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Pharmaceutically active 3-hydroxypyrid-2-and-4-ones

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(58) Field of search
C2C

GB 2 118 176 B

PHARMACEUTICALLY ACTIVE 3-HYDROXYPYRID-2- AND -4-ONES

This invention relates to compounds for use in pharmaceutical compositions.

Certain pathological conditions such as thalassaemia, sickle cell anaemia, idiopathic haemochromatosis and aplastic anaemia are treated by regular blood transfusions. It is commonly found that such transfusions lead to a widespread iron overload, which condition can also arise through increased iron absorption by the body in certain other circumstances. Iron overload is most undesirable since, following saturation of the ferritin and transferrin in the body, deposition of iron can occur and many tissues can be adversely affected, particular toxic effects being degenerative changes in the myocardium, liver and endocrine organs. Such iron overload is most often treated by the use of desferrioxamine. However, this compound is an expensive natural product obtained by the culture of Streptomyces and, as it is susceptible to acid hydrolysis, it cannot be given orally to the patient and has to be given by a parenteral route. Since relatively large amounts of desferrioxamine may be required daily over an extended period, these disadvantages are particularly relevant and an extensive amount of research has been directed towards the development of alternative drugs. However, work has been concentrated on three major classes of iron chelating agents or siderophores, namely hydroxamates, ethylenediamine tetra-acetic acid (EDTA) analogues and catechols. The hydroxamates generally suffer from the same defects as desferrioxamine, being expensive and acid labile, whilst the other two classes are ineffective at removing iron from intracellular sites. Moreover, some cathechol derivatives are retained by the liver and spleen and EDTA analogues possess a high affinity for calcium and so are also likely to have associated toxicity problems.

We have accordingly studied the iron chelating ability of a wide range of compounds and have identified a group of compounds as being of particular use for the treatment of conditions involving iron overload.

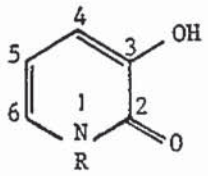
Accordingly the present invention comprises a compound being a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or a salt thereof containing a physiologically acceptable cation, for use in medicine.

The 3-hydroxypyrid-2- and -4-ones may carry more than one type of aliphatic hydrocarbon group and, in particular, the group attached to the nitrogen atom may be different from any aliphatic hydrocarbon group or groups attached to ring carbon atoms. Groups attached to carbon atoms are, however, more often the same when more than one is present. The aliphatic hydrocarbon groups, whether attached to a nitrogen or a carbon atom, may be cyclic or acyclic, having a branched chain or especially a straight chain in the latter case, and may be unsaturated or especially saturated. Groups of from 1 to 4 carbon atoms and particularly of 1 to 3 carbon atoms are of most interest. Alkyl groups are preferred, for example cyclic groups such a cyclopropyl and especially cyclohexyl but, more particularly preferred are acyclic alkyl groups such as methyl, ethyl, n-propyl and isopropyl. Where the ring carbon atoms are substituted by an aliphatic hydrocarbon group or groups, these groups are preferably methyl but in the case of the group substituting the nitrogen atom larger groups may more often be utilised with particular advantage. Substitution of the ring carbon atoms, which is preferably by one rather than two or three aliphatic hydrocarbon groups, is of particular interest in the case of the 3-hydroxypyrid-4-ones, for example at the 6- or particularly the 2-position, whilst the 3-hydroxypyrid-2-ones may more often be used without any additional aliphatic hydrocarbon group substitutent on the ring carbon atoms. Particularly if the ring carbon atoms are substituted by the larger aliphatic hydrocarbon groups, however, there may be an advantage in avoiding substitution on a

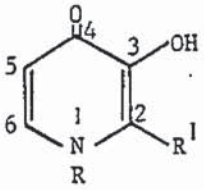
carbon atom alpha to the $-\overset{O}{\overset{\|}{C}}-\overset{OH}{\overset{|}{C}}<$ system. This system is involved in the complexing with iron and the close proximity of one of the larger aliphatic hydrocarbon groups may lead to steric effects which inhibit complex formation.

The compounds may, if desired, be used in the form of salts thereof containing a physiologically acceptable cation, for example the cation of an alkali metal such as sodium, quaternary ammonium ions or protonated amines such as the cation derived from tris (tris represents 2-amino-2-hydroxymethyl propane 1,3-diol). Salt formation may be advantageous in increasing the water solubility of a compound but, in general, the use of the compounds themselves, rather than their salts, is preferred.

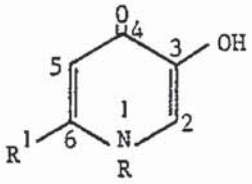
Examples of specific compounds which may be used in compositions according to the present invention are shown by the following formulae (I), (II) and (III):-



(I)



(II)



(III)

in which R is an alkyl group, for example methyl, ethyl, n-propyl or isopropyl, and R^1 is hydrogen or an alkyl group, for example methyl. Among these compounds and others of use in compositions according to the present invention, the 3-hydroxypyrid-4-ones are of particular interest.

Certain of the compounds described herein are novel and the present invention thus also includes as compounds, per se, (a) a 3-hydroxypyrid-2-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and, optionally, in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, and (b) a 3-hydroxypyrid-4-one in which the hydrogen atom attached to the nitrogen atom is replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms and in which one or more of the hydrogen atoms attached to ring carbon atoms are also replaced by an aliphatic hydrocarbon group of 1 to 6 carbon atoms, or a salt of such a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one containing a physiologically acceptable cation, but excluding specifically 3-hydroxy-1-methylpyrid-2-one, 3-hydroxy-1,6-dimethylpyrid-4-one and 3-hydroxypyrid-4-ones in which the only ring carbon atom substituent is a methyl group at the 2-position, and salts thereof.

The 3-hydroxy-pyrid-2-one compounds may conveniently be prepared by nucleophilic substitution at the nitrogen atom of the corresponding 2,3-dihydroxypyridine, for example using an organic halide R'X in which R' represents the aliphatic hydrocarbon group present on the nitrogen atom of the desired 3-hydroxypyrid-2-one and X represents an iodo group. The 3-hydroxypyrid-4-one compounds may conveniently be prepared similarly or preferably from the more readily accessible corresponding 3-hydroxy-4-pyrone. Thus, the 3-hydroxy-4-pyrone may conveniently be converted to the 3-hydroxypyrid-4-one through protection of the hydroxy group, for example as an ether group such as a benzyloxy group, reaction of the protected compound with a compound $R'NH_2$, in which R' represents the aliphatic hydrocarbon group present on the nitrogen atom of the desired 3-hydroxypyrid-4-one, in the presence of a base, for example an alkali metal hydroxide such a sodium hydroxide. The protecting group may then be removed. The compounds may be converted to salts formed at the hydroxy group thereof through its conversion to the anion ($OH \longrightarrow O^-$) by reaction with the appropriate base according to standard procedures.

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