Lithiation of 4-Methoxy-2-pyridones. Synthetic Entry to Tenellin and Funiculosin, and Related Natural 3,5-Disubstituted 4-Oxy-2-pyridones

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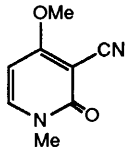
Lithiation of 4-methoxy-2-pyridone with butyllithium at −78 °C occurs at the C-3 position exclusively. Subsequent reactions with MeOD, MeI, CO_2, benzaldehyde or (*E*)-but-2-enal then lead to the corresponding C-3-substituted derivatives. In a one-pot procedure, treatment of 1,2-dihydro-4-methoxy-1-methyl-2-oxopyridine-3-carboxylic acid with ammonia in the presence of a polyphosphate buffer at 80 °C produced natural ricinine in 58% overall yield.

A convenient three-step synthesis of 5-aryl- and 5-alkyl-substituted 4-methoxy-2-pyridones is described. Lithiation of these substrates, followed by reaction with electrophiles, provided a convenient route to 3,5-disubstituted 4-oxy-2-pyridones, and a synthetic entry to natural products, *e.g.* tenellin and funiculosin, containing this structural feature.

4-Oxy-2-pyridones occur widely in Nature, and vary in structural complexity from the simple ricinine **1**[1] to the more elaborate elfamycins, *e.g.* aurodox **2** (also known as goldinomycin and antibiotic X5108) produced by *Streptomyces*.[2] Other, more substituted members include tenellin **3a**, bassianin **3b**[3] and illicicolin **4**,[4] together with the unusual metabolite funiculosin **5**[5] isolated from *Penicillium funiculosum*. In connection with a projected total synthesis of funiculosin **5**[6] we required a procedure for the direct substitution at C-3 in a 5-substituted 4-methoxy-2-pyridone. The metallation of precursor molecules such as compound **7**, followed by reaction with an appropriate electrophile appeared an attractive strategy. This was made the more so in view of our earlier successes with related substitution reactions with β-methoxyacrylate and tetronic acid derivatives leading, for example, to total syntheses of aspertetronin and gregatin natural products.[7] In this paper we describe a synthetic route to 5-aryl- and 5-alkyl-substituted 4-methoxy-2-pyridones, and the further substitution of these



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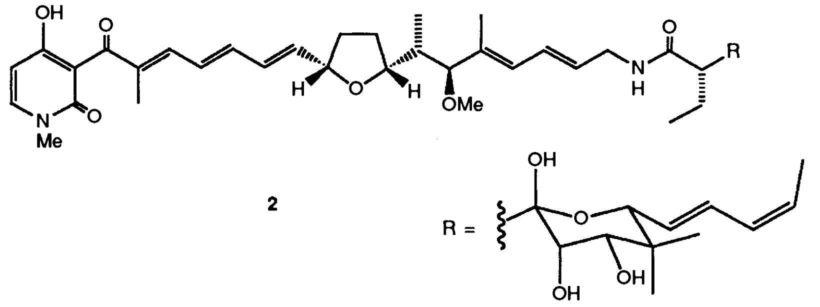

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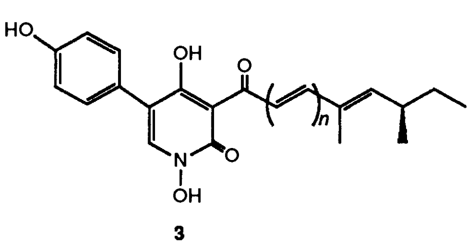
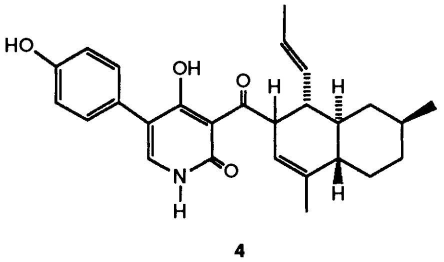


3
a; *n* = 1
b; *n* = 2



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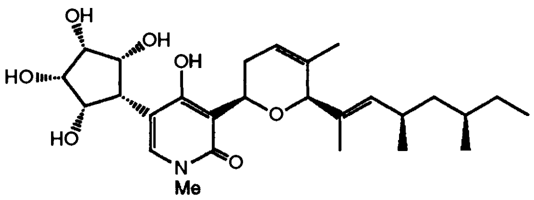
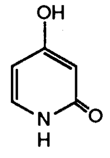


5

molecules following lithiation in the presence of butyllithium and reaction with electrophiles.[8]

We began our investigations by first studying the specificity of lithiation of 4-methoxy-1-methyl-2-pyridone **7** which was easily prepared by methylation of commercial 3-deazauracil **6**. Treatment of a solution of compound **7** in tetrahydrofuran (THF) with butyllithium at −80 °C, followed by quenching with MeOD and work-up, produced exclusively the C-3-deuteriated derivative **9** in almost quantitative yield. In a similar manner when the aryllithium species **8** was quenched with methyl iodide or carbon dioxide, good yields of the corresponding C-3 methyl- and carboxy-substituted derivatives, **10** and **11** respectively, were obtained. We were gratified to find no evidence for the co-formation of products, *e.g.* **12**, resulting from simultaneous lithiation at the *N*-methyl group in the substrate in any of these reactions.[9]



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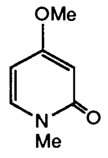

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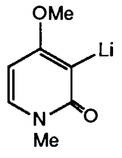

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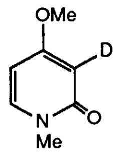

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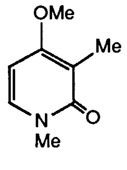

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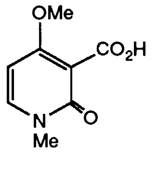

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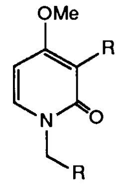
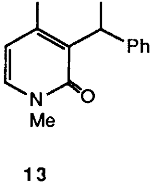


12

When a solution of the vinyllithium **8** was quenched with either benzaldehyde or (*E*)-but-2-enal, satisfactory yields of the secondary alcohol products, **13** and **14** respectively, were produced. Furthermore, when the alcohols **13** and **14** were treated with manganese dioxide, they underwent smooth oxidation to the corresponding 3-acyl derivatives, **15a** and **15b** respectively, in good yields. The direct acylation of compound **8** to ketones **15a**/**15b** by using esters or acid chlorides was not achieved. Finally, when the 3-carboxy derivative **11** was treated with ammonia gas in the presence of ethyl polyphosphate at 80 °C, it underwent conversion into ricinine **1** in a one-pot reaction and in 56% overall yield. We believe that this synthesis of ricinine **1** from compound **6** *via* the organo-lithium **8** must be the shortest route to this historically important natural product reported so far.[10]



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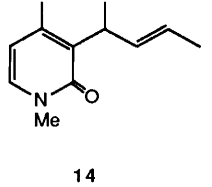

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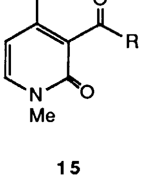
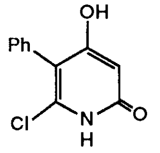


15
a; R = Ph
b; R = CH=CHMe

To investigate further the lithiation of 4-oxy-2-pyridones, and particularly those 2-pyridones more related to funiculosin **5** and tenellin **3a**, we required a synthesis of both 5-alkyl- and 5-aryl-substituted 4-oxy-2-pyridones. To achieve this, we modified and extended some literature work reported by Elvidge *et al.*[11] Thus, condensation between phenylacetonitrile and malonyl dichloride first produced the known 6-chloropyridone **16**, which on methylation with dimethyl sulfate in the presence of aq. sodium hydroxide next led to the *N*-methyl derivative **17**. Further treatment of compound **17** with diazomethane then gave the 4-methoxy derivative **18a** together with a small amount of the enol ether tautomer **19**. The enol ether tautomers **18a** and **19**, and related tautomers (see below), were distinguished on the basis of their UV, IR and ^1H NMR data, and comparison of these data with those reported for isomeric pyridones described in the literature.[12] In an alternative route the pyridone **16** could be converted directly to the dimethyl derivative **18a** by using excess of diazomethane. The 6-chloro residue was smoothly removed from compound **18a** leading to compound **18b** following treatment of a hot solution of the substrate **18a** in benzene with tributyltin hydride in the presence of azoisobutyronitrile (AIBN).



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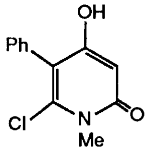
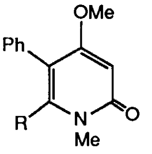
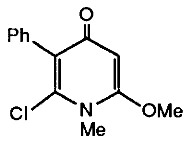


17



18
a; R = Cl
b; R = H



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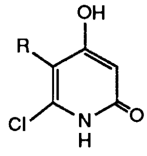
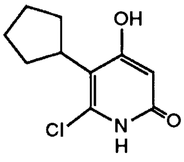


20
a; R = C_6H_4OMe-*p*
b; R = Me



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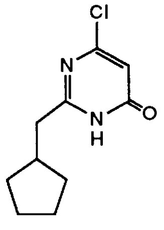
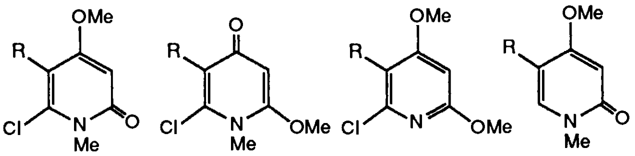


22

In a similar manner the 5-(4-methoxyphenyl) **20a**, 5-methyl **20b**, and 5-cyclopentyl **21** derivatives, corresponding to the phenyl compound **16**, were produced from condensation reactions between malonyl dichloride and 4-methoxyphenylacetonitrile, propiononitrile, and cyclopentylacetonitrile respectively. Interestingly, in the latter case we also isolated the pyrimidone **22** as a by-product (~10%); the formation of pyrimidones in these reactions is known, and the mechanism of their formation has been discussed in detail by several authors.[11,13]

Methylation of compound **20a** by using an excess of diazomethane led to a mixture of the required 4-methoxy-N-methylpyridone **23a** and the isomers **24a** and **25a**, which could be separated by chromatography. Dechlorination of compound **23a** with tributyltin hydride–AIBN then produced compound **26a**. Similarly, the 5-methyl derivative **20b** was converted into the 1,4,5-trimethylpyridone **26b** by using an identical sequence of reactions.

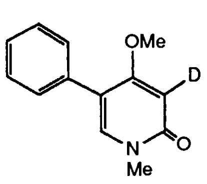
Deprotonation of compound **18b** in the presence of butyllithium at −78 °C, like that of the unsubstituted 4-methoxy-2-pyridone **7**, occurred exclusively at C-3 leading to the corre-



23 **24** **25** **26**

a; R = C_6H_4OMe-*p*
b; R = Me

sponding vinyllithium species which could be deuteriated with MeOD, thereby producing the C-3-deuteriated pyridone **27** in 75% yield. Interestingly, by using an excess of butyllithium the 4-methoxyphenyl derivative **26a** produced both 3-deuterio compounds **28a** and **28b** following treatment of the intermediate vinyllithium species with MeOD. Lithiation of substrate **26b**, followed by quenching with MeOD, produced only the 3-deuterium derivative **29** uncontaminated by products resulting from competitive lithiation at any other sites in the starting material.



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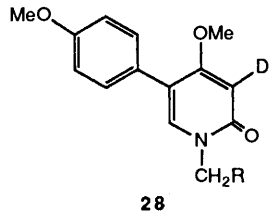
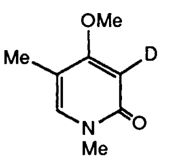


28
a; R = H
b; R = D



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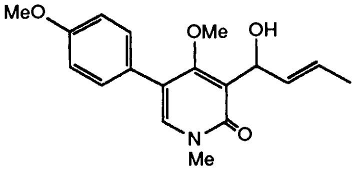

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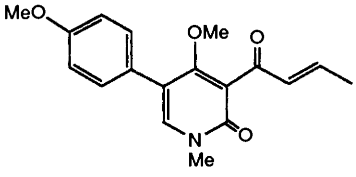

31

As a corollary, we also treated the vinyllithium species derived from the 5-(4-methoxyphenyl)pyridone **26a** with (*E*)-but-2-enal which led to the secondary alcohol **30** as a pale yellow oil. Oxidation of compound **30** using manganese dioxide then produced the corresponding butenone **31** in 83% yield. Studies are now in progress to extend this methodology for the preparation of C-3, C-5-disubstituted 4-methoxy-2-pyridones *via* 3-lithium intermediates, in a synthesis of funiculosin **5** and related naturally occurring 4-oxy-2-pyridones.

Experimental

For general details see ref. 6.

4-Methoxy-1-methyl-2(1H)-pyridone **7**.—A vigorously stirred mixture of deazauracil **6** (2.2 g), 40% aq. sodium hydroxide (40 cm^3), dimethyl sulfate (7.6 cm^3), triethylbenzylammonium bromide (0.65 g) and benzene (60 cm^3) was heated at 70 °C for 4 d, and was then cooled to room temperature. The two layers were separated, and the aq. layer was then extracted continuously with methylene dichloride for 2 d. The combined organic layers were washed with brine and evaporated to dryness to leave the pyridone **7** (1.4 g, 50%) as a solid, which was recrystallised from toluene, m.p. 107–108 °C (lit.,[12b] 113–114 °C); λ_{max}(EtOH)/nm 284 (4020), 225sh (3700) and 210 (33 100); ν_{max}(Nujol)/cm^{-1} 1660, 1590, 1350 and 1230; δ_H 7.26 (d, *J* 8, C*H*=CH), 5.95 (=CH), 5.85 (d, *J* 8, CH=C*H*), 3.82 (OMe) and 3.52 (NMe) (Found: C, 60.2; H, 6.7; N, 10.3%; M^+, 139.0633. Calc. for $C_7H_9NO_2$: C, 60.4; H, 6.5; N, 10.1%; M, 139.0633).

Metallation of 4-Methoxy-1-methyl-2(1H)-pyridone **7**.—*General procedure*. A solution of 4-methoxy-1-methyl-2(1*H*)-pyridone (1 mol equiv.) in dry THF (2 cm^3/mmol) was added dropwise to a solution of butyllithium (1.6 mol equiv.; 1.4–1.6 mol dm^{-3} solution in hexane) in dry THF (3 cm^3/mmol) maintained at −78 °C under nitrogen. After 30 min had been allowed for metallation to occur, the pale yellow-coloured solution of the corresponding vinyl lithium species was then used as required.

3-Deuterio-4-methoxy-1-methyl-2(1H)-pyridone **9**.—The vinyllithium species **8** was prepared from 4-methoxy-1-methyl-2(1*H*)-pyridone (0.1 g) according to the general procedure. After 15 min monodeuteriomethanol (0.5 cm^3) was added and the mixture was then left to warm to 23 °C during 30 min. The mixture was then poured into pH 7 phosphate buffer (3 cm^3), and was then extracted with methylene dichloride (3 × 3 cm^3). The combined extracts were washed with brine, dried, and the solvent was then evaporated off to give the *deuteriopyridone* **9** (0.07 g, 70%) as a solid, δ_H 7.17 (d, *J* 8, C*H*=CH), 5.93 (d, *J* 8, CH=C*H*), 3.78 (OMe) and 3.48 (NMe) (Found: M^+, 140.0697. $C_7H_8DNO_2$ requires M, 140.0696).

4-Methoxy-1,3-dimethyl-2(1H)-pyridone **10**.—Methyl iodide (0.04 cm^3) was added to a solution of the vinyllithium species prepared from 4-methoxy-1-methyl-2(1*H*)-pyridone (0.1 g). After 2 h, the reaction mixture was allowed to warm to 23 °C during 2 h and was then poured into water. The solution was extracted with methylene dichloride (3 × 3 cm^3), and the combined extracts were then washed with brine and dried. The solvent was evaporated off, and the residue was then purified by flash column chromatography on silica, with chloroform–methanol (49:1) as eluent, to give the *dimethylpyridone* **10** (26 mg, 24%) as an oil, ν_{max}(film)/cm^{-1} 1645 and 1590; δ_H 7.34 (d, *J* 8, C*H*=CH), 6.16 (d, *J* 8, CH=C*H*), 3.88 (OMe), 3.56 (NMe) and 2.03 (Me) (Found: M^+, 153.0779. $C_8H_{11}NO_2$ requires M, 153.0790).

1,2-Dihydro-4-methoxy-1-methyl-2-oxopyridine-3-carboxylic Acid **11**.—Carbon dioxide was passed into a solution of the vinyllithium species prepared from 4-methoxy-1-methyl-2(1*H*)-pyridone (0.1 g). After 15 min, the reaction mixture was warmed to 23 °C, then poured into water (5 cm^3) and the aq. solution was washed with methylene dichloride (2 × 10 cm^3). The aq. layer was next acidified with 2 mol dm^{-3} hydrochloric acid, then saturated with sodium chloride and exhaustively extracted with methylene dichloride (8 × 10 cm^3). The combined extracts were washed with brine, then dried and evaporated to leave a solid, which was recrystallised from methanol to give the *title acid* (0.08 g, 80%) as needles, m.p. 214–216 °C; ν_{max}(Nujol)/cm^{-1} 3450, 1725 and 1480; δ_H([$^2H_4$]MeOH) 7.95 (d, *J* 8, C*H*=CH), 6.56 (d, *J* 8, CH=C*H*), 4.09 (OMe) and 3.68 (NMe) (Found: C, 51.9; H, 5.0; N, 7.5. $C_8H_9NO_4$ requires C, 52.5; H, 4.95; N, 7.65%).

3-(α-Hydroxybenzyl)-4-methoxy-1-methyl-2(1H)-pyridone **13**.—Benzaldehyde (0.2 cm^3) was added to a solution of the vinyllithium species prepared from 4-methoxy-1-methyl-2(1*H*)-pyridone (0.1 g). After 30 min, the reaction mixture was warmed up to 23 °C and was then poured into water (3 cm^3) and extracted with methylene dichloride (3 × 3 cm^3). The combined extracts were washed with brine, and then dried. The solvent was evaporated off to leave a yellow oil, which was purified by flash column chromatography on silica with chloroform–methanol (49:1) as eluent to give the *title alcohol* (0.08 g, 70%) as a solid, that was recrystallised from toluene–hexane as crystals, m.p. 127–128 °C; ν_{max}(Nujol)/cm^{-1} 3300, 1640, 1570 and 1260; δ_H 7.65–7.24 (m, 5 × ArH and OH), 6.59 (d, *J* 9, C*H*=CH), 6.16 (d, *J* 7, C*H*OH), 6.06 (d, *J* 9, CH=C*H*), 3.99 (OMe) and 3.48 (NMe) (Found: M$^+$, 254.1064; $C_{14}H_{15}NO_3$ requires *M*, 245.1052).

3-Benzoyl-4-methoxy-1-methyl-2(1H)*-pyridone* **15a**.—A solution of the alcohol **13** (88 mg) in methylenedichloride (2 cm^3) was stirred with manganese dioxide (0.8 g) for 18 h and was then filtered. The filtrate was evaporated to dryness to leave the *ketone* **15a** (78 mg, 99%) as an oil, ν_{max}(film)/cm^{-1} 1660, 1600 and 1360; δ_H 8.04–7.90 (m, 2 × ArH), 7.64–7.34 (m, 3 × ArH and C*H*=CH), 6.18 (d, J 8, CH=C*H*), 3.71 (OMe) and 3.44 (NMe) (Found: M$^+$, 243.0895. $C_{14}H_{13}NO_3$ requires M, 243.0894).

(E)*-4-Methoxy-1-methyl-3-(1-oxobut-2-enyl)-2-*(1H)*-pyridone* **15b**.—Crotonaldehyde (0.16 g) was added to a solution of the vinyllithium species prepared from 4-methoxy-1-methyl-2(1*H*)-pyridone (0.21 g). After 15 min, the reaction mixture was warmed to 23 °C, then poured into water and extracted with methylene dichloride (3 × 3 cm^3). The combined extracts were washed with brine, then dried, and the solvent was evaporated off. The residue was purified by flash column chromatography on silica (10 g) with chloroform–methanol (49:1) as eluent to give a mixture of the alcohol and starting material (0.14 g). The mixture was dissolved in methylene dichloride (10 cm^3), and manganese dioxide (1.2 g) was then added. The mixture was stirred for 18 h, then was filtered, and the filtrate was evaporated to dryness. The residue was purified by flash column chromatography on silica with chloroform–methanol (49:1) as eluent to give the *ketone* **15b** (0.08 g, 26%) as a yellow oil, ν_{max}(CHCl$_3$)/cm^{-1} 1650, 1590 and 1360; δ_H 7.51 (d, *J* 8, C*H*=CH), 6.89 (dq, *J* 16 and 7, CH=C*H*Me), 6.50 (dq, *J* 16 and 2, C*H*=CHMe), 6.18 (d, *J* 8, CH=C*H*), 3.89 (OMe), 3.57 (NMe) and 1.95 (dd, *J* 7 and 2, CH=CH*Me*) (Found: M$^+$, 207.0888. $C_{11}H_{13}NO_3$ requires M, 207.0895).

1,2-Dihydro-4-methoxy-1-methyl-2-oxopyridine-3-carbonitrile (*Ricinine*) **1**.—A mixture of the acid **11** (20 mg), ethylpolyphosphate (60 mg) and chloroform (5 cm^3) was mechanically stirred whilst a stream of ammonia gas was passed over the reaction mixture. After 2 h, when amide formation was complete, more ethyl polyphosphate (100 mg) was added, and the reaction mixture was heated to 80 °C for 4 h.[14] The mixture was stirred with 10% sodium carbonate (10 cm^3) and was then extracted with methylene dichloride (5 × 5 cm^3). The combined extracts were washed with brine, then dried and evaporated to leave the *nitrile* **1** (10 mg, 56%) as a solid, m.p. 195–196 °C (lit.,[10b] 201.5 °C); λ_{max}(EtOH)/nm 315 (7000), 255 (2820) and 220 (25 600); ν_{max}(Nujol)/cm^{-1} 2240 and 1650; δ_H([^{2}H$_4$]-MeOH) 7.82 (d, *J* 8, C*H*=CH), 6.30 (d, *J* 8, CH=C*H*), 4.07 (OMe) and 3.59 (NMe) (Found: M$^+$, 165.0558. $C_8H_8N_2O_2$ requires M, 165.0586).

6-Chloro-4-hydroxy-5-phenyl-2(1H)*-pyridone* **16**.—Malonyl dichloride (8.0 cm^3, 82 mmol) and phenylacetonitrile (4.7 cm^3, 39 mmol) were stirred together under anhydrous conditions for 96 h. The solid product was triturated with dry dioxane (15 cm^3), filtered off under reduced pressure, and washed with diethyl ether (2 × 20 cm^3). Recrystallisation from aqueous dioxane gave the pyridone (4.92 g, 57%) as a buff solid, m.p. 297–299 °C (lit.,[11] 310 °C); λ_{max}(EtOH)/nm 289 (8900), 229 (42 200) and 206 (90 400); λ_{max}(EtOH–KOH)/nm 289 (12 200), 206 (93 900); ν_{max}(Nujol)/cm^{-1} 1655, 1585 and 1305; δ_H(CD$_3$SOCD$_3$) 6.20 (C=CH), 7.25–7.60 (m, ArH) and 9.3–10.9 (OH, NH) (Found: M$^+$, 221.0227. Calc. for $C_{11}H_8ClNO_2$: M, 221.0244).

6-Chloro-4-hydroxy-1-methyl-5-phenyl-2(1H)*-pyridone* **17**.—Dimethyl sulfate (0.47 cm^3, 5.0 mmol) was added dropwise, at room temperature, to a stirred solution of 6-chloro-4-hydroxy-5-phenyl-2(1*H*)-pyridone (1.0 g, 4.5 mmol) in aq. sodium hydroxide (2 mol dm^{-3}; 15 cm^3). The mixture was stirred vigorously for 3.5 h and was then acidified with conc. hydrochloric acid (2.8 cm^3). The solid precipitate was filtered off under reduced pressure and purified by column chromatography on silica gel G with 10% methanol in chloroform as eluent to give the 1-methylpyridone (0.58 g, 55%) as a solid, which was crystallised from 10% methanol in chloroform as buff crystals, m.p. 274–276 °C; ν_{max}(CHCl$_3$)/cm^{-1} 3200 and 1645; δ_H 7.18–7.53 (m, ArH), 5.98 (C=CH), 4.65 (OH) and 3.70 (NMe) (Found: M$^+$, 235.0375. $C_{12}H_{10}ClNO_2$ requires M, 235.0400).

6-Chloro-4-methoxy-1-methyl-5-phenyl-2(1H)*-pyridone* **18a**, *2-Chloro-4,6-dimethoxy-3-phenylpyridine and 2-Chloro-6-methoxy-1-methyl-3-phenyl-4*(1H)*-pyridone* **19**.—A solution of diazomethane [prepared from *N*-methyl-*N*-nitrosourea (6.0 g)] in diethyl ether (60 cm^3) was added, during 2 min, to a stirred suspension of 6-chloro-4-hydroxy-5-phenyl-2(1*H*)-pyridone (1.49 g, 6.3 mmol) in 10% methanol in chloroform (50 cm^3) at 5 °C, and the mixture was then allowed to warm to 20 °C during 15 h. Glacial acetic acid (1.0 cm^3) was added and the solvent was evaporated off under reduced pressure. The residue was dissolved in chloroform (50 cm^3) and the solution was then washed with saturated aq. sodium carbonate (3 × 10 cm^3) and dried (MgSO$_4$). The solvent was evaporated off under reduced pressure and the residue was purified by chromatography on silica gel G with chloroform as eluent to give: (i) 2-chloro-4,6-dimethoxy-3-phenylpyridine (**25**; R = Ph) (0.19 g, 12%) (eluted first), which was crystallised from diethyl ether as a waxy solid, λ_{max}(EtOH)/nm 243sh (17 800) and 203 (69 600); ν_{max}(CHCl$_3$)/cm^{-1} 1605, 1595 and 1580; δ_H 7.13–7.44 (m, ArH), 6.17 (5-H), 3.90 (OMe) and 3.66 (OMe) (Found: M$^+$, 249.0539. $C_{13}H_{12}ClNO_2$ requires M, 249.0557); (ii) *6-chloro-4-methoxy-1-methyl-5-phenyl-2*(1H)*-pyridone* **18a** (1.09 g, 69%) (eluted second), which was crystallised from acetone as pale yellow crystals, m.p. 165–166 °C; λ_{max}(EtOH)/nm 296 (6500), 233 (18 800) and 210 (41 800); ν_{max}(CHCl$_3$)/cm^{-1} 1650 and 1600; δ_H 7.20–7.56 (m, ArH), 6.06 (C=CH) and 3.76 (OMe + NMe) (Found: C, 62.2; H, 4.8; N, 5.6%; M$^+$, 249.0551. $C_{13}H_{12}ClNO_2$ requires C, 62.5; H, 4.8; N, 5.6%; M, 249.0557).

Further elution with 5% methanol in chloroform gave *2-chloro-6-methoxy-1-methyl-3-phenyl-4*(1H)*-pyridone* **19** (0.06 g, 4%) as a brown oil, λ_{max}(EtOH)/nm 260 (16 300), 227 (31 100) and 204 (46 300); ν_{max}(CHCl$_3$)/cm^{-1} 1625 and 1575; δ_H 7.24–7.51 (m, ArH), 5.98 (5-H), 3.93 (OMe) and 3.69 (NMe) (Found: M$^+$, 249.0543. $C_{13}H_{12}ClNO_2$ requires M, 249.0557).

4-Methoxy-1-methyl-5-phenyl-2(1H)*-pyridone* **18b**.—Tributyltin hydride (3.1 cm^3, 11.5 mmol) was added dropwise, during 10 min, to a refluxing solution of 6-chloro-4-methoxy-1-methyl-5-phenyl-2-(1*H*)-pyridone (1.44 g, 5.8 mmol) in dry benzene (15 cm^3) containing a catalytic amount of AIBN (~10 mg). The mixture was stirred under reflux for 25 h, and then the solvent was evaporated off under reduced pressure. The residue was purified by chromatography on silica gel G with 50% diethyl ether in chloroform as eluent to give: (i) recovered starting material (0.23 g, 16%) and (ii) *4-methoxy-1-methyl-5-phenyl-2(1H)-pyridone* **18b** (1.01 g, 81.5%) (eluted second) as a solid, which crystallised from acetone as needles, m.p. 115–116 °C; λ_{max}(EtOH)/nm 296 (10 300), 256 (36 000), 236 (51 600) and 208 (82 800); ν_{max}($CHCl_3$)/cm^{-1} 1655 and 1590; δ_H 7.33 (ArH), 7.13 (6-H), 5.98 (3-H), 3.76 (OMe) and 3.50 (NMe) (Found: C, 72.4; H, 6.3; N, 6.4%; M$^+$, 215.0957. $C_{13}H_{13}NO$ requires C, 72.6; H, 6.1; N, 6.5%; M, 215.0946).

*2-Chloro-4-hydroxy-5-(*p*-methoxyphenyl)-2(1H)-pyridone* **20a**.—Malonyl dichloride (12.4 g, 88 mmol) and *p*-methoxyphenylacetonitrile (7.5 g, 51 mmol) were stirred together under anhydrous conditions, at room temperature, for 1 week. Methanol (10 cm^3, 247 mmol) was added dropwise to the mixture (slight exotherm) and the solvent was then evaporated off under reduced pressure. The residue was dissolved in 40% aq. potassium hydroxide (50 cm^3) and the solution was washed with diethyl ether (3 × 15 cm^3). The layers were separated and the aq. solution was then acidified with conc. hydrochloric acid. The precipitated solid was filtered off under reduced pressure, and was then washed successively with chloroform (2 × 10 cm^3) and diethyl ether (2 × 10 cm^3). Chromatography on silica gel G with 10% methanol in chloroform as eluent gave the *pyridone* **20a** (6.88 g, 47%), which was crystallised from methanol as a buff, crystalline solid, m.p. 305–306 °C (sublimation); λ_{max}(EtOH)/nm 299 (4700), 280sh (7900), 249 (23 400), 228sh (22 900), 207sh (48 600) and 200 (50 400); λ_{max}(EtOH–KOH)/nm 281 (21 100) and 206 (90 700); ν_{max}(Nujol)/cm^{-1} 1650, 1605 and 1595; δ_H(CD_3COCD_3) 10.80–11.20 (br, OH, NH), 7.09 (d, *J* 9, ArH), 6.87 (d, *J* 9, ArH), 6.07 (C=CH) and 3.73 (ArO*Me*) (Found: C, 57.1; N, 4.3; N, 5.6%; M$^+$, 251.0323. $C_{12}H_{10}ClNO_3$ requires: C, 57.3; H, 4.0; N, 5.6%; M, 251.0349).

6-Chloro-4-hydroxy-5-methyl-2(1H)-pyridone **20b**.—Propiononitrile (5.25 cm^3, 69 mmol) and malonyl dichloride (9.75 cm^3, 100 mmol) were stirred together under anhydrous conditions for 1 week. The residue was triturated with diethyl ether–dioxane and filtered off under reduced pressure. Recrystallisation from methanol gave the pyridinone **20b** (5.7 g, 52%) as buff crystals, m.p. 302–303 °C (sublimation) (lit.,[11] 302 °C); λ_{max}(EtOH)/nm 290 (7600), 278 (7500) and 207 (49 000); λ_{max}(EtOH–KOH)/nm 281 (6800) and 210 (73 000); ν_{max}(Nujol)/cm^{-1} 1660 and 1600; δ_H(CD_3SOCD_3) 7.20–9.00 (OH + NH), 6.06 (C=CH) and 2.01 (Me) (Found: M$^+$, 159. Calc. for $C_6H_6ClNO_2$: M, 159).

6-Chloro-5-cyclopentyl-4-hydroxy-2(1H)-pyridone **21** *and* *4-Chloro-2-(cyclopentylmethyl)-6(1H)-pyrimidone* **22**.—Cyclopentylacetonitrile (1.02 g, 9.36 mmol) and malonyl dichloride (1.3 cm^3, 13.40 mmol) were stirred under anhydrous conditions for 12 d. Methanol (3 cm^3) was added (slight exotherm) and the solvent was then evaporated off under reduced pressure. The residue was dissolved in 14 mol dm^{-3} sodium hydroxide (60 cm^3) and the solution was then washed with diethyl ether (3 × 10 cm^3) to remove non-polar material. Acidification of the aq. layer with conc. hydrochloric acid and removal of the solvent under reduced pressure left a buff solid, which was purified by flash chromatography on silica, with 5% methanol in chloroform as eluent, to give *4-chloro-2-(cyclopentylmethyl)-6(1H)-pyrimidone* **22** (178 mg, 9%), which was crystallised from chloroform as pale yellow needles, m.p. 177–178 °C; λ_{max}(EtOH)/nm 280 (12 600), 226 (13 800) and 200 51 300); ν_{max}(KBr)/cm^{-1} 1675 and 1580; δ_H 13.50 (NH), 6.38 (5-H), 2.67 (d, *J* 7.9, R_2CHCH_2R'), 2.32 (septet, *J* 7.9, R_2CHCH_2R') and 1.12–1.84 (8 H, m, 4 × CH_3); δ_C 24.93, 32.29, 38.71, 41.10, 110.71, 160.67, 163.32 and 165.04 (Found: C, 56.3; H, 6.1; N, 12.9%; M$^+$, 212.0566. $C_{10}H_{13}ClN_2O$ requires C, 56.5; H, 6.1; N, 13.2%; M, 212.0716). Further elution gave *6-chloro-5-cyclopentyl-4-hydroxy-2(1H)-pyridone* **21** (110 mg, 6%), which was crystallised from methanol as crystals, m.p. 358–360 °C (sublimation); λ_{max}(EtOH)/nm 292 (6300), 279 (5800) and 211 (45 900); ν_{max}(KBr)/cm^{-1} 3200–2500, 1660, 1605 and 1590; δ_H(CD_3SOCD_3) 10.80 (OH + NH), 5.96 (3-H) and 1.46–1.95 (m, C_5H_9); δ_C(CD_3SOCD_3) 26.15, 29.72, 37.97, 94.81, 116.84, 146.13, 161.68 and 166.48 (Found: C, 56.3, H, 5.6; N, 6.3%; M$^+$, 213.0547. $C_{10}H_{12}ClNO_2$ requires C, 56.2; H, 5.6; N, 6.6%; M, 213.0557).

Use of 1.5 mol equiv. of malonyl dichloride in subsequent preparations together with lithium perchlorate (0.3 mol equiv.) increased the yield of the pyridinone **21** to 27%.

*6-Chloro-4-methoxy-5-(*p*-methoxyphenyl)-1-methyl-2(1H)-pyridone* **23a**.—Dimethyl sulfate (1.51 g, 12.0 mmol) was added, in one portion, to a stirred solution of 6-chloro-4-hydroxy-5-(*p*-methoxyphenyl)-2(1*H*)-pyridone (2.77 g, 11.0 mmol) in a mixture of dioxane (15 cm^3) and 20% aq. sodium hydroxide (6 cm^3) at 18 °C. The mixture was stirred at room temperature for 20 h, then acidified with hydrochloric acid (2 mol dm^{-3}; 3 cm^3) and the precipitated solid was filtered off, suspended in a mixture of diethyl ether–methanol–chloroform (30:2:5) (37 cm^3) and treated with excess of ethereal diazomethane [prepared from *N*-methyl-*N*-nitrosourea (4 g)] in diethyl ether (40 cm^3). After 2 h, the solvent was evaporated off under reduced pressure. The residue was dissolved in chloroform (20 cm^3) and the solution was washed successively with saturated aq. sodium hydrogen carbonate (3 × 10 cm^3) and brine (2 × 10 cm^3), and then dried ($MgSO_4$). The solvent was evaporated off under reduced pressure and the residue was purified by chromatography on silica gel G with chloroform as eluent to give the *pyridone* **23a** (1.11 g, 36%), which was crystallised from acetone as crystals, m.p. 221–222 °C; λ_{max}(EtOH)/nm 299 (11 100), 249 (30 900), 230sh (41 200), 213 (74 000) and 197 (82 300); ν_{max}($CHCl_3$)/cm^{-1} 1640 and 1605; δ_H 7.2 (d, *J* 9, ArH), 7.02 (d, *J* 9, ArH), 6.01 (C=CH), 3.87 (C_6H_4OMe) and 3.73 (NMe + pyr-OMe) (Found: C, 60.1, H, 5.0, N, 4.9; Cl, 12.3%; M$^+$, 279.0653. $C_{14}H_{14}ClNO_3$ requires C, 60.1; H, 5.0; N, 5.0; Cl, 12.7%; M, 279.0662).

*6-Chloro-4-methoxy-5-(*p*-methoxyphenyl)-1-methyl-2(1H)-pyridone* **23a**, *2-Chloro-4,6-dimethoxy-3-(*p*-methoxyphenyl)pyridine* **25a** *and* *2-Chloro-6-methoxy-3-(*p*-methoxyphenyl)-1-methyl-4(1H)-pyridone* **24a**.—A suspension of the pyridone **20a** (0.96 g, 3.8 mmol) in 10% methanol in chloroform (10 cm^3) was cooled to 0 °C and ethereal diazomethane [prepared from *N*-nitroso-*N*-methylurea (2.5 g)] (25 cm^3) was added. The mixture was maintained at 0 °C for 3 h, then treated with the same quantity of diazomethane and allowed to warm to 18 °C during 14 h. Glacial acetic acid (1.0 cm^3) was added and the solvent was then evaporated off under reduced pressure. The residue was dissolved in chloroform (10 cm^3) and the solution was washed with saturated aq. sodium hydrogen carbonate (4 × 5 cm^3), and then dried ($MgSO_4$). Evaporation of the solvent left a yellow gum, which was purified by chromatography on silica gel G with chloroform as eluent to give *2-chloro-4,6-dimethoxy-3-(*p*-methoxyphenyl)pyridine* **25a** (0.26 g, 25%), which was crystallised from chloroform as pale yellow crystals, m.p. 108–109 °C; λ_{max}(EtOH)/nm 250 (8200), 244 sh (11 700) and 198 (42 800); ν_{max}($CHCl_3$)/cm^{-1} 1595 and 1545; δ_H 7.14 (d, *J* 9, ArH), 6.88 (d, *J* 9, ArH), 6.16 (C=CH), 3.89 (C_6H_4OMe), 3.76 (OMe) and 3.64 (OMe) (Found: C, 60.1; H, 5.1; N, 4.9%; M$^+$, 279.0639. $C_{14}H_{14}ClNO_3$ requires C, 60.1; H, 5.0; N, 5.0%; M, 279.0653).

Further elution gave 6-chloro-4-methoxy-5-(*p*-methoxyphenyl)-1-methyl-2(1H)-pyridone **23a** (0.55 g, 52%), and elution with 5% methanol in chloroform gave *2-chloro-6-methoxy-3-(*p*-

methoxyphenyl)-1-*methyl*-4(1H)-*pyridone* **24a** (70 mg, 7%) as a brown oil, λ_{max}(EtOH)/nm 258sh (17 100), 235 (28 000) and 201 (48 000); ν_{max}($CHCl_3$)/cm^{-1} 1625; δ_H 7.26 (d, *J* 9, ArH), 7.00 (d, *J* 9, ArH), 6.20 (5-H), 3.95 (C_6H_4OMe), 3.83 (pyr-O*Me*) and 3.69 (NMe) (Found: M$^+$, 279.0672. $C_{14}H_{14}ClNO_3$ requires M, 279.0662).

4-*Methoxy*-5-(p-*methoxyphenyl*)-1-*methyl*-2(1H)-*pyridone* **26a**.—Tributyltin hydride (2.8 cm^3, 10.4 mmol) was added dropwise, during 2 min to a stirred solution of the pyridinone **23a** (1.45 g, 5.2 mmol) in benzene (15 cm^3). The mixture was heated under reflux, and a solution of AIBN ($\sim$20 mg) in benzene (5 cm^3) was added dropwise during 1 h. The mixture was heated under reflux for 40 h with further additions of AIBN after 8, 21, and 29 h. The solvent was evaporated off under reduced pressure and the residue was then purified by chromatography on silica gel G with 10% methanol in chloroform as eluent to give: (i) recovered starting material (0.25 g, 17%) (eluted first) and (ii) the *pyridone* **26a** (1.03 g, 81%), which was crystallised from acetone as pale yellow crystals, m.p. 158–159 °C; λ_{max}(EtOH)/nm 301sh (9900), 254 (61 000), 229 (38 000), 212 (93 400) and 197 (89 400); ν_{max}($CHCl_3$)/cm^{-1} 1655, 1605 and 1590; δ_H 7.34 (d, *J* 9, ArH), 7.20 (6-H), 6.98 (d, *J* 9, ArH), 6.04 (3-H), 3.88 (C_6H_4OMe), 3.82 (pyr-O*Me*) and 3.56 (NMe) (Found: C, 68.4; H, 6.3; N, 5.5%; M$^+$, 245.1063. $C_{14}H_{15}NO_3$ requires C, 68.5; H, 6.2; N, 5.7%; M, 245.1052).

2-*Chloro*-4,6-*dimethoxy*-3-*methylpyridine* **25b**, 6-*Chloro*-4-*methoxy*-1,5-*dimethyl*-2(1H)-*pyridone* **23b** *and* 2-*Chloro*-6-*methoxy*-1,3-*dimethyl*-4(1H)-*pyridone* **24b**.—A solution of diazomethane [prepared from 'Diazald' (30 g)] in diethyl ether (250 cm^3) was added in three portions, at 1 h intervals, to a stirred suspension of the pyridone **20b** (3.82 g, 24 mmol) in ethanol (20 cm^3). The mixture was stirred at 5 °C for 6 h and was then allowed to warm to room temperature during 15 h. The solvent was evaporated off under reduced pressure and the residue was then purified by flash chromatography on silica, with chloroform as eluent, to give 2-*chloro*-4,6-*dimethoxy*-3-*methylpyridine* **25b** (0.77 g, 17%), which was crystallised from diethyl ether as pale yellow crystals, m.p. 91–92 °C; λ_{max}(EtOH)/nm 268 (5 800), 221sh (11 800) and 202 (51 800); ν_{max}($CHCl_3$)/cm^{-1} 1600; δ_H 6.11 (C=CH), 3.89 (OMe), 3.82 (OMe) and 2.13 (Me) (Found: M$^+$, 187.0374. $C_8H_{10}ClNO_2$ requires M, 187.0399). Further elution with 10% methanol in chloroform gave 6-*chloro*-4-*methoxy*-1,5-*dimethyl*-2(1H)-*pyridone* **23b** (2.41 g, 54%), which was crystallised from acetone as yellow needles, m.p. 141–142 °C; λ_{max}(EtOH)/nm 296 (14 800), 232sh (11 200) and 211 (56 600); ν_{max}($CHCl_3$)/cm^{-1} 1645; δ_H 5.97 (C=CH), 3.84 (OMe), 3.69 (NMe) and 2.09 (Me) (Found: C, 51.4; H, 5.6; N, 7.42%; M$^+$, 187.0410. $C_8H_{10}ClNO_2$ requires C, 51.2; H, 5.3; N, 7.5%; M, 187.0400). Further elution with 5% methanol in chloroform gave 2-*chloro*-6-*methoxy*-1,3-*dimethyl*-4(1H)-*pyridone* **24b** (0.31 g, 7%) as a pale yellow oil, λ_{max}(EtOH)/nm 261 (20 400), 219 (27 800) and 202 (38 500); ν_{max}($CHCl_3$)/cm^{-1} 1625 and 1560; δ_H 5.78 (5-H), 3.87 (OMe), 3.60 (NMe) and 2.10 (Me) (Found: M$^+$, 187.0388. $C_8H_{10}ClNO_2$ requires M, 187.0400).

4-*Methoxy*-1,5-*dimethyl*-2(1H)-*pyridone* **26b**.—Tributyltin hydride (2.47 cm^3, 9.2 mmol) was added dropwise, during 2 min, to a stirred solution of 6-chloro-4-methoxy-1,5-dimethyl-2(1*H*)-pyridone (0.86 g, 4.6 mmol) in dry benzene (15 cm^3). The mixture was heated under reflux and a 1% solution of AIBN in benzene (10 cm^3) was then added dropwise during 4 h. The mixture was heated under reflux for a total of 40 h, with further addition of AIBN solution after 24 h. The solvent was evaporated off under reduced pressure and the residue was then purified by flash chromatography on silica with hexane (200 cm^3) as eluent to remove tin compounds. Further elution with chloroform (300 cm^3) gave recovered starting material (0.19 g, 22%), followed by the *pyridone* **26b** (0.51 g, 72%), which was crystallised from acetone as pale yellow crystals, m.p. 122–123 °C; λ_{max}(EtOH)/nm 288 (7400), 299sh (8500) and 210 (47 300); ν_{max}($CHCl_3$)/cm^{-1} 1665 and 1590; δ_H 6.98 (6-H), 5.94 (3-H), 3.80 (OMe), 3.47 (NMe) and 1.94 (Me) (Found: M$^+$, 153.6804. $C_8H_{11}NO_2$ requires M, 153.0750).

3-*Deuterio*-4-*methoxy*-1-*methyl*-5-*phenyl*-2(1H)-*pyridone* **27**.—A solution of 1-methyl-4-methoxy-5-phenyl-2(1*H*)-pyridone (172 mg, 0.8 mmol) in anhydrous THF (3.0 cm^3) was added dropwise, during 5 min, to a stirred solution of butyllithium (1.60 mol dm^{-3} in hexanes; 0.8 cm^3, 1.28 mmol) in THF (5.0 cm^3) at −78 °C under nitrogen. The mixture was stirred at −78 °C, under nitrogen, for 45 min, to ensure complete anion formation. The pale orange solution of the anion was quenched by the dropwise addition of monodeuteriomethanol (0.5 cm^3, 12.3 mmol) during 2 min, at −78 °C. The decolourised solution was warmed to 18 °C during 30 min, then was poured into pH 7.0 phosphate buffer. The THF was evaporated off under reduced pressure and the residue was then extracted with dichloride (3 × 3 cm^3). The combined extracts were washed with brine (3 × 2 cm^3), then dried ($MgSO_4$), and the solvent was removed under reduced pressure to leave the *pyridone* **27** (162 mg, 75%) as a red oil, ν_{max}($CHCl_3$)/cm^{-1} 1655 and 1590; δ_H 7.41 (ArH), 7.22 (6-H), 6.04 (0.33 H, 3-H), 3.80 (OMe) and 3.54 (NMe) (Found: M$^+$, 216.1027. $C_{13}H_{12}DNO_2$ requires M, 216.1009).

3-*Deuterio*-4-*methoxy*-5-(p-*methoxyphenyl*)-1-*methyl*-2(1H)-*pyridone* **28a** *and* 3-*Deuterio*-1-(*deuteriomethyl*)-4-*methoxy*-5-(p-*methoxyphenyl*)-2(1H)-*pyridone* **28b**.—A solution of 4-methoxy-3-(*p*-methoxyphenyl)-1-methyl-2(1H)-pyridinone (63.2 mg, 0.26 mmol) in anhydrous THF (3.0 cm^3) was added dropwise, during 5 min, to a stirred solution of butyllithium (1.55 mol dm^{-3} in hexane; 0.26 cm^3, 0.40 mmol) in THF (8 cm^3) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 50 min and then the resulting pale orange solution of the pyridone vinyl anion was quenched with [^{2}H]methanol (0.5 cm^3, 12.3 mmol). The mixture was allowed to warm to room temperature during 30 min, and was then poured into pH 7 phosphate buffer (5 cm^3) and THF was evaporated off under reduced pressure. The residue was extracted with methylene dichloride (5 × 3 cm^3), and the combined extracts were then washed with brine (2 × 3 cm^3) and dried ($MgSO_4$). The extracts were evaporated under reduced pressure to leave a mixture of mono- and di-deuteriopyridones as a pale pink oil (57 mg), ν_{max}($CHCl_3$)/cm^{-1}, 1650, 1605 and 1590; δ_H 7.32 (d, *J* 9, ArH), 7.18 (6-H), 6.96 (d, *J* 9, ArH), 3.83 (C_6H_4OMe), 3.78 (pyr-O*Me*) and 3.52 (2.5 H, NMe + CH_2DN) (Found: M$^+$, 247.1171 (33.7), 246.1111 (100). $C_{14}H_{13}D_2NO_3$ requires M, 247.1177; $C_{14}H_{14}DNO_3$ requires M, 246.1115).

3-*Deuterio*-4-*methoxy*-1,5-*dimethyl*-2(1H)-*pyridone* **29**.—Butyllithium (1.6 mol dm^{-3} in hexane; 0.35 cm^3, 0.56 mmol) was added dropwise, during 1 min, to a solution of 4-methoxy-1,5-dimethyl-2(1*H*)-pyridone (65 mg, 0.43 mmol) in anhydrous THF (5 cm^3) −78 °C under argon and the mixture was then stirred at −78 °C for 40 min. Monodeuteriomethanol (0.5 cm^3) was added dropwise and the orange solution was decolourised immediately. The mixture was warmed to 18 °C during 40 min, then was poured onto pH 7 phosphate buffer (4 cm^3). THF was evaporated off under reduced pressure and the residue was then extracted with chloroform (3 × 3 cm^3). The combined extracts were washed with water (2 × 2 cm^3), then dried ($MgSO_4$), and evaporated under reduced pressure to leave 3-*deuterio*-4-*methoxy*-1,5-*dimethyl*-2(1H)-*pyridone* **29** (60 mg, 92%) as a pale yellow oil, ν_{max}($CHCl_3$)/cm^{-1} 1655 and 1585; δ_H 7.00 (6-H), 3.80

(OMe), 3.47 (NMe) and 1.96 (Me) (Found: M$^+$, 154.0840. $C_8H_{10}DNO_2$ requires M, 154.0853).

(E)-3-(1-*Hydroxybut*-2-*enyl*)-4-*methoxy*-5-(p-*methoxyphenyl*)-1-*methyl*-2(1H)-*pyridone* **30**.—A solution of the pyridone **26a** (105 mg, 0.43 mmol) in anhydrous THF (4.0 cm^3) was added dropwise, during 5 min, to a stirred solution of butyllithium (1.60 mol dm^{-3} in hexane; 0.30 cm^3, 0.48 mmol) in THF (5.0 cm^3) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 1 h, and then freshly distilled crotonaldehyde (0.04 cm^3, 0.48 mmol) was added dropwise during 2 min. The mixture was stirred at −78 °C for 45 min, then was allowed to warm to room temperature during 1 h and poured into pH 7 phosphate buffer (5 cm^3). THF was evaporated off under reduced pressure and the residue was then extracted with methylene dichloride (5 × 3 cm^3). The combined extracts were washed with brine (2 × 3 cm^3), dried ($MgSO_4$), and then evaporated under reduced pressure to leave a yellow oil, which was purified by chromatography on silica gel G with 2% methanol in chloroform as eluent to give the alcohol **30** (56.2 mg, 41%) as a pale yellow oil, λ_{max}(EtOH)/nm 292 (7800) 271sh (12 400), 235sh (39 500) and 205 (106 000); ν_{max}($CHCl_3$)/cm^{-1} 3400, 1640, 1605, 1575 and 965; δ_H 7.28 (d, *J* 9, ArH), 7.16 (6-H), 6.90 (d, *J* 9, ArH), 5.73–5.87 (m, C*H*=C*H*Me), 5.27–5.40 [m, C*H*(OH)C=C], 3.81 (OMe), 3.53 (OMe), 3.36 (NMe) and 1.69 (d, *J* 5.4, *Me*CH=C) (Found: M$^+$, 315.1499. $C_{18}H_{21}NO_4$ requires M, 315.1471).

(E)-4-*Methoxy*-5-(p-*methoxyphenyl*)-1-*methyl*-3-(1-*oxobut*-2-*enyl*)-2(1H)-*pyridone* **31**.—A solution of the alcohol **30** (47.6 mg, 0.15 mmol) in dry methylene dichloride (8.0 cm^3) was stirred at room temperature with manganese dioxide (500 mg, 38 mol equiv.) for 20 h, and the mixture was then filtered through a pad of Kieselguhr. The filter pad was washed with methylene dichloride (2 × 3 cm^3) and the combined filtrates were then evaporated under reduced pressure. The residue was purified by chromatography on silica gel G with chloroform as eluent to give the pyridone **31** (39.2 mg, 83%) as an orange oil, λ_{max}(EtOH)/nm 320 (9400), 255 (40 500), 231 (40 800), 210sh (57 900) and 198 (91 500); ν_{max}($CHCl_3$)/cm^{-1} 1640, 1605 and 970; δ_H 7.31 (d, *J* 9, ArH), 7.29 (6-H), 6.95 (d, *J* 9, ArH), 6.1–6.7 (m, C*H*=CH), 3.84 (OMe), 3.58 (OMe), 3.76 (NMe) and 1.97 (d, *J* 6.8, *Me*CH=C) (Found: M$^+$, 313.1279. $C_{18}H_{19}NO_4$ requires M, 313.1314).

Acknowledgements

We thank Pfizer Central Research for a research scholarship (to J. P. M.) and for generous financial support. We also thank the SERC for a studentship (to J. B.) and Dr. P. J. Whittle (Pfizer Central Research) for his interest in this study.

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Paper 1/03890G
Received 29th *July* 1991
Accepted 5th *September* 1991