Simple Synthesis of the Potent Iron Chelators 1-Alkyl-3-hydroxy-2-methylpyrid-4-ones

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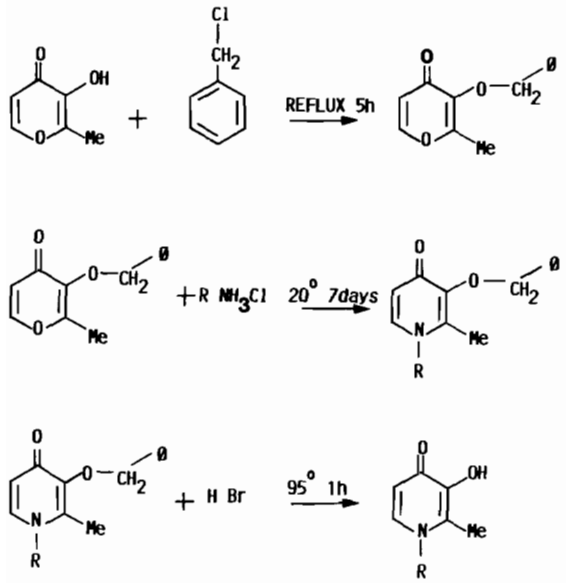
The current treatment of transfusional iron overload using desferrioxamine is limited to a small number of patients worlwide because this chelator is highly expensive and thus unobtainable by most countries that need it and also orally inactive [1, 2]. One of the most promising experimental groups of chelators which could replace desferrioxamine are the 1-alkyl-3-hydroxy-2-methylpyrid-4-one derivatives which are orally and parenterally effective in the removal of iron *in vivo* from rabbits [3] and mice [4] and also from transferrin [5] and ferritin [7] *in vitro*.

Although several methods for the preparation of these chelators have already been reported [7–9] including one shown in Scheme 1 [9], the need for an inexpensive synthesis and the knowledge that these hydroxypyridones and maltol are generally highly stable and in particular stable at high alkali concentrations, prompted us to attempt a direct one-step preparation.



R=Me, Et, nPr.

Scheme 1. The long synthetic route of 1-alkyl-3-hydroxy-2-methylpyrid-4-ones.

Experimental

Synthesis of the 1-Alkyl-2-methyl-3-hydroxypyrid-4-ones

1,2-Dimethyl-3-hydroxypyrid-4-one was prepared from the reflux for 6.5 h of 3-hydroxy-2-methylpyr-4-one (maltol) (10 g) with 3 equivalents of aqueous methylamine (40%) in 200 ml of water. Decolourising charcoal was added after refluxing and the mixture left for 0.5 h. This was then filtered and the dark brown filtrate was evaporated *in vacuo* to give a dark brown solid. Crystallisation from hot water gave fine white needles of 1,2-dimethyl-3-hydroxypyrid-4-one (50% yield). ^{1}H NMR (60 MHz; D_2O); δ 2.35 (3 H, s, 2-CH_3), 3.70 (3 H, s, 1-CH_3), 6.36 and 7.48 (2 H, ABq *J* 7 Hz, H-5 and H-6).

1-Ethyl-3-hydroxy-2-methylpyrid-4-one was prepared in a similar manner to 1,2-dimethyl-3-hydroxypyrid-4-one using 3 equivalents of aqueous ethylamine (70%). Crystallisation from hot methanol gave brown crystals which on recrystallisation from the same solvent gave 1-ethyl-3-hydroxy-2-methylpyrid-4-one as white octahedra (24% yield). ^{1}H NMR (60 MHz; D_2O): δ 1.26 (3 H, t *J* 7 Hz, $-CH_2CH_3$), 2.28 (3 H, s, 2-CH_3), 3.94 (2 H, q *J* 7 Hz, $-CH_2CH_3$), 6.32 and 7.43 (2 H, ABq *J* 7 Hz, H-5 and H-6).

3-Hydroxy-2-methyl-1-propylpyrid-4-one was prepared in a similar manner to 1,2-dimethyl-3-hydroxypyrid-4-one using 3 equivalents of neat n-propylamine. Crystallisation from hot acetone gave an orange brown solid which on recrystallisation yielded colourless blades (21% yield). ^{1}H NMR (60 MHz, D_2O): δ 0.82 (3 H, ~t *J* 7 Hz, $-CH_2CH_2CH_3$), 1.36–1.95 (2 H, m, $-CH_2CH_2CH_3$), 2.29 (3 H, s, 2-CH_3), 3.88 (2 H, ~t *J* 7 Hz, $-CH_2CH_2CH_3$), 6.33 and 7.42 (2 H, ABq *J* 7 Hz, H-5 and H-6).

Although the yields reported here are lower than those reported from other methods of the preparation of the 1-methyl derivative (55–57%) [7, 8] or the 1-methyl (48%), 1-ethyl (48%) 1-propyl (36%) derivatives [9], no attempts have been made to optimise them.

Partition Coefficients of the Chelators and Red Blood Cell Permeability Studies of the Chelator Iron Complexes

The partition coefficients of the chelators and their iron complexes were determined using a mixture of n-octanol and phosphate buffer saline at pH 7.3 as previously described [9, 10]. The effect of the chelators on the incorporation of iron containing traces of ^{59}Fe into red blood cells was studied as

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TABLE I. Properties of the Chelators and their Iron Complexes

Derivatives of 3-hydroxy-2-methylpyrid-4-ones	Lethal dose (range)[b] (mg/kg)	K_{par}[a] chelator	K_{par}[a] iron complex	^{59}Fe incorporation (%)	
				20 min	1 h
1-Methyl	600–700	0.19	0.24	5.0	5.0
1-Ethyl	400–500	0.47	0.52	5.0	10
1-Propyl	150–200	3.16	4.12	85	86

[a]K_{par} is the n-octanol/phosphate buffer saline (pH 7.3) partition coefficient of the chelator. [b]Range of doses, the higher being lethal and the lower a non-lethal dose. [c]The percentage incorporation of traces of ^{59}Fe mixed with iron (2.5×10^{-5} M) into red blood cells in the presence of the chelators (18×10^{-5} M) was estimated from the total ^{59}Fe count of red blood cells plus supernatant/oil (100% ^{59}Fe 1.4×10^3 cpm).

previously described [10] by incubating the chelator iron complexes with packed red blood cells at 37 °C, withdrawing aliquots, centrifuging and measuring the incorporation of ^{59}Fe into the red blood cells.

Studies in Animals

The three 1-alkyl-3-hydroxy-2-methylpyrid-4-ones dissolved in phosphate buffer saline were administered intraperitoneally to groups of three male Sprague Dawley rats (60–90 g), at different doses until a near maximum non-lethal dose was established.

Results and Discussion

Although the yields reported here for the preparation of 1-alkyl-2-methyl-3-hydroxypyrid-4-ones are lower than those reported from other methods of the preparation of the 1-methyl derivative (55–57%) [7, 8] or the 1-methyl (48%), 1-ethyl (48%) and 1-propyl (36%) derivatives [9], no attempts have been made to optimise them. It should be emphasised however, that this single step synthetic pathway is much easier and overall less expensive than any of the other ones previously proposed.

The partition coefficients of the chelators and their iron complexes were shown to increase as the chain length of the *N*-alkyl substituents was increasing (Table I).

The lower lethal dose observed in rats treated with the propyl derivative in comparison to those treated with the other two derivatives may be related to the higher K_{par} of the former (Table I). Although doses of up to 200 mg/kg of the 1-methyl and 1-ethyl hydroxypyridones were shown to be effective in increasing iron excretion in iron loaded mice and rabbits [3] and also in non iron loaded mice [4], further studies are required to establish therapeutic and lethal doses in rats and other animals.

The red blood cell membrane permeability of iron in the presence of the chelators seems also to be related to the partition coefficient of the chelator iron complexes (Table I) which is in agreement with previous observations [9]. Lipophilic iron chelator complexes such as that of 1-propyl-2-methyl-3-hydroxypyrid-4-one which could easily diffuse through membranes may have a use in the treatment of iron deficiency anaemia by increasing iron absorption.

The oral activity, low cost and easy method of preparation of the 1-alkyl-3-hydroxy-2-methylpyrid-4-ones increase the prospects for the use of these 'orphan' drugs [2] in the treatment of iron overload and other forms of iron imbalance and also their use as probes for studying many aspects of iron metabolism. Further attempts are needed to improve the yield of the synthetic route described.

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