Tetraacyl hydrazines and 3,3′-biquinazoline-4,4′-diones; synthesis, studies of rotational barriers and deracemisation

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The barrier to rotation around the N–N bond in 3,3′-biquinazoline-4,4′-dione is estimated to be 96 kJ mol^{-1}, significantly higher than in acyclic tetraacyl hydrazines (84 kJ mol^{-1}). Both dynamic chiroptical and NMR studies of 3,3′-biquinazoline-4,4′-diones which have an additional ring bridging the 2,2′ positions indicate that these compounds have a significantly higher barrier to rotation than the parent 3,3′-biquinazoline-4,4′-dione. Deracemisation of certain 3,3′-biquinazoline-4,4′-diones is possible *via* treatment with chiral acids at high temperature.

Introduction

Atropisomeric compounds,[1] that is those whose chirality arises from hindered rotation around a bond, have provoked a large range of work since the earliest *ortho*-substituted biaryls[2] were investigated. Apart from the purely academic interest in these aesthetically pleasing molecules, atropisomers, and particularly the binaphthyls, have formed the core of many important ligands for metals in asymmetric catalysis.[3] After years of domination of the field by binaphthyls, a range of other atropisomeric systems have come into favour, some close analogues of the binaphthyls,[4,5] others wider ranging.[6–8]

While the more traditional[2–6] systems display hindered rotation around C–C bonds, there is increasing interest in ligand systems which rely upon hindered rotation around other bonds, notably C–N[7] and N–N.[8] Although the majority of these systems display hindered rotation due to steric factors, certain N–N bonds may also have an electronic barrier to rotation and it is upon these systems which this paper is focused.

Multiple acylations of hydrazine increase the barrier to rotation around the N–N bond and an origin arising from overlap of lone pairs at planarity has been proposed.[9] However the systems which have been studied contain at least one ring. In early work the 1,1-diacyl substituents were constrained in cyclic imides (*e.g.* Fig. 1[10]); in later work[11] quinazolinone rings formed one end of the chiral axis. Locking the conformation at one end of the axis in this way may give a distorted picture of the true barrier to rotation, as, according to theoretical studies,[12] the fixed conformation of the imide carbonyls (in *e.g.* Fig. 1) increases the barrier to rotation. A stereostable chiral axis in such compounds could allow the design of novel ligands for metals in catalytic asymmetric reactions.

In order to probe the barrier to rotation around the N–N bond a re-examination of the simplest possible such systems was undertaken. While a small number of acyclic tetraacyl hydrazines have been reported[13] no attention has been paid to the possibility of chirality in these simple systems.

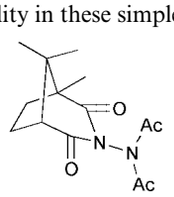

Fig. 1

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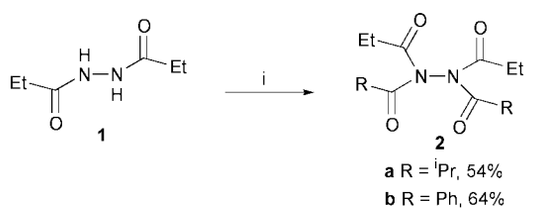
Results and discussion

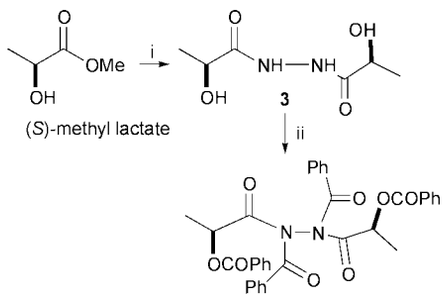
Acyclic tetraacyl hydrazines

1,2-Dipropionylhydrazine **1**[14] was acylated with both isobutyryl chloride and benzoyl chloride to give 1,2-diisobutyryl-1,2-dipropionylhydrazine **2a** and 1,2-dibenzoyl-1,2-dipropionylhydrazine **2b** respectively (Scheme 1). Disappointingly, there



Scheme 1 *Reagents*: (i) RCOCl (4 equiv.), pyridine, a) 16 h, 60 °C; b) 60 h, RT.

was no evidence of diastereotopicity in either the proton or carbon (the methyl groups of the isobutyryl fragment are in principle diastereotopic in the presence of a chiral axis) NMR spectra of **2a**. Gratifyingly, however, **2b** shows an ABX_3 system for the methylene groups indicative of slow rotation around the N–N axis, and thus chirality, at least on the NMR timescale. The presence of the chiral axis which was confirmed by the diastereotopicity of methylene signals in **2b** should give rise to diastereoisomers if an asymmetric carbon is incorporated in the same molecule, and it was to such systems that attention turned. Reaction of hydrazine hydrate with an excess of (*S*)-(−)-methyl lactate at reflux gave (*S*,*S*)-1,2-bis(hydroxypropanoyl)hydrazine **3**, which was perbenzoylated to (*S*,*S*)-1,2-bis-(2-benzoyloxypropanoyl)-1,2-dibenzoylhydrazine **4** (Scheme 2).



Scheme 2 *Reagents*: (i) $H_2NNH_2{\cdot}H_2O$ (0.2 mol. equiv.), 150 °C, 16 h, 47%; (ii) PhCOCl (8 mol. equiv.), pyridine, 96 h, RT, 57%.

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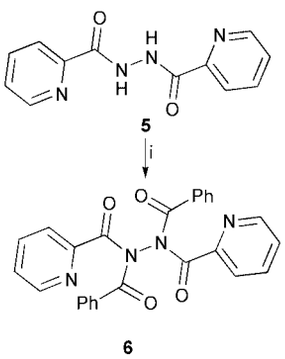
The proton and carbon NMR spectra of **4** indicated that it had been formed as a *ca.* 2:1 mixture of diastereoisomers (this atroposelectivity was unexpected, and appears to represent a thermodynamic ratio as it is unaltered by heating–cooling cycles). The 2-pyridylcarbonyl group is the core of many important ligand systems and a derived tetraacyl hydrazine was readily accessible. In an attempt to synthesise potential ligands for metals based around this system, benzoylation of 1,2-bis-(2-pyridylcarbonyl)hydrazine **5**[15] gave 1,2-dibenzoyl-1,2-bis-(2-pyridylcarbonyl)hydrazine **6** (Scheme 3).



Scheme 3 *Reagents*: (i) PhCOCl, NEt_3, DCM, 12% after recrystallisation.

Both the ^1H and ^{13}C NMR spectra of **6** showed significant broadness at ambient temperature and were only resolved upon heating to 70 °C. Attempts to determine the dynamic process responsible for this phenomenon by the low temperature NMR are made difficult by the low solubility of **6** at low temperatures. We attribute this isomerism to the orientation of the aromatic rings which may have slow rotation about the C–C bonds—the 2-pyridyl group renders the rotamers isomeric and its environment may be sufficiently congested to hinder rotation. This explanation is favoured over the more common phenomenon of hindered rotation around amide C–N bonds, as no such broadening was observed in analogues **2a**,**b** or **4**. N–N rotation is unlikely to be occurring at room temperature at a sufficient rate to cause this broadening given the barriers to rotation which were determined for analogue **4** and calculated for tetraformylhydrazine.[12]

Although the existence of diastereoisomers and diastereotopicity in the NMR of **2b** and **4** and the known molecular geometries of both cyclic and acyclic tetraacyl hydrazines[16,17] point towards the existence of a chiral axis, from theoretical work[12] it is expected that the purely electronic component of the barrier to rotation will not be large enough to ensure stereostability and a substantial steric component will be required too. In order to distinguish between chirality on the NMR timescale and the real timescale the interconversion of the diastereoisomers of **4** was studied at high temperature. VT NMR (400 MHz) studies showed that the methyl doublets (J = 6.8 Hz) of **4** which are separated by *ca.* $\Delta\nu$ = 52 Hz under a slow exchange regime (ambient temperature to 90 °C) coalesce between T_c = 135 and 140 °C when studied as a DMSO solution. This correlates to a free energy barrier of 82–84 kJ mol^{-1} (82.3 ± 0.3 to 83.6 ± 0.3) for the interconversion of the isomers according to eqn. (1),[18]‡ which is in good agreement with the

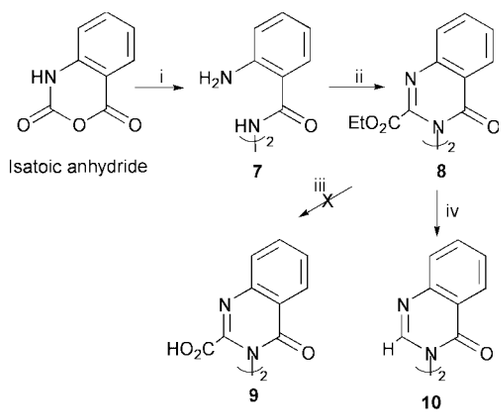
$$\Delta G^{ts} = 19.2T_c\{9.67 + \log [T_c/(\Delta\nu^2 + 6J^2)^{1/2}]\} \qquad (1)$$

theoretically determined value,[12] and somewhat lower than the cyclic imide containing species previously studied.[10] This supports the theoretical[12] finding that the large barriers to rotation in these systems are associated with O–O contacts and in systems which can avoid these interactions the residual barrier due to orbital overlap is around 80 kJ mol^{-1}, which, while significant, does not represent stereostability.

‡ Units: T_c (K); $\Delta\nu$, J (Hz); ΔG^{ts} (kJ mol^{-1}).

3,3′-Biquinazoline-4,4′-diones

Tetracyl hydrazines having proved to have too low a barrier to racemisation to be attractive as ligand systems, attention turned to 3,3′-biquinazoline-4,4′-diones. These were attractive as they were anticipated to be very stable materials and their molecular geometry dictates that the carbonyl oxygen is in a conformation which is known to increase the barrier to rotation.[12] While a range of 3,3′-biquinazoline-4,4′-diones have been reported, some of which contained substituents which could be expected to show diastereotopicity in their NMR spectra, no such phenomenon has been reported.[19] The literature[19] method for the synthesis of 3,3′-biquinazoline-4,4′-diones required dianthraniloylhydrazine **7**; however as literature methods for the synthesis of **7** are tedious a simplified method was devised (Scheme 4). For any study of chirality substituents which may



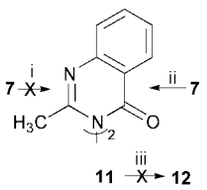
Scheme 4 *Reagents*: (i) 0.5 equiv. hydrazine hydrate, EtOH, 84%; (ii) diethyl oxalate, 180 °C, 16 h, 81%; (iii) LiOH or KOH or HCl; (iv) LiOH or MeMgBr or PhCOMe–NaH.

show diastereotopicity are useful, as are functional groups which allow resolution to be performed. For these reasons the first target was 2,2′-diethoxycarbonyl-3,3′-biquinazoline-4,4′-dione **8**. An adaptation of the literature[20] method for the synthesis of monomeric ethoxycarbonylquinazolinones, gave **8** in good yield by treating **7** at high temperature with an excess of diethyl oxalate. No diastereotopicity was observed in the ^1H NMR spectrum of the methylene group of the ethyl ester. As the lack of diastereotopicity could be attributed to accidental degeneracy of the methylene protons (due to the distance from the chiral axis), attempts were made to access the parent acid **9** which could be resolved with chiral amines if the system proved to possess a stable chiral axis. Base hydrolysis of **8**, however, gave not the parent acid **9**, but the formal decarboxylation product **10** (Scheme 4). This spontaneous decarboxylation is at odds with the stability of monomeric oxoquinazoline-2-carboxylic acids,[20] accessible *via* base hydrolysis of the analogous esters. An explanation for this behaviour is suggested by the observation that both addition of Grignards to, and attempted Claisen reactions of, **8** also gave **10** (Scheme 4).

One interpretation of these data is that the electron withdrawing 3-substituent (*i.e.* quinazolinone) renders the 4-oxoquinazolin-2-yl anion a better leaving group than ethoxide, and C–C cleavage occurs in preference to C–O. In addition to electrostatic stabilisation of the anion, the quinazolin-4-one carbonyl oxygen may bind to the metal counterion endowing further stability.

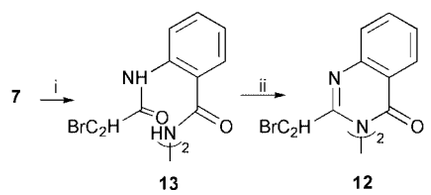
A 3,3′-biquinazoline-4,4′-dione was sought which would have a methylene group closer to the chiral axis than in **8** and thus more likely to demonstrate diastereotopicity and which additionally would be more straightforward to functionalise. A 2-bromomethyl substituent was selected as the methylene group

is as close to the chiral axis as possible, the pseudo-benzylic bromide should be readily substituted by a range of nucleophiles, and α-bromination of the known 2,2′-dimethyl-3,3′-biquinazoline-4,4′-dione **11** should provide simple access to 2,2′-bis(bromomethyl)-3,3′-biquinazoline-4,4′-dione **12**. In fact, the literature preparation of **11** proved problematical, and although an alternative route acetylating **7** in acetic anhydride solvent, then relying upon the reaction conditions to dehydrate to the product, provided good yields of this material (Scheme 5), specific mono-bromination of each methyl group of **11**



Scheme 5 *Reagents*: (i) AcOH (ref. 19); (ii) Ac_2O, Δ, 16 h, 94%; (iii) Br_2, AcOH.

was never achieved. In the event **12** was synthesised *via* acid catalysed dehydration of the unstable bis-bromoacetamide **13** under Dean and Stark conditions (Scheme 6).

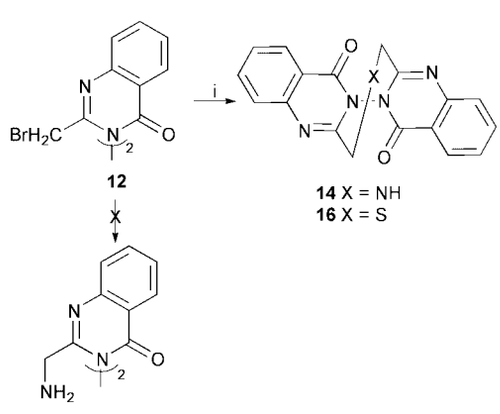


Scheme 6 *Reagents*: BrAcBr, NEt_3, DMF; (ii) PhH, TsOH (cat.), Dean and Stark, 16 h, 58%, 2 steps.

The 2,2′-bromomethylene protons of **12** are observed as an AB system (δ 4.43, 4.32, J = 12.0 Hz) indicating chirality (slow rotation around the N–N bond on the NMR timescale). VT NMR (400 MHz, $\Delta\nu$ = 44 Hz) showed line broadening above 60 °C, however even at 135 °C free rotation was not observed around the N–N bond (non-coalescence) which according to eqn. (1) indicates a *minimum* barrier to rotation of the order of 83 kJ mol^{-1} (82.6 ± 0.2). While this would not be a sufficient barrier to rotation to endow stereostability at room temperature, this figure is a minimum value and the true value may be significantly higher.

2,2′-Bridged 3,3′-biquinazoline-4,4′-diones

Treatment of a solution of **12** in THF with aqueous ammonia gave (±)-6,8,14,17-tetrahydro-7*H*-[1,2,5]triazepino[3,2-*b*:7,1-*b*′]diquinazoline-14,17-dione **14** in 74% yield; none of the anticipated diamine **15** was detected (Scheme 7). This cyclisation was unexpected as it had been anticipated by analogy with the N–N axis of tetraformyl hydrazine that the preferred geometry of the 3,3′-biquinazoline-4,4′-dione system would have the planar quinazolinone units orthogonal, which would render the methylene units of **12/14** too distant for cyclisation to occur. Clearly for the saturated ring in **14** not to experience prohibitive strain some deviation from orthogonality is necessary, however it is possible to minimise this ring without approaching planarity (maximum overlap of the quinazolinones) and it is apparent from the rapid cyclisation that the preferred conformation of **12** may be far from orthogonal. This cyclisation is extremely rapid and the intramolecular reaction occurs to the exclusion of a second intermolecular amination; regardless of the concentration of ammonia none of the uncyclised diamine **15** could be detected, even when the reaction was performed by slow addition of a THF solution of **12** to liquid ammonia.



Scheme 7 *Reagents*: (i) a) NH_3 (aq.), THF, 74% (**14**), b) Li_2S, THF–H_2O, 52% (**16**).

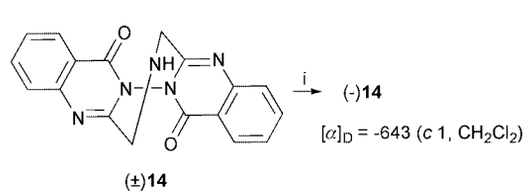
In **14** the diastereotopic protons in each methylene unit (δ 4.00, 3.93, J = 13.2 Hz) confirmed that rotation around the N–N bond was slow on the NMR timescale, and in this case VT NMR (400 MHz, $\Delta\nu$ = 28 Hz, J = 13.2 Hz) did not even show any broadening of lines at 130 °C, even less coalescence, (T_c > 403 K) which according to eqn. (1) again gives a minimum barrier to rotation of 82 kJ mol^{-1} (82.3 ± 0.3). Treatment of **12** with lithium sulfide gave the analogous cyclic sulfide **16** (Scheme 7), which again showed diastereotopicity in the methylene groups (4.45, 3.74, J = 13.6 Hz). In this case the separation between the diastereotopic protons is sufficient to allow selective saturation of one of the signals in the proton NMR spectrum (this had proved impossible for **12** and **14**). Attempts to measure the rate of mutual exchange between the diastereotopic protons using spin saturation transfer techniques,[21] whereby one proton of the diastereotopic pair is exclusively saturated and the effect of this on the integral of the other signal is measured against a constant intensity peak over a range of temperatures, showed no discernible reduction in signal intensity even at 120 °C. Assuming a worst case of residual signal intensity of 95% of non-irradiated intensity, and that ^{1}H T_1 = 0.1 s (unrealistically short), eqn. (2) (M_{oa} = equilibrium magnetisation intensity, M_a = observed magnetisation intensity) gives a rate of exchange (= k) (rotation) at 120 °C of 0.5 s^{-1}.[21]

$$k = 1/T_1\,(M_{oa}/M_a - 1) \qquad (2)$$

For a first order process with no entropy change (ΔS = 0) a rate of 0.5 s^{-1} at 120 °C correlates with a free energy barrier to rotation in the order of 99 kJ mol^{-1}, or a half-life for racemisation at 20 °C of around 13 hours. Bearing in mind that this was again a minimum barrier and that the estimates of T_1 and of M_a were unrealistically pessimistic, it seems clear that **16** exists as a pair of atropisomers on the real timescale.

Racemisation/deracemisation processes

The development of the acid catalysed deracemisation of **14** has been recorded elsewhere[22] and only the optimum conditions are recorded here (Scheme 8). With (−)-**14** available a kinetic study of the rate of racemisation was undertaken *via* the loss of optical activity, at elevated temperatures, however the barrier to racemisation (rotation) appears to be so large that



Scheme 8 *Reagents*: (i) (+)-CSA (2 equiv.), PhH (3.8 ml mol^{-1}, reflux, 40 h).

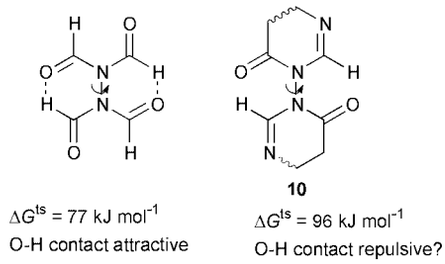
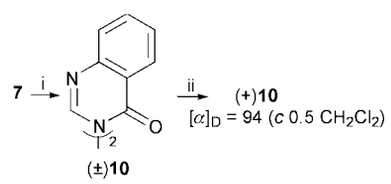


Fig. 2

thermal decomposition dominates, and at temperatures at which decomposition is negligible (110 °C) racemisation is extremely slow ($t_{1/2}$ ≈24 h). For rotation (racemisation) to be frozen at 110 °C implies a very large barrier to rotation ($t_{1/2}$ = 24 h at 110 °C correlates to a free energy barrier of over 130 kJ mol^{-1}), a greater magnitude than expected for these atropisomeric systems. This barrier is expected to be atypical for 3,3′-biquinazoline-4,4′-diones as the low energy rotation pathway for such systems implied from the theoretical work[12] is not available here. Any rotation must involve two high energy O–O contacts rather than the lower energy O–H (or here O–CH_2) contacts available in uncyclised systems as the alternative rotation would over-stretch the alicyclic tether.

In order to obtain a more representative value for the rotation barrier of 3,3′-biquinazoline-4,4′-diones, the parent system **10** was synthesised, again by an improvement to the literature[19] procedure (Scheme 9) which involves formylation of



Scheme 9 *Reagents*: (i) $POCl_3$, DMF, 91%; (ii) (+)-CSA (5 equiv.), PhMe, Δ, 72 h.

7 which dehydrates to the required product under the reaction conditions ($POCl_3$–DMF). Deracemisation of (±)-**10** to (+)-**10** ($[a]_D$ = 94 (c = 1, DCM), not raised by crystallisation) was again achieved at high temperatures in the presence of (+)-CSA (Scheme 9) in this case, however, the deracemisation was simply the formation of the thermodynamically favoured diastereoisomeric salt, as crystallisation processes were not involved (the deracemisation takes place in solution). As **10** is thermally stable the most effective conditions for deracemisation were found to be at higher temperatures and for longer than for **14**. (+)-**10** as a dilute solution (to minimise any intramolecular effects) in dichloromethane at 25 °C has a half life for racemisation (as followed by loss of optical activity) of 58 minutes. This gives a rate of racemisation k_{rac} of approximately 2×10^{-4} s^{-1} which implies a rate of interconversion of atropisomers, that is rotation, of $k_{rot} = 1 \times 10^{-4}$ s^{-1} [22] and implies a free energy barrier to rotation of around 96 kJ mol^{-1}. This value confirms that simple 3,3′-biquinazoline-4,4′-diones such as **10** exist as a pair of atropisomers on the real timescale and in the solid state no loss of optical activity was observed over one month. It is interesting that this barrier is significantly higher than that calculated[12] for rotation around the N–N bond of tetraformylhydrazine when in a conformation which mimics that of 3,3′-biquinazoline-4,4′-dione (77 kJ mol^{-1}). It was proposed that the barrier to rotation around the N–N bond in that case was purely electronic, and that O–H contacts were attractive. If this is the case then either the electronic barrier in **10** must be higher than in tetraformylhydrazine, for reasons which are not at the moment clear, or the substitution of iminyl for carbonyl renders the O–H contacts repulsive (Fig. 2).

Conclusion

As **10** represents the least substituted, and thus least sterically hindered (with regard to rotation) member of the 3,3′-biquinazoline-4,4′-diones, it is reasonable to assume that 96 kJ mol^{-1} represents a minimum barrier to rotation for this family of compounds and that *all* analogues can be regarded as stable atropisomers. Given the ease of lithiation–substitution of the 2-position of monomeric quinazolinones, which has been used to introduce phosphorus and sulfur donor atoms as a strategy in ligand synthesis,[7] 3,3′-biquinazoline-4,4′-diones are an appealing new class of atropisomers for ligand design. Further studies in this area are ongoing.

Experimental

General

Mps were recorded on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured using a Jasco P1020 polarimeter. Infrared spectra were recorded using a Perkin-Elmer 1600 FTIR. NMR experiments were variously measured at 200 MHz on a Varian Mercury 200, at 250 MHz on a Brüker AM 250, at 300 MHz on a Varian Unity 300, at 400 MHz on a Varian VXR400 and at 500 MHz on a Varian INOVA500. Variable temperature NMR experiments were performed on the Varian VXR 400 calibrated against ethylene glycol assumed to be accurate to ±1 °C with digital resolution taken to be ±0.5 Hz. ^{13}C NMR spectra were recorded on the same instruments at the frequencies stated in the text. Mass spectra were measured using a MICROMASS AUTOSPEC. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry Service, Swansea. Prior to use in moisture sensitive reactions THF was distilled from sodium–benzophenone ketyl, DCM was distilled from calcium hydride, triethylamine was distilled from sodium hydroxide pellets, DMF was distilled from calcium hydride and pyridine was distilled from molecular sieves, all these procedures being conducted under an atmosphere of nitrogen. Other solvents and reagents were used as supplied without prior purification. Light petroleum refers to that fraction of petroleum ether which boils in the range 40–60 °C. Column chromatography was performed on silica gel (Kieselgel 60).

1,2-Diisobutanoyl-1,2-dipropanoylhydrazine 2a

To a stirred solution of 1,2-dipropanoylhydrazine **1** (0.5 g, 3.4 mmol) in pyridine (2 ml) under an atmosphere of nitrogen was added isobutyryl chloride (1 ml, 1.02 g, 9.5 mmol) and stirring was continued for 48 hours. The reaction mixture was then treated with dilute hydrochloric acid (2 M, 20 ml), extracted into DCM (2 × 10 ml), and the extracts were washed with further dilute hydrochloric acid (2 M, 2 × 10 ml), sodium hydrogen carbonate (saturated, aqueous, 2 × 20 ml) and brine (10 ml saturated), dried ($MgSO_4$) and evaporated *in vacuo*. The crude residue was crystallised from light petroleum to give the title compound as a white solid (0.51 g, 54%). Mp 66.6–67.0 °C, δ_H (400 MHz, $CDCl_3$) 3.31 (2H, septet, J = 6.8 Hz, C*H*(CH_3)$_2$), 2.45 (4H, q, J = 7.2 Hz, C*H*$_2$CH$_3$), 1.09 (12H, d, J = 6.8 Hz, CH(C*H*$_3$)$_2$), 1.07 (6H, t, J = 7.2 Hz, CH$_2$C*H*$_3$); δ_C (62.9 MHz, $CDCl_3$) 177.9, 174.9, 34.4, 29.3, 19.0, 8.3; ν_{max} (neat) 1725 cm^{-1}; *m*/*z* (%) 285 (3.0, M + H$^+$) 284 (1.2, M$^+$), 229 (12.7), 215 (10.4), 197 (10.8), 159 (21.4), 141 (77.7), 127 (31.2), 102 (11.7), 71 (96.5), 57 (57.4), 43 (100); $C_{14}H_{25}N_2O_4$ (M + H)$^+$ requires 285.1814, found 285.1811.

1,2-Dibenzoyl-1,2-dipropanoylhydrazine 2b

To a stirred solution of 1,2-dipropanoylhydrazine **1** (279 mg, 1.9 mmol) in pyridine (2 ml) under an atmosphere of nitrogen was added benzoyl chloride (1 ml, 1.2 g, 8.5 mmol) and stirring continued for 48 hours. The reaction mixture was then treated

with dilute hydrochloric acid (2 M, 20 ml), extracted into DCM (2 × 10 ml) and the extracts were washed with further dilute hydrochloric acid (2 M, 2 × 10 ml), sodium hydrogen carbonate (saturated, aqueous, 2 × 20 ml) and brine (10 ml saturated), dried ($MgSO_4$) and evaporated *in vacuo*. The crude residue was purified by flash chromatography ($R_f = 0.8$, DCM) to give **2b** as a colourless oil (427 mg, 64%); δ_H (400 MHz, $CDCl_3$) 8.17 (4H, dd, $J = 1.6$, 9.6 Hz, Ar*H-ortho*), 7.68 (2H, m, Ar*H-para*), 7.44 (4H, m, Ar*H-meta*), 2.60 (2H, dq, $J = 17.3$, 7.5 Hz, 2 × 1/2 × CH_2CH_3), 2.57 (2H, dq, $J = 17.3$, 7.5 Hz, 2 × 1/2 × CH_2CH_3), 1.05 (6H, t, $J = 7.5$ Hz, CH_3); δ_C (62.9 MHz, $CDCl_3$) 174.8, 162.2, 134.5, 132.3, 130.5, 128.8, 128.7, 127.6, 30.8, 8.8; ν_{max} (neat) 3063, 2984, 2880, 1787, 1723 cm^{-1}; *m/z* (%) 352 (2.7, M^+), 240 (5.5), 226 (11.2), 222 (10.0), 198 (17.0), 192 (1.6), 182 (4.6), 174 (37.7), 122 (1.6), 105 (100), 77 (83.8); $C_{20}H_{20}N_2O_4$ requires 352.1423, found 352.1431.

(*S*,*S*)1,2-Bis(2-hydroxypropanoyl)hydrazine 3

To a flask containing methyl lactate (10 ml) was added hydrazine monohydrate (1 ml, 1.03 g, 20 mmol) and the mixture heated at reflux for 3 hours. The condenser was then allowed to warm to room temperature and all material volatile at 80 °C removed by evaporation. The residue was then heated at reflux for 16 h with a bath temperature of 150 °C. After this time the excess methyl lactate was removed *in vacuo* to give a crystalline residue. The residue was recrystallised from ethanol to give the title compound **3** (1.65 g, 47%) as a white solid, mp 185.3–186.4 °C, $[\alpha]_D = +29$ ($c = 0.2$, acetone); δ_H (300 MHz, DMSO) 9.47 (2H, s, 2 × NH), 5.45 (2H, d, $J = 6.0$ Hz, O*H*), 4.06 (2H, dq, $J = 6.0$, 6.7 Hz, C*H*(OH)CH_3), 1.22 (6H, d, $J = 6.7$ Hz, CH_3); δ_C (250 MHz, DMSO) 173.9, 67.4, 22.0; ν_{max} (Nujol) 3200 (broad), 1658; *m/z* (%) 176 (2.0, M^+), 131 (1.7), 113 (1.8), 104 (14.9), 86 (5.0), 69 (3.5), 55 (2.7), 45 (100); $C_6H_{12}N_2O_4$ requires C, 40.9; H, 6.8; N, 15.9%; found C, 40.9; H, 6.9; N, 15.7%.

(*S*,*S*)-1,2-Bis(2-benzoyloxypropanoyl)-1,2-dibenzoylhydrazine 4

To a stirred solution of (*S*,*S*)-1,2-bis(2-hydroxypropanoyl)-hydrazine (500 mg, 2.8 mmol) in pyridine (5 ml) under nitrogen was slowly added benzoyl chloride. The mixture was sealed under nitrogen and stirring continued for 96 h. After this time the reaction mixture was treated with dilute hydrochloric acid (2M, 50 ml), extracted into dichloromethane (3 × 20 ml), washed with further dilute hydrochloric acid (3 × 100 ml), sodium hydrogen carbonate (saturated, aqueous, 3 × 50 ml) then brine (saturated 20 ml), dried ($MgSO_4$) and evaporated to give a solid residue which was crystallised from acetone to give the title compound **4** (940 mg, 57%), mp 173.2–175.5 °C, $[\alpha]_D = +75$ ($c = 0.38$, acetone); δ_H (250 MHz, $CDCl_3$) 8.05 (4H, d, $J = 7.0$ Hz, ArH), 7.56–7.31 (16H, m, ArH), 6.08 (major isomer, 2H, q, $J = 7.0$ Hz, C*H*CH_3), 5.83 (minor isomer, 2H, q, $J = 6.8$ Hz, C*H*CH_3), 1.66 (major isomer, 6H, d, $J = 7.0$ Hz, CH_3), 1.58 (minor isomer, 6H, d, $J = 6.8$ Hz, CH_3); δ_C 171.7 (minor), 171.6 (major), 170.2 (minor), 170.0 (major), 165.4 (major), 165.1 (minor), 135.4, 138.3, 132.9, 132.8, 132.8, 132.2, 130.5, 130.1, 129.8, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 70.9 (major), 70.4 (minor), 16.77 (minor), 16.70 (major); ν_{max} (Nujol) 1748, 1715 cm^{-1}; *m/z* (%) 592 (2.0, M^+), 443 (2.3), 294 (1.2), 261 (0.6), 222 (0.9), 189 (6.0), 177 (46.2), 149 (6.0), 122 (1.0), 105 (100); $C_{34}H_{28}N_2O_8$ requires C, 68.9; H, 4.7; N, 4.7%; found C, 68.9; H, 4.7; N 4.6%.

1,2-Dibenzoyl-1,2-bis(2-pyridylcarbonyl)hydrazine 6

To a stirred suspension of **5** (2.44 g, 10 mmol) in DCM (20 ml) was added triethylamine (5 ml, 3.63 g, 36 mmol) then benzoyl chloride (2.5 ml, 3 g, 22 mmol) dropwise over 10 minutes. The reaction was sealed under an atmosphere of nitrogen and stirring continued for a further 36 hours. The mixture was then treated with potassium hydrogen carbonate (saturated, aqueous, 25 ml) and concentrated *in vacuo* until all the volatile organics had been removed and water had started to evaporate. After cooling the product was collected as a slate grey powder by filtration, dissolved in boiling ethanol (400 ml) and cooled over 16 hours. Filtration gave **6** as fawn crystals 560 mg, 12%, mp 213 °C (decomp.); δ_H (400 MHz, DMSO-d_6, ambient temperature) 8.26 (2H, br s), 7.87 (4H, br s), 7.55 (4H, br s), 7.41 (4H, br s), 7.32 (4H, br s); δ_H (400 MHz, DMSO-d_6, 70 °C) 8.28 (2H, d, $J = 3.6$ Hz), 7.87 (4H, d, $J = 3.6$ Hz), 7.61 (4H, d, $J = 7.6$ Hz), 7.44 (4H, m), 7.32 (4H, m); δ_C (100.5 Hz, DMSO-d_6, 70 °C) 170.2, 168.6, 149.6, 148.0, 137.2, 133.8, 132.2, 128.3, 128.27, 128.22, 128.1, 126.6, 124.6; ν_{max} (Nujol) 2853, 1713, 1693 cm^{-1}; *m/z* (%) 450 (2.8, M^+), 329 (4.4), 223 (25.2), 212 (7.5), 167 (6.0), 148 (3.0), 105, (100), 77 (60.0); $C_{26}H_{18}N_4O_4$ requires C, 69.3; H, 4.0; N, 12.4%; found C, 69.6; H, 4.0; N, 12.1%.

1,2-Dianthraniloylhydrazine 7

To an efficiently stirred suspension of isatoic anhydride (163 g, 1 mol) in ethanol (500 ml) was added hydrazine monohydrate (24.3 ml, 25.0 g, 0.5 mmol) and the mixture heated at reflux for 16 h. Evaporation of the ethanol followed by recrystallisation from DMF gave the title compound **7** as colourless needles (113.5 g, 84%), mp 208 °C (lit.,[19] mp 212 °C).

2,2′-Diethoxycarbonyl-3,3′-biquinazoline-4,4′-dione 8

A suspension of dianthraniloylhydrazine **7** (2.26 g, 8.4 mmol) in diethyl oxalate (40 ml) was heated to a bath temperature of 180 °C for 16 hours after which the excess diethyl oxalate was removed *in vacuo* and the brown tarry residue treated with ethanol (5 ml) then cooled to give a precipitate of a white crystalline solid which proved to be the title compound **8** (2.93 g, 6.8 mmol, 81%), mp 133.5 °C (EtOH); δ_H (300 MHz, $CDCl_3$) 8.35 (2H, dd, $J = 8.1$, 1.2 Hz, 2 × H6), 7.94 (2H, dd, $J = 8.3$, 1.2 Hz, H7), 7.92 (2H, dd, $J = 6.9$, 1.5 Hz, H8), 7.67 (2H, dd, $J = 6.9$, 1.2 Hz, 2 × H9), 4.36 (4H, q, $J = 7.2$ Hz, 2 × CH_2), 1.28 (6H, t, $J = 7.2$ Hz, 2 × CH_3); δ_C (62.9 MHz, $CDCl_3$) 158.8, 158.4, 145.2, 142.9, 135.7, 129.5, 129.2, 127.6, 122.3, 63.5, 13.7; ν_{max} (Nujol mull) 1736, 1700, 1596 cm^{-1}; *m/z* (EI) 434 (22.2%, M^+) 389 (1.8), 362 (23.4), 317 (62.7), 289 (100); $C_{22}H_{18}N_4O_6$ requires C, 60.83; H, 4.18; N, 12.90%; found C, 60.87; H, 4.17; N, 12.95%.

3,3′-Biquinazoline-4,4′-dione 10

To an ice-cold stirred solution of 1,2-dianthraniloylhydrazine **7** (10 g, 38 mmol) in DMF (100 ml) was added $POCl_3$ (7.6 ml, 12.5 g, 82 mmol) dropwise and stirring continued at 0 °C for a further hour. Then the mixture was allowed to attain ambient temperature over one hour. The mixture was then re-cooled in an ice bath before the careful addition of water (100 ml). The product was separated by filtration as a fine white solid, washed with copious quantities of diethyl ether and dried *in vacuo* to give **10** (9.67 g, 89%), mp 292 °C (lit.,[19] mp 295 °C).

2,2′-Dimethyl-3,3′-biquinazoline-4,4′-dione 11

To 1,2-dianthraniloylhydrazine **7** (20 g, 74 mmol) was added acetic anhydride (100 ml) and the mixture heated for 16 hours then cooled for 8 hours and the product collected by filtration. Crystallisation (toluene) gave the title compound **11** as golden crystals (15.4 g, 65%), mp 176 °C (lit.,[19] mp 170–177 °C).

2,2′-Bis(bromomethyl)-3,3′-biquinazoline-4,4′-dione 12

A stirred solution of 1,2-dianthraniloylhydrazine **7** (12.4 g, 45.9 mmol) in dry DMF (120 ml) under an atmosphere of nitrogen was treated with triethylamine (12.8 ml, 9.3 g, 92 mmol) then cooled to 0 °C before the dropwise addition of bromoacetyl bromide (8 ml, 18.6 g, 91.9 mmol) over 30 minutes. The solution

was allowed to attain ambient temperature over a further 90 minutes then treated with ethyl acetate (500 ml), washed with 2 × 500 ml HCl (3 M, aqueous) then a further 3 × 100 ml HCl (3 M, aqueous), 2 × 100 ml sodium hydrogen carbonate (saturated, aqueous) and finally 100 ml brine (saturated). The organic layers were dried ($MgSO_4$) and evaporated to give 1,2-bis(2-bromoacetamidobenzoyl)hydrazine **13** (16.8 g, 33 mmol, 72%). This amide (7.87 g, 15.4 mmol) was suspended in 200 ml of toluene with 500 mg of tosic acid monohydrate and heated under reflux with a condenser equipped with a Dean and Stark trap for 90 minutes. The mixture was allowed to cool to ambient temperature then diluted with ethyl acetate (100 ml), washed with 3 × 100 ml of sodium hydrogen carbonate (saturated, aqueous), 100 ml of brine (saturated), dried ($MgSO_4$) then evaporated to dryness. Crystallisation from ethyl acetate gave the title compound **12** (5.98 g, 12.6 mmol, 81%) (58% from dianthraniloylhydrazine) as colourless blocks, mp 228.6 °C (EtOAc); δ_H (300 MHz, $CDCl_3$) 8.31 (2H, ddd, J = 8.1, 1.5, 0.6 Hz, 2 × H6), 7.93 (4H, m, 2 × H7 + H8), 7.60 (2H, ddd, J = 6.9, 1.5, 1.2 Hz, 2 × H9), 4.43 (2H, d, J = 12.0 Hz, 2 × H2′), 4.32 (2H, d, J = 12.0 Hz, 2 × H2″); δ_C (62.8 MHz, $CDCl_3$) 160.4, 152.0, 147.4, 137.5, 130.0, 129.7, 129.0, 122.2, 28.7; ν_{max} (Nujol mull) 1713, 1693, 1603 cm^{-1}; *m/z* (EI) 476 (5.4%, M^+), 396 (4.4), 383 (62.7), 316 (33.7), 302 (100); $C_{18}H_{12}Br_2N_4O_2$ requires C, 45.4; H, 2.5; N, 11.8%; found C, 45.6; H, 2.5; N, 12.0%.

(±)-6,8,14,17-Tetrahydro-7*H*-[1,2,5]triazepino[3,2-*b*:7,1-*b*′]-diquinazoline-14,17-dione 14

To a rapidly stirred mixture of THF (50 ml) and aqueous ammonia (35%, 70 ml) was added dropwise a solution of 2,2′-bis(bromomethyl)-3,3′-biquinazoline-4,4′-dione **12** (1.9 g, 4.0 mmol) in THF (50 ml) over 30 minutes then stirring was continued for a further 60 minutes. The THF layer was then separated from the aqueous, which was diluted with 200 ml of brine (saturated) and extracted with 3 × 100 ml of DCM. The combined organic layers were washed with a further 2 × 100 ml of brine then dried ($MgSO_4$) and evaporated to dryness to give a red residue. Crystallisation from DCM–ethanol (the use of decolourising charcoal was essential to eliminate highly coloured trace impurities) gave the title compound **14** as colourless needles (1.03 g, 3.1 mmol, 78%), mp 218.2–220.6 °C (decomp.) (EtOH); δ_H (300 MHz, $CDCl_3$) 8.38 (2H, dd, J = 8.1, 1.2 Hz, 2 × H6), 7.91 (2H, ddd, J = 8.1, 7.2, 1.5 Hz, 2 × H7), 7.81 (2H, dd, J = 7.5, 1.5 Hz, 2 × H9), 7.63 (2H, ddd, J = 8.1, 7.5, 1.2 Hz, 2 × H8), 4.08, 4.02 (4H, 2 × d, J = 13.5 Hz, 2,2′-CH_2), 2.01 (broad, NH); δ_C (62.8 MHz, $CDCl_3$) 156.4, 150.7, 146.4, 135.3, 128.0, 127.8, 127.6, 121.4, 48.5; ν_{max} (Nujol mull) 3313, 3263, 1705, 1687, 1620, 1607 cm^{-1}; *m/z* (EI) 331 (100%, M^+), 303 (29.3), 186 (99.9), 160 (39); $C_{18}H_{14}N_5O_2$ $(M + H)^+$ requires 332.1147, found 332.1145.

(±)-6,8,14,17-Tetrahydro[1,4,5]thiadiazepino[3,4-*b*:6,5-*b*′]-diquinazoline-14,17-dione 16

To a stirred solution of lithium sulfide (27 mg, 0.58 mmol) in 20% aqueous THF (1 ml) was added dropwise a solution of 2,2′-bis(bromomethyl)-3,3′-biquinazoline-4,4′-dione **12** (100 mg, 0.21 mmol) in 20% aqueous THF (5 ml) and stirred for 5 hours. The reaction mixture was treated with ammonium chloride (sat. aqueous, 20 ml), extracted into DCM (3 × 20 ml), dried ($MgSO_4$) and evaporated to dryness. Crystallisation of the solid residue from DMF gave the title compound (104 mg, 52%) as a yellow solid, mp 322.2–324.6 °C (decomp.); δ_H (400 MHz, DMSO) 8.17 (2H, d, J = 8.0 Hz, 2 × H6), 7.97 (2H, app t, J = 7.6 Hz, 2 × H7), 7.80 (2H, d, J = 8.4 Hz, 2 × H9), 7.66 (2H, app t, J = 7.6 Hz, 2 × H8), 4.45 (2H, d, J = 13.6 Hz, 2 × 1/2 CH_2S), 3.74 (2H, d, J = 13.6 Hz, 2 × 1/2 CH_2S); δ_C (62.9 MHz, $CDCl_3$) 157.5, 152.1, 147.3, 136.5, 128.8, 128.5, 127.9, 122.3, 30.9; ν_{max} (Nujol mull) 1711m, 1696, 1605 cm^{-1}; *m/z* (EI) 348 (M^+, 100%), 315 (32), 303 (26), 287 (7), 203 (57), 160 (10), 149 (36); $C_{18}H_{12}N_4O_2S$ requires C, 62.1; H, 3.5; N, 16.1; found C, 61.8; H, 3.5; N, 16.1%.

(−)-6,8,14,17-Tetrahydro-7*H*-[1,2,5]triazepino[3,2-*b*:7,1-*b*′]-diquinazoline-14,17-dione 14

To a mixture of (±)-6,8,14,17-tetrahydro-7*H*-[1,2,5]triazepino[3,2-*b*:7,1-*b*′]diquinazoline-14,17-dione **14** (435 mg, 1.3 mmol) and (+)-CSA (458 mg, 2.0 mmol) was added benzene (5 ml) and the mixture heated at reflux for 40 hours. After this period the mixture was dissolved in DCM (50 ml), washed with sodium hydrogen carbonate (2 × 50 ml, saturated aqueous), and brine (1 × 20 ml, saturated) then dried ($MgSO_4$) and evaporated to dryness to give the title compound **14** of $[a]_D = -643$ (c = 0.1, DCM) (357 mg, 82% recovery). The sample was recrystallised from DCM–ethanol to give $[a]_D = -688$ (c = 0.011, DCM) (348 mg, 76% recovery from racemate).

(+)-3,3′-Biquinazoline-4,4′-dione 10

A mixture of **10** (5 g, 17.2 mmol) and (+)-CSA (20 g, 86 mmol) was heated at reflux in toluene (150 ml) for 24 hours, during which time the mixture became a homogeneous solution. After this time the solvent was removed *in vacuo* (cool water bath) the mixture re-dissolved in dichloromethane (100 ml) washed with sodium carbonate (saturated, aqueous, 3 × 50 ml) dried ($MgSO_4$) and evaporated to dryness to give **10** (4.8 g, 96% recovery) with $[a]_D = 80$ (c = 1, DCM). The above procedure was applied to the deracemisation of **10** over the course of 48 hours to give **10** (98% recovery) of $[a]_D = 93$ (c = 1, DCM) and 72 hours (98% recovery) of $[a]_D = 94$ (c = 1, DCM). This rotation could not be increased by crystallisation from low boiling solvents and crystallisation from high boiling solvents led to a loss of optical rotation.

Racemisation of **10** was followed at an average temperature of 25 °C on samples of (+)-**10** (c = 0.005, DCM) with measurements being taken every 300 s over 3 hours. From the gradient of plots of ln $[a_0]/[a_t]$ *vs.* t an average k for racemisation of 1.992×10^{-4} s^{-1}, or $t_{1/2}$ of 3479 s (58 minutes) was obtained.[22]

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References

1 E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, ch. 14.5.
2 G. H. Christie and J. H. Kenner, *J. Chem. Soc.*, 1922, 614.
3 For reviews see R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; K. Tomioka, *Synthesis*, 1990, 451.
4 See *e.g.* S. Vyskocil, M. Smrcina and P. Kocovsky, *Tetrahedron Lett.*, 1998, **39**, 9289; G. Chelucci, A. Bacchi, D. Fabbri, A. Saba and F. Ulgheri, *Tetrahedron Lett.*, 1998, **40**, 553.
5 H. Tsue, H. Fujinami, T. Itakura, R. Tsuchiya, K. Kobayashi, H. Takahashi and K. Hirao, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 3677.
6 See J. Clayden, *Angew. Chem.*, *Int. Ed. Engl.*, 1997, **36**, 949 and references therein.
7 X. Dai and S. Virgil, *Tetrahedron*: *Asymmetry*, 1999, **10**, 25.
8 T. Beninicori, E. Brenna, F. Sannicol, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin, T. Pilati and G. Zotti, *J. Organomet. Chem.*, 1997, **529**, 445.
9 M. J. S. Dewar and W. B. Jennings, *J. Am. Chem. Soc.*, 1969, **91**, 3655; M. J. S. Dewar and W. B. Jennings, *J. Am. Chem. Soc.*, 1973, **95**, 1562; R. S. Atkinson, B. D. Judkins and B. Patwardhan, *J. Chem. Soc.*, *Perkin Trans. 2*, 1979, 1490; R. S. Atkinson, E. Barker, P. J. Edwards and G. A. Thomson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 1047.

10 S. M. Verma and R. Prasad, *J. Org. Chem.*, 1973, **38**, 1004.
11 R. S. Atkinson, E. Barker, C. J. Price and D. R. Russell, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 1159; R. S. Atkinson, E. Barker and M. J. Sutcliffe, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 1051.
12 J. A. Platts and M. P. Coogan, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1075.
13 K. Stolle, *J. Prakt. Chem.*, 1904, **70**, 427; K. Stolle, *Chem. Ber.*, 1899, **32**, 797; J. A. Young, *J. Am. Chem. Soc.*, 1962, **84**, 2105; K. Stolle, *Chem. Ber.*, 1912, **45**, 282.
14 H. Feuer and F. Brown, *J. Org. Chem.*, 1970, **35**, 1468.
15 H. Zhao and T. R. Burke, *Tetrahedron*, 1997, **53**, 4219.
16 M. C. Apreda, C. Foces-Foces, F. H. Cano and S. Garcia-Blanko, *Acta Crystallogr.*, *Sect. B*, 1978, **34**, 3477; G. S. D. King, *J. Chem. Soc. B*, 1966, 1224.
17 A. Hinderer and H. Hess, *Chem. Ber.*, 1974, **107**, 492.
18 G. A. El-Hiti, *Spectrosc. Lett.*, 1999, **32**, 671.
19 P. S. N. Reddy and A. K. Bhavani, *Indian J. Chem.*, *Sect. B*, 1992, **31**, 740.
20 T. George, D. V. Mehta and R. Tahilramani, *Indian J. Chem.*, 1971, **19**, 755.
21 R. L. Jarek, R. J. Flesher and S. K. Shin, *J. Chem. Educ.*, 1997, **74**, 978.
22 M. P. Coogan, D. E. Hibbs and E. Smart, *Chem. Commun.*, 1999, 1991 and references therein.