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Structures of 3-Hydroxy-1-(2-methoxyethyl)-2-methyl-4-pyridinone, its Hydrochloride and 1-Ethyl-3-hydroxy-2-methyl-4-pyridinone Hydrochloride Hydrate

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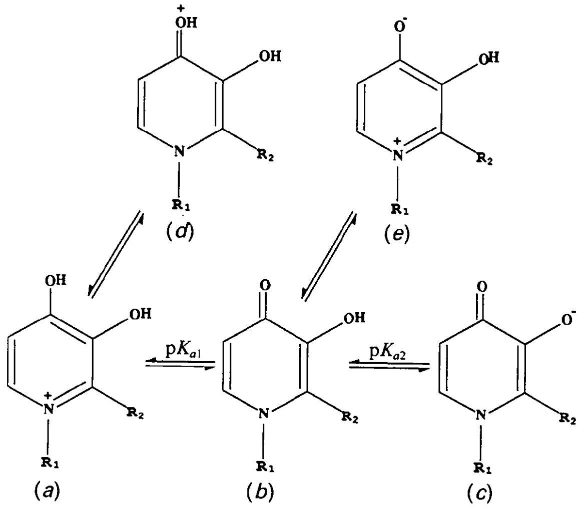
Abstract

3-Hydroxy-1-(2-methoxyethyl)-2-methyl-4(1*H*)-pyridinone (1) exists mainly in the quinoid form with a small contribution from the aromatic zwitterion form, while 3-hydroxy-1-(2-methoxyethyl)-2-methyl-4(1*H*)-pyridinone hydrochloride (2) and 1-ethyl-3-hydroxy-2-methyl-4(1*H*)-pyridinone hydrochloride hydrate (3) are observed to occur in the aromatic form with a minor contribution from the quinoid resonance form. Different substituents at the ring N position do not have significant geometric effects in either the neutral molecules, as a group, or in the hydrochloride salts.

Comment

3-Hydroxy-4-pyridinones are currently being investigated as orally active iron chelators for the treatment of transfusion-induced iron overload and in particular thalassaemia (Porter, Huehns & Hider, 1989). As part of the continuing structural studies (Hider, Taylor, Walkinshaw, Wang & van der Helm, 1990; Xiao, van der Helm, Hider & Dobbin, 1992; Hider, Dobbin, Taylor, Hall, Porter, Saspong, Xiao & van der Helm, 1993) we report here the structural chemistry of the three title compounds. The crystal structure of (3) was determined earlier (Hider *et al.*, 1990) but a more accurate structure is required for the present comparison studies. The chemical syntheses of these compounds have been described elsewhere (Hider, Kontoghiorges & Silver, 1982). Resonance forms of the title molecules are shown below, where $R_1 = (CH_2)_2OCH_3$, $R_2 = CH_3$ for (1) and (2), and $R_1 = CH_2CH_3$, $R_2 = CH_3$ for (3).



In structure (1), the C(3)—O(1), C(3)—C(4) and C(4)—O(2) bond distances are essentially the same as in the other two neutral 2-methyl congeners (Hider *et al.*, 1990; Nelson, Karpishin, Rettig & Orvig, 1988; Nelson, Rettig & Orvig, 1989; Xiao, van der Helm, Hider & Dobbin, 1992). This implies that different alkyl substitutients at the ring N position can be expected to have little effect on the pK_a values of 3-hydroxy-4-pyridinones and their affinities for metal ions. Like other 3-hydroxy-4-pyridinones, the heterocyclic ring of the neutral ligand (1) is mainly in the quinoid form (*b*) (see scheme above). However, the C(4)—O(2) bond is significantly longer [1.262 (2) Å] than a normal ketone bond (1.210 Å), and therefore an aromatic resonance form (*e*) contributes to the structure as well, giving a partial negative charge to O(2) and a partial positive charge to N(1). This zwitterionic resonance form is more pronounced for 3-hydroxy-4-pyridinones than for 3-hydroxy-2-pyridinones (Xiao *et al.*, 1992) and the difference is believed to be the cause of the larger complexation constants of the former compounds. Resonance form (*e*) also makes it possible for the molecule to form a strongly hydrogen-bonded dimeric unit.

In structures (2) and (3), the bond distances in the common part are comparable with each other. A significant delocalization from the C(4)—O(2) bond towards the ring occurs upon protonation of the carbonyl O(2) atom. Furthermore, the C(3)—C(4) and C(4)—C(5) single bonds become shorter while the C(2)—C(3) and C(5)—C(6) double bonds become longer. The main resonance form, therefore, is aromatic (*a*). Nevertheless, the longer C(3)—O(1) bond distance compared to the C(4)—O(2) bond, and longer C(3)—C(4) and C(4)—C(5) bonds compared to the C(2)—C(3) and C(5)—C(6) bonds in the protonated ligands (2) and (3), suggest a contribution from resonance form (*d*) (see scheme above).

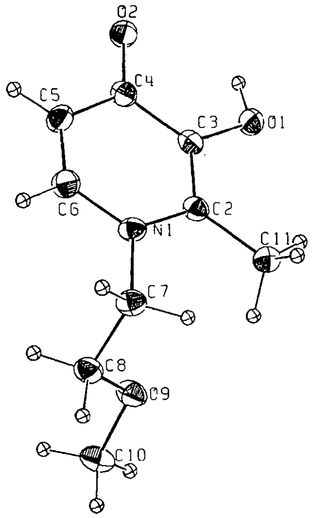


Fig. 1. An *ORTEP* (Johnson, 1976) plot of a single molecule of (1).

Experimental

Compound (1)

Crystal data

$C_9H_{13}NO_3$
$M_r = 183.21$
Monoclinic
$P2_1/a$
$a = 15.158\ (4)$ Å
$b = 8.435\ (2)$ Å
$c = 7.277\ (1)$ Å
$\beta = 103.52\ (1)°$
$V = 904.6\ (6)$ Å^3
$Z = 4$
$D_x = 1.35$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 48 reflections
$\theta = 19$-$48°$
$\mu = 0.851$ mm^{-1}
$T = 138\ (2)$ K
Needle
0.31 × 0.12 × 0.10 mm
Colorless

Data collection

Enraf-Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
1853 measured reflections
1853 independent reflections
1577 observed reflections $[I \geq 2\sigma(I)]$

$\theta_{\max} = 75.0°$
$h = 0 \rightarrow 19$
$k = 0 \rightarrow 10$
$l = -9 \rightarrow 9$
3 standard reflections
frequency: 120 min
intensity variation: 2.4%

Refinement

Refinement on F
Final $R = 0.036$
$wR = 0.047$
$S = 1.80$
1577 reflections
170 parameters
All H-atom parameters refined

$w = 1/\sigma^2(F)$
$(\Delta/\sigma)_{\max} = 0.071$
$\Delta\rho_{\max} = 0.26$ e Å^{-3}
$\Delta\rho_{\min} = -0.19$ e Å^{-3}
Atomic scattering factors from *SHELXS*86 (Sheldrick, 1986)

Compound (2)

Crystal data

$C_9H_{13}NO_3.HCl$
$M_r = 219.67$
Orthorhombic
$P2_12_12_1$
$a = 11.865\ (3)$ Å
$b = 12.174\ (4)$ Å
$c = 7.127\ (2)$ Å
$V = 1029.5\ (9)$ Å^3
$Z = 4$
$D_x = 1.42$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 48 reflections
$\theta = 11$-$15°$
$\mu = 0.357$ mm^{-1}
$T = 138\ (2)$ K
Needle
0.25 × 0.10 × 0.10 mm
Colorless

Data collection

Enraf-Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
1265 measured reflections
1265 independent reflections
1139 observed reflections $[I \geq 2\sigma(I)]$

$\theta_{\max} = 26.5°$
$h = 0 \rightarrow 14$
$k = 0 \rightarrow 15$
$l = 0 \rightarrow 8$
3 standard reflections
frequency: 120 min
intensity variation: 5.7%

Refinement

Refinement on F
Final $R = 0.033$
$wR = 0.039$
$S = 1.41$
1139 reflections
183 parameters
All H-atom parameters refined

$w = 1/\sigma^2(F)$
$(\Delta/\sigma)_{\max} = 0.065$
$\Delta\rho_{\max} = 0.37$ e Å^{-3}
$\Delta\rho_{\min} = -0.39$ e Å^{-3}
Atomic scattering factors from *SHELXS*86 (Sheldrick, 1986)

Compound (3)

Crystal data

$C_8H_{11}NO_2.HCl.H_2O$
$M_r = 207.656$

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å

Monoclinic
$P2_1/c$
$a = 6.6361\ (4)$ Å
$b = 17.115\ (1)$ Å
$c = 9.1024\ (5)$ Å
$\beta = 98.473\ (5)°$
$V = 1022.5\ (1)$ Å^3
$Z = 4$
$D_x = 1.35$ Mg m^{-3}

Cell parameters from 48 reflections
$\theta = 19–31°$
$\mu = 3.148$ mm^{-1}
$T = 138\ (2)$ K
Needle
0.28 × 0.12 × 0.08 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2096 measured reflections
2096 independent reflections
1920 observed reflections $[I \geq 2\sigma(I)]$

$\theta_{\max} = 75.0°$
$h = 0 \rightarrow 8$
$k = 0 \rightarrow 21$
$l = -11 \rightarrow 11$
3 standard reflections
frequency: 120 min
intensity variation: 0.9%

Refinement

Refinement on F
Final $R = 0.035$
$wR = 0.047$
$S = 1.77$
1920 reflections
174 parameters
All H-atom parameters refined

$w = 1/[\sigma^2(F) + 0.0001F_o^2]$
$(\Delta/\sigma)_{\max} = 0.14$
$\Delta\rho_{\max} = 0.34$ e Å^{-3}
$\Delta\rho_{\min} = -0.30$ e Å^{-3}
Atomic scattering factors from *SHELXS*86 (Sheldrick, 1986)

Table 1. *Fractional atomic coordinates and equivalent isotropic thermal parameters* (Å^2)

$$U_{\text{eq}} = \tfrac{1}{3}\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
Compound (1)				
N(1)	0.72184 (7)	0.2127 (1)	0.1953 (2)	0.0206 (3)
C(2)	0.80545 (9)	0.2399 (2)	0.1578 (2)	0.0201 (4)
C(3)	0.86874 (9)	0.3237 (2)	0.2869 (2)	0.0204 (4)
C(4)	0.85130 (9)	0.3876 (2)	0.4583 (2)	0.0212 (4)
C(5)	0.7627 (1)	0.3565 (2)	0.4843 (2)	0.0247 (4)
C(6)	0.70216 (9)	0.2709 (2)	0.3556 (2)	0.0247 (4)
C(7)	0.6494 (1)	0.1221 (2)	0.0658 (2)	0.0226 (4)
C(8)	0.57964 (9)	0.2274 (2)	−0.0573 (2)	0.0247 (4)
O(9)	0.61970 (7)	0.3110 (1)	−0.1862 (1)	0.0270 (4)
C(10)	0.5538 (1)	0.4006 (2)	−0.3150 (2)	0.0320 (4)
C(11)	0.8250 (1)	0.1764 (2)	−0.0212 (2)	0.0253 (4)
O(1)	0.95216 (7)	0.3488 (1)	0.2534 (1)	0.0254 (4)
O(2)	0.91204 (6)	0.4628 (1)	0.5737 (1)	0.0267 (4)
Compound (2)				
N(1)	0.8157 (2)	0.6680 (2)	0.8626 (3)	0.0200 (7)
C(2)	0.8951 (2)	0.5879 (2)	0.8868 (4)	0.0197 (8)
C(3)	0.8591 (2)	0.4802 (2)	0.9091 (5)	0.0210 (7)
C(4)	0.7441 (2)	0.4542 (2)	0.9080 (4)	0.0199 (7)
C(5)	0.6663 (2)	0.5390 (2)	0.8871 (5)	0.0233 (8)
C(6)	0.7044 (2)	0.6442 (2)	0.8649 (4)	0.0226 (8)
C(7)	0.8483 (3)	0.7838 (3)	0.8250 (5)	0.0248 (9)
C(8)	0.8760 (3)	0.8462 (2)	1.0015 (5)	0.0258 (9)
O(9)	0.7784 (2)	0.8521 (2)	1.1140 (3)	0.0279 (6)
C(10)	0.7994 (3)	0.9091 (3)	1.2854 (5)	0.0320 (10)
C(11)	1.0177 (2)	0.6145 (3)	0.8926 (5)	0.0250 (9)
O(1)	0.9401 (2)	0.4029 (2)	0.9269 (4)	0.0302 (7)
O(2)	0.7167 (2)	0.3489 (2)	0.9266 (3)	0.0264 (6)
Cl(12)	0.46592 (6)	0.32538 (6)	0.9028 (1)	0.0251 (2)
Compound (3)				
N(1)	−0.0518 (2)	0.39875 (7)	−0.2171 (1)	0.0235 (4)
C(2)	0.1303 (2)	0.43594 (8)	−0.1805 (2)	0.0236 (4)
C(3)	0.1543 (2)	0.51004 (8)	−0.2382 (2)	0.0242 (4)
C(4)	−0.0087 (2)	0.54708 (8)	−0.3267 (2)	0.0250 (4)
C(5)	−0.1937 (2)	0.50770 (9)	−0.3569 (2)	0.0290 (4)
C(6)	−0.2104 (2)	0.43358 (9)	−0.3028 (2)	0.0283 (4)
C(7)	−0.0821 (3)	0.31735 (8)	−0.1659 (2)	0.0283 (5)
C(8)	−0.1376 (3)	0.3146 (1)	−0.0108 (2)	0.0350 (5)
C(9)	0.3010 (3)	0.3986 (1)	−0.0802 (2)	0.0328 (5)
O(1)	0.3398 (2)	0.54296 (7)	−0.2054 (1)	0.0341 (4)
O(2)	0.0264 (2)	0.61815 (6)	−0.3773 (1)	0.0321 (4)
O(10)	0.4614 (2)	0.68089 (7)	−0.2776 (2)	0.0403 (4)
Cl(11)	0.66465 (6)	0.68547 (2)	−0.56760 (4)	0.0305 (1)

Table 2. *Geometric parameters* (Å, °)

	(1)	(2)	(3)
N(1)—C(2)	1.377 (2)	1.367 (4)	1.363 (2)
N(1)—C(6)	1.361 (2)	1.353 (4)	1.353 (2)
N(1)—C(7)	1.482 (2)	1.490 (4)	1.492 (2)
C(2)—C(3)	1.371 (2)	1.391 (4)	1.391 (2)
C(2)—C(9)			1.490 (2)
C(2)—C(11)	1.501 (2)	1.492 (4)	
C(3)—C(4)	1.439 (2)	1.400 (4)	1.401 (2)
C(3)—O(1)	1.359 (2)	1.353 (3)	1.346 (2)
C(4)—C(5)	1.424 (2)	1.394 (4)	1.392 (2)
C(4)—O(2)	1.262 (2)	1.332 (3)	1.333 (2)
C(5)—C(6)	1.356 (2)	1.370 (4)	1.371 (2)
C(7)—C(8)	1.506 (2)	1.507 (5)	1.511 (2)
C(8)—O(9)	1.418 (2)	1.411 (4)	
O(9)—C(10)	1.418 (2)	1.429 (4)	
N(1)—C(2)—C(3)	118.6 (1)	118.5 (2)	118.7 (1)
N(1)—C(2)—C(9)			121.0 (1)
N(1)—C(2)—C(11)	119.4 (1)	121.3 (2)	
N(1)—C(6)—C(5)	122.4 (1)	121.6 (3)	121.2 (1)
N(1)—C(7)—C(8)	112.8 (1)	112.7 (3)	112.5 (1)
C(2)—N(1)—C(6)	120.4 (1)	121.2 (2)	121.4 (1)
C(2)—N(1)—C(7)	122.62 (9)	121.5 (2)	121.0 (1)
C(2)—C(3)—C(4)	123.1 (1)	120.8 (2)	120.5 (1)
C(2)—C(3)—O(1)	119.3 (1)	116.8 (2)	116.7 (1)
C(3)—C(2)—C(9)			120.3 (1)
C(3)—C(2)—C(11)	122.0 (1)	120.1 (2)	
C(3)—C(4)—C(5)	114.6 (1)	118.5 (2)	118.6 (1)
C(3)—C(4)—O(2)	120.8 (1)	117.1 (2)	116.9 (1)
C(4)—C(3)—O(1)	117.6 (1)	122.3 (2)	122.8 (1)
C(4)—C(5)—C(6)	120.9 (1)	119.3 (2)	119.5 (1)
C(5)—C(4)—O(2)	124.6 (1)	124.4 (2)	124.6 (1)
C(6)—N(1)—C(7)	117.0 (1)	117.3 (2)	117.5 (1)
C(7)—C(8)—O(9)	109.7 (1)	108.8 (2)	
C(8)—O(9)—C(10)	110.9 (1)	111.6 (2)	

Table 3. *Hydrogen-bonding geometry* (Å, °)

D—H$\cdots A$	$D\cdots A$	H$\cdots A$	D—H$\cdots A$
Compound(1)			
O(1)—H$\cdots$O(2$^{\text{i}}$)	2.671 (2)	1.89 (2)	148 (2)
Compound (2)			
O(1)—H$\cdots$Cl$^{\text{ii}}$	3.054 (2)	2.35 (4)	152 (4)
O(2)—H$\cdots$Cl	2.995 (2)	2.17 (5)	175 (2)
Compound (3)			
O(1)—H$\cdots$O(10)	2.610 (2)	1.93 (2)	160 (3)
O(2)—H$\cdots$Cl$^{\text{iii}}$	2.977 (2)	2.10 (2)	173 (2)
HO(10)—H$\cdots$Cl	3.137 (3)	2.36 (3)	172 (3)
HO(10)—H$\cdots$Cl$^{\text{iv}}$	3.154 (1)	2.34 (3)	166 (3)

Symmetry codes: (i) $2 - x, 1 - y, 1 - z$; (ii) $x + \frac{1}{2}, \frac{1}{2} - y, 2 - z$; (iii) $x - 1, y, z$; (iv) $x, \frac{3}{2} - y, z + \frac{1}{2}$.

The title compounds were crystallized from ethanol solution equilibrated with heptane at 277 K. Data were collected at 138 (2) K and corrected for Lorentz and polarization effects, but not for absorption. The structures were determined by direct methods using *SHELXS*86 (Sheldrick, 1986) and refined by a full-matrix least-squares routine (*SHELX*76; Sheldrick, 1976). All H atoms were located from the difference Fourier map and refined isotropically.

Support from the National Institute for General Medical Sciences (GM-21822) and the British Technology Group is gratefully acknowledged.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates, complete geometry and stereoscopic views of all molecules have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71069 (29 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: CD1028]

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Structure of a 6-Tetrahydroxybutyl-Substituted 5,6,7,8-Tetrahydropteridine

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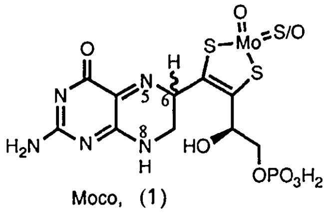
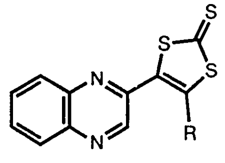
Abstract

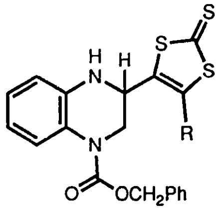
The crystal structure of 2-acetamido-5-benzyloxycarbonyl-3,4,5,6,7,8-hexahydro-4-oxo-6-(D-*arabino*-tetrahydroxybutyl)pteridine tetraacetate, (5), shows that reduction of 2-acetamido-3,4-dihydro-4-oxo-6-(D-*arabino*-tetrahydroxybutyl)pteridine tetraacetate, (4), with sodium cyanoborohydride in the presence of benzyl chloroformate achieves saturation of the pyrazine ring with regioselective protection at nitrogen N(5).

Comment

We are developing a synthetic route (Rowe, Garner, & Joule, 1985; Larsen, Garner & Joule, 1989; Larsen, Rowe, Garner & Joule, 1989; Russell, Garner & Joule, 1992*a*,*b*,*c*) to Moco (Rajagopalan, 1991; Johnson, 1980; Gardlik & Rajagopalan, 1990), (1), the cofactor of all molybdoenzymes except nitrogenase. The cofactor comprises a dihydropteridine carrying a functionalized side chain at C(6) on which are situated the S atoms which coordinate the metal centre. It is planned that the production of the requisite dihydropyrazine oxidation level, *cf.* (1), will involve (*a*) reduction of a precursor pteridine to the 5,6,7,8-tetrahydro level then (*b*) regioselective reoxidation to dihydro level, *i.e.* the introduction of unsaturation at N(5).


Moco, (1)


(2)


(3)

We have shown (Beddoes, Russell, Garner & Joule, 1993; Russell, Garner & Joule, 1992*a*,*b*) that reduction of quinoxalines of the general form (2) in the presence of benzyl chloroformate generates tetrahydroquinoxalines, (3), with the N atom which is remote from the substituent, protected as a urethane. In seeking to clarify both the stage at which the reduction should be carried out and also whether a comparable regiochemical preference would be found in a pteridine, we have reduced 2-acetamido-3,4-dihydro-4-oxo-6-(D-*arabino*-tetrahydroxybutyl)pteridine tetraacetate, (4), with sodium cyanoborohydride in the presence of benzyl chloroformate in methanol. A mixture of diastereoisomers was formed, recrystallization of which produced material