The N–N Bond as a Chiral Axis: 3-(Diacylamino)quinazolin-4(3*H*)ones as Chiral Acylating Agents

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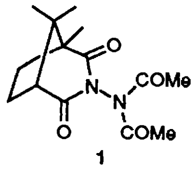
Two diastereoisomers of 3-(diacylamino)quinazolinone **5** are separated and identified by crystal structure determinations which confirm the presence of an N–N chiral axis: one diastereoisomer of enantiopure **8** reacts with racemic 1-phenylethylamine exclusively at the 2-acetoxypropanoyl imide carbonyl group and with kinetic resolution to give a 3.6 : 1 ratio of diastereoisomers of **10**.

The barriers to rotation around N–N bonds in di-, tri-, and tetra-acyl-substituted hydrazines are large by comparison with those around most other single bonds.[1] Verma *et al.*[2] have shown that the barrier to rotation around the N–N bond in *N*,*N*-diacetylaminocamphorimide **1** is in excess of 97 kJ mol^{-1} since no coalescence of the signals from the acetyl methyl groups was observed in its NMR spectrum at 150 °C.

We have prepared a number of 3-(diacylamino)quinazolinones **2** from the corresponding 3-aminoquinazolinones **3** (Scheme 1). The monoacylation products **4** are isolated in good yields because diacylation is a much slower reaction under the same conditions: this allows reaction to be carried out with a second acyl group that is different from the first.

Using the method in Scheme 1, the compound **5** has been prepared by reaction of 2-phenylpropanoyl chloride with the appropriate 3-(acetylamino)quinazolinone as a mixture of diastereoisomers **5a** and **5b** (1.8 : 1). Separation of these diastereoisomers by chromatography provided crystalline samples of each on which X-ray crystal structure determinations have been carried out (Fig. 1).†‡



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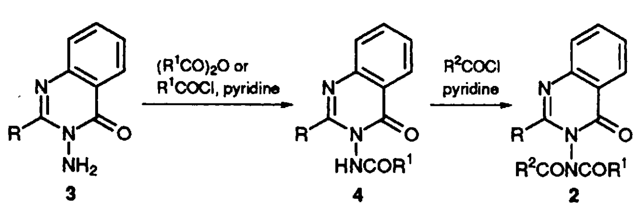
As anticipated, both molecules comprise two orthogonal planes containing the quinazolinone and diacylimide units, respectively, with the N–N bond as a chiral axis, The '*exo–endo*' arrangement of the acyl carbonyl groups with one *cis* to the quinazolinone ring and one *trans*, is known to be the preferred conformation for simple imides.[3]

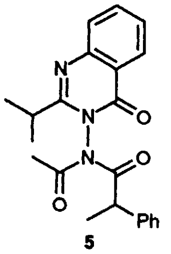
Diastereoisomers **5a** and **5b** are interconverted by rotation around their N–N bonds. Heating **5b** in toluene at three different temperatures and measurement of the rate constants for its interconversion with **5a** at each temperature gave the following: $\Delta G^\ddagger$ = 121.3 kJ mol^{-1}; $\Delta H^\ddagger$ = 77.2 kJ mol^{-1}; $\Delta S^\ddagger$ = −118.2 J K^{-1} mol^{-1}.

Slow rotation around the imide N–CO bonds in **5a** and **5b** gives rise to broadening of some signals in their NMR spectra. From analysis of the NMR spectrum of **6** at low temperature (−83 °C) in [^{2}H$_6$]acetone, the two imide conformations which are in equilibrium are the two (identical) *exo–endo* and *endo–exo* conformations: it is likely that an analogous process is responsible for the broadening of the signals in the NMR spectra of **5a** and **5b**.

These 3-(diacylamino)quinazolinones are readily attacked



Scheme 1



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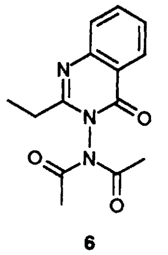

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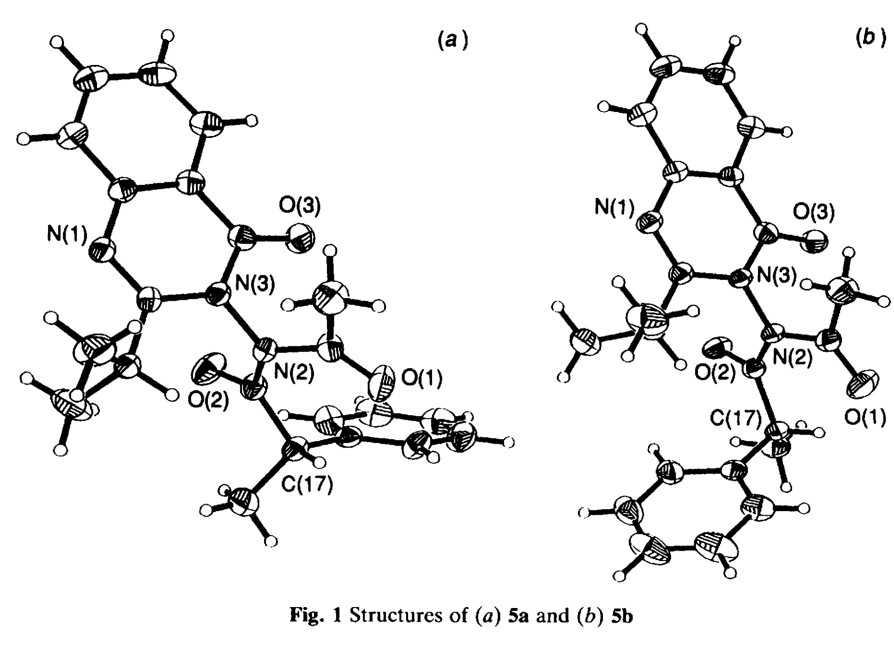
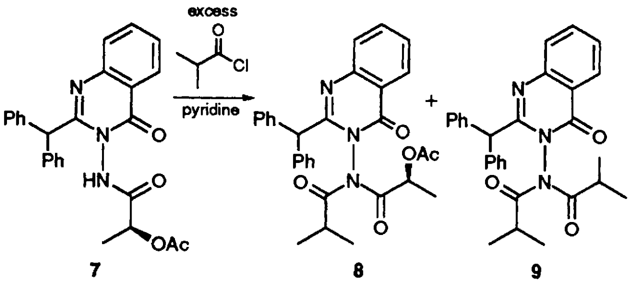
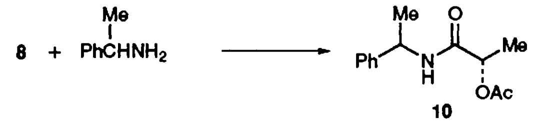


Fig. 1 Structures of (*a*) **5a** and (*b*) **5b**



7 **8** **9**

Scheme 2



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Scheme 3

by nucleophiles. An unexpected by-product **9** in the preparation of **8** illustrates this reactivity (Scheme 2). Acylation of the required 3-aminoquinazolinone (*cf*. Scheme 1) with (*S*)-2-acetoxypropanoyl chloride gave **7**. Further acylation with isobutanoyl chloride followed by flash chromatography allowed separation of the two diastereoisomers of **8** and also gave a product identified as **9** by comparison with an authentic sample. Formation of **9** is believed to arise by selective nucleophilic attack by chloride anion on the 2-acetoxypropanoyl group of one or both diastereoisomers of **8**, followed by re-acylation with isobutanoyl chloride.

The two diastereoisomers of **8**[§] are chiral acylating agents: they react with racemic 1-phenylethylamine exclusively at the 2-acetoxypropanoyl imide carbonyl group with no competitive attack on either the ester or isobutanoyl group (Scheme 3).

When the faster-eluted (R_f 0.3; light petroleum (bp 60–80 °C) : ethyl acetate 5 : 1) (enantiopure) diastereoisomer of **8** is treated with 1-phenylethylamine (2 equiv.) in toluene at −20 °C, the reaction is accompanied by kinetic resolution giving a 3.6 : 1 ratio of diastereoisomers of **10**. From comparison with authentic samples of both diastereoisomers of **10**, it is the (*R*)-enantiomer of the amine which reacts preferentially.

Using the slower-eluted (R_f 0.2, light petroleum : ethyl acetate 5 : 1) diastereoisomer of **8**, a 2.3 : 1 ratio of diastereoisomers of **10** is obtained in which the (*S*)-enantiomer of the amine reacts preferentially.

Clearly, the kinetic resolution obtained in these acylations using 1-phenylethylamine is dominated by the chiral axis since both diastereoisomers of **8** have the (*S*)-configuration at the α-acetoxypropanoyl chiral centre. 2-Acetoxypropanoyl chloride reacts with 1-phenylethylamine with little if any kinetic resolution.

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Footnotes

[†] *Crystal data*: Data were measured at 293 K on a Siemens P4 diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) with an ω scan technique. The data were corrected for Lorentz and polarisation effects.

For **5a**: $C_{22}H_{23}N_3O_3$, M = 377.4, monoclinic, $P2_1/n$, a = 12.181(3), b = 12.712(2), c = 12.991(3) Å, β = 95.12(0.02)°, V = 2003.6(7) Å^3, Z = 4, D_c = 1.251 g cm^{-3}, $F(000)$ = 800, μ = 0.085 mm^{-1}. The intensities of 4565 reflections with $4.0 < 2\theta < 50.6°$ were measured yielding 3616 unique reflections (R_m = 0.0322), of which 2664 had $F > 4\sigma(F)$. The structure was solved by direct methods. All non-hydrogen atoms were refined as anisotropic, hydrogen atoms were included in calculated positions (C–H = 0.95 Å). Final R = 0.0465 and R_w = 0.0640 for 280 variables. $(\Delta/\sigma)_{max}$ = 0.021.

For **5b**: $C_{22}H_{23}N_3O_3$, M = 377.4, triclinic, $P\bar{1}$, a = 8.256(5), b = 8.710(5), c = 14.261(7) Å, α = 93.03(3)°, β = 90.97(3)°, γ = 99.35(5)°, V = 1010.1(11) Å^3, Z = 2, D_c = 1.241 g cm^{-3}, $F(000)$ = 400, μ = 0.085 mm^{-1}. The intensities of 5147 reflections with $4.0 < 2\theta < 50°$ were measured yielding 4299 unique reflections (R_m = 0.0251), of which 2763 had $F > 4\sigma(F)$. The structure was solved by direct methods. All non-hydrogen atoms were refined as anisotropic, hydrogen atoms were included in calculated positions (C–H = 0.95 Å). final R = 0.0605 and R_w = 0.0688 for 257 variables. $(\Delta/\sigma)_{max}$ = 0.009. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

[‡] Compound **5a**, mp 144–147 °C, ν_{max} (Nujol) 1740s, 1705s and 1605s cm^{-1}; δ_H (300 MHz) ($CDCl_3$), 1.13–1.17 (2 × d, J 6.6 Hz, CH_3CHCH_3), 1.59 (d, J 6.9 Hz, CH_3CHPh), 2.20 (s, CH_3CO), 2.49 [h, J 6.6 Hz, $(CH_3)_2CH$], 4.91 (br q, CH_3CHPh), 7.27–7.33 (m, 5 × PhH), 7.48 (ddd, J 8.1, 7.2, and 1.2 Hz, quinaz. H-6), 7.71 (dd, J 8.1 and 0.4 Hz, quinaz. H-8), 7.81 (ddd, J 8.4, 7.0, and 1.5 Hz, quinaz. H-7), and 8.19 (dd, J 8.0 and 1.2 Hz, quinaz. H-5).

Compound **5b**, mp 129–132 °C, ν_{max} (Nujol) 1745s, 1735s, 1705s and 1600s cm^{-1}; δ_H ($CDCl_3$), 0.77 (d, J 6.6 Hz, CH_3CHCH_3), 1.12 (d, J 6.6 Hz, CH_3CHCH_3), 1.54 (d, J 6.6 Hz, CH_3CHPh), 2.45 [Spt, J 6.6 Hz, $(CH_3)_2CH$], 2.59 (s, CH_3CO), 4.08 (br q, J 6.6 Hz, CH_3CHPh). 7.10–7.13 (m, 2 × Ph H), 7.25–7.35 (m, 3 × Ph H), 7.54 (ddd, J 8.3, 7.1 and 1.3 Hz, quinaz. H-6), 7.73 (ddd, J 8.2, 1.3 and 0.8 Hz, quinaz. H-8), 7.85 (ddd, J 8.5, 7.0, and 1.6 Hz, quinaz. H-7) and 8.34 (ddd, J 8.0, 1.5 and 0.8 Hz, quinaz. H-5).

[§] Compound **8**, slower-eluted diastereoisomer (R_f 0.2, light petroleum–ethyl acetate 5:1) ν_{max} (CH_2Cl_2) 1730s, 1700s and 1600s cm^{-1}; δ_H($CDCl_3$, 300 MHz) 0.60 (d, J 5.8 Hz, CH_3CHCH_3), 0.98 (d, J 6.7 Hz, CH_3CHCH_3), 1.58 [d, J 6.7 Hz, $CH_3CH(OAc)$], 2.11 (s, CH_3CO), 2.6–2.75 [m, br, $(CH_3)_2CH$], 5.51 (s, br, Ph_2CH), 5.7–5.75 [m, br, $CH_3CH(OAc)$], 7.16–7.37 (m, 10 × Ph H), 7.44 (ddd, J 8.1, 7.0, and 1.3 Hz, quinaz. H-6), 7.64 (dd, J 8.1 and 0.9 Hz, quinaz. H-8), 7.71 (ddd, J 8.2, 7.0, and 1.5 Hz, quinaz. H-7), and 8.25 (dd, J 8.0 and 1.0 Hz, quinaz. H-5) : faster-eluted diastereoisomer (R_f 0.3, light petroleum–ethyl acetate 5:1) ν_{max} (CH_2Cl_2) 1730s, 1700m and 1605m; δ_H ($CDCl_3$, 300 MHz) 0.19 (d, J 6.2 Hz, CH_3CHCH_3), 0.94 (d, J 6.7 Hz, CH_3CHCH_3), 1.64 [d, J 6 Hz, $CH_3CH(OAc)$], 2.02–2.07 [m, br, $(CH_3)_2CH$], 2.15 (s, CH_3CO), 5.61 (Ph_2CH), 6.07 [q, br, J 6, $CH_3CH(OAc)$], 7.13–7.38 (m, 10 × Ph H), 7.42 (dd, J 8.2, 6.6, and 1.7 Hz, quinaz. H-6), 7.59 (d, J 7.3 Hz, quinaz. H-8), 7.70 (dd, J 8.1 and 1.4 Hz, quinaz. H-7) and 8.18 (d, J 7.7 Hz quinaz. H-5).

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