Synthesis and Structure of the *N*-Alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic Acids

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A range of *N*-alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic acids **XV** have been prepared *via* reactions of primary alkyl amines with differing 2,6-dimethyl-4-oxopyran-3-carboxylate esters **IX**. The quantity of desired product formed and the character of by-products formed are determined by the natures of the amine and ester **IX** respectively. X-ray crystallography data for the *N*-ethyl analogue of **XV** indicates very strong intramolecular hydrogen bonding to be present, with the heterocyclic ring exhibiting considerable aromaticity.

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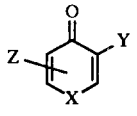
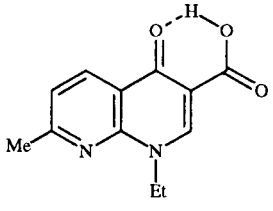
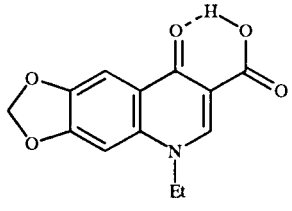
The liganding ability of the highly polarisable 4-oxo group of pyran-4-ones and pyridin-4-ones has proven valuable in the design of clinically useful iron chelators [1]. Bioavailability of ferric iron is enhanced by certain 3-hydroxypyran-4-ones **Ia** [2], whilst related *N*-substituted-3-hydroxypyridin-4-ones **Ib** are currently the leading candidates as orally active replacements for desferrioxamine in the relief of transfusional iron overload [3]. As an extension of our contribution to this work, we wished to explore the chelating properties of 4-oxopyran-3-carboxylic acids **Ic** and corresponding *N*-alkyl-4-oxopyridine-3-carboxylic acids **Id**. These compounds are closely related to the "4-quinolone" class of antibacterial agents (for example, nalidixic acid **II** and oxolinic acid **III**), which have previously been demonstrated to interact with a range of metal cations [4].



Ia, X = O, Y = OH
Ib, X = NR, Y = OH
Ic, X = O, Y = CO_2H
Id, X = NR, Y = CO_2H



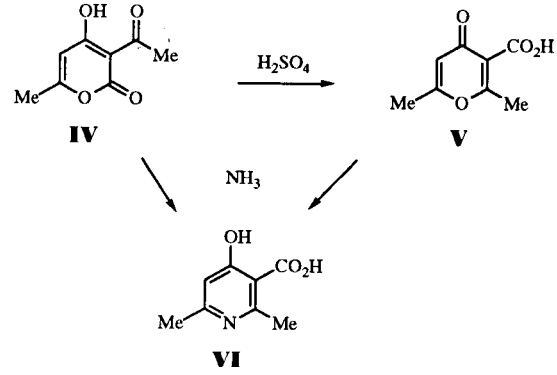
II



III

The rearrangement of readily available dehydroacetic acid (3-acetyl-4-hydroxy-6-methylpyran-2-one) **IV** to give 2,6-dimethyl-4-oxopyran-3-carboxylic acid **V** (Scheme I) in sulphuric acid is the most synthetically convenient route to a compound of type **Ic** [5]. This reaction is believed to proceed *via* acid-catalysed attack of water at the 6-position of **IV** followed by ring-opening [6]. The intermediate diacetylacetonecarboxylic acid can undergo facile deacetylation to give 4-hydroxy-6-methylpyran-2-one, whilst decarboxylation results in the formation of 2,6-dimethylpyran-4-one [7]. We have found reflux of dehydroacetic acid **IV** in 80% sulphuric acid for 1 hour gives the desired product **V** in an average yield of 50%.

Scheme I



IV **V** **VI**

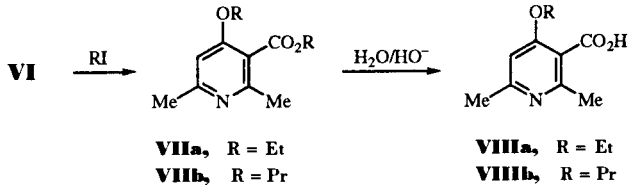
Although treatment of both **IV** and **V** with ammonia produces 2,6-dimethyl-4-hydroxypyridine-3-carboxylic acid **VI** (Scheme I) [8], corresponding reactions with primary alkyl amines give *N*-alkyl-2,6-dimethylpyridin-4-ones. This decarboxylation has been explained in terms of steric hindrance to ring-closure and formation of relatively stable hydrogen bonded 2,6-bis(alkylamino)-2,5-heptadiene-4-ones [9]. A description of the preparation of a range of *N*-aryl-2,6-dimethyl-4-oxopyridine-3-carboxylic acids is available in the patent literature [10], but no information could be found regarding the *N*-alkyl analogues.

Since changes in the ring substitution pattern may alter the affinity of *N*-alkyl-4-oxopyridine-3-carboxylic acids for metal cations, and we wished to make direct comparisons with the 4-oxopyran-3-carboxylic acid **V**, it was decided not to simply follow published procedures for the preparation of other derivatives of **Id** [11]. In this paper we therefore report methods investigated towards the synthesis of such *N*-alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic acids *via* two distinct novel routes, namely: (i) attempted *N*-alkylation of 2,6-dimethyl-4-hydroxypyridine-3-carboxylic acid **VI**; and (ii) reaction of various esters of 2,6-dimethyl-4-oxopyran-3-carboxylic acid **V** with primary alkyl amines in alkaline aqueous ethanolic medium. Products are unambiguously identified by X-ray crystallography.

Method (i).

Reviews centered on the synthesis of *N*-alkyl-4-oxoquinoline-3-carboxylic acids indicate one step often employed to be *N*-alkylation of a corresponding 4-hydroxyquinoline-3-carboxylate ester [12]. These reactions are performed with reagents such as alkyl halides, sulphates and tosylates in a variety of protic and aprotic solvent/base systems. It was decided however for the attempted *N*-alkylations of 2,6-dimethyl-4-hydroxypyridine-3-carboxylic acid **VI** to adopt the conditions recently used by Cooper and coworkers [13], who reported formation of an *N*-ethyl-4-oxoquinoline-3-carboxylate ester in 92% yield. A reaction was hence effected between **VI** and an eight molar excess of ethyl iodide in DMF with potassium carbonate as base, tlc indicating the formation of only one product. Purification by extraction and vacuum distillation gave a colourless oil for which the 90 MHz ^{1}H nmr spectrum exhibited two quartets at δ 4.09 and 4.34, initially believed to correspond to the *N*-substituent and ester group respectively of ethyl *N*-ethyl-2,6-dimethyl-4-oxopyridine-3-carboxylate. The ir spectrum of this oil however showed no band in the 1600 to 1650 cm^{-1} region characteristic of a pyridin-4-one carbonyl stretch, implying alkylation of the 4-hydroxy group (to give **VIIa**, Scheme II) as opposed to the heterocyclic nitrogen may have occurred. Support for this hypothesis was gained from the ^{1}H nmr spectrum of the product obtained from an analogous reaction of propyl iodide with **VI**, neither propyl group exhibiting the distortion present in the spectrum of decarboxylated species *N*-propyl-2,6-dimethylpyridin-4-one (reasoned to result from restricted rotation of the *N*-substituent). Based on the pK_a values of 4.20 for benzoic acid [14] and 6.69 for 2,6-dimethylpyridine [15], it was assumed that the 2,6-dimethyl-4-alkoxypyridine-3-carboxylic acids **VIII** (Scheme II) would be predominantly neutral, although probably zwitterionic, in the *p*H range 5-6. Isolation of these highly hydrophilic products was therefore achieved by adjusting the post-hydrolysis mixture to *p*H 5.5 prior to removal of solvent and solid extraction into DMF. The structure of the *O*-ethyl analogue **VIIIa** was determined by X-ray crystallography, confirming the identity of this compound (see below).

Scheme II



VIIa, R = Et
VIIb, R = Pr

VIIIa, R = Et
VIIIb, R = Pr

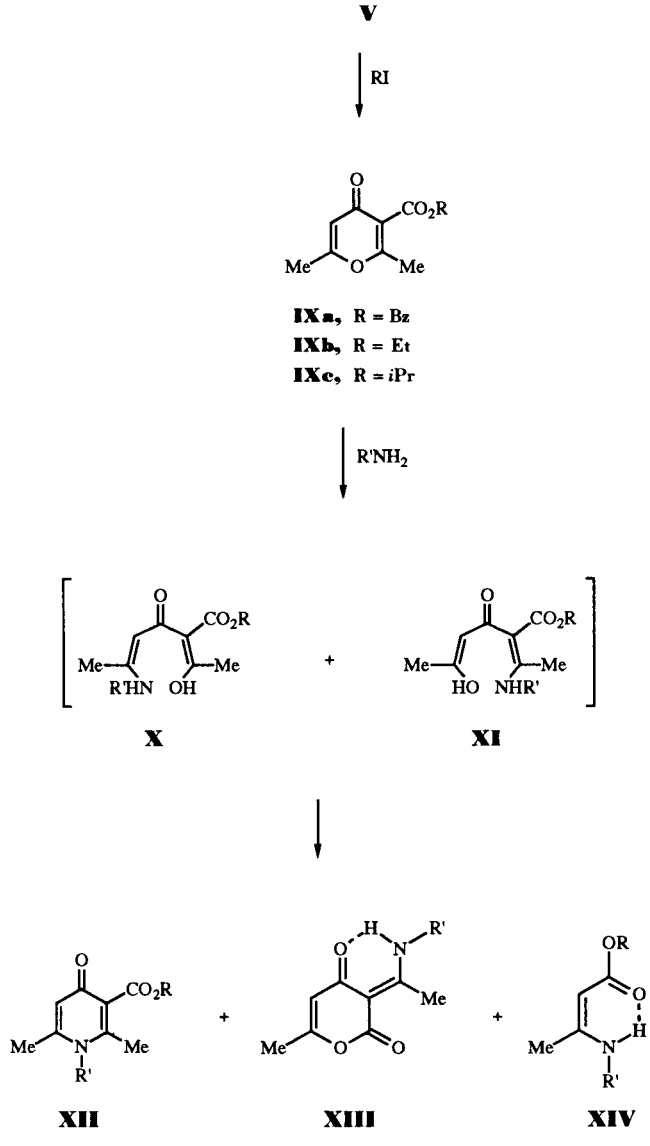
The regiospecific *O*-alkylation of hydroxypyridine **VI** probably occurs by virtue of steric hindrance to electrophilic attack at the heterocyclic nitrogen resulting from the presence of methyl groups at the 2- and 6-positions of the ring. Di-alkylation is most likely disfavoured due to destabilisation of the resulting pyridinium ion by a strongly electron-withdrawing alkoxycarbonyl ring substituent.

Method (ii).

The preparation of *N*-arylpyridin-4-ones from corresponding pyran-4-ones is normally achieved by reaction with primary aryl amines under acidic aqueous reflux conditions [16], protonation of the pyrone supposedly increasing its susceptibility to nucleophilic attack at the 2- and 6-positions [17]. In the patent describing the synthesis of *N*-aryl-2,6-dimethyl-4-oxopyridine-3-carboxylic acids [10] however the carboxyl function of 2,6-dimethyl-4-oxopyran-3-carboxylic acid **V** is protected as a methyl ester, necessitating the use of aprotic solvents and azeotropic distillation of water formed during the reaction. Although this acidic anhydrous methodology proved reasonably successful (the one yield quoted, for the synthesis of methyl *N*-(4-chlorophenyl)-2,6-dimethyl-4-oxopyridine-3-carboxylate, being 47%), a decision was made against its adoption for the preparation of *N*-alkyl analogues based on the following: (a) the fact that acidic conditions are not required for the reaction of more nucleophilic primary alkyl amines with pyran-4-ones; and (b) the assumption that since **V** is a quasi-aromatic carboxylic acid, its esters should be more stable than aliphatic esters, elevated temperature being required for alkaline hydrolysis. Hence under the room temperature conditions sufficient for reaction with alkyl amines [18], the protecting group would probably not be removed. Literature methods for preparation of methyl 2,6-dimethyl-4-oxopyran-3-carboxylate include methylation of the corresponding acid with diazomethane and treatment of dehydroacetic acid with methyl fluorosulphonate [19]. The instability of carboxylic acid **V** in acidic aqueous medium [7] necessitates Fischer esterification conditions for reaction with methanol [10]. The synthesis of benzyl 2,6-dimethyl-4-oxopyran-3-carboxylate **IXa** (selected because the protecting group can be removed by hydrogenolysis in addition to hydrolysis) from **V**

was however achieved using a one molar equivalent of benzyl bromide in an anhydrous DMF/potassium carbonate system (Scheme III), crystallization of the oil obtained only being possible after column chromatography. Owing to the fact that **IXa** was found to have low solubility in water alone, the presence of ethanol in the alkaline aqueous system for reaction with primary alkyl amines was required.

Scheme III



Monitoring by tlc indicated that treatment with a 1.6 molar excess of methylamine for 30 minutes resulted in complete reaction of **IXa** to give three major products. The most hydrophobic of these was found to have rf values identical to benzyl alcohol in both ethanol and ethyl acetate, suggesting hydrolysis of the ester group in the pyran-4-one starting material and/or the anticipated pyridin-4-one product might have occurred. Neither of the other products however had rf values corresponding to 1,2,6-trimethylpyridin-4-one, and both were found to partition into dichloromethane after adjustment of the reaction mixture to *p*H 7. Separation by column chromatography and subsequent characterisation by ^{1}H nmr spectroscopy indicated the less hydrophobic of these species to be benzyl 1,2,6-trimethyl-4-oxopyridine-3-carboxylate **XIIa** (Scheme III, Table I), obtained in a yield of 58%. The ^{1}H nmr spectrum in DMSO-d_6 of the by-product formed by loss of the benzyl group exhibited a methyl group doublet at δ 3.18 which collapsed to a singlet on spin-decoupling from a broad peak at δ 13.40-13.80. Based on this evidence the compound was deduced to be 3-(1-methylamino)ethylidene-6-methylpyran-2,4-dione **XIIIa** (Scheme III, Table I), formed in a yield of 19%. Numerous analogues of **XIII** have previously been prepared from reaction of dehydroacetic acid with equimolar quantities of primary alkyl, aryl and heterocyclic amines [9,20]. The results of nmr studies [21] and X-ray crystallography [22] have suggested predominance of the keto-enamine over the enol-imine (Schiff base) form.

Attack of methylamine, in a Michael-type addition, can theoretically occur at either the 6- or 2-positions of benzyl 2,6-dimethyl-4-oxopyran-3-carboxylate **IXa**, subsequent ring-opening giving the corresponding analogues of **X** and **XI** respectively (Scheme III). Both of these intermediates can then undergo ring-closure to give the pyridin-4-one **XIIa** by a second, intramolecular Michael-type addition. The pyran-2,4-dione by-product **XIIIa** must however be formed *via* **XI**, this open-chain species adopting a different conformer prior to intramolecular nucleophilic attack of enolate anion at the ester group. Analogous reaction of ethylamine with the pyran-4-one benzyl ester **IXa** resulted in pyridin-4-one **XIIb** and pyran-2,4-dione **XIIIb** being obtained in yields of 13% and 59% respectively (Table I). This relatively increased by-product formation was reasoned to be due to steric hindrance, the bulkier *N*-substituent disfavouring ring-closure to give the desired product. Although use of propylamine and butylamine gave some pyridin-4-one **XII** (Table I), the sole species obtained from reaction of **IXa** with isopropylamine was pyran-2,4-dione **XIIIe**. It is likely therefore that only intermediate **XI** is formed in these reactions, this being a reasonable assumption when it is considered that C_2 of the pyran-4-one ester **IXa** is the β-carbon of two α,β-unsaturated carbonyl units, and as such is likely to be more electron deficient and hence more prone to nucleophilic attack than C_6.

In an effort to combat by-product formation, it was decided to prepare ethyl 2,6-dimethyl-4-oxopyran-3-carboxylate **IXb** (by treatment of acid **V** with ethyl iodide) for analogous reactions with primary amines. Since the

Table I

Physical and Analytical Data for the Products **XII** and **XIII** from Reaction of Pyran-4-one Benzyl Ester **IXa** with Various Primary Alkyl Amines

Compound	R	R'	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
XIIa	Bz	Me	58	165-166	$C_{16}H_{17}NO_3$	70.82 70.75	6.33 6.62	5.16 5.11
XIIb	Bz	Et	13	147-148	$C_{17}H_{19}NO_3 \cdot HCl$	63.44 63.08	6.28 6.17	4.35 3.98
XIIc	Bz	Pr	6	153-154	$C_{18}H_{21}NO_3 \cdot HCl$	64.37 64.33	6.62 6.50	4.17 3.93
XIId	Bz	Bu	6	157-158	$C_{19}H_{23}NO_3 \cdot HCl$	65.22 65.12	6.93 7.02	4.00 3.95
XIIIa	–	Me	19	130-131	$C_9H_{11}NO_3$	59.65 59.91	6.13 6.35	7.73 7.78
XIIIb	–	Et	59	91-92	$C_{10}H_{13}NO_3$	61.51 61.63	6.73 6.92	7.18 7.17
XIIIc	–	Pr	59	76-77	$C_{11}H_{15}NO_3$	63.13 63.14	7.24 7.37	6.69 6.53
XIIId	–	Bu	77	–	$C_{12}H_{17}NO_3$	64.54 64.16	7.69 7.62	6.27 6.09
XIIIe	–	*i*-Pr	80	91-92	$C_{11}H_{15}NO_3$	63.13 62.88	7.24 7.32	6.69 6.48

Table II

Physical and Analytical Data for the Products **XII** and **XIV** from Reaction of Pyran-4-one Ethyl Ester **IXb** with Various Primary Alkyl Amines

Compound	R	R'	Yield (%)	Mp or Bp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
XIIe	Et	Me	85	210-211	$C_{11}H_{15}NO_3 \cdot HCl$	53.76 53.86	6.58 6.74	5.70 5 64
XIIf	Et	Et	43	106-107	$C_{12}H_{17}NO_3$	64.54 64.88	7.69 7.79	6.27 6.13
XIIg	Et	Pr	15	184-185	$C_{13}H_{19}NO_3 \cdot HCl$	57.03 56.87	7.38 7.66	5.12 4.89
XIIh	Et	Bu	23	178-179	$C_{14}H_{21}NO_3 \cdot HCl$	58.42 58.59	7.72 7.89	4.87 4.68
XIIi	Et	Pentyl	17	159-160	$C_{15}H_{23}NO_3 \cdot HCl$	59.68 59.35	8.03 8.09	4.64 4.59
XIIj	Et	Hexyl	10	157-158	$C_{16}H_{25}NO_3 \cdot HCl$	60.83 60.45	8.31 8.08	4.44 4.30
XIVa	Et	Et	18	80 (0.1 mm Hg)	$C_8H_{15}NO_2$	61.10 60.83	9.63 9.70	8.91 8.74
XIVb	Et	Pr	54	80 (0.1 mm Hg)	$C_9H_{17}NO_2$	63.11 63.08	10.03 9.76	8.18 7.82
XIVc	Et	Bu	64	82 (0.1 mm Hg)	$C_{10}H_{19}NO_2$	64.81 65.02	10.36 10.57	7.56 7.42

ethoxy anion is an inferior leaving group compared to the benzyloxy anion, it was believed that ring-closure to give pyran-2,4-diones **XIII** would be suppressed. Support for this concept was gained when reaction of pyran-4-one ethyl ester **IXb** with methylamine gave only the desired ethyl 1,2,6-trimethyl-4-oxopyridine-3-carboxylate **XIIe**. Treatment of **IXb** with ethylamine however resulted in the formation of three products, separated by column chromatography and subsequently identified by ^1H nmr as the pyridin-4-one ester **XIIf** (yield 43%), the pyran-2,4-dione **XIIIb** (yield 26%), plus an unknown compound. The salient features of the spectrum of the latter species were the presence of a double-quartet at δ 3.23, which collapsed to a quartet on spin-decoupling from a broad peak at δ 8.25-8.65, and the assignment of only one methyl group singlet. Based on the above, together with the observation that the 35 eV mass spectrum exhibited a peak at m/z 157 with 100% abundance, the second by-product was deduced to be the *Z* isomer of ethyl 3-ethylamino-2-butenoate **XIVa** (Scheme III, Table II). This compound was obtained in a yield of 18%. The mechanism for formation of **XIVa** is that of a retro-Claisen condensation [23],

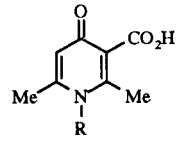
Table III

Physical and Analytical Data for the Products **XII** and **XIV** from Reaction of Pyran-4-one Isopropyl Ester **IXc** with Various Primary Alkyl Amines

Compound	R	R'	Yield (%)	Mp or Bp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
XIIk	*i*-Pr	Et	29	199-200	$C_{13}H_{19}NO_3 \cdot HCl$	57.03	7.38	5.12
						56.74	7.40	4.90
XIIl	*i*-Pr	Pr	24	184-185	$C_{14}H_{21}NO_3 \cdot HCl$	58.42	7.72	4.87
						58.04	7.45	4.69
XIVd	*i*-Pr	Et	49	80 (0.1 mm Hg)	$C_9H_{17}NO_2$	63.11	10.03	8.18
						63.05	10.10	8.28
XIVe	*i*-Pr	Pr	58	82 (0.1 mm Hg)	$C_{10}H_{19}NO_2$	64.81	10.36	7.56
						64.64	10.57	7.74
XIVf	*i*-Pr	*i*-Pr	81	82 (0.1 mm Hg)	$C_{10}H_{19}NO_2$	64.81	10.36	7.56
						64.72	10.23	7.59

Table IV

Physical and Analytical Data for the *N*-Alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic Acids **XV** obtained from alkaline Hydrolysis of the Corresponding Ethyl Esters



Compound	R	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
XVa	Me	83	261-262	$C_9H_{11}NO_3$	59.65	6.13	7.73
					59.60	5.91	7.79
XVb	Et	75	221-222	$C_{10}H_{13}NO_3$	61.51	6.73	7.18
					61.21	6.86	7.09
XVc	Pr	61	143-144	$C_{11}H_{15}NO_3$	63.13	7.24	6.69
					63.16	7.32	6.61
XVd	Bu	81	127-128	$C_{12}H_{17}NO_3$	64.54	7.69	6.27
					64.70	7.86	6.31
XVe	Pentyl	94	181-182	$C_{13}H_{19}NO_3$	65.79	8.09	5.90
					65.55	8.17	5.75
XVf	Hexyl	89	150-151	$C_{14}H_{21}NO_3$	66.89	8.44	5.57
					66.53	8.40	5.41

attack of hydroxide ion on the corresponding intermediate **XI** (a β-keto ester) resulting in carbon-carbon bond cleavage, acetoacetic acid also being produced. Existance of **XIVa** in the *Z* enamine as opposed to imine tautomer is a consequence of intramolecular hydrogen bonding, this situation being the norm for aliphatic α,β-unsaturated-β-keto amines [24].

It may be concluded from the reaction of pyran-4-one ethyl ester **IXb** with ethylamine that although suppression of pyran-2,4-dione **XIIIb** formation had been achieved relative to the analogous experiment using pyran-4-one benzyl ester **IXa**, and moreover the yield of the desired pyridin-4-one ethyl ester **XIIf** was superior to that of pyridin-4-one benzyl ester **XIIb**, another competing reaction of intermediate **XI** had come into play to give the acyclic species **XIVa** as a second by-product. Reaction of pyran-4-one ethyl ester **IXb** with propylamine and butylamine gave increased yields of butenoates **XIV** accompanied by decreased yields of pyridin-4-ones **XII** relative to reaction with ethylamine, whilst similarly low formation of desired product resulted from use of pentylamine and hexylamine (Table II).

The final experiments performed in this series involved analogous treatment of isopropyl 2,6-dimethyl-4-oxopyran-3-carboxylate **IXc** with various primary alkyl amines, the respective yields of products formed being presented in Table III. After reaction with ethylamine, no pyran-2,4-dione **XIIIb** was detected, presumably as a consequence of the isopropoxy anion being an inferior leaving group compared to the ethoxy anion. No more of the desired pyr-

Table V

Spectral Data for the *N*-Alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic Acids **XV** Obtained from Alkaline Hydrolysis of the Corresponding Ethyl Esters

Compound	IR (Nujul) cm^{-1}	^1H NMR in DMSO-d_6 δ (ppm)	35 ev MS m/z (%)
XVa	1690, 1640, 1630, 1615, 1515, 1480	2.50 (*s*, 3H, 6-CH_3), 3.00 (*s*, 3H, 2-CH_3), 3.69 (*s*, 3H, N-CH_3), 6.62 (*s*, 1H, 5-H)	181 (M^+, 34), 137 (100)
XVb	1690, 1640, 1630, 1615, 1515, 1500, 1470	1.02 (t, 3H, ethyl CH_3), 2.54 (*s*, 3H, 6-CH_3), 3.01 (*s*, 3H, 2-CH_3), 4.22 (quartet, 2H, ethyl CH_2), 6.71 (*s*, 1H, 5-H)	195 (M^+, 10), 165 (48), 151 (100), 137 (35), 124 (79) 123 (48), 109 (38)
XVc	1690, 1640, 1600, 1510	0.99 (t, propyl CH_3), 1.72 (sextet, 2H, CH_2-CH_2-CH_3), 2.55 (*s*, 3H, 6-CH_3), 3.02 (*s*, 3H, 2-CH_3), 4.10 (t, 2H, N-CH_2-CH_2), 6.70 (*s*, 1H, 5-H), 17.50-18.50 (broad, 1H, CO_2H)	209 (M^+, 16), 194 (31), 165 (100), 150 (43), 149 (30), 123 (84)
XVd	1690, 1640, 1620, 1590, 1510, 1480	0.96 (t, 3H, butyl CH_3), 1.22-1.88 (m, 4H, CH_2-CH_2-CH_2-CH_3), 2.55 (*s*, 3H, 6-CH_3), 3.02 (*s*, 3H, 2-CH_3), 4.15 (t, 2H, N-CH_2-CH_2), 6.71 (*s*, 1H, 5-H), 17.60-18.20 (broad, 1H, CO_2H)	208 (41), 179 (100), 123 (42)
XVe	1690, 1640, 1620, 1580, 1510	0.90 (t, 3H, pentyl CH_3), 1.15-1.90 (m, 6H, CH_2-CH_2-CH_2-CH_2-CH_3) 2.53 (*s*, 3H, 6-CH_3), 3.02 (*s*, 3H, 2-CH_3), 4.12 (t, 2H, N-CH_2-CH_2), 6.72 (*s*, 1H, 5-H)	222 (56), 193 (100), 149 (30), 123 (56)
XVf	1690, 1635, 1620, 1570, 1510	0.87 (t, 3H, hexyl CH_3), 1.15-1.89 (m, 8H, CH_2-CH_2-CH_2--CH_2-CH_2-CH_3), 2.52 (*s*, 3H, 6-CH_3), 3.00 (*s*, 3H, 2-CH_3), 4.10 (t, 2H, N-CH_2-CH_2), 6.71 (*s*, 1H, 5-H)	251 (M^+, 1.5), 236 (63), 207 (100), 164 (29), 150 (30), 149 (38), 137 (32), 123 (97)

idin-4-one isopropyl ester **XIIk** was however obtained than pyridin-4-one ethyl ester **XIIf** from the analogous reaction of **IXb**, this being due the acyclic by-product **XIVd** forming in a considerable quantity. Reaction of propylamine with **IXc** gave similar results, but only the butenoate **XIVf** was isolated after use of isopropylamine. The reason for this difference is probably steric hindrance to ring-closure caused by the bulky *N*-substituent.

The major conclusions that can be drawn from the reactions of various 2,6-dimethyl-4-oxopyran-3-carboxylate esters **IX** with primary alkyl amines under alkaline aqueous ethanolic conditions (Scheme III) are as follows: (a) three species can be obtained, most probably all resulting from the common intermediate **XI**, which is formed by attack of amine at C_2 of pyran-4-one ester **IX**; (b) the quantity of desired pyridin-4-one ester **XII** formed is determined by the nature of the alkyl group on the amine, an increase in the bulk of which leads to ring-closure of **XI** by Michael-type addition being sterically hindered, thereby increasing the lifetime of this intermediate and hence the probability of by-products forming; and (c) which by-product is formed is determined by the nature of the pyran-4-one ester **IX**; if a good leaving group is present, formation of the pyran-2,4-dione **XIII** will be favoured, whilst if a poor leaving group is present, formation of butenoate **XIV** will be favoured.

The target compounds *N*-alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic acids **XV** (Tables IV and V) were obtained by simple acidic hydrogenolysis and/or alkaline hydrolysis of their corresponding esters. Precipitation of the *N*-methyl, *N*-ethyl, *N*-pentyl and *N*-hexyl analogues **XVa,b,e,f** in the neutral form occurred from *p*H 4.2 aqueous solution, whereas the *N*-propyl and *N*-butyl species **XVc,d** were isolated by extraction. Only the latter two compounds proved sufficiently soluble in DMSO-d_6 for the labile CO_2H proton to be assigned, the very low-field values obtained (Table V) being assumed indicative of intramolecular hydrogen-bonding to the 4-oxo group. This effect was further investigated by X-ray crystallography of the *N*-ethyl compound **XVb**.

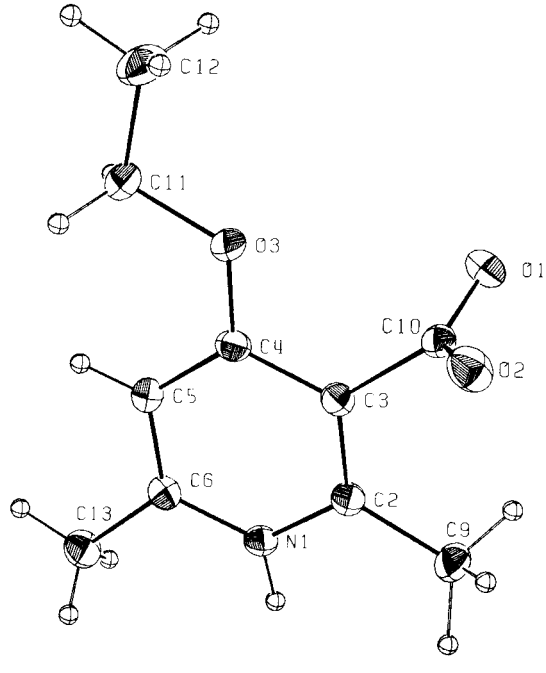


Figure I. ORTEP plot of 2,6-dimethyl-4-ethoxypyridine-3-carboxylic acid (**VIIIa**) with atomic numbering scheme.

X-ray Crystallography.

During the refinement of the structure of 2,6-dimethyl-4-ethoxypyridine-3-carboxylic acid **VIIIa** (Figure I) a hydrogen atom was located on the heterocyclic nitrogen atom as opposed to the carboxyl group, indicating the molecule to exist as a zwitterion. An intermolecular hydrogen bond is formed between this hydrogen atom and O_1 of the negatively charged carboxylate group, whilst further intermolecular attractions occur *via* four water molecules. Although the acceptance of three hydrogen bonds by O_1 is unusual, similar effects have been observed with negatively charged oxygen atoms [25]. The bond distances within the planar (rms deviation = 0.004 Å) pyridinium ring of **VIIIa** (Table VIII) indicate aromaticity to be present. That the carboxyl group is essentially perpendicular (99°) to the ring serves to prevent close contact with the 4-ethoxy group, but also eliminates the possibility of resonance with the aromatic system. The ethoxy side-chain is close to the plane of the ring, and has a *trans* formation for C_4-O_3-C_{11}-C_{12} (179°).

Table VI

Positional Parameters (x 10^4) and Equivalent Isotropic Temperature Factors (x 10^4) for the Non-hydrogren Atoms of **VIIIa**. Estimated Standard Deviations are Within Parentheses

Atom	X	Y	Z	U(EQ)
N(1)	1402(1)	6902(1)	1364(1)	184(3)
C(2)	2013(1)	6146(1)	782(2)	188(4)
C(3)	1709(1)	5151(1)	1018(2)	181(4)
C(4)	775(1)	4952(1)	1862(2)	183(4)
C(5)	173(1)	5754(1)	2464(2)	191(4)
C(6)	501(1)	6736(1)	2185(2)	188(4)
C(9)	2991(1)	6453(2)	-83(2)	285(5)
C(10)	2361(1)	4264(1)	406(2)	183(4)
C(11)	-406(1)	3689(1)	2904(2)	241(4)
C(12)	-447(2)	2545(2)	2883(3)	337(5)
C(13)	-92(1)	7656(2)	2724(2)	257(4)
O(1)	2951(1)	3850(1)	1438(1)	229(3)
O(2)	2273(1)	4013(1)	-1012(2)	271(3)
O(3)	5349(8)	3969(1)	2015(1)	219(3)
O(1W)	1413(1)	4900(1)	-3660(1)	285(4)
O(2W)	2382(1)	3268(1)	4631(2)	350(4)
O(3W)	4290(1)	5186(1)	3220(2)	362(4)
O(4W)	2961(1)	6218(1)	-4783(2)	359(4)

Table VII

Positional Parameters (x 10^4) and Equivalent Isotropic Temperature Factors (x 10^4) for the Non-hydrogren Atoms of **XVb**. Estimated Standard Deviations are Within Parentheses

Atom	X	Y	Z	U(EQ)
N(1)	7106(3)	2135(3)	3651(1)	357(8)
C(2)	8386(3)	2262(4)	3217(2)	355(9)
C(3)	8174(3)	2416(4)	2312(2)	365(9)
C(4)	6611(3)	2524(4)	1833(2)	390(10)
C(5)	5363(3)	2437(4)	2318(2)	440(10)
C(6)	5592(3)	2245(4)	3203(2)	388(9)
C(7)	7322(4)	1928(5)	4635(2)	440(10)
C(8)	7436(6)	3748(5)	5098(2)	590(10)
C(9)	9981(4)	2234(7)	3764(2)	580(10)
C(10)	9536(4)	2492(4)	1801(2)	460(10)
C(13)	4214(4)	2127(7)	3691(2)	600(10)
O(1)	10893(3)	2339(4)	2113(1)	730(10)
O(2)	9129(3)	2755(3)	950(1)	610(10)
O(3)	6338(3)	2732(3)	993(1)	572(9)

Table VIII

Bond Distances (Å) for **VIIIa** and **XVb**. Estimated Standard Deviations are Within Parentheses

	VIIIa	**XVb**
N(1)-C(2)	1.354(2)	1.377(3)
N(1)-C(6)	1.353(2)	1.381(3)
C(2)-C(3)	1.380(3)	1.383(3)
C(3)-C(4)	1.407(2)	1.435(4)
C(4)-C(5)	1.399(3)	1.400(4)
C(5)-C(6)	1.378(3)	1.355(3)
C(2)-C(9)	1.495(2)	1.497(4)
C(6)-C(13)	1.497(3)	1.501(4)
C(3)-C(10)	1.521(2)	1.510(4)
C(10)-O(1)	1.266(2)	1.199(4)
C(10)-O(2)	1.232(2)	1.318(3)
C(4)-O(3)	1.335(2)	1.288(3)
N(1)-C(7)		1.506(3)
C(7)-C(8)		1.504(5)
O(3)-C(11)	1.457(2)	
C(11)-C(12)	1.507(3)	

The bond distances within the approximately planar (rms deviation = 0.009 Å) heterocyclic ring of *N*-ethyl-2,6-dimethyl-4-oxopyridine-3-carboxylic acid **XVb** (Figure II, Table VIII) indicate a basic quinoid structure, but with a considerable amount of resonance (Figure III). This effect is further evidenced by the C_4-O_3 distance of 1.288 (3) Å, which is appreciably longer than the 1.22 Å normal carbonyl bond distance, and moreover the 1.265 (1) Å determined for the corresponding bond in *N*-ethyl-2-methyl-3-hydroxypyridin-4-one [26]. The carboxyl group of **XVb** is essentially co-planar with the ring (3.5°), and a "very strong" [27] intramolecular hydrogen bond is formed with the 4-oxo group (O_2---O_3 = 2.414 (3) Å, O_3---H = 1.43 (4) Å, O_2-H = 1.06 (4) Å, O_2-H---O_3 = 153 (2)°) to give a 6-membered chelate ring. It is presumably this hydrogen bonding which causes increased pyridinium mesomer contribution to the structure of the ring, a greater partial negative charge on O_3 leading to stronger attraction of the proton. Such a hypothesis appears justified by the findings of ^{1}H nmr spectroscopy, the 5-H resonance for acid **XVb** (δ 6.71) being detected appreciably downfield of the corresponding proton in its ethyl ester **XIIf** (δ 6.09). It is noteworthy that the 4-oxo distance determined for **XVb** is similar to that of 1.286 (4) Å found for the equivalent bond in the adduct of 1,2,6-trimethylpyridin-4-one with 1,8-biphenylenediol, which features intermolecular hydrogen bonding [28]. The C_3-C_{10} distance of 1.510 (4) Å in **XVb** is shorter than the 1.521 (2) Å noted for the corresponding bond in **VIIIa**, suggesting some resonance of the carboxyl group with the heterocyclic ring in the former compound.

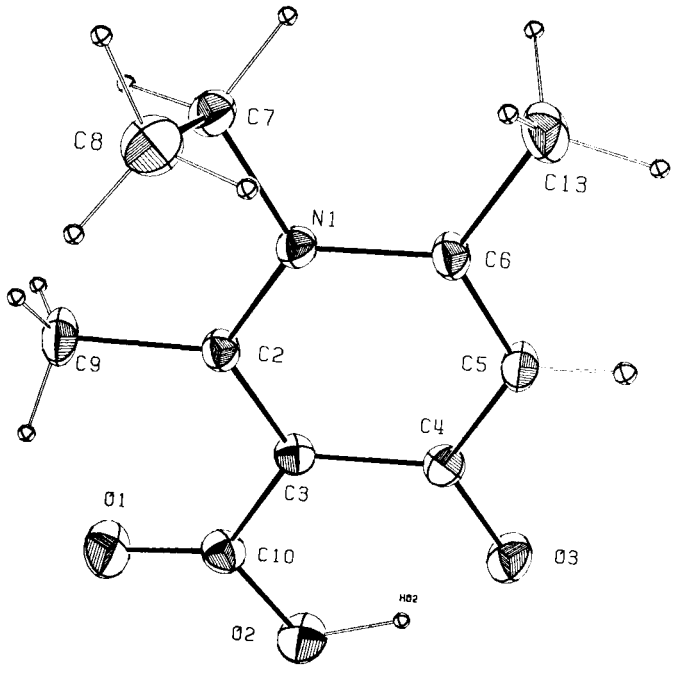


Figure II. ORTEP plot of *N*-ethyl-2,6-dimethyl-4-oxopyridine-3-carboxylic acid (**XVb**) with atomic numbering scheme.

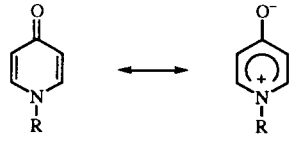


Figure III. Mesomerism of a general *N*-substituted-pyridin-4-one.

Based on the very strong intramolecular hydrogen bonding present in the structure of **XVb**, it might by predicted that this compound will possess a low acidity. Indeed, such interaction has been reasoned to be soley responsible for the elevated carboxyl group pK_a values invariably observed in the "4-quinolone" class of antibacterial agents [4a-d, 29]. The intramolecular hydrogen bonding previously noted in nalidixic acid **II** [30] is appreciably weaker (O---O = 2.528 (3) Å) than that present in **XVb** (O---O = 2.414 (3) Å), yet pK_a values in the region of 6 have been reported for the carboxylic acid group of the former compound [4a-d, 29]. Protonation of the 4-oxo group in both **II** and oxolinic acid **III** has been observed only at *p*H values of less than 1 [4b]. This decreased basicity relative to unsubstituted 4-hydroxyquinoline (quinolin-4-one) (pK_a = 2.27) has also been explained as a consequence of intramolecular hydrogen bonding, and a parallel drawn with the speciation of salicylic acid [4b, 31].

An alternative suggestion however is that anion destabilisation, resulting from conjugation of the lone pair of electrons on the heterocyclic nitrogen atom with the carboxyl group, may be a contributory factor in the decreased acidity of the "4-quinolone" antibacterial agents [4e]. In the light of this proposal it is pertinent to note from the structure of nalidixic acid **II** [30] the significantly shorter N_1-C_2 (1.339 (3) Å), C_3-CO_2H (1.480 (3) Å) and C_4-O (1.254 (3) Å) bond distances, and the significantly longer carboxylic acid carbonyl bond distance (1.214 (3) Å), compared to **XVb** (Table VIII). These differences indicate that whilst aromatic resonance is more significant in **XVb** (Figure III), and indeed appears to be enhanced by intramolecular hydrogen bonding, the lone pair of electrons on N_1 of **II** is in fact preferentially delocalised on the 3-carboxyl group. Such an effect markedly reduces the electron density on the 4-oxo group of **II**, and hence is also probably of importance with respect to the depressed basicity of this compound. The bond distances quoted above for nalidixic acid **II** [30] are similar to those found in oxolinic acid **III** [32].

The isolation of the *N*-alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic acids **XV** by precipitation or extraction from *p*H 4.2 aqueous solution implies that these compounds exist predominantly in the unionised form only under these conditions. An acid-base titration of the *N*-propyl analogue **XVc** monitored by uv spectroscopy indicated speciation changes to be restricted to the *p*H range 3.5-5.0, and pK_a values for the 4-oxo and 3-carboxyl groups of this compound were determined to be 3.8 and 4.6 respectively by standard manual methodology [33]. The close proximity of

Table IX

Intermolecular Hydrogen Bonding for Molecule **VIIIa**

D-H---A	D-H (Å)	H---A (Å)	D---A (Å)	D-H---A (Å)	Symmetry
Molecule VIIIa					
N(1)-H(N1)---O(1)	0.89(3)	1.84(3)	2.696(2)	161(2)	1/2-x, 1/2+y,z
O(1W)-H1(O1W)---O(2)	0.89(3)	1.86(3)	2.728(2)	164(3)	x,y,z
O(2W)-H1(O2W)---O(1)	0.81(4)	2.06(3)	2.860(2)	171(3)	x,y,x
O(3W)-H2(O3W)---O(1)	0.82(4)	2.07(4)	2.870(2)	169(3)	x,y,z
O(4W)-H2(O4W)---O(1W)	0.80(4)	2.00(4)	2.791(2)	168(4)	x,y,z
O(2W)-H2(O2W)---O(1W)	0.80(4)	2.06(4)	2.861(2)	173(3)	x, y, z-1
O(4W)-H1(O4W)---O(2W)	0.81(4)	1.98(4)	2.779(2)	176(3)	1/2-x.y-1/2,1+z

Table X

Bond Angles (°)

	VIIIa	XVb
N(1)-C(2)-C(3)	119.0(1)	120.2(2)
N(1)-C(2)-C(9)	117.0(2)	117.4(2)
N(1)-C(7)-C(8)		112.2(2)
N(1)-C(6)-C(5)	119.6(2)	119.4(2)
N(1)-C(6)-C(13)	116.7(2)	120.3(2)
C(3)-C(2)-C(9)	124.0(2)	122.4(2)
C(3)-C(4)-O(3)	115.0(2)	122.4(2)
C(3)-C(4)-C(5)	120.2(2)	117.4(2)
C(3)-C(10)-O(2)	118.5(1)	114.4(3)
C(3)-C(10)-O(1)	115.3(1)	125.1(2)
O(2)-C(10)-O(1)	126.2(2)	120.5(3)
O(3)-C(4)-C(5)	124.9(1)	120.2(3)
C(5)-C(6)-C(13)	123.7(1)	120.3(3)
C(2)-N(1)-C(7)		120.6(2)
C(2)-N(1)-C(6)	123.4(2)	121.2(2)
C(2)-C(3)-C(4)	119.1(2)	119.4(2)
C(2)-C(3)-C(10)	121.8(1)	122.3(2)
C(7)-N(1)-C(6)		118.1(2)
C(6)-C(5)-C(4)	118.8(1)	122.4(3)
C(4)-C(3)-C(10)	119.1(2)	118.2(2)
C(4)-O(3)-C(11)	118.8(1)	
O(3)-C(11)-C(12)	106.0(1)	

Table XI

Torsion Angles (°)

	VIIIa	XVb
N(1)-C(2)-C(3)-C(4)	-0.3(3)	2.8(3)
N(1)-C(2)-C(3)-C(10)	-179.6(2)	-177.8(3)
N(1)-C(6)-C(5)-C(4)	-1.1(2)	0.2(6)
C(3)-C(2)-N(1)-C(7)		178.7(3)
C(3)-C(2)-N(1)-C(6)	0.5(3)	-3.1(4)
C(3)-C(4)-C(5)-C(6)	1.4(2)	-0.5(5)
O(2)-C(10)-C(3)-C(2)	-81.7(2)	-176.0(3)
O(2)-C(10)-C(3)-C(4)	98.9(2)	3.5(4)
O(3)-C(4)-C(3)-C(2)	179.2(1)	177.6(3)
O(3)-C(4)-C(3)-C(10)	-1.5(2)	-1.9(4)
O(3)-C(4)-C(5)-C(6)	-178.5(2)	-179.1(3)
C(5)-C(6)-N(1)-C(2)	0.2(6)	1.6(4)
C(5)-C(6)-N(1)-C(7)		179.8(4)
C(5)-C(4)-C(3)-C(2)	-0.7(3)	-1.0(4)
C(5)-C(4)-C(3)-C(10)	178.7(1)	179.6(4)
C(5)-C(4)-O3-C(11)	-1.6(2)	
C(13)-C(6)-N(1)-C(2)	-179.1(2)	-179.2(3)
C(13)-C(6)-N(1)-C(7)		-1.0(4)
C(13)-C(6)-C(5)-C(4)	178.1(1)	-179.0(3)
C(9)-C(2)-N(1)-C(7)		-1.5(4)
C(9)-C(2)-N(1)-C(6)	-179.3(2)	176.6(3)
C(9)-C(2)-C(3)-C(4)	179.5(2)	-177.0(3)
C(9)-C(2)-C(3)-C(10)	0.2(4)	2.5(5)
C(2)-N(1)-C(7)-C(8)		88.5(4)
C(2)-C(3)-C(10)-O(1)	98.5(2)	3.9(5)
C(6)-N(1)-C(7)-C(8)		-89.7(4)
C(4)-C(3)-C(10)-O(1)	-80.8(2)	
C(4)-O(3)-C(11)-C(12)	-179.1(2)	
C(3)-C(4)-O(3)-C(11)	178.6(1)	

Table XII

Anisotropic Temperature Factors (x 10^4) of the Non-hydrogen Atoms for **VIIIa** with e.s.d's in Parentheses

Atom	U11	U22	U33	U12	U13	U23
N(1)	193(6)	131(6)	227(5)	-8(5)	5(5)	8(5)
C(2)	188(6)	171(7)	206(6)	1(5)	8(5)	0(5)
C(3)	179(6)	171(7)	193(6)	10(6)	-1(5)	2(5)
C(4)	182(6)	163(7)	205(6)	-3(5)	-23(5)	27(5)
C(5)	165(6)	198(7)	210(6)	1(6)	13(5)	6(6)
C(6)	182(7)	186(7)	196(6)	11(6)	-14(5)	-7(6)
C(9)	253(8)	194(7)	407(9)	-17(6)	122(7)	22(7)
C(10)	179(6)	144(6)	225(6)	-16(5)	32(5)	-1(6)
C(11)	197(7)	216(7)	311(8)	-29(6)	53(6)	26(6)
C(12)	370(10)	219(9)	420(10)	-87(7)	90(8)	4(7)
C(13)	260(8)	171(7)	340(8)	30(6)	44(7)	-29(7)
O(1)	242(5)	178(5)	267(5)	43(4)	-31(4)	-5(4)
O(2)	331(6)	260(6)	222(5)	71(5)	7(4)	-29(4)
O(3)	196(5)	149(5)	311(5)	-13(4)	54(4)	24(4)
O(1W)	259(6)	304(6)	292(6)	-18(5)	19(4)	-75(5)
O(2W)	471(8)	293(7)	286(6)	80(6)	41(6)	47(6)
O(3W)	257(6)	314(7)	514(8)	15(5)	34(6)	-139(6)
O(4W)	274(7)	260(7)	543(9)	15(5)	56(6)	35(6)

Table XIII

Anisotropic Temperature Factors (x 10^3) of the Non-hydrogen Atoms for **XVb** with e.s.d's in Parentheses

Atom	U11	U22	U33	U12	U13	U23
N(1)	32(1)	45(1)	31(1)	2(1)	5(1)	3(1)
C(2)	28(2)	42(2)	36(1)	2(1)	5(1)	0(1)
C(3)	36(2)	40(2)	35(1)	1(1)	8(1)	-3(1)
C(4)	41(2)	42(2)	33(1)	-2(2)	5(1)	-3(1)
C(5)	31(2)	58(2)	41(1)	4(2)	-3(1)	0(1)
C(6)	26(2)	49(2)	42(1)	2(1)	4(1)	-1(1)
C(7)	41(2)	57(2)	35(1)	4(2)	6(1)	6(1)
C(8)	65(3)	68(2)	44(2)	-4(2)	11(2)	-7(2)
C(9)	28(2)	106(4)	39(2)	-1(2)	-1(1)	-4(2)
C(10)	44(2)	51(2)	44(2)	-1(2)	13(1)	-2(1)
C(13)	33(2)	99(3)	52(2)	3(2)	14(2)	-2(2)
O(1)	39(1)	127(2)	56(1)	4(2)	18(1)	6(1)
O(2)	59(2)	89(2)	37(1)	4(2)	18(1)	0(1)
O(3)	54(1)	84(2)	32(1)	-1(1)	0(1)	2(1)

these figures suggest it is unlikely that a uv spectrum corresponding solely to the neutral molecule can be obtained, so only uv parameters for the cationic and anionic species can confidently be determined (Table XVI). Both the non-depressed 4-oxo pK_a value (compare to 1,2,6-trimethylpyridin-4-one, 4.1 [9e], and 1,2-dimethyl-3-hydroxypyridin-4-one, 3.6 [34]) and non-elevated 3-carboxyl pK_a value found for **XVc** suggest that the very strong hydrogen bonding present is of negligible consequence to the acid-base speciation of this compound.

The inherent greater electron density on the 4-oxo group of the *N*-alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic acids **XV** compared to the "4-quinolone" antibacterials is predicted to result in the former compounds being superior chelators of metal cations, and a series of affinity constants are currently being determined in our laborator-

Table XIV

Positional and Isotropic Thermal Parameters (x10^3) of the Hydrogen Atoms for **VIIIa**

Atom	X	Y	Z	U
H(N1)	166(2)	752(2)	116(3)	33(6)
H(O3)	-44(2)	565(2)	301(3)	36(7)
H(91)	302(3)	621(4)	-110(5)	80(10)
H(92)	353(3)	595(4)	15(5)	90(10)
H(93)	304(3)	721(4)	-51(5)	90(10)
H(111)	-32(2)	395(2)	397(3)	30(5)
H(112)	-103(2)	399(2)	236(3)	29(5)
H(121)	-51(2)	224(3)	179(4)	52(8)
H(122)	-109(3)	229(3)	343(5)	80(10)
H(123)	20(3)	225(3)	347(4)	58(9)
H(131)	35(2)	808(2)	340(3)	33(6)
H(132)	-28(2)	804(2)	183(3)	38(6)
H(133)	-70(3)	744(2)	330(4)	49(8)
H1(O1W)	163(3)	470(3)	-269(4)	52(8)
H2(O1W)	78(3)	507(3)	-358(3)	43(7)
H1(O2W)	247(3)	345(2)	372(3)	41(6)
H2(O2W)	206(2)	370(3)	511(4)	52(9)
H1(O3W)	387(3)	555(3)	382(4)	60(9)
H2(O3W)	398(3)	479(3)	264(4)	56(9)
H1(O4W)	283(2)	681(3)	-497(3)	45(7)
H2(O4W)	246(3)	590(3)	-451(3)	48(8)

Table XV

Positional and Isotropic Thermal Parameters (x10^3) of the Hydrogen Atoms for **XVb**

Atom	X	Y	Z	U
H(C5)	431(4)	255(4)	202(2)	49(9)
H1(C6)	325(5)	237(5)	325(3)	90(10)
H2(C6)	416(5)	80(6)	394(2)	110(10)
H3(C6)	433(5)	299(4)	416(3)	90(10)
H1(C7)	827(4)	112(4)	483(2)	60(10)
H2(C7)	637(4)	116(4)	479(2)	56(9)
H1(C8)	833(4)	441(5)	499(2)	80(10)
H2(C8)	653(4)	458(5)	486(2)	80(10)
H3(C8)	742(4)	356(4)	574(2)	65(9)
H1(C9)	1039(6)	104(7)	381(3)	160(20)
H2(C9)	997(4)	269(4)	428(2)	70(10)
H3(C9)	1066(6)	293(5)	343(3)	120(20)
H(O2)	789(6)	273(4)	78(2)	90(10)

Table XVI

UV Parameters for the Cationic and Anionic Forms of *N*-Propyl-2,6-dimethyl-4-oxopyridine-3-carboxylic acid **XVc**

Form of **XVc**	λ max	ε mol^{-1}dm^{-3}cm^{-1}
Cationic (<*p*H 3.4)	245.5	8380
Anionic (>*p*H 5.0)	265.7	21000

ies. With respect to 2,6-dimethyl-4-oxopyran-3-carboxylic acid **V**, the downfield shift of the 5-H resonance (δ 6.58) in the ^{1}H nmr spectrum of this compound relative to the corresponding proton in its ethyl ester **IXb** (δ 6.20) indicates the existance of an increased aromatic mesomer contribution as a result of intramolecular hydrogen bonding, and hence little diversion of electron density to the 3-carboxyl group. Measurement of pK_a values for **V** is however complicated by its instability in acidic aqueous solution [7], a property which may ultimately hamper its usefulness as a chelator.

EXPERIMENTAL

Melting points were taken in capillary tubes on an Electrothermal Digital Melting Point Apparatus and are uncorrected. ^{1}H nmr spectra were determined with a Perkin-Elmer R32 90 MHz nmr spectrometer, with chemical shifts (δ) reported in ppm downfield from internal tetramethylsilane or 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt. Infrared 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.

X-ray Crystallography.

2,6-Dimethyl-4-ethoxypyridine-3-carboxylic acid **VIIIa** was crystallized from methanol equilibrated with hexane. A crystal of dimensions 0.45 x 0.3 x 0.2 mm was used for intensity data collection on a Enraf-Nonius CAD-4 Diffractometer with Ni-filtered Cu Kα radiation; $C_{10}H_{13}NO_3 \cdot 4H_2O$, M_r = 267, orthorhombic, $Pca2_1$, a = 12.746 (1), b = 13.163 (1), c = 8.331 (1) Å, V = 1398 Å^3, z = 4, D_c = 1.268 g cm^{-3}, λ(CuKα) = 1.54178 Å, μ = 8.27 cm^{-1}, F(000) = 576, T = 162 K, R = 0.025 and ωR = 0.027 for 1473 reflections. The cell parameters were refined using 48 reflections in the range $20° \leq \theta \leq 40°$. Three standard reflections monitored periodically (every 2 hours) showed no significant change in intensity. Intensities were measured in the $\omega - 2\theta$ mode with a scan-width (0.7 + 0.2 tan θ)° and an aperture width (4 + 0.86 tan θ) mm in the range $0 \leq 2\theta \leq 75°$. A total of 1769 reflections were collected out of which 1508 reflections were unique. 1473 reflections with $I \geq 1.5\sigma(I)$ were used for the structure solution. Lp-corrections were applied. The structure was solved using MITHRIL [35] and the structure was refined by full-matrix least-squares using SHELX76 [36]. The function minimised was $\Sigma w (|F_o| - |F_c|)^2$ with $\omega = \sigma^{-2}(F)$. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from a difference Fourier and refined isotropically. The maximum Δ/σ is 0.04 for non-hydrogen atoms and the maximum residual density in the final difference map was 0.17 e Å^{-3}. Positional parameters and equivalent isotropic temperature factors for non-hydrogen atoms of **VIIIa** are presented in Table VI.

Crystals of *N*-ethyl-2,6-dimethyl-4-oxopyridine-3-carboxylic acid **XVb** were obtained by slow evaporation of water. Crystal dimensions were 0.5 x 0.35 x 0.3 mm; $C_{10}H_{13}NO_3$, M_r = 195, monoclinic, $P2_{1/n}$, a = 8.612 (1), b = 7.298 (1), c = 15.399 (2) Å, β = 98.78 (1)°, V = 957 Å^3, z = 4, D_c = 1.391 g cm^{-3}, λ(MoKα) = 0.71069 Å, μ = 0.61 cm^{-1}, F(000) = 416, T = 292 K, R = 0.056, ωR = 0.052 for 1129 $I \geq 2\sigma(I)$ reflections. Data collection, unit-cell determination, and structure refinement as in **VIIIa**. Reflections were collected with a scan-width (1.0 + 0.35 tan θ)° and an aperture-width (3.0 + 0.86 tan θ) mm. 2340 reflections were measured out of which 1970 were unique and 1129 reflections with $I \geq 2\sigma(I)$ were considered to be observed and used in the refinement, maximum Δ/σ = 0.01 for non-hydrogen atoms, and the largest density in the final difference map was 0.20 e Å^{-3}. Position-

al parameters and equivalent isotropic temperature factors for non-hydrogen atoms of **XVb** are presented in Table VII.

Details of the intermolecular hydrogen bonding for **VIIIa** (Table IX), bond angles for **VIIIa** and **XVb** (Table X), torsion angles for **VIIIa** and **XVb** (Table XI), anisotropic temperature factors for the non-hydrogen atoms of **VIIIa** (Table XII), and **XVb** (Table XIII), and positional and thermal parameters for the hydrogen atoms of **VIIIa** (Table XIV), and **XVb** (Table XV) are reported.

Preparation of 2,6-Dimethyl-4-oxopyran-3-carboxylic Acid **V**.

Dehydroacetic acid (100 g, 0.595 mole) was refluxed in 500 ml of 80% sulphuric acid for 1 hour, the resultant solution being poured into 1000 ml of water prior to extraction into 2 x 1000 ml of dichloromethane. The organic fractions were dried over anhydrous sodium sulphate, filtered and rotary evaporated to yield a pink solid, recrystallization from ethanol giving **V** as colourless prisms, 50 g (50%), mp 98-99°; ir (Nujol): 1720, 1650, 1560 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.40 (s, 3H, 6-CH_3), 2.70 (s, 3H, 2-CH_3), 6.58 (s, 1H, 5-H), 14.27-14.95 (broad, 1H, CO_2H); ms: (m/z) 168 (M^+, 3.0), 124 (100), 109 (72).

Anal. Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.24; H, 4.66.

Preparation of 2,6-Dimethyl-4-hydroxypyridine-3-carboxylic Acid **VI**.

2,6-Dimethyl-4-oxopyran-3-carboxylic acid **V** (50 g, 0.297 mole) was stirred in 800 ml of 35% aqueous ammonia for 18 hours at room temperature. Removal of solvent by rotary evaporation yielded a pale yellow solid, recrystallization from water giving **VI** as a white powder, 40.7 g (82%), mp 266-267°; ir (Nujol): 1705, 1665, 1605 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.34 (s, 3H, 6-CH_3), 2.72 (s, 3H, 2-CH_3), 6.51 (s, 1H, 5-H); ms: (m/z) 167 (M^+, 35), 149 (79), 123 (100), 121 (36), 93 (26).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.47; H, 5.44; N, 8.38. Found: C, 57.35; H, 5.20; N, 8.52.

General Procedure for the Preparation of Alkyl 2,6-Dimethyl-4-alkoxypyridine-3-carboxylates **VII**.

To a solution of 2,6-dimethyl-4-hydroxypyridine-3-carboxylic acid **VI** (7 g, 0.0419 mole) in 200 ml of dry DMF stirring at 75° in an atmosphere of nitrogen was added anhydrous potassium carbonate (23.2 g, 0.168 mole) followed by the appropriate alkyl iodide (0.366 mole). After continued stirring at this elevated temperature for 20 hours, solvent was removed *in vacuo* and the resultant orange solids taken-up in 250 ml of water prior to extraction into 2 x 250 ml of dichloromethane. The organic fractions were subsequently dried over anhydrous sodium sulphate, filtered and rotary evaporated to give crude products **VII** as orange oils, purification of which was achieved by vacuum distillation.

Ethyl 2,6-Dimethyl-4-ethoxypyridine-3-carboxylate **VIIa**.

This compound was obtained as a colourless oil, 7.12 g (76%), bp 160° (0.1 mm Hg); ir: 1725, 1585, 1570 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.30 (t, 6H, 2 x ethyl CH_3), 2.39 (s, 3H, 2-CH_3), 2.43 (s, 3H, 6-CH_3), 4.09 (quartet, 2H, 4-O-CH_2-CH_3), 4.34 (quartet, 2H, CO_2-CH_2-CH_3), 6.88 (s, 1H, 5-H); ms: (m/z) 223 (M^+, 100), 178 (99), 177 (65), 176 (28), 150 (36), 149 (30).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.69; N, 6.27. Found: C, 64.31; H, 7.79; N, 6.12.

Propyl 2,6-Dimethyl-4-propoxypyridine-3-carboxylate **VIIb**.

This compound was obtained as a colourless oil, 8.66 g (82%), bp 132° (0.1 mm Hg); ir: 1725, 1590, 1570 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.98 (t, 6H, 2 x propyl CH_3), 1.72 (sextet, 4H, 2 x CH_2-CH_2-CH_3), 2.40 (s, 3H, 2-CH_3), 2.44 (s, 3H, 6-CH_3), 4.02 (quartet, 2H, 4-O-CH_2-CH_2), 4.25 (t, 2H, CO_2-CH_2-CH_2), 6.86 (s, 1H, 5-H); ms: (m/z) 251 (M^+, 69), 192 (73), 191 (44), 162 (31), 150 (51), 149 (100).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.89; H, 8.44; N, 5.57. Found: C, 67.03; H, 8.45; N, 5.67.

General Procedure for the Preparation of 2,6-Dimethyl-4-alkoxypyridine-3-carboxylic Acids **VIII**.

The alkyl 2,6-dimethyl-4-alkoxypyridine-3-carboxylates **VII** (5 g) were refluxed in 150 ml of 5% aqueous sodium hydroxide for 12 hours. The resultant solutions were washed with 2 x 150 ml of dichloromethane prior to adjustment to *p*H 5.5 and removal of solvent *in vacuo*. To the yellow solids obtained was added 200 ml of dry DMF and the suspensions stirred for 4 hours at room temperature, subsequent filtration and rotary evaporation giving crude products **VIII** as yellow solids.

2,6-Dimethyl-4-ethoxypyridine-3-carboxylic Acid **VIIIa**.

This compound was obtained as a white powder (water/acetone), 4.38 g (67%), mp 207-208°; ir (Nujol): 1660, 1620 cm^{-1}; ^1H nmr (deuterium oxide): δ 1.45 (t, 3H, ethyl CH_3), 2.61 (s, 3H, 2-CH_3), 2.69 (s, 3H, 6-CH_3), 4.40 (quartet, 2H, ethyl CH_2), 7.28 (s, 1H, 5-H); ms: (m/z) 195 (M^+, 100), 177 (96), 149 (72), 121 (29).

Anal. Calcd. for $C_{10}H_{13}NO_3 \cdot 4H_2O$: C, 44.92; H, 7.93; N, 5.24. Found: C, 45.15; H, 8.20; N, 5.23.

The product was then dried in a vacuum oven (2 hours/130°/-0.1 mm Hg).

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.51; H, 6.73; N, 7.18. Found: C, 61.25; H, 6.51; N, 7.11.

2,6-Dimethyl-4-propoxypyridine-3-carboxylic Acid **VIIIb**.

This compound was obtained as a white powder (water/acetone), 2.56 g (59%), mp 187-188°; ir (Nujol): 1655, 1610, 1590 cm^{-1}; ^1H nmr (deuterium oxide): δ 1.02 (t, 3H, propyl CH_3), 1.86 (sextet, 2H, CH_2-CH_2-CH_3), 2.64 (s, 3H, 2-CH_3), 2.70 (s, 3H, 6-CH_3), 4.32 (t, 2H, O-CH_2-CH_2), 7.30 (s, 1H, 5-H); ms: (m/z) 209 (M^+, 47), 149 (100).

Anal. Calcd. for $C_{11}H_{15}NO_3 \cdot 1/2H_2O$: C, 60.52; H, 7.40; N, 6.42. Found: C, 60.54; H, 7.31; N, 6.57.

General Procedure for the Preparation of Alkyl 2,6-Dimethyl-4-oxopyran-3-carboxylates **IX**.

To a solution of 2,6-dimethyl-4-oxopyran-3-carboxylic acid **V** (50 g, 0.297 mole) in 500 ml of dry DMF stirring at 60° in an atmosphere of nitrogen was added anhydrous potassium carbonate (41.5 g, 0.300 mole) followed by the appropriate alkyl halide (0.297 mole). After continued stirring at this elevated temperature for 4 hours, solvent was removed *in vacuo* and the resultant red solids taken-up in 750 ml of water prior to extraction into 2 x 500 ml of dichloromethane. The organic fractions were subsequently dried over anhydrous sodium sulphate, filtered and rotary evaporated to give crude products **IX** as red oils. Purification was achieved by column chromatography (silica gel-ethyl acetate).

Benzyl 2,6-Dimethyl-4-oxopyran-3-carboxylate **IXa**.

This compound was obtained as pale yellow needles (diethyl ether), 49.3 g (64%), mp 55-56°; ir (Nujol): 1735, 1665, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.22 (s, 3H, 6-CH_3), 2.25 (s, 3H, 2-CH_3), 5.33 (s, 2H, O-CH_2-Ph), 6.22 (s, 1H, 5-H), 7.44 (m, 5H, phenyl H's); ms: (m/z) 258 (M^+, 1.0), 152 (54), 124 (100).

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.47. Found: C, 69.88; H, 5.31.

Ethyl 2,6-Dimethyl-4-oxopyran-3-carboxylate **IXb**.

This compound was obtained as pale yellow needles (diethyl ether), 41.5 g (71%), mp 36-37°; ir (Nujol): 1735, 1670, 1630, 1600 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.29 (t, 3H, ethyl CH_3), 2.26 (s, 3H, 6-CH_3), 2.31 (s, 3H, 2-CH_3), 4.29 (quartet, 2H, ethyl CH_2), 6.20 (s, 1H, 5-H); ms: (m/z) 196 (M^+, 16), 152 (32), 151 (54), 124 (100).

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.18. Found: C, 61.27; H, 6.25.

Isopropyl 2,6-Dimethyl-4-oxopyran-3-carboxylate **IXc**.

This compound was obtained as pale yellow prisms (diethyl ether), 21.0 g (34%), mp 62-63°; ir (Nujol): 1735, 1665, 1625, 1595 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.29 (d, 6H, isopropyl CH_3's), 2.25 (s, 3H, 6-CH_3), 2.29 (s, 3H, 2-CH_3), 5.10 (septet, 1H, isopropyl CH), 6.20 (s, 1H, 5-H); ms: (m/z) 210 (M^+, 5.2), 151 (73), 124 (100), 109 (25).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.83; H, 6.73. Found: C, 62.68; H, 6.80.

General Procedure for the Reaction of Alkyl 2,6-Dimethyl-4-oxopyran-3-carboxylates **IX** with Primary Alkyl Amines.

To a solution of **IX** (x g, n mole) in 20x ml of water/15x ml of ethanol was added the appropriate primary alkyl amine (1.6n moles) followed by 10% aqueous sodium hydroxide (0.04x ml) and the mixture stirred for 4 hours at room temperature. After adjustment to *p*H 7 the resultant aqueous ethanolic solution was extracted into 2 x 20x ml of dichloromethane, the organic fractions subsequently being dried over anhydrous sodium sulphate, filtered and rotary evaporated. If tlc indicated the residue to contain more than one product, separation was achieved by column chromatography (silica gel-ethyl acetate or ethanol or ethyl acetate followed by ethanol). Physical and analytical data of the products obtained are presented in Tables I, II and III.

Reaction of **IXa** (50 g) with Methylamine.

An orange oil (48.1 g) was separated using ethanol to give benzyl alcohol (rf = 0.94), **XIIIa** (rf = 0.57) and **XIIa** (rf = 0.32).

3-(1-Methylamino)ethylidene-6-methylpyran-2,4-dione **XIIIa**.

A 7.12 g sample of this compound was obtained as colourless needles (ethyl acetate) (Table I); ir (Nujol): 1690, 1655, 1610, 1580 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.08 (s, 3H, 6-CH_3), 2.58 (s, 3H, vinyl CH_3), 3.18 (d, 3H, N-CH_3), 5.71 (s, 1H, 5-H), 13.40-13.80 (broad, 1H, N-H); ms: (m/z) 181 (M^+, 100), 124 (27).

Benzyl 1,2,6-Trimethyl-4-oxopyridine-3-carboxylate **XIIa**.

A 30.5 g sample of this compound was obtained as a white powder (ethanol/diethyl ether) (Table I); ir (Nujol): 1730, 1640, 1575, 1545, 1505 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.20 (s, 3H, 2-CH_3), 2.28 (s, 3H, 6 -CH_3), 3.44 (s, 3H, N-CH_3), 5.28 (s, 2H, O-CH_2-Ph), 6.10 (s, 1H, 5-H), 7.43 (m, 5H, phenyl H's); ms: (m/z) 271 (M^+, 5.5), 137 (100).

Reaction of **IXa** (20 g) with Ethylamine.

An orange oil (22.2 g) was separated using ethyl acetate to give benzyl alcohol (rf = 0.88) and **XIIIb** (rf = 0.52), followed by ethanol to give **XIIb** (rf = 0.39).

3-(1-Ethylamino)ethylidene-6-methylpyran-2,4-dione **XIIIb**.

An 8.87 g sample of this compound was obtained as colourless needles (ethyl acetate) (Table I); ir (Nujol): 1690, 1660, 1595, 1570 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.28 (t, 3H, ethyl CH_3), 2.10 (s, 3H, 6-CH_3), 2.70 (s, 3H, vinyl CH_3), 3.58 (d-quartet, 2H, ethyl CH_2), 5.70 (s, 1H, 5-H), 13.60-14.00 (broad, 1H, N-H); ms: (m/z) 195 (M^+, 100), 137 (43).

Benzyl *N*-Ethyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIIb**.

A 3.12 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric acid) (Table I); ir (Nujol): 2300 (broad), 1780, 1740, 1715, 1620, 1580, 1520, 1500, 1480 cm^{-1}; ^1H nmr (deuterium oxide): δ 1.38 (t, 3H, ethyl CH_3), 2.50 (s, 3H, 2-CH_3), 2.68 (s, 3H, 6-CH_3), 4.29 (quartet, 2H, ethyl CH_2), 5.39 (s, 2H, O-CH_2-Ph), 7.02 (s, 1H, 5-H), 7.41 (m, 5H, phenyl H's); ms: (m/z) 285 (M^+, 3.5), 151 (100).

Reaction of **IXa** (20 g) with Propylamine.

An orange oil (23.6 g) was separated using ethyl acetate to give benzyl alcohol and **XIIIc** (rf = 0.58), followed by ethanol to give **XIIc** (rf = 0.59).

3-(1-Propylamino)ethylidene-6-methylpyran-2,4-dione **XIIIc**.

A 9.52 g sample of this compound was obtained as colourless prisms (ethyl acetate) (Table I); ir (Nujol): 1705, 1660, 1580 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.00 (t, 3H, propyl CH_3), 1.18 (sextet, 2H, CH_2-CH_2-CH_3), 2.10 (s, 3H, 6-CH_3), 2.60 (s, 3H, vinyl CH_3), 3.51 (d-t, 2H, N-CH_2-CH_2), 5.70 (s, 1H, 5-H), 13.75-14.10 (broad, 1H, N-H); ms: (m/z) 209 (M^+, 100), 194 (37), 152 (39).

Benzyl *N*-Propyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIIc**.

A 1.82 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric acid) (Table I); ir (Nujol): 2260 (broad), 1790, 1760, 1730, 1630, 1580, 1495, 1475 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.96 (t, 3H, propyl CH_3), 1.72 (sextet, 2H, CH_2-CH_2-CH_3), 2.59 (s, 3H, 2-CH_3), 2.68 (s, 3H, 6-CH_3), 4.24 (t, 2H, N-CH_2-CH_2), 5.42 (s, 2H, O-CH_2-Ph), 7.45 (m, 5H, phenyl H's), 7.54 (s, 1H, 5-H), 9.32-9.78 (broad, 1H, OH); ms: (m/z) 299 (M^+, 2.1), 165 (100).

Reaction of **IXa** (30 g) with Butylamine.

A dark orange oil (34.1 g) was separated using ethyl acetate to give benzyl alcohol and **XIIId** (rf = 0.76), followed by ethanol to give **XIId** (rf = 0.69).

3-(1-Butylamino)ethylidene-6-methylpyran-2,4-dione **XIIId**.

A 19.9 g sample of this compound was obtained as an orange oil (Table I); ir: 1700, 1660, 1610, 1580, 1480 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.93 (t, 3H, butyl CH_3), 1.10-1.85 (m, 4H, CH_2-CH_2-CH_2-CH_3), 2.07 (s, 3H, 6-CH_3), 2.57 (s, 3H, vinyl CH_3), 3.52 (d-t, 2H, N-CH_2-CH_2), 5.68 (s, 1H, 5-H), 13.70-14.05 (broad, 1H, N-H); ms: (m/z) 223 (M^+, 41), 208 (36), 194 (52), 181 (100).

Benzyl *N*-Butyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIId**.

A 2.75 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric acid) (Table I); ir (Nujol): 2210 (broad), 1800, 1770, 1740, 1630, 1620, 1580, 1520 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.93 (t, 3H, butyl CH_3), 1.10-1.95 (m, 4H, CH_2-CH_2-CH_2-CH_3), 2.61 (s, 3H, 2-CH_3),

2.70 (s, 3H, 6-CH_3), 4.29 (t, 2H, N-CH_2-CH_2), 5.43 (s, 2H, O-CH_2-Ph), 7.46 (m, 5H, phenyl H's), 7.56 (s, 1H, 5-H), 11.85-12.35 (broad, 1H, OH); ms: (m/z) 179 (100), 91 (34).

Reaction of **IXa** (5 g) with Isopropylamine.

An orange oil (5.93 g) was separated using ethyl acetate to give benzyl alcohol and **XIIIe** (rf = 0.60).

3-(1-Isopropylamino)ethylidene-6-methylpyran-2,4-dione **XIIIe**.

A 3.24 g sample of this compound was obtained as colourless prisms (ethyl acetate) (Table I); ir (Nujol): 1690, 1665, 1605, 1570 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.29 (d, 6H, isopropyl CH_3's), 2.09 (s, 3H, 6-CH_3), 2.61 (s, 3H, vinyl CH_3), 4.18 (d-septet, 1H, isopropyl CH), 5.70 (s, 1H, 5-H), 13.85-14.15 (broad, 1H, N-H); ms: (m/z) 209 (M^+, 100), 152 (47).

Reaction of **IXb** (10 g) with Methylamine.

The only product formed in this reaction was **XIIe**.

Ethyl 1,2,6-Trimethyl-4-oxopyridine-3-carboxylate **XIIe**.

A 10.7 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric acid) (Table II); ir (Nujol): 2300 (broad), 1790, 1730, 1630, 1590, 1515, 1485 cm^{-1}; ^1H nmr (deuterium oxide): δ 1.43 (t, 3H, ethyl CH_3), 2.70 (s, 3H, 2-CH_3), 2.74 (s, 3H, 6-CH_3), 3.97 (s, 3H, N-CH_3), 4.54 (quartet, 2H, ethyl CH_2), 7.18 (s, 1H, 5-H); ms: (m/z) 209 (M^+, 13), 164 (28), 137 (100).

Reaction of **IXb** (10 g) with Ethylamine.

An orange oil (14.4 g) was separated using ethyl acetate to give **XIVa** (rf = 0.86) and **XIIIb** (1.63 g, 16%), followed by ethanol to give **XIIf** (rf = 0.38).

Z-Ethyl 3-Ethylamino-2-butenoate **XIVa**.

A 1.42 g sample of this compound was obtained as a colourless oil (vacuum distillation) (Table II); ir: 3290, 1725, 1655, 1610, 1500, 1480 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.11 (t, 3H, ethyl CH_3), 1.13 (t, 3H, ethyl CH_3), 1.88 (s, 3H, vinyl CH_3), 3.23 (d-quartet, 2H, N-CH_2-CH_3), 3.96 (quartet, 2H, O-CH_2-CH_3), 4.34 (s, 1H, vinyl H), 8.25-8.65 (broad, 1H, N-H); ms: (m/z) 157 (M^+, 100), 112 (63), 96 (26), 85 (54), 84 (49).

Ethyl *N*-Ethyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIIf**.

A 4.86 g sample of this compound was obtained as a white powder (ethanol/diethyl ether) (Table II); ir (Nujol): 1720, 1640, 1630, 1570, 1535, 1495, 1480 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.24 (t, 3H, ethyl CH_3), 1.25 (t, 3H, ethyl CH_3), 2.30 (s, 3H, 2-CH_3), 2.35 (s, 3H, 6-CH_3), 3.96 (quartet, 2H, N-CH_2-CH_3), 4.22 (quartet, 2H, O-CH_2-CH_3), 6.09 (s, 1H, 5-H); ms: (m/z) 223 (M^+, 20), 179 (30), 178 (38), 166 (36), 151 (100), 123 (33).

Reaction of **IXb** (15 g) with Propylamine.

An orange oil (19.5 g) was separated using ethyl acetate to give **XIVb** (rf = 0.86) and **XIIIc** (2.70 g, 17%), followed by ethanol to give **XIIg** (rf = 0.52).

Z-Ethyl 3-Propylamino-2-butenoate **XIVb**.

A 7.03 g sample of this compound was obtained as a colourless oil (vacuum distillation) (Table II); ir: 3360, 3290, 3190, 1720, 1650, 1610, 1500 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.90 (t, 3H, propyl CH_3), 1.14 (t, 3H, ethyl CH_3), 1.52 (sextet, 2H, CH_2-CH_2-CH_3), 1.90 (s, 3H, vinyl CH_3), 3.17 (d-t, 2H, N-CH_2-CH_2), 3.98 (quartet, 2H, ethyl CH_2), 4.35 (s, 1H, vinyl H), 8.42-8.72 (broad, 1H, N-H); ms: (m/z) 171 (M^+, 100), 142 (51), 126 (59), 96 (97), 84 (35).

Ethyl *N*-Propyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIIg**.

A 3.17 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric acid) (Table II); ir (Nujol): 2240 (broad), 1800, 1735, 1630, 1620, 1585, 1510, 1490 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.00 (t, 3H, propyl CH_3), 1.31 (t, 3H, ethyl CH_3), 1.78 (sextet, 2H, CH_2-CH_2-CH_3), 2.65 (s, 3H, 2-CH_3), 2.72 (s, 3H, 6-CH_3), 4.26 (t, 2H, N-CH_2-CH_2), 4.38 (quartet, 2H, ethyl CH_2), 7.55 (s, 1H, 5-H), 10.70-11.20 (broad, 1H, OH); ms: (m/z) 237 (M^+, 17), 193 (27), 192 (32), 165 (100).

Reaction of **IXb** (30 g) with Butylamine.

A brown oil (39.7 g) was separated using ethyl acetate to give **XIVc** (rf = 0.96) and **XIIId** (0.31 g, 1%), followed by ethanol to give **XIIh** (rf = 0.57).

Z-Ethyl 3-Butylamino-2-butenoate **XIVc**.

A 18.0 g sample of this compound was obtained as a colourless oil (vacuum distillation) (Table II); ir: 3360, 3280, 1690, 1655, 1610, 1500 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.91 (t, 3H, butyl CH_3), 1.14 (t, 3H, ethyl CH_3), 1.42 (m, 4H, CH_2-CH_2-CH_2-CH_3), 1.89 (s, 3H, vinyl CH_3), 3.20 (d-t, 2H, N-CH_2-CH_2), 3.94 (quartet, 2H, ethyl CH_2), 4.34 (s, 1H, vinyl H), 8.35-8.70 (broad, 1H, N-H); ms: (m/z) 185 (M^+, 84), 156 (26), 143 (48), 142 (36), 140 (57), 98 (50), 96 (100), 84 (26), 71 (30).

Ethyl *N*-Butyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIIh**.

A 10.3 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric acid) (Table II); ir (Nujol): 2220 (broad), 1800, 1740, 1625, 1585, 1520, 1490 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.95 (t, 3H, butyl CH_3), 1.30 (t, 3H, ethyl CH_3), 1.30-1.95 (m, 4H, CH_2-CH_2-CH_2-CH_3), 2.65 (s, 3H, 2-CH_3), 2.72 (s, 3H, 6-CH_3), 4.32 (t, 2H, N-CH_2-CH_2), 4.40 (quartet, 2H, ethyl CH_2), 7.55 (s, 1H, 5-H), 10.35-10.90 (broad, 1H, OH); ms: (m/z) 251 (M^+, 6.5), 206 (33), 179 (100).

Reaction of **IXb** (35 g) with Pentylamine.

A brown oil (53.0 g) was separated using ethyl acetate to give two products (rf = 0.95 and 0.85) which were not isolated, followed by ethanol to give **XIIi** (rf = 0.62).

Ethyl *N*-Pentyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIIi**.

A 9.32 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric acid) (Table II); ir (Nujol): 2280 (broad), 1805, 1730, 1630, 1580, 1520, 1490 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.88 (t, 3H, pentyl CH_3), 1.30 (t, 3H, ethyl CH_3), 1.20-1.95 (m, 6H, CH_2-CH_2-CH_2-CH_2-CH_3), 2.65 (s, 3H, 2-CH_3), 2.72 (s, 3H, 6-CH_3), 4.30 (t, 2H, N-CH_2-CH_2), 4.39 (quartet, 2H, ethyl CH_2), 7.57 (s, 1H, 5-H), 8.65-9.25 (broad, 1H, OH); ms: (m/z) 265 (M^+, 6.8), 193 (100).

Reaction of **IXb** (25 g) with Hexylamine.

A brown oil (36.4 g) was separated using ethyl acetate to give two products (rf = 0.96 and 0.86) which were not isolated, followed by ethanol to give **XIIj** (rf = 0.64).

Ethyl *N*-Hexyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIIj**.

A 3.95 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric

acid) (Table II); ir (Nujol): 2230 (broad), 1805, 1765, 1730, 1630, 1585, 1520, 1490, 1475 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.88 (t, 3H, hexyl CH_3), 1.32 (t, 3H, ethyl CH_3), 1.20-1.95 (m, 8H, CH_2-CH_2-CH_2-CH_2-CH_2-CH_3), 2.66 (s, 3H, 2-CH_3), 2.73 (s, 3H, 6-CH_3), 4.30 (t, 2H, N-CH_2-CH_2), 4.39 (quartet, 2H, ethyl CH_2), 7.58 (s, 1H, 5-H), 12.30-12.70 (broad, 1H, OH); ms: (m/z) 279 (M^+, 3.2), 207 (39), 36 (100).

Reaction of **IXc** (5 g) with Ethylamine.

An orange oil (5.11 g) was separated using ethanol to give **XIVd** (rf = 0.88) and **XIIk** (rf = 0.50).

Z-Isopropyl 3-Ethylamino-2-butenoate **XIVd**.

A 2.01 g sample of this compound was obtained as a colourless oil (vacuum distillation) (Table III); ir: 3360, 3290, 3190, 1650, 1610, 1500 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.13 (d, 6H, isopropyl CH_3's), 1.15 (t, 3H, ethyl CH_3), 1.88 (s, 3H, vinyl CH_3), 3.22 (d-quartet, 2H, ethyl CH_2), 4.30 (s, 1H, vinyl H), 4.85 (septet, 1H, isopropyl CH), 8.30-8.62 (broad, 1H, N-H); ms: (m/z) 171 (M^+, 74), 128 (28), 112 (78), 96 (55), 85 (85), 84 (100), 70 (36).

Isopropyl *N*-Ethyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIIk**.

A 1.89 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric acid) (Table III); ir (Nujol): 2280 (broad), 1805, 1770, 1735, 1620, 1580, 1520, 1500 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.31 (d, 6H, isopropyl CH_3's), 1.36 (t, 3H, ethyl CH_3), 2.64 (s, 3H, 2-CH_3), 2.71 (s, 3H, 6-CH_3), 4.39 (quartet, 2H, ethyl CH_2), 5.22 (septet, 1H, isopropyl CH), 7.52 (s, 1H, 5-H), 8.70-9.10 (broad, 1H, OH); ms: (m/z) 237 (M^+, 8.1), 179 (28), 178 (45), 151 (100), 123 (30).

Reaction of **IXc** (5 g) with Propylamine.

An orange oil (6.53 g) was separated using ethanol to give **XIVd** (rf = 0.92) and **XIII** (rf = 0.61).

Z-Isopropyl 3-Propylamino-2-butenoate **XIVd**.

A 2.55 g sample of this compound was obtained as a colourless oil (vacuum distillation) (Table III); ir: 3380, 3280, 3200, 1650, 1610, 1500 cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.90 (t, 3H, propyl CH_3), 1.13 (d, 6H, isopropyl CH_3's), 1.51 (sextet, 2H, CH_2-CH_2-CH_3), 1.88 (s, 3H, vinyl CH_3), 3.17 (d-t, 2H, N-CH_2-CH_2), 4.32 (s, 1H, vinyl H), 4.86 (septet, 1H, isopropyl CH), 8.40-8.70 (broad, 1H, N-H); ms: (m/z) 185 (M^+, 92), 171 (42), 142 (42), 126 (64), 114 (69), 96 (100), 84 (77).

Isopropyl *N*-Propyl-2,6-dimethyl-4-oxopyridine-3-carboxylate **XIII**.

A 1.63 g sample of the hydrochloride salt of this compound was obtained as a white powder (ethanol/diethyl ether/hydrochloric acid) (Table III); ir (Nujol): 2280 (broad), 1795, 1735, 1620, 1580, 1520, 1500, 1475 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.00 (t, 3H, propyl CH_3), 1.32 (d, 6H, isopropyl CH_3's), 1.72 (sextet, 2H, CH_2-CH_2-CH_3), 2.63 (s, 3H, 2-CH_3), 2.71 (s, 3H, 6-CH_3), 4.25 (t, 2H, N-CH_2-CH_2), 5.22 (septet, 1H, isopropyl CH), 7.51 (s, 1H, 5-H); ms: (m/z) 251 (M^+, 5.6), 192 (30), 165 (100).

Reaction of **IXc** (10 g) with Isopropylamine.

The only product formed in this reaction was **XIVf**.

Z-Isopropyl 3-Isopropylamino-2-butenoate **XIVf**.

A 7.12 g sample of this compound was obtained as a colourless oil (vacuum distillation twice); ir: 3360, 3280, 3190, 1650, 1610, 1500 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.13 (d, 12H, 2 x isopropyl CH_3's), 1.90 (s, 3H, vinyl CH_3), 3.70 (d-septet, 1H, N-C*H*-$(CH_3)_2$, 4.28 (s, 1H, vinyl H), 4.85 (septet, 1H, O-C*H*-$(CH_3)_2$), 8.30-8.70 (broad, 1H, N-H); ms: (m/z) 185 (M^+, 100), 171 (27), 142 (47), 128 (42), 126 (60), 124 (27), 110 (73), 99 (69), 98 (88), 84 (75).

General Procedure for the Preparation of *N*-Alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic Acids **XVa,b** by Hydrogenolysis of the Corresponding Benzyl Ester **XIIa,b**.

The benzyl *N*-alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylates **XIIa,b** (2 g, neutral **a**, crude neutral **b**) were dissolved in 75 ml of water and adjusted to *p*H 1 with hydrochloric acid. Palladium on charcoal catalyst (5%) was added (0.1 g) and the mixtures stirred under a constant stream of hydrogen for 3 hours at room temperature. After filtration the solutions were rotary evaporated then reconstituted in 50 ml of water, adjustment to *p*H 4.2 causing precipitation of crude products **XVa,b** as white powders.

1,2,6-Trimethyl-4-oxopyridine-3-carboxylic Acid **XVa**.

This compound was obtained as colourless prisms (water), 1.12 g (84%), mp 261-262°; spectral data as in Table V.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.65; H, 6.13; N, 7.73. Found: C, 59.67; H, 6.37; N, 7.77.

N-Ethyl-2,6-dimethyl-4-oxopyridine-3-carboxylic Acid **XVb**.

This compound was obtained as colourless prisms (water), 0.97 g (71%), mp 221-222°; spectral data as in Table V.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.51; H, 6.73; N, 7.18. Found: C, 61.63; H, 6.57; N, 6.94.

General Procedure for the Preparation of *N*-Alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic Acids **XVa,b,e,f** by Hydrolysis of the Corresponding Ethyl Esters **XIIe,f,i,j**.

The ethyl *N*-alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylates **XIIe,f,i,j** (10 g, hydrochloride salts **e,i,j**, neutral **f**) were refluxed in 300 ml of 5% aqueous sodium hydroxide for 3 hours. The resultant solutions were filtered then adjusted to *p*H 4.2, causing precipitation of crude products as white powders. Recrystallization from water gave **XVa,b,e,f** as colourless prisms (Tables IV and V).

General Procedure for the Preparation of *N*-Alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylic Acids **XVc,d** by Hydrolysis of the Corresponding Ethyl Esters **XIIg,h**.

The ethyl *N*-alkyl-2,6-dimethyl-4-oxopyridine-3-carboxylates **XIIg,h** (5 g, hydrochloride salts) were refluxed in 150 ml of 5% aqueous sodium hydroxide for 3 hours. The resultant solutions were adjusted to *p*H 4.2, reduced in volume to 50 ml by rotary evaporation, and extracted into 200 ml of dichloromethane. The aqueous fractions were then repeatedly re-adjusted to *p*H 4.2 and extracted into 100 ml of dichloromethane until no more product entered the organic layer (by tlc monitoring). Drying of the organic fractions over anhydrous sodium sulphate followed by filtration and rotary evaporation gave crude products as white solids, recrystallization from chloroform/diethyl ether yielding **XVc,d** as white powders (Tables IV and V).

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