(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 093 498**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **26.11.86**

(51) Int. Cl.⁴: **A 61 K 31/44**, C 07 D 213/69

(21) Application number: **83301659.5**

(22) Date of filing: **24.03.83**

(54) **Pharmaceutical compositions containing N-substituted-3-hydroxypyrid-2-one or -4-one derivatives.**

(30) Priority: **24.03.82 GB 8208608**

(43) Date of publication of application:
09.11.83 Bulletin 83/45

(45) Publication of the grant of the patent:
26.11.86 Bulletin 86/48

(84) Designated Contracting States:
BE CH DE FR GB IT LI NL SE

(56) References cited:
Chemical Abstracts vol. 74, no. 5, 1 February 1971, Columbus, Ohio, USA M. YASUE et al. "Sytheses of N-substituted 3-glucosyloxy-2-methyl-4-pyridones and their aglycones" page 339, column 1, abstract no. 23102b

Chemical Abstracts vol. 79, no. 15, 15 October 1973, Columbus, Ohio, USA R.T. BORCHARDT et al. "Catechol O-methyltransferase. 4. In vitro inhibition by 3-hydroxy-4-pyrones, 3-hydroxy-2-pyridones, and 3-hydroxy-4-pyridones" page 60, column 1, abstract no. 87818a

(73) Proprietor: **NATIONAL RESEARCH DEVELOPMENT CORPORATION**
101 Newington Causeway
London SE1 6BU (GB)

(72) Inventor: **Hider, Robert Charles**
257 Point Clear Road
St. Osyth Clacton Essex (GB)
Inventor: **Kontoghiorghes, George**
15 Celia Road
Tufnell Park London N19 (GB)
Inventor: **Silver, Jack**
50 Stanbury Court
Haverstock Hill London NW3 (GB)

(74) Representative: **Stephenson, Gerald Frederick**
Patent Department National Research Development Corporation 101 Newington Causeway
London SE1 6BU (GB)

EP 0 093 498 B1

Courier Press, Leamington Spa, England.

(56) References cited:
Chemical Abstracts vol. 97, no. 11, 13 September 1982, Columbus, Ohio, USA J. BARTULIN et al. "Synthesis and structure of heterocyclic compounds with chelating properties" page 748, column 2, abstract no. 92048a

Chemical Abstracts vol. 94, no. 9, 2 March 1982 Columbus, Ohio, USA D.R. HWANG et al. "Pyridones as potential antitumor agents. II: 4-Pyridones and bioisosteres of 3-acetoxy-2-pyridone" page 704, column 2, abstract no. 65438j

Chemical Abstracts vol. 73, no. 21, 23 November 1970, Columbus, Ohio, USA H. MOEHRLE et al. "Pyridones. I. 1-Methyl-3-hydroxy-2(and 6)-pyridones" pages 357, column 2, abstract no. 109632r

Description

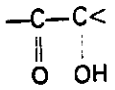
This invention relates to compounds for use in pharmaceutical compositions.

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 (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 siters. 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 3-hydroxypyrid-2- and -4-one compounds as being of particular use for the treatment of conditions involving iron overload. Certain of these compounds have been described in the literature in other contexts as follows: (a) Chambers and Casida, Toxicology and Applied Pharmacology, 1969, *14*, 249—258, disclose 3-hydroxy-1-methylpyrid-2-one; (b) Imafuku *et al*, Bulletin of the Chemical Society of Japan, 1979, *52*, 111—113, discloses 3-hydroxy-1-methylpyrid-4-one and 3-hydroxy-1,6-dimethylpyrid-4-one; (c) Borchardt, Journal of Medicinal Chemistry, 1973, *16*, 581—583, discloses 3-hydroxy-1-methylpyrid-4-one; (d) Kleipool and Wibaut, Recueil des Travaux Chimiques des Pays-Bas, 1950, *69*, 1041—1047, disclose 1-ethyl-3-hydroxypyrid-4-one, 3-hydroxy-1-propylpyrid-4-one and 3-hydroxy-1-(1'-methylethyl)-pyrid-4-one; (e) Bartulin *et al*, Boletin de la Sociedad chilena de Quimica, 1982, *27*, 122—124, disclose 3-hydroxy-2-methyl-1-propylpyrid-4-one, 3-hydroxy-2-methyl-1-hexylpyrid-4-one and 3-hydroxy-2-methyl-1-octylpyrid-4-one) and (f) Yasue *et al*, Yakugaku Zasshi, 1970, *90*, 1222—1225 disclose a range of 3-hydroxy-2-methylpyrid-4-ones substituted at the 1-position by a cyclohexyl group or various alkyl groups. It should be emphasised, however, that none of these papers are concerned with the use of the compounds for the removal of iron from the body, nor do they describe a therapeutic use for any of these compounds. Thus, although Chambers and Casida carry out *in vivo* tests on 3-hydroxy-1-methylpyrid-2-one as a protective agent against certain neurotoxic agents, it was found to be inactive against tubocurarine and not to exhibit a significant effect in prolonging the mean knockdown time (MKDT) with tri-n-butylphosphate (TBP). Moreover, although Borchardt shows 3-hydroxy-1-methylpyrid-4-one to exhibit catechol O-methyltransferase (COMT) inhibitory activity in a chemical test procedure, he gives no indication as to any therapeutic application to which this finding could be put.

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 therapy.

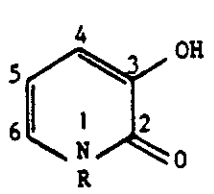
The 3-hydroxypyrid-2- and -4-ones may carry more than one type of aliphatic hydrocarbon group and, in particular, the group attached to the nitrogen atom may be different from any aliphatic hydrocarbon group or groups attached to ring carbon atoms. Groups attached to carbon atoms are, however, more often 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 saturated. Groups of from 1 to 4 carbon atoms and particularly of 1 to 3 carbon atoms are of most interest. Saturated groups are preferred, these being either cyclic such as the cycloalkyl groups cyclopropyl and especially cyclohexyl or, more particularly, acyclic such as the alkyl groups 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 substituent 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



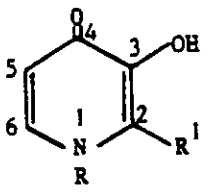
system. This system is involved in the complexing with iron and the close proximity of one of the larger aliphatic hydrocarbon groups may lead to steric effects which inhibit complex formation.

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.

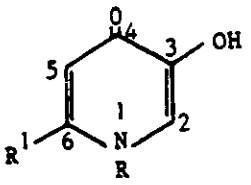
Examples of specific compounds which may be used in compositions according to the present invention are shown by the following formulae (I), (II) and (III):—



(I)



(II)



(III)

in which R is a cycloalkyl or alkyl group, for example methyl, ethyl, n-propyl or isopropyl, and R^2 is hydrogen or a cycloalkyl or 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.

As indicated hereinbefore, although certain of the compounds of use in the present invention are known, many others are novel. 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 atomslon 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 an 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, and 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 ($OH \rightarrow O^-$) by reaction with the appropriate base according to standard procedures.

The compounds may be formulated for use as pharmaceuticals for veterinary or particularly human use by a variety of methods. The pharmaceutical composition may, for example, incorporate water or a medium containing an organic solvent as a diluent, having the form of a solution, suspension or emulsion. Aqueous, oily or emulsified compositions incorporating a liquid diluent will, however, most usually be employed for parenteral administration and therefore may conveniently be sterile and pyrogen free. However, it will be appreciated from the foregoing discussion in relation to desferrioxamine that oral administration is to be preferred and the compounds of the present invention may be given by such a route. Although compositions incorporating a liquid diluent may be used for oral as well as parenteral administration, it is preferred to use compositions incorporating a solid carrier. This may, for example, be a conventional solid carrier material such as starch, lactose, dextrin or magnesium stearate, and the composition may, for example, be formed as tablets.

Other forms of administration than by injection or through the oral route may also be considered in both human and veterinary contexts, for example the use of suppositories for human administration.

The present invention thus further includes a pharmaceutical composition comprising as an active

component thereof 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, together with a physiologically acceptable diluent or carrier but excluding any liquid which is non-sterile and non-pyrogen free.

Compositions may be formulated in unit dosage form, i.e. in the form of discrete portions each comprising a unit dose, or a multiple or sub-multiple of a unit dose. Whilst the dosage of active compound given will depend on various factors, including the particular compound which is employed in the composition, it may be stated by way of guidance that satisfactory control of the amount of iron present in the human body will often be achieved using a daily dosage of about 0.1 g to 5 g, particularly of about 0.5 g to 2 g, veterinary doses being on a similar g/kg body weight ratio. However, it will be appreciated that it may be appropriate under certain circumstances to give daily dosages either below or above these levels. Where desired, more than one compound according to the present invention may be administered in the pharmaceutical composition or, indeed, other active compounds may be included in the composition.

Although 3-hydroxy-1-methylpyrid-4-one has previously been recognised as a siderophore, it has never before been appreciated that compounds such as this might be used in a pharmaceutical context, and with real advantage. We have found that the 3-hydroxypyrid-2- and -4-ones described above are particularly suited to the removal of iron from patients having an iron overload. The compounds form neutral 3:1 iron complexes at most physiological pH values, and have the advantage that they do not co-ordinate calcium or magnesium. Both the compounds and their complexes will partition into n-octanol indicating that they will permeate biological membranes, this property being confirmed in practice by tests of the ability of the ^{59}Fe labelled iron complexes to permeate erythrocytes. The measured coefficients (K_{part}) for partition of various of the compounds and their 3:1 hydroxypyridone:iron (III) complexes are presented in Table 1 of Example 5 hereinafter. Although the ability of both the free compound and its iron complex to permeate membranes is important, it is also desirable for both to possess some degree of water solubility. Preferred compounds show a value of K_{part} for the free compound of about 0.05 but less than 3.0, especially of above 0.2 but less than 1.0, together with a value of K_{part} for the 3:1 hydroxypyridone:iron (III) complex of above 0.02 but less than 6.0, especially of above 0.2 but less than 1.0. Reference to Table 1 will show that the preferences as to the structure of the compounds in compositions according to the present invention which are expressed hereinbefore lead to compounds which have K_{part} values both in the free state and as the 3:1 iron (III) complexes which are broadly in line with the ranges indicated above.

Both the 3-hydroxypyrid-2-ones and the 3-hydroxypyrid-4-ones possess a high affinity for iron (III), as evidenced by log K_{sol} values {log K_{sol} is defined as being equal to log $\beta_{Fe(L)n}$ + 21 − [pK_{sp} + n log $a_{L(H+)}$ + m log $a_{L(Ca++)}$] where log $\beta_{Fe(L)n}$ is the cumulative affinity constant of the ligand in question for iron (III), pK_{sp} is the negative logarithm of the solubility product for $Fe(OH)_3$ and has a value of 39, n and m are the number of hydrogen and calcium ions, respectively, which are bound to the ligand, and $a_{L(H+)}$ and $a_{L(Ca++)}$ are the affinities of the ligand for hydrogen ions and calcium ions, respectively}. In order to solubilise iron (III) hydroxide, log K_{sol} must be greater than 0 and in order to remove iron from transferrin, log K_{sol} should be in excess of 6.0. The log K_{sol} values for 3-hydroxy-1-methylpyrid-2-one and 1,2-dimethyl-3-hydroxypyrid-4-one, by way of example, are 10.0 and 9.5, respectively, thus comparing favourably with those of the bidentate hydroxamates at about 4.0, of catechols at about 8.0, of desferrioxamine at 6.0, and of diethylenetriamine penta-acetic acid (DTPA) at 2.0. Moreover, the ability of the compounds to remove iron efficiently has been confirmed both by *in vitro* tests and also by *in vivo* tests in mice. It is particularly significant that these latter tests are successful whether the compound is given intraperitoneally or orally by stomach tube, the compounds being stable under acidic conditions. Oral activity is not generally present among the other types of compound previously suggested for use as iron co-ordinating drugs and although certain EDTA analogues do show such activity, they possess drawbacks for pharmaceutical use.

Although the major use of the compounds is in the removal of iron, they are also of potential interest for the removal of some other metals present in the body in deleterious amounts. The present invention thus includes the use of a 3-hydroxypyrid-2- or -4-one or salt thereof as described hereinbefore for the manufacture of a medicament for use in effecting a reduction in toxic levels of a metal in a patient's body.

This invention is illustrated by the following Examples.

EXAMPLES

Example 1

The preparation of 3-hydroxy-1-methylpyrid-2-one

2,3-Dihydroxypyridine (5.55 g) is suspended in methyl iodide (20 ml) in sealed tube and heated for 24 hours at 140°C. The reaction is taken to be complete when a dark brown residue forms as a separate phase from the methyl iodide and the tube is then cooled in solid carbon dioxide and opened. The excess methyl iodide is poured off, distilled water (10 ml) is added to the brown residue, and sulphur dioxide gas is bubbled through the mixture until the aqueous phase becomes clear. The pH of the reaction mixture is adjusted to a value of 6 with 1 M aqueous sodium carbonate and the resulting solution then saturated with ammonium sulphate and extracted with chloroform until the chloroform layer no longer gives a blue colouration when added to ferric chloride solution. The chloroform extracts are combined and dried over

sodium sulphate. The solvent is then evaporated under vacuum and the resulting residue is crystallised from petroleum ether (b.p. 100°—120°C) using activated charcoal to give 3-hydroxy-1-methylpyrid-2-one, m.p. 129°—131°C; ν_{max} (nujol) 1660, 3100 cm^{-1}; δ (d_6DMSO) 3.6 (s, 3H), 6.1 (t, 1H), 6.8 (m, 2H), 7.3 (s, 1H); M^+ 125.

Example 2

The preparation of other 3-hydroxypyrid-2-ones

2,3-Dihydroxypyridine is reacted with ethyl iodide, n-propyl iodide and isopropyl iodide under similar conditions to those described in Example 1 for methyl iodide. The reaction mixtures are worked up as described in Example 1 to give the following compounds:—

1-Ethyl-3-hydroxypyrid-2-one: m.p. 130°—132°C; ν_{max} (nujol) 1620, 3100 cm^{-1}; δ(d_6DMSO) 1.2(t, 3H) 3.8(m, 2H), 6.0(t, 2H), 6.8(m, 2H), 8.9(s, 1H), M^+ 139.

3-Hydroxy-1-propylpyrid-2-one: m.p. 148°C; ν_{max} (nujol) 1620, 3150 cm^{-1}; δ(d_6DMSO) 0.7(t, 3H) 1.5(m, 2H), 3.7(t, 2H), 5.8(t, 1H), 6.5—7.0(m, 2H), 8.7(s, 1H); M^+ 153.

3-Hydroxy-1-(1-methylethyl)pyrid-2-one: m.p. 190°C; ν_{max} (nujol) 1660, 3200 cm^{-1}; δ(d_6DMSO) 1.0(d, 6H) 6.0(m, 1H), 6.5(t, 1H), 6.7(m, 2H); M^+ 153.

Example 3

The preparation of 3-hydroxy-1,2-dimethylpyrid-4-one

3-Benzyloxy-2-methyl-4-pyrone

3-Hydroxy-2-methyl-4-pyrone (22.2 g) in methanol 225 ml) is added to aqueous sodium hydroxide (25 ml containing 7.5 g NaOH). Benzyl chloride (25.5 g) is added and the mixture is refluxed for 6 hours and is then allowed to cool overnight. The bulk of the methanol is removed under vacuum and the residue is treated with water (50 ml). The mixture is extracted into dichloromethane (3 × 25 ml). The extracts are combined, washed with 5% w/v NaOH (2 × 25 ml), then water (2 × 25 ml) and dried over magnesium sulphate. Evaporation of the solvent gives crude 3-benzyloxy-2-methyl-4-pyrone (35 g, 92%) which is purified by distillation in nitrogen under reduced pressure to yield a colourless oil (28 g) of b.p. 148°C/26,6 Pa (0.2 mm Hg).

1,2-Dimethyl-3-benzyloxypyrid-4-one

3-Benzyloxy-2-methyl-4-pyrone (4.8 g) and methylamine hydrochloride (1.56 g) are dissolved in water (200 ml) and ethanol (100 ml) containing sodium hydroxide (2 g) is added. The mixture is stirred at room temperature for 6 days and is then acidified with concentrated hydrochloric acid to pH 2, and evaporated to dryness. The resulting colourless solid is washed with water and extracted into chloroform (2 × 50 ml). The chloroform extracts are combined, dried over magnesium sulphate, and evaporated to yield 1,2-dimethyl-3-benzyloxypyrid-4-one (3.2 g).

3-Hydroxy-1,2-dimethylpyrid-4-one

1,2-Dimethyl-3-benzyloxypyrid-4-one (2 g) is added to concentrated hydrobromic acid (10 ml) and heated in a steam bath for 30 minutes. The resulting mixture is then recrystallised from water to yield 3-hydroxy-1,2-dimethylpyrid-4-one (1 g), m.p. 230°C (with decomposition); ν_{max} (nujol) 1620, 3150 cm^{-1}; δ(d_6DMSO) 2.3(s, 3H), 3.8(s, 3H), 6.9(d, 1H), 7.8(d, 1H); M^+ 139.

Example 4

The preparation of other 3-hydroxypyrid-4-ones

3-Benzyloxy-2-methyl-4-pyrone is prepared as described in Example 3 and is reacted with ethylamine, n-propylamine, isopropylamine, n-butylamine and n-hexylamine hydrochloride under similar conditions to those described in Example 3 for methylamine hydrochloride. The The reaction mixture is worked up and the hydroxy group deprotected as described in Example 3 to give the following compounds:

1-Ethyl-3-hydroxy-2-methylpyrid-4-one: m.p. 190°—195°C; ν_{max} (nujol) 1620, 3150 cm^{-1}; δ(d_6DMSO) 1.1(t, 3H), 2.6(s, 3H), 3.5(m, 2H), 7.3(d, 1H), 8.5(d, 1H); M^+ 153.

3-Hydroxy-2-methyl-1-propylpyrid-4-one: m.p. 182°—183°C; ν_{max} (nujol) 1630, 3200 cm^{-1}; δ(d_6DMSO) 0.9(t, 3H), 1.6(m, 2H), 2.43(s, 3H), 4.2(t, 2H), 7.1(d, 1H), 8.15(d, 1H); M^+ 167.

3-Hydroxy-2-methyl-1-(1'-methylethyl)pyrid-4-one: 198°—200°C; ν_{max} (nujol) 1630, 3150 cm^{-1}; δ(d_6DMSO) 1.28(d, 6H), 2.43(s, 3H), 4.8(m, 1H), 7.15(d, 1H), 8.15(d, 1H); M^+ 167.

1-Butyl-3-hydroxy-2-methylpyrid-4-one: m.p. 188°—190°C; ν_{max} (nujol) 1630, 3200 cm^{-1}; δ(d_6DMSO) 0.9(t, 3H), 1.3(m, 4H), 2.41(s, 3H), 4.2(t, 2H), 7.2(d, 1H), 8.3(d, 1H); M^+ 181.

1-Hexyl-3-hydroxy-2-methylpyrid-4-one: m.p. 166°—168°C; ν_{max} (nujol) 1630, 3200 cm^{-1}; δ(d_6DMSO) 0.8(t, 3H), 1.3(m, 8H), 2.5(s, 3H), 4.2(t, 2H), 7.4(d, 1H), 8.3(d, 1H); M^+ 209.

Example 5

Partition data on 3-hydroxypyrid-2- and -4-ones and their iron complexes

The partition coefficient K_{part}, being the ratio (concentration of compound in n-octanol)/(concentration of compound in aqueous phase) on partition between n-octanol and aqueous tris hydrochloride (20 mH, pH 7.4), is measured at 20°C for various of the compounds of Examples 1 to 4 and for their 3:1 hydroxypyridone:iron (III) complexes (at 10^{-4}M) by spectrophotometry. Acid washed glassware is used throughout and, following mixing of 5 ml of the 10^{-4}M aqueous solution with 5 ml n-octanol for 1 minute, the aqueous n-octanol mixture is centrifuged at 1,000 for 30 seconds. The two resulting phases are separated for a concentration determination by spectrophotometry on each. For the free hydroxypyridones, the range 220—340 nm is used for concentration determinations whilst for the iron complexes, the range 340—640 nm is used.

Values typical of those obtained are shown in Table 1 where it will be seen that quite small changes in structure such as the replacement of a 1-propyl group by a 1-(1'-methylethyl) group can produce quite large differences in K_{part} values.

TABLE 1: Partition coefficients

Compound	Partition Coefficient, K_{part}	
	Free Compound	Iron complex [Fe^{III}-(compound)$_3$]
3-hydroxy-1-methylpyrid-2-one	0.44	0.10
1-ethyl-3-hydroxypyrid-2-one	0.52	1.06
3-hydroxy-1-propylpyrid-2-one	0.78	6.20
3-hydroxy-1-(1'-methylethyl)-pyrid-2-one	3.10	13.50
3-hydroxy-1,2-dimethylpyrid-4-one	0.21	0.05
1-ethyl-3-hydroxy-2-methylpyrid-4-one	0.40	0.03
3-hydroxy-2-methyl-1-propylpyrid-4-one	0.67	0.53
3-hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one	0.95	0.20
1-butyl-3-hydroxy-2-methylpyrid-4-one	5.30	7.70

Example 6

In vitro tests of an iron binding capacity

The 3-hydroxypyridones used in this Example were prepared as described in Examples 1 to 4.

(1) *Mobilisation of iron from ferritin*

Horse spleen ferritin (Sigma) was used without further purification and its iron content was estimated spectrophotometrically at 420 nm. The ferritin solution in phosphate buffered saline (Dulbecco-OXOID, 10^{-6} M, pH 7.4) was enclosed in a Visking dialysis tube and dialysed against a 3×10^{-3} M buffered solution of one of various pyridones as indicated as indicated in Table 2. The absorption spectrum of the resulting iron (III) complex in the dialysis solution was recorded after 6 and 24 hours. For comparative purposes, the procedure was repeated using a blank control.

The results are shown in Table 2 where the percentage of ferritin-bound iron removed by the compound under test is shown. For comparative purposes, results reported in the literature for similar tests with 1×10^{-3} M desferrioxamine (Crichton *et al,* J. Inorganic Biochem., 1980, *13,* 305) and with 6×10^{-3} M LICAMS (Tufano *et al,* Biochem. Biophys. Acta, 1981, *668,* 420) are also given in the Table. It will be seen that the pyridone compounds are able to remove iron effectively from ferritin in contrast with desferrioxamine and LICAMS (although the latter will remove iron in the presence of ascorbic acid such a mixture is very difficult to manage clinically). These results shown in Table 2 have been confirmed by separating apoferritin and the 3-hydroxypyridine iron complex from the reaction product in each case by chromatography on Sephadex® G10.

TABLE 2: Removal of iron from ferritin

Compound	Percentage of iron removed	
	6 hours	24 hours
Control	0	0
3-hydroxy-1-methylpyrid-2-one	11	22
1-ethyl-3-hydroxypyrid-2-one	14	24
3-hydroxy-1-propylpyrid-2-one	11	21
3-hydroxy-1-(1'-methylethyl)-pyrid-2-one	11	20
3-hydroxy-1,2-diemthylpyrid-4-one	14	31
1-ethyl-3-hydroxy-2-methyl-pyrid-4-one	19	34
3-hydroxy-2-methyl-1-propylpyrid-4-one	15	26
3-hydroxy-2-methyl-1-(1'-methylethyl)-pyrid-4-one	17	24
1-butyl-3-hydroxy-2-methylpyrid-4-one	6	7
Desferrioxamine (1 mM)	1.5	—
LICAMS (6 mM)	0	—
LICAMS (6 mM+12 mM ascorbic acid)	7	—

(2) *Mobilisation of iron from transferrin*

Human transferrin (Sigma) was loaded with iron (III) by the method of Bates and Schlaback, J. Biol. Chem. (1973) *248*, 3228. ^{59}Iron (III) transferrin (10^{-5} M) was incubated with a $4 + 10^{-3}$ M solution in tris (0.1 M, pH 7.4) of one of various pyridones as indicated in Table 2 for periods of 4 hours and 18 hours. The solution was then dialysed against phosphate buffered saline for 24 hours. The ^{59}Fe remaining in the dialysis tube was then recorded. For comparative purposes, this procedure was repeated with desferrioxamine using incubation for both 4 hours and 18 hours and with EDTA using incubation for 4 hours only.

The results are shown in Table 3 in terms of the percentage of transferrin bound iron removed by the compound under test. It will be seen that the pyrid-4-one compounds are very effective at iron removal, as compared with desferrioxamide or EDTA, after only 4 hours. Although the efficiency at iron removal of the pyrid-2-one compounds is only at a similar level to that of desferrioxamine and EDTA after 4 hours, it increases markedly after 18 hours whereas the level for desferrioxamine at 18 hours is substantially similar to that at 4 hours.

Similar relative levels of efficiency were observed when the iron was measured spectrophotometrically. Moreover, the results shown in Table 3 have been confirmed by separating apotransferrin and the 3-hydroxypyridone iron complex from the reaction product in each case by chromatography on Sephadex® G10.

TABLE 3: Removal of iron from transferrin

Compound	Percentage of iron removed	
	4 hours	18 hours
Control	0	0
3-hydroxy-1-methypyrid-2-one	11	62
1-ethyl-3-hydroxypyrid-2-one	12	52
3-hydroxy-1-propylpyrid-2-one	15	45
3-hydroxy-1-(1'-methylethyl)-pyrid-2-one	17	57
3-hydroxy-1,2-dimethylpyrid-4-one	90	91
1-ethyl-3-hydroxy-2-methylpyrid-4-one	88	90
3-hydroxy-2-methyl-1-propylpyrid-4-one	90	92
3-hydroxy-2-methyl-1-(1'-methylethyl)-pyrid-4-one	94	94
Desferrioxamine	17	22
EDTA	27	—

Example 7

in vivo tests of iron binding capacity

The 3-hydroxypyridones used in this Example were prepared as described in Examples 1, 2 and 3.

Mice were injected intraperitoneally with iron dextran (2 mg) at weekly intervals over a four week period. Two weeks after the final injection, the mice were injected via the tail vein with ^{59}Fe lactoferrin (human lactoferrin, 1 mg per injection $7,4 \times 10^{10}$ Bq = 2 Ci). The mice were then caged individually. After a ten day period, one of the various pyridones listed in Table 4 was administered to groups of mice at 10 mg per mouse either intraperitoneally or intragastrically. The excretion of iron was recorded at either 12 or 24 hourly intervals over a three day period before and a two day period after administration of the compound. For comparative purposes, the procedure was repeated with a blank control and with desferrioxamine, also at 10 mg per mouse.

The results are shown in Table 4, being given on the basis of the control representing 100% excretion, and illustrate the particular advantage of the pyridones as compared with desferrioxamine for oral administration. It should be mentioned that the large standard deviation (SD) values are somewhat misleading as uniformly positive results can yield high SDs which might be taken to suggest that the results are not significantly different from zero. However, this is not the case here, the large SD values being a consequence of the large range among the positive responses (the range of values obtained is given in the Table for each compound).

TABLE 4: Excretion of iron *in vivo*

Compound	Intraperitoneal Administration		Intragastric Administration	
	Number of Mice	Excretion of $^{59}Fe \pm SD$ (Range of values) percent	Number of Mice	Excretion of $^{59}Fe \pm SD$ (Range of values) percent
Control	12	100±10	—	—
3-hydroxy-1-methylpyrid-2-one	7	150±30 (107—192)	3	235±30 (222—240)
1-ethyl-3-hydroxypyrid-2-one	13	223±117 (133—590)	13	188±66 (95—303)
3-hydroxy-1-propylpyrid-2-one	13	169±49 (112—280)	13	149±56 (53—260)
3-hydroxy-1,2-dimethylpyrid-4-one	7	265±70 (181—401)	3	320±90 (242—425)
Desferrioxamine	7	340±90 (172—472)	3	90±20 (80—107)

Claims

1. 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 therapy.

2. A compound according to Claim 1, in which the or each aliphatic hydrocarbon group is of 1 to 4 carbon atoms.

3. A compound according to Claim 1 or 2, in which the or each aliphatic hydrocarbon group is an acyclic group.

4. A compound according to any of Claims 1 or 2, in which the or each aliphatic hydrocarbon group is a cycloalkyl or alkyl group.

5. A compound according to Claim 1, in which the hydrogen atom attached to the nitrogen atom and, optionally, also one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or different substituents selected from methyl, ethyl, n-propyl and isopropyl.

6. A compound according to any of the preceding claims, in which the 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one is substituted either only on the nitrogen atom or on the nitrogen atom and on one only of the ring carbon atoms.

7. A compound according to any of the preceding claims, in which any replacement of a hydrogen atom attached to a ring carbon atom is effected by a methyl group.

8. A compound according to any of the preceding claims, being a 3-hydroxypyrid-2-one substituted only on the nitrogen atom.

9. A compound according to any of Claims 1 to 7, being a 3-hydroxypyrid-4-one.

10. A compound according to Claim 9, in which the 3-hydroxypyrid-4-one is substituted on the nitrogen atom and by a single additional substituent at the 2- or 6-position.

11. A compound according to Claim 10, in which the single additional substituent is a methyl group at the 2-position.

12. A compound according to Claim 1, being 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one, 3-hydroxy-1-(1'-methylethyl)-pyrid-2-one, 3-hydroxy-1,2-dimethylpyrid-4-one, 1-ethyl-3-hydroxy-2-methylpyrid-4-one, 3-hydroxy-2-methyl-1-propylpyrid-4-one or 3-hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one, or a salt thereof containing a physiologically acceptable cation.

13. A compound according to Claim 1, being 3-hydroxy-1,2-dimethylpyrid-4-one, 1-ethyl-3-hydroxy-2-methylpyrid-4-one, 3-hydroxy-2-methyl-1-propylpyrid-4-one or 3-hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one, or a salt thereof containing a physiologically acceptable cation.

14. A compound according to any of the preceding claims being a pyridone in the free form rather than a salt.

15. A pharmaceutical composition comprising as an active component thereof 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, together with a physiologically acceptable diluent or carrier but excluding any liquid which is non-sterile and non-pyrogen free.

16. A pharmaceutical composition comprising as an active component thereof 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, together with a physiologically acceptable solid carrier.

17. A pharmaceutical composition according to Claim 16 which is adapted for oral administration.

18. A pharmaceutical composition according to Claim 17 which is formed as tablets.

19. A pharmaceutical composition according to Claim 16 in suppository form.

20. A pharmaceutical composition comprising as an active component thereof 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, together with a physiologically acceptable diluent the composition being of sterile injectable form.

21. A pharmaceutical composition according to any of Claims 15 to 20 in unit dosage form.

22. A pharmaceutical composition according to any of Claims 15 to 21, in which the or each aliphatic hydrocarbon group is of 1 to 4 carbon atoms.

23. A pharmaceutical composition according to any of Claims 15 to 22, in which the or each aliphatic hydrocarbon group is an acyclic group.

24. A pharmaceutical composition according to any of Claims 15 to 22, in which the or each aliphatic hydrocarbon group is a cycloalkyl or alkyl group.

25. A pharmaceutical composition according to any of Claims 15 to 21, in which the hydrogen atom attached to the nitrogen atom and, optionally, also one or more of the hydrogen atoms attached to ring carbon atoms are replaced by the same or different substituents selected from methyl, ethyl, n-propyl and isopropyl.

26. A pharmaceutical composition according to any of Claims 15 to 25, in which the 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one is substituted either only on the nitrogen atom or on the nitrogen atom and on one only of the ring carbon atoms.

27. A pharmaceutical composition according to any of Claims 15 to 26, in which any replacement of a hydrogen atom attached to a ring carbon atom is effected by a methyl group.

28. A pharmaceutical composition according to any of Claims 15 to 27, in which the pyridine is a 3-hydroxypyrid-4-one substituted on the nitrogen atom and by a single additional substituent at the 2- or 6-position.

29. A pharmaceutical composition according to any of Claims 15 to 21, in which the pyridone is 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one, 3-hydroxy-1-(1'-methylethyl)-pyrid-2-one, 3-hydroxy-1,2-dimethylpyrid-4-one, 1-ethyl-3-hydroxy-2-methylpyrid-4-one, 3-hydroxy-2-methyl-1-propylpyrid-4-one or 3-hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one, or a salt thereof containing a physiologically acceptable cation.

30. A pharmaceutical composition according to any of Claims 15 to 29, in which the pyridone is in the form of the free compound rather than a salt.

31. A compound being (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, or (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-dimethylpryid-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.

32. A compound according to Claim 31, in which the or each aliphatic hydrocarbon group is an acyclic group of 1 to 4 carbon atoms.

33. A compound according to Claim 32, in the aliphatic hydrocarbon group of groups are selected from methyl, ethyl, n-propyl and isopropyl.

34. A compound according to Claim 31, 32 or 33, being a 3-hydroxypyrid-2-one substituted either only on the nitrogen atom or on the nitrogen atom and on one only of the ring carbon atoms.

35. A compound according to Claim 31, 32 or 33, being a 3-hydroxypyrid-4-one substituted on the nitrogen atom and on one only of the ring carbon atoms.

36. A compound according to Claim 31, being 1-ethyl-3-hydroxypyrid-2-one, 3-hydroxy-1-propylpyrid-2-one or 3-hydroxy-1-(1'-methylethyl)-pyrid-2-one, or a salt thereof containing a physiologically acceptable cation.

37. The use of 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 the manufacture of a medicament for use in effecting a reduction in toxic levels of a metal in a patient's body.

38. The use of a compound according to Claim 37, in which the compound is a 3-hydroxypyrid-2-one or 3-hydroxypyrid-4-one as defined in any of Claims 2 to 14.

Patentansprüche

1. Eine Verbindung, nämlich 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das an das Stickstoffatom gebundene Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 mit 6 Kohlenstoffatomen ersetzt ist, und worin gegebenenfalls eines oder mehrere der an die Ringkohlenstoffatome gebundenen Wasserstoffatome durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind, oder ein Salz davon, welches ein physiologisch annehmbares Kation enthält, für die Verwendung in der Therapie.

2. Verbindung nach Anspruch 1, worin die oder jede aliphatische Kohlenwasserstoffgruppe 1 bis 4 Kohlenstoffatome enthält.

3. Verbindung nach Anspruch 1 oder 2, worin die oder jede aliphatische Kohlenwasserstoffgruppe eine acyclische Gruppe ist.

4. Verbindung nach Anspruch 1 oder 2, worin die oder jede aliphatische Kohlenwasserstoffgruppe eine Cycloalkyl- oder Alkylgruppe ist.

5. Verbindung nach Anspruch 1, worin das an das Stickstoffatom gebundene Wasserstoffatom und gegebenenfalls eines oder mehrere der an Ringkohlenstoffatome gebundenen Wasserstoffatome durch die gleichen oder unterschiedliche Substituenten, ausgewählt unter Methyl, Ethyl, n-Propyl und Isopropyl, ersetzt ist bzw. sind.

6. Verbindung nach einem der vorhergehenden Ansprüche, worin das 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on entweder nur an dem Stickstoffatom oder an dem Stickstoffatom und an nur einem der Kohlenstoffringatome substituiert ist.

7. Verbindung nach einem der vorhergehenden Ansprüche, worin die Substitution eines an das Ringkohlenstoffatom gebundenen Wasserstoffatoms durch eine Methylgruppe erfolgt ist.

8. Verbindung nach einem der vorhergehenden Ansprüche, nämlich ein 3-Hydroxypyrid-2-on, welches nur an dem Stickstoffatom substituiert ist.

9. Verbindung nach einem der Ansprüche 1 bis 7, nämlich 3-Hydroxypyrid-4-on.

10. Verbindung nach Anspruch 9, worin das 3-Hydroxypyrid-4-on an dem Stickstoffatom und durch einen einzigen zusätzlichen Substituenten in der 2- oder 6-Stellung substituiert ist.

11. Verbindung nach Anspruch 10, worin der einzige zusätzliche Substituent eine Methylgruppe in der 2-Stellung ist.

12. Verbindung nach Anspruch 11, nämlich 1-Ethyl-3-hydroxypyrid-2-on, 3-Hydroxy-1-propylpyrid-2-on, 3-Hydroxy-1-(1'-methylethyl)-pyrid-2-on, 3-Hydroxy-1,2-dimethylpyrid-4-on, 1-Ethyl-3-hydroxy-2-methylpyrid-4-on, 3-Hydroxy-2-methyl-1-propylpyrid-4-on oder 3-Hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-one, oder ein Salz davon, welches ein physiologisch annehmbares Kation enthält.

13. Verbindung nach Anspruch 1, nämlich 3-Hydroxy-1,2-dimethylpyrid-4-on, 1-Ethyl-3-hydroxy-2-methylpyrid-4-on, 3-Hydroxy-2-methyl-1-propylpyrid-4-on oder 3-Hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-on, oder ein Salz davon, welches ein physiologisch annehmbares Kation enthält.

14. Verbindung nach einem der vorhergehenden Ansprüche, nämlich ein Pyridon in freier Form statt eines Salzes.

15. Pharmazeutische Zubereitung, dadurch gekennzeichnet, daß sie als aktive Komponente ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, bei dem das an das Stickstoffatom gebundene Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen substituiert ist und bei dem gegebenenfalls eins oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen substituiert ist bzw. sind, oder eines ihrer Salze, welches ein physiologisch annehmbares Kation enthält, zusammen mit einem physiologisch annehmbaren Verdünnungsmittel oder Träger, ausgenommen irgendeine Flüssigkeit, welche nicht steril und nicht pyrogenfrei ist, enthält.

16. Pharmazeutische Zubereitung, dadurch gekennzeichnet, daß sie als aktive Komponente ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das an das Stickstoffatom gebundene Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist, und bei der gegebenenfalls eins oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome

gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind, oder ein Salze davon, welches ein physiologisch annehmbares Kation aufweist, zusammen mit einem physiologisch annehmbaren festen Träger, enthält.

17. Pharmazeutische Zubereitung nach Anspruch 16, dadurch gekennzeichnet, daß sie in einer für die orale Verabreichung geeigneten Form vorliegt.

18. Pharmazeutische Zubereitung nach Anspruch 17, dadurch gekennzeichnet, daß sie in Form von Tabletten vorliegt.

19. Pharmazeutische Zubereitung nach Anspruch 16, dadurch gekennzeichnet, daß sie in Form von Suppositorien vorliegt.

20. Pharmazeutische Zubereitung, dadurch gekennzeichnet, daß sie als aktive Komponente ein 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das an das Stickstoffatom gebundene Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist, und gegebenenfalls eins oder mehrere Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind, oder ein Salz davon mit einem physiologisch annehmbaren Kation, zusammen mit einem physiologisch annehmbaren flüssigen Verdünnungsmittel, enthält, wobei die Zubereitung in einer sterilen injizierbaren Form vorliegt.

21. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 20, dadurch gekennzeichnet, daß sie in Dosiseinheitsform vorliegt.

22. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 21, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe 1 bis 4 Kohlenstoffatome enthält.

23. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 22, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine acyclische Gruppe ist.

24. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 22, dadurch gekennzeichnet, daß die oder jede aliphatische Kohlenwasserstoffgruppe eine Cycloalkyl- oder Alkylgruppe ist.

25. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 21, dadurch gekennzeichnet, daß das an das Stickstoffatom gebundene Wasserstoffatom gegebenenfalls eins oder mehrere der an Ringkohlenstoffatome gebundene Wasserstoffatome durch gleiche oder unterschiedliche Substituenten, ausgewählt unter Methyl, Ethyl, n-Propyl und Isopropyl, ersetzt ist bzw. sind.

26. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 25, dadurch gekennzeichnet, daß das 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on entweder nur am Stickstoffatom oder am Stickstoffatom und an nur eines der Ringkohlenstoffatome substituiert ist.

27. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 26, dadurch gekennzeichnet, daß die Substitution des Wasserstoffatoms, welches an ein Ringkohlenstoffatom gebunden ist, durch eine Methylgruppe erfolgt.

28. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 27, dadurch gekennzeichnet, daß das Pyridon ein am Stickstoffatom substituiertes 3-Hydroxypyrid-4-on ist und einen einzigen zusätzlichen Substituenten in der 2- oder 6-Stellung aufweist.

29. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 21, dadurch gekennzeichnet, daß das Pyridon 1-Ethyl-3-hydroxypyrid-2-on, 3-Hydroxy-1-propylpyrid-2-on, 3-Hydroxy-1-(1'-methylethyl)-pyrid-2-on, 3-Hydroxy-1,2-dimethylpyrid-4-on, 1-Ethyl-3-hydroxy-2-methylpyrid-4-on, 3-Hydroxy-2-methyl-1-propylpyrid-4-on oder 3-Hydroxy-1-(1'-methylethyl)-2-methylpyrid-4-on, oder eines seiner Salze, welches ein physiologisch annehmbares Kation enthält, ist.

30. Pharmazeutische Zubereitung nach einem der Ansprüche 15 bis 29, dadurch gekennzeichnet, daß das Pyridon in Form der freien Verbindung anstatt als Salz vorliegt.

31. Verbindung, nämlich (a) ein 3-Hydroxypyrid-2-on, in dem das an das Stickstoffatom gebundene Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist, und daß gegebenenfalls eins oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatomen ersetzt ist, und daß gegebenenfalls eins oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatome ersetzt ist bzw. sind, oder (b) ein 3-Hydroxypyrid-4-on, in dem das an das Stickstoffatom gebundene Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist, wobei eins oder mehrere der Wasserstoffatome, die an Ringkohlenstoffatome gebunden sind, ebenfalls durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist oder sind, oder ein Salz eines solchen 3-Hydroxypyrid-2-ons oder 3-Hydroxypyrid-4-ons, welches ein physiologisch annehmbares Kation enthält, aber ausgenommen spezifisch 3-Hydroxy-1-methylpyrid-2-on, 3-Hydroxy-1,6-dimethylpyrid-4-on und 3-Hydroxypyrid-4-on, in denen nur der Ringkohlenstoffatom-Substituent eine Methylgruppe in 2-Stellung ist, und die Salze davon.

32. Verbindung nach Anspruch 31, worin die oder jede aliphatische Kohlenwasserstoffgruppe eine acyclische Gruppe mit 1 bis 4 Kohlenstoffatomen ist.

33. Verbindung nach Anspruch 32, worin die aliphatische Kohlenwasserstoffgruppe oder -gruppen ausgewählt wird bzw. werden unter Methyl, Ethyl, n-Propyl und Isopropyl.

34. Verbindung nach Anspruch 31, 32 oder 33, nämlich 3-Hydroxypyrid-2-on, welches entweder nur am Stickstoffatom oder an dem Stickstoffatom und nur an einem der Ringkohlenstoffatome substituiert ist.

35. Verbindung nach Anspruch 31, 32 oder 33, nämlich 3-Hydroxypyrid-4-on, welches am Stickstoffatom und nur an einem der Ringkohlenstoffatome substituiert ist.

36. Verbindung nach Anspruch 31, nämlich 1-Ethyl-3-hydroxypyrid-2-on, 3-Hydroxy-1-propylpyrid-2-on oder 3-Hydroxy-1-(1'-methylethyl)-pyrid-2-on, oder eines ihrer Salze, welches ein physiologish annehmbares Kation enthält.

37. Verwendung einer Verbindung, nämlich 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on, worin das an das Stickstoffatom gebundene Wasserstoffatom durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist, und worin gegebenenfalls eins oder mehrere der Wasserstoffatome an Ringkohlenstoffatome gebunden sind, auch durch eine aliphatische Kohlenwasserstoffgruppe mit 1 bis 6 Kohlenstoffatomen ersetzt ist bzw. sind, oder eines ihrer Salze, welches ein physiologisch annehmbares Kation enthält, für die Herstellung eines Arzneimittels für die Verwendung bei der Verringerung der toxischen Wirkung eines Metalls im Körper eines Patienten.

38. Verwendung einer Verbindung nach Anspruch 37, wobei die Verbindung 3-Hydroxypyrid-2-on oder 3-Hydroxypyrid-4-on gemäß einem der Ansprüche 2 bis 14 ist.

Revendications

1. Composé qui est une 3-hydroxypyrid-2-one ou une 3-hydroxypyrid-4-one, dans lesquelles l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, un ou plusieurs des atomes d'hydrogène fixés à des atomes de carbone cycliques est ou sont également remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou un de leurs sels contenant un cation physiologiquement acceptable, destiné à servir en thérapie.

2. Composé selon la revendication 1, dans lequel le ou chaque groupe hydrocarboné aliphatique comporte 1 à 4 atomes de carbone.

3. Composé selon la revendication 1 ou 2, dans lequel le ou chaque groupe hydrocarboné aliphatique est un groupe acyclique.

4. Composé selon l'une des revendications 1 ou 2, dans lequel le ou chaque groupe hydrocarboné aliphatique est un groupe cycloalkyle ou alkyle.

5. Composé selon la revendication 1, dans lequel l'atome d'hydrogène fixé à l'atome d'azote et, éventuellement, aussi un ou plusiers des atomes d'hydrogène fixés à des atomes de carbone cycliques, est ou sont remplacés par des substituants identiques ou différents choisis parmi un groupe méthyle, éthyle, n-propyle et isopropyle.

6. Composé selon l'une quelconque des revendications précédentes, dans lequel la 3-hydroxypyrid-2-one ou la 3-hydroxypyrid-4-one est substituée seulement sur l'atome d'azote ou bien sur l'atome d'azote et sur un seul des atomes de carbone cyclique.

7. Composé selon l'une quelconque des revendications précédentes, dans lequel tout remplacement éventuel d'un atome d'hydrogène fixé sur un atome de carbone cyclique est effectué par un groupe méthyle.

8. Composé selon l'une quelconque des revendications précédentes, qui est une 3-hydroxypyrid-2-one substituée seulement sur l'atome d'azote.

9. Composé selon l'une quelconque des revendications 1 à 7, qui est une 3-hydroxypyrid-4-one.

10. Composé selon la revendication 9, dans lequel la 3-hydroxypyrid-4-one est substituée sur l'atome d'azote et par un seul substituant supplémentaire en position 2 ou 6.

11. Composé selon la revendication 10, dans lequel le seul substituant supplémentaire est un groupe méthyle en position 2.

12. Composé selon la revendication 1, qui est la 1-éthyl-3-hydroxypyrid-2-one, la 3-hydroxy-1-propylpyrid-2-one, la 3-hydroxy-1-(1'-méthyléthyl)-pyrid-2-one, la 3-hydroxy-1,2-diméthylpyrid-4-one, la 1-éthyl-3-hydroxy-2-méthylpyrid-4-one, la 3-hydroxy-2-méthyl-1-propylpyrid-4-one ou la 3-hydroxy-1-(1'-méthyléthyl)-2-méthylpyrid-4-one ou un de leurs sels contenant un cation physiologiquement acceptable.

13. Composé selon la revendication 1, qui est la 3-hydroxy-1,2-diméthylpyrid-4-one, la 1-éthyl-3-hydroxy-2-méthylpyrid-4-one, la 3-hydroxy-2-méthyl-1-propylpyrid-4-one ou la 3-hydroxy-1-(1'-méthyléthyl)-2-méthylpyrid-4-one, ou un de leurs sels, contenant un cation physiologiquement acceptable.

14. Composé selon l'une quelconque des revendications précédentes, qui est une pyridone sous forme libre plutôt que d'être un sel.

15. Composition pharmaceutique comprenant, à titre de composant actif, une 3-hydroxypyrid-2-one ou une 3-hydroxypyrid-4-one dans laquelle l'atome d'hydrogène fixé sur l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone cycliques et ou sont également remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou un de leurs sels contenant un cation physiologiquement acceptable, avec un diluant ou excipient physiologiquement acceptable, mais à l'exclusion de tout liquide qui n'est stérile et qui n'est pas dépourvu de pyrogènes.

16. Composition pharmaceutique comprenant comme composant actif une 3-hydroxypyrid-2-one ou une 3-hydroxypyrid-4-one dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, un ou plusieurs des

atomes d'hydrogène fixés sur des atomes de carbone cycliques et ou sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou un de leurs sels contenant un cation physiologiquement acceptable, avec un excipient solide physiologiquement acceptable.

17. Composition pharmaceutique selon la revendication 16, qui est destinée à l'administration orale.

18. Composition pharmaceutique selon la revendication 17, qui est sous forme de comprimés.

19. Composition pharmaceutique selon la revendication 16, qui est sous forme de comprimés.

20. Composition pharmaceutique comprenant, à titre de composant actif, une 3-hydroxypyrid-2-one ou une 3-hydroxypyrid-4-one dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone cycliques et ou sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou un de leurs sels contenant un cation physiologiquement acceptable, avec un diluant liquide physiologiquement acceptable, la composition étant sous forme injectable stérile.

21. Composition pharmaceutique selon l'une quelconque des revendications 15 à 20, sous forme de doses unitaires.

22. Composition pharmaceutique selon l'une quelconque des revendications 15 à 21, dans laquelle le ou chaque groupe hydrocarboné aliphatique comporte 1 à 4 atomes de carbone.

23. Composition pharmaceutique selon l'une quelconque des revendications 15 à 22, dans laquelle le ou chaque groupe hydrocarboné aliphatique est un groupe acyclique.

24. Composition pharmaceutique selon l'une quelconque des revendications des revendications 15 à 22, dans laquelle le ou chaque groupe hydrocarboné aliphatique est un groupe cycloalkyle ou alkyle.

25. Composition pharmaceutique selon l'une quelconque des revendications 15 à 21, dans laquelle l'atome d'hydrogène fixé à l'atome d'azote et, éventuellement, également un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone cycliques et ou sont remplacés par des substituants, identiques ou différents, choisis parmi un groupe méthyle, éthyle, n-propyle et isopropyle.

26. Composition pharmaceutique selon l'une quelconque des revendications 15 à 25, dans laquelle la 3-hydroxypyrid-2-one ou la 3-hydroxypyrid-4-one est substituée seulement sur l'atome d'azote ou bien sur l'atome d'azote et sur un seulement des atomes de carbone cycliques.

27. Composition pharmaceutique selon l'une quelconque des revendications 15 à 26, dans laquelle tout remplacement éventuel d'un atome d'hydogène fixé sur un atome de carbone cyclique est effectué par un groupe méthyle.

28. Composition pharmaceutique selon l'une quelconque des revendications 15 à 27, dans laquelle la pyridone est une 3-hydroxypyrid-4-one substituée sur l'atome d'azote et par un seul substituant supplémentaire en position 2 ou 6.

29. Composition pharmaceutique selon l'une quelconque des revendications 15 à 21, dans laquelle la pyridone est la 1-éthyle-3-hydroxypyrid-2-one, la 3-hydroxy-1-propylpyrid-2-one, la 3-hydroxy-1-(1'-méthyléthyl)-pyrid-2-one, la 3-hydroxy-1,2-diméthylpyrid-4-one, la 1-éthyl-3-hydroxy-2-méthylpyrid-4-one, la 3-hydroxy-2-méthyl-1-propylpyrid-4-one ou la 3-hydroxy-1-(1'-méthyléthyl)-2-méthylpyrid-4-one ou un de leurs sels contenant un cation physiologiquement acceptable.

30. Composition pharmaceutique selon l'une quelconque des revendications 15 à 29, dans laquelle la pyridone est sous forme du composé libre plutôt que d'un sel.

31. Composé qui est (a) une 3-hydroxypyrid-2-one dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone cycliques est ou sont également remplacés par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou (b) une 3-hydroxypyrid-4-one dans laquelle l'atome d'hydrogène fixé à l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone cyclique est ou sont également remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou un sel d'une telle 3-hydroxypyrid-2-one ou 3-hydroxypyrid-4-one contenant un cation physiologiquement acceptable, mais à l'exclusion spécifiquement de la 3-hydroxy-1-méthylpyrid-2-one, de la 3-hydroxy-1,6-diméthylpyrid-4-one et de 3-hydroxypyrid-4-ones dans lesquelles le seul substituant d'un atome de carbone cyclique est un groupe méthyle en position 2, et leurs sels.

32. Composé selon la revendication 31, dans lequel le ou chaque groupe hydrocarboné aliphatique est un groupe acyclique ayant 1 à 4 atomes de carbone.

33. Composé selon la revendication 32, dans lequel le ou les groupes hydrocarbonés aliphatiques est ou sont choisis parmi un groupe méthyle, éthyle, n-propyle et isopropyle.

34. Composé selon la revendication 31, 32 ou 33, qui est une 3-hydroxypyrid-2-one substituée seulement sur l'atome d'azote ou bien sur l'atome d'azote et sur un seul des atomes de carbone cycliques.

35. Composé selon la revendication 31, 32 ou 33, qui est une 3-hydroxypyrid-4-one substituée sur l'atome d'azote et sur un seul des atomes de carbone cycliques.

36. Composé selon la revendication 31, qui est la 1-éthyl-3-hydroxypyrid-2-one, la 3-hydroxy-1-propylpyrid-2-one ou la 3-hydroxy-1-(1'-méthyléthyl)-pyrid-2-one, ou un de leurs sels contenant un cation physiologiquement acceptable.

37. Utilisation d'un composé qui est une 3-hydroxypyrid-2-one ou une 3-hydroxypyrid-4-one dans

laquelle l'atome d'hydogène fixé sur l'atome d'azote est remplacé par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone et, éventuellement, un ou plusieurs des atomes d'hydrogène fixés sur des atomes de carbone cycliques est ou sont également remplacé(s) par un groupe hydrocarboné aliphatique ayant 1 à 6 atomes de carbone, ou un de leurs sels contenant un cation physiologiquement acceptable, pour la fabrication d'un médicament destiné à servir à effectuer une diminution des taux toxiques d'un métal dans le corps d'un patient.

38. Utilisation d'un composé selon la revendication 37, dans laquelle le composé est une 3-hydroxypyrid-2-one ou une 3-hydroxypyrid-4-one telle que définie dans l'une quelconque des revendications 2 à 14.

THE PATENT OFFICE

State House 66-71 High Holborn London WC1R 4TP

Switchboard 01-831 2525

RENEWAL DETAILS

PATENT No 0093498

RENEWAL DATE ..... ~~6th~~ 24-3-89

RENEWAL FEE PAID FOR ..... 6th ..... YEAR ON 17-2-88

..... B. S. A. .....

FOR THE COMPTROLLER

NOTE: RENEWALS FILED WITHIN THE LAST FEW DAYS MAY NOT APPEAR IN THE RECORDS

(11) (43) Publication No.
0093498 A dated 9 November 1983

(45) Patent Granted: 26 November 1986

(21) (22) Application No.
833016595 filed on 24 March 1983

(30) Priority claimed:
24 March 1982 in United Kingdom doc 8208608

(84) Designated States:
Belgium, Switzerland, Federal Republic of Germany, France, United Kingdom, Italy, Liechtenstein, The Netherlands, Sweden.

(54) Title:
Pharmaceutical compositions containing N-substituted-3-hydroxypyrid-2-one or -4-one derivatives.

(73) Proprietor:
NATIONAL RESEARCH DEVELOPMENT CORPORATION, 101 Newington Causeway, London SE1 6BU,

(72) Inventors:
Hider, Robert Charles, 257 Point Clear Road, St. Osyth Clacton Essex,

Kontoghiorghes, George, 15 Celia Road, Tufnell Park London N19,

Silver, Jack, 50 Stanbury Court, Haverstock Hill London NW3,

(51) Classified to:
A61K 31/44

Address for Service:

G F. Stephenson
National Research Development Corp.
101, Newington
Causeway
LONDON SE1 6BU.

Printed by the Patent Office at St. Mary Cray, 30 OCT 86