Regiospecific electrophilic substitution of aminoquinazolinones: directed lithiation of 3-(pivaloylamino)- and 3-(acetylamino)-2-methylquinazolin-4(3*H*)-ones[1]

Keith Smith,*[a] Gamal A. El-Hiti,[a] Mohamed A. Abdo[b] and Mohamed F. Abdel-Megeed[b]
[a] *Department of Chemistry, University of Wales Swansea,† Swansea SA2 8PP, UK*
[b] *Department of Chemistry, Faculty of Science, Tanta University, Tanta, Egypt*

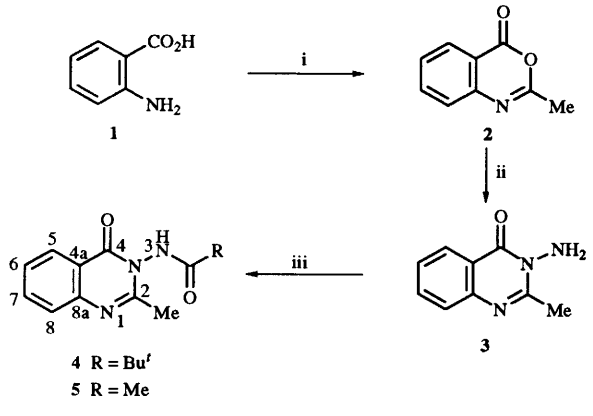
The 2-methyl group in 3-(pivaloylamino)- and in 3-(acetylamino)-2-methylquinazolin-4(3*H*)-ones has been lithiated with butyllithium. The lithium reagents thus obtained react with a variety of electrophiles (benzophenone, methyl iodide, D_2O, cyclohexanone, acetophenone, phenyl isocyanate) to give the corresponding substituted derivatives in very good yields. The amide group has been cleaved in good yield under basic conditions for one model case to provide convenient access to 3-amino-2-ethylquinazolin-4(3*H*)-one. The NMR spectra of the 2-substituted 3-acylaminoquinazolin-4(3*H*)-ones show diastereotopism of the CH_2 group at position 2.

Introduction

The use of directing groups to facilitate lithiation followed by reaction of the organolithium compound thus obtained with electrophiles has found wide application in a variety of synthetic transformations.[2-4] In particular, the pivaloylamino group is useful for directed *ortho* lithiation of aromatic compounds[4] and has been applied to pyridine derivatives.[5,6] However, there are relatively few examples of the use of such groups for directed lithiation of more complicated heterocyclic compounds. The recent report of the synthesis of a series of 11-substituted dibenzoxazepines *via* directed lithiation utilizing the *N*-BOC group as an activator,[7] and our continuing interests in heterocyclic chemistry[8] and the use of directed lithiation for organic synthesis,[9] prompt us to report our studies on the directed lithiation of 2-(acylamino)-2-methylquinazolin-4(3*H*)-ones. Compounds possessing this ring system show a variety of biological activities,[10] which provides additional impetus for the development of new synthetic approaches to substituted derivatives.

Results and discussion

3-(Pivaloylamino)-2-methylquinazolin-4(3*H*)-one **4** and 3-(acetylamino)-2-methylquinazolin-4(3*H*)-one **5**[11] were synthesized according to Scheme 1.

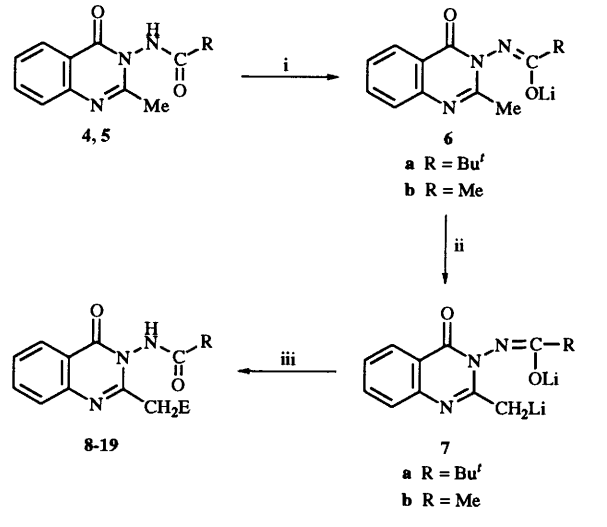


Scheme 1 *Reagents and conditions:* i, Ac_2O, reflux; ii, N_2H_4; iii, acylating agent (pivaloyl chloride or Ac_2O)

† Formerly known as the University College of Swansea.

It was hoped that lithiation would take place as for pivaloylaminobenzenes, so that substitution at the methyl group at position 2 could be achieved,[4] but it was recognized that complications might arise from the fact that the acylamino group was part of an acylhydrazine unit or from the presence of the ring carbonyl group. Fortunately, in practice lithiation of **4** and **5** occurred smoothly and rapidly with BuLi (2 equiv.) at −78 °C in THF, with no nucleophilic attack of BuLi at either the carbonyl group of the acylamino unit or that of the quinazolinone ring. Surprisingly, there was also no lithiation at the methyl group of the acetylamino unit in compound **5**. Such a side reaction is generally encountered in simple acetanilides, which accounts for the preferred use of the pivaloylamino group in directed lithiation reactions.[4] There is still discussion of the fundamental reasons for the enhanced rate and selectivity of lithiation proximate to electron-rich centres,[12] but operation of the effect would be expected to convert the monolithio derivatives **6** into dilithio derivatives **7** in which the additional lithiation has occurred at the 2-methyl group (Scheme 2). This was found to be the case by trapping of the dilithio species with methyl iodide to give 3-acylamino-2-ethylquinazolin-4(3*H*)-ones.

Reaction of the dilithio species **7** with a range of electrophiles (benzophenone, methyl iodide, D_2O, cyclohexanone, aceto-



Scheme 2 *Reagents and conditions:* i, BuLi, THF, −78 °C; ii, BuLi, THF, −78 °C; iii, electrophile, −78 °C

Table 1 Products from reaction of dilithio compounds **7a** and **7b** with electrophiles

Product	R	Electrophile	E	Yield (%)[a]
8	Bu^t[b]	Ph_2CO	$Ph_2C(OH)$	83
9	Bu^t[b]	Me	Me	89
10	Bu^t[b]	D_2O	D	88
11	Bu^t[b]	$CH_2(CH_2)_4CO$	$CH_2(CH_2)_4COH$	80
12	Bu^t[b]	PhCOMe	PhC(OH)Me	81
13	Bu^t[b]	PhNCO	PhNHCO	84
14	Me[c]	Ph_2CO	$Ph_2C(OH)$	80
15	Me[c]	MeI	Me	75
16	Me[c]	D_2O	D	74
17	Me[c]	$CH_2(CH_2)_4CO$	$CH_2(CH_2)_4COH$	79
18	Me[c]	PhCOMe	PhC(OH)Me	84
19	Me[c]	PhNCO	PhNHCO	83

[a] Yields reported are for isolated and purified materials. [b] Compound **7a** is the starting material. [c] Compound **7b** is the starting material.

phenone, phenyl isocyanate) resulted in the production of the corresponding 2-substituted quinazolin-4(3*H*)-one derivatives **8–19** in very good yields (Table 1).

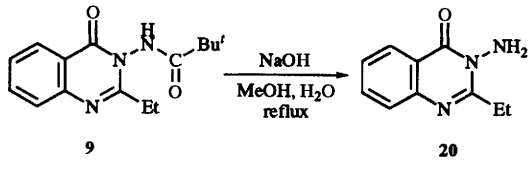
The yields of isolated, purified products **8–19** were extremely good, as indicated in Table 1. The fact that the yields were almost as good in the acetylamino series as they were in the pivaloylamino series was surprising, as was the fact that no *N*-substitution was observed with iodomethane as electrophile. We tentatively ascribe these features to the modified characteristics of the lithiated acylamino group, which is part of an acylhydrazine unit, the other nitrogen of which is flanked by two electron-withdrawing carbonyl or pseudo-carbonyl groups.

The NMR spectra of most of the compounds **8–19** (see Experimental section) show interesting features. Except for the cases in which the electrophile was D_2O (*i.e.* compounds **10** and **16**) the two hydrogen atoms of the CH_2 group at position 2 occur as independent, coupled signals, suggesting that they are diastereotopic. No such diastereotopism is observed in the ^1H NMR spectrum of 2-ethyl(pivaloylamino)benzene and related compounds.

In keeping with the diastereotopism of the CH_2 group, for compounds **8** and **14** the two phenyl groups appear as separated signals, and for compounds **11** and **17** the two sides of the cyclohexane ring appear as separate signals in their NMR spectra. For compounds **12** and **18** the extra complication of the presence of an asymmetric carbon atom causes the appearance in the NMR spectra of two diastereoisomers with unequal proportions.

In order to clarify these phenomena we have carried out variable-temperature ^1H NMR measurements and an X-ray crystal structure determination on compound **8**. The crystal structure clearly shows that the plane of the aromatic ring is orthogonal to the plane of the Bu^{t}CONH group.‡ This renders the N–N bond as a chiral axis. Orthogonal conformations are known to be significantly more stable than their co-planar counterparts for *N,N'*-diacylhydrazines, which has resulted in measured barriers to rotation about the N–N bond[13] as high as 96 kJ mol^{-1}. In the case of compound **8** the ^1H NMR spectrum recorded at 150 °C showed significant line-broadening indicative of the onset of equilibration *via* rotation about the N–N bond, thereby confirming the origin of the non-equivalence of the CH_2 hydrogen atoms.

In order to render the synthetic approach described in this report even more valuable, it would be useful if the acyl group could be removed to reveal a free NH_2 group available for further reaction without the ring system itself being damaged. This turned out to be quite straightforward. The acylhydrazide group could be cleaved by treatment with alkali. Using compound **9** as the model, we found that sodium hydroxide in aqueous methanol at reflux removed the acyl group to give 3-amino-2-ethylquinazolin-4(3*H*)-one **20** in good yield (Scheme 3).



9 **20**

Scheme 3

Conclusion

Directed lithiation of 3-acylamino-2-methylquinazolin-4(3*H*)-ones provides useful access to more complicated 2-substituted 3-acylamino- or 2-substituted 3-aminoquinazolin-4(3*H*)-ones. This should be beneficial for the synthesis of analogues with potentially useful pharmacological properties.

Experimental

Melting points were determined on an electrothermal digital melting point apparatus and are reported uncorrected. IR spectra were recorded on a Perkin-Elmer 1725X spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C measurement. Chemical shifts are reported in parts per million 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 use of ammonia as ionizing gas. Accurate mass data were obtained on a VG ZAB-E-instrument. Elemental analyses were obtained from the laboratories of the University of Wales, Cardiff. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Butyllithium was obtained from Aldrich Chemical Company and was estimated prior to use by the method of Watson and Eastham.[14] THF was distilled from sodium benzophenone ketyl. Other chemicals were obtained from Aldrich Chemical Company and used without further purification. Solvents were purified by standard procedures.[15,16]

‡ The structure was determined by the EPSRC crystallography service in Cardiff; details will be published as part of a more extensive study in due course.

2-Methyl-3-pivaloylaminoquinazolin-4(3*H*)-one 4
A stirred mixture of **3** (6.4 g, 36.3 mmol), pivaloyl chloride (4.8 g, 39.4 mmol) and triethylamine (8 cm^3) in anhydrous toluene (80 cm^3) was heated under reflux for 2 h. The organic layer was washed twice with saturated aqueous $NaHCO_3$ (20 cm^3) and water (25 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Crystallization of the residue from ethyl acetate gave white crystals (8.9 g, 34.0 mmol, 94%), mp 161–163 °C; $\delta_H(CDCl_3)$ 8.51 (s, exch., 1 H, NH), 8.11 (d, *J* 7.9, 1 H, 5-H), 7.70 (t, *J* 7.9, 1 H, 7-H), 7.55 (d, *J* 7.9, 1 H, 8-H), 7.41 (t, *J* 7.9, 1 H, 6-H), 2.39 (s, 3 H, CH_3) and 1.36 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ 178.88 (s, C=O), 160.19 (s, C-4), 155.40 (s, C-2), 146.97 (s, C-8a), 134.85 (d, C-7), 127.17 (d, C-5), 126.57 (d, C-6), 126.55 (d, C-8), 120.53 (s, C-4a), 38.99 [s, $C(CH_3)_3$], 27.18 [q, $C(CH_3)_3$] and 21.08 (q, CH_3); *m/z* (EI) 259 (M^+, 5%), 202 (10), 175 (17), 146 (25), 117 (12) and 57 (100); *m/z* (CI) 260 (MH^+, 100%), 176 (5), 161 (50), 102 (25) (Found: M^+, 259.1321. Calc. for $C_{14}H_{17}N_3O_2$: 259.1321) (Found: C, 64.8; H, 6.5; N, 16.2. Calc. for $C_{14}H_{17}N_3O_2$: C, 64.86; H, 6.56; N, 16.21%); ν_{max}(KBr disc)/cm^{-1} 3443, 1710, 1665, 1606 and 1568.

3-Acetylamino-2-methylquinazolin-4(3*H*)-one 5
Compound **5** was prepared according to the literature method as white crystals, mp 175–176 °C (lit.,[11] 176.5 °C).

General procedure for the synthesis 2-substituted quinazolin-4(3*H*)-ones
To a cooled (−78 °C), stirred solution of **4** or **5** (2 mmol) in THF (20 cm^3) under nitrogen, was added a solution of BuLi (1.6 mol dm^{-3}; 2.56 cm^3, 4.2 mmol) in hexane. Formation of the dianion was observed as an orange–red solution. The mixture was stirred at −78 °C for an additional 30 min, after which an electrophile (2.1 mmol; in solution in THF, if solid) was added. The mixture was stirred for 1 h and then removed from the cooling bath and allowed to warm to room temperature; it was then diluted with ether (15 cm^3) and quenched with aq. saturated ammonium chloride (15 cm^3). The organic layer was separated, washed with water (2 × 20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The products obtained were recrystallized from ethyl acetate to give white crystals.

2-(2-Hydroxy-2,2-diphenylethyl)-3-pivaloylaminoquinazolin-4(3*H*)-one 8. Mp 193–194 °C; $\delta_H(CDCl_3)$ 8.22 (s, exch., 1 H, NH), 7.98 (d, *J* 7.9, 1 H, 5-H), 7.14 (m, 13 H, 6-H, 7-H, 8-H and ArH) 6.97 (s, exch., 1 H, OH), 3.70, 3.59 (2 d, *J* 17.0, 2 H, CH_2) and 1.34 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ 179.18 (s, C=O), 159.62 (s, C-4), 156.15 (s, C-2), 146.81 (s, C-1 of one Ph ring), 146.34 (s, C-1 of other Ph ring), 145.18 (s, C-8a), 134.85 (d, C-7), 128.39 (d, C-5), 127.95 (d, C-2 of a Ph), 127.81 (d, C-2 of a Ph), 127.05 (d, C-3 of a Ph), 126.91 (d, C-3 of a Ph), 126.88 (d, C-4 of a Ph), 126.58 (d, C-4 of a Ph), 126.02 (d, C-6), 125.61 (d, C-8), 120.27 (s, C-4a), 77.24 (s, C–OH), 41.37 (t, CH_2), 39.00 [s, $C(CH_3)_3$] and 27.17 [q, $C(CH_3)_3$]; *m/z* (EI) 423 ($M^+ - H_2O$, 1%), 341 (20), 260 (10), 202 (15), 182 (50), 105 (80), 77 (65), 57 (100); *m/z* (CI), 442 (MH^+, 7%), 424 (5), 325 (4), 260 (100), 200 (30) and 187 (70) (Found: MH^+, 442.2131. Calc. for $C_{27}H_{28}N_3O_3$: 442.2131) (Found: C, 73.2; H, 6.3; N, 9.3. Calc. for $C_{27}H_{27}N_3O_3$: C, 73.46; H, 6.12; N, 9.52%); ν_{max}(KBr disc)/cm^{-1} 3327, 1710, 1673, 1608 and 1571.

2-Ethyl-3-pivaloylaminoquinazolin-4(3*H*)-one 9. Mp 194–195 °C; $\delta_H(CDCl_3)$ 8.42 (s, exch., 1 H, NH), 8.10 (d, *J* 8.0, 1 H, 5-H), 7.69 (t, *J* 8.0, 1 H, 7-H), 7.59 (d, *J* 8.0, 1 H, 8-H), 7.39 (t, *J* 8.0, 1 H, 6-H), 2.68, 2.65 (two overlapping double quartets, *J* 7.5 and 15.0, 2 H, CH_2), 1.36 [s, 9 H, $C(CH_3)_3$] and 1.26 (t, *J* 7.4, 3 H, CH_3); $\delta_C(CDCl_3)$ 179.00 (s, C=O), 160.42 (s, C-4), 158.57 (s, C-2), 147.07 (s, C-8a), 134.73 (d, C-7), 127.48 (d, C-5), 126.52 (d, C-6), 126.48 (d, C-8), 120.48 (s, C-4a), 38.94 [s, $C(CH_3)_3$], 27.21 [q, $C(CH_3)_3$] and 26.67 (t, CH_2); *m/z* (EI) 273 (M^+, 10%), 216 (7), 189 (5), 179 (10), 160 (5), 130 (10), 119 (10) and 57 (100); *m/z* (CI), 274 (MH^+, 100%), 175·(30), 119 (5) and 102 (5) (Found: MH^+, 274.1556. Calc. for $C_{15}H_{20}N_3O_2$: 274.1556) (Found: C, 66.0; H, 7.4; N, 15.3. Calc. for $C_{15}H_{19}N_3O_2$: C, 65.93; H, 6.96; N, 15.38%); ν_{max}(KBr disc)/cm^{-1} 3283, 1709, 1674, 1605 and 1568).

2-[$^2H_1$]Methyl-3-pivaloylaminoquinazolin-4(3*H*)-one 10. Mp 162–163 °C; $\delta_H(CDCl_3)$ 8.31 (s, exch., 1 H, NH), 8.15 (d, *J* 8.0, 1 H, 5-H), 7.73 (t, *J* 8.0, 1 H, 7-H), 7.60 (d, *J* 8.0, 1 H, 8-H), 7.42 (t, *J* 8.0, 1 H, 6-H), 2.42 (1:1:1t, *J* 2.0, 2 H, CH_2D) and 1.39 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$, 179.01 (s, C=O), 160.19 (s, C-4), 155.34 (s, C-2), 147.01 (s, C-8a), 134.88 (d, C-7), 127.19 (d, C-5), 126.66 (d, C-6), 126.61 (d, C-8), 120.56 (s, C-4a), 39.00 [s, $C(CH_3)_3$], 27.22 [q, $C(CH_3)_3$], 21.10, 20.90 and 20.70 (CH_2D); *m/z* (EI) 260 (M^+, 5%), 203 (5), 176 (10), 147 (15), 118 (10), 57 (100); *m/z* (CI), 261 (MH^+, 100%), 162 (35), 119 (5) and 102 (5) (Found: MH^+, 261.1462. Calc. for $C_{14}H_{17}N_3O_2$: 261.1462); ν_{max}(KBr disc)/cm^{-1} 3284, 1700, 1665, 1605 and 1568.

2-[(1-Hydroxycyclohexyl)methyl]-3-pivaloylaminoquinazolin-4(3*H*)-one 11. Mp 179–181 °C; $\delta_H(CDCl_3)$ 9.12 (s, exch., 1 H, NH), 7.99 (d, *J* 8.0,1 H, 5-H), 7.60 (t, *J* 8.0, 1 H, 7-H), 7.46 (d, *J* 8.0, 1 H, 8-H), 7.29 (t, *J* 8.0, 1 H, 6-H), 5.19 (s, exch., 1 H, OH), 2.84, 2.74 (2 d, *J* 16.2, 2 H, CH_2), 1.73–1.43 [m, 10 H, $(CH_2)_5$] and 1.33 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ 177.77 (s, C=O), 159.58 (s, C-4), 156.17 (s, C-2), 145.54 (s, C-8a), 134.58 (d, C-7), 126.88 (d, C-5), 126.75 (d, C-6), 126.59 (d, C-8), 120.56 (S, C-4a), 71.63 (s, C-OH), 41.98 (t, CH_2), 38.83, 36.89, 25.26, 22.11, 21.90 [5 t, $(CH_2)_5$], 38.70 [s, $C(CH_3)_2$] and 27.14 [q, $C(CH_3)_3$]; *m/z* (EI) 358 (MH^+, 5%), 340 (2), 301 (1), 259 (20), 242 (5), 202 (15) and 57 (100); *m/z* (CI) 358 (MH^+, 100%); 340 (10), 318 (20), 260 (50) and 119 (16); (Found: MH^+, 358.2131. Calc. for $C_{20}H_{28}N_3O_3$: 358.2131) (Found: C, 67.0; H, 7.7; N, 11.9. Calc. for $C_{20}H_{27}N_3O_3$: C, 67.22; H, 7.56; N, 11.76%); ν_{max}(KBr disc)/cm^{-1} 3241, 1713, 1683, 1605 and 1571.

2-(2-Hydroxy-2-phenylpropyl)-3-pivaloylaminoquinazolin-4(3*H*)-one 12. Mp 91–92 °C; NMR shows a mixture of 2 diastereoisomers a and b, in a ratio 2:5; $\delta_H(CDCl_3)$ of **12a**, 8.40 (s, exch., 1 H, NH), 8.02 (d, *J* 8.0, 1 H, 5-H), 7.66 (t, *J* 8.0, 1 H, 7-H), 7.54 (d, *J* 8.0, 1 H, 8-H), 7.45–7.16 (m, 6 H, 6-H and Ph), 6.06 (s, exch., 1 H, OH), 3.26, 3.18 (2 d, *J* 17.0, 2 H, CH_2), 1.59 (s, 3 H, CH_3) and 1.37 [s, 9 H, $C(CH_3)_3$]; $\delta_H(CDCl_3)$ of **12b**, 8.23 (s, exch., 1 H, NH), 8.02 (d, *J* 8.0, 1 H, 5-H), 7.66 (t, *J* 8.0, 1 H, 7-H), 7.54 (d, *J* 8.0, 1 H, 8-H), 7.45–7.16 (m, 6 H, 6-H and Ph), 6.05 (s, exch., 1 H, OH), 3.37, 3.07 (2 d, *J* 16.0, 2 H, CH_2), 1.65 (s, 3 H, CH_3) and 1.35 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ of **12a**, 178.83 (s, C=O), 159.66 (s, C-4), 155.98 (s, C-2), 147.19 (s, C-8a), 145.39 (s, C-1 of Ph), 134.81 (d, C-7), 128.16 (d, C-2 of Ph), 126.96 (d, C-5), 126.87 (d, C-6), 127.73 (d, C-8), 126.61 (d, C-3 of Ph), 124.61 (d, C-4 of Ph), 120.47 (s, C-4a), 73.49 (s, C-OH), 42.67 (t, CH_2), 38.89 [s, $C(CH_3)_3$], 31.09 (q, CH_3) and 27.19 [q, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ of **12b**, 178.43 (s, C=O), 159.55 (s, C-4), 155.98 (s, C-2), 147.52 (s, C-8a), 145.51 (s, C-1 of Ph), 134.86 (d, C-7), 128.25 (d, C-2 of Ph), 126.99 (d, C-5), 126.90 (d, C-6), 126.73 (d, C-8), 126.66 (d, C-3 of Ph), 124.45 (d, C-4 of Ph), 120.47 (s, C-4a), 73.93 (s, C-OH), 43.37 (t, CH_2), 38.97 [s, $C(CH_3)_3$], 30.48 (q, CH_3) and 27.19 [q, $C(CH_3)_3$]; *m/z* (EI) 259 (6%), 202 (5), 105 (30), 77 (40) and 57 (100); *m/z* (CI) 380 (MH^+, 5), 362 (5), 318 (3), 260 (100) and 161 (30) (Found: MH^+, 380.1974. Calc. for $C_{22}H_{26}N_3O_3$: 380.974) (Found: C, 69.7; H, 6.8; N, 11.2. Calc. for $C_{22}H_{25}N_3O_3$: C, 69.65; H, 6.59; N, 11.08%); ν_{max}(KBr disc)/cm^{-1} 3294, 1710, 1685, 1604 and 1571.

2-(Anilinocarbonylmethyl)-3-pivaloylaminoquinazolin-4(3*H*)-one 13. Mp 187–188 °C; $\delta_H([^2H_6]DMSO)$ 10.70 (s, exch., 1 H, CONHPh), 10.05 [s, exch., 1 H, $NHCOC(CH_3)_3$], 8.13 (d, *J* 8.0, 1 H, 5-H), 7.82 (t, *J* 8.0, 1 H, 7-H), 7.74–7.40 (m, 7 H, 6-H, 8-H and Ph), 3.85, 3.76 (2 d, *J* 15.9, 2 H, CH_2) and 1.25 [s, 9 H, $C(CH_3)_3$]; $\delta_C([^2H_6]DMSO)$ 176.14 (s, C=O), 158.89 (s, C-4),

157.01 (s, C-2), 152.49 (s, CONHPh), 146.53 (s, C-8a), 139.68 (s, C-1 of Ph), 135.78 (d, C-7), 128.78 (d, C-2 of Ph), 127.44 (d, C-5), 127.16 (d, C-3 of Ph), 126.73 (d, C-6), 126.33 (d, C-8), 123.58 (d, C-4 of Ph), 119.91 (s, C-4a), 42.97 (t, CH_2), 37.74 [s, $C(CH_3)_3$] and 26.86 [q, $C(CH_3)_3$]; *m/z* (EI) 378 (M^+, 2%), 259 (12), 160 (20), 119 (100) and 91 (75); *m/z* (CI), 379 (MH^+, 3), 280 (10), 161 (60), 102 (80) and 94 (100); (Found: MH^+, 379.1770. Calc. for $C_{21}H_{23}N_4O_3$: 379.1770) (Found: C, 66.8; H, 5.7; N, 14.4. Calc. for $C_{21}H_{22}N_4O_3$: C, 66.66; H, 5.82; N, 14.81%); ν_{max}(KBr disc)/cm^{-1} 3269, 1718, 1693, 1670, 1605 and 1575.

3-Acetylamino-2-(2-hydroxy-2,2-diphenylethyl)quinazolin-4(3*H*)-one 14. Mp 169–170 °C; δ_H($CDCl_3$) 8.92 (s, exch., 1 H, NH), 8.03 (d, *J* 8.0, 1 H, 5-H), 7.59 (t, *J* 8.0, 1 H, 7-H), 7.42–7.12 (m, 12 H, 6-H, 8-H and 2 Ph), 7.11 (s, exch., 1 H, OH), 3.76, 3.64 (2 d, *J* 17.5, 2 H, CH_2) and 2.17 (s, 3 H, CH_3); δ_C($CDCl_3$) 170.01 (s, C=O), 160.37 (s, C-4), 156.33 (s, C-2), 146.63, 146.27 (2 s, C-1 of Ph's), 145.23 (s, C-8a), 127.18 (d, C-5), 127.06 (d, C-6), 126.99 (d, C-8), 126.94, 126.67 (2 d, C-3 of Ph's), 126.24, 125.90 (2 d, C-4 of Ph's), 120.22 (s, C-4a), 77.46 (s, C-OH), 41.67 (t, CH_2) and 20.98 (q, CH_3); *m/z* (EI) 217 (10%), 182 (30), 160 (10), 105 (100) and 77 (80); *m/z* (CI), 400 (MH^+, 30), 325 (20), 218 (100), 183 (90), 161 (60) and 105 (10) (Found: MH^+, 400.1661. Calc. for $C_{24}H_{22}N_3O_3$, 400.1661) (Found: C, 72.0; H, 5.2; N, 10.8. Calc. for $C_{24}H_{21}N_3O_3$: C, 72.18; H, 5.26; N, 10.52%); ν_{max}(KBr disc)/cm^{-1} 3223, 1720, 1666, 1608 and 1571.

3-Acetylamino-2-ethylquinazolin-4(3*H*)-one 15. Mp 135–136 °C (lit.,[17] 136–138 °C); δ_H($CDCl_3$) 9.36 (s, exch., 1 H, NH), 8.12 (d, *J* 8.0, 1 H, 5-H), 7.73 (t, *J* 8.0, 1 H, 7-H), 7.66 (d, *J* 8.0, 1 H, 8-H), 7.41 (t, *J* 8.0, 6-H), 2.81, 2.74 (2 dq, *J* 7.4 and 16.2, 2 H, CH_2), 2.24 (s, 3 H, CH_3CO) and 1.30 (t, *J* 7.4, 3 H, CH_3); δ_C($CDCl_3$) 170.69 (s, C=O), 160.86 (s, C-4), 158.69 (s, C-2), 147.10 (s, C-8a), 134.98 (d, C-7), 127.48 (d, C-5), 126.67 (d, C-6), 126.64 (d, C-8), 120.44 (s, C-4a), 26.84 (t, CH_2), 20.91 (q, CH_3) and 10.61 (q, CH_3CO); *m/z* (EI) 232 (MH^+, 30%), 231 (M^+, 35), 189 (100), 173 (65), 160 (25), 130 (40) and 119 (80); *m/z* (CI), 232 (MH^+, 100), 189 (1) and 175 (10) (Found: M^+, 231.1008. Calc. for $C_{12}H_{13}N_3O_2$: 231.1008) (Found: C, 62.4; H, 5.7; N, 18.3. Calc. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.62; N, 18.18%); ν_{max}(KBr disc)/cm^{-1} 3233, 1708, 1679, 1605 and 1570.

3-Acetylamino-2-[$^2H_1$]methylquinazolin-4(3*H*)-one 16. Mp 175–176 °C; δ_H($CDCl_3$) 9.44 (s, exch., 1 H, NH), 8.13 (d, *J* 8.0, 1 H, 5-H), 7.73 (t, *J* 8.0, 1 H, 7-H), 7.62 (d, *J* 8.0, 1 H, 8-H), 7.41 (t, *J* 8.0, 1 H, 6-H), 2.49 (1:1:1 t, *J* 2.0, 2 H, CH_2D) and 2.22 (s, 3 H, CH_3); δ_C($CDCl_3$) 170.58 (s, C=O), 160.60 (s, C-4), 155.47 (s, C-2), 147.06 (s, C-8a), 135.09 (d, C-7), 127.05 (d, C-5), 126.74 (d, C-6), 126.71 (d, C-8), 120.53 (s, C-4a), 21.30, 21.11, 20.91 (3 t, CH_2D) and 20.86 (q, CH_3); *m/z* (EI), 218 (M^+, 30%), 176 (100), 161 (40), 147 (90), 132 (5), 118 (40) and 43 (100); *m/z* (CI) 219 (MH^+, 100), 176 (2) and 162 (60) (Found: M^+, 218.0914. Calc. for $C_{11}H_{10}N_3O_2$: 218.0914); ν_{max}/KBr disc)/cm^{-1} 3279, 1699, 1664, 1609 and 1568.

3-Acetylamino-2-[(1-hydroxycyclohexyl)methyl]quinazolin-4(3*H*)one 17. Mp 174–175 °C; δ_H($CDCl_3$) 9.59 (s, exch., 1 H, NH), 8.04 (d, *J* 8.0, 1 H, 5-H), 7.66 (t, *J* 8.0, 1 H, 7-H), 7.53 (d, *J* 8.0, 1 H, 8-H), 7.34 (t, *J* 8.0, 1 H, 6-H), 5.40 (s, exch., 1 H, OH), 2.92, 2.74 (2 d, *J* 16.4, 2 H, CH_2), 2.22 (s, 3 H, CH_3) and 1.87–1.22 [m, 10 H, $(CH_2)_5$]; δ_C($CDCl_3$) 170.28 (s, C=O), 159.90 (s, C-4), 156.42 (s, C-2), 145.57 (s, C-8a), 134.91 (d, C-7), 127.00 (d, C-5), 126.92 (d, C-6), 126.66 (d, C-8), 120.48 (s, C-4a), 71.34 (s, C-OH), 41.98 (t, CH_2), 38.33, 37.18, 25.61, 22.99 and 21.85 [5 t, $(CH_2)_5$] and 20.85 (q, CH_3); *m/z* (EI), 315 (M^+, 2%), 272 (5), 217 (50), 175 (100), 160 (20) and 117 (20); *m/z* (CI) 316 (MH^+, 100), 298 (20), 285 (15), 218 (80), 161 (30), 116 (10) and 77 (30) (Found: MH^+, 316.1661. Calc. for $C_{17}H_{22}N_3O_3$: 316.1661) (Found: C, 64.9; H, 6.8; N, 13.3. Calc. for $C_{17}H_{21}N_3O_3$: C, 64.76; H, 6.66; N, 13.33%); ν_{max}(KBr disc)/cm^{-1} 3249, 1719, 1668, 1607 and 1572.

3-Acetylamino-2-(2-hydroxy-2-phenylpropyl)quinazolin-4(3*H*)-one 18. Mp 157–157.5 °C; NMR shows a mixture of two isomers, a and b, in a 2:3 ratio: δ_H([$^2H_6$]DMSO) of **18a**, 10.91 (br, exch., 1 H, NH), 8.07 (d, *J* 8.0, 1 H, 5-H), 7.79 (t, *J* 8.0, 1 H, 7-H), 7.63 (d, *J* 8.0, 1 H, 8-H), 7.55–7.12 (m, 6 H, 6-H and Ph), 5.96 (br, exch., 1 H, OH), 3.22, 3.15 (2 d, *J* 16.5, 2 H, CH_2), 2.18 (s, 3 H, CH_3CO) and 1.55 (s, 3 H, CH_3); δ_H([$^2H_6$]DMSO) of **18b**, 10.91 (br, exch., 1 H, NH), 8.07 (d, *J* 8.0, 1 H, 5-H), 7.79 (t, *J* 8.0, 1 H, 7-H), 7.63 (d, *J* 8.0, 1 H, 8-H), 7.55–7.12 (m, 6 H, 6-H and Ph), 5.96 (br, exch., 1 H, OH), 3.43, 2.96 (2 d, *J* 15.8, 2 H, CH_2), 2.14 (s, 3 H, CH_3CO) and 1.54 (s, 3 H, CH_3); δ_C([$^2H_6$]DMSO) of **18a**, 169.25 (s, C=O), 158.57 (s, C-4), 156.48 (s, C-2), 148.09 (s, C-8a), 145.31 (s, C-1 of Ph), 134.73 (d, C-7), 127.55 (d, C-2 of Ph), 126.74 (d, C-5), 126.26 (d, C-6), 126.24 (d, C-8), 126.12 (d, C-3 of Ph), 124.75 (d, C-4 of Ph), 120.40 (s, C-4a), 72.79 (s, C-OH), 43.43 (t, CH_2), 30.56 (q, CH_3) and 20.50 (q, CH_3CO); δ_C([$^2H_6$]DMSO) of **18b**, 169.12 (s, C=O), 158.63 (s, C-4), 156.78 (s, C-2), 148.62 (s, C-8a), 145.37 (s, C-1 of Ph), 134.79 (d, C-7), 127.77 (d, C-2 of Ph), 126.74 (d, C-5), 126.26 (d, C-6), 126.12 (d, C-8), 126.01 (d, C-3 of Ph), 124.51 (d, C-4 of Ph), 120.42 (s, C-4a), 73.12 (s, C-OH), 43.19 (t, CH_2), 30.23 (q, CH_3) and 20.45 (q, CH_3CO); *m/z* (EI) 217 (15%), 175 (63), 146 (50), 105 (75) and 43 (100); *m/z* (CI) 338 (MH^+, 10), 321 (1), 218 (100) and 161 (10) (Found: MH^+, 338.1505. Calc. for $C_{19}H_{20}N_3O_3$: 338.1505) (Found: C, 67.5; H, 5.9; N, 12.3. Calc. for $C_{19}H_{19}N_3O_3$: C, 67.65; H, 5.63; N, 12.46%); ν_{max}(KBr disc)/cm^{-1} 3209, 1722, 1675, 1605 and 1571.

3-Acetylamino-2-(anilinocarbonylmethyl)quinazolin-4(3*H*)-one 19. Mp 195–196 °C; δ_H([$^2H_6$]DMSO) 10.90 (s, exch., 1 H, $NHCOCH_3$), 10.60 (s, exch., 1 H, CONHPh), 8.04 (d, *J* 8.0, 1 H, 5-H), 7.79 (t, *J* 8.0, 1 H, 7-H), 7.64 (d, *J* 8.0, 1 H, 8-H), 7.55–7.12 (m, 6 H, 6-H and Ph), 3.22, 3.15 (2 d, *J* 16.4, 2 H, CH_2) and 2.11 (s, 3 H, CH_3); δ_C([$^2H_6$]DMSO) 169.11 (s, C=O), 158.63 (s, C-4), 156.48 (s, C-2), 148.62 (s, CONHPh), 148.09 (s, C-8a), 145.31 (s, C-1 of Ph), 134.79 (d, C-7), 127.77 (d, C-2 of Ph), 127.55 (d, C-5), 126.64 (d, C-3 of Ph), 126.26 (d, C-6), 126.24 (d, C-8), 124.51 (d, C-4 of Ph), 120.40 (s, C-4a), 43.19 (t, CH_2) and 20.50 (q, CH_3); *m/z* (EI) 337 (MH^+, 15%), 336 (M^+, 8), 217 (75), 176 (60), 93 (100) and 43 (60); *m/z* (CI) 337 (MH^+, 100), 280 (20), 202 (21) and 94 (25) (Found: MH^+, 337.1300. Calc. for $C_{18}H_{17}N_4O_3$: 337.1301) (Found, C, 64.4; H, 4.8; N, 16.6. Calc. for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.76; N, 16.66%); ν_{max}(KBr disc)/cm^{-1} 3215, 1728, 1719, 1656, 1604 and 1582.

3-Amino-2-ethylquinazolin-4(3*H*)-one 20. A mixture of compound **9** (0.20 g, 0.73 mmol), methanol (10 cm^3) and aqueous sodium hydroxide (20%; 5 cm^3) was heated under reflux for 1 h and then evaporated under reduced pressure. The residue was extracted with ethyl acetate (10 cm^3) and the extract washed with water (2 × 8 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give compound **20** (0.13 g, 72%), which was recrystallized from methanol, mp 126–128 °C (lit.,[18] 128 °C).

Acknowledgements

We thank the Egyptian Government for a studentship to G. A. El-Hiti, the EPSRC for the grant which supplied the NMR equipment used in this study and the EPSRC Mass Spectrometry Centre in Swansea for the mass spectra.

References

1 Part 37 in the series *Novel Heterocyclic Systems*; for part 36 see, 'A convenient synthesis of 2-substituted thiazolo[4,5-*b*]pyridines *via* directed metalation', K. Smith, D. Anderson and I. Matthews, *Sulfur Lett.*, 1995, **18**, 79.
2 P. Beak, W. J. Zajdel and D. B. Reitz, *Chem. Rev.*, 1984, **84**, 471.
3 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
4 W. Führer and H. W. Gschwend, *J. Org. Chem.*, 1979, **44**, 1133.

5 J. A. Turner, *J. Org. Chem.*, 1983, **48**, 3401.
6 K. Smith, C. M. Lindsay and I. K. Morris, *Chem Ind. (London)*, 1988, 302; K. Smith, C. M. Lindsay, I. K. Morris, I. Matthews and G. J. Pritchard, *Sulfur Lett.*, 1994, 197.
7 T. J. Hagen, M. F. Rafferty, J. T. Collins, D. J. Garland, J. J. Li, M. B. Norton, D. B. Reitz, S. Tsymbalov, B. S. Pitzele and E. A. Hallinan, *Heterocycles*, 1994, **38**, 601.
8 See for example: K. Smith, I. Matthews, N. M. Hulme and G. E. Martin, *J. Chem. Soc., Perkin Trans. 1*, 1986, 2075; C. M. Lindsay, K. Smith and G. E. Martin, *J. Heterocycl. Chem.*, 1987, **24**, 211; I. Matthews, K. Smith and G. E. Martin, *J. Chem. Soc., Perkin Trans. 1*, 1988, 77; K. Smith, M. E. W. Hammond, D. M. James, I. J. Ellison and M. G. Hutchings, *Chem. Lett.*, 1990, 351; K. Smith, A. Small and M. G. Hutchings, *Chem. Lett.*, 1990, 347; K. Smith, A. Small and M. G. Hutchings, *Synlett.*, 1991, 485; K. Smith, D. M. James, A. G. Mistry, M. R. Bye and D. J. Faulkner, *Tetrahedron*, 1992, **48**, 7479.
9 K. Smith, C. M. Lindsay and G. J. Pritchard, *J. Am. Chem. Soc.*, **111**, 665; K. Smith and G. J. Pritchard, *Angew. Chem.*, 1990, **102**, 298; *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 282.
10 See for example: E. F. Harrison and A. A. Larsen, U.S.P., 3, 560, 619 (1971) (*Chem. Abstr.*, 1971, **75**, 5929); R. J. Alaimo, U.S.P., 3, 997, 538 (1976) (*Chem. Abstr.*, 1977, **86**, 121366); D. P. Gupta, S. Ahmad, A. Kumar and K. Suanker, *Indian J. Chem., Sect. B.*, 1988, **27**, 1060; J. S. Shukla and M. Fadayan, *Asian J. Chem.*, 1989, **1**, 208.
11 M. T. Bogert and R. A. Gortner, *J. Am. Chem. Soc.*, 1909, **31**, 943.
12 N. J. R. v. E. Hommes and P. v. R. Schleyer, *Tetrahedron*, 1994, **50**, 5917.
13 R. S. Atkinson, in *Comprehensive Organic Chemistry*, ed. D. H. R. Barton and W. D. Ollis, Pergamon, Oxford, 1978, vol. 2, p. 225; Y. Shvo in *The Chemistry of the Hydrazo, Azo and Azoxy Groups*, ed. S. Patai, Interscience, New York, 1975, part 2.
14 S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, 1967, **9**, 165.
15 *Vogel's Textbook of Practical Organic Chemistry*, 4th edn., Longman Scientific and Technical, John Wiley and Sons, New York, 1978.
16 D. D. Perrin, W. L. F. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon, Oxford, 1966.
17 J. Klosa, *J. Prakt. Chem.*, 1961, **31**, 140.
18 A. Sammour, M. I. Selim, M. Elkasaby and M. Abdalla, *Acta Chim. (Budapest)*, 1973, **78**, 293 (*Chem. Abstr.*, 1973, **79**, 137061).

Paper 4/06923D
Received 14*th November* 1994
Accepted 3*rd January* 1995