 1370, 1105, 1020, 1000, 900	99	
50	Colorless prism crystals 150.0-152.0°C (methanol)	1.90(2H,m), 2.48(2H,t, J=7.3Hz), 2.55-2.70(4H,m), 2.95(2H,t, J=5.3 Hz), 3.15-3.30(4H,m), 3.45-3.65(4H,m), 3.78(3H,s), 3.85(3H,s), 6.34(1H,d, J=2.6Hz), 6.41(1H,dd, J=7.9Hz, 1.9Hz), 6.47(1H,t, J=1.9Hz), 6.53(1H,dd, J=7.9Hz, 1.9Hz), 6.65(1H,d, J=2.6Hz), 7.16(1H,t, J=7.9Hz), 10.28(1H,br.s)	3580, 2950, 2840, 1615, 1480, 1440, 1380, 1165, 1000, 965, 910	96	

*1: Measured in CDCl₃ with TMS as an internal standard.

*2: Measured as a CHCl₃ solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
51	Colorless needle crystals 175.0-176.0°C (methanol)	1.91(2H,m), 2.50(2H,t,J=7.3Hz), 2.60-2.75(4H,m), 2.96(2H,t, J=5.9Hz), 3.05-3.20(4H,m), 3.45-3.75(4H,m), 3.76(3H,s), 3.86(3H,s), 6.35(1H,d,J=2.6Hz), 6.66(1H,d,J=2.6Hz), 6.83(2H,d, J=9.3Hz), 6.91(2H,d,J=9.3Hz), 10.10(1H,br.s)	3570, 2940, 2820, 1620, 1500, 1470, 1000, 905	94	
52	Colorless needle crystals 108.0-112.0°C (methanol-ethyl ether)	1.80-2.30(8H,m), 2.45-2.65(3H,m), 3.03(2H,t,J=5.3Hz), 3.10-3.25 (2H,m), 3.50-3.65(4H,m), 3.88(3H,s), 6.42(1H,d,J=7.2Hz), 6.70(1H,d,J=2.7Hz), 7.15-7.30 (5H,m), 9.20(1H,br.s)	3570, 2920, 1620, 1470, 1425, 1370, 1100, 1000, 960, 900	99	
53	Colorless prism crystals 161.0-162.0°C (methanol)	1.50-2.10(8H,m), 2.17(2H,m), 2.40-2.65(3H,m), 2.95(2H,t, J=5.3Hz), 3.16(2H,m), 3.45- 3.65(4H,m), 3.87(3H,s), 6.38(1H,d,J=2.6Hz), 6.69(1H, d,J=2.6Hz), 7.10-7.40(5H,m), 8.70(1H,br.s)	3570, 2930, 1620, 1470, 1430, 1375, 1105, 995, 900	64	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
54	Pale yellow prism crystals 193.0-194.0°C (methanol)	1.50-1.80(4H,m), 2.51(2H,t, J=7.3Hz), 2.50-2.80(4H,m), 2.94(2H,t, J=5.2Hz), 3.10-3.35(4H,m), 3.40-3.65(4H,m), 3.87(3H,s), 6.36(1H,d, J=2.6Hz), 6.68(1H,d, J=2.6Hz), 6.86(1H,t, J=7.2Hz), 6.92(2H,d, J=7.2Hz), 7.26(2H,t, J=7.2Hz), 8.80(1H,br.s)	3570, 2930, 2820, 1620, 1600, 1470, 1430, 1370, 1120, 990, 900	73	
55	Colorless powdery crystals 197.5-198.0°C (ethanol)	1.89(2H,m), 2.38-2.57(6H,m), 2.98(2H,m), 3.50-3.62(4H,m), 3.84(4H,m), 3.88(3H,s), 6.38(1H,d, J=3.3Hz), 6.48(1H,m), 6.70(1H,d, J=3.3Hz), 7.72(1H,br.s), 8.30(2H,d, J=4.6Hz)	(KBr) 3240, 1583, 1544, 1503, 1488, 1442, 1360, 1312, 1267, 1256, s ² , 965, 916, 803, 784	96	
56	Colorless prism crystals 167.5-169.5°C (ethanol)	1.89(2H,quint, J=7.3Hz), 2.48(2H,t, J=7.3Hz), 2.65(4H,m), 2.98(2H,m), 3.58(4H,m), 3.87(3H,s), 6.33(1H,d, J=2.6Hz), 6.67(1H,d, J=2.6Hz), 6.82-7.03(4H,m), 9.54(1H,br.s)	(KBr) 3248, 1597, 1508, 1472, 1433, 1239, 1158, 928, 819, 783	98	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
57	Colorless prism crystals 150.5-151.5°C (ethanol)	1.39(3H,t,J=7.3Hz), 1.89(2H,m), 2.48(2H,t,J=7.3Hz), 2.64(4H,m), 2.97(2H,m), 3.16(4H,m), 3.43-3.68(4H,m), 4.29(2H,t,J=7.3Hz), 6.35(1H,d,J=3.0Hz), 6.76(1H,d,J=3.0Hz), 6.81-7.04(4H,m), 9.13(1H,bs)	(KBr) 2940, 2830, 1630, 1510, 1475, 1440, 1370, 1235, 1160, 1010, 970, 925	91	
58	Pale yellow oil	1.87(4H,m), 2.02(2H,m), 2.33(2H,m), 2.44(2H,m), 2.76(2H,m), 2.99(2H,m), 3.50-3.63(4H,m), 3.87(3H,s), 4.24(1H,m), 6.39(1H,d,J=2.6Hz), 6.69(1H,d,J=2.6Hz), 6.84(2H,m), 6.95(2H,m), 8.75(1H,br.s)	(film) 1624, 1504, 1477, 1434, 1372, 1248, 1206, 1044, 1004, 963, 829, 763	98	
59	Pale yellow oil	1.49-1.98(6H,m), 2.06(2H,m), 2.38(2H,m), 2.80-3.06(5H,m), 3.54(4H,m), 3.86(3H,s), 6.42(1H,d,J=2.6Hz), 6.69(1H,d,J=2.6Hz), 6.99(2H,dt,J=2.0Hz,9.2Hz), 7.40(1H,dd,J=2.6Hz,9.2Hz), 7.42(1H,dd,J=2.6Hz,9.2Hz), 9.15(1H,br.s)	(film) 1624, 1489, 1431, 1374, 1248, 1220, 1155, 1003, 776, 754	99	

*1: Measured in CDCl_3 with TMS as an internal standard.*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR*1 (δ ppm/270MHz)	IR*2 (cm^{-1})	Yield (%)	Structural formula
60	Colorless prism crystals 155.0-156.0°C (methanol-ethyl ether)	1.53-1.90(4H,m), 2.01(2H,m), 2.66(1H,m), 2.75-2.95(2H,m), 2.97(2H,t, J=5.3Hz), 3.56(2H,t, J=5.3Hz), 3.61(2H,t, J=7.2Hz), 3.87(3H,s), 4.19(2H,t, J=7.2Hz), 4.20-4.35(2H,m), 6.38(1H,d, J=2.6Hz), 6.68(1H,d, J=2.6Hz), 7.10-7.35(5H,m), 7.50(1H,br.s)	3570, 2940, 1690, 1630, 1470, 1430, 1280, 1110	99	
61	Colorless oil	2.01(2H,t, J=7.2Hz), 2.98(2H,t, J=5.3Hz), 3.00-3.15(4H,m), 3.57(2H,t, J=5.3Hz), 3.62(2H,t, J=7.2Hz), 3.65-3.80(4H,m), 3.87(3H,s), 3.88(3H,s), 4.20(2H,t, J=7.2Hz), 6.38(1H,d, J=2.7Hz), 6.70(1H,d, J=2.7Hz), 6.85-7.10(4H,m), 8.80(1H,br.s)	3560, 2960, 1690, 1620, 1500, 1470, 1420, 1100	91	

*1: Measured in CDCl_3 with TMS as an internal standard.

*2: Measured as a CHCl_3 solution unless otherwise specifically indicated.

Table 1 (Cont'd)

Comp'd No.	Property Melting point (recrystallization solvent)	NMR ^{*1} (δ ppm/270MHz)	IR ^{*2} (cm ⁻¹)	Yield (%)	Structural formula
62	Colorless needle crystals 176.0-176.5°C (methanol)	2.01(2H,tt,J=7.6Hz, 7.3Hz), 2.98(2H,t,J=5.3Hz), 3.10-3.25(4H,m), 3.57(2H,t,J=5.3Hz), 3.60-3.80(m), 3.63(t,J=7.3Hz), (6H in total), 3.87(3H,s), 4.20(2H,t,J=6.6Hz), 6.38(1H,d,J=2.7Hz), 6.70(1H,d,J=2.7Hz), 6.97(1H,t,J=7.3Hz), 7.06(2H,d,J=7.3Hz), 7.30(2H,t,J=7.3Hz), 9.30(1H,br.s)	3570, 2930, 1690, 1620, 1600, 1470, 1420, 1120, 990	96	

*1: Measured in CDCl₃ with TMS as an internal standard.

*2: Measured as a CHCl₃ solution unless otherwise specifically indicated.

Test

With respect to the compounds of the present invention, their anti- α_1 action and anti-serotonin (5-HT) action were investigated by the testing methods which will be described below. The test results of some representative compounds are tabulated below.

(1) Anti- α_1 action

The thoracic aorta of each Hartley male guinea pig (body weight: 300-500 g) was excised. A sample cut in a helical form was suspended under 1 g load in a Magnus cylinder filled with the Tyrode solution of 37°C which had been saturated with a mixed gas consisting of 95% O₂ + 5% CO₂. Using an isometric transducer ("TB-612J"/NIHON KOHDEN) and a pressure preamplifier ("AP-620G"/NIHON KOHDEN), variations in tension were measured. The measurement results were recorded on a thermal pen-writing recorder ("WT-647G"/NIHON KOHDEN).

Taking the tonic contraction induced by 10⁻⁵ M norepinephrine (NE) as 100%, the percent contractions upon addition of each test drug at 10⁻⁸ and 10⁻⁷ M were determined as anti- α_1 action.

(2) Anti-serotonin action (anti-5-HT action)

The superior mesenteric artery of each Hartley male guinea pig (body weight: 300-500 g) was excised. A sample cut in a helical form was suspended under

0.3 g load in a Magnus cylinder filled with the Tyrode solution of 37°C which had been saturated with a mixed gas consisting of 95% O₂ + 5% CO₂. Using an isometric transducer ("UL-10"/SHINKOH K.K.) and a pressure
5 preamplifier ("DSA-605A"/SHINKOH K.K.), variations in tension were measured. The measurement results were recorded on a pen-writing recorder ("VP-6537A"/NATIONAL K.K.). Taking the contraction induced by 10⁻⁵ M serotonin (5-HT) as 100%, the percent contractions in
10 the presence of each test drug at 10⁻⁷ and 10⁻⁶ M were determined as anti-5-HT action.

15

20

25

(Results)

Comp'd No.	Anti α_1 action (% of Control)		Anti 5-HT action (% of Control)	
	$10^{-8}M$	$10^{-7}M$	$10^{-7}M$	$10^{-6}M$
18*	100.0	85.5	52.8	16.3
19*	100.0	90.1	60.3	12.4
39	99.3	80.5	34.3	8.7
40	100.0	94.5	24.2	12.5
43	73.3	37.9	43.1	8.7
45	79.8	23.8	11.2	-
46	78.7	28.0	59.5	12.8
47	100.0	81.9	5.2	-
48	98.9	60.5	52.8	5.1
50	57.6	38.8	60.0	18.4
52	97.2	62.6	39.1	9.9

* The test compound was obtained by converting the compound to its hydrochloride with excess hydrogen chloride in an organic solvent and, if necessary, subjecting the hydrochloride to recrystallization.

(3) Anti-platelet-aggregating action

Blood was drawn from the auricular artery of Japanese white house rabbit (male, about 3 kg), whereby a platelet rich plasma sample (PRP) was prepared. Platelet aggregating ability was measured using a platelet aggregation measuring

apparatus ("PAM-8C"/MEBANIX).

Found under the presence of 1 mM of CaCl₂ was a controlling action of the test drug (10⁻⁷ M) against the maximum reaction (100%) of the platelet aggregation induced by 10⁻⁶ M of ADP + 10⁻⁵ M of 5-HT.

5

(Results)

Compound No.	Inhibitory rate of platelet aggregation (%)
39	33
43	18
45*	30
47	34
Ketanserin tartrate	20

* The test compound was obtained by converting the compound to its hydrochloride with excess hydrogen chloride in an organic solvent and, if necessary, subjecting the hydrochloride to recrystallization.

Industrial Applicability

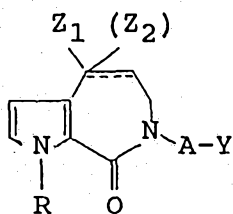
The pyrroloazepine compounds according to the present invention are drugs having excellent anti-serotonin action. Coupled with their high safety, they can therefore be used as novel therapeutics for ischemic heart diseases.

10

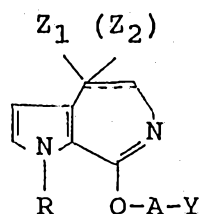
Particularly, these compounds according to the present invention include those having strong anti- α_1 action in addition to the excellent anti-serotonin action. Such compounds are effective as hypotensive drugs. Pyrroloazepine compounds according to the present invention are therefore useful as therapeutics for various circulatory diseases.

CLAIMS

1 1. A pyrroloazepine compound represented by
2 the following formula (I) or (II):



(I)



(II)

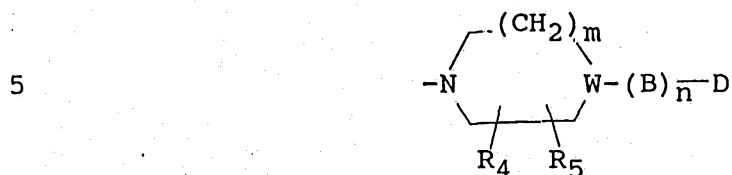
4 wherein the dashed line indicates the presence or
5 absence of a bond and when the bond indicated by
6 the dashed line is present, Z₁ represents a
7 hydrogen atom but, when the bond indicated by the
8 dashed line is absent, Z₁ represents a hydrogen
9 atom and Z₂ represents a hydroxyl group or Z₁ and
10 Z₂ are taken together to form an oxygen atom or a
11 group NOR₁, in which R₁ represents a hydrogen
12 atom, an alkyl group, a substituted or un-
13 substituted aryl group or a substituted or un-
14 substituted aralkyl group; R represents an alkyl
15 group, a cycloalkyl group, a cycloalkyl-alkyl
16 group, a substituted or unsubstituted aryl group,
17 or a substituted or unsubstituted aralkyl group; A
18 represents an alkylene, alkenylene or alkynylene
19 group; and Y represents a substituted or un-

20 substituted heterocyclic group or a group:



22 in which R₂ and R₃ may be the same or different
23 and individually represent a hydrogen atom, an
24 alkyl group which may be substituted by a lower
25 alkoxy group or a substituted or unsubstituted
26 aryloxy group, a substituted or unsubstituted aryl
27 group or a substituted or unsubstituted aralkyl
28 group; or a salt thereof.

1 2. A pyrroloazepine compound or a salt
2 thereof according to claim 1, wherein in the for-
3 mula (I) or (II), Y represents a heterocyclic
4 group represented by the following formula:



6 in which R₄ and R₅ may be the same or different
7 and individually represent a hydrogen atom or an
8 alkyl group; W represents a group C-R₆, in which
9 R₆ represents a hydrogen atom or an alkyl group,
10 or a nitrogen atom and when W represents C-R₆, m
11 stands for 0, 1 or 2, B represents an oxygen atom,
12 a sulfur atom, a carbonyl group, a sulfinyl group,
13 a sulfonyl group, an alkylene group, an alkenylene

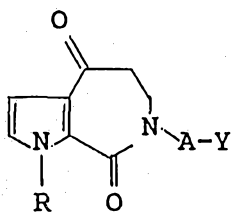
14 group, a substituted or unsubstituted phenyl-
15 methylene group, a substituted or unsubstituted
16 hydroxymethylene group or a substituted or un-
17 substituted, cyclic or noncyclic acetal group but,
18 when W represents a nitrogen atom, m stands for 1
19 or 2, B represents a carbonyl group, a sulfonyl
20 group, an alkylene group, an alkenylene group or a
21 substituted or unsubstituted phenylmethylene
22 group; n stands for 0 or 1; and D represents a
23 substituted or unsubstituted aryl group or sub-
24 stituted or unsubstituted aromatic heterocyclic
25 group.

1 3. A pyrroloazepine compound or a salt
2 thereof according to claim 1, wherein in the for-
3 mula (I) or (II), Z_1 and Z_2 are taken together to
4 form an oxygen atom or a group NOR_1 , in which R_1
5 has the same meaning as defined above.

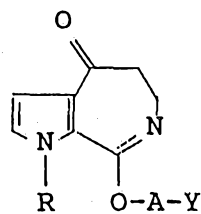
1 4. A pyrroloazepine compound or a salt
2 thereof according to claim 1, wherein in the for-
3 mula (I) or (II), Y represents a substituted or
4 unsubstituted piperidinyl or piperazinyl group.

1 5. A process for the preparation of a
2 pyrroloazepine compound represented by the follow-
3 ing formula (Ia) or (IIa):

4



(Ia)



(IIa)

5

wherein A, R and Y have the same meanings as defined above, which comprises:

6

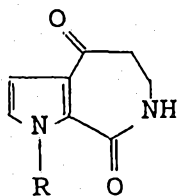
7

reacting a compound represented by the fol-

8

lowing formula (III):

9



(III)

10

wherein R has the same meaning as defined above

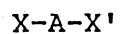
11

with a compound represented by the following for-

12

mula (IV):

13



(IV)

14

wherein A has the same meanings as defined above

15

and X and X' may be the same or different and in-

16

dividually mean a substituent easily replaceable

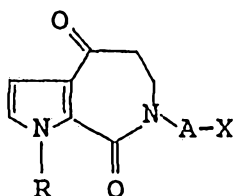
17

with an amino group, thereby obtaining a compound

18

represented by the following formula (V):

19



(V)

20

wherein A, R and X have the same meanings as

21

defined above; and then

22

reacting the compound of the formula (V)

23

with a nitrogen-containing compound represented by

24

the following formula (VI):

25



26

wherein Y has the same meaning as defined above.

1

6. A process for the preparation of a

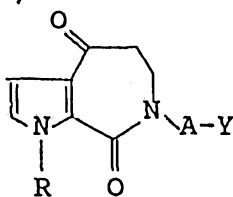
2

pyrroloazepine compound represented by the follow-

3

ing formula (Ia):

4



(Ia)

5

wherein A, R and Y have the same meanings as

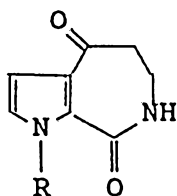
6

defined above, which comprises reacting a compound

7

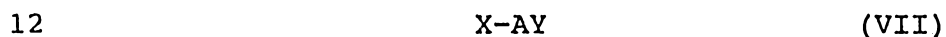
represented by the following formula (III):

8



(III)

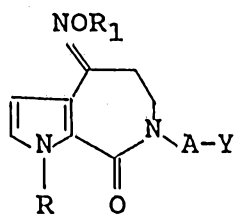
9 wherein R has the same meaning as defined above
10 with a compound represented by the following for-
11 mula (VII):



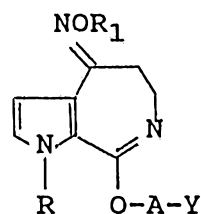
13 wherein A, X and Y have the same meanings as
14 defined above.

1 7. A process for the preparation of a
2 pyrroloazepine derivative represented by the fol-
3 lowing formula (Ib) or (IIb):

4



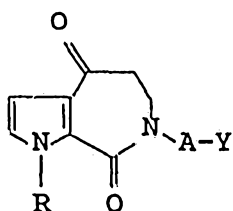
(Ib)



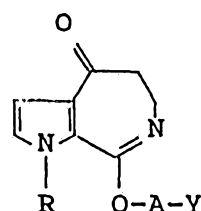
(IIb)

5 wherein A, R, R₁ and Y have the same meanings as
6 defined above, which comprises reacting a pyr-
7 roloazepine compound represented by the following
8 formula (Ia) or (IIa):

9



(Ia)



(IIa)

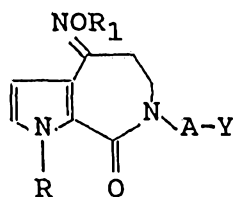
10 wherein A, R and Y have the same meanings as
11 defined above with hydroxylamine or a derivative
12 thereof, which is represented by the following
13 formula (VIII):



15 wherein R_1 has the same meaning as defined above.

1 8. A process for the preparation of a pyr-
2 roloazepine compound represented by the following
3 formula (Ib):

4



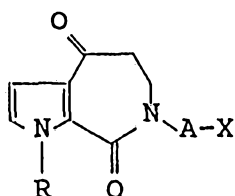
(Ib)

5 wherein A, R, R_1 and Y have the same meanings as
6 defined above, which comprises:

7 causing hydroxylamine or a derivative there-
8 of, which is represented by the following formula
9 (VIII):

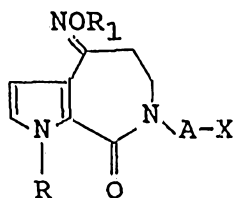


11 wherein R₁ has the same meaning as defined above,
12 to act on a compound represented by the following
13 formula (V):



(V)

15 wherein A, R and X have the same meanings as
16 defined above to obtain a compound represented by
17 the following formula (IX):



(IX)

19 wherein A, R, R₁ and X have the same meanings as
20 defined above; and then

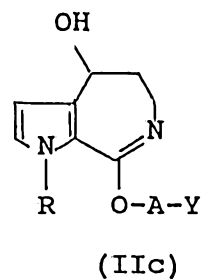
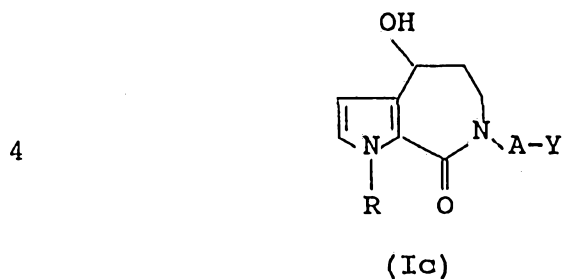
21 reacting the compound of the formula (IX)
22 with a nitrogen-containing compound represented by
23 the following formula (VI):



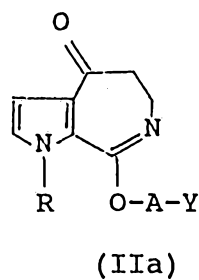
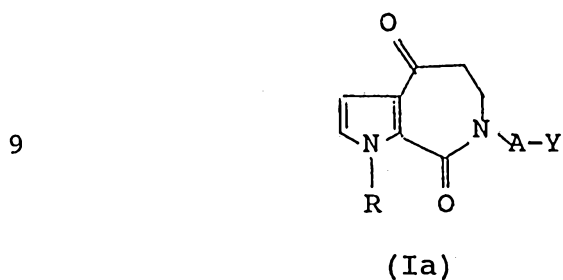
25 wherein Y has the same meaning as defined above.

26 9. A process for the preparation of a

2 pyrroloazepine derivative represented by the fol-
3 lowing formula (Ic) or (IIc):



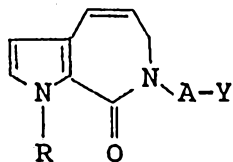
5 wherein A, R and Y have the same meanings as
6 defined above, which comprises reducing a pyr-
7 roloazepine compound represented by the formula
8 (Ia) or (IIa):



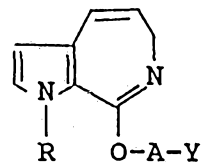
10 wherein A, R and Y have the same meanings as
11 defined above.

1 10. A process for the preparation of a pyr-
2 roloazepine compound represented by the following
3 formula (Id) or (IIId):

4



(Id)



(IIId)

5

wherein A, R and Y have the same meanings as

6

defined above, which comprises subjecting to

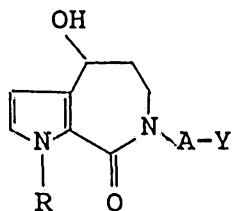
7

dehydration a pyrroloazepine compound represented

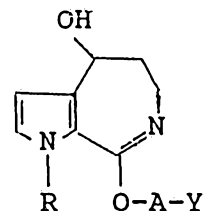
8

by the following formula (Ic) or (IIc):

9



(Ic)



(IIc)

10

wherein A, R and Y have the same meanings as

11

defined above.

1

11. An intermediate suitable for use in the

2

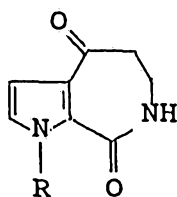
production of a pharmaceutical product, said in-

3

termediate being represented by the following for-

4

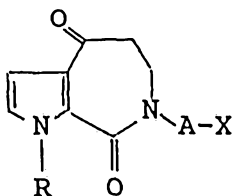
mula (III):



(III)

6 wherein R has the same meanings as defined above.

1 12. An intermediate suitable for use in the
2 production of a pharmaceutical product, said in-
3 termediate being represented by the following for-
4 mula (V):

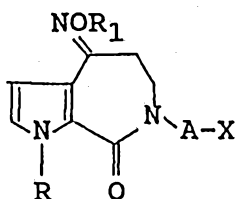


(V)

6 wherein A, R and X have the same meanings as
7 defined above.

1 13. An intermediate suitable for use in the
2 production of a pharmaceutical product, said in-
3 termediate being represented by the following for-
4 mula (IX):

5



(IX)

6

wherein A, R, R₁ and X have the same meanings as defined above.

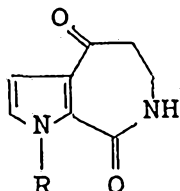
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1

14. A process for the preparation of a pyrroloazepine compound represented by the following formula (III):

2

3



4

(III)

5

wherein R has the same meaning as defined above, which comprises:

6

7

causing β -alanine or a derivative thereof,

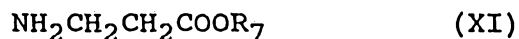
8

which is represented by the following formula

9

(XI):

10



11

wherein R₇ represents a hydrogen atom or a

12

carboxyl-protecting group, to act on a 1-

13

substituted pyrrole-2-carboxylic acid or a deriva-

14 tive thereof, which is represented by the follow-
15 ing formula (X):



(X)

17 wherein R has the same meaning as defined above
18 and Q represents a hydroxyl group or an elimina-
19 tive substituent easily replaceable with an amino
20 group, thereby forming a compound represented by
21 the following formula (XII):



(XII)

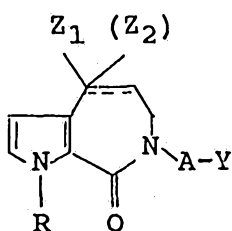
23 wherein R and R₇ have the same meanings as defined
24 above; and

25 subjecting the compound of the formula (XII)
26 to ring closure.

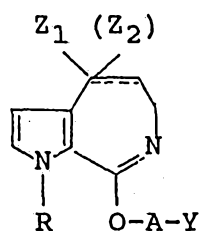
1 15. A therapeutic for circulatory diseases,
2 comprising as an active ingredient a pyr-
3 roloazepine derivative (I) or (II) or a salt
4 thereof as described in claim 1.

ABSTRACT

This invention provides a pyrroloazepine compound represented by the following formula (I) or (II):

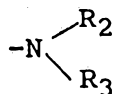


(I)



(II)

5 wherein, when the bond indicated by the dashed line is present, Z₁ represents H but, when the bond indicated by the dashed line is absent, Z₁ represents H and Z₂ represents OH or Z₁ and Z₂ are taken together to represent O or a group NOR₁, in
10 which R₁ represents H or an alkyl, aryl or aralkyl group; R represents an alkyl, cycloalkyl, cycloalkyl-alkyl, aryl, or aralkyl group; A represents an alkylene, alkenylene or alkynylene group; and Y represents a substituted or un-
15 substituted heterocyclic group or a group:



in which R₂ and R₃ represent H or an alkyl, lower-alkoxy- or aryloxy-substituted alkyl, aryl or

aralkyl group; or a salt thereof; a preparation
20 process thereof; and a therapeutic for circulatory
diseases, said therapeutic containing as active
ingredient the pyrroloazepine compound or the salt
thereof.

25 The pyrroloazepine compounds according to
the present invention are drugs having excellent
anti-serotonin action. Coupled with their high
safety, they can therefore be used as novel
therapeutics for ischemic heart diseases. In ad-
30 dition, the compounds of the present invention in-
clude those having anti- α_1 action. Such compounds
are effective as hypotensive drugs. Pyrrolo-
azepine compounds according to the present inven-
tion are therefore extremely useful as
35 therapeutics for a wide variety of circulatory
diseases.

