The N–N bond as a chiral axis: 3-diacylaminoquinazolinones as chiral acylating agents

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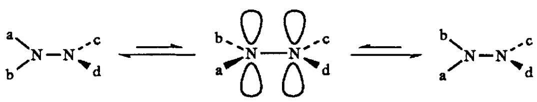
3-Diacylaminoquinazolinones 10 and 15 have high enough barriers to rotation around their N–N bonds to allow separation of each into diastereoisomers. Interconversion of diastereoisomers 10a and 10b occurs on heating in boiling toluene and thermodynamic parameters for this process have been measured. The barriers to rotation around the N–N bonds in analogous monoacylaminoquinazolinones are not sufficient to permit isolation of stereoisomers at room temperature unless the exocyclic nitrogen is additionally substituted *e.g.* by an alkyl group as in 28. X-Ray crystal structure determinations carried out on 10a, 10b, 15a and 28b confirm the presence of chiral axes. Reaction of both diastereoisomers 15a and 15b with 1-phenylethylamine takes place with exclusive reaction at the 1-acetoxypropionyl carbonyl group and with partial kinetic resolution: the preferred sense of enantioselectivity obtained is dominated by the N–N axis.

The barrier to rotation around an N–N bond is maximised when both nitrogens are acylated.[1] This increased barrier to rotation can be rationalised in terms of a destabilising interaction in the transition state for rotation arising from eclipsing of the filled orbitals on each sp^2-hybridised nitrogen constituting the N–N bond (Scheme 1).

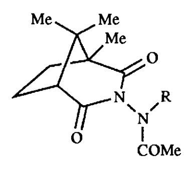


Scheme 1

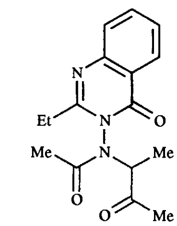
Verma and Prasad[2] have shown that the barrier to rotation around the N–N bond in *N,N*-diacetylcamphorimide **2** is in excess of 97 kJ mol^{-1} since no coalescence of the acetyl methyl signals was observed in its proton NMR spectrum at 150 °C.

We have previously shown that the barrier to N–N bond rotation in *N*-acyl-*N*-alkylquinazolinones *e.g.* **3** is sufficient to allow separation of diastereoisomers when another chiral element (chiral centre) was present in the molecule. Thus the keto amide **3** has been separated into two diastereoisomers which did not interconvert on heating briefly at 200 °C.[3]

In this paper we report that the N–N bond in 3-aminoquinazolinones *N*-substituted with two different acyl groups is also a chiral axis on the real time scale and that these compounds when used in enantiopure form are chiral acylating agents and bring about the partial kinetic resolution of a racemic amine.[4]



2 R = COMe
7 R = H



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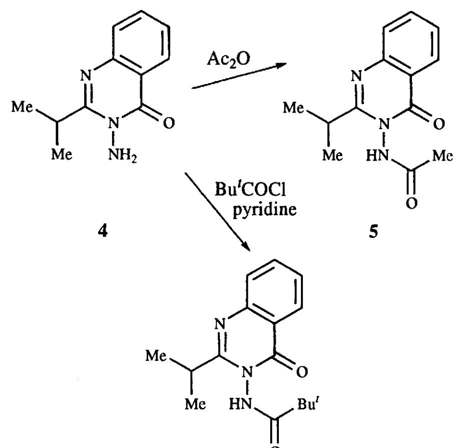


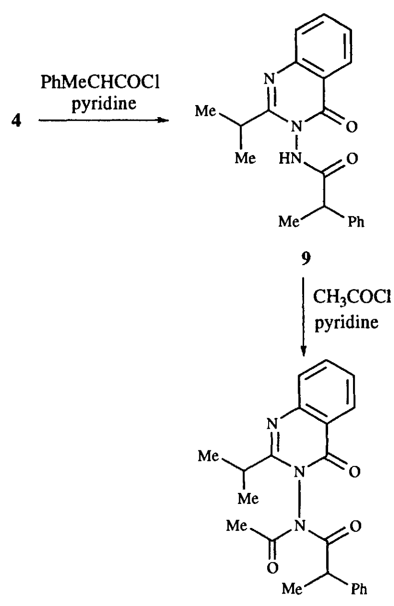
4 **5** **6**

Scheme 2

Results and discussion

3-Amino-2-isopropylquinazolinone **4** reacts with acetic anhydride to give the 3-acetylamino derivative **5** in 66% yield (Scheme 2): diacetylation is a much slower reaction under these conditions, which facilitates the synthesis of 3-diacylaminoquinazolinones bearing different *N*-acyl groups. The presence of a chiral axis in compound **5** is revealed in its NMR spectrum, in which the methyl groups of the isopropyl substituent are non-equivalent and present in a 1 : 1 ratio. A similar acylation of 3-aminoquinazolinone **4** with pivaloyl chloride (2,2-dimethylpropanoyl chloride)–pyridine leads to the corresponding 3-acylaminoquinazolinone **6** in 55% yield (Scheme 2). In the NMR spectrum of compound **6**, the methyl groups of the isopropyl group are also diastereotopic and present in a 1 : 1 ratio. Complete coalescence of the isopropyl methyl group signals in the NMR spectrum of compound **5** was not observed even at 110 °C (although some broadening of these signals was apparent at this temperature) and hence the associated barrier is > 85 kJ mol^{-1}. Verma and Prasad[2] have assigned the barrier giving rise to non-equivalent $COCH_3$ signals in the NMR spectrum of the *N*-acetylaminocamphorimide (*N*-acetylamino-1,2,2-trimethylcyclopentane-1,3-dicarboximide) **7** to slow rotation around the N–CO bond (fast N–N bond rotation assumed). A similar explanation for the NMR data of compounds **5** and **6** is untenable in view of the 1:1 intensity ratios for the isopropyl group methyl signals in both compounds **5** and **6**. Moreover, the magnitude of this barrier in compound **5** is significantly greater than that found for amide rotamer interconversion in *N,N*-dialkylamides (69–73 kJ mol^{-1}).[5]

Reaction of 3-aminoquinazolinone **4** first with 2-phenylpropanoyl chloride–pyridine to give compound **9** and then with acetyl chloride–pyridine gave the 3-diacylaminoquinazolinone **10** as a 1.8:1 ratio of diastereoisomers **10a** and **10b** (Scheme 3).



Scheme 3

Separation of these diastereoisomers by chromatography gave crystalline samples of each on which X-ray crystal determinations were carried out (Fig. 1).† As anticipated, both molecules comprise two orthogonal planes, containing the quinazolinone and imide respectively, with the N–N bond as a chiral axis. The *endo-exo* arrangement of imide carbonyl groups with one *cis* and one *trans* to the quinazolinone ring is also the preferred conformation for simple imides.[6]

Diastereoisomers **10a** and **10b** are interconverted by rotation around their N–N bond. Heating **10a** in toluene at three different temperatures and measurement of the rate constants for its interconversion with **10b** at each temperature by NMR spectroscopy gave the following: $\Delta G^{\ddagger} = 121$ kJ mol^{-1}, $\Delta H^{\ddagger} =$ 77 kJ mol^{-1} and $\Delta S^{\ddagger} = 118$ kJ mol^{-1}.

We have also prepared the 3-diacylaminoquinazolinone **15** from 3-aminoquinazolinone **13** and separated the two diastereoisomers **15a** and **15b**. 3-Aminoquinazolinone **13** was prepared from diphenylacetyl chloride *via* the anthranilate **11** and hydrazide **12** in the usual way (Scheme 4). In the second acylation **14** ⟶ **15**, compounds **16** and **17** were obtained as by-products (see below) and the more polar diastereoisomer **15b** was not completely freed from compound **17**.

An X-ray crystal structure determination on **15a** (Fig. 2) reveals the absolute configuration around the N–N chiral axis in this compound.‡

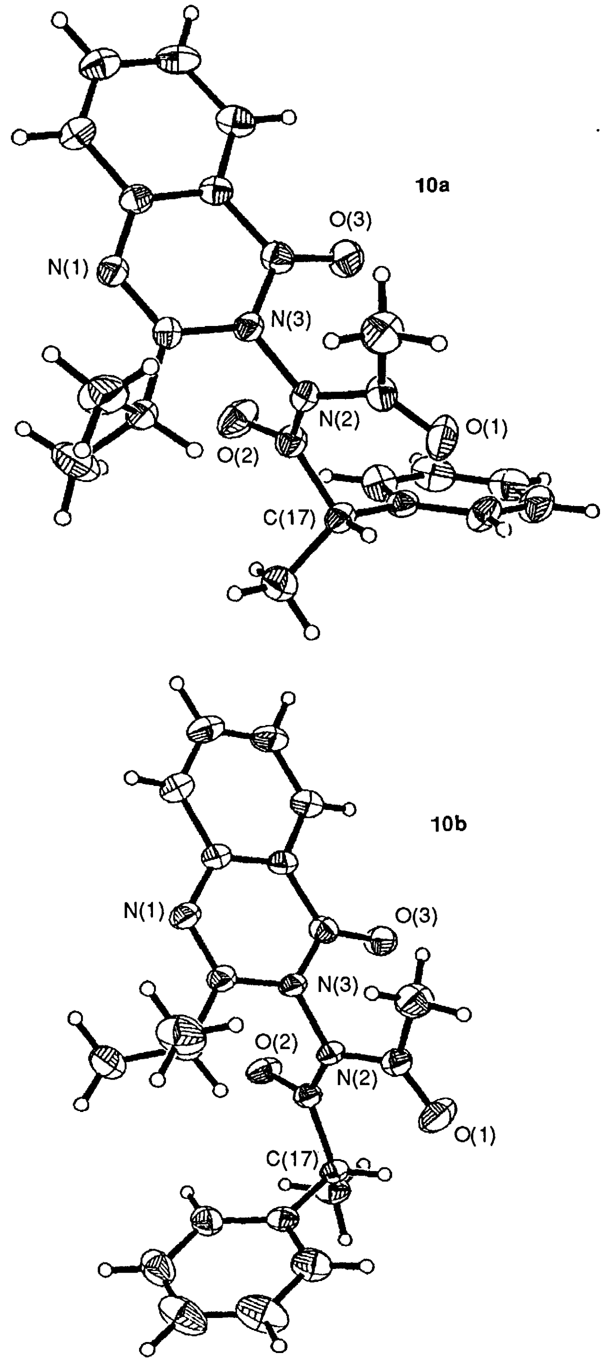
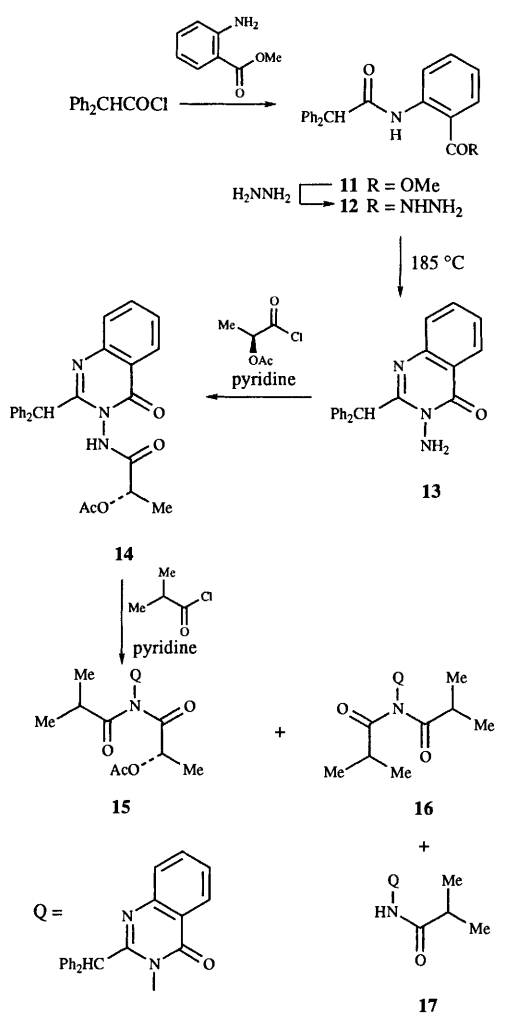


Fig. 1 Structures of **10a** (mp 129–132 °C) and **10b** (mp 144–147 °C), two diastereoisomers of 3-[*N*-acetyl-*N*-(2-phenylpropanoyl)amino]-2-isopropyl-3,4-dihydroquinazolin-4-one

† The melting points and NMR data for **10a** and **10b** in our preliminary communication (ref. 4; footnote for **5a** and **5b**) are incorrect and should be reversed.

‡ Crystal data for **15a**: Data were measured at 293 K on a Siemens P4 diffractometer using graphite monochromated Mo-Kα radiation ($\lambda =$ 0.710 73 Å) with an ω scan technique. The data were corrected for Lorentz and polarisation effects. The structures were solved by direct methods and refined by full-matrix least-squares using the program SHELXTL-PC (G. M. Sheldrick, SHELXTL-PC Release 4.2 Siemens Analytical X-ray Instruments Inc. Madison, WI, 1991). For **15a**: $C_{30}H_{29}N_3O_5 \cdot 0.333C_2H_5OH$, M = 526.93, Orthorhombic, $C222_1$, a = 11.632(1), b = 20.088(2), c = 25.189(3) Å, V = 5856(1) Å^3, Z = 8, D_c = 1.189 Mg m^{-3}, $F(000)$ = 2229.3, μ = 0.086 mm^{-1}. The intensities of 3490 reflections with $\theta \leqslant 25°$ were measured yielding 3369 unique reflections (R_{int} = 0.0144) of which 2312 had $F > 4\sigma(F)$. The ethanol solvent molecule was refined to have $\frac{1}{3}$ site occupancy with two atoms and on a two fold axis. The hydrogen atoms of the solvent molecule were not included in the refinement; all other hydrogen atoms were included in calculated positions (C–H = 0.96 Å) with a common fixed isotropic displacement parameter (0.08 Å^2). With the exception of the solvent molecule all non-hydrogen atoms were refined with anisotropic displacement parameters. Final R = 0.056 and R_w = 0.0621 for 351 parameters.

Atomic coordinates, bond lengths and angles, and thermal parameters for compounds **15a** and **28b** have been deposited at the Cambridge Crystallographic Data Centre. For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1.



Scheme 4

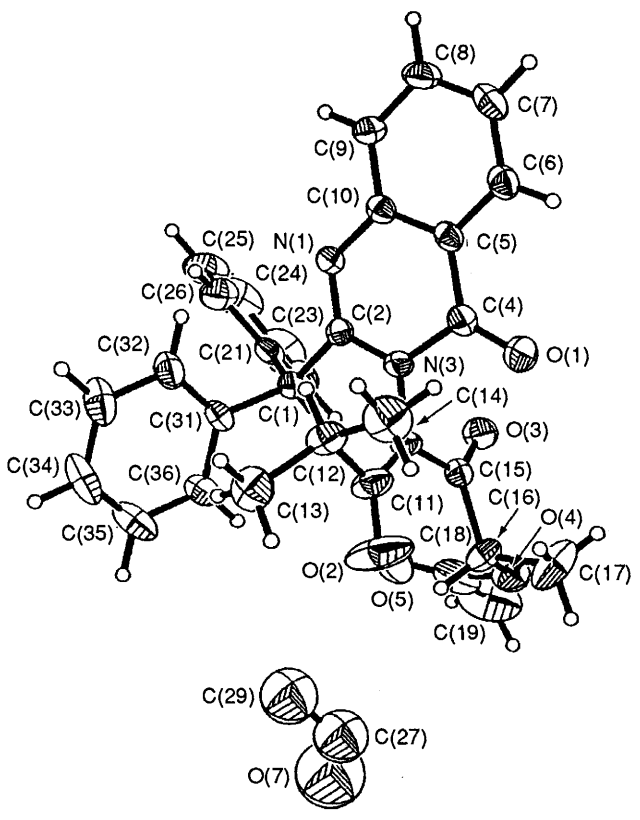
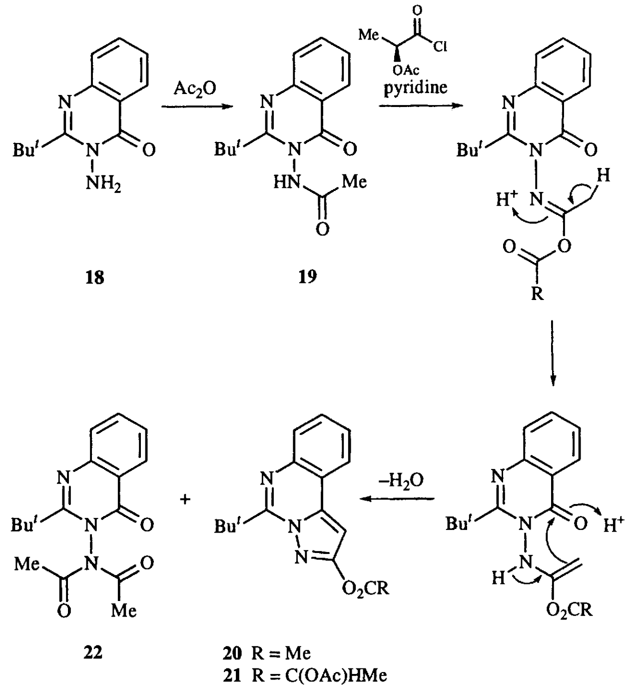


Fig. 2 Crystal structure of **15a** (mp 141–143 °C) containing a molecule of ethanol of crystallisation

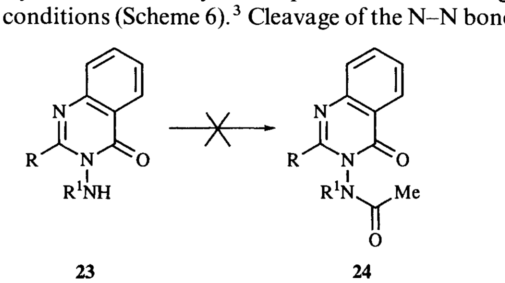
An attempt was also made to synthesise chiral 3-diacylamino-quinazolinones bearing a *tert*-butyl group in the 2-position of the quinazolinone ring. 3-Amino-2-*tert*-butylquinazolinone **18** was treated with acetic anhydride to give the 3-acetylamino derivative **19** (Scheme 5). Further acylation was attempted



Scheme 5

using (*S*)-2-acetoxypropanoyl chloride but the only homogeneous products isolated were compounds **20** (8%) and **21** (3%) and the 3-diacetylaminoquinazolinone **22** (9%). Assignments of structures to compounds **20** and **21** are based on spectroscopic data: it appears that the bulk of the 2-*tert*-butyl group may result in competitive acylation at the amide carbonyl oxygen, as in the mechanism depicted in Scheme 5, and this leads to the formation of compounds **20** and **21**. However, both acetyl groups are bonded to the exocyclic nitrogen in compound **22** (rather than *N*,*O*-diacylation) as shown by the ^{13}C NMR spectrum which contains only a single carbonyl and methyl carbon resonance for both acetyl groups.

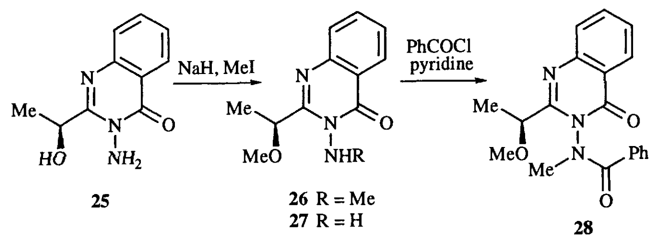
Although mono- and di-acylation of 3-aminoquinazolinones, therefore, is successful, we have previously been unable to effect the *N*-acetylation of 3-alkylaminoquinazolinones using a variety of conditions (Scheme 6).[3] Cleavage of the N–N bond in



Scheme 6

3-alkylaminoquinazolinones was important to us in connection with other work[7] and the N–N bond in compounds such as **24** is known to be more easily reductively cleaved than in compound **23**.

It was surprising, therefore, to find that reaction of the 3-methylaminoquinazolinone **26** with benzoyl chloride–pyridine gave the *N*-benzoyl derivative **28** in good yield (73%) as a mixture of diastereoisomers (1.24:1) which were separated by flash chromatography (Scheme 7). A by-product in the *N*,*O*-dimethylation of the 3-aminoquinazolinone **25** was the *O*-methylated compound **27**.



Scheme 7

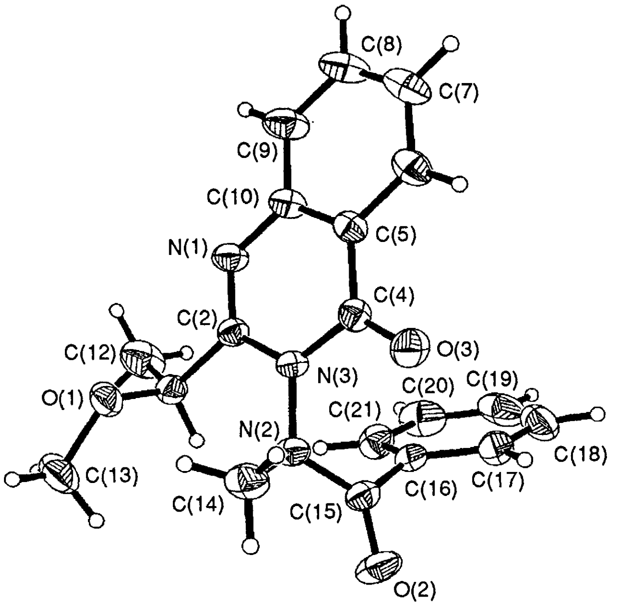
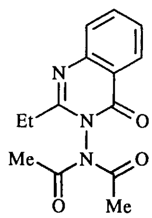


Fig. 3 Crystal structure of **28b** (mp 123–127 °C)

An X-ray crystal structure of diastereoisomer **28b** (the more polar on silica chromatography) was obtained (Fig. 3).§ Again there is orthogonality of the two planes containing the quinazolinone ring and the exocyclic amide unit, which gives rise to the chirality of the N–N axis. An unexpected feature of this crystal structure was the centric space group $P\bar{1}$ to which it belonged, indicating that the material was racemic: the starting 3-aminoquinazolinone **25** from which it was prepared was believed to be enantiopure.[7] The small number of crystals obtained by setting aside a dilute ethanol solution of diastereoisomer **28b**, one of which was used for the X-ray crystal structure determination, were subsequently found to have a melting point of 123–127 °C, which is considerably lower than that obtained previously for this material after crystallisation from ethanol in bulk (mp 142–144 °C). This depression of melting point is in accord with the racemic nature of the sample on which the crystal structure was carried out but the origin of this racemic material is not clear.

Evidence for an *exo-endo* imide conformation for 3-diacylaminoquinazolinones in solution

The ^{1}H NMR spectra of both diastereoisomers of 3-(*N*-methyl-*N*-benzoylamino)quinazolinone **28** at room temperature showed the presence of both amide rotamers (ratios 3.2:1 for **28a**; 4.1:1 for **28b**). Corresponding separated signals from imide rotamers were not visible in the NMR spectrum of 3-diacylaminoquinazolinones **10a**, **10b**, **15a** and **15b** at room temperature although some signals in the proton NMR spectra of these compounds were broadened. In the proton NMR



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spectrum of 3-diacetylaminoquinazolinone **29** at room temperature, the acetyl methyl signals are present as a broadened singlet at δ 2.41. At −83 °C in [$^2H_6$]-acetone, this broadened singlet has separated into two singlets of equal intensity which are assigned to the two methyl groups in *endo* and *exo* positions, respectively. Significantly, the two methylene protons of the quinazolinone 2-ethyl substituent also become non-equivalent (diastereotopic) since the N–N bond becomes a chiral axis on the NMR time-scale at this temperature.

It appears that, as in the crystalline form (Figs. 1 and 3), the preferred conformation for these 3-diacylaminoquinazolinones in solution is the *endo-exo* arrangement which is also preferred for simple imides.[6] We assume that the broadening of some signals in the NMR spectra of other 3-diacylaminoquinazolinones, referred to above, is also the result of rotation around N–CO bonds in these compounds not being fast on the NMR timescale. The larger barrier to rotation around the amide N–CO bonds in compounds **28a** and **28b** than around the corresponding bonds in imides **10a**, **10b**, **15a**, **15b** and **29** is to be expected.

3-Diacylaminoquinazolinones as selective acylating agents

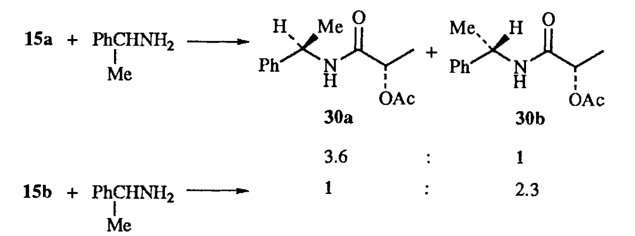
3-Diacylaminoquinazolinones are acylating agents towards nucleophiles. An indication of their reactivity in this respect was the isolation of 3-[bis(2-methylpropanoyl)amino]quinazolinone **16** as an unexpected by-product in the preparation of compound **15** (Scheme 4). An authentic sample of this by-product **16** was prepared from 3-aminoquinazolinone **13** in the more usual way (see Experimental section).

The origin of this material we believe to be one or both diastereoisomers of 3-diacylaminoquinazolinone **15** which are presumably slowly attacked by chloride anion at the more reactive 2-acetoxypropanoyl carbonyl group (see below): re-acylation of **17** by isobutyryl chloride then gives the product **16**. Evidence to support this proposed route was the presence of an impurity in the more polar diastereoisomer of 3-diacylaminoquinazolinone **15b** which was identified as the 3-(2-methylpropanoylamino)quinazolinone **17** by comparison with the ^{1}H and ^{13}C NMR spectra of an authentic sample prepared from 3-aminoquinazolinone **13**.

These 3-diacylaminoquinazolinones are acylating agents for amines. We have shown elsewhere that they show high selectivity for reaction with primary over secondary amines and selective reaction with one secondary amine over another.[8] In enantiopure form they can be used to bring about enantioselective acylation of racemic amines by kinetic resolution. Thus when the faster-eluted enantiopure diastereoisomer **15a** is treated with 1-phenylethylamine (2 equiv.) in toluene at −20 °C, the product consists of a 3.6:1 ratio of diastereoisomers of amide **30**. From comparison with authentic samples of both diastereoisomers **30a** and **30b** of this amide prepared independently, it is the (*R*)-enantiomer of the racemic amine that reacts preferentially.

Using the more polar diastereoisomer **15b** (contaminated

§ Crystal data for **28b**: $C_{19}H_{19}N_3O_3$, M = 337.37, Triclinic, $P\bar{1}$, a = 9.899(2), b = 9.939(2), c = 10.429(2) Å, α = 84.95(3), β = 64.43(3), γ = 69.18(3)°, V = 862.5 Å^3, Z = 2, D_c = 1.30 Mg m^{-3}, F(000) = 356, μ = 0.053 mm^{-1}. The intensities of 3881 reflections with $\theta \leqslant 26°$ were measured yielding 3378 unique reflections (R_{int} = 0.0174) of which 2520 had $F > 4\sigma(F)$. The structure was solved by direct methods. All hydrogen atoms were included in calculated positions (C–H = 0.96 Å) with a common fixed isotropic displacement parameter (0.08 Å^2). All other atoms were refined with anisotropic displacement parameters. Final R = 0.0457 and R_w = 0.0501 for 235 parameters.



with *ca.* 10% monoacylquinazolinone **17**), a 1:2.3 ratio of amide diastereoisomers **30a**:**30b** is obtained in which the (*S*)-enantiomer of the amine reacts preferentially. Clearly the kinetic resolution obtained in these acylations is dominated by the N–N chiral axis since both diastereoisomers of 3-diacylaminoquinazolinone **15** have the same (*S*)-configuration at the chiral centre. A control experiment in which 2-acetoxypropanoyl chloride was reacted with 1-phenylethylamine gave little, if any, kinetic resolution.

Experimental

For instrumentation used and general experimental details, see refs. 3 and 7. Unless otherwise indicated, ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ using tetramethylsilane as internal standard and ^{13}C spectra at 75 MHz in the same solvent; *J* values are given in Hz. 'Q' refers to nuclei that are part of the quinazolinone ring system. Assignment of ^{13}C resonances was assisted by the use of DEPT. IR spectra were recorded using Nujol mulls unless otherwise indicated. Mass spectra were obtained using a Kratos Concept mass spectrometer and high resolution masses were obtained by peak-matching using perfluorokerosene. Magnesium sulfate was used as the drying agent. (±), (+) and (−) α-Methylbenzylamine (1-phenylethylamine) and diphenylacetyl chloride were purchased (Aldrich) and used as received. Light petroleum refers to the fraction bp 60–80 °C, ether refers to diethyl ether.

General procedure for the monoacylation of 3-aminoquinazolinones

The carboxylic acid (1 equiv.) was treated with an excess of freshly distilled thionyl chloride and 1 drop of dimethylformamide and the mixture heated at 40 °C until conversion to the acid chloride was complete [1–2 h as monitored by ν_{max}/cm^{-1} 1835 and 1780 in the IR (film)]. Excess thionyl chloride was removed under reduced pressure, the residual acid chloride diluted with dichloromethane (*ca.* 1 cm^3 g^{-1}) and added dropwise with stirring over 2 min to the 3-aminoquinazolinone (0.9 equiv.) in dichloromethane (2 cm^3 g^{-1}) and pyridine (1 equiv.). The resulting mixture was stirred for 5 h at room temperature then further dichloromethane (40 cm^3) added and the solution washed with saturated aqueous sodium hydrogen carbonate, then water, dried and the solvent removed under reduced pressure.

General procedure for preparation of 3-diacylamino- from 3-monoacylaminoquinazolinones

To a solution of the 3-acylaminoquinazolinone (1 equiv.), prepared as described above, in pyridine (3 cm^3 g^{-1}) was added the acid chloride (2–3 equiv.) (prepared as described above) dropwise over 10 min and the mixture stirred for 1–2 days at room temperature, monitoring the disappearance of the starting 3-monoacylaminoquinazolinone by TLC. Dichloromethane (40 cm^3) was added, the solution washed with saturated aqueous sodium hydrogen carbonate, then water, dried and the dichloromethane removed under reduced pressure. The bulk of the residual pyridine was removed using an oil pump (0.5 mmHg) and the product purified by flash chromatography over silica gel.

3-Acetylamino-2-isopropyl-3,4-dihydroquinazolin-4-one 5

3-Amino-2-isopropyl-3,4-dihydroquinazolin-4-one **4** (20.82 g)[3] was dissolved in acetic anhydride (100 cm^3) and stirred for 48 h. The solution was poured into water (1 dm^{-3}), excess acetic anhydride decomposed by stirring (*ca.* 10 min) and the solid obtained was separated and dried. Crystallisation gave the title *quinazolinone* **5** (16.6 g, 66%) as a colourless solid hydrate, mp 74–76 °C (from chloroform–light petroleum) (Found: C, 59.1; H, 6.5; N, 15.9. $C_{13}H_{15}N_3O_2{\cdot}H_2O$ requires C, 59.3; H, 6.5; N, 16.0%); δ_H([^{2}H$_6$]-DMSO) 1.22 (2 × overlapping d, *J* 6.7, C*H*$_3$CHC*H*$_3$), 2.12 (s, C*H*$_3$CON), 3.13 (heptet, *J* 6.7, CH$_3$C*H*CH$_3$), 3.32 (br s, *H*$_2$O of crystallisation), 7.53 (dd, *J* 8.0 and 1.0, Q 6-H), 7.67 (d, *J* 8.1, Q 8-H), 7.85 (ddd, *J* 8.1, 8.0 and 1.6, Q 7-H), 8.10 (dd, *J* 8.0 and 1.6, Q 5-H) and 10.95 (br s, N*H*, D$_2$O exch.); δ_C([^{2}H$_6$]-DMSO) 24.02, 24.54, 25.04 (*C*H$_3$CH*C*H$_3$, *C*H$_3$CON), 34.38 (CH$_3$*C*HCH$_3$), 124.46 [*C*CO (Q)], 130.28, 130.59, 131.13 and 138.80 [4 × *C*H (Q)], 150.42 [*C*N=C (Q)], 162.97 [*C*N (Q)], 166.53 [*C*O (Q)] and 173.51 (CH$_3$*C*ON); ν_{max}/cm^{-1} 3420s br, 3180m, 1700s and 1677s; *m*/*z* 245 (M$^+$, 63%), 203 (45), 202 (22), 188 (50), 187 (61), 186 (31) and 175 (100).

3-(2,2-Dimethylpropanoyl)amino-2-isopropyl-3,4-dihydroquinazolin-4-one 6

The general procedure for monoacylation was followed using 3-amino-2-isopropyl-3,4-dihydroquinazolin-4-one **4** (3 g), pyridine (1.3 cm^3), dichloromethane (6 cm^3) and pivaloyl chloride (2,2-dimethylpropanoyl chloride) (1.94 g) (prepared from the corresponding acid). An oil was obtained on work-up which solidified on standing overnight (4.07 g). Crystallisation from ethyl acetate gave the *product* **6** as a colourless solid (2.32 g, 55%), mp 168–170 °C (Found: C, 66.85; H, 7.35; N, 14.65. $C_{16}H_{21}N_3O_2$ requires C, 66.9; H, 7.35; N, 14.6%); δ_H 1.16 and 1.24 (2 × d, *J* 6.8, C*H*$_3$CHC*H*$_3$), 1.33 [s, (CH$_3$)$_3$C], 3.01 (heptet, *J* 6.8, CH$_3$C*H*CH$_3$), 7.36 (ddd, *J* 8.0, 6.9 and 1.1, Q 6-H), 7.60 (d, *J* 7.6, Q 8-H), 7.68 (ddd, *J* 7.6, 6.9 and 1.1, Q 7-H), 8.10 (dd, *J* 8.0 and 1.1, Q 5-H) and 8.63 (s, N*H*; D$_2$O exch.); δ_C 20.13 (*C*H$_3$CHCH$_3$), 20.97 (CH$_3$CH*C*H$_3$), 27.12 [(*C*H$_3$)$_3$C], 30.92 (CH$_3$*C*HCH$_3$), 38.83 [(CH$_3$)$_3$*C*], 120.40 [*C*CO (Q)], 126.31, 126.44, 127.52 and 134.54 [4 × CH (Q)], 147.04 [*C*N=C (Q)], 160.58 [*C*N (Q)], 161.78 [*C*O (Q)] and 179.06 [(CH$_3$)$_3$C*C*ON]; ν_{max}/cm^{-1} 3285m br, 1715m, 1675s and 1600s; *m*/*z* 287 (M$^+$, 53%), 230 (50), 188 (38), 187 (54), 175 (69), 129 (22), 97 (20), 91 (100), 85 (49), 83 (27), 73 (31), 71 (30) and 69 (36).

3-(2-Phenylpropanoyl)amino-2-isopropyl-3,4-dihydroquinazolin-4-one 9

The general procedure for monoacylation was followed using 3-amino-2-isopropyl-3,4-dihydroquinazolin-4-one **4** (3.85 g), pyridine (2 cm^3), dichloromethane (8 cm^3) and 2-phenylpropanoyl chloride (3.16 g) (prepared from the corresponding acid). A yellow oil was obtained on work-up which solidified on standing overnight (7.17 g). Trituration using ethyl acetate–light petroleum and crystallisation of the insoluble material obtained gave the title *product* **9** (3.62 g, 57%) as a colourless solid hydrate, mp 73.5–76 °C (from ethyl acetate) (Found: C, 67.8; H, 6.55; N, 11.9. $C_{20}H_{21}N_3O_2{\cdot}H_2O$ requires C, 67.95; H, 6.55; N, 11.9%); δ_H(major diastereoisomer) 0.98 and 1.15 (2 × d, *J* 6.7, C*H*$_3$CHC*H*$_3$), 1.57 (d, *J* 7.1, C*H*$_3$CHPh), 1.9 (br s, *H*$_2$O), 2.70 (heptet, *J* 6.7, CH$_3$C*H*CH$_3$), 3.93 (q, *J* 7.1, CH$_3$C*H*Ph), 7.27–7.46 [m, Q, 6-H and 5 × C*H* (Ph)], 7.62–7.74 (m, Q 8- and 7-H), 8.14 (dd, *J* 8.0 and 1.0, Q 5-H) and 8.56 (s, N*H*); (minor diastereoisomer, observable peaks) 1.21 and 1.31 (2 × d, *J* 6.8, C*H*$_3$CHC*H*$_3$), 1.66 (d, *J* 7.2, C*H*$_3$CHPh), 3.07 (heptet, *J* 6.8, CH$_3$C*H*CH$_3$), 3.88 (q, *J* 7.2, CH$_3$C*H*Ph) and 8.20 (s, N*H*); The ratio of major:minor diastereoisomers was 2:1 from comparison of the intensities of signals at δ 3.93 and 3.88 in the spectrum above. δ_C(major diastereoisomer) 17.65 (*C*H$_3$), 19.90 (*C*H$_3$), 20.83 (*C*H$_3$), 30.76 (CH$_3$*C*HCH$_3$), 45.04

(CH_3CHPh), 120.45 [*C*CO (Q)], 140.10 [*C* (Ph)], 147.10 [*C*N=C (Q)], 160.94 [*C*N (Q)], 161.93 [*C*O (Q)] and 174.24 (COCH); (minor diastereoisomer, observable peaks) 18.62 (CH_3), 20.19 (CH_3), 21.13 (CH_3), 31.01 (CH_3CHCH_3), 45.36 (CH_3CHPh), 120.50 [*C*CO (Q)], 134.65 [*C*H (Q)], 139.30 [C (Ph)], 147.04 [*C*N=C (Q)], 160.50 [*C*N (Q)], 161.75 [*C*O (Q)] and 174.80 (*C*OCHPh), (both diastereoisomers) 126.45, 126.57, 126.61, 127.51, 127.63, 127.81, 128.85, 128.91 and 134.73 [10 × *C*H (Ph, Q)]; ν_{max}/cm^{-1} 3480m, 3410m, 1685s, 1670s and 1610s; *m/z* 335 (M^+, 30%), 230 (99), 132 (19) and 105 (100).

3-[*N*-Acetyl-*N*-(2-phenylpropanoyl)amino]-2-isopropyl-3,4-dihydroquinazolin-4-one 10

The general procedure for diacylation was followed using **9** (1 g) and acetyl chloride (0.47 g) in pyridine (4 cm^3) and the black oil obtained after work-up was purified by column chromatography on silica using light petroleum–ethyl acetate (5:1) as eluent to give the product **10** (0.69 g, 61%) as a mixture of diastereoisomers (1.8:1, from comparison of the intensities of signals at δ 4.08 and 4.91 in the NMR spectrum, see below). Separation of these diastereoisomers was carried out using a Chromatotron with light petroleum–ether (7:1) as eluent to give the major diastereoisomer of the title *imide* **10a** (R_f 0.20) mp 129–132 °C (from ethanol)† (Found: C, 70.0; H, 6.2; N, 11.1. $C_{22}H_{23}N_3O_3$ requires C, 70.0; H, 6.15; N, 11.15%); δ_H 0.77 (d, *J* 6.7, CH_3CHCH_3), 1.12 (d, *J* 6.7, CH_3CHCH_3), 1.54 (d, *J* 6.6, CH_3CHPh), 2.45 (heptet, *J* 6.7, CH_3CHCH_3), 2.59 (s, CH_3CO), 4.08 (br q, *J* 6.6, CH_3CHPh), 7.10–7.13 [m, 2 × *CH* (Ph)], 7.25–7.35 [m, 3 × *CH* (Ph)], 7.54 (ddd, *J* 8.0, 7.1 and 1.3, Q 6-H), 7.73 (ddd, *J* 8.2, 1.3 and 0.5, Q 8-H), 7.85 (ddd, *J* 8.2, 7.1 and 1.5, Q 7-H) and 8.34 (ddd, *J* 8.0, 1.5 and 0.5, Q 5-H) [at −20 °C $\delta_H(CD_3OD)$ 4.05 (CH_3CHPh) and 0.65 (CH_3CHCH_3) signals are broadened by comparison with the corresponding signals at δ 4.08 and 0.77 in the spectrum above]; δ_C 20.36, 21.21, 21.80 and 25.27 (4 × CH_3), 30.84 (CH_3CHCH_3), 45.53 (CH_3CHPh), 120.44 [*C*CO (Q)], 126.76, 127.18, 127.34, 127.53, 127.59, 128.96 and 135.15 [9 × *C*H (Ph, Q)], 138.62 [*C* (Ph)], 146.92 [*C*N=C (Q)], 159.87 [*C*N (Q)], 161.44 [*C*O (Q)], 169.95 (N*C*O) and 175.04 (N*C*O); ν_{max}/cm^{-1} 1745s, 1735s, 1705s and 1600s; *m/z* 377 (M^+, 4%), 230 (22), 132 (100) and 105 (59). Crystals of **10a** suitable for X-ray crystal structure determination were obtained by crystallisation from ethanol.

Further elution gave the minor diastereoisomer of the title *imide* **10b** (R_f 0.14) mp 144–147 °C (from ethanol)† (Found: C, 69.95; H, 6.15; N, 11.10. $C_{22}H_{23}N_3O_3$ requires C, 70.00; H, 6.15; N, 11.15%); δ_H 1.14 and 1.16 (2 × d, *J* 6.6, CH_3CHCH_3), 1.59 (d, *J* 6.9, CH_3CHPh), 2.20 (s, CH_3CO), 2.49 (heptet, *J* 6.6, CH_3CHCH_3), 4.91 (br q, CH_3CHPh), 7.27–7.33 [5 × *CH* (Ph)], 7.48 (ddd, *J* 8.1, 7.2 and 1.2, Q 6-H), 7.71 (d, *J* 8.1, Q 8-H), 7.81 (ddd, *J* 8.1, 7.2 and 1.5, Q 7-H) and 8.19 (dd, *J* 8.1 and 1.5, Q 5-H); δ_C 19.48, 21.43, 21.58 and 24.16 (4 × CH_3), 30.08 (CH_3CHCH_3), 46.34 (CH_3CHPh), 120.63 [*C*CO (Q)], 126.83, 127.21, 127.49, 127.53, 128.01, 128.58 and 135.12 [9 × *C*H (Ph, Q)], 139.21 [C (Ph)], 146.87 [*C*N=C (Q)], 159.55 [*C*N (Q)], 161.32 [*C*O (Q)] and 170.80 and 173.85 (2 × *C*O); ν_{max}/cm^{-1} 1740s, 1705s and 1605s; *m/z* 377 (M^+, 4%), 230 (35), 228 (25), 132 (100) and 105 (63). Crystals of **10b** suitable for X-ray crystal structure determination were obtained by crystallisation from ethanol. Heating the major diastereoisomer in [$^2H_8$]toluene (120, 105 and 100 °C in separate experiments) and interconversion with the minor diastereoisomer was followed by recording changes in intensity of the signal δ 4.91 (**10b**) and 4.08 (**10a**) with time. The initial rate constants were: 2.92×10^{-4}, 0.97×10^{-4} and 0.81×10^{-4} s^{-1} respectively. From these values the $\Delta G^{\ddagger}$ value for N–N bond rotation was calculated to be 121 kJ mol^{-1}.

3-Amino-2-diphenylmethyl-3,4-dihydroquinazolin-4-one 13

Diphenylacetic acid (30 g) was converted to its acid chloride as described in the general procedure. The acid chloride was dissolved in dry ether (25 cm^3) and then added rapidly with efficient stirring to methyl anthranilate (47.01 g) dissolved in dry ether (800 cm^3). After stirring for 3 h, insoluble methyl anthranilate hydrochloride was separated and the ether solution washed twice with hydrochloric acid (2 mol dm^{-3}; 200 cm^3) then with water, dried and evaporated under reduced pressure. Crystallisation of the product gave *anthranilate* **11** (33.16 g, 69%) as a colourless solid (from light petroleum), mp 58–60 °C (Found: C, 76.55; H, 5.65; N, 3.9. $C_{22}H_{19}NO_3$ requires C, 76.5; H, 5.55; N, 4.05%); δ_H([$^2H_6$]-DMSO) 3.71 (s, OCH_3), 5.36 (s, Ph_2CH), 7.16 [ddd, *J* 8.0, 7.1 and 1.0, H-6 (Ar)], 7.25–7.49 [m, 10 × *CH* (Ph)], 7.58 [ddd, *J* 7.8, 7.1 and 1.5, H-7 (Ar)], 7.89 [dd, *J* 8.0, 1.5, H-5 (Ar)], 8.40 [d, *J* 7.8, H-8 (Ar)] and 10.97 (br s, N*H*); δ_C([$^2H_6$]-DMSO) 52.09 (OCH_3), 58.50 (Ph_2CH), 117.72 (CCO_2Me), 121.03, 123.24, 126.87, 128.34, 128.62, 130.41 and 133.71 [14 × *C*H (Ar, Ph)], 139.33 [*C*NHCO (Ar), *C* (Ph)] and 167.26 and 170.19 (2 × *C*O); ν_{max}/cm^{-1} 3260w, 1680s, 1605m and 1590s; *m/z* 345 (M^+, 9%), 178 (80), 167 (42), 165 (34) and 146 (100). The anthranilate (31.91 g) was dissolved in ethanol (60 cm^3), hydrazine monohydrate (12.41 cm^3) was added and the mixture heated under reflux for 2 h, then cooled to room temperature and the bulk of the ethanol removed under reduced pressure. Crystallisation of the residue gave 2-(*diphenylacetylamino*)*benzohydrazide* **12** (28.87 g, 91%) as a colourless solid, mp 179–181 °C (from ethanol) (Found: C, 72.75; H, 5.7; N, 11.95. $C_{21}H_{19}N_3O_2$ requires C, 73.05; H, 5.55; N, 12.15%); δ_H([$^2H_6$]-DMSO) 4.70 (br s, NH_2NH), 5.23 (s, Ph_2CH), 7.14 [ddd, *J* 7.9, 7.7 and 1.1, H-6 (Ar)], 7.25–7.49 [m, H-7 (Ar), 10 × *CH* (Ar), NH_2], 7.72 [dd, *J* 7.9 and 1.4, H-5 (Ar)], 8.51 [d, *J* 7.8, H-8 (Ar)] and 11.61 (s, NHCO); δ_C([$^2H_6$]-DMSO) 58.82 (Ph_2CH), 119.92 [*C*CC (Ar)], 120.40, 122.82, 126.85, 127.50, 128.35, 128.54 and 131.58 [14 × *C*H (Ar)], 138.52 and 139.40 [*C* (Ph), CONH*C*], 166.92 (Ph_2CHCO) and 169.85 (NH_2NHCO); ν_{max}/cm^{-1} 3320w, 3230m, 1660s, 1630w and 1600s; *m/z* 345 (M^+, 4%), 313 (24), 312 (20), 178 (55), 168 (31), 167 (100), 166 (27), 165 (70), 152 (26), 149 (20) and 146 (89). The hydrazide (27.16 g), in ethanol (100 cm^3), was heated in a closed steel vessel at 185 °C for 2 days. After cooling to room temperature, the solid obtained gave the 3-*aminoquinazolinone* **13** as colourless crystals (22.38 g, 87%) mp 211–213 °C (from ethanol) (Found: C, 77.0; H, 5.3; N, 12.8. $C_{21}H_{17}N_3O$ requires C, 77.05; H, 5.25; N, 12.85%); δ_H([$^2H_6$]-DMSO) 4.80 (br s, NH_2), 6.31 (s, Ph_2CH), 7.22–7.37 [m, 10 × *CH* (Ph)], 7.44 (ddd, *J* 8.2, 7.9 and 1.7, Q 6-H), 7.62–7.71 (m, Q 7- and 8-H) and 8.22 (ddd, *J* 7.9, 1.4 and 0.7, Q 5-H); δ_C([$^2H_6$]-DMSO) 53.76 (Ph_2CH), 119.87 [*C*CO (Q)], 126.30, 126.64, 127.07, 127.99, 128.51, 129.43 and 134.01 [14 × *C*H (Ph, Q)], 139.78 [2 × *C* (Ph)], 146.39 [*C*N=C (Q)], 157.83 [*C*=N (Q)] and 161.55 [*C*O (Q)]; ν_{max}/cm^{-1} 3330w, 3280w, 1675s and 1600m; *m/z* 328 (M + 1, 23%), 327 (M^+, 100), 311 (24), 310 (29), 235 (39), 167 (26) and 165 (37).

3-[(*S*)-2-Acetoxypropanoyl]amino-2-diphenylmethyl-3,4-dihydroquinazolin-4-one 14

The general procedure for monoacylation was followed using 3-aminoquinazolinone **13** (1.73 g), (*S*)-2-acetoxypropanoyl chloride (0.88 g), dichloromethane (5 cm^3) and pyridine (0.43 cm^3). After work-up, the solid obtained was purified by flash chromatography over silica using light petroleum–ethyl acetate (2:1) as eluent to give the title 3-*acylaminoquinazolinone* **14** as colourless crystals (R_f 0.32) (1.82 g, 78%), mp 181–184 °C (from ethanol) (Found: C, 70.4; H, 5.3; N, 9.45. $C_{26}H_{23}N_3O_4$ requires C, 70.7; H, 5.25; N, 9.5%); δ_H([$^2H_6$]-DMSO) (mixture of N–N bond rotamers, major rotamer) 1.54 (d, *J* 6.8, CH_3CH), 2.19 (s, CH_3CO), 5.12 (q, *J* 6.8, CH_3CH), 5.85 (s, Ph_2CH), 7.23–7.50 [m, 10 × *CH* (Ph)], 7.54–7.59 (m, Q 6-H), 7.64 (d, *J* 7.9, Q 8-H), 7.84 (ddd, *J* 8.2, 7.9 and 1.4, Q 7-H), 8.15 (m, Q 5-H) and 11.46 (s, N*H*); (minor rotamer, observable peaks), 2.17 (s, CH_3CO), 5.22 (q, *J* 6.8, CH_3CH), 5.70 (s, Ph_2CH) and 11.37 (s, N*H*); δ_C([$^2H_6$]-DMSO) (major rotamer) 16.63 and 20.43

($2 \times CH_3$), 51.67 (Ph_2CH), 58.54 (CH_3CHOAc), 120.31 [CCO (Q)], 126.29, 126.51, 126.61, 127.19, 127.49, 127.63, 127.93, 128.48, 128.68, 128.73, 129.12, 129.31, 135.01 and 135.97 [$14 \times CH$ (Ph, Q)], 139.09 and 139.96 [$2 \times C$ (Ph)], 145.82 [CN=C (Q)], 158.56 [CN (Q)], 158.75 [CO (Q)] and 170.05 and 171.00 ($2 \times CO$); (minor rotamer, observable peaks), 17.27 and 20.38 ($2 \times CH_3$), 51.76 (Ph_2CH), 69.58 (CH_3CHOAc), 123.77 [CCO (Q)], 139.05 and 140.12 [$2 \times C$ (Ph)], 145.42 [CN=C (Q)], 158.65 [CO (Q)] and 170.02 and 170.07 ($2 \times CO$); ν_{max}/cm^{-1} 3320w, 1720s, 1690s and 1595s; m/z 441 (M^+, 100%), 328 (51), 327 (59), 312 (21), 311 (50), 310 (30), 309 (20), 167 (48), 165 (56), 152 (22), 115 (22) and 87 (43).

(*S*)-3-[*N*-(2-Acetoxypropanoyl)-*N*-(2-methylpropanoyl)amino]-2-diphenylmethyl-3,4-dihydroquinazolin-4-one 15

The monoacylaminoquinazolinone **14** (1 g), prepared as described above, was treated with isobutyryl chloride (1.08 g) in dichloromethane (1 cm^3) and pyridine (2 cm^3), according to the general procedure. After work-up the dark brown oil obtained was purified by column chromatography over silica eluting with light petroleum–ethyl acetate (5:1) to give 3-[N,N-*bis*(2-*methylpropanoyl*)*amino*]-2-*diphenylmethyl*-3,4-*dihydroquinazolin*-4-*one* **16** (R_f 0.38) as colourless crystals (0.11 g, 10%) mp 154–156 °C (from ethanol) (Found: M^+, 467.2206. $C_{29}H_{29}N_3O_3$ requires M^+, 467.2209); δ_H 0.85 and 1.23 (d, $4 \times CH_3CH$), 2.98–3.03 ($2 \times$ br heptet, $2 \times CH_3CHCH_3$), 5.32 (s, Ph_2CH), 7.24–7.42 [m, $10 \times CH$ (Ph)], 7.48 (ddd, *J* 8.0, 6.8 and 1.5, Q 6-H), 7.68–7.78 (m, Q 7- and 8-H) and 8.25 (ddd, *J* 8.0, 1.2 and 0.4, Q 5-H); δ_C 18.65 and 19.92 ($4 \times CH_3CH$), 34.46 ($2 \times CH_3CHCH_3$), 52.93 ($CHPh_2$), 120.79 [CCO (Q)], 127.08, 127.23, 127.38, 128.11, 128.55, 129.16 and 134.99 [$14 \times CH$ (Ph, Q)], 138.60 [$2 \times C$ (Ph)], 146.21 [CN=C (Q)], 157.26 [CN (Q)], 159.81 [CO (Q)] and 178.38 ($2 \times CO$); ν_{max}/cm^{-1} 1730s, 1690s, 1610s and 1600s; m/z 468 (M + 1, 32%), 467 (M^+, 100), 397 (65), 380 (55), 354 (22), 327 (50), 311 (34), 310 (28), 309 (26), 306 (20), 230 (38), 167 (55), 165 (39) and 71 (27). An authentic sample of **16** was prepared from **13** (0.5 g) and isobutyryl chloride (0.48 cm^3) in dichloromethane (4 cm^3) and pyridine (1 cm^3), following the general diacylation procedure. The solid obtained gave colourless crystals of *diacylquinazolinone* **16** (0.55 g, 77%).

Further elution with the same solvent mixture above gave a single diastereoisomer **15a** of the title 3-*diacylaminoquinazolinone* (R_f 0.30) as an oil (0.30 g, 26%). On setting aside for several weeks the oil crystallised, mp 141–143 °C (from ethanol) (Found: M^+, 511.2106. $C_{30}H_{29}N_3O_5$ requires M^+, 511.2107); δ_H 0.19 (d, *J* 6.7, CH_3CHCH_3), 0.94 (d, *J* 6.7, CH_3CHCH_3), 1.64 (d, *J* 6.2, CH_3CHOAc), 2.02–2.07 (br m, CH_3CHCH_3), 2.15 (s, CH_3CO), 5.61 (s, $CHPh_2$), 6.07 (br q, *J* 6.2, CH_3-CHOAc), 7.13–7.38 [m, $10 \times CH$ (Ph)], 7.42 (ddd, *J* 8.1, 7.7 and 1.7, Q 6-H), 7.59 (d, *J* 7.3, Q 8-H), 7.70 (ddd, *J* 8.1, 7.7 and 1.4, Q 7-H) and 8.18 (d, *J* 7.7, Q 5-H); δ_C 16.74, 19.25, 21.06 and 21.19 ($4 \times CH_3$), 34.10 (CH_3CHCH_3), 52.58 (Ph_2CH), 72.34 (CH_3CHOAc), 121.31 [CCO (Q)], 127.35, 127.68, 128.05, 128.55, 128.62, 129.01, 129.95, 130.10 and 135.93 [$14 \times CH$ (Ph, Q)], 138.45 and 141.25 [$2 \times C$ (Ph)], 147.04 [CN=C (Q)], 157.90 [CN (Q)], 160.81 [CO (Q)] and 171.91, 173.40 and 180.26 ($3 \times CO$); ν_{max}/cm^{-1} (CH_2Cl_2) 1730s, 1700m, 1605m and 1595m; m/z 512 (M + 1, 31%), 511 (M^+, 94), 442 (11), 441 (38), 397 (40), 354 (73), 327 (61), 312 (32), 311 (82), 310 (41), 309 (31), 235 (20), 167 (100), 166 (28), 165 (79), 152 (34), 115 (23), 87 (41) and 71 (33). Crystals of **15a** suitable for X-ray structure determination were obtained by crystallisation from ethanol.

Further elution with the same solvent mixture gave a second diastereoisomer **15b** as an oil (R_f 0.20) (0.36 g, 31%) containing *ca.* 10% of the monoacylquinazolinone **17** (see below) (Found: M^+, 511.2105. $C_{30}H_{29}N_3O_5$ requires M^+, 511.2107); δ_H 0.60 (d, *J* 6.7, CH_3CHCH_3), 0.98 (d, *J* 6.7, CH_3CHCH_3), 1.58 (d, *J* 5.8, CH_3CHOAc), 2.11 (s, CH_3CO), 2.61–2.75 (br m, CH_3CHCH_3), 5.51 ($CHPh_2$), 5.70–5.75 (br m, CH_3CHOAc), 7.16–7.37 [m, $10 \times CH$ (Ph)], 7.44 (ddd, *J* 8.0, 7.0 and 0.9, Q 6-H), 7.64 (dd, *J* 8.1 and 0.9, Q 8-H), 7.71 (ddd, *J* 8.1, 7.0 and 1.0, Q 7-H) and 8.24 (dd, *J* 8.0 and 1.0, Q 5-H); δ_C 16.45, 18.45, 19.77 and 20.50 ($4 \times CH_3$), 34.06 (CH_3CHCH_3), 52.88 (Ph_2CH), 72.13 (CH_3CHOAc), 120.70 [CCO (Q)], 126.92, 127.28, 127.44, 127.71, 128.07, 128.12, 128.90, 129.06, 129.26, 129.43 and 135.16 [$14 \times CH$ (Ph, Q)], 137.51 and 139.75 [$2 \times C$ (Ph)], 145.97 [CN=C (Q)], 156.73 [CN (Q)], 159.76 [CO (Q)] and 169.96, 171.51 and 177.55 ($3 \times CO$); ν_{max}/cm^{-1} (CH_2Cl_2) 1730s, 1700s and 1600s; m/z 512 (M + 1, 34%), 511 (M^+, 100), 441 (40), 354 (72), 327 (39), 312 (28), 311 (73), 310 (34), 309 (26), 168 (83), 166 (22), 165 (62), 152 (26), 87 (34) and 71 (25).

An authentic sample of monoacylquinazolinone **17** was prepared from **13** (0.5 g) and isobutyryl chloride (0.24 cm^3) in dichloromethane (2 cm^3) and pyridine (0.2 cm^3), following the general monoacylation procedure. The solid obtained gave colourless crystals of 2-(*diphenylmethyl*)-3-[(2-*methylpropanoyl*)*amino*]-3,4-*dihydroquinazolin*-4-*one* **17** (0.44 g, 73%), mp 78–80 °C (from ethanol) (Found: C, 75.2; H, 5.9; N, 10.5. $C_{25}H_{23}N_3O_2$ requires 75.55; H, 5.85; N, 10.6%); δ_H 1.27 and 1.32 ($2 \times$ d, *J* 6.8, CH_3CHCH_3), 2.69 (h, *J* 6.8, CH_3CHCH_3), 5.66 (s, Ph_2CH), 7.26–7.40 [m, $10 \times CH$ (Ph, Q)], 7.44 (ddd, *J* 8.1, 7.1 and 1.2, Q 6-H), 7.66 (dd, *J* 7.7 and 1.2, Q 8-H), 7.73 (ddd, *J* 7.7, 7.1 and 1.1, Q 7-H), 8.11 (dd, *J* 8.1 and 1.1, Q 5-H) and 8.30 (s, NH); δ_C 18.73 and 19.41 (CH_3CHCH_3), 33.63 (CH_3CHCH_3), 53.76 (Ph_2CH), 120.57 [CCO (Q)], 126.59, 126.63, 126.70, 127.25, 127.89, 128.11, 128.77, 128.79, 129.63, 134.54 [$14 \times CH$ (Ph, Q)], 139.05 and 139.56 [$2 \times C$ (Ph)], 146.44 [CN=C (Q)], 157.65 [C=N (Q)], 160.44 [CO (Q)] and 177.12 (NHCO); ν_{max}/cm^{-1} 3240w, 1720m, 1660s and 1600s; m/z 397 (M^+, 100%), 327 (69), 311 (24), 310 (26), 235 (20), 167 (24) and 165 (30). From comparison of the intensities of signals at δ 0.98 (**15b**) and 1.27 (**17**), the ratio of these two compounds in the sample of **15b** eluted from the column is > 10:1.

3-Acetylamino-2-*tert*-butyl-3,4-dihydroquinazolin-4-one 19

3-Amino-2-*tert*-butyl-3,4-dihydroquinazolin-4-one **18** (1 g) was dissolved in acetic anhydride (3 cm^3) and heated at 50 °C for 8 h. Water was added, the excess acetic anhydride allowed to hydrolyse, dichloromethane (20 cm^3) added and the organic layer separated, washed with saturated aqueous sodium hydrogen carbonate, dried and the solvent evaporated to give a pale yellow oil (0.94 g), which solidified on standing overnight. Crystallisation gave the *monoacylquinazolinone* **19** as a colourless hydrate (0.84 g, 71%), mp 90–92 °C (from ethanol–water) (Found: C, 60.75; H, 6.9; N, 15.15. $C_{14}H_{17}N_3O_2 \cdot H_2O$ requires C, 60.65; H, 6.90; N, 15.15%); δ_H([$^2H_6$]-DMSO) 1.48 [s, $(CH_3)_3C$], 2.22 (s, CH_3CO), 7.62 (ddd, *J* 7.9, 7.3 and 1.1, Q 6-H), 7.75 (d, *J* 7.7, Q 8-H), 7.93 (ddd, *J* 7.7, 7.3 and 1.3, Q 7-H), 8.19 (dd, *J* 7.9 and 1.3, Q 5-H) and 10.92 (s, NH); δ_C([$^2H_6$]-DMSO) 20.78 (CH_3CO), 28.64 [$(CH_3)_3C$], 38.58 [$(CH_3)_3C$], 120.28 [CCO (Q)], 126.17, 126.82, 127.57 and 134.74 [$4 \times CH$ (Q)], 145.87 [CN=C (Q)], 159.88 [C=N (Q)], 162.58 [CO (Q)] and 170.50 ($COCH_3$); ν_{max}/cm^{-1} 3460m, 3380m, 3280w, 3180w, 1695s, 1670s, 1610m and 1590s; m/z 259 (M^+, 47%), 202 (100), 201 (77), 187 (23), 175 (68), 160 (30), 132 (35), 119 (20) and 103 (20).

Attempted *N*-acylation of 19 with (*S*)-2-acetoxypropanoyl chloride

To the monoacylaminoquinazolinone **19** prepared above (0.5 g) in pyridine (2 cm^3), was added (*S*)-2-acetoxypropanoyl chloride (0.87 g) in dichloromethane (1 cm^3), following the general procedure for diacylation. After work-up, the black oil obtained was purified by flash chromatography using light petroleum–ether (7:1) as eluent to give, in order of elution: 2-*acetoxy*-5-tert-*butylpyrazolo*[1,5-c]*quinazoline* **20** as colourless crystals (R_f 0.47) (0.045 g, 8%) mp 117–120 °C (from ethanol) (Found: M^+, 283.1317. $C_{16}H_{17}N_3O_2$ requires M^+, 283.1321); δ_H 1.68 [s, $(CH_3)_3C$], 2.42 (s, CH_3CO), 6.92 (s, C=CH), 7.52

[ddd, J 7.8, 7.3 and 1.2, CH (Ar)], 7.62 [ddd, J 8.3, 7.3 and 1.6, CH (Ar)] and 7.88–7.95 [m, 2 × CH (Ar)]; δ_C 21.25 (CH$_3$CO), 27.68 [(CH$_3$)$_3$C], 38.85 [(CH$_3$)$_3$$C$], 88.24 (C=$C$H), 118.89 ($C$), 122.69, 127.20, 128.65 and 129.73 [4 × CH (Ar)], 139.21, 141.59, 155.09 and 156.78 (4 × C) and 167.80 (COCH$_3$); ν_{max}/cm^{-1} (CH_2Cl_2) 1770s, 1620m and 1600m; m/z 283 (M$^+$, 32%), 241 (37), 240 (22), 226 (40) and 199 (100): 2-{[(S)-2-*acetoxypropanoyl*]*oxy*}-5-tert-*butylpyrazolo*[1,5-c]*quinazoline* **21** as a colourless oil (R_f 0.29) (0.022 g, 3%) (Found: M$^+$, 355.1532. $C_{19}H_{21}N_3O_4$ requires M^+, 355.1532); δ_H 1.81 [s, ($C$$H_3$)$_3$C], 1.85 (d, J 7.0, CH_3CHOAc), 2.34 (s, CH_3CO), 5.50 (q, J 7.0, CH$_3$CHOAc), 7.10 (s, C=CH), 7.62 [ddd, J 7.6, 6.4 and 1.2, CH (Ar)], 7.66 [ddd, J 7.7, 6.5 and 1.2, CH (Ar)] and 7.73–8.07 [m, 2 × CH (Ar)]; ν_{max}/cm^{-1} (CH_2Cl_2) 1780m, 1745m, 1710s, 1620m and 1605m; m/z 355 (M$^+$, 26%), 241 (45), 240 (24), 226 (39) and 199 (100): 2-tert-*butyl*-3-*diacetylamino*-3,4-*dihydroquinazolinone* **22** as a colourless oil (R_f 0.24) (0.05 g, 9%) (Found: M$^+$, 301.1427. $C_{16}H_{19}N_3O_3$ requires M^+, 301.1426); δ_H 1.41 [s, (CH_3)$_3$C], 2.42 (s, 2 × CH_3CO), 7.49 (ddd, J 7.9, 7.0 and 1.4, Q 6-H), 7.71 (ddd, J 8.2, 1.4 and 0.5, Q 8-H), 7.80 (ddd, J 8.2, 7.0 and 1.5, Q 7-H) and 8.21 (ddd, J 7.9, 1.5 and 0.5, Q 5-H); δ_C 24.85 (2 × CH$_3$CO), 29.51 [(CH$_3$)$_3$C], 39.65 [(CH$_3$)$_3$$C$], 120.25 [$C$CO (Q)], 126.97, 127.16, 128.08 and 135.09 [4 × CH (Q)], 146.22 [CN=C (Q)], 160.43 [C=N (Q)], 160.69 [CO (Q)] and 171.51 (2 × CH$_3$$C$O); ν_{max}/cm^{-1} (CH_2Cl_2) 1740s, 1690s, 1605m, 1590s and 1580m; m/z 301 (M$^+$, 1%) and 202 (100).

(*S*)-2-(1-Methoxyethyl)-3-methylamino-3,4-dihydroquinazolin-4-one 26

To a stirred solution of sodium hydride (3 g, 5 equiv.) in freshly distilled THF (50 cm^3) under an argon atmosphere, was added (*S*)-3-amino-2-(1-hydroxyethyl)-3,4-dihydroquinazolin-4-one **25**[7] (5.13 g). The mixture was stirred for 30 min during which time a white solid formed. To this stirred slurry was added methyl iodide (17.78 g) and the stirring continued overnight. After addition of dry ether (50 cm^3), the insoluble sodium iodide was separated and the solution evaporated under reduced pressure. The residue was dissolved in dichloromethane (60 cm^3), the solution washed with water and the organic layer dried and evaporated under reduced pressure to give a 1:1 mixture of the O-*methyl*- and O,N-*dimethyl*-*quinazolinones* **26** and **27** respectively (3.02 g, 55%). Fractional crystallisation from ethyl acetate–light petroleum gave 3-*amino*-2-[(S)-1-*methoxyethyl*]-3,4-*dihydroquinazolin*-4-*one* **27**: $[\alpha]_D = -22.9$ (c 2.4, CH_2Cl_2) (Found: C, 61.8; H, 6.6; N, 17.85. $C_{12}H_{15}N_3O_2$ requires C, 61.8; H, 6.5; N, 18.0%); δ_H 1.57 (d, J 6.4, CH_3CHOCH$_3$), 2.79 (br s, CH_3NH), 3.43 (s, OCH_3), 4.94 (q, J 6.4, CH$_3$CHOCH$_3$), 5.54 (br s, NH), 7.42 (ddd, J 8.1, 7.1 and 1.3, Q 6-H), 7.70 (ddd, J 8.2, 7.1 and 1.5, Q 7-H), 7.78 (dd, J 8.2 and 1.3, Q 8-H) and 8.21 (dd, J 8.1 and 1.5, Q 5-H); δ_C 19.17 (CH$_3$CHOCH$_3$), 38.24 (CH$_3$NH), 56.95 (CH$_3$O), 74.51 (CH$_3$$C$HOCH$_3$), 120.79 [$C$CO (Q)], 126.11, 126.51, 127.72 and 134.11 [4 × CH (Q)], 146.75 [CN=C (Q)], 157.28 [C=N (Q)] and 161.08 [CO (Q)]; ν_{max}/cm^{-1} (CH_2Cl_2) 3317w, 1675s and 1597s; m/z 233 (M$^+$, 6%), 174 (100), 173 (42) and 146 (20).

(*S*)-3-(*N*-Benzoyl-*N*-methylamino)-2-(1-methoxyethyl)-3,4-dihydroquinazolin-4-one 28

The *O*,*N*-dimethylquinazolinone **26** (0.19 g) was dissolved in benzoyl chloride (10 cm^3), dry pyridine (0.11 g) added and the solution left at room temperature for 6 days. After removal of the bulk of the remaining pyridine and benzoyl chloride by distillation under reduced pressure (0.2 mmHg; 90 °C bath temp.), the residue was dissolved in dichloromethane (20 cm^3) and the solution washed with saturated aqueous sodium hydrogen carbonate, then water, dried and the solvent removed under reduced pressure. Chromatography of the residue over silica, with ethyl acetate–light petroleum (1:2) as eluent, gave a single diastereoisomer **28a** of the title *quinazolinone* (R_f 0.41) as colourless crystals (0.11 g, 40%), mp 119–121 °C (from ethyl acetate–light petroleum) $[\alpha]_D = -146.3$ (c 10.4, CH_2Cl_2) (Found: C, 67.5; H, 5.75; N, 12.45. $C_{19}H_{19}N_3O_3$ requires C, 67.65; H, 5.7; N, 12.45%); δ_H(mixture of amide rotamers, major rotamer) 1.64 (d, J 6.7, CH_3CHOCH$_3$), 3.42 (s, CH_3N), 3.46 (s, CH_3O), 4.63 (q, J 6.7, CH$_3$CHOCH$_3$), 7.43–7.58 [m, Q 6-H and 3 × CH (Ph)], 7.69–7.85 [m, Q 7- and 8-H and 2 × CH (Ph)] and 8.32 (ddd, J 7.9, 1.3, 0.7, Q 5-H); (minor rotamer, observable peaks), 1.63 (d, J 6.4, CH_3CHOCH$_3$), 3.25 (s, CH_3N), 3.50 (s, CH_3O), 4.72 (q, J 6.4, CH$_3$CHOCH$_3$), 7.15–7.28 [m, 4 × CH (Ph)] and 8.16 (dd, J 7.9, 1.3, Q 5-H); the ratio of major:minor rotamers is 4.1:1 from comparison of the intensities of the signals at δ 8.32 (major) and 8.16 (minor); δ_C(major rotamer) 17.16 (CH$_3$CHOCH$_3$), 40.62 (CH$_3$N), 56.24 (CH$_3$O), 75.12 (CHOCH$_3$), 121.89 [CCO (Q)], 126.23, 126.93, 127.36, 128.13, 128.69 and 131.06 [8 × CH (Ph, Q)], 133.48 [CCO (Ph)], 134.79 [CH (Q)], 146.42 [CN=C (Q)], 155.62 [C=N (Q)], 159.02 [CO (Q)] and 170.81 (PhCON); (minor rotamer, observable peaks), 37.00 (CH$_3$N), 56.16 (CH$_3$O), 73.85 (CHOCH$_3$), 121.18 [CCO (Q)], 130.55 and 134.93 [2 × CH (Q)], 145.72 [CN=C (Q)], 154.48 [C=N (Q)], 160.00 [CO (Q)] and 172.70 (PhCON); ν_{max}/cm^{-1} 1700s and 1606s; m/z 337 (M$^+$, 3%), 307 (24), 174 (38), 105 (100) and 77 (33).

Further elution with ethyl acetate–light petroleum gave the second diastereoisomer of **28b** of the title *quinazolinone* (R_f 0.32) as colourless crystals (0.089 g, 37%), mp 142–144 °C (from ethanol) $[\alpha]_D = +59.5$ (c 8.6, CH_2Cl_2) (Found: M$^+$, 337.1431. $C_{19}H_{19}N_3O_3$ requires M^+, 337.1426); δ_H(mixture of amide rotamers, major rotamer) 1.65 (d, J 6.4, CH_3CHOCH$_3$), 3.45 (s, CH_3N), 3.47 (s, CH_3O), 4.64 (q, J 6.4, CH$_3$CHOCH$_3$), 7.45–7.57 [m, Q 6-H and 3 × CH (Ph)], 7.65–7.73 (m, Q 7- and 8-H), 7.74–7.85 [m, 2 × CH (Ph)] and 8.31 (ddd, J 8.6, 2.1 and 0.9, Q 5-H); (minor rotamer, observable peaks) 1.54 (d, J 6.4, CH_3CHOCH$_3$), 3.46 (s, CH_3N), 3.56 (s, CH_3O), 4.81 (q, J 6.4, CH$_3$CHOCH$_3$), 7.14–7.24 [m, 2 × CH (Ph)], 7.37–7.45 [m, CH (Ph)] and 8.18 (ddd, J 8.6, 2.1 and 0.9, Q 5-H); this compound exists as a 3.2:1 ratio of rotamers from comparison of intensities of signals at δ 8.31 (major) and 8.18 (minor); δ_C(major rotamer) 19.74 (CH$_3$CHOCH$_3$), 41.06 (CH$_3$N), 57.41 (CH$_3$O), 77.07 (CHOCH$_3$), 121.78 [CCO (Q)], 127.05, 127.27, 127.60, 127.89, 128.70 and 131.21 [8 × CH (Ph, Q)], 133.30 [CCO (Ph)], 135.10 [CH (Q)], 146.56 [CN=C (Q)], 156.82 [C=N (Q)], 159.15 [CO (Q)] and 170.92 (PhCON); (minor rotamer, observable peaks), 18.71 (CH$_3$CHOCH$_3$), 38.24 (CH$_3$N), 56.67 (CH$_3$O), 73.84 (CHOCH$_3$), 126.97, 127.21, 128.04, 128.14, 130.76, 133.20, 134.91 [5 × CH (Ph) and 4 × CH (Q)] and 156.00 [CN (Q)]; ν_{max}/cm^{-1} (CH_2Cl_2) 1700s, 1680s and 1600s; m/z 337 (M$^+$, 3%), 174 (40), 105 (100) and 77 (33). An X-ray crystal structure determination was carried out on one of a small number of crystals of **28b** which crystallised from ethanol; these were subsequently found to have mp 123–127 °C and $[\alpha]_D = 0$.

3-Diacetylamino-2-ethyl-3,4-dihydroquinazolin-4-one 29

The general procedure for diacylation was applied using 3-amino-2-ethylquinazolinone **20** (2 g), acetic anhydride (6.16 g) and pyridine (2.45 cm^3). The reaction mixture was heated at 50 °C for 24 h then stirred at room temperature overnight. The solution was poured into water (20 cm^3), the excess acetic anhydride decomposed by stirring (*ca.* 10 min), then the product extracted into dichloromethane (60 cm^3). The organic layer was washed with saturated aqueous sodium hydrogen carbonate, then water, dried and the solvent removed under reduced pressure to yield a yellow oil (2.27 g). This oil solidified on standing and crystallisation from ethanol gave the title *quinazolinone* **29** as colourless crystals (1.94 g, 67%), mp 75–76 °C (from ethanol) (Found: C, 61.4; H, 5.6; N, 15.35. $C_{14}H_{15}N_3O_3$ requires C, 61.5; H, 5.55; N, 15.4%); δ_H([$^2H_6$]-DMSO) 1.27 (br t, CH_3CH$_2$), 2.41 (s, 2 × CH_3CO), 2.68 (br q, CH$_3$CH_2), 7.56–7.60 (m, Q 6-H), 7.76 (d, J 7.9, Q 8-H), 7.88–

7.93 (m, Q 7-H) and 8.17 (d, J 7.7, Q 5-H); δ_C([$^2H_6$]-DMSO) 9.72 (CH_3CH_2), 24.28 (2 × CH_3CO), 25.14 (CH_3CH_2), 120.08 [CCO (Q)], 126.62, 127.09, 127.33 and 135.50 [4 × CH (Q)], 146.24 [CN=C (Q)], 157.23 [C=N (Q)], 158.80 [CO (Q)] and 170.12 (2 × CH_3CO); ν_{max}/cm^{-1} 1740s, 1700s, 1605s and 1570w; m/z 273 (M^+, 33%), 231 (26), 214 (52), 189 (100), 173 (20), 130 (22) and 119 (26).

Kinetic resolution of 1-phenylethylamine by acylation using 3-diacylaminoquinazolinones 15a and 15b

To the imide **15a** (0.05 g, 0.5 equiv.) dissolved in toluene (1.5 cm^3) was added racemic 1-phenylethylamine (0.025 cm^3, 1 equiv.) and the solution set aside at −20 °C for 2 days. The solution was allowed to warm to ambient temperature with stirring and then the bulk of the solvent was removed under reduced pressure. The residue was diluted with dichloromethane (10 cm^3) and the solution washed with hydrochloric acid (2 mol dm^{-3}; 5 cm^3) and water, dried and the solvent removed under reduced pressure. Examination of the residue by NMR spectroscopy showed the presence of (2*S*,1′*R*)- and (2*S*,1′*S*)-2-acetoxy-*N*-(1-phenylethyl)propanamide **30a** and **30b** in a ratio of 3.6 : 1 respectively from comparison of the intensity of signals at δ 2.10 and 2.11 (CH_3CO) and by comparison with authentic samples prepared as follows. (*S*)-2-Acetoxypropanoyl chloride (1.24 g) in dichloromethane (2 cm^3) was added to a stirred and ice-cooled solution of (*S*)-1-phenylethylamine (1 g) in pyridine (0.74 cm^3) and dichloromethane (2 cm^3). After 1 h further dichloromethane (30 cm^3) was added, the solution washed successively with saturated aqueous sodium hydrogen carbonate (10 cm^3), hydrochloric acid (2 mol dm^{-3}; 10 cm^3) and water (10 cm^3), then dried and the solvent removed under reduced pressure to give a yellow solid. Crystallisation twice from ethyl acetate gave pale yellow crystals of *amide* **30a** (7.1 g, 88%) $[\alpha]_D$ = −78 (c 6, CH_2Cl_2) (Found: MH^+, 236.1286. $C_{13}H_{18}N_1O_3$ requires MH^+, 236.1287); δ_H 1.47 (d, J 6.9, CH_3CH), 1.52 (d, J 7.0, CH_3CH), 2.11 (s, CH_3CO), 5.08–5.20 (m, 2 × CH_3CH), 6.39 (br d, J 6.8, NHCHCH$_3$) and 7.23–7.37 [m, 5 × CH (Ph)]; δ_C 18.2, 21.5 and 22.1 (3 × CH_3), 48.8 and 71.0 (2 × CH_3CH), 126.4, 126.5, 127.8 and 129.1 [5 × CH (Ph)], 143.2 [C (Ph)] and 169.9 and 170.0 (2 × CO); ν_{max}/cm^{-1} 3440m, 1745s and 1630s cm^{-1}; m/z [CI(NH_3)] 253 ($M + NH_4)^+$ and 236 (MH^+, 100%). Repetition of the above procedure using (*R*)-1-phenylethylamine gave amide **30b** as a yellow oil (1.67 g, 86%) $[\alpha]_D$ = +14 (c 6, CH_2Cl_2) (Found: MH^+, 236.1286. $C_{13}H_{18}N_1O_3$ requires MH^+, 236.1287); δ_H 1.44 (d, J 6.9, CH_3CH), 1.49 (d, J 7.0, CH_3CH), 2.10 (s, CH_3CO), 5.07–5.16 (m, CH_3CHNH), 5.19 (q, J 6.9, CH_3-CHCO), 6.48 (br d, J 7.0, NHCHCH$_3$) and 7.19–7.42 [m, 5 × CH (Ph)]; δ_C 18.3, 21.5 and 22.0 (3 × CH_3), 48.8 and 71.1 (2 × CH_3CH), 126.5, 127.9 and 129.1 [5 × CH (Ph)], 143.1 [C (Ph)] and 169.9 and 170.0 (2 × CO); ν_{max}/cm^{-1} 3440m, 1750s and 1680s; m/z [CI(NH_3)] 253 ([$M + NH_4]^+$) and 236 (MH^+, 100%).

The same reaction described above but using **15b** (containing *ca.* 10% of monoacylquinazolinone **16**, see previously) gave a 2.3 : 1 ratio of diastereoisomers **30b** : **30a** respectively from comparison of the same signals in the NMR spectrum of the crude reaction mixture. Reaction of (*S*)-2-acetoxypropionyl chloride with racemic 1-phenylethylamine using the procedure given above gave a 1.05 : 1 ratio of **30a** : **30b** from comparison of the same signals in the NMR spectrum of the crude reaction mixture.

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References

1 Y. Shvo, in *The Chemistry of Hydrazo, Azo and Azoxy Groups*, ed. S. Patai, Interscience, New York, 1974, part 2.
2 S. M. Verma and R. Prasad, *J. Org. Chem.*, 1973, **38**, 1004.
3 R. S. Atkinson, P. J. Edwards and G. A. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3209.
4 Preliminary communication: R. S. Atkinson, E. Barker, C. Price and D. R. Russell, *J. Chem. Soc., Chem. Commun.*, 1994, 1159.
5 M. D. Wunderlich, L. K. Leung, J. A. Sandberg, K. D. Meyer and C. H. Yoder, *J. Am. Chem. Soc.*, 1978, **100**, 1500.
6 E. A. Noe and M. Raban, *J. Am. Chem. Soc.*, 1975, **77**, 5811.
7 R. S. Atkinson, B. J. Kelly and J. Williams, *Tetrahedron*, 1992, **48**, 7713.
8 R. S. Atkinson and E. Barker, unpublished work.

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