Hetero-ring Lithiation of *N*-Methyl-4-quinolone and *N*-Methylquinoline-4-thione

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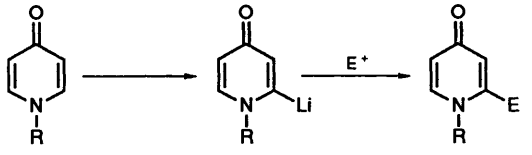
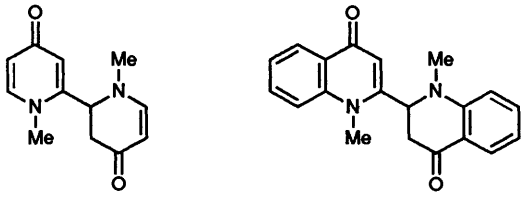
Lithiation of 1-methyl-4-quinolone and 1-methylquinoline-4-thione with lithium diisopropylamide (LDA) at −78 °C takes place at C-2. The resulting lithio-species react with a variety of electrophiles to give 2-substituted-4-quinolones and -quinolines-4-thiones respectively. 1-Methylquinoline-4-thione is easily converted into 1-methyl-4-quinolone in protic solution.

We have shown [1] that low temperature lithiation of 4-pyridones provides a route for the introduction of electrophiles at the 2-position (**1**→**2**→**3**). 2-Acylated pyridones, thus obtained, can provide the means for the further construction of polycyclic heterocyclic quinones [2] of relevance to the total synthesis of sea alkaloids.[3]



1 **2** **3**

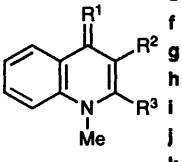
Encouraged by the pyridone results, and motivated by plans for the construction of sea alkaloids containing both quinoline and quinone moieties, we have now examined the lithiation of 1-methyl-4-quinolone, **4a**, and thereby the synthesis of 2-substituted quinolones.[4] A difficulty, which could be largely avoided in the pyridone work, was the side-production of 'dimers', *e.g.* **5**, in which lithiated heterocycle had added, in a



5 **6**

Michael sense, to unchanged pyridone, and it was anticipated that this might be a greater problem in the quinolone series, there being retention of a full benzene ring in a dimer to be derived comparably from a quinolone, **6** from **4a**.

Exchange at C-2 in quinoline in strong acid is considered to involve C-2-deprotonation of the 1-protoquinolinium cation.[5] Lithio derivatives of quinoline, where the metal is at the hetero-ring 2-, 3-, and 4-positions were first described by Spatz[6] and Gilman,[7] produced *via* reaction of the corresponding bromo-quinolines with butyllithium. The direct *ortho C*-lithiation of 2-, 3- and 4-fluoro-[8] 2-, 3- and 4-chloroquinolines,[9] adjacent to a 2-pivaloylamino group,[10] and to 2-, 3-, 4-, 5-, 6-, 7- and 8-dimethylaminocarbonyloxyquinolines[11] have been described. Lithiations *ortho* to a 2-ethoxy[12] and between the two oxygen substituents of 2,4-dimethoxyquinoline[13] have been recorded, but there does not seem to have been a description of metallation of a benzene-ring-alkoxyquinoline. Quinoline- and substituted-quinoline-2-, 7- and 8-aurio derivatives were prepared



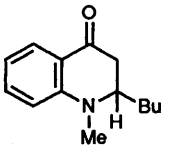
4

	R^1	R^2	R^3
a	O	H	H
b	S	H	H
c	O	H	D
d	O	H	Et
e	O	H	PhCH(OH)
f	O	H	4-$O_2NC_6H_4CH(OH)$
g	O	H	4-$MeOC_6H_4CH(OH)$
h	O	H	3-pyridyl-CH(OH)
i	O	H	PhCO
j	O	H	3-pyridyl-CO
k	O	H	$H_2C(OH)$
l	O	H	PhC(Me)(OH)
m	O	PhC(Me)(OH)	H
n	O	H	$Ph_2C(OH)$
o	O	H	Bu
p	S	H	PhCH(OH)
q	S	H	3-pyridyl-CH(OH)
r	S	H	4-$MeOC_6H_4CH(OH)$
s	O	H	4-$MeOC_6H_4CO$

from the lithio species.[14] Transformation of 3-lithioquinoline to the quinolin-3-yl tributylborate provided a means for 3-allylation.[15] There are no reports of the lithiation of *N*-substituted 2- or 4-quinolones at any position.

Results

Attempts to lithiate *N*-methyl-4-quinolone with butyllithium were unsatisfactory; for example, after reaction at −78 °C, and subsequent addition of benzaldehyde, only a trace of the substitution product **4e** was obtained, along with **7** and **4o**; the last two must result from a Michael-type nucleophilic addition of the organometallic reagent to the 'enone' of the quinolone (→**7**), with subsequent dehydrogenation to afford the major product **4o**. The location of the butyl substituent in **4o** followed from the singlet at δ 6.59, corresponding to a quinolone 3-H, and in **7** from the multiplet at δ 4.10 for one hydrogen and the two-hydrogen multiplet at higher field, δ 3.00. Attempted use of methyllithium was also attended by addition problem, and neither *sec*-butyllithium or mesityllithium effected any deprotonation of the quinolone.



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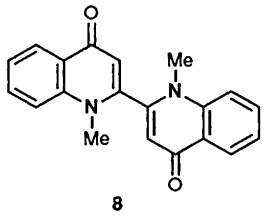
The reverse addition of quinolone to 3 equiv. of lithium diisopropylamide (LDA) at −78 °C was however efficient for the lithiation of *N*-methyl-4-quinolone, the excess of organometallic being necessary to minimise dimer formation (see below), and after quenching with CD_3OD, three products were obtained in proportions and structure determined by ^1H NMR and mass spectroscopic analysis: (i) mono-deuteriated quinolone, **4c**, which showed 63% deuteration, the location of the label being shown to be C-2 by the remaining 3-H signal, at δ 6.28, now a singlet, (ii) dimer, **6**, 18% (see below), and (iii) dehydro dimer, **8**, 18% (see below). Deuteriated quinolone **4c** was isolated in 15% yield by column chromatography of the crude reaction mixture.

In all reactions of the lithiated quinolone with electrophiles, some of the dimer **6** was always produced and this compound could be prepared in 74% yield by treatment of the quinolone with 0.5 mol equiv. of LDA. The regiochemistry of linking follows from (a) the residual quinolone 3-H singlet at δ 6.12 and (b) from the CH_2CH unit of the dihydroquinolone portion represented by signals for the geminal pair at δ 2.91 and 3.30 and for the methine at lower field, δ 5.01.



8

The formation of fully aromatic 'dimer' **8** may involve oxidation of **6**, but we suggest that a more likely source is *via* the dimerisation of an anion radical produced by addition of an electron (from $Pr^i_2N^-$) to starting quinolone; such processes have good precedent [16] in pyridine chemistry, but not, so far as we are aware, in pyridone/quinolone chemistry.

The reaction of lithiated quinolone with typical electrophilic reagents proved variable in efficiency, and was always accompanied by dimer formation and consequent lower yields of substituted products. Attempted simple methylation gave rise to 2-ethyl-1-methyl-4-quinolone **4d** presumably by a second alkylation at the activated methyl in 1,2-dimethyl-4-quinolone, the initial product; a comparable process has been observed before.[1] Aromatic aldehydes reacted well, giving alcohols **4e–h** in good yields, with the exception that from both 2- and 4-methoxycarbonylbenzaldehydes very complex mixtures were obtained from which no useful products could be isolated. Two aromatic acid chlorides reacted less well to afford ketones **4i** and **4j**. Reaction with gaseous formaldehyde produced the expected alcohol **4k**.

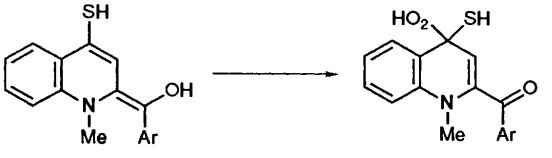
Benzophenone reacted as anticipated to form **4n**; however, from acetophenone two products, **4l** and **4m**, were obtained the second of which proved to be the alcohol resulting from substitution at C-3. The key measurement which established the isomeric nature of **4l** and **4m** are the multiplicities of the hetero-ring carbons: in **4l** C-2 and C-3 are singlet and doublet and in **4m** they are doublet and singlet respectively. It is difficult to rationalise (a) the formation of a 3-substituted product at all and (b) only with this particular electrophile. One possible explanation is that initial 2-substitution assists a second lithiation, at C-3, that this is followed by a second alkylation and then by a dealkylation at the originally substituted C-2.

There appear to be no reported examples of the lithiation of pyridinethiones or quinolinethiones. In anticipation that the regiochemistry of lithiation might be different, 1-methylquinoline-4-thione was prepared by thionation of the quinolone using Lawesson's reagent and its lithiation studied. Lithiation proceeded in acceptable yield and with three typical aromatic aldehydes, alcohols **4p–r** were obtained.

The chemical shifts (δ 7.28 and 7.41) of the hetero-ring protons in quinolinethione **4b** differ by only 0.13 ppm; this can be compared with the comparable protons in the quinolone **4a** [δ 6.32 (3-H) and 7.56 (2-H)] where the difference was clearly of sufficient magnitude to allow unambiguous structural assignments to be made to substitution products. In order to assign the signals of the quinolinethione unequivocally, an NOE experiment was conducted and thus the proton giving the signal at δ 7.41 shown to be adjacent to the *N*-methyl group.

Even with this knowledge of the shifts of the quinolinethione heterocyclic-ring protons it was clearly not feasible to utilise the chemical shift of the remaining ring proton alone to assign structures to the substitution products **4p–r**, indeed for **4p** (δ 7.72) and **4r** (δ 7.78) the shifts tended to suggest that lithiation and substitution had indeed taken place at C-3 (the residual hetero-ring proton signal in **4q** was obscured by other signals).

Assignments **4p–r** were secured by the transformation of these products, simply by recrystallisation from dichloromethane, or column chromatography over silica, or by stirring solutions of **4p–r** in dichloromethane with silica gel, into the 2-acyl-substituted quinolones **4i**, **4j** and **4s**. These conversions must involve an oxidation, perhaps of a tautomer **9** generating **10** as an intermediate. The quinolinethione **4b** itself was converted into the quinolone **4a** simply by stirring in alcoholic solution with silica gel overnight at room temperature.



9 **10**

Experimental

M.p.s were determined in open capilliaries on a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-200 or Bruker AC-300 spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal standard, *J* values are given in Hz. IR spectra were taken with a Perkin-Elmer 1430 spectrophotometer, and only structurally significant absorptions (ν_{max}/cm^{-1}) are listed. UV spectra were determined using a Perkin-Elmer Lambda 5 spectrophotometer. Low-resolution mass spectra were measured on a Hewlett-Packard 5930A mass spectrometer and high-resolution measurements made on a MS-9 AEI mass spectrometer updated by VG. Column chromatography was carried out on silica gel 60 (0.063–0.200 mm), flash chromatography on silica gel 60 (0.040–0.063 mm), and TLC was carried out on silica gel 60 F254 (0.063–0.200 mm); the spots were located with iodoplatinate reagent or UV light. Purification of reagents and solvents was effected according to standard methods. All reactions were conducted under a nitrogen or argon atmosphere. Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous magnesium or sodium sulfate. Microanalyses were performed on a Carlo-Erba 1106 analyser by the Instituto de Química Bio-Orgánica, Barcelona. ^{13}C NMR spectroscopic data for compounds **4a–s**, **6** and **7** are given in Table 1.

1-*Methyl*-4-*quinolone* **4a**.—Methyl iodide (16.8 cm^3, 270 mmol) was added in one aliquot to a solution of 4-quinolone (4 g, 27.5 mmol) and KOH (2.28 g, 40.7 mmol) in methanol (12 cm^3) and the mixture was stirred for 2 h at room temperature. The precipitate was removed by filtration, the solvent was

Table 1 ^{13}C NMR[a] Chemical shifts of compounds **4a–s**, **6** and **7**

	δ_C															
Compd.	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	N–Me	Other					
4a	143.76	109.52	178.08	126.66	123.46	126.31	132.01	115.32	140.37	40.19						
4b	136.82	125.42	194.88	133.95	130.79	125.78	132.98	116.14	133.95	41.66						
4c	147.14	112.91	177.69	—	124.86	127.24	133.43	115.91	141.34	35.93						
4d	156.24	109.95	178.09	126.35	123.40	126.55	132.21	115.41	141.97	33.73	12.58	27.54[b]				
4e	156.25	112.78	177.95	125.26	123.78	127.89	132.64	115.60	139.88	35.40	74.74	126.00	126.12	128.81	142.00[c]	
4f	—	111.41	—	—	124.82	127.13	133.59	115.88	—	37.00	53.36	124.38	131.64[d]			
4g	156.47	110.30	178.89	125.75	124.01	126.01	132.75	115.65	142.21	34.82	55.00	73.22	114.13	127.78	131.77	159.42[e]
4h	154.26	112.90	178.54	125.50	123.69	125.84	132.65	115.49	141.91	35.10	72.90	123.69	134.16	135.83	147.73	149.11[f]
4i	150.00	110.52	177.71	129.20	124.48	127.09	133.20	115.74	134.94	36.80	129.32	130.62	135.39	141.65[g]		
4j	148.59	111.30	177.71	133.78	124.08	127.10	133.46	115.86	171.78	36.86	124.68	130.68	137.60	151.90	155.39	190.20[h]
4k[i]	154.37	109.41	178.50	125.46	124.04	125.88	132.87	115.61	—	34.10	62.07[j]					
4l	157.42	111.72	178.31	124.77	122.89	127.08	132.26	115.56	142.22	36.84	34.45	124.31	125.64	128.72	146.27[k]	
4m	140.82	—	—	—	124.04	125.35	132.62	115.25	—	41.05	28.92	126.85	126.99	128.15[l]		
4n	157.60	115.58	177.91	125.10	123.03	125.48	133.13	115.78	142.34	38.04	81.65	127.21	127.52	128.50	144.86[m]	
4o	150.65	144.66	162.48	122.49	121.95	124.99	130.39	119.97	140.10	29.05	13.62	22.38	31.54	50.71[n]		
4p	139.27	125.43	191.52	132.69	130.20	127.52	132.89	116.27	138.30	36.19	73.84	126.30	128.21	128.93	149.10[o]	
4q	—	125.61	192.30	—	130.06	127.08	133.14	116.29	—	36.11	71.81	123.84	134.45	147.55	149.15[p]	
4r	138.12	125.33	191.02	131.21	130.01	126.73	132.80	116.27	133.25	35.95	55.13	72.94	114.19	127.94	149.70[q]	
4s	—	110.10	—	127.60	124.44	127.09	133.13	115.73	—	36.69	55.72	114.60	133.27[r]			
6	150.76	113.08	177.93	126.43	124.22	126.77	132.90	115.69	142.83	38.24	34.26	41.26	61.85	190.31[s]		
7	146.48	111.66	176.96	126.27	124.11	126.37	132.72	115.29	140.61	35.22						

[a] δ Values are given in ppm downfield from Me_4Si. Measured in $CDCl_3$ solution at 50.3 MHz. [b] Signals due to CH_2CH_3. [c] Signals due to CHOH, 4′-CH, 2′- and 6′-CH, 3′- and 5′-CH, and 1′-C. [d] Signals due to CH–OH, 2′- and 6′-CH, and 3′- and 5′-CH. [e] Signals due to OCH_3, CHOH, 3′- and 5′-CH, 2′- and 6′-CH, 1′-C, and 4′-C. [f] Signals due to CHOH, 5′-CH, 4′-CH, 3′-C, 6′-CH, and 2′-CH. [g] Signals due to 2′- and 6′-CH, 3′- and 5′-CH, 4′-CH, and 1′-C. [h] Signals due to 5′-CH, 3′-C, 4′-CH, 6′-CH, 2′-CH, and C=O. [i] Measured in $CDCl_3$ + CD_3OD. [j] Signal due to CH_2OH. [k] Signals due to CH_3, 2′- and 6′-CH, 4′-CH, 3′- and 5′-CH, and 1′-C. [l] Signals due to CH_3, 2′- and 6′-CH, 4′-CH, and 3- and 5′-CH. [m] Signals due to COH, 2′- and 6′-CH, 4′-CH, 3′- and 5′-CH, and 1′-C. [n] Signals due to $CH_2CH_2CH_2CH_3$. [o] Signals due to CHOH, 2′- and 6′-CH, 4′-CH, 3′- and 5′-CH, and 1′-C. [p] Signals due to CHOH, 5′-CH, 4′-CH, 6′-CH, and 2′-CH. [q] Signals due to OCH_3, CHOH, 3′- and 5′-CH, 2′- and 6′-CH, and 1′-C. [r] Signals due to OCH_3, 3′- and 5′-CH, and 2′- and 6′-C. [s] Signals due to N′–CH_3, 3′-CH_2, 2′-CH, and 4′-C.

evaporated from filtrate, and the resulting residue was digested with chloroform. The chloroform solution was evaporated and the residue was purified by flash chromatography, elution with chloroform affording 1-methyl-4-quinolone **4a** (4 g, 88%), m.p. 150–151 °C (from Me_2CO/Pr^i_2O) (lit.,[17] 151–152 °C) (b.p. 185–185 °C at 0.2 mmHg), ν_{max}(film)/cm^{-1} 2990, 1625, 1585 and 1550; δ_H(200 MHz; $CDCl_3$) 3.83 (3 H, s, NCH_3), 6.32 (1 H, d, *J* 7.7, 3-H), 7.41 (1 H, dd, *J* 8.0, 7.5, 6-H), 7.43 (1 H, d, *J* 8.0 8-H), 7.56 (1 H, d, *J* 7.7, 2-H), 7.71 (1 H, ddd, *J* 8.0, 7.5, 1.6, 7-H), and 8.47 (1 H, dd, *J* 8.0 and 1.6 5-H); λ_{max}(MeOH)/nm 219, 237, 323 and 337 (log ε 4.42, 4.36, 4.19 and 4.22); *m/z* (EI, %) 160 (20), 159 ($M^{\bullet+}$, 100), 131 (90), 130 (61), 116 (11), 90 (13), 89 (20) and 77 (25).

1-*Methylquinoline*-4-*thione* **4b**.—A solution of 1-methyl-4-quinolone **4a** (1.01 g, 6.3 mmol) and Lawesson's reagent (1.25 g, 3.1 mmol) in dry pyridine (50 cm^3) was refluxed for 3 h with stirring. The solvent was removed under reduced pressure and the residue was digested with chloroform (25 cm^3). The organic solution was evaporated and the residue was purified by flash chromatography eluting with chloroform to give a yellow solid (1.07 g, 97%) identified as the quinolinethione, m.p. 210–212 °C (from Me_2CO/Pr^i_2O) (lit.,[18] 209–210 °C), ν_{max}(KBr)/cm^{-1} 1590, 1525 and 1505; δ_H(300 MHz; $CDCl_3$) 3.90 (3 H, s, NCH_3), 7.28 (1 H, d, *J* 7.0, 3-H), 7.41 (1 H, d, *J* 7.0, 2-H), 7.43–7.52 (2 H, m, 6-H and 8-H), 7.71 (1 H, ddd, *J* 8.0, 7.5 and 1.5, 7-H) and 8.98 (1 H, dd, *J* 8.0, 1.5, 5-H); λ_{max}(MeOH)/nm 259, 274, 282 and 419 (log ε 3.73, 3.74, 3.75 and 4.22); *m/z* (EI, %) 176 (12), 175 ($M^{\bullet+}$, 100), 131 (43), 130 (18) and 98 (14).

Typical Procedure for Lithiation of 1-*Methyl*-4-*quinolone and* 1-*Methylquinoline*-4-*thione and Reaction of* 2-*Lithio*-1-*methyl*-4-*quinolone and* 2-*Lithio*-1-*methylquinoline*-4-*thione with Electrophiles; Synthesis of Compounds* **4d–s** *and* **6**.—Diisopropylamine (0.24 cm^3, 1.86 mmol) was added by syringe to a solution of BuLi (1.16 cm^3, 1.86 mmol) in dry tetrahydrofuran (THF) (10 cm^3) at −78 °C and the solution was stirred at this temperature for 30 min. A solution of 1-methyl-4-quinoline **4a** (100 mg, 0.62 mmol) in THF (20 cm^3) was added very slowly, the mixture stirred for a further 30 min at −78 °C, and then a solution of the electrophile in THF was added. The reaction mixture was stirred for 30 min at −78 °C and then for 1 h at room temperature. Aqueous ammonium chloride was added and the organic solvent removed under reduced pressure. The resulting aqueous solution was extracted with methylene dichloride and the resulting organic solution dried and evaporated to afford a residue which was purified as described.

1-*Methyl*-2-(1-*methyl*-4-*oxo*-1,2,3,4-*tetrahydro*-2-*quinolyl*)-4-*quinolone* **6**. From LDA (0.62 mmol) and quinolone **4a** (1.25 mmol) was obtained a crude yellow solid (193 mg). Purification by column chromatography, eluting with CH_2Cl_2–MeOH (9:1), gave the *dimer* **6** (157 mg, 74%), m.p. 257–258 °C (from CH_2Cl_2), ν_{max}(film)/cm^{-1} 1675, 1605, 1570 and 1510; δ_H(300 MHz; $CDCl_3$) 2.91 (1 H, dd, *J* 16.0, 5.0, 3′-H), 3.03 (3 H, s, N′CH_3), 3.30 (1 H, dd, *J* 16.0, 7.0, 3′-H), 3.60 (3 H, s, NCH_3), 5.01 (1 H, dd, *J* 7.0, 5.0, 2′-H), 6.12 (1 H, s, 3-H), 6.78 (1 H, ddd, *J* 8.5, 7.0, 1.0, 6′-H), 7.37 (1 H, ddd, *J* 8.5, 7.0, 1.0, 6-H), 7.42–7.50 (2 H, m, 7′-H and 8′-H), 7.52 (1 H, dd, *J* 8.0, 1.0, 8-H), 7.68 (1 H, ddd, *J* 8.0, 7.0, 2.0, 7-H), 7.79 (1 H, dd, *J* 8.5, 2.0, 5′-H) and 8.35 (1 H, dd, *J* 8.5, 2.0, 5-H); λ_{max}($CHCl_3$)/nm 325, 339 and 382 (log ε 4.12, 4.23 and 3.65); *m/z* (EI, %) 318 ($M^{\bullet+}$, 10), 227 (43), 160 (60), 159 (100), 131 (57), 130 (37), 89 (22), 77 (27), 75 (21), 73 (23) and 40 (26) (Found: C, 74.4; H, 5.6; N, 8.6%; M^+, 318.1369. $C_{20}H_{18}N_2O_2$ requires C, 75.4; H, 5.7; N, 8.8%; *M*, 318.1368).

2-*Ethyl*-1-*methyl*-4-*quinolone* **4d**. From LDA (1.25 mmol), quinolone **4a** (0.62 mmol), then iodomethane (3.1 mmol), and after purification by column chromatography eluting with $CHCl_3$–MeOH (94:6), 2-*ethyl*-1-*methyl*-4-*quinolone* **4d** (74 mg, 64%) was isolated, m.p. 148–150 °C (from $CHCl_3$–hexane), ν_{max}($CHCl_3$)/cm^{-3} 1620 and 1590; δ_H(200 MHz; $CDCl_3$) 1.32 (3

H, t, *J* 7.5, CH_3CH_2), 2.76 (2 H, q, *J* 7.5, CH_3CH_2), 3.74 (3 H, s, NCH_3), 6.27 (1 H, s, 3-H), 7.37 (1 H, ddd, *J* 8.0, 7.5, 1.5, 6-H), 7.51 (1 H, dd, *J* 8.5, 1.5, 8-H), 7.67 (1 H, ddd, *J* 8.5, 7.5, 1.7, 7-H) and 8.44 (1 H, dd, *J* 8.0, 1.7, 5-H); λ_{max}($CHCl_3$)/nm 243, 288, 324 and 338 (log ε 4.19, 3.20, 4.02 and 4.09); *m/z* (Cl, %) 205 (M + H_4N^+, 100), 188 (M + 1, 74) and 173 (9) (Found: C, 74.1; H, 6.7; N, 7.2. $C_{12}H_{13}NO{\cdot}0.5H_2O$ requires C, 73.5; H, 7.2; N, 7.1%).

2-(α-*Hydroxybenzyl*)-1-*methyl*-4-*quinolone* **4e**. From LDA (1.25 mmol) and quinolone **4a** (0.62 mmol) then benzaldehyde (3.1 mmol), and after column chromatography on eluting with chloroform, dimer **6** (25 mg, 12%) and 2-(α-*hydroxybenzyl*)-1-*methyl*-4-*quinolone* **4e** (115 mg, 71%) were obtained; the alcohol had m.p. 177–178 °C (from $CHCl_3$–hexane), ν_{max}(film)/cm^{-1} 3220, 1620, 1600, 1560 and 1500; δ_H(200 MHz, $CDCl_3$) 3.44 (3 H, s, NCH_3), 5.88 (1 H, s, CH), 6.42 (1 H, s, 3-H), 7.08 (1 H, dd, *J* 8.2, 8-H), 7.20–7.60 (7 H, m, ArH) and 8.27 (1 H, dd, *J* 8.2, 1.5, 5-H); λ_{max}(MeOH)/nm 213, 242, 325 and 327 (log ε 4.45, 4.44, 4.06 and 4.10); *m/z* (El, %) 266 (21), 265 ($M^{\bullet+}$, 100), 248 (20), 159 (53), 130 (23), 107 (23), 105 (34), 97 (28), 91 (75), 89 (35), 79 (38) and 77 (81) (Found: C, 76.6; H, 5.6; N, 5.0. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3).

2-(α-*Hydroxy*-4-*nitrobenzyl*)-1-*methyl*-4-*quinolone* **4f**. From LDA (2.13 mmol) and quinolone **4a** (0.71 mmol) then 4-nitrobenzaldehyde (1.29 mmol) and after chromatographic purification, eluting with methylene dichloride, 4-nitrobenzyl alcohol (187 mg) was obtained, and then with CH_2Cl_2–MeOH (95:5) *benzylic alcohol* **4f** (69 mg, 36%) was isolated, δ_H(200 MHz; $CDCl_3$) 3.71 (3 H, s, NCH_3), 4.80 (1 H, br, OH), 5.31 (1 H, s, CH), 6.31 (1 H, s, 3-H), 7.50 (1 H, ddd, *J* 8.0, 7.5, 0.9, 6-H), 7.59 (1 H, dd, *J* 8.8, 0.9, 8-H), 7.81 (1 H, ddd, *J* 8.8, 7.5, 1.6, 7-H), 8.18 (2 H, d, *J* 8.9, 2′-H and 6′-H), 8.39 (2 H, d, *J* 8.9, 3′-H and 5′-H) and 8.49 (1 H, dd, *J* 8.0, 1.6, 5-H); λ_{max}(CH_2Cl_2)/nm 270 and 333 (log ε 4.03 and 3.62); *m/z* (El, %) 310 ($M^{\bullet+}$, 1.2), 308 (44), 295 (14), 279 (23), 233 (29), 192 (44), 191 (74), 167 (100), 165 (50), 152 (27), 150 (30), 132 (24), 120 (25), 115 (24), 92 (27) and 76 (79) (Found: C, 63.8; H, 4.9; N, 8.4. $C_{17}H_{14}N_2O{\cdot}0.5H_2O$ requires C, 63.7; H, 5.0; N, 8.7%).

2-(α-*Hydroxy*-4-*methoxybenzyl*)-1-*methyl*-4-*quinolone* **4g** *and* 1-*methyl*-2-(1-*methyl*-4-*oxo*-2-*quinolyl*)-4-*quinolone* **8**. From LDA (2.52 mmol) and quinolone **4a** (0.84 mmol) then 4-methoxybenzaldehyde (3.33 mmol) and after column chromatography, elution with methylene dichloride gave 1-*methyl*-2-(1-*methyl*-4-*oxo*-2-*quinolyl*)-4-*quinolone* **8** (23 mg, 8%) m.p. 234–236 °C (from $CHCl_3$–ether), ν_{max}($CHCl_3$)/cm^{-1} 1620, 1600 and 1495; δ_H(200 MHz; $CDCl_3$) 3.64 (6 H, s, 2 × NCH_3), 6.43 (2 H, s, 2 × 3-H), 7.47 (2 H, dd, *J* 8.0, 7.2, 2 × 6-H), 7.60 (2 H, d, *J* 8.5, 2 × 8-H), 7.80 (2 H, ddd, *J* 8.5, 7.2, 1.4, 2 × 7-H) and 8.52 (2 H, dd, *J* 8.0, 1.4, 2 × 5-H); λ_{max}(MeOH)/nm 214, 239, 324 and 337 (log ε 4.43, 4.47, 4.09 and 4.12); *m/z* (El, %) 317 (24), 316 ($M^{\bullet+}$, 100), 301 (90), 184 (90), 158 (25), 154 (22), 144 (22), 132 (27), 77 (53) and 57 (36) (Found: C, 71.5; H, 4.95; N, 8.2%; M^+, 316.1222. $C_{20}H_{16}N_2O_2{\cdot}H_2O$ requires C, 71.84; H, 5.42; N, 8.37%; $C_{20}H_{16}N_2O_2$ requires *M*, 316.1212), elution with CH_2Cl_2–MeOH (98:2) gave *benzylic alcohol* **4g** (35 mg, 14%), m.p. 231–233 °C (from $CHCl_3$–hexane), ν_{max}(KBr)/cm^{-1} 3120, 1625, 1580 and 1520; δ_H(200 MHz; $CDCl_3$–CD_3OD) 3.61 (3 H, s, NCH_3), 3.80 (3 H, s, OCH_3), 5.86 (1 H, s, CH), 6.66 (1 H, s, 3-H), 6.90 (2 H, d, *J* 6.8, 3′-H and 5′-H), 7.29 (2 H, d, *J* 6.8, 2′-H and 5′-H), 7.44 (1 H, dd, *J* 8.0, 7.0, 6-H), 7.50 (1 H, d, *J* 8.7, 8-H), 7.69 (1 H, ddd, *J* 8.7, 7.0, 1.5, 7-H), 8.41 (1 H, dd, *J* 8.0, 1.5, 5-H); λ_{max}(CH_2Cl_2)/nm 211, 239 and 324 (log ε 3.72, 3.70 and 3.37); *m/z* (El, %) 296 (14), 295 ($M^{\bullet+}$, 30), 159 (100), 137 (32), 132 (20), 131 (20), 130 (23), 117 (20), 109 (22), 89 (24) and 77 (37) (Found: C, 70.2; H, 5.45; N, 4.8. $C_{18}H_{17}NO_3{\cdot}0.6H_2O$ requires C, 70.6; H, 6.0; N, 4.6%), and finally, elution with CH_2Cl_2–MeOH (95:5) afforded 4-methoxybenzyl alcohol (21 mg).

2-[*Hydroxy*(3-*pyridyl*)*methyl*]-1-*methyl*-4-*quinolone* **4h**. From LDA (1.76 mmol) and quinolone **4a** (1.42 mmol) then nicotinaldehyde (4.36 mmol) and after column chromatography, on elution with $CHCl_3$–MeOH (95:5), *compound* **4h** (228 mg, 60%) was obtained, m.p. 181–182 °C (from $CHCl_3$) ν_{max}($CHCl_3$)/cm^{-1} 3200, 1620, 1580, 1550, 1480 and 1450; δ_H(200 MHz; $CDCl_3$) 3.45 (3 H, s, NCH_3), 5.91 (1 H, s, CH), 6.36 (1 H, s, 3-H), 7.05 (1 H, d, *J* 8.5, 8-H), 7.25–7.52 (3 H, m, 6-H, 7-H and 5′-H), 7.78 (1 H, d, *J* 7.9, 4′-H), 8.26 (1 H, dd, *J* 7.7 and 1.7, 5-H), 8.54 (1 H, br d, *J* 4.1, 6′-H) and 8.62 (1 H, br s, 2′-H); λ_{max}($CHCl_3$)/nm 248, 274, 328 and 414 (log ε 3.29, 3.81, 3.75 and 3.38); *m/z* (El, %) 266 ($M^{\bullet+}$, 7), 123 (15), 105 (12), 78 (54), 77 (24), 53 (21), 52 (34) and 51 (100) (Found: C, 70.5, H, 5.2; N, 10.2. $C_{16}H_{14}N_2O_2{\cdot}0.3H_2O$ requires C, 70.6; H, 5.4; N, 10.3%).

2-*Benzoyl*-1-*methyl*-4-*quinolone* **4i**. From LDA (5 mmol) and quinolone **4a** (1.24 mmol) then benzoyl chloride (2.5 mmol), and after normal work up and column chromatography elution with chloroform gave the *ketone* **4i** (54 mg, 17%), m.p. 154 °C (from CH_2Cl_2–Pr^i_2O), ν_{max}(KBr)/cm^{-1} 1700, 1620, 1600, 1500 and 1470; δ_H(200 MHz; $CDCl_3$) 3.80 (3 H, s, NCH_3), 6.34 (1 H, 3-H), 7.48–7.60 (4 H, m, 3′-H, 4′-H, 5′-H and 6′-H), 7.65–7.83 (2 H, m, 7-H and 8-H), 7.98 (2 H, dd, *J* 7.9, 1.4, 2′-H and 6′-H) and 8.50 (1 H, dd, *J* 8.0, 1.5, 5-H); *m/z* (Cl, %) 281 (M + H_4N^+, 7), 280 (26), 264 (M + 1, 7), 263 (22), 197 (100), 188 (41), 181 (23), 177 (61), 160 (23), 118 (52) and 101 (44) (Found: C. 64.8; H, 5.9; N, 4.7. $C_{17}H_{13}NO_2{\cdot}4H_2O$ requires C, 64.3; H, 6.0; N, 4.4%).

1-*Methyl*-2-*nicotinoyl*-4-*quinolone* **4j**. From LDA (1 mmol) and quinolone **4a** (0.62 mmol) then nicotinoyl chloride (2.5 mmol), following the general procedure and after purification by column chromatography elution with chloroform gave the *ketone* **4j** (41 mg, 25%), as an oil, ν_{max}(film)/cm^{-1} 1670, 1630, 1600 and 1580; δ_H(200 MHz; $CDCl_3$) 3.72 (3 H, s, NCH_3), 6.34 (1 H, s, 3-H), 7.40–7.60 (3 H, m, 6-H, 5-H and 5′-H), 7.81 (1 H, dd, *J* 8.0, 7.5, 7-H), 8.30 (1 H, dd, *J* 8.0, 1.8, 4′-H), 8.51 (1 H, d, *J* 8.0, 5-H), 8.92 (1 H, d, *J* 4.3, 6′-H) and 9.19 (1 H, d, *J* 1.8, 2′-H); λ_{max}(MeOH)/nm 237 and 318 (log ε 5.92 and 4.95); *m/z* (Cl, %) 265 (M + 1, 13), 264 (67), 236 (22), 235 (49), 207 (17), 132 (15), 130 (14), 106 (70), 98 (49) and 78 (100) (Found: C, 67.9; H, 5.1; N, 9.5. $C_{16}H_{14}N_2O_2{\cdot}H_2O$ requires C, 68.1; H, 5.0; N, 9.9%).

2-*Hydroxymethyl*-1-*methyl*-4-*quinolone* **4k**. From LDA (2.31 mmol) and quinolone **4a** (0.77 mmol) then bubbling an excess of gaseous formaldehyde there was obtained, after column chromatography eluting with CH_2Cl_2–MeOH (95:5), 2-*hydroxymethyl*-1-*methyl*-4-*quinolone* **4k** (58 mg, 40%), m.p. 190–192 °C (from Me_2CO–Pr^i_2O), ν_{max}($CHCl_3$)/cm^{-1} 3200, 1610, 1590 and 1495; δ_H(200 MHz; $CDCl_3$) 3.78 (3 H, s, NCH_3), 4.63 (2 H, s, CH_2), 6.30 (1 H, s, 3-H), 7.42 (1 H, ddd, *J* 8.0, 7.6, 0.9, 6-H), 7.54 (1 H, dd, *J* 8.5, 0.9, 8-H), 7.70 (1 H, ddd, *J* 8.5, 7.6, 1.5, 7-H) and 8.31 (1 H, dd, *J* 8.0, 1.5, 5-H); λ_{max}(CH_2Cl_2)/nm 242, 327 and 340 (log ε 3.69, 3.43 and 3.49); *m/z* (El, %) 190 (4); 189 ($M^{\bullet+}$, 31), 161 (13), 144 (44), 77 (24) and 51 (20) (Found: C, 66.9; H, 5.8; N, 6.6. $C_{11}H_{11}NO_2{\cdot}0.5H_2O$ requires: C, 66.7; H, 6.1; N, 7.0%).

2-(1-*Hydroxy*-1-*phenylethyl*)-1-*methyl*-4-*quinolone* **4l** *and* 3-(1-*hydroxy*-1-*phenylethyl*)-1-*methyl*-4-*quinolone* **4m**. From LDA (1.25 mmol) and quinolone **4a** (0.62 mmol) then acetophenone (3.2 mmol) following the general procedure and after purification by column chromatography, elution with $CHCl_3$ gave the oily *alcohol* **4m** (36 mg, 20%), ν_{max}(film)/cm^{-1} 3300, 1610, 1550, 1530 and 1480; δ_H(200 MHz; $CDCl_3$) 1.86 (3 H, s, CCH_3), 3.87 (3 H, s, NCH_3), 6.90 (1 H, br, OH), 7.10–7.60 (7 H, m, ArH), 7.56 (1 H, s, 2-H), 7.70 (1 H, ddd, *J* 8.0, 7.5, 1.5, 7-H) and 8.42 (1 H, dd, *J* 8.5, 1.0, 5-H); λ_{max}(CH_2Cl_2)/nm 244, 252, 279, 291, 329 and 344 (log ε 4.35, 4.31, 3.70, 3.68, 4.07 and 4.15); *m/z* (Found: C, 69.9; H, 6.4; N, 4.3. $C_{18}H_{17}NO_2{\cdot}6H_2O$ requires C, 69.9; H, 6.6; N, 4.5%), and on elution with $CHCl_3$–MeOH (95:5) the isomeric *alcohol* **4l** (56 mg, 31%) was obtained, m.p. 240–242 °C (from Me_2CO–Pr^i_2O), ν_{max}($CHCl_3$)/cm^{-1} 3350, 1620, 1610 and 1490; δ_H(200 MHz; $CDCl_3$) 2.00 (3 H, s, CCH_3), 3.23 (3 H, s, NCH_3), 6.50 (1 H, br,

OH), 6.71 (1 H, s, 3-H), 6.79 (1 H, dd, *J* 8.7, 1.9, 8-H), 7.20–7.32 (7 H, m, ArH) and 8.18 (1 H, dd, *J* 7.0, 1.8, 5-H); $\lambda_{max}(CH_2Cl_2)$/nm 246, 253, 328 and 340 (log ε 4.36, 4.38, 4.06 and 4.13); *m/z* (El, %) 279 ($M^{\bullet+}$, 13), 159 (28), 121 (13), 89 (25), 77 (19), 75 (45), 51 (25) and 43 (100) (Found: C, 72.0; H, 5.8; N, 4.3. $C_{18}H_{17}NO_2 \cdot 1.5H_2O$ requires C, 72.2; H, 6.2; N, 4.3%).

2-[*Hydroxy(diphenyl)methyl*]-1-*methyl*-4-*quinolone* **4n**. From LDA (1.88 mmol) and quinolone **4a** (0.62 mmol) then benzophenone (3.2 mmol) following the general procedure and after purification by column chromatography, elution with CH_2Cl_2–MeOH (98:2) gave *alcohol* **4n** (74 mg, 35%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3220, 1620, 1600 and 1560; δ_H(200 MHz; $CDCl_3$) 3.47 (3 H, s, NCH_3), 5.70 (1 H, s, OH), 6.75–7.0 (m, 2 H, 3-H and 8-H), 7.10–7.50 (2 H, m, 6-H and 7-H), 8.20 (1 H, dd, *J* 8.0 and 1.0, 5-H); λ_{max}(MeOH)/nm 327, 340 and 370 (log ε 4.23, 4.21 and 2.15); *m/z* (El, %) 342 (16), 341 ($M^{\bullet+}$, 63), 236 (29), 183 (34), 159 (870), 130 (20), 105 (100), 78 (17) and 77 (93) (Found: C, 80.7; H, 5.8; N, 4.3. $C_{23}H_{19}NO_2$ requires C, 80.9; H, 5.6; N, 4.1%).

Interaction of Quinolone **4a** *with* BuLi *and then with Benzaldehyde; 2-Butyl-1-methyl-2,3-dihydroquinolin-4-one* **7** *and 2-Butyl-1-methyl-4-quinolone* **4o**.—A solution of quinolone **4a** (100 mg, 0.62 mmol) in dry THF (15 cm^3) was slowly added to a solution of BuLi (1.56 cm^3, 2.5 mmol) in THF (15 cm^3) cooled at −75 °C, and the resulting mixture maintained at this temperature for 30 min. Benzaldehyde (0.31 cm^3, 3.1 mmol) was added in one portion and the mixture was stirred at −78 °C for a further 30 min and then at room temperature for 1 h. Aqueous ammonium chloride was added and the organic solvent was removed under reduced pressure. The aqueous solution was extracted with methylene dichloride and the resulting organic solution dried and evaporated. The residue was purified by column chromatography, elution with $CHCl_3$ gave *2-butyl-1-methyl-2,3-dihydroquinolin-4(1H)-one* **7** (15 mg, 11%), ν_{max}(film)/cm^{-1} 1673 and 1606; $\delta_H(CDCl_3)$ 0.7–0.9 (3 H, m, CH_3), 1.10–2.20 [6 H, m, $(CH_2)_3$], 2.80–3.20 (2 H, m, 3-H_2), 3.76 (3 H, s, N-CH_3), 4.10 (1 H, m, 2-H), 7.20 (1 H, m, 6-H), 7.43 (1 H, d, *J* 8.8, 8-H), 7.63 (1 H, d, *J* 8.8, 7-H) and 7.75 (1 H, d, *J* 8.0, 5-H); *m/z* (Cl, %) 218 (M + 1, 71), 217 (3), 216 (14), 176 (15) and 169 (18), and *2-butyl-1-methyl-4-quinolone* **4o** (49 mg, 36%), $\nu_{max}(CHCl_3)/cm^{-1}$ 1635 and 1575; δ_H(200 MHz; $CDCl_3$) 0.97 (3 H, t, *J* 7.3, CH_3CH_2), 1.45 (2 H, m, CH_2), 1.68 (2 H, m, CH_2), 2.81 (2 H, t, *J* 8.0, CH_2), 3.69 (3 H, s, NCH_3), 6.59 (1 H, s, 3-H), 7.26 (1 H, ddd, *J* 8.0, 7.5, 1.1, 6-H), 7.38 (1 H, dd, *J* 8.0, 1.1, 8-H), 7.57 (1 H, ddd, *J* 8.0, 7.5, 1.1, 7-H) and 7.75 (1 H, dd, *J* 8.0, 1.1, 5-H); $\lambda_{max}(CHCl_3)$/nm 216, 220, 244 and 276 (log ε 3.42, 4.27, 3.49 and 3.89); *m/z* (El, %) 218 (3), 217 ($M^{\bullet+}$, 10), 174 (43), 160 (40), 86 (21), 84 (33), 51 (32) and 49 (100); lastly, elution with $CHCl_3$–MeOH (97:3) gave 2-[hydroxy(phenyl)methyl]-1-methyl-4-quinolone **4e** (7 mg, 4%).

2-[*Hydroxy(phenyl)methyl*]-1-*methylquinoline*-4-*thione* **4p** *and 2-benzoyl-1-methyl-4-quinolone* **4l**. From LDA (1.25 mmol) and thioquinolone **4b** (0.49 mmol) then benzaldehyde (5 mmol) following the general procedure and after purification by column chromatography, elution with $CHCl_3$–MeOH 99:1 gave the *alcohol* **4p** (55 mg, 40%) as an oil, ν_{max}(film)/cm^{-1} 3200, 1570, 1520 and 1155; δ_H(200 MHz; $CDCl_3$) 3.55 (3 H, s, NCH_3), 5.97 (1 H, s, CHOH), 7.0–7.6 (8 H, m, ArH), 7.72 (1 H, s, 3-H) and 8.85 (1 H, dd, *J* 8.2, 1.5, 5-H); λ_{max}(MeOH)/nm 230, 284 and 409 (log ε 3.46, 2.84 and 3.25); *m/z* (Cl, %) 300 (M + NH_3 + 2, 0.4), 281 ($M^{\bullet+}$, 1), 153 (23), 136 (19), 93 (24) and 69 (100). After crystallization from CH_2Cl_2 the hydroxythioquinolone **4p** was converted into 2-benzoyl-1-methyl-4-quinolone **4l**.

2-[1-*Hydroxy*(3-*pyridyl*)*methyl*]-1-*methylquinoline*-4-*thione* **4q** *and 1-methyl-2-nicotinoyl-4-quinolone* **4j**. From LDA (1.1 mmol) and quinolionethione **4b** (0.33 mmol) then nicotinaldehyde (2 mmol) following the general procedure and after purification by column chromatography, elution with $CHCl_3$ gave the *alcohol* **4q** (77 mg, 82%), ν_{max}(film)/cm^{-1} 3300, 1580, 1530 and 1170; δ_H(200 MHz; $CDCl_3$) 3.63 (3 H, s, NCH_3), 6.01 (1 H, s, CHOH), 7.10–7.80 (4 H, m, ArH), 8.30–8.60 (4 H, m, ArH) and 8.82 (1 H, dd, *J* 8.3, 1.5, 5-H); λ_{max}(MeOH)/nm 230, 269, 283, 336 and 411 (log ε 4.38, 3.89, 3.90, 3.15 and 4.15); *m/z* (El, %) 282 ($M^{\bullet+}$, 1), 279 (2), 204 (4), 174 (9), 151 (14), 134 (25), 110 (11), 93 (100), 76 (33) and 74 (56). After crystallization from CH_2Cl_2 compound **4q** was converted into 1-methyl-2-nicotinoyl-4-quinolone **4j**.

2-(α-*Hydroxy*-4-*methoxybenzyl*)-1-*methylquinoline*-4-*thione* **4r** *and* 2-(4-*methoxybenzoyl*)-1-*methyl*-4-*quinoline* **4s**. From LDA (1.1 mmol) and thioquinolone **4b** (0.42 mmol) then 4-methoxybenzaldehyde (5 mmol) following the general procedure and after purification by column chromatography, elution with $CHCl_3$ gave the *alcohol* **4r** (62 mg, 46%) as an oil, ν_{max}(KBr)/cm^{-1} 3440, 1580 and 1140; δ_H(200 MHz; $CDCl_3$) (3 H, s, NCH_3), 3.76 (3 H, s, OCH_3), 5.96 (1 H, s, CHOH), 6.82 (2 H, d, *J* 8.8, 3′-H and 5′-H), 7.20–7.30 (3 H, m, 8-H, 2′-H and 6′-H), 7.40 (1 H, dd, *J* 8.0, 7.5, 6-H), 7.54 (1 H, ddd, *J* 8.0, 7.5, 1.5, 7-H), 7.78 (1 H, s, 3-H) and 8.86 (1 H, dd, *J* 7.5, 1.5, 5-H); λ_{max}(MeOH)/nm 238, 313, 372 and 399 (log ε 3.12, 2.76, 2.23 and 2.33); *m/z* (El, %) 312 (3), 311 ($M^{\bullet+}$, 2), 134 (100), 117 (22) and 73 (15) (Found: C, 68.0; H, 5.4; N, 4.1. $C_{18}H_{17}NO_2S \cdot 0.3H_2O$ requires C, 68.1; H, 5.6; N, 4.4%).

After dissolution in CH_2Cl_2, alcohol **4r** was converted into 2-(4-*methoxybenzoyl*)-1-*methyl*-4-*quinolone* **4s**, δ_H(200 MHz; $CDCl_3$) 3.68 (3 H, s, NCH_3), 3.92 (3 H, s, OCH_3), 6.34 (1 H, s, 3-H), 7.00 (2 H, d, *J* 9.0, 3′-H and 5′-H), 7.48 (1 H, dd, *J* 8.7, 7.0, 6-H), 7.56 (1 H, d, *J* 8.7, 8-H), 7.77 (1 H, ddd, *J* 8.7, 8.0, 1.9, 7-H), 7.95 (2 H, d, *J* 9.0, 2′-H and 6′-H) and 8.50 (1 H, dd, *J* 8.0, 1.9, 5-H); *m/z* (El, %) 294 (5), 293 ($M^{\bullet+}$, 27), 292 (10), 276 (12), 164 (11), 191 (14), 135 (100), 107 (11), 92 (38), 89 (28), 77 (63) and 62 (20) (Found: C, 73.5; H, 5.0; N, 5.0; $C_{18}H_{15}NO_3$ requires C, 73.7; H, 5.2; N, 4.8%).

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