CONVENIENT SYNTHESIS OF MORE COMPLEX 2-SUBSTITUTED 4(3*H*)-QUINAZOLINONES *via* LITHIATION OF 2-ALKYL-4(3*H*)-QUINAZOLINONES

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2-Methylquinazolin-4(3*H*)-one has been doubly lithiated, at nitrogen and in the 2-methyl group, with n-butylithium. The lithium reagent thus obtained reacts with a variety of electrophiles (iodomethane, D_2O, phenyl isocyanate, benzaldehyde, benzophenone, cyclopentanone, 2-butanone, carvone) to give the corresponding 2-substituted derivatives in very good yields. Reaction of the dilithio reagent with acetonitrile gives an α,β-unsaturated imine by tautomerization of the initial addition product. Double lithiation of 2-ethyl- and 2-propyl-4(3*H*)-quinazolinones can be achieved using lithium diisopropylamide and the lithiated reagents thus obtained react with similar electrophiles to give the corresponding products in very good yields. In the reaction of the dianion of the 2-ethyl-4(3*H*)-quinazolinone with iodine, an oxidatively dimerised product was obtained. Lithiation of 2-unsubstituted 4(3*H*)-quinazolinone does not take place on C-2 under similar conditions.

Key words: Quinazolinones; Metallation; Double lithiation; Nucleophilic additions; Ketones; Carbanions.

The rapid expansion of the list of functionalities capable of directing metalation[1] has made this an important strategy for the synthesis of regiospecifically substituted benzenes and heterocycles, but there are relatively few reports concerning the metalation of pyrimidine compounds[2–13]. In a continuation of our own interests in heterocyclic chemistry[14], particularly in the use of directed lithiation for heterocyclic synthesis[15], we have recently shown the lithiation of 3-acylamino-, 3-amino- and 3-methylamino-2-alkyl-4(3*H*)-quinazolinones[16–18]. Lithiation of 3-unsubstituted

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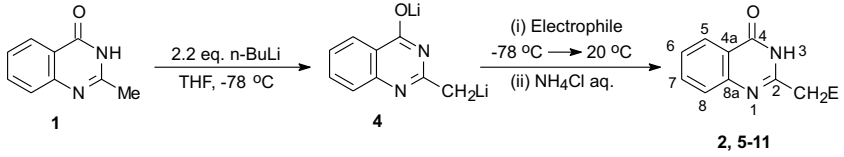
2-methyl-4(3*H*)-quinazolinone has been reported previously[19], but the lithiated species has been reacted with only a limited range of electrophiles and other 2-alkyl-4(3*H*)-quinazolinones were not investigated at all. We now report the extension of this approach to encompass a wider range of products.

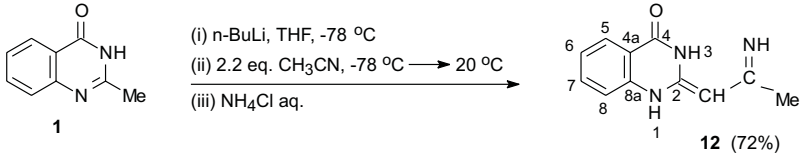
2-Alkyl-4(3*H*)-quinazolinones (**1**–**3**) were prepared according to the literature procedures[20]. Double lithiation of 2-methyl-4(3*H*)-quinazolinone (**1**) occurred smoothly and rapidly with 2.2 equivalents of n-BuLi at –78 °C in THF with no nucleophilic attack at either the carbonyl or the imine group of the quinazolinone ring. Initial addition of n-BuLi provided a reddish solution until approximately one equivalent had been added, then gave a very deep red solution of the dianion **4** as the remaining n-BuLi was added. Reactions of the dianion **4** with a range of electrophiles (iodomethane, D_2O, phenyl isocyanate, benzaldehyde, benzophenone, cyclopentanone, 2-butanone, *R*-(–)-carvone) resulted in the production of the corresponding 2-substituted 4(3*H*)-quinazolinone derivatives **2** and **5**–**11**, respectively (Scheme 1) in very good yields (Table I).



SCHEME 1

The yields of isolated, purified products were extremely good. No *N*-substitution was observed, even with excess iodomethane (3.3 equivalents) as electrophile.

Reaction of the dilithio reagent of compound **1** with excess acetonitrile (2 equivalents) proceeded in an interesting manner to give compound **12** in 72% isolated yield (Scheme 2).

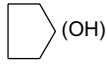
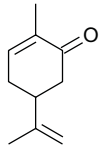
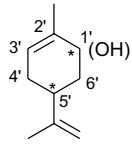


SCHEME 2

The NMR and mass spectra confirm the structure of compound **12**. The ^{1}H NMR spectrum shows the presence of three exchangeable singlets due to three NH protons which resonate in the 11.40–9.26 ppm region, while the ^{13}C NMR spectrum shows all the appropriate carbon resonances. The CI mass spectrum shows an intense pseudo molecular ion peak (MH^+) at *m/z* 202, and there is a molecular ion peak at *m/z* 201 in the EI spectrum. The accurate mass of the molecular ion confirms the formula as $C_{11}H_{11}N_3O$. The unusual stability of compound **12** is presumably a result of intramolecular hydrogen bonding.

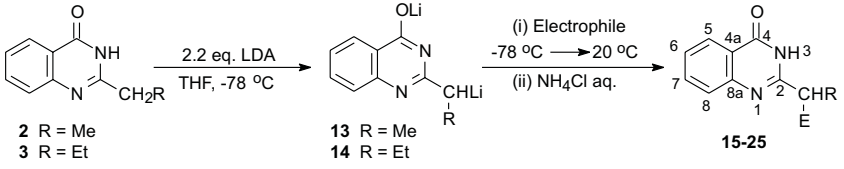
Attention was next turned to lithiation of 2-ethyl-4(3*H*)-quinazolinone (**2**) and 2-propyl-4(3*H*)-quinazolinone (**3**). It was hoped that lithiation would take place as for compound **1**, which would suggest that the process was tolerant of a variety of primary alkyl groups at position 2, but attempts to lithiate compound **2** with n-BuLi gave only low yields of the products of reaction with a number of electrophiles (D_2O, Ph_2CO and MeI). However, successful lithiation was achieved with 2.2 equivalents of LDA in THF at

TABLE I
Products from the reactions of the dilithio reagent **4** with electrophiles according to Scheme 1[a]

Compound	Electrophile	E	Yield[b], %
2	MeI	Me	89
5	D_2O	D	90
6	PhNCO	PhNHCO	80
7	PhCHO	PhCH(OH)	77
8	Ph_2CO	$Ph_2C(OH)$	79
9			81
10	EtCOMe	EtC(OH)Me	80
11			82[c]

[a] See Experimental for details. [b] Yields reported are for isolated, purified materials. [c] NMR spectra indicate a mixture of two diastereoisomers in a ratio 1 : 4.

–78 °C under nitrogen for 2 h. Initial addition of LDA provided a brownish yellow solution when approximately one equivalent had been added and then a red solution of the dilithio reagent **13** or **14** as the remaining LDA was added. Addition of iodomethane to **13** or **14** gave the corresponding *C*-methyl compounds **15** and **16** in 82 and 79% isolated yields, respectively, with no *N*-substitution, as had been observed with dianion **4**. In order to test the versatility of the intermediate dilithio reagents **13** and **14**, they were reacted with several electrophiles (Scheme 3) to give the corresponding 2-substituted 4(3*H*)-quinazolinone derivatives **15**–**25** in very good yields (Table II).



SCHEME 3

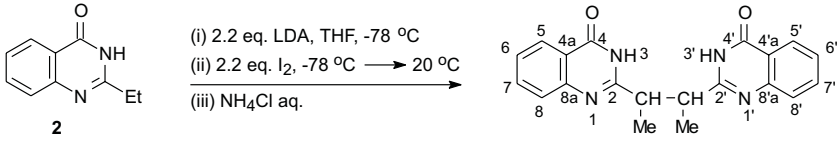
TABLE II
Products from the reactions of the dilithio reagents **13** and **14** with electrophiles according to Scheme 3[a]

Compound	R	Electrophile	E	Yield[b], %
15	Me	MeI	Me	82
16	Et	MeI	Me	79
17	Me	D_2O	D	87
18	Et	D_2O	D	77
19	Me	Ph_2CO	$Ph_2C(OH)$	78
20	Et	Ph_2CO	$Ph_2C(OH)$	88
21	Me	PhCOMe	PhC(OH)Me	70
22	Et	PhCOMe	PhC(OH)Me	77[c]
23	Me	PhCHO	PhCH(OH)	73[c]
24	Et	PhCHO	PhCH(OH)	79[c]
25	Me	PhNCO	PhNHCO	62

[a] See Experimental for details. [b] Yields reported are for isolated, purified materials. [c] NMR spectra indicate a mixture of two diastereoisomers.

The NMR spectra of compounds **22**–**24** show the expected presence of two racemic diastereoisomers in unequal proportions. However, for compound **21** the spectra indicate only one racemic diastereoisomer, which is clearly not expected when two asymmetric centres are introduced during the reaction. Similar observations have been made previously for 3-aminoquinazolinone derivatives[18]. We are currently attempting to establish the cause of the diastereoselectivity.

Reaction of the dilithio reagent of compound **2** with iodine resulted in oxidative dimerization to give compound **26** in 71% crude yield (Scheme 4). The EI spectrum of compound **26** shows an intense molecular ion peak (M^+) at *m/z* 346. After extraction with hot methanol, the yield was reduced to 60%. ^{1}H and ^{13}C NMR spectra of the product, before or after washing suggested that it was a single racemic diastereoisomer. We have not determined which one because of the low solubility of the compound, which prevented crystallisation to obtain suitable crystals for X-ray studies and also impaired the use of a chiral shift reagent in NMR studies.



SCHEME 4

Attention was next turned to lithiation of 4(3*H*)-quinazolinone itself, to see if substitution of the hydrogen at position 2 could be achieved. It was found that the double lithiation of 4(3*H*)-quinazolinone did not take place under conditions similar to those used for lithiation of compounds **1**–**3** with n-BuLi and LDA. No further attempts were made to try to find conditions under which such lithiations could be effected.

EXPERIMENTAL

Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. The laboratories of the University of Wales Cardiff carried out microanalyses. IR spectra were recorded on a Perkin–Elmer 1725X spectrometer. ^{1}H and ^{13}C NMR spectra (ppm, δ-scale; *J* in Hz) were recorded on a Bruker AC spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C measurements. Chemical shifts are reported relative to tetramethylsilane. Assignments of signals are based on coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low-resolution

mass spectra were recorded on a VG 12-253 spectrometer, electron impact (EI) at 70 eV and chemical ionization (CI) by the use of ammonia as ionization gas. Accurate mass data were obtained on a VG ZAB-E instrument. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Lithium diisopropylamide, n-butyllithium and other chemicals were obtained from Aldrich Chemical Company and n-butyllithium was estimated prior to use by the method of Watson and Eastham[21]. THF was distilled from sodium benzophenone ketyl. Other solvents were purified by standard procedures[22,23]. The IR spectra were in agreement with the assigned structure.

2-Substituted 4(3*H*)-Quinazolinones **2** and **5**–**12**. General Procedure

A 1.6 M solution of n-BuLi (2.75 ml, 4.4 mmol) was added in a dropwise manner to a stirred solution of **1** (0.32 g, 2.0 mmol) in anhydrous THF (40 ml) maintained at –78 °C under nitrogen. Formation of the dianion was observed as a very deep red solution. The mixture was stirred at –78 °C for an additional 1 h, after which an electrophile (2.2 mmol), in THF (8 ml) if solid, otherwise neat, was added. The mixture was stirred for 2 h, then removed from the cooling bath and allowed to warm to room temperature, diluted with ethyl acetate (20 ml) and quenched with aqueous saturated ammonium chloride solution (20 ml). The organic layer was washed with water (2 × 20 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The products were recrystallized from methanol to give the yields quoted in Table I.

2-Ethyl-4(3H)-quinazolinone (**2**): m.p. 236 °C (ref.[20] gives m.p. 235 °C).

2-Monodeuteriomethyl-4(3H)-quinazolinone (**5**): m.p. 238–239 °C. EIMS, *m/z*: 161. ^{1}H NMR (DMSO-d_6): 12.21 s, exch., 1 H (NH); 8.07 d, 1 H, *J* = 7.9 (H-5); 7.74 t, 1 H, *J* = 7.9 (H-7); 7.54 d, 1 H, *J* = 7.9 (H-8); 7.42 t, 1 H, *J* = 7.9 (H-6); 2.34 1 : 1 : 1 t, 2 H, *J* = 2.2 (CH_2D). ^{13}C NMR (DMSO-d_6): 161.63 s (C-4), 154.03 s (C-2), 148.80 s (C-8a), 133.96 d (C-7), 126.35 d (C-5), 125.58 d (C-6), 125.53 d (C-8), 120.62 s (C-4a), 21.31, 21.26, 20.87 1 : 1 : 1 t (CH_2D). HRMS: for $C_9H_7N_2OD$ calculated: 161.0699; found: 161.0699. Analysis: for $C_9H_7N_2OD$ (161.2) calculated: 67.07% C 5.63% H, 17.38% N; found: 67.00% C, 5.54% H, 17.33% N.

2-[(Phenylamino)carbonylmethyl]-4(3H)-quinazolinone (**6**): m.p. >250 °C. EIMS, *m/z*: 279. ^{1}H NMR (DMSO-d_6): 12.33 s, exch., 1 H (NH); 10.27 s, exch., 1 H (PhNH); 8.11 d, 1 H, *J* = 7.9 (H-5); 7.76 t, 1 H, *J* = 7.9 (H-7); 7.60 m, 3 H (H-8 and H-2 of Ph); 7.47 t, 1 H, *J* = 7.9 (H-6); 7.30 t, 2 H, *J* = 7.5 (H-3 of Ph); 7.04 t, 1 H, *J* = 7.5 (H-4 of Ph); 3.78 s, 2 H (CH_2). ^{13}C NMR (DMSO-d_6): 165.58 s (PhNHCO), 161.45 s (C-4), 152.01 s (C-2), 148.57 s (C-8a), 138.86 s (C-1 of Ph), 134.07 d (C-7), 128.56 d (C-3 of Ph), 126.62 d (C-5), 126.07 d (C-6), 125.67 d (C-8), 123.20 d (C-4 of Ph), 120.94 s (C-4a), 118.97 d (C-2 of Ph), 42.97 t (CH_2). HRMS: for $C_{16}H_{13}N_3O_2$ calculated: 279.1008; found: 279.1008. Analysis: for $C_{16}H_{13}N_3O_2$ (279.3) calculated: 68.81% C, 4.69% H, 15.04% N; found: 69.00% C, 4.47% H, 15.22% N.

2-(2-Hydroxy-2-phenylethyl)-4(3H)-quinazolinone (**7**): m.p. 204 °C. EIMS, *m/z*: 266. ^{1}H NMR (DMSO-d_6): 12.19 s, exch., 1 H (NH); 8.09 d, 1 H, *J* = 8.0 (H-5); 7.76 t, 1 H, *J* = 8.0 (H-7); 7.61 d, 1 H, *J* = 8.0 (H-8); 7.35 t, 1 H, *J* = 7.5 (H-2 of Ph); 7.27–7.22 m, 4 H (H-6, H-3 and H-4 of Ph); 5.54 s, exch., 1 H (OH); 5.19 m, 1 H (CH); 2.90 m, 2 H (CH_2). ^{13}C NMR (DMSO-d_6): 161.65 s (C-4), 155.22 s (C-2), 148.80 s (C-8a), 144.89 s (C-1 of Ph), 134.03 d (C-7), 127.95 d (C-3 of Ph), 126.87 d (C-4 of Ph), 126.63 d (C-5), 125.74 d (C-6), 125.70 d (C-8), 125.85 d (C-2 of Ph), 120.87 s (C-4a), 70.69 d (CH-OH), 44.77 t (CH_2). HRMS: for $C_{16}H_{15}N_2O_2$ calculated: 267.1134; found: 267.1134. Analysis: for $C_{16}H_{14}N_2O_2$ (266.3) calculated: 72.17% C, 5.30% H, 10.52% N; found: 72.25% C, 5.46% H, 15.52% N.

2-(2,2-Diphenyl-2-hydroxyethyl)-4(3H)-quinazolinone (**8**): m.p. 178 °C (ref.[19] gives 163–164 °C). EIMS, *m/z*: 342. ^{1}H NMR (DMSO-d_6): 12.15 s, exch., 1 H (NH); 8.01 d, 1 H, *J* = 7.9 (H-5); 7.70 t, 1 H, *J* = 7.9 (H-7); 7.53–7.11 m, 13 H (H-6, H-8, OH and 2 Ph); 3.64 s, 2 H (CH_2). ^{13}C NMR (DMSO-d_6): 166.85 s (C-4), 155.61 s (C-2), 147.36 s (C-8a), 146.59 s (C-1 of Ph), 134.34 d (C-7), 127.86 d (C-3 of Ph), 126.54 d (C-4 of Ph), 126.34 d (C-5), 126.20 d (C-6), 125.60 d (C-8), 125.48 d (C-2 of Ph), 120.59 s (C-4a), 76.84 s (C-OH), 43.76 t (CH_2). HRMS: for $C_{22}H_{19}N_2O_2$ calculated: 343.1425; found: 343.1425. Analysis: for $C_{22}H_{18}N_2O_2$ (342.4) calculated: 77.16% C, 5.30% H, 8.19% N; found: 76.95% C, 5.28% H, 8.09% N.

2-[(1-Hydroxycyclopentyl)methyl]-4(3H)-quinazolinone (**9**): m.p. 158–159 °C. EIMS, *m/z*: 244. ^{1}H NMR ($CDCl_3$): 11.81 s, exch., 1 H (NH); 8.26 d, 1 H, *J* = 8.0 (H-5); 7.76 t, 1 H, *J* = 8.0 (H-7); 7.67 d, 1 H, *J* = 8.0 (H-8); 7.49 t, 1 H, *J* = 8.0 (H-6); 4.74 s, exch., 1 H (OH); 3.06 s, 2 H (CH_2); 1.88–1.71 m, 8 H ((CH_2)$_4$). ^{13}C NMR ($CDCl_3$): 163.43 s (C-4), 155.36 s (C-2), 148.67 s (C-8a), 134.85 d (C-7), 127.12 d (C-5), 126.62 d (C-6), 126.27 d (C-8), 120.37 s (C-4a), 81.08 s (C-OH), 44.95 t (CH_2), 39.88, 23.73 2 t ((CH_2)$_4$). HRMS: for $C_{14}H_{17}N_2O_2$ calculated: 245.1290; found: 245.1290. Analysis: for $C_{14}H_{16}N_2O_2$ (244.3) calculated: 68.83% C, 6.60% H, 11.47% N; found: 68.69% C, 6.69% H, 11.60% N.

2-(2-Hydroxy-2-methylbutyl)-4(3H)-quinazolinone (**10**): m.p. 150–151 °C. EIMS, *m/z*: 232. ^{1}H NMR (DMSO-d_6): 11.77 s, exch., 1 H (NH); 8.09 d, 1 H, *J* = 8.0 (H-5); 7.77 t, 1 H, *J* = 8.0 (H-7); 7.60 d, 1 H, *J* = 8.0 (H-8); 7.46 t, 1 H, *J* = 8.0 (H-6); 4.84 s, exch., 1 H (OH); 2.75, 2.71 2 d, 2 H, *J* = 13.7 (C**H**$_2$COH); 1.50 (2 overlapping dq's, 2 H, *J* = 7.5 and 15.5 (C**H**$_2$CH$_3$); 1.16 s, 3 H, (C**H**$_3$COH); 0.90 t, 3 H, *J* = 7.5 (C**H**$_3$CH$_2$). ^{13}C NMR (DMSO-d_6): 161.24 s (C-4), 155.46 s (C-2), 148.35 s (C-8a), 134.11 d (C-7), 126.59 d (C-5), 125.88 d (C-6), 125.60 d (C-8), 120.77 s (C-4a), 77.52 s (C-OH), 45.12 t (**C**H$_2$COH), 34.39 t (**C**H$_2$CH$_3$), 25.95 q (**C**H$_3$COH), 8.16 q (**C**H$_3$CH$_2$). HRMS: for $C_{13}H_{17}N_2O_2$ calculated: 233.1290; found: 233.1290. Analysis: for $C_{13}H_{16}N_2O_2$ (232.3) calculated: 67.22% C, 6.94% H, 12.06% N; found: 67.09% C, 7.02% H, 11.92% N.

2-[(1-Hydroxy-5-isopropenyl-2-methylcyclohex-2-en-1-yl)methyl]-4(3H)-quinazolinone (**11**): m.p. 65–67 °C. EIMS, *m/z*: 310. Compound **11** appears in its NMR spectra as a mixture of two isomers, **a** and **b**, in a ratio of 1 : 4. ^{1}H NMR ($CDCl_3$): **11a**, 11.36 s, exch., 1 H (NH); 8.27 d, 1 H, *J* = 7.9 (H-5); 7.77 t, 1 H, *J* = 7.9 (H-7); 7.68 d, 1 H, *J* = 7.9 (H-8); 7.47 t, 1 H, *J* = 7.9 (H-6); 5.69 m, 1 H (H-3′); 4.62 m, 2 H (CH_2=C); 4.42 s, exch., 1 H (OH); 3.40, 2.68 2 d, 2 H, *J* = 14.6 (CH_2); 2.40 m, 1 H (H-5′); 2.13 m, 1 H (1 H of H-4′); 2.03 m, 2 H (H-6′); 1.88 s, 3 H (CH_3); 1.68 m, 4 H (1 H of H-4′ and C**H**$_3$C=CH$_2$); **11b**, 11.67 s, exch., 1 H (NH); 8.27 d, 1 H, *J* = 7.9 (H-5); 7.77 t, 1 H, *J* = 7.9 (H-7); 7.68 d, 1 H, *J* = 7.9 (H-8); 7.47 t, 1 H, *J* = 7.9 (H-6); 5.57 m, 1 H (H-3′); 4.62 m, 2 H (CH_2=C); 4.42 s, exch., 1 H (OH); 3.26, 2.98 2 d, 2 H, *J* = 14.8 (CH_2); 2.51 m, 1 H (H-5′); 2.17 m, 1 H (1 H of H-4′); 2.00 m, 2 H (H-6′); 1.84 s, 3 H (CH_3); 1.61 m, 4 H (1 H of H-4′ and CH_3C=CH$_2$). ^{13}C NMR ($CDCl_3$): **11a**, 163.07 s (C-4), 155.13 s (C-2), 148.59 s (C-8a), 148.44 s (**C**=CH$_2$), 137.08 s (C-2′), 135.17 d (C-7), 127.15 d (C-5), 126.68 d (C-6), 126.31 d (C-8), 124.99 d (C-3′), 120.75 s (C-4a), 109.48 t (**C**H$_2$=C), 72.34 s (C-1′), 44.70 t (CH_2), 40.60 t (C-6′), 36.97 d (C-5′), 30.93 t (C-4′), 20.65 q (**C**H$_3$C=CH$_2$), 17.88 q (CH_3); **11b**, 163.12 s (C-4), 154.71 s (C-2), 148.71 s (C-8a), 148.33 s (**C**=CH$_2$), 137.08 s (C-2′), 134.85 d (C-7), 127.15 d (C-5), 126.68 d (C-6), 126.36 d (C-8), 124.99 d (C-3′), 120.75 s (C-4a), 109.33 t (**C**H$_2$=C), 74.27 s (C-1′), 42.69 t (CH_2), 40.66 t (C-6′), 39.29 d (C-5′), 30.80 t (C-4′), 20.57 q (**C**H$_3$C=CH$_2$), 17.24 q (CH_3). HRMS: for $C_{19}H_{23}N_2O_2$ calculated: 311.1760; found: 311.1760. Analysis: for $C_{19}H_{22}N_2O_2$ (310.4) calculated: 73.52% C, 7.14% H, 9.03% N; found: 73.74% C, 7.39% H, 8.94% N.

2-(2-Iminopropylidene)-1,2-dihydro-4(3H)-quinazolinone (**12**): yield 72%; m.p. >250 °C. EIMS, *m/z*: 201. ^{1}H NMR (DMSO-d_6): 11.40 s, exch., 1 H (NHCO); 9.60 br s, exch., 1 H (NH); 9.26 s, exch., 1 H (NH=CH); 7.94 d, 1 H, *J* = 8.0 (H-5); 7.60 t, 1 H, *J* = 8.0 (H-7); 7.42 d, 1 H, *J* = 8.0 (H-8); 7.19 t, 1 H, *J* = 8.0 (H-6); 4.62 s, 1 H (CH); 1.94 s, 3 H (CH_3). ^{13}C NMR (DMSO-d_6): 161.68 s (C-4), 157.19 s (C=NH), 155.22 s (C-2), 149.78 s (C-8a), 133.66 d (C-7), 125.51 d (C-5), 125.12 d (C-6), 122.87 d (C-8), 118.86 s (C-4a), 83.42 d (CH), 22.19 q (CH_3). HRMS: for $C_{11}H_{11}N_3O$ calculated: 201.0900; found: 201.0900. Analysis: for $C_{11}H_{11}N_3O$ (201.2) calculated: 65.66% C, 5.51% H, 20.88% N; found: 65.53% C, 5.45% H, 20.83% N.

2-Substituted 4(3*H*)-Quinazolinones **15**–**26**. General Procedure

A 1.6 M solution of LDA in heptane (2.75 ml, 4.4 mmol) was added in a dropwise manner to a stirred solution of **2** or **3** (2.0 mmol) in anhydrous THF (40 ml) maintained at –78 °C under nitrogen. Formation of the dianion was observed as a very deep red solution. The mixture was stirred at –78 °C for 2 h, after which an electrophile (2.2 mmol), as a solution in THF (8 ml) if solid, was added. The mixture was stirred for 4 h, then removed from the cooling bath and allowed to warm to room temperature, diluted with ethyl acetate (30 ml) and quenched with aqueous saturated ammonium chloride solution (25 ml). The organic layer was washed with water (2 × 25 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The products were recrystallised from methanol to give the yields recorded in Table II.

2-(1-Methylethyl)-4(3H)-quinazolinone (**15**): m.p. 229–231 °C. EIMS, *m/z*: 188. ^{1}H NMR (DMSO-d_6): 12.13 s, exch., 1 H (NH); 8.09 d, 1 H, *J* = 8.0 (H-5); 7.75 t, 1 H, *J* = 8.0 (H-7); 7.60 d, 1 H, *J* = 8.0 (H-8); 7.44 t, 1 H, *J* = 8.0 (H-6); 2.90 sept, 1 H, *J* = 6.9 (C**H**$(CH_3)_2$); 1.28 d, 6 H, *J* = 6.9 (CH(C**H**$_3)_2$). ^{13}C NMR (DMSO-d_6): 161.88 s (C-4), 161.38 s (C-2), 148.87 s (C-8a), 133.98 d (C-7), 126.87 d (C-5), 125.70 d (C-6), 125.57 d (C-8), 120.94 s (C-4a), 33.24 d (**C**H$(CH_3)_2$), 20.31 q (CH(**C**$H_3)_2$). HRMS: for $C_{11}H_{12}N_2O$ calculated: 188.0949; found: 188.0949. Analysis: for $C_{11}H_{12}N_2O$ (188.2) calculated: 70.19% C, 6.43% H, 14.88% N; found: 70.21% C, 6.26% H, 15.00% N.

2-(1-Methylpropyl)-4(3H)-quinazolinone (**16**): m.p. 176–177 °C. EIMS, *m/z*: 202. ^{1}H NMR (DMSO-d_6): 12.16 s, exch., 1 H (NH); 8.11 d, 1 H, *J* = 8.0 (H-5); 7.77 t, 1 H, *J* = 8.0 (H-7); 7.62 d, 1 H, *J* = 8.0 (H-8), 7.46 t, 1 H, *J* = 8.0 (H-6); 2.69 sext, 1 H, *J* = 6.9 (CH); 1.82, 15.9 2 overlapping m's, 2 H (CH_2); 1.27 d, 3 H, *J* = 6.9 (C**H**$_3$CH); 0.87 t, 3 H, *J* = 7.4 (C**H**$_3$CH$_2$). ^{13}C NMR (DMSO-d_6): 161.94 s (C-4), 160.87 s (C-2), 148.93 s (C-8a), 134.12 d (C-7), 126.91 d (C-5), 125.79 d (C-6), 125.63 d (C-8), 120.91 s (C-4a), 40.34 d (CH), 27.49 t (CH_2), 18.21 q (**C**H_3CH), 11.65 q (**C**H_3CH$_2$). HRMS: for $C_{12}H_{14}N_2O$ calculated: 202.1106; found: 202.1106. Analysis: for $C_{12}H_{14}N_2O$ (202.3) calculated: 71.26% C, 6.98% H, 13.85% N; found: 71.09% C, 6.95% H, 13.66% N.

2-(1-Monodeuterioethyl)-4(3H)-quinazolinone (**17**): m.p. 235 °C. EIMS, *m/z*: 175. ^{1}H NMR (DMSO-d_6): 12.15 s, exch., 1 H (NH); 8.08 d, 1 H, *J* = 8.1 (H-5); 7.75 t, 1 H, *J* = 8.1 (H-7); 7.58 d, 1 H, *J* = 8.1 (H-8); 7.43 t, 1 H, *J* = 8.1 (H-6); 2.63 m, 1 H (CHD); 1.27 m, 3 H (CH_3). ^{13}C NMR (DMSO-d_6): 161.74 s (C-4), 158.10 s (C-2), 148.95 s (C-8a), 133.96 d (C-7), 126.71 d (C-5), 125.63 d (C-6), 125.59 d (C-8), 120.78 s (C-4a), 27.72, 27.52, 27.33 1 : 1 : 1 d (CH), 11.21 q (CH_3). HRMS: for $C_{10}H_9N_2OD$ calculated: 175.0871; found: 175.0856. Analysis: for $C_{10}H_9N_2OD$ (175.2) calculated: 68.54% C, 6.33% H, 16.00% N; found: 68.37% C, 6.21% H, 15.95% N.

2-(1-Monodeuteriopropyl)-4(3H)-quinazolinone (**18**): m.p. 207 °C. EIMS, *m/z*: 189. ^{1}H NMR (DMSO-d_6): 12.16 s, exch., 1 H, (NH); 8.07 d, 1 H, *J* = 8.0 (H-5); 7.74 t, 1 H, *J* = 8.0 (H-7);

7.58 d, 1 H, *J* = 8.0 (H-8); 7.44 t, 1 H, *J* = 8.0 (H-6); 2.57 m, 1 H (CHD); 1.75 m, 2 H (CH_2); 0.94 t, 3 H, *J* = 7.3 (CH_3). ^{13}C NMR (DMSO-d_6): 161.76 s (C-4), 157.16 s (C-2), 148.91 s (C-8a), 134.08 d (C-7), 126.90 d (C-5), 125.74 d (C-6), 125.59 d (C-8), 120.76 s (C-4a), 36.30, 35.97, 35.77 1 : 1 : 1 d (CH), 120.18 t (CH_2), 13.54 q (CH_3). HRMS: for $C_{11}H_{11}N_2OD$ calculated: 189.1012; found: 189.1012. Analysis: for $C_{11}H_{11}N_2OD$ (189.2) calculated: 69.80% C, 6.93% H, 14.81% N; found: 69.77% C, 6.88% H, 14.77% N.

2-[1-(Diphenylhydroxymethyl)ethyl]-4(3H)-quinazolinone (**19**): m.p. 181–182 °C. EIMS, *m/z*: 356. ^{1}H NMR (DMSO-d_6): 12.01 s, exch., 1 H (NH); 8.08 d, 1 H, *J* = 8.0 (H-5), 7.70–7.00 m, 14 H (H-6, H-7, H-8, OH and 2 Ph); 4.10 q, 1 H, *J* = 6.9 (CH); 1.29 d, 3 H, *J* = 6.9 (CH_3). ^{13}C NMR (DMSO-d_6): 161.85 s (C-4), 161.12 s (C-2), 148.01, 147.52 2 s (C-1 of Ph), 145.27 s (C-8a), 134.08 d (C-7), 127.94, 127.82 2 d (C-3 of Ph), 126.36 d (C-5), 126.18, 125.98 2 d (C-4 of Ph), 125.70 d (C-6), 125.68 d (C-8), 125.22, 125.06 2 d (C-2 of Ph), 120.78 s (C-4a), 78.80 s (C-OH), 44.35 d (CH), 15.43 q (CH_3). HRMS: for $C_{23}H_{21}N_2O_2$ calculated: 357.1603; found: 357.1603. Analysis: for $C_{23}H_{20}N_2O_2$ (356.4) calculated: 77.49% C, 5.66% H, 7.86% N; found: 77.45% C, 5.65% H, 7.82% N.

2-[1-(Diphenylhydroxymethyl)propyl]-4(3H)-quinazolinone (**20**): m.p. 17–175 °C. EIMS, *m/z*: 370. ^{1}H NMR ($CDCl_3$): 12.66 s, exch., 1 H (NH); 8.34 d, 1 H, *J* = 8.0 (H-5); 7.80 t, 1 H, *J* = 8.0 (H-7); 7.78–6.88 m, 12 H (H-6, H-8 and 2 Ph); 6.69 s, exch., 1 H (OH); 3.89 dd, 1 H, *J* = 3.0 and 11.0 (CH); 2.14, 1.80 2 m, 2 H (CH_2); 0.87 t, 3 H, *J* = 7.5 (CH_3). ^{13}C NMR ($CDCl_3$): 163.91 s (C-4), 159.56 s (C-2), 148.26, 147.34 2 s (C-1 of Ph), 145.12 s (C-8a), 135.11 d (C-7), 128.36, 128.04 2 d (C-3 of Ph), 127.10 d (C-5), 126.83 d (C-6), 126.62 d (C-8), 126.47, 126.16 2 d (C-4 of Ph), 125.19, 125.16 2 d (C-2 of Ph), 120.17 s (C-4a), 79.56 s (C-OH), 53.82 d (CH), 23.49 t (CH_2), 12.30 q (CH_3). HRMS: for $C_{24}H_{23}N_2O_2$ calculated: 371.1760; found: 371.1760. Analysis: for $C_{24}H_{22}N_2O_2$ (370.4) calculated: 77.81% C, 5.99% H, 7.56% N; found: 77.80% C, 5.99% H, 7.71% N.

2-(2-Hydroxy-1-methyl-2-phenylpropyl)-4(3H)-quinazolinone (**21**): m.p. 139–141 °C. EIMS, *m/z*: 294. ^{1}H NMR ($CDCl_3$): 11.75 s, exch., 1 H (NH), 8.33 d, 1 H, *J* = 8.0 (H-5); 7.82 t, 1 H, *J* = 8.0 (H-7); 7.75 d, 1 H, *J* = 8.0 (H-8); 7.58 d, 2 H, *J* = 8.4 (H-2 of Ph); 7.52 t, 1 H, *J* = 8.0 (H-6); 7.42 t, 2 H, *J* = 8.4 (H-3 of Ph); 7.31 t, 1 H, *J* = 8.4 (H-4 of Ph); 5.18 s, exch., 1 H (OH); 3.25 q, 1 H, *J* = 7.1 (CH); 1.61 s, 3 H (C**H**$_3$COH), 1.17 d, 3 H, *J* = 7.1 (C**H**$_3$CH). ^{13}C NMR ($CDCl_3$): 163.46 s (C-4), 159.72 s (C-2), 148.65 s (C-1 of Ph), 145.92 s (C-8a), 135.04 d (C-7), 128.34 d (C-3 of Ph), 127.25 d (C-4 of Ph), 126.87 d (C-5), 126.82 d (C-6), 126.39 d (C-8), 124.84 d (C-2 of Ph), 120.84 s (C-4a), 75.81 s (C-OH), 49.55 d (CH), 30.11 q (**C**H_3COH), 14.92 q (**C**H_3CH). HRMS: for $C_{18}H_{19}N_2O_2$ calculated: 295.1447; found: 295.1447. Analysis: for $C_{18}H_{18}N_2O_2$ (294.3) calculated: 73.45% C, 6.16% H, 9.52% N; found: 73.42% C, 5.99% H, 9.41% N.

2-(1-Ethyl-2-hydroxy-2-phenylpropyl)-4(3H)-quinazolinone (**22**): m.p. 139–141 °C. EIMS, *m/z*: 308. Compound **22** appears in its NMR spectra as a mixture of two isomers, **a** and **b**, in a ratio of 1 : 3. ^{1}H NMR ($CDCl_3$): **22a**, 11.72 s, exch., 1 H (NH); 8.20 d, 1 H, *J* = 8.0 (H-5); 7.87–7.29 m, 8 H (H-5, H-6, H-8 and Ph); 5.05 s, exch., 1 H (OH); 3.12 dd, 1 H, *J* = 5.8 and 9.2 (CH); 2.22 m, 1 H, 1 H (1 H of CH_2); 1.66 s, 3 H (CH_3); 1.11 m, 1 H (1 H of CH_2); 0.95 t, 3 H, *J* = 7.4 (C**H**$_3$CH$_2$); **22b**, 11.83 s, exch., 1 H (NH); 8.36 d, 1 H, *J* = 8.0 (H-5); 7.87–7.29 m, 8 H (H-5, H-6, H-8 and Ph); 5.05 s, exch., 1 H (OH); 3.04 dd, 1 H, *J* = 3.5 and 11.5 (CH); 1.92 m, 1 H, 1 H (1 H of CH_2); 1.51 s, 3 H (CH_3); 1.40 m, 1 H (1 H of CH_2); 0.72 t, 3 H, *J* = 7.4 (C**H**$_3$CH$_2$). ^{13}C NMR ($CDCl_3$): **22a**, 163.35 s (C-4), 158.90 s (C-2), 148.40 s (C-8a), 147.66 s (C-1 of Ph), 133.90 d (C-7), 128.33 d (C-3 of Ph), 127.02 d (C-5), 126.57 d (C-6), 126.46 d (C-8), 126.12 d (C-4 of Ph), 124.49 d (C-2 of Ph), 120.17 s (C-4a), 75.99 d (C-OH), 56.21 d

(CH), 27.59 q (CH_3), 22.17 t (CH_2), 12.33 q (**C**H_3CH_2); **22b**, 163.39 s (C-4), 158.81 s (C-2), 148.61 s (C-8a), 146.23 s (C-1 of Ph), 135.05 d (C-7), 128.33 d (C-3 of Ph), 127.84 d (C-5), 127.35 d (C-6), 126.82 d (C-8), 126.37 d (C-4 of Ph), 124.81 d (C-2 of Ph), 120.82 s (C-4a), 75.99 s (C-OH), 57.23 d (CH), 30.47 q (CH_3), 22.33 t (CH_2), 12.09 q (**C**H_3CH_2). HRMS: for $C_{19}H_{21}N_2O_2$ calculated: 309.1603; found: 309.1603.

2-(2-Hydroxy-1-methyl-2-phenylethyl)-4(3H)-quinazolinone (**23**): m.p. 181–182 °C. EIMS, *m/z*: 280. Compound **23** appears in its NMR spectra as a mixture of two isomers, **a** and **b**, in a ratio of 1 : 2. ^{1}H NMR ($CDCl_3$): **23a**, 12.05 s, exch., 1 H (NH); 8.03 d, 1 H, *J* = 8.0 (H-5); 7.73 t, 1 H, *J* = 8.0 (H-7); 7.59 d, 1 H, *J* = 8.0 (H-8); 7.48–7.13 m, 6 H (H-6 and Ph); 5.49 d, exch., 1 H, *J* = 4.6 (OH); 4.99 dd, 1 H, *J* = 4.6 and 10.9 (C**H**OH); 3.00 dq, 1 H, *J* = 6.9 and 10.9 (C**H**CH_3); 1.25 d, 3 H, *J* = 6.9 (CH_3); **23b**, 12.12 s, exch., 1 H (NH); 8.11 d, 1 H, *J* = 8.0 (H-5); 7.76 t, 1 H, *J* = 8.0 (H-7); 7.63 d, 1 H, *J* = 8.0 (H-8); 7.48–7.13 m, 6 H (H-6 and Ph); 5.46 d, exch., 1 H, *J* = 4.2 (OH); 4.80 dd, 1 H, *J* = 4.6 and 9.4 (C**H**OH); 3.00 dq, 1 H, *J* = 7.0 and 9.4 (C**H**CH_3); 0.96 d, 3 H, *J* = 7.0 (CH_3). ^{13}C NMR ($CDCl_3$): **23a**, 161.58 s (C-4), 158.99 s (C-2), 148.60 s (C-8a), 143.69 s (C-1 of Ph), 133.99 d (C-7), 127.54 d (C-3 of Ph), 127.25 d (C-5), 126.84 d (C-6), 126.64 d (C-4 of Ph), 125.74 d (C-8), 125.48 d (C-2 of Ph), 120.79 s (C-4a), 74.06 d (CHOH), 46.13 d (**C**HCH$_3$), 13.51 q (CH_3); **23b**, 161.69 s (C-4), 160.20 s (C-2), 149.01 s (C-8a), 143.78 s (C-1 of Ph), 133.99 d (C-7), 127.96 d (C-3 of Ph), 127.25 d (C-5), 126.84 d (C-6), 126.70 d (C-4 of Ph), 125.74 d (C-8), 125.60 d (C-2 of Ph), 121.03 s (C-4a), 76.07 d (CHOH), 46.84 d (**C**HCH$_3$), 15.71 q (CH_3). HRMS: for $C_{17}H_{17}N_2O_2$ calculated: 281.1290; found: 281.1290. Analysis: for $C_{17}H_{16}N_2O_2$ (280.3) calculated: 72.84% C, 5.75% H, 9.99% N; found: 72.88% C, 5.97% H, 10.06% N.

2-(1-Ethyl-2-hydroxy-2-phenylethyl)-4(3H)-quinazolinone (**24**): m.p. 72–74 °C. EIMS, *m/z*: 294. Compound **24** appears in its NMR spectra as a mixture of two isomers, **a** and **b**, in a ratio of 1 : 2. ^{1}H NMR ($CDCl_3$): **24a**, 11.70 s, exch., 1 H (NH); 8.29 d, 1 H, *J* = 8.0 (H-5); 7.79–7.13 m, 8 H (H-6, H-7, H-8 and Ph); 5.11 br s, exch., 1 H (OH); 4.85 br s, 1 H (C**H**OH); 3.02 m, 1 H (C**H**CH_2); 1.95 m, 1 H (1 H of CH_2); 1.75 m, 1 H (1 H of CH_2); 0.97 t, 1 H, *J* = 7.5 (CH_3); **24b**, 11.78 s, exch., 1 H (NH); 8.24 d, 1 H, *J* = 8.0 (H-5); 7.79–7.13 m, 8 H (H-6, H-7, H-8 and Ph); 5.28 d, exch., 1 H, *J* = 2.2 (OH); 4.78 d, 1 H, *J* = 7.2 (C**H**OH); 2.94 m, 1 H (C**H**CH_2); 1.75 m, 1 H, (1 H of CH_2); 1.25, 1.75 m, 1 H (1 H of CH_2); 0.80 t, 1 H, *J* = 7.5 (CH_3). ^{13}C NMR ($CDCl_3$): **24a**, 163.53 s (C-4), 158.88 s (C-2), 148.69 s (C-8a), 142.76 s (C-1 of Ph), 134.91 d (C-7), 128.36 d (C-3 of Ph), 127.48 d (C-5), 127.78 d (C-4 of Ph), 126.58 d (C-6), 126.26 d (C-8), 126.01 d (C-2 of Ph), 120.67 s (C-4a), 75.05 d (CHOH), 54.00 d (**C**HCH$_2$), 19.69 t (CH_2), 11.90 q (CH_3); **24b**, 163.53 s (C-4), 157.96 s (C-2), 148.62 s (C-8a), 141.62 s (C-1 of Ph), 134.81 d (C-7), 128.26 d (C-3 of Ph), 127.41 d (C-5), 127.20 d (C-4 of Ph), 126.69 d (C-6), 126.33 d (C-8), 125.84 d (C-2 of Ph), 120.80 s (C-4a), 74.20 d (CHOH), 53.43 d (**C**HCH$_2$), 24.94 t (CH_2), 11.96 q (CH_3). HRMS: for $C_{18}H_{19}N_2O_2$ calculated: 295.1447; found: 295.1442.

2-(1-Phenylaminocarbonylethyl)-4(3H)-quinazolinone (**25**): m.p. >250 °C. EIMS, *m/z*: 293. ^{1}H NMR (DMSO-d_6): 12.17 s, exch., 1 H (NH); 10.11 s, exch., 1 H (PhNH); 8.09 d, 1 H, *J* = 8.0 (H-5); 7.76 t, 1 H, *J* = 8.0 (H-7); 7.61 m, 3 H (H-8 and H-2 of Ph); 7.47 t, 1 H, *J* = 8.0 (H-6); 7.28 t, 2 H, *J* = 7.6 (H-3 of Ph); 7.03 t, 1 H, *J* = 7.6 (H-4 of Ph); 3.90 q, 1 H, *J* = 7.1 (CH); 1.56 d, 3 H, *J* = 7.1 (CH_3). ^{13}C NMR (DMSO-d_6): 168.81 s (CONHPh), 161.54 s (C-4), 155.55 s (C-2), 148.47 s (C-8a), 139.02 s (C-1 of Ph), 134.06 d (C-7), 128.48 d (C-3 of Ph), 127.03 d (C-5), 126.13 d (C-6), 125.61 d (C-8), 123.13 d (C-4 of Ph), 121.12 s (C-4a), 119.13 d (C-2 of Ph), 46.22 d (CH), 15.63 q (CH_3). HRMS: for $C_{17}H_{16}N_3O_2$ calculated: 294.1243;

found: 294.1243. Analysis: for $C_{17}H_{15}N_3O_2$ (293.3) calculated: 69.61% C, 5.15% H, 14.33% N; found: 69.40% C, 5.10% H, 14.10% N.

2,2′-(2,3-Butanediyl)bis-4(3H)-quinazolinone (**26**): yield 60%, m.p. >250 °C. EIMS, *m/z*: 346. ^{1}H NMR (DMSO-d_6): 12.26 s, exch., 2 H (2 NH); 8.02 d, 2 H, *J* = 8.0 (H-5 and H-5′); 7.70 t, 2 H, *J* = 8.0 (H-7 and H-7′); 7.51 d, 2 H, *J* = 8.0 (H-8 and H-8′); 7.40 t, 2 H, *J* = 8.0 (H-6 and H-6′); 3.36 m, 2 H (2 CH); 1.30 d, 6 H, *J* = 6.4 (2 CH_3). ^{13}C NMR (DMSO-d_6): 161.58 s (C-4 and C-4′), 159.90 s (C-2 and C-2′), 148.48 s (C-8a and C-8a′), 134.10 d (C-7 and C-7′), 126.69 d (C-5 and C-5′), 125.87 d (C-6 and C-6′), 125.54 d (C-8 and C-8′), 120.67 s (C-4a and C-4a′), 41.20 d (CH), 15.40 q (CH_3). HRMS: for $C_{20}H_{18}N_4O_2$ calculated: 346.1430; found: 346.1430. Analysis: for $C_{20}H_{18}N_4O_2$ (346.4) calculated: 69.34% C, 5.24% H, 16.18% N; found: 69.33% C, 5.03% H, 15.92% N.

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