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).^{†‡}

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 'exoendo' 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: $\Delta G^{\ddagger} = 121.3 \text{ kJ mol}^{-1}$; $\Delta H^{\ddagger} = 77.2 \text{ kJ mol}^{-1}$; $\Delta S^{\ddagger} = -118.2 \text{ J K}^{-1} \text{ mol}^{-1}$.

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

6

(b)

O(1)



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

NH₂

3

1160



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)-2acetoxypropanoyl 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 reacylation 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-K α radiation ($\lambda = 0.71073$ 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, P_{21}/n , a = 12.181(3), b = 12.712(2), c = 12.991(3) Å, $\beta = 95.12(0.02)^\circ$, V = 2003.6(7) Å³, Z = 4, $D_c = 1.251$ g cm⁻³, F(000) = 800, $\mu = 0.085$ mm⁻¹. The intensities of 4565 reflections with $4.0 < 2\theta < 50.6^\circ$ 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. ($\Delta/a)_{max} = 0.021$

0.0640 for 280 variables. $(\Delta/\sigma)_{max} = 0.021$. For 5b: C₂₂H₂₃N₃O₃, M = 377.4, triclinic, $P\overline{1}$, a = 8.256(5), b = 8.710(5), c = 14.261(7) Å, $\alpha = 93.03(3)^{\circ}$, $\beta = 90.97(3)^{\circ}$, $\gamma = 99.35(5)^{\circ}$, V = 1010.1(11) Å³, Z = 2, $D_c = 1.241$ g cm⁻³, F(000) = 400, $\mu = 0.085$ mm⁻¹. The intensities of 5147 reflections with $4.0 < 20 < 50^{\circ}$ 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, v_{max} (Nujol) 1740s, 1705s and 1605s

 \ddagger Compound 5a, mp 144–147 °C, ν_{max} (Nujol) 1740s, 1705s and 1605s cm $^{-1}$; δ_{H} (300 MHz) (CDCl₃), 1.13–1.17 (2 \times d, J 6.6 Hz, CH₃CHCH₃), 1.59 (d, J 6.9 Hz, CH₃CHPh), 2.20 (s, CH₃CO), 2.49 [h, J 6.6 Hz, (CH₃)₂CH], 4.91 (br q, CH₃CHPh), 7.27–7.33 (m, 5 \times 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).

7), and 8.19 (dd, J 8.0 and 1.2 Hz, quinaz. H-5). Compound 5b, mp 129–132 °C, v_{max} (Nujol) 1745s, 1735s, 1705s and 1600s cm⁻¹; δ_{H} (CDCl₃), 0.77 (d, J 6.6 Hz, CH₃CHCH₃), 1.12 (d, J 6.6 Hz, CH₃CHCH₃), 1.54 (d, J 6.6 Hz, CH₃CHPh), 2.45 [Spt, J 6.6 Hz, (CH₃)₂CH], 2.59 (s, CH₃CO), 4.08 (br q, J 6.6 Hz, CH₃CHPh). 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) v_{max} (CH₂Cl₂) 1730s, 1700s and 1600s cm⁻¹; δ_{H} (CDCl₃, 300 MHz) 0.60 (d, *J* 5.8 Hz, CH₃CHCH₃), 0.98 (d, *J* 6.7 Hz, CH₃CHC₃, 0.98 (d, *J* 6.7 Hz, CH₃CHC₃, 0.98 (d, *J* 6.7 Hz, CH₃CH(OAc)], 2.11 (s, CH₃CO), 2.6–2.75 [m, br, (CH₃)₂CH], 5.51 (s, br, Ph₂CH), 5.7–5.75 [m, br, CH₃CH(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) v_{max} (CH₂Cl₂) 1730s, 1700m and 1605m; δ_H (CDCl₃, 300 MHz) 0.19 (d, *J* 6.2 Hz, CH₃CHCH₃), 0.94 (d, *J* 6.7 Hz, CH₃CHCHA₃), 1.64 [d, *J* 6 Hz, CH₃CH(OAc)], 2.02–2.07 [m, br, (CH₃)₂CH], 2.15 (s, CH₃CO), 5.61 (Ph₂CH), 6.07 [q, br, *J* 6. (CH₃CH(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).

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 E. A. Noe and M. Raban, J. Am. Chem. Soc., 1975, 77, 5811.