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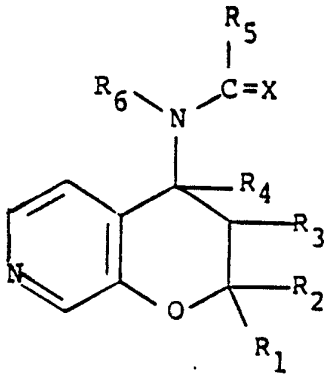
(54) Title: PYRANO (3,2-c) PYRIDINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)

(57) Abstract

Compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein, R_1 is hydrogen or alkyl; R_2 is alkyl or R_1 and R_2 are polymethylene; R_3 is hydrogen, hydroxy, alkoxy, acyloxy; R_4 is hydrogen or R_3 and R_4 are a bond; R_5 is hydrogen, optionally substituted alkyl, alkenyl, optionally substituted amino, optionally substituted aryl or heteroaryl, carboxy, alkoxycarbonyl or aminocarbonyl; R_6 is hydrogen or alkyl or R_5 and R_6 together are $-CH_2-(CH_2)_n-Z-(CH_2)_m-$, wherein m and n are 0 to 2, m + n is 1 or 2, Z is CH_2, O, S, NR; R is hydrogen, alkyl, alkanoyl, phenyl-alkyl, naphthycarbonyl, phenylcarbonyl, benzylcarbonyl, or heteroarylcarbonyl; X is O, S or R_5, R_6, X and N together are tetrahydroisoquinolinone or tetrahydroisoquinolinthione. These compounds show anti-hyper tensive activity.

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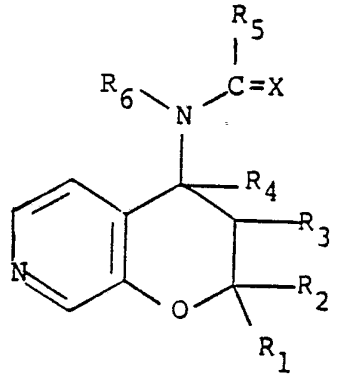
Pyrano (3,2-c) pyridine derivatives, process for their preparation and pharmaceutical compositions containing them.

The present invention relates to novel pyranopyridines having pharmacological activity, to a process and intermediates for preparing them, to pharmaceutical compositions containing them, and to their use in the treatment of mammals.

European Patent Publications 76075, 91748, 93535, 95316, 107423, 120426, 120427, 126311 and 126367 disclose classes of compounds that are described as having blood pressure lowering activity or anti-hypertensive activity.

A structurally distinct class of compounds has now been discovered which are [2,3-c]pyranopyridines substituted in the 4-position by a cyclic or acyclic amide, the nitrogen atom of the amide moiety being bonded directly to the carbon atom in the 4-position. Such pyranopyridines have been found to have blood pressure lowering activity, useful in the treatment of hypertension. In addition, these compounds are believed to be K^+ channel activators which indicates that they are of potential use in the treatment of disorders associated with smooth muscle contraction of the gastro-intestinal tract, respiratory system, uterus or urinary tract. Such disorders include peptic ulcers, irritable bowel syndrome and diverticular disease, reversible airways obstruction and asthma; premature labour; and incontinence. They are also indicated as of potential use in the treatment of cardiovascular disorders other than hypertension, such as congestive heart failure, angina, peripheral vascular disease and cerebral vascular disease.

Accordingly, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

one of R_1 and R_2 is hydrogen or C_{1-4} alkyl and tne other is C_{1-4} alkyl or R_1 and R_2 together are C_{2-5} polymethylene;

either R_3 is hydrogen, hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy and R_4 is hydrogen or R_3 and R_4 together are a bond;

R_5 is hydrogen; C_{1-6} alkyl optionally substituted by up to three halo atoms, by hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, or amino optionally substituted by one or two independent C_{1-6} alkyl groups or disubstituted by C_{4-5} polymethylene; C_{2-6} alkenyl; amino optionally substituted by a C_{1-6} alkyl or C_{1-6} alkenyl group or by a C_{1-6} alkanoyl group optionally substituted by up to three halo atoms, by a phenyl group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen; or aryl or heteroaryl, either being optionally substituted by one or more groups or atoms selected from the class of C_{1-6} alkyl, C_{1-6} alkoxy,

hydroxy, halogen, trifluoromethyl, nitro, cyano, C_{1-12} carboxylic acyl, or amino or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups; or (when X is O), R_5 is selected from the class of carboxy, C_{1-6} alkoxycarbonyl, or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups; and

R_6 is hydrogen or C_{1-6} alkyl; or

R_5 and R_6 together are $-CH_2-(CH_2)_n-Z-(CH_2)_m-$ wherein m and n are 0 to 2 such that m + n is 1 or 2 and Z is CH_2, O, S or NR wherein R is hydrogen, C_{1-9} alkyl, C_{2-7} alkanoyl, phenyl C_{1-4}-alkyl, naphthylcarbonyl, phenylcarbonyl or benzyl-carbonyl optionally substituted in the phenyl or naphthyl ring by one or two of C_{1-6} alkyl, C_{1-6} alkoxy or halogen; or R is heteroarylcarbonyl;

X is oxygen or sulphur; or

R_5, R_6, X and N together are tetrahydroisoquinolinone or tetrahydroisoquinolin-thione optionally substituted in the phenyl ring as defined for R above;

the nitrogen-containing group in the 4-position being trans to the R_3 group when R_3 is hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy.

Preferably, R_1 and R_2 are both C_{1-4} alkyl, in particular both methyl.

When R_3 is C_{1-6} alkoxy and R_4 is hydrogen, preferred examples of R_3 include methoxy and ethoxy, of which methoxy is more preferred. When R_3 is C_{1-7} acyloxy and R_4 is hydrogen, a preferred class of R_3 is

unsubstituted carboxylic acyloxy, such as unsubstituted aliphatic acyloxy. However, it is more preferred that R_3 and R_4 together are a bond, or that R_3 and R_4 are both hydrogen, or, in particular, that R_3 is hydroxy and R_4 is hydrogen.

Examples of R_5, when C_{1-6} alkyl, include methyl, ethyl and n- and iso-propyl. Preferably such R_5 is methyl.

A sub-group of R_5, when C_{1-6} alkyl substituted by halogen is C_{1-6} alkyl substituted by fluoro, chloro or bromo. Examples thereof include methyl or ethyl terminally substituted by one, two or three fluoro, chloro or bromo.

Examples of R_5, when C_{1-6} alkyl substituted by hydroxy, include methyl or ethyl terminally substituted by hydroxy.

A sub-group of R_5, when C_{1-6} alkyl substituted by C_{1-6} alkoxy is C_{1-6} alkyl substituted by methoxy or ethoxy. Examples thereof include methyl or ethyl terminally substituted by methoxy or ethoxy.

A sub-group of R_5, when C_{1-6} alkyl substituted by C_{1-6} alkoxycarbonyl is C_{1-6} alkyl substituted by methoxycarbonyl or ethoxycarbonyl. Examples thereof include methyl or ethyl terminally substituted by methoxycarbonyl or ethoxycarbonyl.

Examples of R_5, when C_{1-6} alkyl substituted by carboxy include methyl or ethyl terminally substituted by carboxy.

Examples of R_5 when alkyl substituted by amino optionally substituted by one or two independent C_{1-6}

alkyl groups include a group $(CH_2)_nNR_9R_{10}$ where n is 1 to 6, and R_9 and R_{10} are each independently hydrogen or C_{1-6} alkyl or together are C_4 or C_5 polymethylene. Examples of n include 1 and 2, in particular 1. Preferably R_9 and R_{10} are each independently selected from hydrogen and methyl.

Examples of R_5, when C_{2-6} alkenyl include vinyl, prop-1-enyl, prop-2-enyl, 1-methylvinyl, but-1-enyl, but-2-enyl, but-3-enyl, 1-methylenepropyl, or 1-methylprop-2-enyl, in both their E and Z forms where stereoisomerism exists.

Examples of R_5 when amino optionally substituted as hereinbefore defined include an amino optionally substituted by a methyl, ethyl, propyl, butyl, allyl or trichloroacetyl group or by a phenyl group optionally substituted by one methyl, methoxy or chloro group or atom, in particular amino, methylamino, and phenylamino optionally substituted in the phenyl ring by one methyl, methoxy or chloro group or atom.

Examples of R_5 when aryl include phenyl and naphthyl, of which phenyl is preferred.

A sub-group of R_5 heteroaryl or heteroaryl for an R moiety in Z, is 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaryl of which 5- or 6-membered monocyclic heteroaryl is preferred. In addition, 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaryl preferably contains one, two or three heteroatoms which are selected from the class of oxygen, nitrogen and sulphur and which, in the case of there being more than one heteroatom, are the same or different.

Examples of 5- or 6-membered monocyclic heteroaryl containing one, two or three heteroatoms which are selected from the class of oxygen, nitrogen and sulphur include furyl, thienyl, pyrryl, oxazolyl, thiazolyl, imidazolyl and thiadiazolyl, and pyridyl, pyridazyl, pyrimidyl, pyrazyl and triazyl. Examples of such groups include furanyl, thienyl, pyrryl and pyridyl, in particular 2- and 3-furyl, 2- and 3-pyrryl, 2- and 3-thienyl, and 2-, 3- and 4-pyridyl.

Examples of 9- or 10-membered bicyclic heteroaryl containing one, two or three heteroatoms which are selected from the class of oxygen, nitrogen and sulphur include benzofuranyl, benzothienyl, indolyl and indazolyl, quinolyl and isoquinolyl, and quinazonyl. Preferred examples of such groups include 2- and 3-benzofuryl, 2- and 3-benzothienyl, and 2- and 3-indolyl, and 2- and 3-quinolyl.

Preferably, the number of groups or atoms for optional substitution of aryl or heteroaryl is one, two, three or four.

Preferred examples of the groups or atoms for optional substitution of aryl or heteroaryl include methyl, methoxy, hydroxy, chloro, fluoro, nitro or cyano, most preferably fluoro.

A sub-group of R_5 is phenyl or naphthyl or a 5- or 6-membered monocyclic or a 9- or 10-membered bicyclic heteroaryl, the phenyl, naphthyl or heteroaryl group being optionally substituted by one, two, three or four groups or atoms selected from the class of C_{1-6} alkyl, C_{1-6} alkoxy, halogen, trifluoromethyl, nitro or cyano.

A preferred subgroup of phenyl optionally substituted as hereinbefore defined is phenyl, 4-substituted phenyl, 3-substituted phenyl, 2-substituted phenyl, 2,4, 2,6 and 3,4-disubstituted phenyl and 3,4,5-trisubstituted phenyl.

A preferred sub-group of 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaryl optionally substituted as hereinbefore defined is unsubstituted or mono-substituted 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaryl, in particular unsubstituted 5- or 6-membered monocyclic or 9- or 10-membered bicyclic heteroaryl.

When X is O, examples of R_5 also include carboxyl, methoxycarbonyl, ethoxycarbonyl, aminocarbonyl, methylamino-carbonyl and dimethylaminocarbonyl.

R_5 and R_6, when together are $-CH_2-(CH_2)_n-Z-(CH_2)_m-$ as defined the resulting radical substituting the pyranopyridine in the 4-position is preferably either pyrrolidonyl or piperidonyl. Other examples of 4-substituents when R_5 and R_6 are joined together include those described in EP-A-107423.

When Z is other than CH_2, m is often 0 or 1 and n is often 0 or 1. Suitable examples of R when Z is NR include hydrogen, methyl, ethyl, n- and iso-propyl, n-, sec- and tert- butyl, benzyl, phenylcarbonyl or benzylcarbonyl optionally substituted in the phenyl ring by methyl, methoxy, chloro or bromo; furylcarbonyl, thienylcarbonyl, pyrrolylcarbonyl or indolylcarbonyl. Preferably R is hydrogen, methyl, n-butyl, acetyl, benzyl, benzylcarbonyl, phenylcarbonyl or furylcarbonyl. Most preferably R is hydrogen.

Preferred examples of R_5 and R_6 are R_5 is methyl or halophenyl, such as 2- or 4-fluorophenyl and R_6 hydrogen and R_5 and R_6 together are C_3 or C_4 polymethylene.

Preferably, X is oxygen.

Examples of a pharmaceutically acceptable salt of a compound of formula (I), when the compound contains a salifiable substituent which is an optionally substituted amino group, include acid addition salts such as the hydrochloride and hydrobromide salts. Such a salifiable group may be within an R_5 group. A carboxy group within R_5 may also be salified to form metal salts, such as alkali metal salts, or optionally substituted ammonium salts.

It will also be appreciated that the pyridine in the compound of formula (I) is also salifiable, to give pyridine salts with acids, such as those with HCl and HBr. Alternatively, internal salts such as the N-Oxide may be formed by per-acid oxidation of the corresponding compound of formula (I).

The compounds of formula (I) may also exist as solvates such as hydrates and the invention extends to these; such solvates are included wherever a compound of formula (I) is herein referred to.

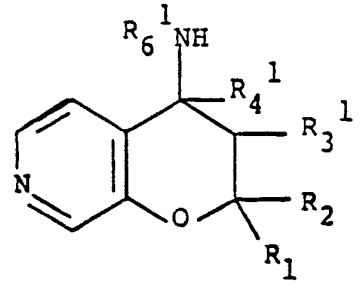
The compounds of formula (I), wherein R_3 is hydrogen, hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy and R_4 is hydrogen, are asymmetric, and, therefore, can exist in the form of optical isomers.

The present invention extends to all such isomers individually and as mixtures, such as racemates.

Examples of compounds of formula (I) include the compounds prepared in the Examples hereinafter.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises;

i) acylating a compound of formula (II) or an N-oxide thereof:



(II)

wherein, R_1 and R_2 are as hereinbefore defined, R_3^1 is hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy, and R_6^1 is hydrogen or C_{1-6} alkyl, the R_6^1NH group being <u>trans</u> to the R_3^1 group,

a) with an acylating agent of formula (III):

$$R_8\text{-}CO\text{-}L_1 \qquad \text{(III)}$$

wherein L_1 is a leaving group, and R_8 is hydrogen, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl optionally substituted by halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy or amino optionally substituted as hereinbefore defined for R_5, C_{2-6} alkenyl or optionally substituted aryl or heteroaryl as hereinbefore defined for R_5, or a group

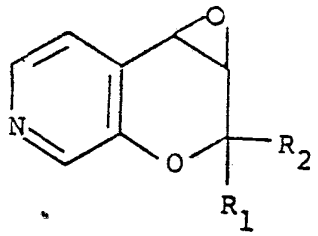
convertible to R_5 as hereinbefore defined, and thereafter, when R_6 is hydrogen and R_8 is $Y(CH_2)_z$, where z is 3 or 4 and Y is a leaving group, cyclising the resultant compound;

b) with a compound of formula (IV)

$$X=C=N.R_{11} \qquad (IV)$$

wherein R_{11} is hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkanoyl optionally substituted by up to three halo atoms, or phenyl optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen; and X is oxygen or sulphur, and thereafter when R_{11} is hydrogen, optionally converting R_{11}; or

ii) where, in the resultant compound of formula (I), R_5 and R_6 are joined together or R_5 is aminocarbonyl, reacting a compound of formula (V) or an N-oxide thereof:



(V)

wherein R_1 and R_2 are as hereinbefore defined, with a compound of formula (VI):

$$R_{13}NHCOR_{12} \qquad (VI)$$

wherein R_{13} is R_6 as defined and R_{12} is aminocarbonyl; R_{12} and R_{13} together are $-CH_2-(CH_2)_n-Z-(CH_2)_m-$ or $R_{13}NHCOR_{12}$ is tetrahydroisoquinolinone;

optionally converting R_3 in the resulting compound into another R_3; in the case where R_3 and R_4 in the resulting compound are hydroxy and hydrogen respectively, optionally dehydrating the compound to give another compound wherein R_3 and R_4 together are a bond, and optionally reducing the resulting compound wherein R_3 and R_4 together are a bond, to give another compound, wherein R_3 and R_4 are each hydrogen; and optionally thiating the R_6-N-CO-R_5 group in the resulting compound to give a compound wherein X is sulphur; and optionally forming a pharmaceutically acceptable salt thereof.

In the process variant i) a) acylation of a compound of formula (II) with an acylating agent of formula (III), the leaving group L_1 is a group that is displaceable by a primary or secondary amino nucleophile. Examples of such a group include C_{1-4} alkanoyloxy, and halogen, such as chloro and bromo or hydroxy. When the leaving group L_1 is either of these examples, the acylating agent of formula (III) is either an acid anhydride or an acid halide. When it is an acid anhydride, it may be a mixed or simple anhydride. If it is a mixed annydride, it may be prepared in situ from a carboxylic acid and an acid halide, although this is less preferred than using the halide itself. When L_1 is hydroxy, conventional coupling methods using dicyclohexylcarbodiimide are suitable.

In process variant i) a), when R_5 in the desired compound of formula (I) is an R_5 optionally substituted amino-substituted alkyl group as hereinbefore defined, it is preferred that R_8 is a group convertible to the R_5 substituted alkyl group as hereinbefore defined, in particular that it is C_{1-6} alkyl substituted by halo, especially bromo. The R_8 halo substituent in the

resultant compound of process variant i) a) may be converted to an R_5 substituent which is amino optionally substituted as hereinbefore defined by a conventional amination reaction with ammonia or a corresponding alkyl- or dialkylamine. When R_8 is C_{1-6}alkoxycarbonyl, this may be converted to R_5 is carboxy by conventional hydrolysis.

Less favourably R_8 may be C_{1-6} alkyl substituted by protected amino, protected C_{1-6} alkylamino or amino substituted by two independent C_{1-6} alkyl groups, it being necessary to protect the R_8 amino function in process variant i) a).

When the acylating agent of formula (III) is an acid anhydride, the acylation of the compound of formula (II) may be carried out in the presence of an acid acceptor, such as sodium acetate, optionally using the anhydride as the solvent.

When the acylating agent of formula (III) is an acid halide, the acylation of the compound of formula (II) is, preferably, carried out in a non-aqueous medium, such as dichloromethane, in the presence of an acid acceptor, such as triethylamine, trimethylamine, or calcium, potassium or sodium carbonate.

When the acylating agent of formula (III) is an acid the acylation of a compound of formula (II) is conveniently performed in the presence of a dehydrating agent, such as dicyclohexyldicarbodiimide in an inert solvent, such as dimethylformamide at a temperature of $0^{o}C$ to ambient.

When R_3^1 in a compound of formula (II) is hydroxy, there is a risk of a side-reaction between the

hydroxy group and the acylating agent of formula (III). However, the reaction may be carried out under controlled conditions such that only the amine, R_6^1NH- is acylated, for example, by using a C_{2-9} acyloxy group as the leaving group L_1, in the acylating agent of formula (III) in the manner as previously described for an acid anhydride, and/or effecting the reaction at relatively low temperature, e.g. at below 10°C. Alternatively R_3^1 may be C_{1-7} acyloxy in a compound of formula (II), although less preferably if R_3 in the resultant compound of formula (I) is to be hydroxy, and, after reaction with the acylating agent of formula (III), be converted into hydroxy, as described hereinafter.

When R_8 is $Y(CH_2)_z$ where the variables are as hereinbefore defined, the leaving group Y is a group that is displaceable by a secondary amino nucleophile adjacent to a carbonyl function. A preferred example is chloro.

The cyclisation reaction when R_8 is $Y(CH_2)_z$ where the variables are as hereinbefore defined is preferably carried out in an inert solvent such as dimethylformamide.

In process variant i) b), when R_{11} in a compound of formula (IV) is C_{1-6} alkyl, C_{1-6} alkanoyl optionally substituted as hereinbefore defined, or phenyl optionally substituted as hereinbefore defined, the reaction between the compounds of formulae (II) and (IV) is, preferably, carried out in a solvent, such as methylene chloride, at below room temperature, in particular below 10°C.

When R_{11} is hydrogen, the reaction between the compounds of formulae (II) and (IV) is, preferably, carried out using a corresponding alkali metal cyanate or thiocyanate, for example that of sodium or potassium, in an optionally methanolic aqueous medium acidified with a mineral acid, such as dilute hydrochloric acid. A slightly elevated temperature such as 50 to 90°C is apt.

In the process variant ii) reaction of a compound of formula (V) with a compound of formula (VI), it is particularly preferred that the reaction is carried out under basic conditions so as to facilitate the formation of the anion of the compound of formula (VI), for example, in the presence of sodium hydride.

The reaction of the compounds of formulae (II) with (III) or (IV) results in a compound of formula (I) wherein R_3 is hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy, whereas the reaction of the compounds of formulae (V) and (VI) results in a compound of formula (I) wherein R_3 is hydroxy. Examples of an optional conversion of R_3 in a compound of formula (I) into another R_3 are generally known in the art. For example, when R_3 is hydroxy, it may be alkylated using an alkyl iodide in an inert solvent, such as toluene, in the presence of a base, such as potassium hydroxide, or it may be acylated using a carboxylic acid chloride or annydride in a non-hydroxylic solvent in the presence of an acid acceptor. Alternatively, when R_3 is C_{1-7} acyloxy or C_{1-6} alkoxy, it may be converted into hydroxy by conventional hydrolysis or dealkylation respectively.

The optional denydration of the resulting compound of formula (I), wherein R_3 and R_4 are hydroxy and hydrogen respectively, into another compound of formula (I),

wherein R_3 and R_4 together are a bond, may be carried out under conventional dehydration conditions, for example, by using a dehydrating agent, such as sodium hydride, in an inert solvent, such as dry tetrahydrofuran, at reflux temperature.

The optional reduction of the resulting compound of formula (I), wherein R_3 and R_4 together are a bond, into another compound of formula (I), wherein R_3 and R_4 are each hydrogen, may be carried out by hydrogenation using a catalyst of palladium on charcoal.

The optional thiation of the R_6-N-CO-R_5 group in a compound of formula (I) to give another compound of formula I, wherein X is sulphur, is, preferably, carried out with conventional thiation agents, such as hydrogen sulphide, phosphorus pentasulphide and Lawesson's reagent (p-methoxyphenylthiophosphine sulphide dimer). The use of hydrogen sulphide and phosphorus pentasulphide may lead to side-reactions and, therefore, the use of Lawesson's reagent is preferred.

The thiation reaction conditions are conventional for the thiation agent employed. For example, the use of hydrogen sulphide is, preferably, acid catalysed by, for example, hydrogen chloride in a polar solvent, such as acetic acid or ethanol. The preferred use of Lawesson's reagent is, preferably, carried out under reflux in a dry solvent, such as toluene or methylene chloride.

The optional formation of a pharmaceutically acceptable salt may be carried out conventionally. It should be appreciated that formation of an N-Oxide by oxidation may affect other substituents and appropriate

modification of reaction conditions and/or protection will be taken where necessary.

A compound of formula (II) may be prepared by reacting a compound of formula (V), or an N-oxide thereof, as hereinbefore defined, with a compound of formula (VII):

$$R_6^1NH_2 \qquad (VII)$$

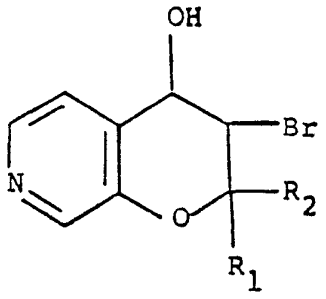
wherein R_6^1 is as hereinbefore defined; and optionally converting R_3^1 hydroxyl in the resulting compound of formula (II) into another R_3^1.

The reaction is normally carried out in a solvent, such as a C_{1-4} alcohol, in particular methanol, ethanol or propanol at an ambient or an elevated temperature, for example 12 to 100°C. The reaction proceeds particularly smoothly if carried out in ethanol under reflux.

The resulting compound of formula (II) may be removed from the reaction mixture by removal of the solvent, for example, by evaporation under reduced pressure. Any epoxide impurity may be removed conventionally, for example by chromatography.

The optional conversion of the hydroxy group for R_3^1 in the resulting compound of formula (II) into a C_{1-6} alkoxy or C_{1-7} acyloxy group may be carried out as hereinbefore described in relation to the corresponding conversion of R_3 in a compound of formula (I).

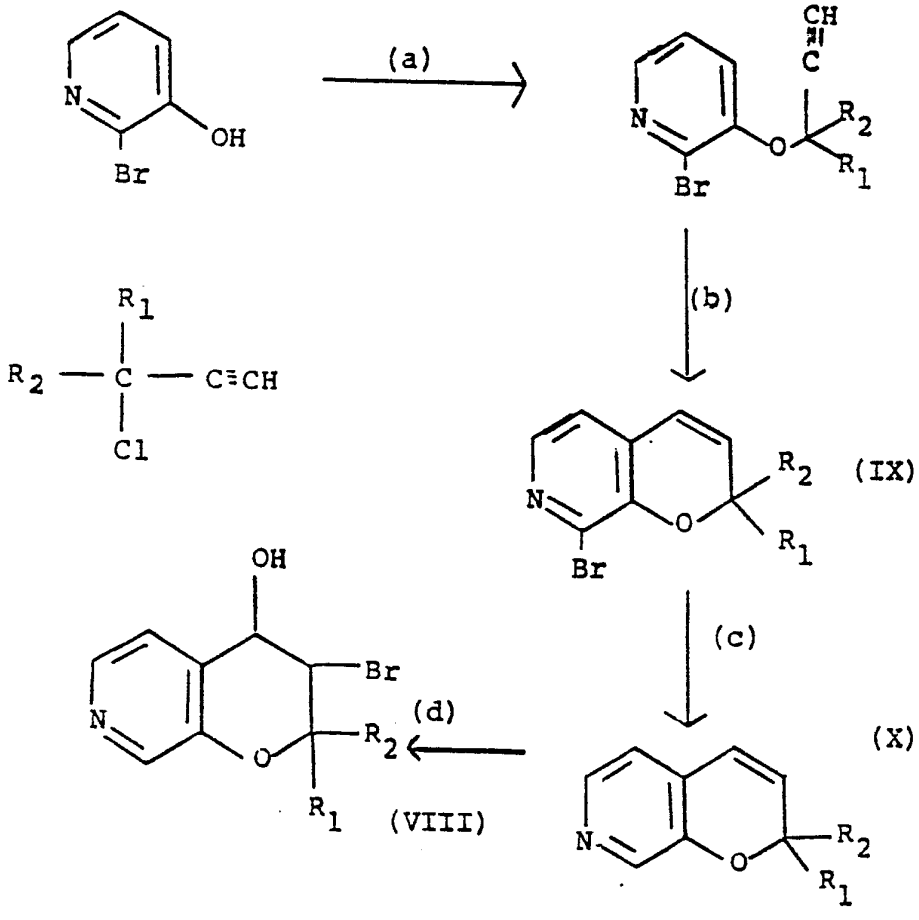
A compound of formula (V) may be prepared by reacting a compound of formula (VIII) or an N-oxide therof:



(VIII)

wherein R_1 and R_2 are as hereinbefore defined, the bromine atom being trans to the hydroxy group, with a base, such as potassium hydroxide, in a solvent, such as aqueous dioxan. It is preferred that the compound of formula (V) is used directly in the reaction with (VI).

A compound of formula (VIII) may be prepared in accordance with analogous processes to those described in the aforementioned European publications, i.e. by the process depicted below:



(a) Room temperature; NaOH/40% benzyltrimethyl-ammonium hydroxide in methanol;

(b) Heat in o-dichlorobenzene;

(c) BuLi; anhydrous ether; -78°C, quench with water;

(d) N-bromosuccinimide/dimethylsulphoxide/water;

It is necessary to introduce a blocking moiety such as bromo, in order to direct the cyclisation (b) to produce the required product. The bromo moiety may be removed at a convenient later stage, using butyl lithium. The intermediates in the above scheme are preferably in the form of the N-oxide. The N-oxide formation is favourably carried out between stages (c) and (d) and subsequent reduction to form the unoxidised form may be carried out at a convenient later stage, by reduction, using hydrogenation or, in particular, a reducing agent such as that described in J. Am Chem. Soc. 91, 2788, 1969.

As mentioned previously, some of the compounds of formula (I) may exist in optically active forms, and the processes of the present invention produce mixtures of such forms. The individual enantiomers may be resolved by conventional methods.

It is preferred that the compounds of formula (I) are isolated in substantially pure, pharmaceutically acceptable form.

The intermediates of formulae (II), (V), (VIII), (IX) and (X) are believed to be novel and represent part of the present invention. The intermediates of formulae

(III), (IV), (VI) and (VII) are known or may be prepared in accordance with an appropriate known process for preparing structurally similar known compounds.

As mentioned previously, the compounds of formula (I) have been found to have blood-pressure lowering activity. They are therefore useful in the treatment of hypertension. They may also be of potential use in the treatment of other disorders hereinbefore described.

The present invention accordingly provides a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In particular, the present invention provides an anti-hypertensive pharmaceutical composition which comprises an anti-hypertensive effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The compositions are preferably adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration for patients suffering from heart failure.

The form and preparation of compositions are as described for the compounds of EP-A-205292.

The present invention further provides a method of prophylaxis or treatment of hypertension in mammals including man, which comprises administering to the suffering mammal an anti-hypertensive effective amount

of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

An effective amount will depend on the relative efficacy of the compounds of the present invention, the severity of the hypertension being treated and the weight of the sufferer. However, a unit dose form of a composition of the invention may contain from 1 to 100 mg of a compound of the invention and more usually from 2 to 50 mg, for example 5 to 25 mg such as 6, 10, 15 or 20mg. Such compositions may be administered from 1 to 6 times a day, more usually from 2 to 4 times a day, in a manner such that the daily dose is from 5 to 200 mg for a 70 kg human adult and more particularly from 10 to 100 mg.

No toxicological effects are indicated at the aforementioned dosage ranges.

The present invention further provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of hypertension.

The following examples relate to the preparation of compounds of formula (I); the following descriptions relate to the preparation of intermediates thereto.

All temperatures therein are in ^{o}C.

Descriptions

1. 8-Bromo-2,2-dimethyl-2H-pyrano[2,3-c]pyridine (D1)

2-Bromo-3-hydroxypyridine (25 g), 40% benzyltrimethylammonium hydroxide in methanol (50 ml) and 3-chloro-3-methylbut-1-yne (22 g) were dissolved in dichloromethane (150 ml). To this stirred solution was added sodium hydroxide pellets (10 g) dissolved in water (150 ml), and the resulting mixture stirred at room temperature for 6 days. The layers were separated and the aqueous layer further extracted with chloroform. The combined organic layers were evaporated and the resulting oil taken up in ether and washed successively with 10% sodium hydroxide solution, water, brine, then dried over anhydrous magnesium sulphate. Evaporation of solvents, after filtration, gave the crude propargyl ether which was heated under reflux in o-dichlorobenzene for 1 hour. Solvent was evaporated in vacuo and the residue distilled to give the title pyranopyridine (12.2 g) of b.p. 60-62°C/0.1 mmHg.

NMR ($CDCl_3$) δ 1.47 (s, 6H)
5.78 (d, J=11Hz, 1H)
6.23 (d, J=11Hz, 1H)
6.79 (d, J=4Hz, 1H)
7.73 (d, J=4Hz, 1H)

2. 2,2-Dimethyl-2H-pyrano[2,3-c]pyridine (D2)

To a solution of 8-bromo-2,2-dimethyl-2H-pyrano[2,3-c]pyridine (12.2 g) dissolved in dry ether (50 ml) at -78°C was added n-butyl lithium (41 ml, 1.6 M in nexane) dropwise with stirring under nitrogen during 15 min. After an additional 45 min under these

conditions, water was added cautiously and the mixture allowed to attain room temperature. The layers were separated, and the aqueous layer further extracted with ether. The combined organic extracts were washed with water, then brine, and dried over anhydrous magnesium sulphate. Filtration and evaporation gave the crude title compound as an oil (8.64 g). A portion was distilled to give the purified sample of b.p. 70°C/0.1 mmHg.

NMR ($CDCl_3$) δ 1.42 (s, 6H)
5.67 (d, J=10Hz, 1H)
6.18 (d, J=10Hz, 1H)
6.68 (d, J=5Hz, 1H)
7.93 (d, J=5Hz, 1H)
7.97 (m, 1H)

3. 2,2-Dimethyl-2H-pyrano[2,3-c]pyridine oxide (D3)

m-Chloroperbenzoic acid (9.15 g) was added to a stirred chloroform (150 ml) solution of 2,2-dimethyl-2H-pyrano [2,3-c]pyridine (8.64 g) during 15 min. The solution was then heated under reflux for 1 h. The solution was cooled and evaporated and the residue chromatographed on silica gel (500 g). Elution with 5% methanol-chloroform gave the title oxide (5.96 g) as a chromatographically homogeneous colourless gum.

NMR ($CDCl_3$) δ 1.45 (s, 6H)
5.73 (d, J=10Hz, 1H)
6.27 (d, J=10Hz, 1H)
6.87 (d, J=6Hz, 1H)
7.75 (irregular m, 2H)

4. trans-3-Bromo-3,4-dihydro-2,2-dimethyl-2H-pyrano[2,3-c]pyridin-4-ol oxide (D4)

To the pyranopyridine N-oxide of description 3 (5.35 g) in dimethyl sulphoxide (25 ml) and water (0.54 ml) was added N-bromosuccinimide (5.25 g) with stirring at room temperature. The reaction mixture was stirred for 20 min when a precipitate formed. The solution was diluted with water and extracted with chloroform. The organic phase was washed with water, brine, and dried over anhydrous magnesium sulphate. The solution was filtered and evaporated to give the bromohydrin as a brown solid (5.87 g). A small portion was triturated with ethyl acetate, and recrystallised from ethyl acetate-methanol to give crystals of m.p. 185-187°C.

5. 3,4-Epoxy-3,4-dihydro-2,2-dimethyl-2H-pyrano[2,3-c]pyridin-4-ol oxide (D5)

The bromohydrin of description 4 (1.56 g) and powdered potassium hydroxide pellets (2.0 g) were heated under reflux and stirred during 4 h. The solution was cooled, filtered and evaporated to give a gum which crystallised (1.01 g) on standing.

NMR ($CDCl_3$) δ 1.31 (s, 3H)
1.58 (s, 3H)
3.51 (d, J=4Hz, 1H)
3.88 (d, J=4Hz, 1H)
7.20 (d, J=7Hz, 1H)
7.75 (irregular m, 2H)

6. trans-4-Amino-3,4-dihydro-2,2-dimethyl-2H-pyrano[2,3-c]pyridin-3-ol oxide (D6)

The epoxide of description 5 (1.01 g) was dissolved in dry ethanolic ammonia (30 ml) and the mixture stirred at room temperature for 7 days. Evaporation and trituration with ethyl acetate gave the aminoalcohol (0.62 g) as a pale yellow solid. A portion recrystallised from ethyl acetate-ethanol had m.p. 206-208°C (with decomposition).

7. trans-4-Chlorovaleroylamino-3,4-dihydro-2,2-dimethyl-2H-pyrano[2,3-c]pyridin-3-ol oxide (D7)

The aminoalcohol of description 6 (0.55 g) and triethylamine (0.40 ml) were stirred in dichloromethane (600 ml) with ultrasonication. 4-Chlorovaleryl chloride (0.37 ml) was added dropwise to the solution during 1 h, and the stirring and sonication continued for 10 min. The solution was evaporated and chromatographed on silica gel and eluted with chloroform containing up to 10% methanol in a gradient elution. The title compound of description 7 was obtained as a crude solid (0.44 g).
Mass spectrum E.I. M^+-H_2O at m/z 310.

8. trans-4-(4-chlorobutyroylamino)-3,4-dihydro-2,2-dimethyl-2H-pyrano[2,3-c]pyridin-3-ol oxide (D8)

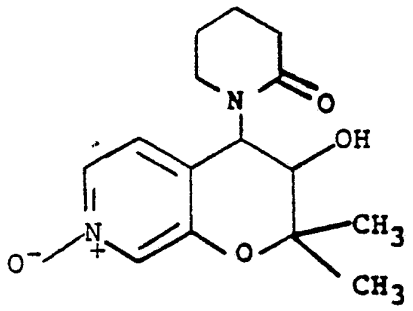
To an ultrasonicated, stirred solution of the aminoalcohol of description 6 (1.54 g) dissolved in dichloromethane (600 ml) and triethylamine (0.64 ml) was added chlorobutyryl chloride (0.91 ml). The conditions were maintained for a further 1 h. The solution was evaporated and the residue chromatographed

on silica gel (200 g) and eluted with chloroform—10% methanol-chloroform in a gradient elution, to give the title compound (1.0 g).

NMR ($CDCl_3$ + CD_3OD) δ 1.38 (s, 3H)
1.53 (s, 3H)
2.15 (m, 2H)
2.43 (m, 2H)
3.62 (m, 3H)
4.92 (d, J=10Hz, 1H)
7.10 (d, J=6Hz, 1H)
7.73 (m, 2H)

Example 1

trans-3,4-Dihydro-2,2-dimethyl-4-(2-oxypiperidinyl)-2H-pyrano[2,3-c]pyridin-3-ol oxide (E1)



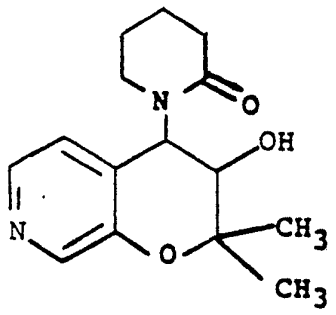
(E1)

The valeroylamino compound of description 7 (0.44 g) was dissolved in dry tetrahydrofuran (10 ml) and sodium hydride (45 mgm; 80% dispersion in oil) was added to the stirred solution under nitrogen. The reaction mixture was stirred for 16 h. Water was cautiously added and the solution reduced in volume and extracted with chloroform (4x). The material from the first two extractions was chromatographed on the chromatotron (chloroform—methanol gradient, silica gel) and the desired material (140 mgm) combined with the product of the last two extractions (110 mgm). Recrystallisation from ethyl acetate-methanol gave the piperidone compound of example 2 as crystals (120 mgm) of m.p. 258-259°C.

NMR ($(CD_3)SO$) δ 1.23 (s, 3H)
1.47 (s, 3H)
1.83 (m, 4H)
2.46 (m, 2H)
2.78 (m, 1H)
3.22 (m, 1H)
3.73 (q, J=10,6Hz, 1H)
5.67 (m, 2H)
6.90 (d, J=6Hz, 1H)
7.75 (d, J=6Hz, 1H)
7.79 (s, 1H)

Example 2

trans-3,4-Dihydro-2,2-dimethyl-4-(2-oxopiperidinyl)-2H-pyrano[2,3-c]pyridin-3-ol (E2)



(E2)

To the N-oxide of example 2 (66 mgm) in dry chloroform (20 ml) was added hexachlorodisilane (0.4 ml) dropwise with stirring under nitrogen. The mixture was stirred for 1 h at room temperature then cooled to 0°C. Aqueous sodium nydroxide solution (5 ml; 10%) was added cautiously to the chloroform solution and the layers separated. The aqueous layer was further extracted with chloroform, and the combined organic layers were dried over annydrous magnesium sulphate. Filtration and evaporation and trituration with diethyl ether gave the compound of example 3 as an off-white powder (11 mgm).

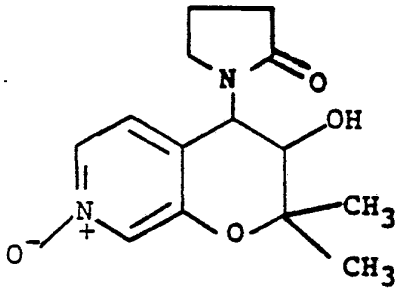
Mass spectrum E.I. M^+ at m/z 276.1467.

$C_{15}H_{20}N_2O_3$ requires 276.1474.

NMR ($CDCl_3$) δ 1.27 (s, 3H)
1.55 (s, 3H)
1.84 (irreg m, 4H)
2.60 (t, J=6Hz, 2H)
2.93 (irreg m, 1H)
3.10 (irreg m, 1H)
3.82 (d, J=10Hz, 1H)
5.93 (d, J=10Hz, 1H)
6.90 (d, J=4Hz, 1H)
8.16 (m, 1H)
8.23 (m, 1H)

Example 3

trans-3,4-Dihydro-2,2-dimethyl-4-(2-oxopyrrolidinyl)-2H-pyran[2,3-c]pyridin-3-ol oxide (E3)



(E3)

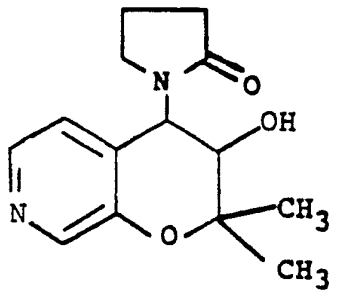
The chlorobutyroylamino compound of description 8 (487 mgm) was dissolved in dry dimethyl sulphoxide (10 ml) and dry tetrahydrofuran (10 ml), and to this solution, under nitrogen, was added sodium hydride (50 mgm, 80% dispersion in oil), and the reaction was stirred for 16 hours. Water was added cautiously to the reaction mixture, and the resulting solution extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulphate filtered and evaporated to give a residue (390 mg) which was recrystallised from ethyl acetate-methanol to give the compound of example 3 as needles (135 mg) of m.p. 268-271°C.

Mass spectrum EI M^+ at m/z 278.1259.

$C_{14}H_{18}N_2O_4$ requires 278.1267.

Example 4

trans-3,4-Dihydro-2,2-dimethyl-4-(2-oxopyrrolidinyl)-2H-pyrano[2,3-c]pyridin-3-ol (E4)



(E4)

To the N-oxide of example 1 (240 mgm) in dichloromethane (200 ml) was added hexachlorodisilane (0.4 ml) in dichloromethane (20 ml) dropwise with stirring under nitrogen. The mixture was stirred for 1 h and 10% aqueous sodium hydroxide solution (0.5 ml) was added to it. The solution was stirred for 10 min and evaporated to dryness. Extraction with chloroform, and with methanol and combination of the solutions and evaporation gave a gummy solid which was purified (chromatotron : gradient elution chloroform — 6% methanol - chloroform) to give the title compound (110 mgm) as a crystalline solid m.p. 221-225°C.

Mass spectrum (EI) M^+ at m/z 262.1316.

$C_{14}H_{18}N_2O_3$ requires 262.1318.

NMR (CD_3OD) δ 1.29 (s, 3H)
1.55 (s, 3H)
2.13 (m, 2H)
2.58 (m, 2H)
3.07 (m, 1H)
3.38 (m, 1H)
3.76 (d, J=10Hz, 1H)
5.22 (d, J=10Hz, 1H)
6.93 (d, J=5Hz, 1H)
8.07 (d, J=5Hz, 1H)
8.13 (s, 1H)

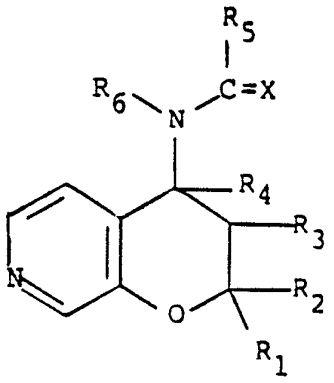
PHARMACOLOGICAL DATA

Systolic blood pressures were recorded by a modification of the tail cuff method described by I.M. Claxton, M.G. Palfreyman, R.H. Poyser, R.L. Whiting, European Journal of Pharmacology, 37, 179 (1976). A W+W BP recorder, model 8005 was used to display pulses. Prior to all measurements rats were placed in a heated environment (33.5 ± 0.5°C) before transfer to a restraining cage. Each determination of blood pressure was the mean of at least 6 readings. Spontaneously hypertensive rats (ages 12-18 weeks) with systolic blood pressures >170 mmHg were considered hypertensive.

The compound of example 1 lowered systolic blood pressure by 40 ± 1% at 4 h post dose, on administration of a dose of 10 mg/kg p.o. to a group of 6 rats.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

one of R_1 and R_2 is hydrogen or C_{1-4} alkyl and the other is C_{1-4} alkyl or R_1 and R_2 together are C_{2-5} polymethylene;

either R_3 is hydrogen, hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy and R_4 is hydrogen or R_3 and R_4 together are a bond;

R_5 is hydrogen; C_{1-6} alkyl optionally substituted by up to three halo atoms, by hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy, or amino optionally substituted by one or two independent C_{1-6} alkyl groups or disubstituted by C_{4-5} polymethylene; C_{2-6} alkenyl; amino optionally substituted by a C_{1-6} alkyl or C_{1-6} alkenyl group or by a C_{1-6} alkanoyl group optionally substituted by up to three halo atoms, by a phenyl group optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen; or aryl or heteroaryl, either being optionally substituted by one or more groups or atoms selected from the class of C_{1-6} alkyl, C_{1-6} alkoxy,

hydroxy, halogen, trifluoromethyl, nitro, cyano, C_{1-12} carboxylic acyl, or amino or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups; or (when X is 0), R_5 is selected from the class of carboxy, C_{1-6} alkoxycarbonyl, or aminocarbonyl optionally substituted by one or two C_{1-6} alkyl groups; and

R_6 is hydrogen or C_{1-6} alkyl; or

R_5 and R_6 together are $-CH_2-(CH_2)_n-Z-(CH_2)_m-$ wherein m and n are 0 to 2 such that m + n is 1 or 2 and Z is CH_2, O, S or NR wherein R is hydrogen, C_{1-9} alkyl, C_{2-7} alkanoyl, phenyl C_{1-4}-alkyl, naphthylcarbonyl, phenylcarbonyl or benzyl-carbonyl optionally substituted in the phenyl or naphthyl ring by one or two of C_{1-6} alkyl, C_{1-6} alkoxy or halogen; or R is heteroarylcarbonyl;

X is oxygen or sulphur; or

R_5, R_6, X and N together are tetrahydroisoquinolinone or tetrahydroisoquinolin-thione optionally substituted in the phenyl ring as defined for R above;

the nitrogen-containing group in the 4-position being trans to the R_3 group when R_3 is hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy.

2. A compound according to claim 1 wherein R_1 and R_2 are both methyl.

3. A compound according to claim 1 or 2 wherein R_5 is hydroxy and R_6 is hydrogen, or R_5 and R_6 together are a bond.

4. A compound according to any one of claims 1 to 3 wherein R_5 and R_6 are joined to form $-CH_2-(CH_2)_n-Z-(CH_2)_m-$ as defined in claim 1.

5. A compound according to any one of claims 1 to 4 wherein R_5 is methyl or R_5 is phenyl or amino either being optionally substituted as defined in claim 1; and R_6 is methyl, ethyl or hydrogen.

6. trans-3,4-Dihydro-2,2-dimethyl-4-(2-oxypiperidinyl)-2H-pyrano[2,3-c]pyridin-3-ol oxide,

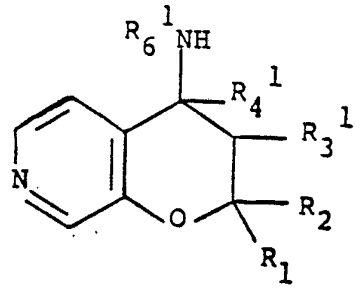
trans-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidinyl)-2H-pyrano[2,3-c]pyridin-3-ol,

trans-3,4-dihydro-2,2-dimethyl-4-(2-oxopyrrolidinyl)-2H-pyran[2,3-c]pyridin-3-ol oxide or

trans-3,4-dihydro-2,2-dimethyl-4-(2-oxopyrrolidinyl)-2H-pyrano[2,3-c]pyridin-3-ol.

7. A process for the preparation of a compound according to claim 1 or a pharmaceutically acceptable salt thereof, which comprises;

i) acylating a compound of formula (II) or an N-oxide thereof:



(II)

wherein, R_1 and R_2 are as defined in claim 1, R_3^1 is hydroxy, C_{1-6} alkoxy or C_{1-7} acyloxy, and R_6^1 is hydrogen or C_{1-6} alkyl, the R_6^1NH group being trans to the R_3^1 group,

a) with an acylating agent of formula (III):

$$R_8\text{-}CO\text{-}L_1 \qquad \text{(III)}$$

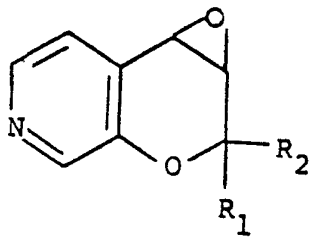
wherein L_1 is a leaving group, and R_8 is hydrogen, C_{1-6} alkoxycarbonyl, C_{1-6} alkyl optionally substituted by halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, carboxy or amino optionally substituted as hereinbefore defined for R_5, C_{2-6} alkenyl or optionally substituted aryl or heteroaryl as defined in claim 1 for R_5, or a group convertible to R_5 as defined in claim 1, and thereafter, when R_6 is hydrogen and R_8 is $Y(CH_2)_z$, where z is 3 or 4 and Y is a leaving group, cyclising the resultant compound;

b) with a compound of formula (IV)

$$X{=}C{=}N.R_{11} \qquad \text{(IV)}$$

wherein R_{11} is hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkanoyl optionally substituted by up to three halo atoms, or phenyl optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy or halogen; and X is oxygen or sulphur, and thereafter when R_{11} is hydrogen, optionally converting R_{11}; or

ii) where, in the resultant compound of formula (I), R_5 and R_6 are joined together or R_5 is aminocarbonyl, reacting a compound of formula (V) or an N-oxide thereof:



(V)

wherein R_1 and R_2 are as defined in claim 1, with a compound of formula (VI):

$$R_{13}NHCOR_{12} \qquad (VI)$$

wherein R_{13} is R_6 as defined and R_{12} is aminocarbonyl; R_{12} and R_{13} together are $-CH_2-(CH_2)_n-Z-(CH_2)_m-$ or $R_{13}NHCOR_{12}$ is tetrahydroisoquinolinone;

optionally converting R_3 in the resulting compound into another R_3; in the case where R_3 and R_4 in the resulting compound are hydroxy and hydrogen respectively, optionally dehydrating the compound to give another compound wherein R_3 and R_4 together are a bond, and optionally reducing the resulting compound wherein R_3 and R_4 together are a bond, to give another compound, wherein R_3 and R_4 are each hydrogen; and optionally thiating the $R_6-N-CO-R_5$ group in the resulting compound to give a compound wherein X is sulphur; and optionally forming a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. A compound according to any one of claims 1 to 6 for use as an active therapeutic substance.

10. Use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for use in the treatment of hypertension.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 87/00386

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC [4] C 07 D 491/04; 491/10; A 61 K 31/435; 31/47,//(C 07 D 491/04, 311:00, 221:00);(C 07 D 491/10, 311:00, 221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC [4]	C 07 D 491/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0095316 (BEECHAM) 30 November 1983 see claim 1; page 18, lines 17-24; cited in the application	1,8
P,A	EP, A, 0205292 (BEECHAM) 17 December 1986 see claim 1; column 1, lines 11-17; column 2, lines 1-14	1,8

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
31st August 1987	25 SEP 1987
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	L. ROSSI

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 87/00386 (SA 17429)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/09/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0095316	30/11/83	AU-A-	1468683	24/11/83
		JP-A-	59001475	06/01/84
		US-A-	4481214	06/11/84
		US-A-	4568692	04/02/86
		AU-B-	564152	06/08/87
EP-A- 0205292	17/12/86	AU-A-	5845786	11/12/86
		JP-A-	61293984	24/12/86