Study of Hydrogen Bonding in 1-Ethyl-2-methyl-4-oxo-1,4-dihydropyridin-3-yloxyethanoic Acid and 3-(1,2-Diethyl-4-oxo-1,4-dihydropyridin-3-yloxy)propanoic Acid by ^{1}H NMR Spectroscopy and X-Ray Crystallography

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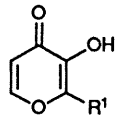
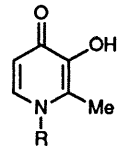
A series of 1,2-dialkyl-4-oxo-1,4-dihydropyridin-3-yloxyethanoic acids and 3-(1,2-dialkyl-4-oxo-1,4-dihydropyridin-3-yloxy)propanoic acids have been synthesized *via* the corresponding pyran-4-ones. Ring proton chemical shifts indicate hydrogen bonding between the side-chain carboxylic acid proton and the 4-oxo group of the heterocycle to be present only for the pyridinone species in DMSO solution. X-Ray crystallography demonstrates the hydrogen bonding in 1-ethyl-2-methyl-4-oxo-1,4-dihydropyridin-3-yloxyethanoic acid to be very strong (O—O = 2.441 Å) and intramolecular, giving a unique 8-membered chelate ring. The analogous hydrogen bonding in 3-(1,2-diethyl-4-oxo-1,4-dihydropyridin-3-yloxy)propanoic acid is however strong (O—O = 2.541 Å) and intermolecular, giving an infinite structure.

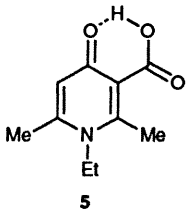
The quasi-aromaticity of pyran-4-one **1** and *N*-substituted pyridin-4-one **2** causes the 4-oxo groups of these molecules to be highly polarisable, and hence the carbonyl oxygen atoms to be endowed with incipient basicity (Fig. 1). The resultant liganding potential has recently proven valuable in the design of clinically useful iron chelators.[1] Maltol [3-hydroxy-2-methylpyran-4(4*H*)-one] **3a** has been demonstrated to increase dramatically the bioavailability of ferric iron,[2] whilst analogues of 3-hydroxy-1,2-dimethylpyridin-4(1*H*)-one **4a** are currently



3a; R^1 = Me
3b; R^1 = Et



4a; R = Me
4b; R = Et



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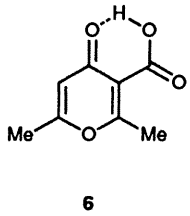

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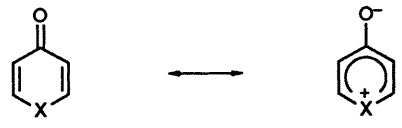
the prime candidates to succeed desferrioxamine in the relief of transfusional iron overload.[3,4] Both **3a** and **4a** are bidentate ligands which form 3:1 neutral complexes with iron(III).[5] The enhanced ability of the heterocyclic nitrogen atom of pyridin-4-ones to support a positive charge compared to the corresponding oxygen atom of pyran-4-ones is manifested in greater affinity for both protonation and Lewis acids. This effect is evidenced by the elevated 4-oxo pK_a value of 3.56 found for **4a**,[6] and its increased log β_3 value (36.9)[6] for iron(III) relative to **3a** (28.5).[7]

The carbonyl oxygen atoms of pyran-4-ones and pyridin-4-ones are frequently used as hydrogen bond acceptors.[8] We have recently reported[9] the existence of 'very strong'[10] intramolecular hydrogen bonding (O—O = 2.414 Å) between the carboxy and 4-oxo groups of 1-ethyl-2,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid **5**, and furthermore discussed ^{1}H NMR data which suggests a similar effect is present in 2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxylic acid **6**. Both of these compounds form thermodynamically favourable 6-membered 'chelate rings' with a proton, which are also observed in the enol tautomers of the β-diketones.[11] As an extension of our interest in the pyran-4-one and pyridin-4-one moieties, we now report investigations of the hydrogen bonding in compounds closely related to the higher homologues of **5** and **6**. Since it was anticipated that intramolecular hydrogen bonding would most probably occur in such species to give 7-membered chelate rings with a proton,[12] efforts were concentrated on compounds which might give unprecedented 8- and 9-membered chelate rings. These were prepared as shown in Scheme 1, the starting materials being readily available maltol **3a** and ethyl maltol **3b**.



1; X = O
2; X = N–R

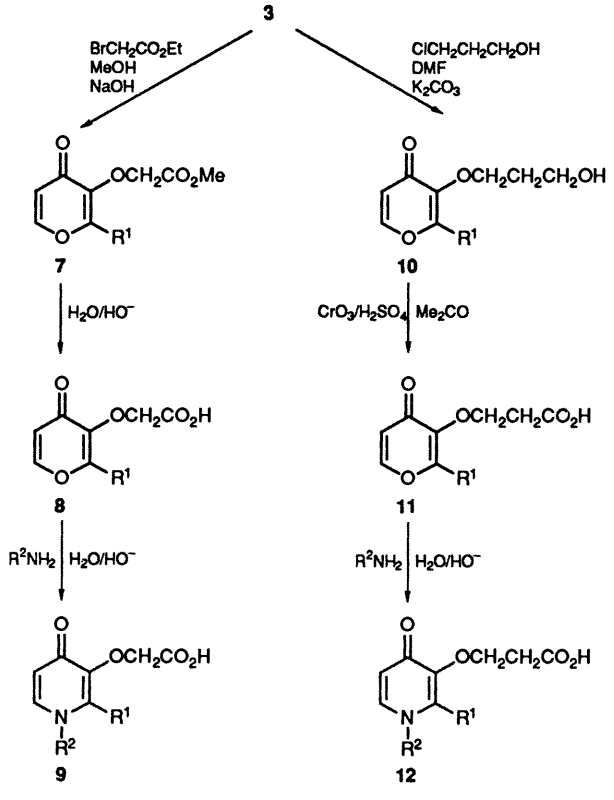
Fig. 1 Mesomerism of pyran-4-one **1** and *N*-substituted pyridin-4-one **2**

Experimental

Instruments.—M.p.s were taken on an Electrothermal Digital Melting Point apparatus and are uncorrected. ^{1}H NMR spectra were determined with a Perkin-Elmer R32 90 MHz spectrometer, with chemical shifts (δ) reported in ppm downfield of internal tetramethylsilane. IR spectra were taken with a Perkin-Elmer 298 IR spectrophotometer using sodium chloride plates. Mass spectra were determined using a Vacuum Generators 16F mass spectrometer, electron energy 35 eV. Elemental analyses were performed by Butterworth Laboratories Limited, Teddington, Middlesex, UK.

Table 1 Analytical and spectral data for compounds **7–12**

Compound (Formula)	R^1	R^2	Yield (%)	M.p./(°C) (Recryst. solvent)	ν_{max}/cm^{-1}	$\delta_H([^2H_6]$-DMSO) 5-H	6-H	*m/z* (%)	Found (%) (Required) C	H	N
7a ($C_9H_{10}O_5$)	Me	—	32	53–54 (Diethyl ether)	1760	6.38	8.09	198 (M^+, 12), 139 (100)	55.0 (54.5	5.6 5.1	— —)
7b ($C_{10}H_{12}O_5$)	Et	—	36	—	1765	6.37	8.10	212 (M^+, 27), 139 (100)	56.4 (56.6	6.1 5.7	— —)
8a ($C_8H_8O_5$)	Me	—	85	136–137 (Ethanol)	1750	6.37	8.04	184 (M^+, 1.4), 126 (100)	52.15 (52.2	4.4 4.4	— —)
8b ($C_9H_{10}O_5$)	Et	—	89	121–122 (Ethanol)	1760	6.39	8.07	198 (M^+, 4.2), 140 (100)	54.7 (54.5	5.2 5.1	— —)
9a ($C_{10}H_{13}NO_4$)	Me	Et	52	142–143 (Chloroform–hexane)	1690	6.52	7.96	211 (M^+, 2.8), 125 (100)	56.0 (56.85	6.25 6.2	6.5 6.6)
9b ($C_{11}H_{15}NO_4$)	Me	Pr	58	136–137 (Chloroform)	1700	6.51	7.94	225 (M^+, 4.3), 125 (100)	58.0 (58.65	6.75 6.7	6.1 6.2)
9c ($C_{11}H_{15}NO_4$)	Et	Et	74	116–117 (Chloroform–hexane)	1720	6.55	7.96	225 (M^+, 36), 166 (100)	58.6 (58.65	6.9 6.7	6.2 6.2)
9d ($C_{12}H_{17}NO_4$)	Et	Pr	72	136–137 (Chloroform–hexane)	1645	6.53	7.96	239 (M^+, 15), 138 (100)	59.9 (60.2	7.3 7.2	5.8 5.85)
10a ($C_9H_{12}O_4$)	Me	—	50	—	3600–3200	6.38	8.06	84 (M^+, 11), 126 (100)	57.2 (58.7	6.9 6.6	— —)
10b ($C_{10}H_{14}O_4$)	Et	—	56	—	3600–3200	6.36	8.08	198 (M^+, 44), 140 (100)	59.9 (60.6	7.75 7.1	— —)
11a ($C_9H_{10}O_5$)	Me	—	46	113–114 (Ethyl acetate)	1725	6.35	8.03	198 (M^+, 52), 126 (100)	54.3 (54.5	5.2 5.1	— —)
11b ($C_{10}H_{12}O_5$)	Et	—	48	102–103 (Ethyl acetate)	1725	6.35	8.09	212 (M^+, 69), 139 (100)	56.6 (56.6	6.0 5.7	— —)
12a ($C_{12}H_{17}NO_4$)	Et	Et	33	149–150 (Chloroform–diethyl ether)	1710	6.30	7.72	239 (M^+, 7.2), 167 (100)	59.3 (60.2	7.2 7.2	5.5 5.85)
12b ($C_{13}H_{19}NO_4$)	Et	Pr	30	158–159 (Chloroform–diethyl ether)	1675	6.22	7.69	253 (M^+, 7.0), 138 (100)	61.3 (61.6	7.5 7.6	5.3 5.5)



Scheme 1

General Synthetic Procedures.—These are given below. Analytical and selected spectral data for novel compounds are presented in Table 1.

Methyl 2-Alkyl-4-oxo-4H-pyran-3-yloxyethanoates **7a**, **b**.—To solutions of pyran-4-ones **3a**, **b** (0.395 mol) in methanol (600 cm^3) were added sodium hydroxide (24 g, 0.600 mol) in water (60 cm^3) and ethyl bromoacetate (100 g, 0.599 mol), the mixtures then being refluxed for 18 h. After removal of solvent by rotary evaporation, the residues were taken-up in water, adjusted to pH 12, and extracted into dichloromethane. The organic fractions were dried and rotary evaporated prior to vacuum distillation, which gave the desired products as yellow oils (134 °C/0.1 mmHg **7a**, 136 °C/0.1 mmHg **7b**). Only **7a** solidified on storage at 4 °C.

2-Alkyl-4-oxo-4H-pyran-3-yloxyethanoic Acids **8a**, **b**.—The methyl esters **7a**, **b** (0.150 mol) were added to water (600 cm^3), adjusted to pH 10.5, and stirred at room temperature. More alkali was added until a steady value of pH 10.5 was achieved, then stirring continued for 1 h. After adjustment to pH 7 and washing with dichloromethane, the aqueous solutions were further adjusted to pH 1 and extracted into dichloromethane. The organic fractions were subsequently dried and rotary evaporated to give the desired products as white solids.

1,2-Dialkyl-4-oxo-1,4-dihydropyridin-3-yloxyethanoic Acids **9a–d**.—To solutions of pyran-4-ones **8a**, **b** (0.0500 mol) in water (300 cm^3) were added primary alkyl amines (0.100 mol) followed by aqueous sodium hydroxide solution (2 mol dm^{-3}; 2 cm^3), and the mixtures stirred at room temperature for 18 h. After adjustment to pH 1, the aqueous solutions were washed with dichloromethane, reduced in volume to 50 cm^3 by rotary evaporation, then repeatedly adjusted to pH 4/extracted into dichloromethane. The organic fractions were subsequently dried and rotary evaporated to give the desired pyridin-4-one products as yellow solids.

3-(2-Alkyl-4-oxo-4H-pyran-3-yloxy)propanols **10a**, **b**.—To solutions of pyran-4-ones **3a**, **b** (0.395 mol) in DMF (500 cm^3)

Table 2 Crystal data: details of intensity measurement and structure refinement for compounds **9a** and **12a**

	9a	**12a**
Mol. formula	$C_{10}H_{13}NO_4$	$C_{12}H_{17}NO_4$
Mol. wt.	211	239
Crystal system	Orthorhombic	Monoclinic
Space group	$Pca2_1$	$P2_1/n$
a/Å	14.362(7)	15.287(2)
b/Å	4.341(1)	8.198(1)
c/Å	15.908(8)	9.851(3)
β/°	—	104.52(1)
Cell parameters from	50 reflections	32 reflections
V/Å^3	989.5	1195.1
D/g cm^{-3}	1.42	1.33
Z	4	4
Radiation	Cu-Kα	Mo-Kα
λ/Å	1.5418	0.710 69
μ	8.3	0.7
T/K	163	163
Diffractometer	CAD4	CAD4
$2\theta_{max}$/°	150	53
Scan width/°	(0.8 + 0.34 tanθ)	(0.70 + 0.2 tanθ)
Scan type	ω-2θ	ω-2θ
Aperture width/mm	(3.0 + 0.86 tanθ)	(3.0 + 0.86 tanθ)
Max. time/s	90	90
Standard reflections	3	3
Frequency/min	120	120
Intensity variation (%)	2.9	1.4
Unique data	1062	2481
Data with $I > 2\sigma(I)$	1029	2055
Correction	Lorentz and polarization	
Refinement on F		
R	0.031	0.039
wR	0.039	0.048
S	1.6	1.7
No. parameters	187	222
$(\Delta/\sigma)_{max}$	0.03	0.01
w	$1/\sigma^2(F_o)$	$1/\sigma^2(F_o)$
Max. peaks height in diff. four/e Å^{-3}	±0.15	±0.22

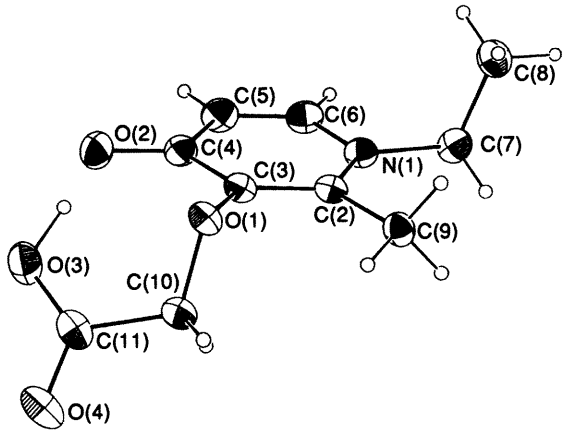


Fig. 2 ORTEP plot of acid **9a**

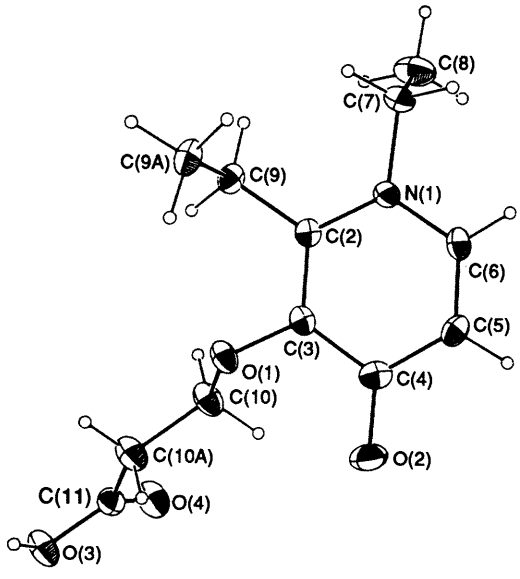


Fig. 3 ORTEP plot of acid **12a**

were added anhydrous potassium carbonate (80 g, 0.579 mol) and 3-chloropropanol (55 g, 0.581 mol), the mixtures then being stirred at 80 °C for 18 h in an atmosphere of nitrogen. After removal of solvent by rotary evaporation, the residues were taken-up in water, adjusted to pH 12, and extracted into dichloromethane. The organic fractions were dried and rotary evaporated prior to vacuum distillation, which gave the desired products as yellow oils (158 °C/0.1 mmHg **10a**, 160 °C/0.1 mmHg **10b**).

3-(2-*Alkyl*-4-*oxo*-4H-*pyran*-3-*yloxy*)*propanoic Acids* **11a**, **b**.—To solutions of the alcohols **10a**, **b** (0.0870 mol) in acetone (300 cm^3) stirring at 0 °C was added Jones' reagent (0.115 mol) dropwise over 15 min. After continued stirring at room temperature for 1 h, inorganic materials were removed and the filtrates rotary evaporated. The residues were subsequently taken-up in water and extracted into dichloromethane; drying and rotary evaporation of the organic fractions yielded the desired products as white solids.

Table 3 Bond lengths for compounds **9a** and **12a** (esds in parentheses)

Bond	9a	12a
O(1)–C(3)	1.376(3)	1.375(2)
O(2)–C(4)	1.286(4)	1.275(1)
C(3)–C(4)	1.426(3)	1.434(2)
N(1)–C(2)	1.374(3)	1.375(2)
N(1)–C(6)	1.360(3)	1.359(2)
N(1)–C(7)	1.484(4)	1.487(2)
C(2)–C(3)	1.376(4)	1.373(2)
C(2)–C(9)	1.494(3)	1.506(2)
C(4)–C(5)	1.411(4)	1.417(2)
C(5)–C(6)	1.355(3)	1.354(2)
C(7)–C(8)	1.515(4)	1.512(2)
C(9)–C(9a)		1.529(2)
O(1)–C(10)	1.433(4)	1.449(2)
C(10)–C(10a)		1.500(2)
C(10a)–C(11)		1.507(2)
C(10)–C(11)	1.526(4)	
C(11)–O(3)	1.294(2)	1.320(2)
C(11)–O(4)	1.218(4)	1.210(2)

Table 4 Ring proton chemical shifts of compounds **3a**, **13**, **14** and the hydrochloride salt of **14**

	δ_H([$^2H_6$]-DMSO)	
Compound	5-H	6-H
3a	6.39	8.03
13	6.36	8.06
14	6.17	7.67
14 HCl salt	7.67	8.66

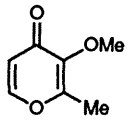
3-(1,2-*Dialkyl*-4-*oxo*-1,4-*dihydropyridin*-3-*yloxy*)*propanoic Acids* **12a**, **b**.—These pyridin-4-ones were obtained from reaction of the pyran-4-one **11b** with primary alkyl amines by analogous methodology to that used in the preparation of **9a–d** from **8a**, **b**.

2-*Methyl*-3-*methoxypyran*-4(4H)-*one* **13** *and* 1-*Ethyl*-2-*methyl*-3-*methoxypyridin*-4(1H)-*one* **14**.—These compounds were prepared by methods previously described.[4]

Crystallography.—Suitable crystals of both compounds **9a** and **12a** were obtained by equilibrating ethanol solutions with hexane. The structure of **9a** was solved with MITHRIL,[13] whilst for **12a** SHELX-86[14] was used. All the non-hydrogen atoms were refined anisotropically. The location of all hydrogen atoms was determined from successive difference Fourier syntheses and refined isotropically. Crystal data, details of intensity measurements and structure refinement parameters for both compounds are presented in Table 2. ORTEP plots of the molecules are shown in Figs 2 and 3, and bond lengths are listed in Table 3. Final fractional coordinates and isotropic equivalent temperature factors for non-hydrogen atoms of **9a** and **12a**, bond angles, torsion angles, final atomic parameters for hydrogen atoms and anisotropic thermal parameters for non-hydrogen atoms are available on request from the Cambridge Crystallographic Data Centre.

Results and Discussion

^{1}H *NMR Spectroscopy*.—The spectrum of 2-methyl-4-oxo-4*H*-pyran-3-yloxyethanoic acid **8a** in [$^2H_6$]DMSO exhibited a broad peak at δ 11.10–13.40. This chemical shift corresponds to a 'normal' carboxylic acid proton (typical values 11.5 ± 3.0),[15] and therefore implies that hydrogen bonding between the carboxylic acid proton and 4-oxo group of the pyran-4-one ring of **8a** probably does not occur in DMSO solution. Such an effect should cause the proton to be more deshielded and hence appear further downfield, as evidenced by the CO_2H resonance for 2,6-dimethyl-4-oxo-4*H*-pyran-3-carboxylic acid **6** being detected at δ 14.27–14.95.[9] Furthermore, the chemical shifts of the 5-H and 6-H doublets (J = 6 Hz) for **8a** do not vary significantly from the corresponding values in the spectra of its ethyl analogue **8b**, the methyl esters **7a**, **b**, maltol **3a**, and 2-methyl-3-methoxypyran-4(4*H*)-one **13** (Tables 1 and 4). This imples that similar heterocyclic ring character exists for all the above compounds, and hence that the substituent differences are of little consequence to the mesomeric equilibrium.



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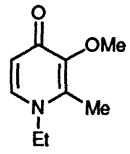

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The 1,2-dialkyl-4-oxo-1,4-dihydropyridin-3-yloxyethanoic acids **9a–d** were isolated by extraction into dichloromethane at pH 4. Under these aqueous conditions it was anticipated that the molecules should be predominantly in the neutral form, based on the pK_a values of 3.56 for the 4-oxo group of **4a**[6] and 4.88 for ethanoic acid.[16] Although **9a–d** were found to have high solubility in [$^2H_6$]DMSO, the CO_2H resonances could not initially be detected. Compression of the spectrum of **9a** (sweep range δ 0–50) however revealed a peak at δ 14.00–15.75, believed indicative of a hydrogen bonded carboxylic acid proton. Support for this hypothesis came from the chemical shifts of the 5-H and 6-H doublets for **9a** appearing 0.35 and 0.29 ppm respectively downfield of the values for the corresponding protons in 1-ethyl-2-methyl-3-methoxypyridin-4(1*H*)-one **14** (Tables 1 and 4), suggesting pyridinium mesomer contribution in **9a** to be enhanced by hydrogen bonding. Whether this hydrogen bonding was intramolecular or intermolecular could not be deduced at this stage. That the 5-H and 6-H doublets in the spectrum of the hydrochloride salt of **14** (Table 4) are at values some 1.15 and 0.70 ppm respectively downfield of the corresponding protons in **9a** precludes the possibility of the latter species existing as a zwitterion in DMSO solution, although fast exchange of the labile proton between the 4-oxo and carboxy groups cannot be ruled out. The hydrogen bonding present in **9a** was then further investigated by X-ray crystallography (see below).

The CO_2H, 5-H and 6-H resonances in the spectra of the 3-(2-alkyl-4-oxo-4*H*-pyran-3-yloxy)propanoic acids **10a**, **b** in [$^2H_6$]-DMSO were comparable with those of the lower homologues **7a**, **b**, implying hydrogen bonding not to be present.

When a similar isolation technique as that employed for **9a–d** was applied to the 3-(1,2-dialkyl-4-oxo-1,4-dihydropyridin-3-yloxy)propanoic acids **12a**, **b**, the latter compounds were found to have low extractability. Indeed, lower alkylated analogues were virtually non-extractable. Furthermore, **12a**, **b** were found to be sparingly soluble in [$^2H_6$]DMSO, and the CO_2H peaks could not be detected in even compressed spectra. However, based on the evidence of the 5-H and 6-H chemical shifts appearing slightly downfield of those for the analogous protons in **14** (Tables 1 and 4), it was assumed that some weak hydrogen bonding was exhibited in DMSO solutions of **12a**, **b**. This effect was subsequently investigated further by X-ray crystallography of **12a**.

Crystallography.—As was suspected from differences in isolation chemistry, ^{1}H NMR spectra, and solubilities, X-ray crystallography demonstrates **9a** to form an intramolecular

Table 5 Hydrogen bonding parameters for compounds **9a** and **12a**

	9a Intramolecular	**12a** Intermolecular
O(2)—O(3)/Å	2.441(4)	2.541(1)
O(2)—H/Å	1.34(5)	1.62(2)
O(3)—H/Å	1.13(5)	0.93(2)
O(2)—H—O(3)/°	165(4)	175(2)

hydrogen bond between the side chain carboxy group and the 4-oxo group of the heterocyclic ring, whilst the structure **12a** features an analogous intermolecular hydrogen bond (Table 5).

In the structure of **9a** the side chain at C(3) is 'folded back' in order to facilitate intramolecular hydrogen bonding, giving an 8-membered chelate ring (Fig. 2). The five non-hydrogen atoms in the side chain lie approximately in the same plane (r.m.s. = 0.102 Å), which makes an angle of 46° with the pyridin-4-one ring. The resulting O—O distance of 2.441 Å is significantly longer than that of 2.414 Å found in the 6-membered chelate ring of **5**,[9] yet the hydrogen bonding present in **9a** may also be classed as 'very strong'.[10] The C(4)–O(2) distance of 1.286 Å in **9a** is slightly shorter than that of 1.292 Å determined previously for the corresponding bond in **5**, but is nevertheless appreciably elongated with respect to the 4-oxo bond distances of 1.271 Å and 1.265 Å in the 3-hydroxypyridin-4-ones **4a**[6] and **4b**.[17] This implies increased pyridinium mesomer contribution to the ring system of **9a** relative to **4a** and **4b**, presumably as a consequence of proton 'chelation'.

In the structure of **12a** the six atoms of the side chain at C(3) lie in the same plane (r.m.s. = 0.024 Å), which is approximately perpendicular (70°) to the heterocyclic ring (Fig. 3). Intermolecular hydrogen bonding to a neighbouring molecule ($\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$) results in an O—O distance of 2.541 Å, which is significantly longer than the corresponding distance in **9a** (Table 5). The hydrogen bonding present in **12a** can only therefore be termed as 'strong'.[10] The 4-oxo bond distance of 1.275 Å present in **12a** is shorter than that in **9a**, suggesting lower aromatic character. This effect is also evidenced by the longer C(3)–C(4) and C(4)–C(5) bond distances in **12a** when compared to **9a**, and presumably occurs as a consequence of the weaker, intermolecular hydrogen bonding present in the former compound.

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