Simultaneous double 1,3-dipolar cycloaddition reactions involving bisnitrones or bisdipolarophiles. ^{1}H NMR investigation of the conformational preferences of *N*-methyl- and *N*-phenyl-isoxazolidines

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Bisnitrones **1a** and **1b** reacted with *N*-methylmaleimide giving bisisoxazolidines. Diastereospecific reaction of the phenyl substituted dipole **1a** gave **3a** whilst the *N*-methyl dipole **1b** furnished diastereomeric adducts **3b**, **4** and **7** classified as *trans*,*trans*, **3b**, *cis*,*cis*, **4** and *cis*,*trans* adducts **7** (major) according to the relative orientation of the 3-H and 4-H protons on each isoxazolidine ring. Similar behaviour was observed in reaction of mono dipoles *N*-benzylideneaniline *N*-oxide and *N*-benzylidenemethylamine *N*-oxide with phenylenedimaleimide **2**. The *N*-phenyl dipole reacted highly selectively furnishing the *trans*,*trans* adduct **8a** whilst the *N*-methyl dipole again gave *trans*,*trans* **8b**, *cis*,*cis* **10** and *cis*,*trans* adducts **9** (major). Some of the *N*-methyl substituted isoxazolidines (**3b**, **7**, **8b**, **9b**) displayed a number of very broad signals in their rt ^{1}H NMR spectra which sharpened (and duplicated) on cooling. By analogy to the corresponding ^{1}H NMR data of the "hemi-adducts" **5** and **6**, and with reference to crystal structure data for **5c** [Fig. 1], it was shown that for this group of adducts the 3-H and 4-H protons are *trans* orientated. The isoxazolidine ring in these adducts equilibrates between the *o*- and *i*-conformations [Fig. 2] and at −40 °C each conformer can be clearly identified in the ^{1}H NMR spectrum. No line broadening was observed in the ^{1}H NMR spectra of any of the *N*-phenyl substituted adducts. The conformational freedom of the adducts is thus dictated by the size of the *N*-isoxazolidine substituent and the relative orientation of the 3-H and 4-H protons. All new cycloadducts reported, **3**–**10**, are prepared as racemic mixtures and stereochemical information portrayed in the drawings implies relative and not absolute relations.

Introduction

As part of an ongoing programme to prepare macrostructures incorporating sub-isoxazolidine rings [1] we have been exploring double cycloaddition reactions of bifunctional nitrones and bisdipolarophiles. Recent successes by other workers in related areas include a two step quadruple cycloadditive macrocyclisation of *in situ* generated nitrile oxides,[2] preparation of a small library of oligoisoxazoles using dipolar nitrile oxide cycloadditions [3] and formation of bispyrroles *via* a double azomethine ylide cycloaddition reaction.[4] This paper reports on the synthesis of bisisoxazolidines from bisnitrones **1** and *N,N′*-1,4-phenylenedimaleimide **2** and on the conformational dichotomy between the resulting *N*-methyl and *N*-phenyl substituted 3,4-heterofused isoxazolidines.

Results and discussion

The aryl linked nitrones were trapped with *N*-methylmaleimide. The *N,N′*-diphenyl dipole **1a** exhibited poor solubility in common solvents so cycloaddition was performed in DMF (120 °C). A single diastereoisomeric adduct, **3a**, resulted (26%). The simplicity of the ^{1}H NMR spectrum, showing only three non-aromatic protons, indicated that **3a** has C_2-symmetry. Relative stereochemistry of **3a** was assigned following nuclear Overhauser enhancement difference spectroscopy (NOEDS) and was supported by the appearance of 3-H as a singlet (δ_H 5.51 ppm) in the ^{1}H NMR spectrum. The adduct **3a** is classified as a *trans*,*trans* bisadduct as the 3-H and 4-H protons on each isoxazolidine ring are *trans* orientated. Reaction of the *N,N′*-dimethyl nitrone **1b** with *N*-methylmaleimide proceeded (toluene, 110 °C) in much higher yield, albeit in a much less selective manner, and three diastereoisomeric adducts were isolated, **4**, **3b**, and **7**. The minor diastereomer **4** (4%) could only be obtained as an enriched sample together with **7**, however from the ^{1}H NMR data of the mixture it is evident that **4** has a highly symmetrical structure and that 3-H and 4-H are *cis* orientated on both rings; the vicinal coupling constant $^3J_{3,4}$ is 8.8 Hz. The rt NMR spectral data of the second adduct **3b** (25%) displayed some odd features: the number of distinct ^{13}C resonance signals (five) was much smaller than expected and some signals were not sharp. In the ^{1}H NMR spectrum a number of broad signals were observed, especially for *N*-methyl (isoxazolidine) and 3-H. Such signal broadening was unexpected and initially it was considered that **3b** may arise from opening of a primary isoxazolidine product to an imine with two available C=N configurations. To probe this possibility the monoadducts **5** and **6** were prepared from reaction between *N*-benzylideneaniline *N*-oxide and *N*-benzylidenemethylamine *N*-oxide with *N*-substituted maleimides. Of this family of 4,5-fused isoxazolidines the *N*-phenyl adducts **5a** and **6a** (obtained in the ratio 5 : 1) displayed the expected ^{1}H NMR data for both the *trans*- and *cis*-isomers. Two adducts were obtained from the *N*-methyl dipole with each of *N*-phenylmaleimide and *N*-methylmaleimide. One pair of adducts, **6b**, **6c** exhibits the expected ^{1}H NMR signals whilst the other pair **5b**, **5c** had the same pattern of broad signals as had previously been observed with **3b**.[5] Compound **5c** crystallised as colourless cubic crystals from diethyl ether–petroleum spirit and its structure was exposed by single crystal X-ray analysis,[6–8] Fig. 1, simply to be the bicyclic adduct with 3-H and 4-H *trans* disposed; the dihedral angle 3-H–C–C–4-H has been calculated as 97.121°. The isoxazolidine ring adopts an envelope shape and its carbon atoms and the oxygen atom are

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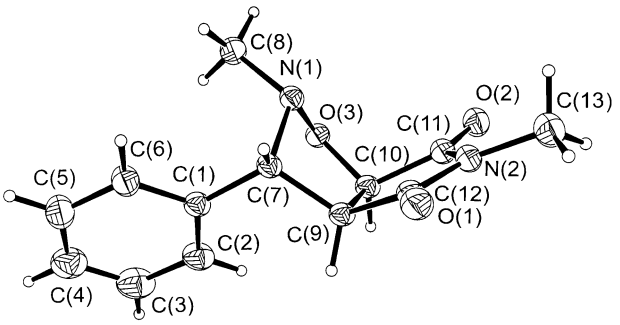
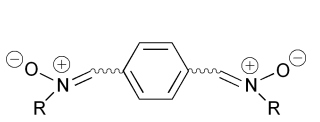


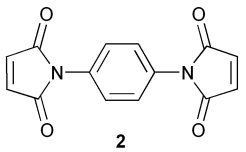
Fig. 1 X-Ray crystallographic projection of **5c**. Crystallographic numbering scheme shown and isoxazolidine ring numbering underlined.

coplanar with the dihedral angle O3–C10–C9–C7 being −1.445° with a standard deviation of 0.164° and the isoxazolidine nitrogen atom points inside the ring.



dipole geometry undefined

1a R = Ph
b R = Me



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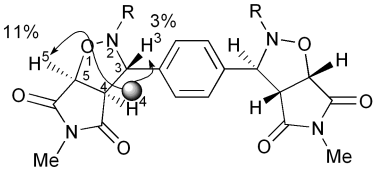
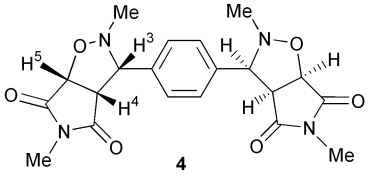


3a R = Ph
b R = Me

NOEDS results shown for 3a
Isoxazolidine ring numbering



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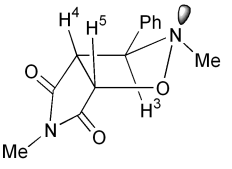
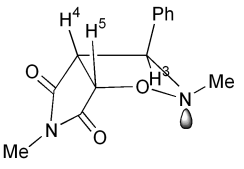
The likely reason for the broad NMR signals in the rt spectra of **3b** and **5b**,**5c** is a conformationally mobile isoxazolidine ring. With this in mind variable temperature NMR spectra of **5c** were recorded and, predictably, at lower temperatures the signals begin to sharpen whilst at elevated temperatures signal broadening becomes less pronounced and the number of ^{13}C resonance signals returns to the expected number. At +10 °C the ^{1}H NMR spectrum begins to show the presence of two equilibrating isomers and at −40 °C their ratio is ~1 : 1.9. At this low temperature the proton signals for each conformer are clearly resolved (Table 1) and in the ^{13}C NMR spectrum there are two sharp sets of signals, one for each invertomer. Comparing the ^{1}H NMR data (resonance position as well as coupling constant) of the minor and major conformers of **5c**, **A′** and **B′** (−40 °C) with those obtained at +50 °C, paying particular attention to 3-H and *N*-methyl (isoxazolidine), it is apparent that the latter are an average of the contributing forms. The high temperature proton NMR data of the bisadduct **3b** (Table 1) closely mirror those of the "hemi-adduct" **5c** and therefore **3b** is confidently assigned as a *trans*,*trans* bisadduct [*i.e.* 3-H and 4-H are *trans* orientated on each isoxazolidine ring]. The low temperature spectra (−35 °C) of **3b** are complex, the proton NMR showing a total of four *N*-methyl (isoxazolidine) signals [2.37 and 2.31 (major) and 2.70 and 2.68 ppm], and the

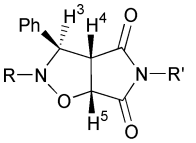


Minor (*o*-) Conformation A'

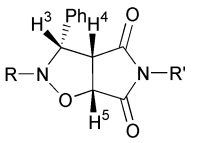


Major (*i*-) Conformation B'

Fig. 2 Conformations of the adduct **5c**.



5a R = R' = Ph
b R = Me, R' = Ph
c R = R' = Me



6

^{13}C spectrum has 25 distinct carbon resonance signals. The large number of signals is a consequence of desymmetrisation as each isoxazolidine ring can independently assume either conformation.

The most significant differences in the ^{1}H NMR data for the invertomers **A′** and **B′** of **5c** are the position and multiplicity of the 3-H signal; in the minor adduct, **A′** 3-H resonates upfield (δ_H 3.64 ppm) of the same proton in **B′** (δ_H 4.51 ppm) and $^{3}J_{3,4}$ ~7.7 Hz for **A′** whilst for **B′** $^{3}J_{3,4}$ is ~0 Hz. These differences can be explained on consideration of the available isoxazolidine ring conformations. Due to the 4,5-fused (planar) pyrrolidindione the isoxazolidine ring adopts an envelope conformation and, allowing for inversion, its nitrogen atom will either extend out from the envelope, *o*-conformation, or point inside the envelope, *i*-conformer.[5] The *o*-conformer has the N-lone pair antiperiplanar to, and therefore capable of shielding, 3-H, and so this conformation is assigned to the minor conformer **A′**. The *i*-conformer permits a 3-H–C–C–4-H dihedral angle of close to 90° and hence this is the conformation of the major conformer **B′** (Fig. 2).

Ali and Wazeer have conducted a thorough investigation into the N-inversion process on a range of monocyclic isoxazolidines with varying substitution patterns and have concluded that the inversion barrier decreases as the size and the conjugative ability of the nitrogen substituent increases. The trend is attributed to a reduction in the energy gap between the ground state (sp^3-N, pyramidal geometry) and transition state (sp^2-N, planar geometry) because of (i) a more effective relief of steric stain as the size of the N-group increases and (ii) delocalisation of the N-lone pair, *e.g* into a phenyl substituent, bringing the ground state closer to the sp^2 transition state.[9] On their own these characteristics could be expected to facilitate rapid nitrogen inversion in **3a** with respect to **3b**. However the ^{1}H NMR spectrum of **3a** shows a series of sharp signals suggesting the presence of a single invertomer (Table 1); that 3-H is not shielded and appears as a singlet suggests the *i*-conformer is favoured. Based on a Dreiding scale model it seems plausible that π-stacking (of the phenyl rings on N-2 and C-3) could be promoting the observed conformation.

The major adduct from reaction of **1b** with *N*-methylmaleimide, **7** (36%), has a more complicated ^{1}H NMR spectrum than either **4** or **3b**; firstly every non-aromatic proton displays a unique signal, further a selected number of the resonance signals appear broad. For this adduct, 3-H and 4-H on one isoxazolidine ring are *cis* orientated whilst on the other ring the corresponding protons have a *trans* relationship—**7** is thus a *cis*,*trans* bisadduct. The broad signals are associated with the isoxazolidine ring having 3-H and 4-H *trans* orientated and at rt the signal for 3-H appears to be completely missing from the ^{1}H NMR spectrum. Consequently the adduct is characterised from low temperature spectral data. The ^{13}C NMR spectrum (−40 °C) of **7** displays a multitude of signals and the proton

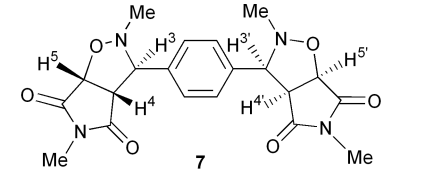
Table 1 Selected ^{1}H NMR data for the isoxazolidines **5c**, **3b**, **8b**, and **9b**

	Proton resonance position (ppm); multiplicity, coupling constant/Hz			
Recording temp., adduct	5-H	3-H	4-H	*N*-Methylisoxazolidine
−40 °C, **5c** minor invertomer **A′**	5.06, d, *J* 7.3	3.64, d, *J* 7.7	3.77, m	2.67, s
−40 °C, **5c** major invertomer **B′**	5.02, d, *J* 7.3	4.51, s	3.81, d, *J* 7.3	2.37, s
+50 °C, **5c**	4.91, d, *J* 7.3	4.1, br s	3.69, dd, *J* 7.3 and 4.0	2.48, br s
+55 °C, **3b**[a]	4.90, d, *J* 7.3	4.05, br s	3.65, dd, *J* 7.3 and 4.3	2.48, br s
rt, **3a**	4.97, d, *J* 7.1.	5.51, s	3.80, d, *J* 7.1	—
−40 °C, **8b** minor invertomer	5.21, d, *J* 7.8	3.95, d, *J* 7.6	3.83, m	2.76
−40 °C, **8b** major invertomer	5.17, d, *J* 7.6	4.64, s	3.98, d, *J* 7.6	2.33
+50 °C, **8b**[a]	5.06, d, *J* 7.6	4.25, br s	3.86, dd, *J* 3.8 and 7.6	2.54, br s
+40 °C, **9b** signals due to *trans* ring[a]	Overlapping 5.05, 2 × d	4.23, br s	Overlapping 3.85, m	2.53, br s
+40 °C, **9b** signals due to *cis* ring	3.96, d, *J* 9.8	2.71, s		

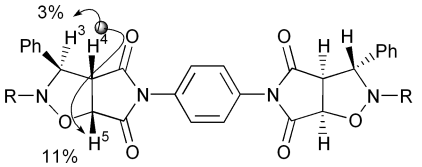
[a] Equilibrating *i*- and *o*-conformers.

spectrum shows several *N*-methyl (pyrrolidinedione) signals [~3.1 ppm]; this multiplication of signals is due to the different diastereomers of **7** which present on freezing-out of the conformational possibilities of the *trans* orientated isoxazolidine ring.

N,N′-1,4-Phenylenedimaleimide is an attractive candidate for investigation as an aryl linked bisdipolarophile. Its cycloadditive ability was tested with *N*-benzylideneaniline *N*-oxide and *N*-benzylidenemethylamine *N*-oxide. Under kinetic conditions (CH_2Cl_2, rt, 24 h) two adducts were isolated from reaction with *N*-benzylideneaniline *N*-oxide. The major diastereomer **8a**

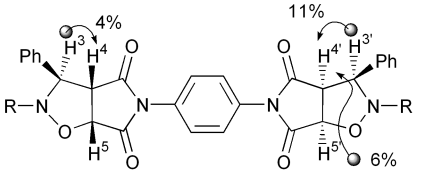


7



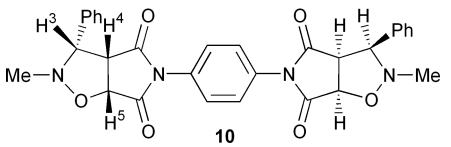
8a R = Ph
b R = Me

NOEDS results shown for 8a



9a R = Ph
b R = Me

NOEDS results shown for 9a



10

(36%) exhibits a remarkably simple ^{1}H NMR spectrum confirming the symmetrical character of the molecule: it has 3-H and 4-H *trans* orientated in both rings. The minor adduct **9a** (17%) has lost this symmetry element and 3-H and 4-H are *cis* orientated on one ring and *trans* orientated on the second ring. NOEDS results for these adducts are summarised in the drawings. That the *trans* isoxazolidine rings of **8a** and **9a** adopt the *i*-conformation is apparent from the proton resonance position and multiplicity of the 3-H signal (~5.7 ppm, s). The *cis* ring of **9a** must also have *i*-conformation; this can be gleaned from the shielded resonance of the 3-H signal (4.8 ppm) suggesting it to be antiperiplanar to the N-lone pair. Repeating the reaction under more forcing conditions (toluene, 110 °C, 6 h) improves the diastereoselectivity and the *trans*,*trans* bisadduct **8a** results in 50% yield accompanied by only a trace amount of **9a**. The thermodynamic preference for *trans* stereochemistry has been observed for related adducts and *cis*-fused adducts have been seen to convert to *trans*-analogues following heating in boiling *p*-xylene.[10]

As with the bisnitrone the *N*-methyl dipole reacts less selectively but furnishes higher (chemical) yields than its electron poor *N*-phenyl analogue. The *cis*,*trans* adduct **9b** is the dominant product (44%), the *trans*,*trans* adduct **8b** is the intermediate product (26%). The minor product **10** could only be obtained as an enriched sample with **9b** (8%), it is tentatively assigned as the *cis*,*cis* isomer by virtue of the size of the 3-H–4-H coupling constant [$^3J_{3,4}$ 8.8 Hz]. ^{1}H NMR spectra associated with the *N*-phenylisoxazolidines **8a**, **9a** exhibit sharp signals for all protons whilst the *N*-methylisoxazolidines display broad signals for the protons associated with rings having 3-H and 4-H *trans* orientated *i.e.* **8b** and **9b**. The variable temperature data for the isoxazolidine ring protons of **8b** are summarised in Table 1; clearly the trend mirrors that seen for **5c** and **3b**. The *cis*,*trans* adduct **9b** has a complex spectrum with some signals overlapping at all temperatures ranging from +40 to –40 °C. At higher temperatures "two sets" of signals representing the *cis*- and the rapidly equilibrating *trans*-ring can be discerned (Table 1). Predictably at low temperature, as discrete diastereomers associated with N-inversion in the *trans*-ring present themselves, the total number of resonance signals increases and the spectra become more crowded.

Conclusion

In conclusion we have prepared bisisoxazolidines **3**, **4** and **7**–**10** from one-pot double cycloaddition reactions on bifunctional nitrones and bismaleimides. *N*-Methyl dipoles (mono and bifunctional) are more reactive, but less selective than their *N*-phenyl analogues. Adducts with an *N*-methyl substituent on the isoxazolidine ring and *trans* disposed 3-H, 4-H protons **3b**, **7**, **8b** and **9b** exhibit conformational flexibility at rt. That the mobility of the bisadducts is associated with the component bicyclic units and is not somehow a feature of the structure at large has been confirmed by studying the "hemi-adducts" **5** and **6**. As the latter show dynamic behaviour at rt it is apparent that a small isoxazolidine *N*-substituent and 3,4-*trans* protons are necessary and sufficient conditions for permitting fluctuation of the NO-heterocyclic ring of isoxazolo-fused pyrrolidinediones. Conformational assignment of *trans*-adducts as *i*- or *o*-conformers can reliably be made following measurement of the resonance position and multiplicity of the 3-H signal with

an upfield doublet (~3.8 ppm, J ~8 Hz) being typical of an *o*-conformer whilst a downfield singlet (~4.5 ppm) characterises the *i*-conformation. Dreiding scale models of *cis*-adducts show that the 3-H signal will always present as a doublet, with an upfield location (indicating shielding by an antiperiplanar N-lone pair) being expected for an *i*-conformer and a more downfield resonance being anticipated for an *o*-conformer. The success of **1** and **2** as discrete bifunctional reagents encourages us in continuing investigation of these substrates as building blocks for macrocyclic structures. Interestingly previous workers report polymerisation of *N*-benzylideneaniline *N*-oxide with *m*-phenylenebismaleimide in the presence of a trace amount of phenyl-β-naphthylamine.[11]

Experimental

All melting points were determined on a Stuart Scientific melting point apparatus and are uncorrected. Mass spectra were recorded on a Profile Kratos Analytical Instrument. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA400 spectrometer (operating at 400 and 100 MHz respectively). Samples were prepared in $CDCl_3$ with TMS as internal standard. Chemical shifts are given in ppm and coupling constants are given in Hz. Elemental analyses were performed on a Perkin-Elmer model 240 CHN analyser. Flash column chromatography was carried out on silica gel (200–400 mesh; Kieselgel 60, E Merck) with air pump pressure and separated compounds are described in order of elution. Analytical TLC plates were purchased from Merck and were visualised under UV light using a Spectroline ENF 240C/F lamp at 254 nm. Solvents were purified by standard methods and petroleum spirit refers to that fraction of light petroleum boiling between 40 and 60 °C. *N*-Methylhydroxylamine hydrochloride, *N*-methylmaleimide, *N*-phenylmaleimide and *N,N′*-1,4-phenylenedimaleimide were purchased from Sigma Aldrich and used without further purification.

Nitrone preparation

Nitrones were synthesised by condensation of the parent aldehyde with the appropriate hydroxylamine.

N-Phenylhydroxylamine

In a slight modification of a literature procedure [12] an aqueous solution of NH_4Cl (320 cm^3, 0.6 mol) was treated with nitrobenzene (20.0 g, 0.16 mol). The mixture was stirred vigorously with heating until the temperature reached ~60 °C. The heat was then removed and activated zinc powder (23.6 g, 0.36 mol) added portion-wise over a 20 min period, ensuring the temperature did not exceed 80 °C. Stirring for a further 20 min afforded a grey suspension which was filtered whilst still hot and washed with hot water (90 °C). The filtrate was saturated with NaCl (120 g) and cooled in an ice bath for 2 h. A pale yellow solid precipitated, and was suspended in ether. Following filtration and solvent removal the crude product crystallised as colourless needles (12.3 g, 71%), mp 80–82 °C (from toluene) [lit. 79.8 °C [13]], δ_H: 6.40 (2H, br, OH and NH), 7.60–6.85 (5H, m, Ar-H). The hydroxylamine was used immediately as it deteriorates on standing.

N-Benzylideneaniline *N*-oxide

A solution of *N*-phenylhydroxylamine (12.00 g, 0.11 mol) in EtOH (22 cm^3) was warmed briefly to between 40 and 60 °C. Benzaldehyde (11.65 g, 0.11 mol) was added to the clear solution and the flask stoppered, shaken vigorously for a few min and stored at rt in the dark for 12 h. Colourless needles of the title nitrone precipitated, were filtered at the pump, washed with EtOH (10 cm^3) and crystallised to yield pure nitrone (19.2 g, 89%), mp 112–114 °C (from EtOH) [lit. 114 °C [14]]. δ_H: 7.35 (6H, m, Ar-H), 7.70 (2H, m, Ar-H), 7.88 (1H, s, CH), 8.40 (2H, m, Ar-H).

N-Benzylidenemethylamine *N*-oxide

A modification of the procedure of Torssell and Zeuthen was used.[15] Benzaldehyde (4.24 g, 0.04 mol) was added to a solution of *N*-methylhydroxylamine hydrochloride (4.18 g, 0.05 mol) in CH_2Cl_2 (40 cm^3). $NaHCO_3$ (10.08 g, 0.12 mol) was added and the mixture heated at reflux for 12 h. On termination of heating the suspension was filtered and the solid washed with CH_2Cl_2. The organics were combined and the solvent removed to afford a yellow solid which crystallised, to give the title dipole as yellow cubic crystals (3.94 g, 73%), mp 83–85 °C (from hexane–dichloromethane) [lit., 84–86 °C [16]], δ_H: 3.85 (3H, s, CH_3), 7.32 (4H, m, Ar-H and CH), 8.15 (2H, m, Ar-H).

N-Phenyl(4-{[phenyl(oxido)iminio]methyl}phenyl)methylideneamine *N*-oxide 1a

A solution of *N*-phenylhydroxylamine (6.00 g, 0.05 mol) in EtOH (25 cm^3) was warmed briefly to between 40 and 60 °C before adding terephthalaldehyde (3.35 g, 0.025 mol). The flask was stoppered, shaken vigorously for a few min and stored at rt in the dark for 12 h after which a bright yellow solid precipitated. The crude product was filtered at the pump, washed with EtOH (10 cm^3) and crystallised to afford yellow cubic crystals (7.03 g, 73%). Mp >250 °C (from DMF) [Found: C, 75.89; H, 5.23; N, 8.76. $C_{20}H_{16}N_2O_2$ requires C, 76.00; H, 5.06; N, 8.86%], *m*/*z* 316 (M^+), 300 (M − O), 196 (M − CHNOPh). Due to poor solubility NMR spectra could not be recorded.

N-Methyl(4-{[methyl(oxido)iminio]methyl}phenyl)methylideneamine *N*-oxide 1b

Terephthalaldehyde (1.34 g, 10 mmol) was added to a solution of *N*-methylhydroxylamine hydrochloride (2.09 g, 25 mmol) in CH_2Cl_2 (50 cm^3). $NaHCO_3$ (2.52 g, 30 mmol) was added and the mixture heated at reflux for 18 h. The solution was filtered while still hot and the inorganic solid washed with boiling $CHCl_3$. The title nitrone crystallised from the filtrate as a white solid and was collected at the pump.

The inorganic solid was returned to the reaction flask and heated in boiling $CHCl_3$ (50 cm^3) for 1 h. The suspension was filtered (hot) and following cooling a second batch of nitrone crystallised from the filtrate and was collected.

The filtrates from collection of each crop of dinitrone were combined and concentrated to yield an off-white solid which was crystallised from $CHCl_3$ to yield a third batch of dinitrone. The total yield of dinitrone was 1.42 g, 74%, mp >250 °C [Found C, 62.58; H, 6.01; N, 14.83. $C_{10}H_{12}N_2O_2$ requires C, 62.47; H, 6.30; N, 14.58%], *m*/*z* 192 (M^+), 176 (M − O), 134 (M − $CHNOCH_3$). δ_H: 3.89 (6H, s, 2 × CH_3), 7.40 (2H, s, 2 × CH), 8.24 (4H, s, Ar-H); δ_C: 54.58 (2 × CH_3), 128.29 (4 × Ar-C), 131.81 (2 × Ar-C), 134.66 (2 × N=C).

3-[4-(5-Methyl-4,6-dioxo-2-phenylhexahydro-2*H*-pyrrolo[3,4-*d*]-isoxazol-3-yl)phenyl]-5-methyl-2-phenyldihydro-2*H*-pyrrolo-[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-dione 3a

N-Phenyl(4-{[phenyl(oxido)iminio]methyl}phenyl)methylideneamine *N*-oxide **1a** (80 mg, 0.25 mmol) and *N*-methylmaleimide (84 mg, 0.76 mmol) were placed in DMF (15 cm^3) and the mixture stirred with heating at 120 °C for 12 h. Removal of the solvent afforded a brown solid which was separated by flash chromatography (Et_2O–MeOH, 19 : 1) to yield **3a**. Crystallisation gave the product as a white solid (26%), mp 229–231 °C (from Et_2O–MeOH) [Found C, 66.82; H, 5.03; N, 10.11. $C_{30}H_{26}N_4O_6$ requires C, 66.65; H, 5.23; N, 10.37%]. δ_H: 2.68 (6H, s, 2 × CH_3), 3.80 (2H, d, J 7.08, 2 × 4-H), 4.97 (2H, d, J 7.08, 2 × 5-H), 5.51 (2H, s, 2 × 3–H), 6.92 (4H, t, Ar-H), 7.00 (4H, d, Ar-H), 7.20 (4H, t, Ar-H), 7.48 (4H, s, Ar-H); δ_C: 24.99, 56.96, 69.31, 77.42, 114.70, 122.94, 127.40, 128.97, 138.24, 174.68.

General procedure for preparation of dihydro-2*H*-pyrrolo[3,4-*d*]-isoxazole-4,6(3*H*,5*H*)-diones 5 and 6

A solution of the appropriate maleimide (1.8 mmol) and nitrone (1.8 mmol) in toluene (30 cm^3) was heated at reflux for 3 h under an N_2 atmosphere. Removal of the solvent under reduced pressure yielded the crude products which were purified by flash chromatography [Et_2O– petroleum spirit (for **5a/6a** 1 : 2; for **5b/6b** 1 : 1; for **5c/6c** 1 : 1)] to yield pure samples of all adducts.

5a, white needles (507 mg, 76%), mp 153–154 °C (from Et_2O–petroleum spirit) [lit. 150–151 °C [17]]. δ_H: 4.01 (1H, d, *J* 7.32, 4-H), 5.10 (1H, d, *J* 7.32, 5-H), 5.76 (1H, s, 3-H), 6.61 (2H, m, Ar-H), 6.99 (1H, t, Ar-H), 7.58–7.14 (12H, m, Ar-H); δ_C: 57.27, 69.94, 77.28, 114.33, 122.91, 126.12, 126.49, 128.14, 128.96, 129.00, 129.39, 130.84, 138.57, 148.82, 172.63, 174.15; **6a** a white solid (100 mg, 15%), mp 203–204 °C (from Et_2O–petroleum spirit) [lit. 201–202 [17]]. δ_H: 3.99 (1H, dd, *J* 9.16 and 8.06, 4-H), 4.87 (1H, d, *J* 9.16, 3-H), 5.21 (1H, d, *J* 8.06, 5-H), 7.40–6.94 (15H, m, Ar-H); δ_C: 54.58, 71.40, 76.92, 118.74, 124.77, 125.87, 125.91, 127.48, 128.80, 129.01, 129.10, 134.45, 147.31, 171.30, 173.42.

5b, colourless cubic crystals from Et_2O–petroleum spirit (289 mg, 52%), mp 182–184 °C [Found C, 70.00; H, 5.28; N, 9.01. $C_{18}H_{16}N_2O_3$ requires C, 70.11; H, 5.24; N, 9.09%]. δ_H and δ_C values at various temperatures are given in Table 2.

6b, white needles (205 mg, 37%), mp 153–155 °C (from Et_2O–petroleum spirit) [Found C, 70.36; H, 5.31; N, 8.86. $C_{18}H_{16}N_2O_3$ requires C, 70.11; H, 5.24; N, 9.09%]. δ_H: 2.68 (3H, s, N-CH_3), 3.78 (1H, br dd, *J* 8.79 and 7.69, 4-H), 3.90 (1H, d, *J* 8.79, 3-H), 4.96 (1H, d, *J* 7.32, 5-H), 7.43–7.19 (10H, m, Ar-H); δ_C: 42.61, 54.37, 75.51, 76.41, 126.04, 127.74, 128.63, 128.84, 128.91, 129.14, 131.35, 133.64, 172.07, 174.70; **5c**, colourless cubic crystals (226 mg, 51%), mp 142–143 °C (from Et_2O–petroleum spirit) [Found C, 63.56; H, 6.01; N, 11.15. $C_{13}H_{14}N_2O_3$ requires C, 63.39; H, 5.74; N, 11.38%], *m*/*z* 246 (M^+). δ_H and δ_C values at various temperatures are given in Table 2; **6c**, colourless cubic crystals (182 mg, 41%), mp 129–131 °C (from Et_2O–petroleum spirit) [Found C, 63.21; H, 5.51; N, 11.25. $C_{13}H_{14}N_2O_3$ requires C, 63.39; H, 5.74; N, 11.38%], *m*/*z* 308 (M^+). δ_H: 2.59 (3H, s, $ONCH_3$), 2.94 (3H, s, (O=C)NCH_3), 3.67 (1H, br dd, *J* 8.42 and 7.32, 4-H), 3.79 (1H, d, *J* 8.42, 3-H), 4.83 (1H, d, *J* 7.32, 5-H), 7.15 (2H, m, Ar-H), 7.31 (3H, m, Ar-H); δ_C: 24.61, 42.35, 54.28, 75.17, 76.15, 127.53, 128.63, 133.47, 173.00, 175.42.

X-Ray crystal determination of 5c‡

The structure was solved by direct methods, SHELXS-97,[6] and refined by full matrix least squares using SHELXL-97.[7] SHELX operations were rendered paperless using ORTEX which was also used to obtain the drawings.[8] Data were corrected for Lorentz and polarization effects but not for absorption. Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they were attached. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a Pentium PC. Crystal data for **5c** are given in Table 3.

3-[4-(2,5-Dimethyl-4,6-dioxohexahydro-2*H*-pyrrolo[3,4-*d*]-isoxazol-3-yl)phenyl]-2,5-dimethyldihydro-2*H*-pyrrolo[3,4-*d*]-isoxazole-4,6(3*H*,5*H*)-diones 3b, 7 and 4

A solution of *N*-methyl(4-{[methyl(oxido)iminio]methyl}-phenyl)methylideneamine *N*-oxide (150 mg, 0.78 mmol) and *N*-methylmaleimide (191 mg, 0.17 mmol) in toluene (60 cm^3) was stirred at reflux under N_2 for 4 h. Removal of solvent under reduced pressure yielded the crude product as an off-white solid. Separation by flash chromatography [gradient from Et_2O through Et_2O–MeOH, 19 : 1) yielded three products. **3b** was isolated as a white solid (80 mg, 25%), mp 179–181 °C (from EtOH) [Found C, 57.74; H, 5.53; N, 13.46. $C_{20}H_{22}N_4O_6$ requires C, 57.96; H, 5.36; N, 13.52%]. δ_H and δ_C values are given in Table 2. **7** was isolated as a white solid (116 mg, 36%), mp 196–198 °C (from EtOH) [Found C, 57.89; H, 5.15; N, 13.37. $C_{20}H_{22}N_4O_6$ requires C, 57.96; H, 5.36; N, 13.52%]. δ_H (−40 °C): 2.31 and 2.68 (6H, 2 × br s, $ONCH_3$), 3.03. 3.05, 3.07, 3.09, 3.12 (6H, 5 × s, (C=O)NCH_3), 3.74 ($3\frac{1}{2}$ H, m, 4-H, 4′-H, 3′-H and $\frac{1}{2}$3-H), 4.51 ($\frac{1}{2}$H, s, 3-H), 5.01 (2H, m, 5-H and 5′-H), 7.21–7.32 ($3\frac{1}{2}$H, m, Ar-H), 7.45 ($\frac{1}{2}$H, m, Ar-H); δ_C (−40 °C): 25.20, 25.54, 39.42, 42.74, 43.46, 54.28, 54.37, 55.47, 55.60, 58.11, 70.63, 74.75, 75.00, 75.73, 76.19, 77.25, 127.99, 129.52, 134.06, 135.59, 172.50, 173.42, 175.08, 175.59, 175.89, 175.97. **4** was isolated as an enriched sample with **7** (13 mg, 4%). δ_H: 2.64 (6H, s, 2 × $ONCH_3$), 2.99 (6H, s, 2 × (O=C)NCH_3), 3.72 (2H, br dd, 2 × 4-H), 3.83 (2H, d, *J* 8.79, 2 × 3-H), 4.89 (2H, d, *J* 7.32, 2 × 5-H), 7.17 (4H, s, Ar-H); δ_C: 24.90, 42.61, 54.37, 75.00, 76.28, 128.21, 134.23, 172.79, 175.38.

2,3-Diphenyl-5-[4-(4,6-dioxo-2,3-diphenylhexahydro-2*H*-pyrrolo[3,4-*d*]isoxazol-5-yl)phenyl]dihydro-2*H*-pyrrolo[3,4-*d*]-isoxazole-4,6(3*H*,5*H*)-diones 8a and 9a

A solution of *N,N′*-1,4-phenylenedimaleimide (68 mg, 0.25 mmol) and *N*-benzylideneaniline *N*-oxide (100 mg, 0.51 mmol) in CH_2Cl_2 (60 cm^3) was stirred at rt for 24 h. Separation of the crude mixtures by flash chromatography [Et_2O–petroleum spirit, 1 : 1] yielded pure samples of **8a** (60 mg, 36%) and **9a** (28 mg, 17%). Repeating the reaction on the same scale in boiling toluene (60 cm^3, 3 h) gave **8a** (84 mg, 50%) and only a trace amount of **9a**. **8a**, a white solid, mp 244–246 °C (from Et_2O–petroleum spirit) [Found C, 72.28; H, 4.29; N, 8.68. $C_{40}H_{30}N_4O_6$ requires C, 72.49; H, 4.57; N, 8.46%]. δ_H 4.01 (2H, d, *J* 7.57, 2 × 4-H), 5.09 (2H, d, *J* 7.57, 2 × 5-H), 5.75 (2H, s, 2 × 3-H), 6.60 (4H, s, 4 × Ar-H), 7.56–6.95 (20H, m, Ar-H); δ_C 57.21, 69.95, 77.13, 114.32, 122.94, 126.46, 126.63, 128.16, 128.97, 129.39, 131.05, 138.35, 148.71, 172.19, 173.68. **9a**, a white solid, mp 211–212 °C (from ether–petroleum spirit) [Found C, 72.47; H, 4.77; N, 8.36. $C_{40}H_{30}N_4O_6$ requires C, 72.49; H, 4.57; N, 8.46%]. δ_H 3.97 (2H, m, 4-H and 4′-H), 4.84 (1H, d, *J* 9.15, 5′-H), 5.03 (1H, d, *J* 7.68, 5-H), 5.18 (1H, d, *J* 8.06, 3′-H), 5.68 (1H, s, 3-H), 6.61 (2H, dd, *J* 8.79 and 1.83, Ar-H), 7.50–6.88 (22H, m, Ar-H); δ_C 54.54, 57.26, 69.99, 71.48, 76.79, 77.21, 112.18, 114.36, 115.38, 118.95, 123.03, 124.94, 129.29, 126.51, 126.80, 127.48, 128.21, 128.84, 128.97, 129.10, 129.44, 130.80, 131.35, 134.32, 138.44, 147.14, 148.76, 170.96, 173.76.

2-Methyl-3-phenyl-5-[4-(2-methyl-4,6-dioxo-3-phenylhexahydro-5*H*-pyrrolo[3,4-*d*]isoxazol-5-yl)phenyl]dihydro-2*H*-pyrrolo[3,4-*d*]isoxazole-4,6(3*H*,5*H*)-diones 8b, 9b and 10

A solution of *N,N′*-1,4-phenylenedimaleimide (100 mg, 0.37 mmol) in toluene (60 cm^3) was heated to reflux to ensure maximum dissolution of the maleimide. *N*-Benzylidene-methylamine *N*-oxide (101 mg, 0.74 mmol) was then added and the solution stirred at reflux for 4 h. Removal of solvent at reduced pressure yielded the crude product as a brown solid. This was purified by flash chromatography [gradient from Et_2O through Et_2O–MeOH, 19 : 1) to yield three products. **8b**, a white solid (52 mg, 26%), mp 187–188 °C (from EtOH) [Found C, 66.73; H, 4.91; N, 10.50; $C_{30}H_{26}N_4O_6$ requires C, 66.90; H, 4.88; N, 10.40%]. δ_H and δ_C values at various temperatures are given in Table 2. **9b**, a white solid (88 mg, 44%), mp 238–240 °C (from EtOH) [Found C, 67.16; H, 4.84; N, 10.63. $C_{30}H_{26}N_4O_6$ requires C, 66.90; H, 4.88; N, 10.40%]. δ_H: 2.55 (3H, br, N-CH_3), 2.72 (3H, s, N-CH_3), 3.89 (2H, m, 4-H and 4′-H), 3.98 (1H, d, *J* 8.79, 3′-H), 4.50 (1H, br, 3-H), 5.07 (2H, m, 5-H and 5′-H), 7.29–7.49 (14H, m, Ar-H); δ_C: 33.99, 44.09, 54.33, 76.28, 76.96, 126.46, 126.76, 127.61, 128.76, 128.88, 128.97, 131.00, 133.00, 175.08. **10** was obtained as an enriched

‡ CCDC reference number 188/284. See http://www.rsc.org/suppdata/p2/b0/b0071641/ for crystallographic data in .cif format.

Table 2 ^{1}H and ^{13}C NMR data for **5b**, **5c**, **3b** and **8b**

Compound	Temp./°C	δ_H	δ_C
5b	rt	2.46 (3H, br, N-CH_3), 3.80 (1H, dd, *J* 7.32 and 3.66, 4-H), 4.40 (1H, br, 3-H), 5.00 (1H, d, *J* 7.32, 5-H), 7.27–7.44 (10H, m, Ar-H)	
5b *i*-conformer	−40	3.96 (1H, d, *J* 7.69, 4-H), 4.64 (1H, s, 3-H), 5.15 (1H, d, *J* 7.69, 5-H), 7.24–7.56 (10H, m, Ar-H)	39.30, 43.08, 55.52, 57.89, 71.23, 75.51, 75.90, 76.79, 126.04, 126.21, 127.48, 127.57, 128.55, 128.63, 128.84, 129.05, 129.27, 129.39, 130.37, 130.75, 134.70, 135.64, 171.17, 173.76, 174.61, 175.08
5b *o*-conformer		2.74 (3H, s, N-CH_3), 3.82 (1H, d, *J* 7.82, 3-H), 3.93 (1H, m, 4-H), 5.19 (1H, d, *J* 7.69, 5-H), 7.50–7.33 (10H, m, Ar-H)	
5c	rt	2.47 (3H, br, $ONCH_3$), 3.08 (3H, s, (C=O)NCH_3), 3.72 (1H, dd, *J* 7.32 and 3.66, 4-H), 4.40 (1H, br, 3-H), 4.95 (1H, d, *J* 7.32, 5-H), 7.36–7.40 (5H, m, Ar-H)	25.12, 41.76 (br), 57.09 (br), 75.94, 105–120[a] (br), 128.67, 128.84, 135.85 (br)
5c	+50	2.48 (3H, br s, $ONCH_3$), 3.06 (3H, s, (C=O)NCH_3), 3.69 (1H, dd, *J* 7.32 and 4.03, 4-H), 4.08 (1H, br, 3-H), 4.92 (1H, d, *J* 7.32, 5-H), 7.41–7.31 (m, Ar-H)	24.99, 41.13 (br), 57.43, 73.60 (br), 76.11, 77.13, 110–120[a] (br), 128.21, 128.63, 128.84, 136.10, 175.21
5c *i*-conformer	−40	2.32 (3H, s, $ONCH_3$), 3.14 (3H, s, (O=C)NCH_3), 3.81 (1H, d, *J* 7.32, 4-H), 4.52 (1H, s, 3-H), 5.03 (1H, d, *J* 7.32, 5-H), 7.21–7.44 (5H, m, Ar-H)	25.12, 25.29, 39.17, 42.86, 55.52, 57.94, 70.76, 75.22, 75.51, 75.85, 127.48, 128.50, 128.76, 129.01, 134.74, 135.55, 172.40, 174.66, 175.46, 175.80
5c *o*-conformer		2.67 (3H, s, $ONCH_3$), 3.09 (3H, s, (O=C)NCH_3), 3.65 (1H, d, *J* 7.68, 3-H), 3.77 (1H, m, 4-H), 5.06 (1H, d, *J* 7.33, 5-H), 7.21–7.44 (5H, m, Ar-H)	
3b	rt	2.49 (6H, br, 2 × $ONCH_3$), 3.08 (6H, s, 2 × (O=C)-NCH_3), 3.71 (2H, dd, *J* 7.32 and 3.66, 2 × 4-H), 4.40 (2H, br, 2 × 3-H), 4.96 (2H, d, *J* 7.32, 2 × 5-H), 7.36 (4H, br, Ar-H)	
3b	−35	2.31, 2.37, 2.67 and 2.69 (6H, 4 × s, 2 × $ONCH_3$), 3.10 and 3.15 (6H, 2 × s, 2 × (C=O)NCH_3), 3.66–3.82 (3H, m, 2 × 4-H, 3-H), 4.53 (1H, s, 3-H), 5.04 (2H, m, 2 × 5-H), 7.28 (2H, m, Ar-H), 7.48 (2H, m, Ar-H)	25.24, 25.41, 39.17, 42.99, 55.39, 57.94, 70.33, 74.71, 75.51, 75.85, 127.74, 128.29, 129.10, 129.65, 135.30, 135.64, 136.53, 172.19, 174.70, 175.33, 175.67
8b	rt	2.52 (6H, br, 2 × NCH_3), 3.90 (2H, dd, *J* 7.32 and 3.42, 2 × 4-H), 4.50 (2H, br, 2 × 3-H), 5.10 (2H, d, *J* 7.32, 2 × 5-H), 7.37–7.44 (10H, m, Ar-H), 7.54 (4H, s, Ar-H)	

[a] Very broad baseline peak.

Table 3 Crystal data and structure refinement for **5c**

Formula	$C_{13}H_{14}N_2O_3$
Formula weight	246.26
Temperature/K	293(2)
Crystal system	Monoclinic
Space group	*P*21/*n*
Unit cell dimensions	*a* = 11.858(2) Å, *α* = 90.000(9)° *b* = 7.7841(11) Å. *β* = 97.595(11)° *c* = 13.3660(11) Å, *γ* = 90.000(13)°
Volume/Å^3	1222.9(3)
Z	4
Absorption coefficient/mm^{-1}	0.096
Reflections collected	2519
Independent reflections	2286 [*R*(int) = 0.0144]
Reflections observed (>2*σ*)	1455
Data/restraints/parameters	2286/0/165
Final *R* indices [>2*σ*(*I*)][a]	$R_1 = 0.0530$, $wR_2 = 0.1282$
R indices (all data)	$R_1 = 0.0845$, $wR_2 = 0.1410$

[a] *R* indices; $R_1 = [\Sigma||F_o| - |F_c||]/\Sigma|F_o|$ (based on *F*), $wR_2 = [[\Sigma_w(|F_o^2 - F_c^2|)^2]/[\Sigma_w(F_o^2)^2]]^{1/2}$ (based on F^2). $w = 1/[(\sigma F_o)^2 + (0.0867P)^2]$.

sample with **9b** (16 mg, 8%). δ_H: 2.71 (6H, s, 2 × N-CH_3), 3.87 (2H, br dd, *J* 8.79 and 7.33, 2 × 4-H), 3.96 (2H, d, *J* 8.79, 2 × 3-H), 5.05 (2H, d, *J* 7.33, 2 × 5-H), 7.37 (4H, s, Ar-H), 7.49–7.30 (10H, m, Ar-H); δ_C: 42.63, 54.39, 75.66, 76.30, 126.40, 136.99, 127.67, 129.03, 131.61, 133.41, 171.62, 174.25.

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