Ring Lithiation of Pyridones

Premji Meghani and John A. Joule*
Chemistry Department, Manchester University, Manchester M13 9PL

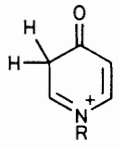
Lithiation of 1-methyl-2-pyridone takes place mainly at the methyl group which then leads to a dimer (**11**) by addition to a second mol equivalent of pyridone at C-6. Lithiation of 1-methyl-4-pyridone takes place cleanly and efficiently at C-2; this lithio derivative gave a dimer (**13**) with a second mol equivalent of the pyridone and reacted with a variety of carbon electrophiles to produce 2-substituted 4-pyridones (**14c—n**). 1-Methoxymethyl-, 1-benzyloxymethyl-, and 1-(2-trimethylsilylethoxy)-methyl-4-pyridones also lithiate at C-2, though these lithio derivatives were much less reactive towards electrophiles.

The preparation of unsymmetrically substituted pyridones has formerly had to rely on ring-synthetic methods,[1] for there are few examples of the introduction of carbon substituents onto a preformed pyridone. It occurred to us that the ring lithiation of 4- and/or 2-pyridones might provide such a means and we have accordingly carried out a study of the feasibility of applying this methodology. Before commencing, we felt that the question as to the position at which deprotonation would take place, in either system, was an open one, but realised that lithiation at either the 2- or 3-positions of a 4-pyridone or the 3- or 6-positions of a 2-pyridone would be synthetically useful. In looking to make the approach more generally useful we have examined the lithiation of some *N*-masked 4-pyridones; however, most of this paper is concerned with *N*-methylpyridones.

In early work[2] it was shown that pyridine itself undergoes exchange most rapidly at C-4, with hot, concentrated aqueous sodium hydroxide but at C-2, in neutral[3] or acidic[2] solutions, the difference lying in the intermediacy in the latter cases of an *N*-protonated-C-2-deprotonated ylide species. The exchange studies were later followed by preparative, strong base-deprotonating, ring-lithiations of oxazolino-,[4] ethoxycarbonyl-,[5] halogeno-,[6] dialkylaminocarbonyl-,[7] and diethylaminocarbonyloxypyridines,[8] at positions governed mainly by the substituent, and recently of pyridine itself, mainly at C-2 and C-4, the exact ratio depending on the detailed conditions.[9] 2-H Exchange and preparative 2-lithiation of pyridine *N*-oxides[10] and 2-H exchange of pyridinium salts[2,11] have also been described but these must necessarily involve ylide species.

There were reports outside pyridone chemistry, which conflicted in the guidance they gave as to the position of lithiation to be expected for pyridones, most, however, suggesting that it would be α to the ring nitrogen. Lithiation of 1-phenyl-1,4-dihydropyridine[12] and of 3-cyano-1-methyl-1,4-dihydropyridine[13] also took place α to nitrogen, and in the latter case, regioselectively at C-2. Treatment of 1-methylsulphonyl-1,4-dihydropyridine with butyl-lithium resulted[12] only in lithiation of the methyl, and of the *N*-phenylsulphonyl analogue, only at the allylic carbon, C-4.[12] However, 1-t-butoxycarbonyl-1,4-dihydropyridines could be lithiated[14] at C-2 and the resulting derivatives made to undergo useful reactions with electrophiles. Lithiation of 2′-deoxyuridines[15] at C-6, *via* a dilithiated species, is of considerable relevance to the present study; one may speculate that the second C-lithiation may involve intramolecular assistance from a sugar oxygen; the lithio derivatives were successfully allowed to react at C-6 with a range of electrophiles. In work[16] on flavones and isoflavones the alternative regio-sense of metallation was observed, thus lithiation both α to the ring oxygen and also α to the carbonyl group was observed, with a preference for the latter.

Turning to relevant pyridone chemistry, exchange reactions of 2- and 4-pyridones were reported[17–19] some while ago: in acidic solution, presumably *via* an intermediate (**1**) produced by enamine-like protonation, exchange in 4-pyridone and 1-methyl-4-pyridone was observed[17] at C-3/C-5 whereas under strong aqueous basic conditions, 1-methyl-4-pyridone underwent[18]



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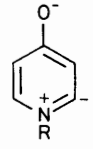

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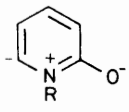
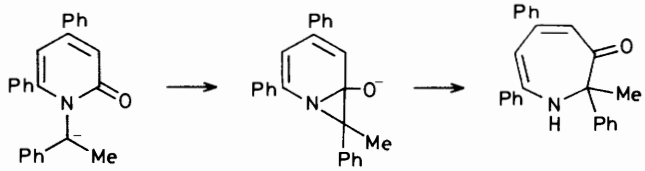


(3)

exchange at C-2/C-6 and its 2-isomer underwent[19] exchange at C-6, though at about one tenth the rate; one may rationalise these regio-preferences in terms of the ylide-like character of the deprotonated forms as expressed in resonance contributors (**2**) and (**3**). No exchange at *N*-methyl was reported for either isomer.

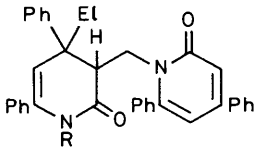
Katritzky has made studies[20–22] of the *N*-substituent-α-lithiation of 1-benzyl-and 1-alkyl-4,6-diphenyl-2-pyridones. He showed[20] that the former readily lithiate at the benzylic methylene and that the resultant organometallic derivatives are stable in solution and react normally with electrophiles. Attempts[20] to utilise potassium dimsylate in DMSO produced 3-methyl derivatives; this was interpreted as involving initial addition of dimsylate anion at the conjugate position C-4, followed by a rearrangement (see also below). Lithiation of 1-(1-phenylethyl)-4,6-diphenyl-2-pyridone produced[20] an azepinone (**4**) by rearrangement of the initial anion (**5**) ⟶ (**6**) ⟶ (**4**).



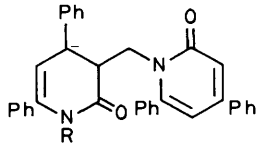
(5) (6) (4)

The reactions[21,22] of 1-alkyl-4,6-diphenyl-2-pyridones were more complex. Thus, for reaction with aldehydes, ketones, and iodomethane, metallation in the usual way, with subsequent addition of the electrophile, was sufficient to effect substitution at the *N*-substituent. For reaction with esters and nitriles it

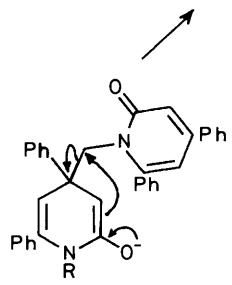
was necessary to utilise a regime in which the lithium di-isopropylamide (LDA) was added to an equimolar mixture of the 2-pyridone and the carbon electrophile. This last variation was made necessary by the discovery that treatment of 1-alkyl-4,6-diphenyl-2-pyridones with LDA at −89 °C followed by addition of electrophiles produced products (**7**) in which the added electrophile (El) was located at C-4 and a second mol of the *N*-alkyl-lithiated pyridone had added at C-3. This unexpected result was interpreted as involving initial Michael-type addition at C-4 to give anion (**8**), a rearrangement to anion (**9**), and finally trapping by the electrophile to produce the reported products (*cf.* the potassium dimsylate reaction, above).



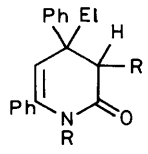
(**7**) El = added electrophile



(**9**)



(**8**)



(**10**) R = Et or Bu

When ethyl- or butyl-lithium were employed[21,22] in attempts to lithiate 1-methyl- and 1-ethyl-4,6-diphenyl-2-pyridone, with subsequent addition of electrophiles, analogous rearrangement products (**10**) were again obtained, and their formation rationalised, as above, *via* initial alkyl-lithium addition to C-4.

Of greatest relevance to the work reported here, is a paper by Katritzky,[23] of which we were unaware * for most of our studies, in which he showed that 1-methyl- and 1-benzyl-2-pyridones could be substituted on the *N*-substituent by the addition of LDA to a mixture of the pyridone and an electrophile. Katritzky also reported that treatment of these simpler pyridones with LDA alone at −78 °C produced purple colours which were, however, discharged within seconds as a result, it was suggested, of polymerisation; in any event subsequent addition of electrophiles gave none of the expected products. The greater acidity of the *N*-benzyl methylene protons was illustrated by showing that some condensation (10% yield) could be achieved even with potassium t-butoxide in DMF.

Results

For synthetic reasons, our principal interest was in the ring-lithiation of 4-pyridones; however, we examined 1-methyl-2-pyridone briefly. In our hands, treatment of 1-methyl-2-pyridone with butyl-lithium at −78 °C gave a red solution, which was stable for 1 h. Quenching with water produced recovered pyridone (15%) together with a 61% yield of a dimer. In the hope that the proportion of dimer could be reduced, reactions with LDA and s-butyl-lithium were conducted; however, comparable quantities of dimer and recovered pyridone were obtained in each case.

Lithiation with butyl-lithium followed by quenching with D_2O, with n.m.r. and m.s. analyses of the recovered 1-methyl-2-pyridone, showed unambiguously that one deuterium had been incorporated regioselectively at C-6 by the disappearance of the signal at δ 7.13 and the simplification of the signal at δ 6.15, corresponding to 5-H. This result confirmed C-6-lithiation, but only as a minor pathway.

The dimer, having only one *N*-methyl group, was clearly formed by the addition of an *N*-methyl-metallated species to a second molecule of pyridone. Initially we proposed to consider only the conjugate positions, C-4 and C-6, as reasonable possibilities for the point of addition; however, in the light of the rearrangement products reported by Katritzky[21,22] it is necessary to exclude the other two possibilities.

The ^1H n.m.r. spectrum of the dimer showed, in addition to signals for an intact pyridone ring, only one *N*-methyl (δ 3.02), signals for two olefinic protons (δ 5.90), and signals for a CH_2CH unit, confirmed by decoupling experiments, in which the shifts, respectively δ 4.28 and 4.46, allowed expansion of this part structure to $NCH_2CH(N)$. This sequence is consistent only with a structure formed by conjugate addition at C-6 of the second pyridone. It is interesting that efforts[25] to add organocuprates in a conjugate fashion to thi-in-4-one were unsuccessful; addition *was* successful for 3-methoxycarbonylthi-in-4-one (See also later for addition to 1-methyl-4-pyridone).

It remained to establish the position of the double bond, 3,4- or 4,5-, in the dihydropyridone ring. The similarity of chemical shifts for the two alkene protons suggested that the double bond was not conjugated to the carbonyl group, yet it seemed unlikely that this non-conjugated isomer † should have emerged from the alkali and therefore we initially assumed an equilibrating reaction medium during work-up. Indeed our first attempts to verify this by exposing the dimer to more vigorous, potentially equilibrating, conditions—hot aqueous lithium hydroxide or hot aqueous hydrochloric acid (2M)—led to recovery of the unchanged dimer. However with aqueous sodium hydroxide (2M), over a period of 2 days at room temperature, the dimer was transformed into an inseparable equilibrium mixture of isomers (90% recovery) in which the new isomer predominated by 3:1 (n.m.r.). The difference in chemical shifts for the two alkene protons in the new isomer, δ 5.00 and 5.50 respectively, clearly showed the double bond now to be in conjugation with the carbonyl group and the isomeric structure therefore to be (**12**), leaving (**11**) to represent the original conjugate addition product.

The lithiation of 1-methyl-4-pyridone proved to be much

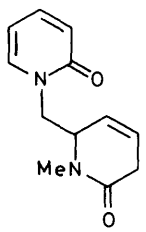
* This paper had not been abstracted by Chemical Abstracts up to the end of Volume 103, 1985. We thank Professor Katritzky for calling our attention to this paper after the publication of our preliminary communication.[24]

† Since the original submission of this paper it has been reported[26] that alkyl-lithiums can be added at C-6, albeit in poor yields, to 2-pyridone itself, giving products with the remaining double bond in the unconjugated 4,5-position. This contrasts with an earlier report[27] of the addition of a chiral organolithium species to 1-benzyl-2-pyridone, at C-4.

Table. Reactions of 2-lithio-1-methyl-4-pyridone (**14a**) with carbon electrophiles

Electrophile	Time/t (°C)	Product(s) (% yield)	m.p. (°C)	Recryst. from†	Mol. Formula	Found C	Found H	Found N	Required C	Required H	Required N	Found M^+	Required M
MeI	3 h/−78 then 3 days/0	**14c** (43)	50—53		$C_7H_9NO·H_2O$	59.5	7.9	9.8	59.6	7.8	9.9		
		14d (6)	Gum		$C_8H_{11}NO$							137.0837	137.0841
$PhCH_2Br$	3 h/−78 then 3 days/0	**14e** (15)	86—92		$C_{13}H_{13}NO$							199.0997	199.0998
		14f (58)	188—191	(EtOAc)	$C_{20}H_{19}NO$	83.0	6.7	4.7	83.0	6.6	4.8		
PhCHO	3 h/−78 then 2 days/0	**14g** (78)	165—170	(EtOAc)	$C_{13}H_{13}NO_2·0.6H_2O$	68.8	5.9	6.1	69.1	6.2	6.2		
Ph_2CO	3 h/−78 then 1 day/0	**14h** (76)	284—285	(EtOAc–EtOH)	$C_{19}H_{17}NO_2$	77.9	6.1	4.5	78.3	5.8	4.8		
PhCOCl	3 h/−78 then 3 days/0	**14i** (48)	126—132	(EtOAc–LP)	$C_{13}H_{11}NO_2$	73.4	5.3	6.4	73.2	5.2	6.6		
Phthalide	3 h/−78 then 2 days/0	**14j*** (34)	168—171		$C_{14}H_{13}NO_3$							243.0895	243.0895
Phthalic anhydride	3 h/−78 then 2 days/0	**14k** (68)	185—186	(EtOAc–LP)	$C_{14}H_{11}NO_4$							257.0693	257.0688
4-Methoxycarbonyl-3-pyridylcarbonyl chloride	3 h/−78 then 2 days/0	**14l** (44)	Gum		$C_{14}H_{12}N_2O_4$							272.0798	272.0797
2-Methoxycarbonyl-2-pyridylcarbonyl chloride	3 h/−78 then 2 days/0	**14m** (40)	Gum		$C_{14}H_{12}N_2O_4$							272.0798	272.0797
Me_2NCHO	2 h/−78 then 1 day/0	**14n** (70)	136—140		$C_7H_7NO_2$							131.0476	137.0477

* Isolated as an inseparable mixture of hydroxy ketone and cyclic hemiacetal forms. † LP = light petroleum.



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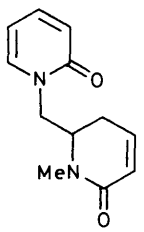

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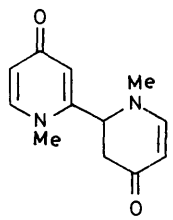

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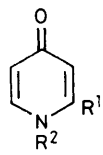

(14)

easier to control; however, here also, in some reactions, traces of a dimer were formed* and, moreover, a 94% yield of this compound could be obtained by treating the pyridone with 0.5 mol equivalents of butyl-lithium. Since this dimer had ^1H n.m.r. signals for two *N*-methyl groups and since it was established (see below) that 1-methyl-4-pyridone lithiates exclusively at C-2, only two structural possibilities needed to be considered. A decision in favour of (**13**) was based on the CH_2CH system shown in its ^1H n.m.r. spectrum and confirmed by decoupling experiments, in which the chemical shifts, δ 2.52 and δ 3.05 for the methylene protons, and δ 4.60 for the methine, located these protons on carbons adjacent to carbonyl and nitrogen respectively. This dimer too, then, was formed by conjugate addition in the anticipated sense.

Lithiation of 1-methyl-4-pyridone with 1 mol equivalent of butyl-lithium at −78 °C proceeded smoothly, generating a yellow solution, becoming brown on reaching 0 °C. Quenching with D_2O at −78 °C produced unchanged pyridone (91% recovery), carrying one deuterium (>98% incorporation) located at C-2 (**14b**) as evidenced by the halving of the integral for pyridone α-proton signals at δ 7.22 and the change of the β-proton signals at δ 6.23 into an overlapping doublet and singlet.

* Formation of dimer could be minimised in subsequent reactions by utilising an excess of electrophile.

	R^1	R^2
a	Li	Me
b	D	Me
c	Me	Me
d	Et	Me
e	CH_2Ph	Me
f	$CH(CH_2Ph)Ph$	Me
g	CH(OH)Ph	Me
h	$C(OH)Ph_2$	Me
i	COPh	Me
j	$2\text{-}HOCH_2C_6H_4CO$	Me
k	$2\text{-}HO_2CC_6H_4CO$	Me
l	$4\text{-}MeO_2CC_5H_3NCO\text{-}3$	Me
m	$2\text{-}MeO_2CC_5H_3NCO\text{-}3$	Me
n	CHO	Me
o	CH(OMe)OH	Me
p	H	COOPh
q	H	CH_2OMe
r	H	CH_2OCH_2Ph
s	H	$CH_2OCH_2CH_2SiMe_3$
t	D	CH_2OMe
u	D	CH_2OCH_2Ph
v	D	H
w	D	$CH_2OCH_2CH_2SiMe_3$
x	H	$C(Ph)_3$
y	COPh	CH_2OMe
z	CHO	CH_2OMe
aa	$4\text{-}MeO_2CC_5H_3NCO\text{-}3$	CH_2OMe
ab	$C_6H_4CO·OC(OMe)$	Me

These data confirm that 2-lithio-1-methyl-4-pyridone (**14a**) had been efficiently generated in solution.

We next examined the trapping of the 2-lithiated-4-pyridone with carbon electrophiles (Table). Reaction with alkyl halides was complicated by the subsequent deprotonation of the alkylated-pyridone product followed by further side-chain alkylation; thus reaction with iodomethane gave 2-ethyl-1-methyl-4-pyridone (**14d**) and the reaction with benzyl bromide gave 2-(1,2-diphenylethyl)-1-methyl-4-pyridone (**14f**) in addition to the straightforward products (**14c**) and (**14e**). Comparable side-chain alkylation of products was noted [6a] in studies on the alkylation of lithiated halogeno-pyridines. There is ample precedent for the acidity of protons on alkyl groups at the 2/6-positions of 4-pyridones.

Condensations of (**14a**) with benzaldehyde, benzophenone, phthalide, phthalic anhydride, acid chlorides, and dimethylformamide all proceeded straightforwardly, though in some cases in only moderate yields (Table), giving products (**14g—n**). The last of these, the aldehyde (**14n**) showed a strong tendency to form hemiacetals; simply boiling in methanol, for example, produced (**14o**) quantitatively.

Next, our attention was turned to the possibility of preparing and lithiating an *N*-masked 4-pyridone. Attempts to prepare *N*-phenylsulphonyl-4-pyridone by reaction of the sodium salt of 1*H*-4-pyridone with benzenesulphonyl chloride produced only 1-(4-pyridyl)-4-pyridone in high yield, presumably by *O*-phenylsulphonylation followed by attack at C-4 by the nitrogen of a second mol equivalent of pyridone anion.

In an attempt to prepare 1-t-butoxycarbonyl-4-pyridone, (*cf.* ref. 14) 1-phenoxycarbonyl-4-pyridone (**14p**), prepared from the sodium salt of 1*H*-4-pyridone and phenyl chloroformate following a procedure [28] for 1-ethoxycarbonyl-4-pyridone, was treated with potassium t-butoxide, but only 4-pyridone itself and t-butyl phenyl carbonate were obtained.

More success was found in the preparation of substituted alkyl-masked pyridones, thus 1-methoxymethyl- (**14q**), 1-benzyloxymethyl- (**14r**), and 1-(2-trimethylsilylethoxymethyl)-4-pyridones (**14s**), were prepared by reactions of the sodium salt of 4-pyridone with the appropriate halide in DMF solution. It was further shown that the masking groups could be removed by treatment with concentrated hydrochloric acid or concentrated sulphuric acid, 6M hydrochloric acid, and boron trifluoride–diethyl ether followed by sodium hydroxide, respectively.

Lithiation of 1-methoxymethyl-4-pyridone with 1 mol equivalent of butyl-lithium at −78 °C proceeded smoothly generating a yellow solution becoming brown on reaching 0 °C. Quenching with D_2O at −78 °C produced the protected pyridone (**14t**) (99% recovery), carrying one deuterium (>98% incorporation) located at C-2 as evidenced by n.m.r. data. Clearly lithiation was taking place as efficiently as with the simpler *N*-methyl analogue, however trapping the lithiated species with some representative electrophiles gave disappointingly low yields of the condensation products (**14y**, **z**, and **aa**).

Lithiation of 1-benzyloxymethyl-4-pyridone also proceeded smoothly, despite our doubts as to the relative acidities of the 2-H and the benzylic methylene protons. The purple solution produced at −78 °C was quenched with D_2O, and worked up to provide a 70% recovery of the starting masked pyridone with one deuterium per molecule (**14u**) (>98% incorporation) located at C-2; the latter conclusion was based on the change in the pattern of signals for the C-3/C-5 protons, those of the pyridone α-protons being masked by the phenyl group resonances. Further confirmation for the location of the label was provided by quantitatively removing the masking group with 6 M hydrochloric acid at 95 °C, producing 4-pyridone, which had a completely interpretable ^{1}H n.m.r. spectrum in accord with structure (**14v**).

Lithiation of 1-(2-trimethylsilylethoxymethyl)-4-pyridone was conducted in the usual way, D_2O work-up producing monodeuteriated (>98%) masked pyridone (**14w**) (86% recovery). Once again, location of the label of C-2 was straightforward by the usual ^{1}H n.m.r. analysis.

Although the experiments described above showed clearly that efficient lithiation of the three *N*-masked 4-pyridones (**14q—s**) was taking place, considerably less success was encountered in attempts to bring about useful reactions of the lithiated species [for (**14r** and **s**) even less than for (**14q**)]. We considered that this might be due to intramolecular complexation of the lithium by the protecting group ether oxygens rendering the lithio reagents less reactive. In an attempt to circumvent this difficulty, 1-triphenylmethyl-4-pyridone (**14x**) was prepared; however, no ring-deuteriated material could be obtained from lithiation attempts with butyl-lithium, with or without tetramethylethylenediamine present, or with lithium di-isopropylamide. Only partial recovery of the tritylpyridone was achieved in these attempts. Addition and dimerisation products were formed, though not fully characterised, the latter showing that some ring lithiation must have occurred.

Experimental

M.p.s were determined on a Kofler hot-stage microscope and are uncorrected. Wet organic solutions/extracts were dried with anhydrous $MgSO_4$, Na_2SO_4, or K_2CO_3 and evaporated at *ca.* 20 mmHg and *ca.* 40—70 °C using a rotary evaporator. U.v. spectra were measured using a Shimadzu UV/VIS 260 instrument; i.r. spectra were measured using Pye-Unicam SP3-200 or Perkin-Elmer 1710 FT spectrometers; ^{1}H n.m.r. spectra were measured on Perkin-Elmer R12B (60 MHz), Perkin-Elmer R34 (220 MHz), Varian SC 300 (300 MHz) or Varian XL 300 (300 MHz) spectrometers. Mass spectra were determined by the electron impact method on an AEI MS 30 instrument coupled to a DS 55 data system. For i.r. and ^{1}H n.m.r. spectra only clearly distinguished and unambiguously assignable absorptions/signals are given, in particular those which are of greatest importance for the establishment of structure. Only ions of >10% of base peak are given for mass spectra, except where a less intense ion is of importance for structure establishment. The homogeneity of non-crystalline products was confirmed by t.l.c. analysis.

6-*Lithio*-1-*methyl*-2-*pyridone and* 1-(1,2,5,6-*Tetrahydro*-1-*methyl*-6-*oxo*-2-*pyridylmethyl*)-2-*pyridone* (**11**).—To a stirred solution of 1-methyl-2-pyridone (0.33 g, 3.1 mmol) in dry THF (40 ml) under nitrogen, maintained at −78 °C, was added rapidly by syringe, a solution of butyl-lithium (1.65M in hexane; 2.04 ml, 3.1 mmol) causing the solution to turn immediately red. The reaction mixture was stirred at −78 °C for 1 h, after which water (2 ml) was injected causing an immediate decolourisation. After the solution had been allowed to warm to room temperature, the precipitated salts were filtered off, and the filtrate evaporated to give a pale yellow oil which was purified by chromatography over silica: elution with $CHCl_3$–MeOH (9:1) gave first 1-methyl-2-pyridone (51 mg, 15%) and then a colourless oil which was crystallised from ethyl acetate to give the *dimer* (**11**) (0.20 g, 61%), m.p. 135—140 °C; $\lambda_{max.}$(EtOH) 303 and 225 nm (log ε 3.70 and 3.89); $\nu_{max.}$(Nujol) 1 650 and 1 580 cm^{-1}; δ[$(CD_3)_2CO$] 7.46 (2 H, d + t, *J* 6 Hz, 6-H and 4-H), 6.43 (1 H, d, *J* 6 Hz, 3-H), 6.22 (1 H, t, *J* 6 Hz, 5-H), 5.90 (2 H, m, CH=CH), 4.46 [1 H, m, $NCH_2CH(N)$], 4.28 [2 H, dd, *J* 5, 15 Hz, $NCH_2CH(N)$], 3.02 (3 H, s, NMe), and 2.55 and 2.79 (2 H, 2 × d, *J* 18 Hz, CH_2CO); *m/z* 218 ($M^{+\bullet}$, 2), 217 (9), 188 (3), 160 (2), 123 (14), 110 (100), 94 (8), and 81 (10) (Found: C, 65.9; H, 6.6; N, 12.4. $C_{12}H_{14}N_2O_2$ requires C, 66.0; H, 6.4; N, 12.8%).

In repetition of the lithiation, but using D_2O for quenching the recovered 1-methyl-2-pyridone had δ($CDCl_3$) 7.34 (1 H, t, *J* 6 Hz, 4-H), 6.57 (1 H, d, *J* 6 Hz, 3-H), and 6.15 (1 H, d, *J* 6 Hz, 5-H); *m/z* 110 ($M^{+\bullet}$, 100), 82 (65), 54 (16), and 43 (32).

2-Lithio-1-methyl-4-pyridone (**14a**) *and 2-Deuterio-1-methyl-4-pyridone* (**14b**).—1-Methyl-4-pyridone (0.39 g, 3.5 mmol) previously melted and dried *in vacuo* (0.1 mmHg) in a flame dried 3-necked round-bottom flask (500 ml) was dissolved in dry THF (100 ml) under nitrogen. Butyl-lithium (1.6M in hexane; 3.45 ml, 3.5 mmol) was rapidly syringed into the magnetically stirred solution at −78 °C causing the solution to turn immediately yellow. The reaction mixture was stirred for 0.5 h and then allowed to warm to 0 °C, over 15 min, causing the solution to turn dark brown. The temperature of the solution was then immediately returned to −78 °C for the electrophile to be syringed into the solution of 2-lithio-1-methyl-4-pyridone (**14a**).

Deuterium oxide (2 ml) when syringed into a stirred solution of 2-lithio-1-methyl-4-pyridone prepared as described above, at −78 °C, caused an immediate decolourisation of the solution. The reaction mixture was then allowed to warm slowly to room temperature after which it was filtered and evaporated under reduced pressure to give crude material as a pale yellow oil. This was purified by passage through a short column of silica gel in chloroform–methanol (2:1) to give the pure 2-deuteriopyridone (**14b**) (0.35 g, 91%) as a colourless crystalline solid, m.p. 91—93 °C; δ($CDCl_3$) 7.22 (1 H, d, *J* 8 Hz, 6-H), 6.37 (1 H, d, *J* 8 Hz, 5-H), 6.37 (1 H, s, 3-H), and 3.62 (3 H, s, NMe); *m/z* 110 ($M^{+\bullet}$, 100), 82 (23), 55 (8), and 42 (13).

2-(1,2,3,4-Tetrahydro-1-methyl-4-oxo-2-pyridyl)-1-methyl-4-pyridone (**13**).—To a stirred solution of 1-methyl-4-pyridone (0.71 g, 6.5 mmol) in dry THF (110 ml) under nitrogen, maintained at −78 °C, was added rapidly by syringe, a solution of butyl-lithium (1.6M in hexane; 2.04 ml, 3.3 mmol) causing the solution to turn immediately yellow. After the solution had been allowed to warm slowly to room temperature over 30 min, it was stirred for a further 30 min and then returned to −78 °C before quenching with water (3 ml); this caused an immediate decolourisation of the dark red–brown solution. The solution was warmed to room temperature, the precipitated salts filtered off, and the filtrate evaporated under reduced pressure to leave a pale yellow gum, which was purified by chromatography over silica: elution with $CHCl_3$–MeOH (1:1) gave 1-methyl-4-pyridone (40 mg) and then the dimer (**13**) as a pale yellow solid. The latter when recrystallised from EtOH–light petroleum (b.p. 60—80 °C) gave fine white needles (0.67 g, 94%), m.p. 204—208 °C; $\lambda_{max.}$(EtOH) 264 and 325 nm (log ε 4.15 and 4.08); $\nu_{max.}$(Nujol) 1 630 and 1 585 cm^{-1}; δ($CDCl_3$) 7.35 (1 H, d, *J* 8 Hz, 6-H), 7.14 (1 H, d, *J* 7 Hz, 6′-H), 6.44 (1 H, s, 3-H), 6.34 (1 H, d, *J* 8 Hz, 5-H), 5.03 (1 H, d, *J* 7 Hz, 5′-H), 4.6 (1 H, t, *J* 6 Hz, NC*H*CH_2), 3.62 (3 H, s, 1-Me), 2.98 (3 H, s, 1′-Me), and 3.05 and 2.52 (2 × 1 H, dd, *J* 7, 16 Hz, NCHCH_2); *m/z* 218 ($M^{+\bullet}$, 8), 217 (14), 189 (21), 176 (73), 136 (14), 110 (76), and 83 (38) (Found: C, 65.7; H, 6.5; N, 12.7. $C_{12}H_{14}N_2O_2$ requires C, 66.0; H, 6.4; N, 12.8%).

Condensations of 2-Lithio-1-methyl-4-pyridone (**14a**) *with Electrophiles; Typical Procedures and Particular Purifications.*—(a) *With an aldehyde: 2-(1-hydroxyphenylmethyl)-1-methyl-4-pyridone* (**14g**). Benzaldehyde (1.5 ml, 15 mmol) was syringed into a stirred solution of 2-lithio-1-methyl-4-pyridone [from 1-methyl-4-pyridone (0.32 g, 2.9 mmol) in THF (120 ml)], prepared in the usual manner, at −78 °C; there was an immediate colour change from brown to purple. The reaction mixture was stirred at −78 °C for 3 h and then at 0 °C for 2 days over which time the colour of the solution gradually turned yellow. The mixture was diluted with water (4 ml), filtered, and evaporated to leave a yellow gum. Excess of benzaldehyde was removed by washing the gum with diethyl ether (2 × 10 ml), and the residue purified by chromatography over silica; elution with $CHCl_3$–MeOH (2:1) gave the *alcohol* (**14g**) (0.48 g, 78%), m.p. 165—170 °C (from ethyl acetate); $\lambda_{max.}$(EtOH) 265 nm (log ε, 4.20); $\nu_{max.}$(Nujol), 3 000—3 400, 1 640, and 1 560 cm^{-1}; δ($CDCl_3$) 8.11 (1 H, d, *J* 7 Hz, 6-H), 7.60—7.20 (5 H, m, ArH), 6.62 (1 H, s, 3-H), 6.40 (1 H, d, *J* Hz, 5-H), 5.75 [1 H, s, C*H*(OH)] and 3.45 (3 H, s, NMe); *m/z* 215 ($M^{+\bullet}$, 100), 170 (23), 110 (22), and 77 (22).

(b) *With DMF: 2-formyl-1-methyl-4-pyridone* (**14n**). Dimethylformamide (1 ml, 12.6 mmol) was syringed rapidly into a stirred solution of 2-lithio-1-methyl-4-pyridone [from 1-methyl-4-pyridone (0.46 g, 4.2 mmol) in THF (200 ml)], prepared in the usual manner, at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and then at 0 °C for 12 h over which time the colour of the solution gradually turned yellow. Hydrochloric acid (2M; 2 ml) was added and the mixture evaporated to leave a dark brown gum. This was purified by passage through a short column of silica gel in $CHCl_3$–MeOH (2 : 1) to give the *aldehyde* (**13n**), in the form of a hemiacetal (**14o**) (0.5 g, 70%) as a colourless foam. After partitioning the foam between 5% aqueous $NaHCO_3$ (10 ml), continuous extraction into chloroform over a period of 24 h and evaporation of the solvent under reduced pressure gave 2-formyl-1-methyl-4-pyridone (**14n**) (0.45 g, 70%) as a colourless crystalline solid; δ($CDCl_3$) 9.55 (1 H, s, CHO), 7.55 (1 H, d, *J* 8 Hz, 6-H), 6.65 (1 H, d, *J* 4 Hz, 3-H), 6.20 (1 H, dd, *J* 8, 4 Hz, 5-H), and 3.7 (3 H, s, NMe); $\nu_{max.}$(Nujol) 1 642 and 1 531 cm^{-1}; *m/z* 137 ($M^{+\bullet}$, 79), 108 (100), 80 (33), and 53 (52). The aldehyde (**13h**) dissolved in methanol (10 ml) was refluxed for 1 h; evaporation of the solvent under reduced pressure gave the *hemiacetal* (**14o**) in quantitative yield, δ(CD_3OD) 7.3 (1 H, d, *J* 8 Hz, 6-H), 6.25 (1 H, d, *J* 4 Hz, 3-H), 5.90 (1 H, d, *J* 8 Hz, 4 Hz, 5-H), 5.10 [1 H, s, *CH*(OH)(OMe)], 3.40 (3 H, s, NMe), and 2.90 (3 H, s, OMe); $\nu_{max.}$(Nujol) 3 084, 1 642, and 1 531 cm^{-1}.

(c) *With alkyl halides: 1,2-dimethyl-4-pyridone* (**14c**) *and 2-ethyl-1-methyl-4-pyridone* (**14d**). After reaction as in (a) above but with iodomethane, evaporation of the solvent and excess of iodomethane under reduced pressure gave a crude, pale-yellow gum. Water (15 ml) was added and the crude product was obtained by continuous extraction into chloroform over a period of 8 h. Purification by chromatography over silica gel eluting with $CHCl_3$–MeOH (2:1) first gave 2-ethyl-1-methyl-4-pyridone (**14d**) (6%) as a brown gum; $\lambda_{max.}$(EtOH) 263 nm; $\nu_{max.}$(Nujol) 1 630 and 1 540 cm^{-1}; δ($CDCl_3$) 7.25 (1 H, d, *J* 8 Hz, 6-H), 6.30 (2 H, d + s, *J* 8 Hz, 3-H, 5-H), 3.62 (3 H, s, NMe), 2.20 (2 H, q, *J* 6.5 Hz, CH_2Me), and 1.10 (3 H, t, *J* 6.5 Hz, CH_2*Me*); *m/z* 137 ($M^{+\bullet}$, 37), 123 (100), 108 (21), 94 (84), and 82 (6); followed closely by 1,2-dimethyl-4-pyridone (**14c**) (43%) as a pale yellow crystalline solid; $\lambda_{max.}$(EtOH) 262 nm (log ε 4.29); $\lambda_{max.}$(EtOH + HCl) 242 nm (log ε 4.02); $\nu_{max.}$(Nujol) 1 635 and 1 535 cm^{-1}; δ($CDCl_3$) 7.27 (1 H, d, *J* 8 Hz, 6-H), 6.26 (1 H, d, *J* 8 Hz, 5-H), 6.26 (1 H, s, 3-H), 3.63 (3 H, s, NMe), and 2.23 (3 H, s, C-Me); *m/z* 123 (M^+, 100), 94 (80), 82 (9.5), and 42 (16).

2-Benzyl-1-methyl-4-pyridone (**14e**) *and 1-methyl-2-(1,2-diphenylethyl)-4-pyridone* (**14f**). After reaction as in (a) above but with benzyl bromide (0.6 g), evaporation of the solvent under reduced pressure gave a crude, pale-yellow gum. Excess of benzyl bromide was removed by washing the gum with diethyl ether (3 × 10 ml) and the residue purified by chromatography over silica, eluting with $CHCl_3$–MeOH (2:1) to give 2-(1,2-diphenylethyl)-1-methyl-4-pyridone (**14f**) (62%) as a white solid; $\nu_{max.}$(Nujol) 1 630 and 1 560 cm^{-1}; $\lambda_{max.}$(EtOH) 264 nm (log ε 4.23); δ($CDCl_3$) 7.22 (7 H, m, 6-H, 6 × ArH), 7.0 (4 H, m, ArH), 6.84 (1 H, s, 3-H), 6.25 (1 H, d, *J* 8 Hz, 5-H), 4.08 (1 H, apparent t, *J* 6 Hz, C*H*Ph), 3.32 (3 H, s, NMe), 3.32 (1 H, dd, *J* 12, 6 Hz,

CH_2Ph), and 3.10 (1 H, dd, *J* 12, 6 Hz, CH_2Ph); *m/z* 289 ($M^{+\bullet}$, 61), 198 (100), 170 (23), and 91 (61).

The second fraction collected contained 2-benzyl-1-methyl-4-pyridone (**14e**) (15%) as a pale yellow gum; $\lambda_{max.}$ 265 nm (log ε 4.22); $\nu_{max.}$(Nujol) 1 640 and 1 550 cm^{-1}; δ($CDCl_3$) 7.5—7.18 (6 H, m, 6-H, 5 × ArH), 6.37 (2 H, d + s, *J* 6 Hz, 5-H, 3-H), 3.91 (2 H, s, CH_2Ph), and 3.46 (3 H, s, NMe); *m/z* 199 ($M^{+\bullet}$, 63), 170 (29), 94 (100), and 91 (31).

(d) *With a ketone:* 2-*hydroxydiphenylmethyl*-1-*methyl*-4-*pyridone* (**14h**). After reaction as in (a) above but with benzophenone (0.6 g) and addition of water (2 ml), evaporation of the solvents under reduced pressure gave a crude, pale-yellow gum. Chromatography of this over silica gel eluting with $CHCl_3$–MeOH (9:1) gave the crystalline *alcohol* (**14h**) (76%); $\lambda_{max.}$(EtOH) 267 nm (log ε 4.25); $\nu_{max.}$(Nujol) 3 495, 3 361, 1 632, and 1 538 cm^{-1}; δ[$(CD_3)_2SO$] 7.6 (1 H, d, *J* d, 8 Hz, 6-H), 7.3 (10 H, m, ArH), 6.0 (1 H, dd, *J* 8, 4 Hz, 5-H), 5.4 (1 H, d, *J* 4 Hz, 3-H), and 2.1 (3 H, s, NMe); *m/z* 291 ($M^{+\bullet}$, 71), 274 (20), 258 (10), 214 (78), 198 (37), 182 (51), 136 (73), 105 (74), 94 (38), 84 (78), 77 (79), and 51 (100).

(e) *With a lactone:* 2-(2-*hydroxymethylbenzoyl*)-1-*methyl*-4-*pyridone* (**14j**). After reaction as in (a) above but with phthalide (0.43 g), evaporation of the solvent under reduced pressure gave a crude, dark-brown foam. Chromatography of this over silica gel eluting with $CHCl_3$–MeOH (2:1) gave (**14j**) (34%) as a mixture of keto alcohol and cyclic hemiacetal in a 1:2 ratio, $\lambda_{max.}$(EtOH) 267 nm (log ε 4.25); keto alcohol form δ($CDCl_3$) 7.60—7.00 (5 H, m, 6-H, ArH), 6.60 (1 H, s, 3-H), 6.30 (1 H, d, *J* 6 Hz, 5-H), 4.66 (2 H, s, CH_2O), and 3.68 (3 H, s, NMe); cyclic hemiacetal form δ($CDCl_3$) 7.60—7.60 (5 H, m, 6-H, ArH), 6.22 (1 H, s, 3-H), 6.22 (1 H, d, 5-H), 5.21 (1 H, d, *J* 12 Hz, CH_2O), 4.95 (1 H, d, *J* 12 Hz, CH_2O), and 3.72 (3 H, s, NMe); *m/z* 243 ($M^{+\bullet}$, 23), 226 (13), 212 (25), 198 (21), 184 (18), 135 (35), 105 (100), and 77 (91).

The keto alcohol–cyclic hemiacetal mixture (**14j**) was converted into a single compound, the cyclic ketal (**14ab**), for full characterisation.

The (1:2) keto alcohol–cyclic hemiacetal mixture (**14j**) (30 mg, 0.12 mmol) was treated with a catalytic amount of toluene-*p*-sulphonic acid in dry methanol (5 ml) with a few drops of 2,2-dimethoxypropane at reflux for 4 h. After evaporation of the solvents under reduced pressure, the residue was taken up in chloroform (10 ml) and treated with 5% aqueous potassium carbonate (5 ml). It gave, after separation and removal of the solvent under reduced pressure, the cyclic ketal (**14ab**) as a pale-yellow gum (30 mg, 95%); $\lambda_{max.}$(EtOH) 269 mm (log ε, 4.21); $\nu_{max.}$(Nujol) 1 640s cm^{-1}; δ($CDCl_3$) 7.6—7.0 (5 H, m, 6-H, 4 × ArH), 6.27 (1 H, d, *J* 8 Hz, 5-H), 6.23 (1 H, s, 3-H), 5.04 and 5.24 (2 H, 2 × d, *J* 12 Hz, ArCH_2), 3.88 (3 H, s, NMe), and 3.06 (3 H, s, OMe); *m/z* 257 ($M^{+\bullet}$, 19), 149 (80), 134 (33), 105 (100), 84 (94), 77 (50), and 49 (92) (Found: M^+, 257.1058. $C_{15}H_{15}NO_3$ requires 257.1052).

(f) *With an anhydride:* 2-(2-*carboxybenzoyl*)-1-*methyl*-4-*pyridone* (**14k**). After reaction as in (a) above but with phthalic anhydride (0.52 g) and addition of 2M HCl solution, evaporation of the solvents under reduced pressure gave a crude pale-yellow gum. Chromatography of this over silica gel eluting with $CHCl_3$–MeOH, 2:1, gave the *keto acid* (**14k**) (68%) as a white solid, (m.p. 185—188 °C from EtOAc/light petroleum (b.p. 60—80 °C) $\lambda_{max.}$(EtOH) 224, 284sh, and 315sh nm (log ε 4.18, 3.64, and 3.11); $\nu_{max.}$(Nujol) 3 600—2 300, 1 695, 1 678, 1 635, and 1 540 cm^{-1}; δ(CD_3OD) 8.75 (1 H, d, *J* 6 Hz, ArH), 8.21 (1 H, d, *J* 7 Hz, 6-H), 8.00—7.80 (3 H, m, ArH), 7.31 (1 H, d, *J* 7 Hz, 5-H), 6.85 (1 H, s, 3-H), and 4.44 (3 H, s, NMe); *m/z* 257 ($M^{+\bullet}$, 100), 212 (48), 184 (57), 149 (79), and 108 (55).

(g) *With acid chlorides.* The acid chloride (1.5 equiv.) was syringed into a stirred solution of 2-lithio-1-methyl-4-pyridone at −78 °C. The reaction mixture was stirred for 3 h at −78 °C and for 2 days at 0 °C for 2 days after which it was evaporated under reduced pressure to leave a gum. This was dissolved in water and the solution made slightly basic by the addition of sodium hydrogen carbonate. The aqueous layer was extracted with chloroform and the extract dried (Na_2SO_4) and evaporated under reduced pressure to give a crude, brown gum.

2-*Benzoyl*-1-*methyl*-4-*pyridone* (**14i**). After reaction as in (g) above, chromatography of the crude material over silica gel eluting with $CHCl_3$–MeOH (2:1) gave (**14i**) (48%), as a pale yellow solid; $\lambda_{max.}$(EtOH) 260 and 238sh nm (log ε 4.32 and 4.15); $\nu_{max.}$(Nujol) 1 660, 1 620, and 1 550 cm^{-1}; δ($CDCl_3$) 7.95 (2 H, d, *J* 7 Hz, *o*-ArH), 7.70 (1 H, t, *J* 7 Hz, ArH), 7.54 (2 H, t, *J* 7 Hz, ArH), 7.41 (1 H, d, *J* 6 Hz, 6-H), 6.50 (2 H, d + s, *J* 6 Hz, 5-H, and 3-H), and 3.59 (3 H, s, NMe); *m/z* 213 ($M^{+\bullet}$, 54), 212 (64), 184 (93), 105 (100), and 77 (85).

2-(4-*Methoxycarbonyl*-3-*pyridylcarbonyl*)-1-*methyl*-4-*pyridone* (**14l**). After reaction as in (g) above, chromatography of the crude material over silica gel eluting with $CHCl_3$–MeOH (2:1) gave the pure *keto ester* (**14l**) (44%) as a pale yellow gum; $\lambda_{max.}$(EtOH) 315sh, 265, and 232 nm (log ε 3.55, 3.97, and 4.19); $\nu_{max.}$(liquid film) 1 730, 1 695, 1 635, and 1 575 cm^{-1}; δ($CDCl_3$) 8.97 (1 H, d, *J* 5 Hz, 6′-H), 8.88 (1 H, s, 1′-H), 7.87 (1 H, d, *J* 5 Hz, 5′-H), 7.49 (1 H, d, *J* 7 Hz, 6-H), 6.45 (1 H, d, *J* 7 Hz, 5-H), 6.18 (1 H, s, 3-H), 4.00 (3 H, s, OMe), and 3.85 (3 H, s, NMe); *m/z* 272 ($M^{+\bullet}$, 39), 242 (42), 213 (35), 185 (40), 64 (100), 136 (17), 108 (50), and 78 (42).

2-(2-*Methoxycarbonyl*-3-*pyridylcarbonyl*)-1-*methyl*-4-*pyridone* (**14m**). Following the same work-up procedure as above gave the pure *keto ester* (**14m**) (40%) as a pale yellow gum; $\lambda_{max.}$(EtOH) 315, 264, and 220sh nm, (log ε 3.51, 3.97, and 4.15); $\lambda_{max.}$(EtOH + HCl) 315sh and 255sh nm (log ε 3.33, and 3.93); $\nu_{max.}$(liq. film) 1 720, 1 650, 1 635, and 1 570 cm^{-1}; δ($CDCl_3$) 8.92 (1 H, d, *J* 5 Hz, 6′-H), 8.00 (1 H, d, *J* 6 Hz, 4′-H), 7.71 (1 H, t, *J* 5 Hz, 5′-H), 7.45 (1 H, d, *J* 7 Hz, 6-H), 6.40 (1 H, d, *J* 7 Hz, 5-H), 6.12 (1 H, s, 3-H), 4.00 (3 H, s, OMe), and 3.88 (3 H, s, NMe); *m/z* 272 ($M^{+\bullet}$, 35), 242 (15), 213 (58), 185 (100), 164 (15), 136 (37), 108 (46), and 78 (60).

1-*Phenoxycarbonyl*-4-*pyridone* (**14p**). Oil-free sodium hydride (0.31 g, 13.0 mmol) was added at once to a stirred solution of 4-pyridone (0.95 g, 10 mmol) in dry t-butyl alcohol (4 ml) which was then heated to 50 °C, while phenyl chloroformate (1.65 g, 13.0 mmol) was added dropwise. The heating bath was then removed and the reaction mixture stirred at room temperature for 3 h. After dilution with water (10 ml) the pH of the solution was immediately adjusted to 6.9 with a few drops of 2% HCl. The mixture was extracted with chloroform (5 × 20 ml) and the extract dried and evaporated under reduced pressure to give 1-*phenoxycarbonyl*-4-*pyridone* (**14p**) (1.62 g, 75%) as a white crystalline solid, m.p. 70—73 °C; $\lambda_{max.}$(EtOH) 257 nm (log ε 3.80); $\nu_{max.}$(Nujol) 1 770, 1 645, and 1 600 cm^{-1}; δ($CDCl_3$) 8.10 (2 H, d, *J* 8 Hz, 2-H and 6-H), 7.20 (5 H, m, ArH), and 6.25 (2 H, d, *J* 8 Hz, 3-H and 5-H); *m/z* 215 ($M^{+\bullet}$, 9) 214 (63), 171 (5), 170 (39), 169 (24), 143 (3), 142 (28), 141 (52), 115 (6), 94 (22), 77 (100), and 65 (38) (Found: M^+, 215.0578. $C_{12}H_9NO_3$ requires *M*, 215.0582).

1-*Methoxymethyl*-4-*pyridone* (**14g**). Oil-free sodium hydride (0.70 g, 29.2 mmol) was added carefully to a stirred solution of 4-pyridone (2.00 g, 21.1 mmol) in dry DMF (20 ml), which was then heated to 50 °C on a water-bath. The mixture was cooled to room temperature and chloromethyl methyl ether (5 ml, 63.3 mmol) was added dropwise with stirring over 10 min. After 6 h the mixture was diluted with water (20 ml) and evaporated under reduced pressure. The crude product was extracted continuously into chloroform over a period of 36 h and the extract then evaporated under reduced pressure to give a pale yellow oil. Distillation of this under reduced pressure gave 1-*methoxymethyl*-4-*pyridone* (**14q**) (2.70 g, 92%) as a colourless oil, b.p. 180 °C at 0.3 mm Hg; $\lambda_{max.}$(EtOH) 263 nm (log ε 4.28);

$\nu_{max.}$(Nujol) 1 640 and 1 550 cm^{-1}; δ($CDCl_3$) 7.50 (2 H, d, *J* 8 Hz, 2-H, 6-H), 6.35 (2 H, d, *J* 8 Hz, 3-H, 5-H), 5.05 (2 H, s, NCH_2O), and 3.31 (3 H, s, OMe); *m/z* 139 ($M^{+\bullet}$, 33), 108 (31), 82 (10), and 45 (100) (Found: M^+, 139.0632. $C_7H_9NO_2$ requires *M*, 139.0633).

1-*Benzyloxymethyl*-4-*pyridone* (**14r**). Oil-free sodium hydride (0.76 g, 25.4 mmol) was added at once to a stirred solution of 4-pyridone (1.86 g, 19.6 mmol) in dry DMF (10 ml), which was then heated to 50 °C on a water-bath. Benzyl chloromethyl ether (3.0 g, 21.5 mmol) was added dropwise with stirring over 10 min after which the heating bath was removed and the reaction mixture stirred at room temperature. After 6 h the mixture was diluted with water (20 ml) and the pH of the resulting solution immediately adjusted to 6.9 with a few drops of 2% HCl. The mixture was repeatedly extracted with chloroform (5 × 20 ml) and the extract dried and evaporated under reduced pressure to give a crude, pale-yellow oil. Distillation of this under reduced pressure gave pure 1-*benzyloxymethyl*-4-*pyridone* (**14r**) (3.73 g, 89%), as a colourless, crystalline solid, b.p. 230—240 °C, 0.1 mmHg, m.p. 93—95 °C; $\lambda_{max.}$(EtOH) 261 nm (log ε 4.30); $\nu_{max.}$(Nujol) 1 640 and 1 570 cm^{-1}; δ($CDCl_3$) 7.41 (2 H, d, *J* 8 Hz, 2-H and 6-H), 7.40—7.24 (5 H, m, ArH), 6.32 (2 H, d, *J* 8 Hz, 3-H and 5-H), 5.06 (2 H, s, NCH_2O), and 4.46 (2 H, s, OCH_2Ph); *m/z* 215 ($M^{+\bullet}$, 17), 185 (9), and 91 (100) (Found C, 72.3; H, 5.85; N, 6.3%. $C_{13}H_{13}NO_2$ requires C, 72.6; H, 6.0; N, 6.5%).

1-(2-*Trimethylsilylethoxymethyl*)-4-*pyridone* (**14s**). Oil-free sodium hydride (0.40 g, 17.5 mmol) was added at once to a stirred solution of 4-pyridone (1.23 g, 12.9 mmol) in dry DMF (8 ml). The mixture was then heated to 50 °C while 2-trimethylsilylethoxymethyl chloride (2.52 ml, 14.2 mmol) was added dropwise: the mixture was subsequently allowed to return to room temperature. After 5 h it was diluted with water (20 ml) and the pH of the resulting solution was immediately adjusted to 6.9 with a few drops of 2% HCl. The mixture was repeatedly extracted with chloroform (5 × 20 ml) and the extract dried and evaporated under reduced pressure to give a yellow, semicrystalline oil. Distillation of this under reduced pressure gave pure 4-*pyridone* (**14s**) as a colourless, crystalline solid (2.7 g, 93%), b.p. 185—190 °C at 0.1 mmHg, m.p. 72—75 °C; $\lambda_{max.}$(EtOH) 264 nm (log ε 4.31); $\nu_{max.}$(Nujol) 1 630 and 1 570 cm^{-1}; δ($CDCl_3$) 7.43 (2 H, d, *J* 8 Hz, 2-H and 6-H), 6.37 (2 H, d, *J* 8 Hz, 3-H and 5-H), 5.04 (2 H, s, NCH_2O), 3.51 (2 H, t, *J* 5 Hz, OCH_2CH_2), 0.90 (2 H, t, *J* 5 Hz, $SiCH_2$), and 0.00 (9 H, s, $SiMe_3$); *m/z* 225 ($M^{+\bullet}$, 12), 182 (2), 152 (22), 108 (40), and 73 (100) (Found C, 58.7; H, 8.7; N, 6.1 $C_{11}H_{19}NO_2Si$ requires C, 58.7; H, 8.4; N, 6.2%).

Attempted N-*Phenylsulphonylation of* 4-*Pyridone: Formation of* 1-(4-*Pyridyl*)-4-*pyridone*.—Oil-free sodium hydride (0.30 g, 13.7 mmol) was added to a stirred solution of 4-pyridone (0.92 g, 9.7 mmol) in dry t-butyl alcohol (10 ml). The mixture was heated to 50 °C on a water-bath when benzenesulphonyl chloride (1.60 ml, 12.6 mmol) was added dropwise; the mixture was then allowed to return to room temperature. After 2 h it was diluted with water (15 ml) and extracted continuously into chloroform over a period of 24 h. Evaporation of the organic solvent under reduced pressure gave 1-(4-pyridyl)-4-pyridone (0.38 g, 82%) as a white solid, m.p. 169—173 °C (lit.,[29] 177—178 °C), identical spectroscopically with an authentic sample.

2-*Lithio*-1-*methoxymethyl*-4-*pyridone and* 2-*Deuterio*-1-*methoxymethyl*-4-*pyridone* (**14t**).—1-Methoxymethyl-4-pyridone (**12g**) (0.068 g, 0.49 mmol) previously dried and heated *in vacuo* (0.1 mmHg) in a flame-dried 3-necked round-bottom flask (100 ml) was dissolved in dry THF (10 ml) under nitrogen. Butyllithium (1.54M in hexane; 0.35 ml, 0.5 mmol) was rapidly syringed into the magnetically stirred solution at −78 °C causing it immediately to turn yellow. The reaction mixture was stirred at this temperature for 30 min and then slowly allowed to warm to 0 °C when it turned light brown. The solution was then immediately cooled to −78 °C when D_2O was syringed into it causing an immediate decolourisation. The reaction mixture was then allowed to warm slowly to room temperature. The mixture was filtered and evaporated under reduced pressure to give a crude, pale-yellow oil. Purification of this by passage through a short column of silica gel in chloroform–methanol (2:1) gave the pure 2-deuteriopyridone (**14t**) (0.067 g, 98%) as a colourless oil; δ($CDCl_3$) 7.4 (1 H, d, *J* 8 Hz, 6-H), 6.4 (2 H, d + s, *J* 8 Hz, 5-H, 3-H), 5.01 (2 H, s, NCH_2O), and 3.4 (3 H, s, OMe); $\lambda_{max.}$(EtOH) 263 nm (log ε 4.30); $\nu_{max.}$(Nujol) 1 640 and 1 550 cm^{-1}; *m/z* 140 ($M^{+\bullet}$,14), 109 (22), 83 (10), 82 (12), and 45 (100).

1-*Benzyloxymethyl*-2-*lithio*-4-*pyridone*, 1-*Benzyloxymethyl*-2-*deuterio*-4-*pyridone*, *and* 2-*Deuterio*-4-*pyridone* (**14v**); *Typical Procedure for Lithiation of* N-*Masked*-4-*pyridones*.—1-Benzyloxymethyl-4-pyridone (**14r**) (0.28 g, 1.30 mmol), previously melted and dried *in vacuo* (0.1 mmHg) in a flame-dried 3-necked round-bottom flask (100 ml), was dissolved in dry THF (20 ml) under nitrogen. Butyl-lithium (1.65M in hexane; 0.87 ml, 1.30 mmol) was then rapidly syringed into the magnetically stirred solution at −78 °C causing it to turn immediately purple. The reaction mixture was allowed to stir at this temperature for 30 min and then to slowly warm to 0 °C when it turned deep purple. The solution was then immediately cooled to −78 °C and deuterium oxide (1 ml) was syringed into it causing an immediate decolourisation. The reaction mixture was allowed to warm slowly to room temperature when the precipitated salts were filtered off and the filtrate evaporated under reduced pressure to give a pale-yellow gum. This was purified by passage in $CHCl_3$–MeOH (2:1) through a short column of silica gel to give the pure 2-*deuteriated* 4-*pyridone* (**14u**) (0.2 g, 70% recovery) as a colourless oil; δ($CDCl_3$) 7.60—7.00 (6 H, m, 6-H, ArH), 6.44 (2 H, d + s, 3-H and 5-H), 5.11 (2 H, s, NCH_2O), and 4.54 (2 H, s, OCH_2Ph); *m/z* 216 ($M^{+\bullet}$, 7), 186 (4), and 91 (100).

1-Benzyloxymethyl-2-deuterio-4-pyridone (**14u**) (50 mg, 0.23 mmol) was dissolved in 6M HCl (2 ml) and heated on a steam-bath for 3 h. Evaporation of the aqueous acid at 100 °C under reduced pressure gave 2-deuterio-4-pyridone (**14v**) (22 mg, 100%) as a pale yellow gum which slowly crystallised; δ(CD_3OD) 7.90 (1 H, d, *J* 8 Hz, 6-H) and 6.75 (2 H, d + s, *J* 8 Hz, 3-H and 5-H); *m/z* 96 ($M^{+\bullet}$, 67), 82 (17), 80 (16), 69 (19), and 36 (100).

2-*Benzoyl*-1-*methoxymethyl*-4-*pyridone* (**14y**).—Benzoyl chloride (0.1 ml) was syringed into a stirred solution of 2-lithio-1-methoxymethyl-4-pyridone [from 1-methoxymethyl-4-pyridone (0.077 g, 0.55 mmol), in dry THF (10 ml), prepared in the usual manner] at −78 °C over 1 h; a purple colour developed which slowly disappeared when the solution was allowed to warm to room temperature over several hours. Evaporation of the solution under reduced pressure afforded a brown gum which was chromatographed over silica gel, eluting with $CHCl_3$–MeOH (9:1) to give the *ketone* (**14y**) (0.03 g, 22%) as a pale yellow gum; $\lambda_{max.}$(EtOH) 259 and 310sh nm; $\nu_{max.}$(film) 1 672, 1 629, 1 596, and 1 580 cm^{-1}; δ($CDCl_3$) 7.75 (1 H, d, *J* 8 Hz, 6-H), 7.50 (5 H, m, 5 × ArH)), 6.45 (2 H, d + s, *J* 8 Hz, 3-H, 5-H), 5.2 (2 H, s, NCH_2O), and 3.20 (3 H, s, OMe); *m/z* 243 ($M^{+\bullet}$, 11), 212 (6), 198 (11), 183 (9), 170 (4), 155 (6), 105 (27), 77 (30), and 45 (100) (Found: M^+, 243.0888. $C_{14}H_{13}NO_3$ requires *M*, 243.0895).

2-*Formyl*-1-*methoxymethyl*-4-*pyridone* (**14z**).—Dimethylformamide (0.3 ml) was syringed into a stirred solution of 2-lithio-1-methoxymethyl-4-pyridone [from 1-methoxymethyl-

4-pyridone (0.2 g, 1.80 mmol), in dry THF (15 ml), prepared in the usual manner] at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and then left at 0 °C overnight during which time it gradually turned yellow. The mixture was diluted with water (1 ml), filtered, and evaporated under reduced pressure to leave a green gum. Purification of this material over silica gel using $CHCl_3$–MeOH (2:1) gave the *aldehyde* (**14z**) (0.086 g, 34%) as a pale brown gum; $\lambda_{max.}$(EtOH) 266 nm (log ε 4.30); $\nu_{max.}$(film), 1 636 and 1 555 cm^{-1}; δ($CDCl_3$) 9.60 (1 H, s, CHO), 7.40 (1 H, d, *J* 8 Hz, 6-H), 6.75 (1 H, d, *J* 3 Hz, 3-H), 6.35 (1 H, dd, *J* 8, 3 Hz, 5-H), 5.50 (2 H, s, NCH_2O), and 3.30 (3 H, s, OMe); *m/z* 167 ($M^{+\bullet}$, 4), 108 (3), and 45 (100) (Found: M^+, 167.0579. $C_8H_9NO_3$ requires *M*, 167.0582).

2-(4-*Methoxycarbonyl*-3-*pyridylcarbonyl*)-1-*methoxymethyl*-4-*pyridone* (**14aa**).—4-Methoxycarbonyl-2-pyridylcarbonyl-chloride (1.1 g, 5.5 mmol) in dry THF (10 ml) was syringed into a stirred solution of 2-lithio-1-methoxymethyl- 4-pyridone [from 1-methoxymethyl-4-pyridone (0.69 g, 4.96 mmol), in dry THF (20 ml), prepared in the usual manner] at −78 °C, causing it to turn immediately dark brown. The reaction mixture was stirred at −78 °C for 3 h and then left at 0 °C overnight during which time its colour gradually turned orange. The mixture was diluted with water (1 ml) and evaporated under reduced pressure to leave a brown foam. Chromatography of this over silica gel eluting with $CHCl_3$–MeOH (9:1) gave the *keto ester* (**14aa**) (0.30 g, 20%) as a pale yellow gum; $\lambda_{max.}$(EtOH) 264 and 320sh nm; $\nu_{max.}$(film) 1 732, 1 688, 1 629, and 1 584 cm^{-1}; δ($CDCl_3$) 8.85 (1 H, d, *J* 5 Hz, 6′-H), 8.75 (1 H, s, 1′-H), 7.7 (2 H, d + d, *J* 5, 8 Hz, 5′-H, 6-H), 6.35 (1 H, dd, *J* 8, 3 Hz, 5-H), 6.1 (1 H, d, *J* 3 Hz, 3-H), 5.45 (2 H, s, NCH_2O), 3.8 (3 H, s, CO_2Me), and 3.5 (3 H, s, OMe); *m/z* 302 ($M^{+\bullet}$, 4), 270 (7), 257 (4), 243 (12), 229 (5), 213 (7), 199 (2), 164 (7), and 45 (100) (Found: M^+, 302.0900. $C_{15}H_{14}N_2O_5$ requires *M*, 302.0903).

4-*Pyridone*.—(a) *By deprotection of* 1-*methoxymethyl*-4-*pyridone* (**14q**). 1-Methoxymethyl-4-pyridone (**14q**) (100 mg, 0.72 mmol) was dissolved in conc. H_2SO_4 (2 ml) and the solution heated to 100 °C for 30 min. The mixture was cooled to room temperature, poured onto ice, and basified with K_2CO_3. T.l.c. analysis indicated the clean formation of 4-pyridone. The deprotection could also be carried out in conc. HCl at 100 °C for 2 h followed by quenching onto ice and basification with K_2CO_3; t.l.c. again showing a clean formation of 4-pyridone in >90% yield.

(b) *By deprotection of* 1-(2-*trimethylsilylethoxymethyl*)-4-*pyridone* (**14s**). 1-(2-Trimethylsilylethoxymethyl)-4-pyridone (**14s**) (300 mg, 1.33 mmol) dissolved in THF (10 ml) was treated with a few drops of $BF_3{\cdot}OEt_2$ at reflux for 4 h; it was then quenched with water and basified with 2M NaOH (0.5 ml) to give 4-pyridone, homogeneous by t.l.c. analysis, in >90% yield.

1-*Triphenylmethyl*-4-*pyridone* (**14x**).—Oil-free sodium hydride (39 mg, 1.64 mmol) was added at once to a stirred solution of 4-pyridone (104 mg, 1.09 mmol) in dry DMF (5 ml) at room temperature and the mixture was then heated to 50 °C. It was then cooled to room temperature when chlorotriphenylmethane (335 mg, 1.2 mmol) was added portionwise over 5 min. After 5 h at room temperature, the mixture was diluted with water (5 ml) and extracted with chloroform. The dried extracts were evaporated under reduced pressure to give a crude white solid. Recrystallisation of this from EtOAc gave 1-*triphenylmethyl*-4-*pyridone* (**14x**) (300 mg, 81%), m.p. 250—252 °C, as white needles; $\lambda_{max.}$(EtOH) 270 nm (log ε 4.25); $\lambda_{max.}$(Nujol) 1 637 and 1 590 cm^{-1}; δ($CDCl_3$) 7.5—7.0 (17 H, m, ArH, 2-H, 6-H), and 6.1 (2 H, d, *J* 8 Hz, 3-H, 5-H); *m/z* 243 ($M^{+\bullet} - C_5H_4NO$, 100), 228 (54), 215 (43), 202 (23), 165 (99), 139 (22), 115 (35), 95 (84), 78 (51), and 67 (66) (Found: C, 84.15; H, 5.6; N, 3.9%, $C_{24}H_{19}NO{\cdot}0.25H_2O$ requires C, 84.3; H, 5.7; N, 4.1%).

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