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# 3-Hydroxy-1-(3-imidazolylpropyl)-2-methyl-4-pyridinone dihydrochloride dihydrate

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**Key indicators**

Single-crystal X-ray study
$T$ = 293 K
Mean $\sigma$(C–C) = 0.006 Å
$R$ factor = 0.062
$wR$ factor = 0.151
Data-to-parameter ratio = 19.4

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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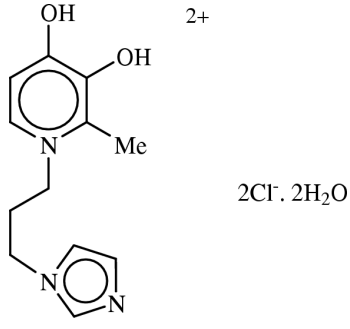
The crystal structure of the title compound, $C_{12}H_{17}N_3O_2^{2+}\cdot 2Cl^-\cdot 2H_2O$, has been determined. The effects of protonating the ketonic oxygen with regard to bond distances within the hydroxypyridinone moiety are discussed and compared to the equivalent bond distances in the parent compounds 3-hydroxy-1,2-dimethyl-4-pyridinone hydrochloride monohydrate and hydrobromide monohydrate and 3-hydroxy-1,2-dimethyl-4-pyridinone itself.

## Comment

3-Hydroxy-4-pyridinones and several of their metal complexes are proving of considerable value and interest in relation to the control of metal levels (particularly of iron) and the introduction of metal ions (*e.g.* Ga, In, Gd) into the body for diagnosis or therapy (Hider & Hall, 1998). Appropriate substitution is needed to maximize effectiveness while minimizing undesirable side effects; the incorporation of acidic ($-SO_3H$ and $-CO_2H$) or basic (nitrogen-containing) moieties confers a useful degree of hydrophilicity and the possibility of pH control (Molenda *et al.*, 1994). The attachment of imidazole-containing moieties to the N atom of the pyridinone ring has recently been shown to be advantageous in the development of chelators for targetting lysosome iron (Lu *et al.*, 2000). We report here the structure of such an imidazole-containing hydroxypyridinone, in a doubly protonated form in a hydrated hydrochloride salt, specifically 3-hydroxy-1-(3-imidazolylpropyl)-2-methyl-4-pyridinone dihydrochloride dihydrate, (I); this complements the published information on ligand synthesis and properties.




(I)

The pyridinone is, as expected, essentially planar. Bond distances and angles in the hydroxypyridinone moiety are the same, within experimental uncertainty, as those in the parent compounds 3-hydroxy-1,2-dimethyl-4-pyridinone hydrochloride monohydrate (Parsons, 1993) and hydrobromide

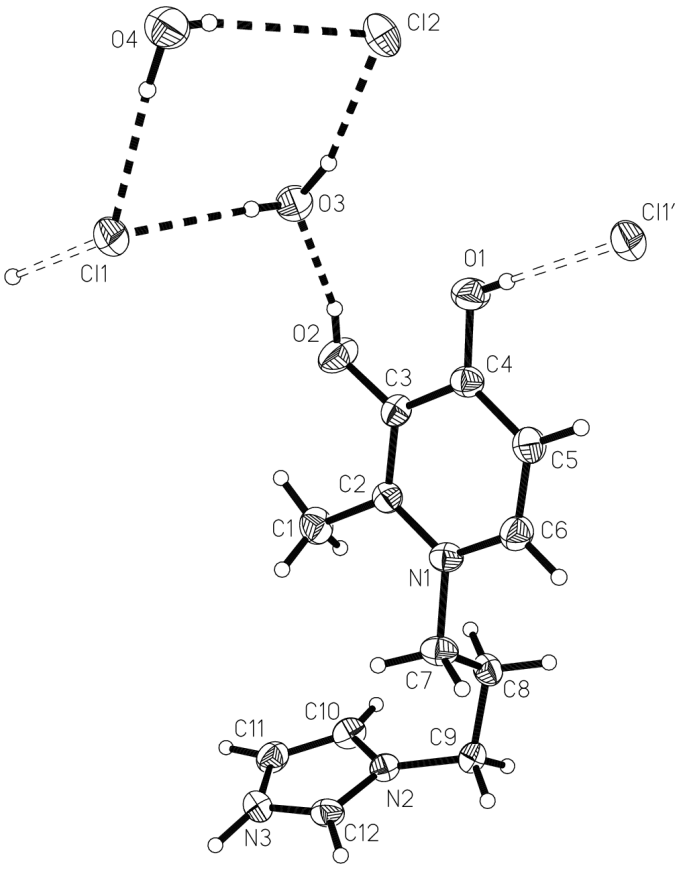



**Figure 1**
The molecular structure of (I) showing the atom-numbering scheme and 30% displacement ellipsoids. Hydrogen bonds are shown dashed and H atoms are drawn as spheres of arbitrary radii.

monohydrate (Hider *et al.*, 1990). This is shown in Table 2, where selected bond distances in the hydroxypyridinone moieties of these hydrohalide salts are compared with each other and with the analogous bond distances in 3-hydroxy-1,2-dimethyl-4-pyridinone (L1) itself (Clarke *et al.*, 1992). Protonation of the ketonic oxygen, O1, results in an extension of the C4—O1 bond to a length almost that of C3—O2. Both C—O bonds are considerably shorter than the sum of the covalent radii of carbon and oxygen (1.43 Å). The double-bond character of C3—C4 is significantly reduced as a result of protonation of O1. Other bonds in the pyridinone ring, and the N—C bond connecting the 1-substituent to the pyridinone ring, are not significantly affected by protonation.

In the title compound, as in L1·H*X*·$H_2O$ (*X* = Cl or Br), the hydroxypyridinone moiety and halide ions are linked by hydrogen bonding, as shown in Fig. 1. The hydrogen-bonded chloride–water–chloride– columns lie parallel to the columns of the imidazole-hydroxypyridinone molecules; both sets of columns lie parallel to the *b* axis.

The imidazole ring approximates closely to planarity. Its C—N and C—C bond distances are within the ranges established from structure determinations for a large number of organic and organometallic derivatives. In particular, the interatomic distances in the imidazole ring of (I) are very similar to those in several imidazolium salts, such as 1-methylimidazolium hydrogen–D-tartrate (Fuller *et al.*, 1995) and trichloromethylphosphonate (Holmes *et al.*, 1992), and 3-ethyl-1-methylimidazolium nitrite (Wilkes & Zaworotko, 1992). Such imidazolium salts tend to have the shortest C12—N2 bonds, *i.e.* most double-bond character to this bond.

## Experimental

The title compound was prepared by the so-called 'protected route' (Harris, 1976; Farber *et al.*, 1994). A solution of 30 g of maltol (Aldrich), 10.5 g sodium hydroxide, and 33.3 g benzyl chloride, dissolved in 150 ml of 70/30 (by volume) methanol/water was refluxed for 8 h. The resultant solution was allowed to cool, then most of the methanol was removed under reduced pressure. Water (100 ml) was added, and the product extracted into dichloromethane (2 × 100 ml portions). The extracts were combined, washed with 100 ml of dilute sodium hydroxide solution, then 100 ml water, and dried over anhydrous magnesium sulfate. Evaporation of the dichloromethane solvent left a residue of crude benzyl-protected intermediate. 20 g of this intermediate were refluxed in ethanol (50 ml) with a threefold excess of imidazole for 6 h. The pH of the product solution was reduced to 2 with dilute hydrochloric acid and the resulting solution washed with diethyl ether to recover unreacted intermediate. The pH was then raised to 7 (ammonium hydroxide) and the benzyl derivative of the required product extracted into dichloromethane (2 × 100 ml portions). The dichloromethane was removed from the combined extracts under reduced pressure prior to the removal of the protecting group. This was achieved by hydrogenolysis of a solution of the benzyl derivative, in 100 ml of ethanol containing hydrogen chloride (2%), using a palladium (10%)-activated charcoal catalyst. The resulting solution was filtered, the ethanol reduced under reduced pressure, and the product recrystallized from 50/50 (by volume) ethanol/water. A crystal suitable for X-ray examination was selected from this product.

*Crystal data*

$C_{12}H_{17}N_3O_2^{2+}\cdot 2Cl^-\cdot 2H_2O$
$M_r$ = 342.22
Triclinic, $P\overline{1}$
$a$ = 7.324 (6) Å
$b$ = 7.342 (9) Å
$c$ = 15.559 (10) Å
$\alpha$ = 77.95 (1)°
$\beta$ = 86.43 (1)°
$\gamma$ = 78.09 (1)°
$V$ = 800.4 (13) Å$^3$
$Z$ = 2
$D_x$ = 1.420 Mg m$^{-3}$
Mo $K\alpha$ radiation
Cell parameters from 38 reflections
$\theta$ = 5.2–12.5°
$\mu$ = 0.42 mm$^{-1}$
$T$ = 293 (2) K
Block, pale orange
0.34 × 0.22 × 0.12 mm

*Data collection*

Bruker *P*4 diffractometer
$\omega$ scans
4551 measured reflections
3686 independent reflections
1858 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.069
$\theta_{max}$ = 27.5°
$h = -1 \rightarrow 9$
$k = -9 \rightarrow 9$
$l = -20 \rightarrow 20$
3 standard reflections every 100 reflections
intensity decay: <1%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.062
$wR(F^2)$ = 0.151
$S$ = 1.00
3686 reflections
190 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0467P)^2 + 0.4761P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.28 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.36 e Å$^{-3}$

**Table 1**
Hydrogen-bonding geometry (Å, °).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| O1—H1···Cl1$^{i}$ | 0.82 | 2.11 | 2.932 (4) | 176 |
| O2—H2···O3 | 0.82 | 1.79 | 2.580 (4) | 162 |
| O3—H3$A$···Cl1 | 0.84 | 2.33 | 3.153 (4) | 169 |
| O3—H3$B$···Cl2 | 0.98 | 2.22 | 3.166 (3) | 163 |
| O4—H4$B$···Cl1 | 0.99 | 2.19 | 3.151 (4) | 166 |
| O4—H4$A$···Cl2 | 0.95 | 2.24 | 3.139 (4) | 158 |
| N3—H3···O4$^{ii}$ | 0.95 | 2.03 | 2.776 (5) | 135 |
| N3—H3···Cl2$^{iii}$ | 0.95 | 2.69 | 3.348 (4) | 127 |

Symmetry codes: (i) $x, 1+y, z$; (ii) $-x, 1-y, 1-z$; (iii) $x, y-1, 1+z$.

**Table 2**
Comparison of selected bond distances (Å) in the hydropyridinone moiety of (I) with analogous distances in the hydrochloride and hydrobromide of L1 and in free L1.

| | C4—O1 | C3—O2 | $\Delta^{a}$ | C3—C4 | C5—C6 | N1—C7 |
|---|---|---|---|---|---|---|
| (I) | 1.315 (5) | 1.330 (5) | 0.015 | 1.393 (5) | 1.358 (6) | 1.474 (5) |
| L1·HCl | 1.338 (3) | 1.342 (3) | 0.004 | 1.408 (4) | 1.347 (5) | 1.484 (3) |
| L1·HBr | 1.328 (5) | 1.343 (5) | 0.015 | 1.385 (6) | 1.349 (7) | 1.479 (7) |
| L1 | 1.278 (3) | 1.363 (3) | 0.085 | 1.431 (4) | 1.356 (4) | 1.469 (4) |

Notes: (*a*) Δ is the difference between the CO bond distances to the ketonic and hydroxylic O atoms, C4—O1 and C3—O2, respectively.

Data collection: *XSCANS* (Fait, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXL*97; software used to prepare material for publication: *SHELXL*97.

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