Nitrogen containing heterocycles from aldoximes; a one-pot route to isoxazolobenzodiazepinones, *N*-substituted and *N*-unsubstituted isoxazoloquinolinones

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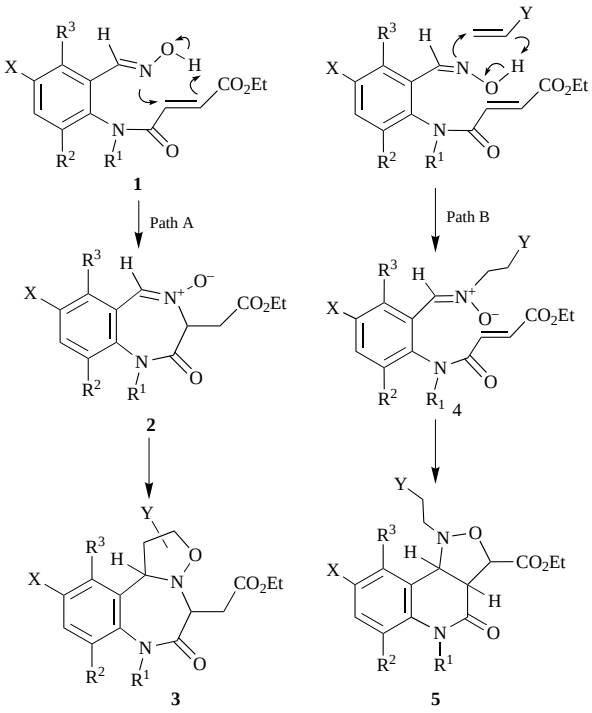
The aldoximes 1 in the presence of electron poor olefins react to form either the 5,6,7-tricyclic isoxazolobenzodiazepinone 3 or the 5,6,6-tricyclic isoxazoloquinolinone 5 ring skeleton. In each case the ring system formed depends on the relative electrophilicity of the added and internal olefin. The oximes 1a,b,c react with *N*-methylmaleimide, methyl acrylate or phenyl vinyl sulfone to afford the corresponding regioisomeric isoxazolobenzodiazepinones by a tandem intramolecular dipole formation–intermolecular cycloaddition sequence. With the more electrophilic olefin, methyl vinyl ketone, intermolecular nitrone generation precedes intramolecular cycloaddition and the isoxazoloquinolinone skeleton results and for each oxime reaction proceeds smoothly in a regio- and stereo-specific manner. Steric control of chemoreactivity is observed with the ring or chain substituted aldoximes 1d,e,f. These oximes react in the presence of phenyl vinyl sulfone to give the isoxazolobenzodiazepines 15 and 16 together with varying quantities of the *N*-unsubstituted isoxazoloquinolines 14. The latter arise *via* an oxime–nitrone-cycloaddition sequence, in each case the cycloaddition proceeds in a regio- and stereo-specific manner. The oximes 1d,e,f react with methyl vinyl ketone to give single regio- and stereo-isomers of the *N*-unsubstituted and -substituted isoxazoloquinolinones 14 and 17. The high degree of chemo-, regio- and stereo-selectivity with which the one-pot reaction of the oximes 1 with electron poor olefins proceeds represents a convenient method for the construction of the title tricyclic molecular frameworks.

Introduction

The oxime functionality with its contiguous nucleophilic atoms may react with electron poor olefins and acetylenes to form *N*- or *O*-addition products.[1] When monosubstituted electrophilic olefins are employed this reaction is synthetically useful for the preparation of open chain nitrones. Intramolecular variants of the process have also been developed and the reaction proceeds by an APT (azaprotio cyclotransfer) mechanism.[2] We have prepared the amidobenzaldehyde oximes **1** with a view to studying their utility as precursors to benzodiazepinone *N*-oxides **2** and ultimately to the relatively uncommon isoxazolobenzodiazepinone ring system **3**. The benzodiazepine nucleus constitutes the basic skeleton of some of the most therapeutically and financially successful anti-anxiety medicines, *e.g.* librium and valium, and much effort has been directed to molecular modifications in search of enhanced biological activity.[3] Recently a paper has appeared on the preparation and evaluation of libraries of 1,4-benzodiazepines.[4] Our interest in the ring systems **3** arises since there is some suggestion that the medicinal properties of the benzodiazepine ring skeleton may be enhanced through the fusion of an additional ring at the edges of the diazepine nucleus.[3b,3c]

We have reported that the aldoximes **1** upon thermal activation readily cyclize to the stable, isolable 6,7-bicyclic dipoles **2**[5a] and it is anticipated that an intermolecular cycloaddition would yield the targeted ring system. In an effort to optimize the efficiency of the process we were attracted to the possibility that these two reactions could occur consecutively in a single pot; our preliminary results in this area have been the subject of a recent communication.[5b] The success of the one-pot reaction relies heavily on substrate (oxime) discrimination, between the internal unsaturated centre in **1** and the added dipolarophile, in the initial dipole formation step. Factors promoting the generation of the cyclic dipole include the entropic advantage of the intramolecular reaction and the moderate degree of electrophilicity conferred on the olefinic centre by the ester substituent. Dipole formation by intermolecular reaction will clearly become more favourable as the electron attracting power of the substituent on the added olefin increases. In the first case scenario the desired 5,7,6-tricyclic isoxazolobenzodiazepinones **3** will result (Scheme 1, path A) whilst in the second case 5,6,6-tricyclic isoxazoloquinolinones **5** will be formed (Scheme 1, path B). In this paper we report on the factors which control the chemoreactivity of the oximes **1**.



Scheme 1

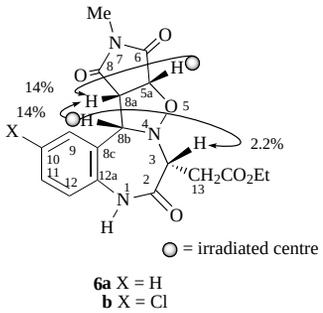


Fig. 1 NOEDS results for **6a**

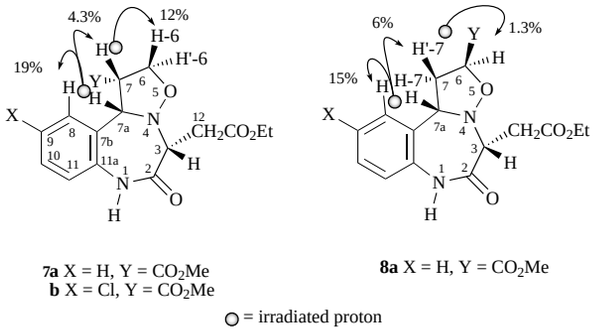


Fig. 2 NOEDS results for **7a** and **8a**

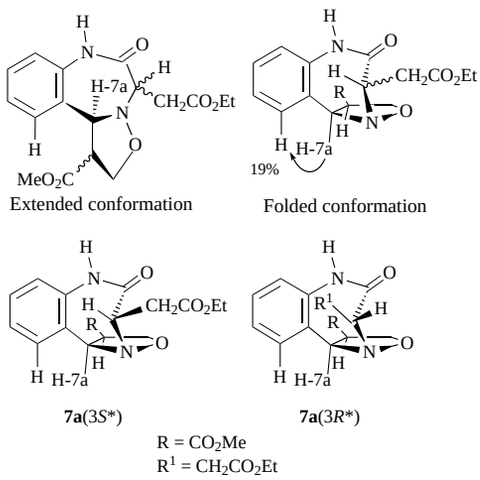


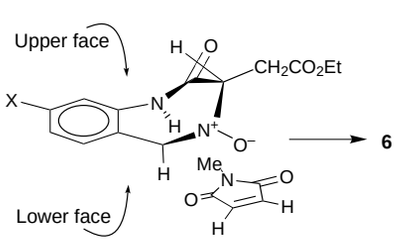
Fig. 3 Conformational possibilities for isobenzodiazepinone **7**

Results and discussion

The *o*-amidobenzaldehyde oxime **1a**, its 5-chloro **1b** and its 3-methyl **1c** derivatives show a clear pattern in their reaction toward *N*-methylmaleimide, methyl acrylate, phenyl vinyl sulfone and methyl vinyl ketone. For each oxime, reaction with any one of *N*-methylmaleimide or the ester or sulfone substituted olefin proceeds by an intramolecular dipole formation–intermolecular cycloaddition route giving the corresponding isoxazolobenzodiazepinones **6**–**10**. With methyl vinyl ketone the chemoselectivity of the reaction is reversed and the isoxazoloquinolinones **11** arise following an intermolecular dipole forming reaction–intramolecular cycloaddition sequence.

N-Methylmaleimide shows limited susceptibility to the APT reaction yet it is a reactive dipolarophile,[6] it was therefore an obvious choice to encourage the oximes to react *via* path A. Additionally as a consequence of its symmetry there exists no possibility for formation of regioisomeric 1,3-dipolar cycloaddition products.

Following stirring in boiling xylene for 8 h, each of **1a** and **1b** react with *N*-methylmaleimide in a chemo- and regio-specific fashion to furnish single diastereoisomeric cycloadducts **6a** and **6b** in 89 and 69% yield, respectively. The relative stereochemistry at C-3, C-5a, C-8a and C-8b in **6a** is assigned on the basis of NOEDS results (nuclear Overhauser enhancement difference spectroscopy) (Fig. 1).† A 14% enhancement on H-8a following saturation of H-8b suggests a *cis* relationship between these protons; irradiation of H-5a causes a similar enhancement, confirming the expected *cis* relationship between H-5a and H-8a; a 2% enhancement on the signal for H-3 upon saturation of H-8b suggests these cross ring protons also have a *cis* arrangement. That **6b** has the same relative stereochemistry as **6a** is inferred from the close agreement of the resonance position and coupling constants for the key signals, H-3, H-5a, H-8a and H-8b, in **6a** and **6b**. Analysis of product stereochemistry indicates that **6a**,**b** arise *via* an *endo* addition of the dipolarophile to the lower face of the dipole (Scheme 2).



Scheme 2

Methyl acrylate, like the olefinic moiety in **1**, owes its electrophilicity to its ester substituent and since both the internal and the external 'olefin' are similarly activated it can be expected that the initial dipole forming reaction (APT) ought to proceed in an intramolecular fashion. Heating a toluene solution of **1a**,**b** in turn with methyl acrylate (110 °C, 18 h) results in the formation of novel isoxazolobenzodiazepinones. Reaction proceeds quantitatively with **1a** and the regioisomeric adducts **7a** and **8a** were formed in a 2:1 ratio; for each regioisomer a single diastereoisomeric adduct results (Fig. 2). The regioselectivity of the reaction is in accordance with the predictions of FMO theory and favours the 4-substituted ring.[7] The multiplicity and the resonance positions of the isoxazolidine ring protons is a sensitive probe for regiochemical assignment. The chloro-substituted dipole **1b** reacts to furnish **7b** as a single regio- and stereo-isomer. The chlorine substituent does affect the solubility of the dipole which is reflected in the low chemical yield (53%). However, the origin of the observed regiospecificity is not obvious, the chlorine atom is too far removed from the reacting centres to exert any steric influence nor is it able to bring to bear any significant (electronic) stabilising effect on the dipole.

Two distinct conformational possibilities available to isoxazolobenzodiazepinones have been identified, the extended and the folded conformations shown in Fig. 3.[8] The ^{1}H NMR spectra of the adducts **7** and **8** show sharp signals indicating that these compounds exist in one preferred conformation at room temperature and this conformational rigidity may argue well for their biological activity—related molecules show facile conformational equilibration under NMR conditions.[8,9] Examination of the NOEDS results of the adducts **7a** and **8a** suggest these molecules adopt the less hindered folded conformation (shown for **7a**), the alternative extended conformation would be incompatible with the observed 19% enhancement on the *o*-ArH following saturation of the benzylic proton H-7a. The relative stereochemistry at C-6/C-7 and C-7a of the regioisomeric adducts **7a**, **8a** can reliably be made following inspection

† The numbering system for compounds used throughout this paper and in the NMR assignments are as shown in Figs. 1, 2 and 4 and do not follow IUPAC guidelines. Correct IUPAC numbering is used for the compound names in the Experimental section only.

Table 1 Characteristic proton resonances and coupling constants for the adducts **7**–**10**, **12**, **13**, **15** and **16**

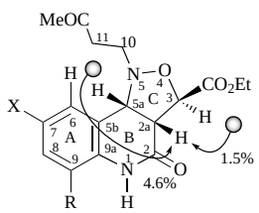
Compound	H-7a	H-7	H-6	H′-6	Compound	H-7a	H-7	H′-7	H-6
7a	4.91	3.75	4.42	4.07	**8a**	4.78	2.95	2.95	4.89
	$J_{7a,7}$ 8.80	$J_{7,6}$ 8.79	$J_{6,6'}$ 8.79	$J_{7,6'}$ 8.79		$J_{7a,7'}$ 9.17	$J_{7a,7}$ 9.17	$J_{7',6}$ 8.78	$J_{7,6}$ 3.67
7b	5.01	3.73	4.48	4.10	**10a**	5.01	3.08	3.08	5.18
	$J_{7a,7}$ 8.77	$J_{7,6}$ 8.77	$J_{6,6'}$ 8.77	$J_{7,6'}$ 8.77		$J_{7a,7'}$ 8.42	$J_{7a,7}$ 8.42	m	m
9a	4.95	4.43	4.43	4.43	**10b**	5.02	3.47	3.05	5.11
	$J_{7a,7}$ 6.59	m*	m	m		$J_{7a,7'}$ 8.49	$J_{7a,7}$ 8.49	$J_{7',6}$ 7.13	$J_{7,6}$ 2.14
9b	5.01	4.49	4.49	4.49	**13**	4.58	2.82	2.33	4.58
	$J_{7a,7}$ 6.27	m	m	m		m	m	m	m
12	4.85	4.01	4.41	4.01	**16a**	5.01	3.10	2.75	5.21
	$J_{7a,7}$ 7.39	m	$J_{6,6'}$ 8.42	m		$J_{7a,7'}$ 8.27	$J_{7a,7}$ 8.12	$J_{7',6}$ 7.69	$J_{7,6}$ 2.20
15a	4.83	4.05	4.41	4.41	**16b**	5.01	3.11	3.11	5.18
	$J_{7a,7}$ 7.33	m	m	m		$J_{7a,7'}$ 8.49	$J_{7a,7}$ 8.49	$J_{7',6}$ 8.26	$J_{7,6}$ 2.20
15b	5.39	4.59	4.22	4.22	**16c**	5.04	3.47	3.05	5.17
	$J_{7a,7}$ 8.06	m	m	m		$J_{7a,7'}$ 8.43	$J_{7a,7}$ 8.43	$J_{7',6}$ 7.33	$J_{7,6}$ 2.21
15c	4.83	4.46	4.46	4.46					
	$J_{7a,7}$ 6.60	m	m	m					

* m multiplets, meaning the coupling constant could not be determined.

of NOEDS results (Fig. 2); stereochemical assignment at the corresponding positions in **7b** was deemed to be as in **7a** by comparison of the chemical shift position and coupling pattern of the relevant protons (Table 1). The cross ring relationship between the protons on C-7a and C-3 in this family of adducts is more tentatively assigned. For each isomer saturation of H-7a causes no effect on the signal for H-3 and irradiation of H-3 causes enhancements only on the signals representing the adjacent exocyclic methylene protons. Examination of Dreiding stereomodels of the folded conformation of the C-3 stereoisomers **7a**(3*S**) and **7a**(3*R**) indicate that on steric grounds the ethoxy group should be oriented away from the plane of the aromatic ring. With this restriction in place an enhancement on the methylene protons upon irradiation of the benzylic signal is expected for the isomer **7a**(3*R**) but not for **7a**(3*S**). No such enhancement was observed thus suggesting H-7a and H-3 have a *cis* relationship; this stereochemical assignment is consistent with that established for the tetracyclic analogue **6a** following NOEDS experiments.

The diastereospecificity observed in the generation of each regioisomer (**7** and **8**) is rationalized following inspection of Dreiding stereomodels, the transition state leading to the formation of the 4-substituted isomer experiences no steric encumbrance when the dipolarophile approaches the lower face of the dipole in an *endo* orientation and cycloaddition proceeds exclusively by this mode. In contrast significant steric clashes between the substituent at C-3 of the dipole and the ester group on the dipolarophile in the transition state leading to the 5-substituted isomer prohibit an *endo* approach and cycloaddition occurs solely by an *exo* addition of methyl acrylate to the lower face of the dipole. Clearly both steric and electronic factors are important in orientating the dipolarophile in the cycloaddition.

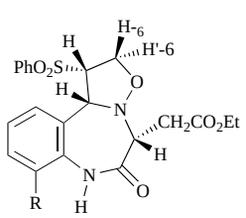
The enhanced electrophilicity of sulfone-activated vinyl compounds compared to ester-substituted olefins[10] suggests that in a competitive situation a reacting nucleophile should preferentially attack the former. In a one-pot reaction of **1** with phenyl vinyl sulfone however the situation is complicated by the fact that nucleophilic attack on the ester-substituted moiety is an intramolecular reaction whilst attack on phenyl vinyl sulfone involves a bimolecular process and as such will suffer from a large negative entropy of activation. Whether dipole formation will occur by path A or path B (Scheme 1) presents an interesting problem. Following heating in boiling toluene, phenyl vinyl sulfone reacts with each of **1a** and **1c** in turn to furnish regioisomeric mixtures of the 5,6,7-tricyclic isoxazolobenzodiazepinones **9** and **10** indicating that phenyl vinyl sulfone was not able to compete with the internal olefin in **1a**,**c** as an effective dipole generating component; no isoxazoloquinolinones were formed. The relative stereochemistry of the regioisomeric tricycles is understood to parallel that observed for **7a** and **8a** on the basis of the close agreement of the characteristic proton resonances and coupling patterns for this series of molecules (Table 1). As observed with methyl acrylate the regioselectivity of the reaction favours formation of the 4-substituted cycloadduct and for each regioisomer a single diastereoisomer results, with **9** arising from *endo* and **10** from *exo* addition of the dipolarophile to the lower face of the dipole.



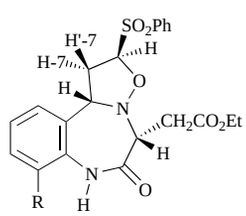
11a R = H, X = Cl
b R = Me, X = H
c R = X = H

○ = irradiated proton

Fig. 4 NOEDS results for **11c**



9a R = H
b R = Me



10a R = H
b R = Me

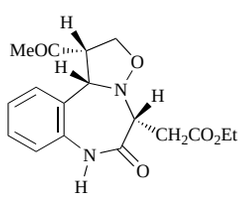
Methyl vinyl ketone is much more susceptible to nucleophilic attack than phenyl vinyl sulfone[10] and in a one-pot reaction with either **1b** or **1c** chemospecific formation of a single isomer of the 5,6,6-tricyclic isoxazoloquinolinones **11a** and **11b** (Fig. 4) arises *via* a tandem intermolecular dipole formation–intramolecular cycloaddition sequence (Scheme 1, path B). Reaction between methyl vinyl ketone and **1a** was highly chemoselective and the 5,6,6- and 5,6,7-tricycles **11c** and **12** were formed in a 9:1 ratio. It is thus apparent that, despite the acknowledged entropic and reactivity advantage of the intramolecular reaction, intermolecular addition to an unsaturated ketone is a lower energy path than intramolecular addition to an unsaturated ester in the dipole generating step (APT reaction). That the BC rings of **11** are *cis* fused is evident from the magnitude of the cross ring coupling constant, $^3J_{2a,5a}$ is ~6 Hz, for this series which by comparison with related molecules indicates *cis* fusion.[11] Retention of the stereochemistry of the dipolarophile

Table 2 Vicinal coupling constants ($^3J_{2a,5a}$, $^3J_{2a,3}$) for the adducts **11**, **14** and **17**

Compound	$^3J_{2a,5a}$ (Hz)	$^3J_{2a,3}$ (Hz)
11a	6.33	2.24
11b	6.23	2.25
11c	6.05	3.12
14a	13.50	8.79
14b	7.32	2.93
14c	8.10	2.64
17a	5.98	2.76
17b	5.92	3.45
17c	5.96	3.20

upon cycloaddition suggests H-2a and H-3 should be in a *trans* relationship.[12] A coupling constant, $^3J_{2a,3}$ 2.2–3.4 Hz, supports this assignment (Table 2). The results of a number of NOEDS experiments carried out to support these assignments are included in the experimental section.

In an effort to increase the yield of the acyl substituted isoxazolobenzodiazepinone **12** the reaction was carried out in two steps involving isolation of the dipole followed by cycloaddition. When **2a** reacts with methyl vinyl ketone in boiling THF the regioisomeric adducts **12** and **13** result in 64 and 26% yield,



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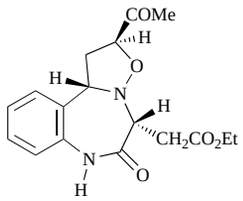
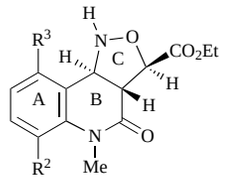
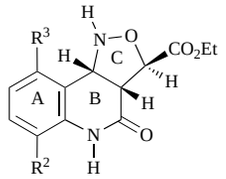


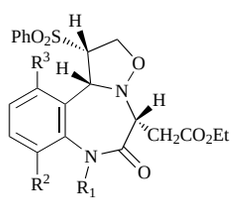
13



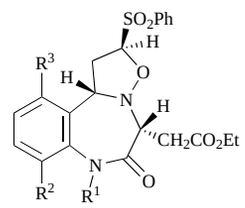
14a R^2, R^3 = H



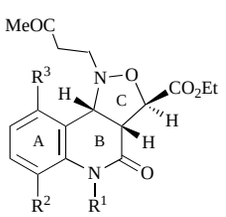
14b R^2, R^3 = Me
c R^2 = H, R^3 = Me



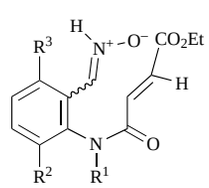
15a R^1 = Me, R^2, R^3 = H
b R^1 = H, R^2, R^3 = Me
c R^1, R^2 = H, R^3 = Me



16a R^1 = Me, R^2, R^3 = H
b R^1 = H, R^2, R^3 = Me
c R^1, R^2 = H, R^3 = Me



17a R^1 = Me, R^2, R^3 = H
b R^1 = H, R^2, R^3 = Me
c R^1, R^2 = H, R^3 = Me



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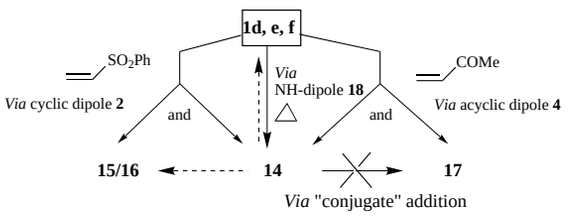
respectively. As previously observed in the one-pot reaction with both methyl acrylate and phenyl vinyl sulfone, the regiochemical preference is for formation of the 4-substituted isomer and the stereochemistry of the reaction is such that an *endo* approach of the dipolarophile to the lower face of the dipole operates in the formation of **12**, whilst an *exo* approach of the dipolarophile to the lower face of the dipole is involved in the generation of the 5-substituted isoxazolidine **13**.

The behaviour of the oximes **1d–f** toward electron deficient olefins is shrouded by a degree of complexity not experienced by **1a–c**. In a recent paper we have shown that these oximes are transformed, simply on heating, to the *N*-unsubstituted isoxazoloquinolinones **14** by an IOOC sequence (*i*ntramolecular *o*xime *o*lefin *c*ycloaddition) involving the tautomeric NH-dipoles **18**.[5a] Oxime–nitrone isomerization is an equilibrium process which lies well to the side of the oxime but in substrates like **1d–f** where there is an internal 'dipolarophile' and ring/chain substituents (R^1–R^3) in place to assist in the attainment of the transition state required for cycloaddition, then the effective concentration of the nitrone is increased through formation of the cycloadduct. When **1d–f** are stirred in solution with phenyl vinyl sulfone or methyl vinyl ketone the possible reaction products therefore include the *N*-unsubstituted (by an IOOC reaction sequence[13]) and *N*-substituted isoxazoloquinolinones (by Scheme 1, path B), as well as isoxazolobenzodiazepinones (by Scheme 1, path A). Competition for reaction of these oximes is therefore between dipole formation by tautomerism or by an intra- or an inter-molecular APT reaction, and the steric bulk of the substituents R^1–R^3 is expected to significantly influence the chemoselectivity of the reaction. The ease with which **1d–f** undergo the IOOC reaction sequence will of course influence their level of interaction with any external component. Of the three oximes **1d** is the most reactive converting to **14a** in 53% yield after 4 h at room temp., the 3,6-dimethyl substrate **1e** is transformed to **14b** in 49% after 16 h heating in boiling ethanol whilst the monomethyl derivative **1f** is the least reactive converting to **14c** in only 23% yield (80 °C, 12 h).[5a] This relative propensity for the unimolecular reaction is retained in the reaction of **1d–f** with either of phenyl vinyl sulfone or methyl vinyl ketone.

The regioisomeric isoxazolobenzodiazepinones **15a–c** and **16a–c** accompanied by the isoxazoloquinolinones **14a–c** are formed on treatment of **1d–f** with phenyl vinyl sulfone in boiling toluene (24 h). None of the alternative *N*-substituted isoxazoloquinolinones were found indicating, as observed above for **1a–c**, that with these oximes phenyl vinyl sulfone is not an effective reactive dipole generating agent, *i.e.* reaction *via* path B is not a low energy alternative. As is expected from molecular orbital analysis of the cycloaddition reaction, the 4-substituted isoxazolidine is the major regioisomer in each case, the ratio **15**:**16** varies from 3:1 for **1d** to 7:6 for **1e**. The adducts **15** and **16** display dependable ^{1}H NMR characteristics and their stereochemical assignment is made by comparison of the chemical shift position and coupling pattern of the key protons H-3, H-6/7 and H-7a with the corresponding signals in **7a** and **8a** (Table 1). Significantly the ratio of isoxazoloquinolinone: isoxazolobenzodiazepinone decreases in the order **1d**:**1e**:**1f** reflecting the tendency of these substances to undergo the IOOC reaction. The relative stereochemistry of the isoxazoloquinolinones is assigned on the basis of the magnitude of the cross ring coupling constant $J_{2a,5a}$ and the vicinal coupling constant $J_{2a,3}$ (Table 2); the value of $^3J_{2a,5a}$ of 6–8 Hz is indicative of a *cis* fused BC ring junction whilst $^3J_{2a,3}$ 2–3 Hz is consistent with a *trans* arrangement of these protons.

That methyl vinyl ketone is an effective dipole generating agent with oximes like **1** has been demonstrated above and so in its reaction with **1d–f** *N*-substituted isoxazoloquinolinones may be expected among the reaction products. The oximes **1d–f**, in turn, react with methyl vinyl ketone following heating in boiling toluene to give varying amounts of *N*-substituted and -unsubstituted isoxazoloquinolinones (**14a–c** and **17a–c**), no isoxazolobenzodiazepinones were formed. For the adducts **17a–c** the

small magnitude of the vicinal coupling constant $J_{2a,5a}$ is diagnostic of *cis* fused BC rings and that H-2a and H-3 are *trans* is also evident from their coupling pattern (Table 2). The parallel between the relative ease of the IOOC reaction sequence for **1d–f**, and the ratio of the products **14**:**17** is striking. The most reactive substrate in the IOOC reaction, **1d**, shows little interest in reaction with methyl vinyl ketone (**14a**:**17a**, 74:15) whilst **1f**, the least reactive IOOC substrate prefers the bimolecular reaction with methyl vinyl ketone and **14c** and **17c** result in a 13:63 ratio. The close alliance between the relative rate of the IOOC reaction and the ratio of the products **14**:**17** lends credence to the proposal that **17** is indeed formed by a tandem intermolecular APT–intramolecular cycloaddition sequence (Scheme 1, path B) rather than by an alternative Michael type addition of **14** to methyl vinyl ketone (Scheme 3). This hypothesis is



Scheme 3

further supported following examination of the relative stereochemistry of the adducts **14a** and **17a**. In **14a** the BC ring junction is *trans* fused ($^3J_{2a,5a}$ 13.5 Hz) whilst for **17a** these rings are *cis* fused. The adduct **14a** is thermally stable (at least to 140 °C) and therefore it is not likely that **17a** arises indirectly from **14a**. Whether the isoxazolobenzodiazepinones **15** and **16** arise from **1** *via* a retro IOOC reaction of initially formed **14** or if direct formation of the cyclic dipoles **2d–f** occurs simultaneously under the more vigorous reaction conditions (110 °C *vs.* room temp. or 80 °C) is not obvious.

Conclusions

The one-pot tandem intramolecular APT–intermolecular cycloaddition of the oximes **1a–c** with *N*-methylmaleimide, methyl acrylate or phenyl vinyl sulfone represents a technically simple route to benzodiazepinones with an isoxazolidine ring fused to the *d*-edge of the diazepine nucleus. The same oximes react with methyl vinyl ketone highly chemoselectively by an intermolecular APT–intramolecular cycloaddition sequence giving isoxazoloquinolinones. Methyl vinyl ketone is therefore the only olefin sufficiently reactive to overcome the entropic advantage of the intramolecular reaction in the dipole forming step. With the oximes **1d–f** there is a substituent induced shift in reactivity and these substrates react with phenyl vinyl sulfone to give a mixture of isoxazolobenzodiazepinones and *N*-unsubstituted isoxazoloquinolinones, with the more electrophilic methyl vinyl ketone only *N*-substituted and *N*-unsubstituted isoxazoloquinolinones resulted. The title compounds are complex tricyclic molecular frameworks with potential biological activity: their synthesis by a one-pot reaction of the oximes **1** and a carefully chosen olefin has been demonstrated.

Experimental

Mps were determined on an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer model 240 CHN analyser. NMR Spectra were recorded using a JEOL EX90 FT NMR and a JEOL EX270 FT NMR spectrometer at probe temperatures with tetramethylsilane as internal reference; *J* values are given in Hz. Infrared spectra were recorded on a Perkin-Elmer 1600 series FT IR spectrophotometer, samples were prepared as Nujol mulls. Flash column chromatography was carried out on silica gel (200–400 mesh; Kieselgel 60, E Merck) with air pump pressure; analytical TLC plates were purchased from Merck. Samples were located by UV illumination using a portable Spectroline Hanovia lamp (λ 254 nm) or by the use of iodine staining. All solvents used were purified by standard procedures and pet. spirit refers to that fraction of light petroleum boiling between 40–60 °C. The aldoximes **1** were prepared according to the procedure described in an earlier paper.[5a]

7-Ethoxycarbonylmethyl-9a,10,11,12,12a,12b-hexahydro-11-methyl-7*H*-10,12-dioxopyrrolo[3′,4′:4,5]isoxazolo[2,3-*d*][1,4]-benzodiazepin-6(5*H*)-one 6a†

A solution of ethyl {*N*-[2-(hydroxyiminomethyl)phenyl]carbamoyl}acrylate **1a** (100 mg, 0.38 mmol) in xylene (30 ml) was treated with *N*-methylmaleimide (0.042 mg, 0.38 mmol) and heated at reflux (138 °C) under a nitrogen atmosphere for 8 h. Removal of the solvent under reduced pressure afforded a dark yellow oil. ^{1}H NMR Spectral analysis shows the crude product comprised a single compound, **6a**, which was isolated as a cream solid (129 mg, 89%), mp 224–225 °C (from Et_2O–pet. spirit, 1:1) (Found: C, 57.88; H, 5.13; N, 11.25. $C_{18}H_{19}N_3O_6$ requires C, 57.91; H, 5.09; N, 11.26%); ν_{max}(Nujol mull)/cm^{-1} 3318.4 (NH), 1716.5 (CO_2Et), 1708.9 ($CONCH_3$), 1707.4 ($CONCH_3$) and 1676.8 (N*CHO*); δ_H(270 MHz; $CDCl_3$) 9.31 (1H, s, NH), 7.44 (2H, m, ArH), 7.25 (1H, m, ArH), 7.14 (1H, d, *J* 8.06, ArH), 5.13 (1H, d, *J* 8.06, 5a-H), 4.85 (1H, d, *J* 5.13, 8b-H), 4.10 (1H, dd, *J* 8.79 and 5.14, 3-H), 4.02 (3H, m, OCH_2, 8a-H), 3.24 (1H, dd, *J* 8.79 and 17.22, 13-H), 3.00 (3H, s, NCH_3), 2.74 (1H, dd, *J* 5.14 and 17.22, 13-H′), 1.20 (3H, t, *J* 7.32, CH_3); δ_C(67.5 MHz; $CDCl_3$) 176.29 (NHCO), 174.46 (CONMe), 174.36 (CONMe), 170.35 (CO_2Et), 137.70 (C-12a), 126.82 (C-8c), 129.85, 127.57, 125.42 and 121.94 (Ar), 75.63 (C-5a), 64.62 (C-8b), 60.25 (C-3), 59.94 (OCH_2), 50.86 (C-8a), 33.86 (C-13), 24.82 (NCH_3), 13.94 (CH_3). NOEDS Results for **6a**: irradiation of H-8b caused an enhancement on the signals for the following protons H-8a (14.5%), H-5a (6.7%), H-3 (2.2%), *o*-ArH (17%); irradiation of H-8a caused an enhancement on H-8b (6.5%) and H-5a (4.5%) and irradiation of H-5a caused a 14.6% enhancement on the signal for H-8a.

2-Chloro-7-ethoxycarbonylmethyl-9a,10,11,12,12a,12b-hexahydro-11-methyl-7*H*-10,12-dioxopyrrolo[3′,4′:4,5]isoxazolo-[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 6b

A solution of ethyl {*N*-[4-chloro-2-(hydroxyiminomethyl)-phenyl]carbamoyl}acrylate **1b** (112 mg, 0.38 mmol) in xylene (30 ml) was treated with *N*-methylmaleimide (0.042 mg, 0.38 mmol) and heated at reflux (138 °C) under a nitrogen atmosphere for 8 h. Removal of the solvent under reduced pressure affords a yellow oil. ^{1}H NMR Spectral analysis shows the crude product comprised a single compound, **6b**, which was isolated as a white solid (95 mg, 69%), mp 192–194 °C (from Et_2O–pet. spirit, 1:1) (Found: C, 52.98; H, 4.43; N, 10.27. $C_{18}H_{18}N_3O_6Cl$ requires C, 53.01; H, 4.42; N, 10.31%); ν_{max}(Nujol mull)/cm^{-1} 3312.0 (NH), 1710.2 (CO_2Et), 1693.2 ($CONCH_3$), 1683.2 ($CONCH_3$) and 1652.0 (NCHO); δ_H(270 MHz; $CDCl_3$) 8.97 (1H, s, NH), 7.45 (2H, m, ArH), 7.05 (1H, d, *J* 8.79, ArH), 5.09 (1H, d, *J* 8.09, 5a-H), 4.82 (1H, d, *J* 5.13, 8b-H), 4.09 (3H, m, OCH_2, 3-H), 3.92 (1H, dd, *J* 5.13 and 8.09, 8a-H), 3.22 (1H, dd, *J* 8.79 and 17.58, 13-H), 3.02 (3H, s, NCH_3), 2.74 (1H, dd, *J* 5.13 and 17.58, 13-H′), 1.22 (3H, t, *J* 7.33, CH_3); δ_C(67.5 MHz; $CDCl_3$) 175.33 (NHCO), 172.92 (CONMe), 172.67 (CONMe), 134.71 (C-12a), 130.59 (C-8c), 124.52 (C-10), 171.98 (CO_2Et), 131.86 and 131.65 (Ar), 77.89 (C-5a), 70.99 (C-8b), 61.56 (C-3), 60.24 (OCH_2), 56.69 (C-8a), 34.87 (C-13), 25.94 (NCH_3), 14.81 (CH_3).

5-Ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-1-methoxy-carbonylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 7a and 5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-2-methoxy-carbonylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 8a

Ethyl {*N*-[2-(hydroxyiminomethyl)phenyl]carbonyl}acrylate **1a**

(100 mg, 0.38 mmol) and methyl acrylate (32 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a dark yellow oil. Analysis of the ^1H NMR spectral data of the crude products shows a 2:1 mixture of regioisomeric adducts **7a** and **8a**. Purification by flash chromatography (100% Et_2O) afforded the pure products. Isoxazolobenzodiazepinone **7a** was isolated as colourless prisms (87 mg, 65%), mp 109–110 °C (from Et_2O–pet. spirit, 3:2) (Found: C, 58.59; H, 5.80; N, 8.06. $C_{17}H_{20}N_2O_6$ requires C, 58.62; H, 5.75; N, 8.05%); ν_{max}(Nujol mull)/cm^{-1} 3312.0 (NH), 1719.4 (CO_2Et) 1710.6 (CO_2Me) and 1665.2 (NHCO); δ_H(270 MHz; $CDCl_3$) 8.86 (1H, s, NH), 7.34 (2H, m, ArH), 7.20 (1H, d, *J* 7.33, ArH), 7.08 (1H, d, *J* 7.33, ArH), 4.91 (1H, d, *J* 8.80, 7a-H), 4.42 (1H, dd, *J* 8.79 and 8.79, 6-H), 4.07 (4H, m, OCH_2, 3-H, 6-H′), 3.75 (1H, ddd, *J* 8.79, 8.79 and 8.79, 7-H), 3.65 (3H, s, OCH_3), 3.22 (1H, dd, *J* 8.79 and 16.75, 12-H), 2.77 (1H, dd, *J* 5.10 and 16.75, 12-H′), 1.22 (3H, t, *J* 7.33, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 173.39 (NHCO), 171.65 (CO_2Et), 171.19 (CO_2Me), 136.25 (C-11a), 130.12 (C-7b), 131.96, 129.99, 125.69 and 122.78 (Ar), 70.39 (C-7a), 69.32 (C-6), 60.71 (OCH_2), 59.76 (C-3), 53.40 (OCH_3), 52.42 (C-7), 34.15 (C-12), 14.21 (CH_3). NOEDS Results for **7a**: due to problems with overlapping signals NOE data were acquired in both $CDCl_3$ and C_6D_6. Irradiation of H-7a ($CDCl_3$) caused an enhancement on the signals for the following protons H-7 (4.3%) and *o*-ArH (18.9%); irradiation of H-7 caused an enhancement on H-7a (5.9%) and H-6 (11.9%) and irradiation of H-6 caused a 12.3% enhancement on the signal for H-7 and 24.3% on its partner H′-6. Irradiation of H-3 (C_6D_6) caused a 5.0% enhancement on H-12 and 9.5% enhancement on H′-12. Isoxazolobenzodiazepinone **8a** was isolated as a white solid (41 mg, 31%), mp 122–123 °C (from Et_2O–pet. spirit, 3:2) (Found: C, 58.57; H, 5.80; N, 8.08. $C_{17}H_{20}N_2O_6$ requires C, 58.62; H, 5.75; N, 8.05%); ν_{max}(Nujol mull)/cm^{-1} 3312.8 (NH), 1716.2 (CO_2Et), 1709.0 (CO_2Me) and 1654.1 (NHCO); δ_H(270 MHz; $CDCl_3$) 8.71 (1H, s, NH), 7.34 (2H, m, ArH), 7.20 (1H, d, *J* 7.32, ArH), 7.08 (1H, d, *J* 7.88, ArH), 4.89 (1H, dd, *J* 3.67 and 8.78, 6-H), 4.78 (1H, dd, *J* 9.17 and 9.17, 7a-H), 4.08 (3H, m, *J* 7.13, 3-H, OCH_2), 3.80 (3H, s, OCH_3), 3.31 (1H, dd, *J* 9.89 and 17.22, 12-H), 2.95 (2H, m, 7-H, 7-H′), 2.77 (1H, dd, *J* 4.40 and 17.22, 12-H′), 1.22 (3H, t, *J* 7.14, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 173.40 (NHCO), 171.69 (CO_2Et), 171.67 (CO_2Me), 136.51 (C-11a), 130.12 (C-7b), 131.64, 129.99, 125.69 and 122.78 (Ar), 75.83 (C-6), 66.66 (C-7a), 60.71 (OCH_2), 60.08 (C-3), 52.67 (OCH_3), 38.76 (C-7), 34.39 (C-12), 14.21 (CH_3). NOEDS Results for **8a**: due to problems with overlapping signals NOE data were acquired in both $CDCl_3$ and C_6D_6. Irradiation of H-7a ($CDCl_3$) caused an enhancement on the signals for the following protons H′-7 (5.8%) and *o*-ArH (15.5%); irradiation of H-6 caused an enhancement on H-7 (5.3%) and H′-7 (1.5%). Irradiation of H-7 (C_6D_6) caused a 19.7% enhancement on H′-7 and 11.5% enhancement on H-6, irradiation of H′-7 caused an 8.9% enhancement on the signal for H-7a, 1.3% on H-6 and 23.3% on its partner H-7. Irradiation of H-3 caused enhancement on the adjacent exocyclic methylene group.

10-Chloro-5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-1-methoxycarbonylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 7b

Ethyl {*N*-[4-chloro-2-(hydroxyiminomethyl)phenyl]carbamoyl}acrylate **1b** (112 mg, 0.38 mmol) and methyl acrylate (32 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a dark yellow oil. Analysis of ^1H NMR spectral data of the crude mixture indicated the presence of a single new product. Purification by flash chromatography (100% Et_2O) afforded the pure product, **7a**, as a cream solid (67 mg, 53%), mp 163–167 °C (from Et_2O–pet. spirit, 1:1) (Found: C, 53.39; H, 4.97; N, 7.27. $C_{17}H_{19}N_2O_6Cl$ requires C, 53.33; H, 4.98; N, 7.32%); δ_H(270 MHz; $CDCl_3$) 9.32 (1H, s, NH), 7.36 (2H, m, ArH), 7.10 (1H, d, *J* 8.06, Ar-H), 5.01 (1H, d, *J* 8.77, 7a-H), 4.48 (1H, dd, *J* 8.77 and 8.77, 6-H), 4.10 (4H, m, OCH_2, 3-H, 6-H′), 3.78 (1H, ddd, *J* 8.77, 8.77 and 8.77, 7-H), 3.68 (3H, s, OCH_3), 3.26 (1H, dd, *J* 8.54 and 16.89, 12-H), 2.77 (1H, dd, *J* 4.98 and 16.89, 12-H′), 1.22 (3H, t, *J* 7.33, CH_3); δ_C(67.5 MHz; $CDCl_3$) 172.76 (NHCO), 171.44 (CO_2Et), 171.09 (CO_2Me), 135.98 (C-11a), 130.06 (C-7b), 133.76, 130.29, 125.69 and 122.78 (Ar), 70.69 (C-7a), 69.42 (C-6), 60.60 (OCH_2), 59.74 (C-3), 53.37 (OCH_3), 52.39 (C-7), 34.10 (C-12), 14.19 (CH_3).

5-Ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-1-phenylsulfonylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 9a and 5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-2-phenylsulfonylisoxazolo-[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 10a

Ethyl {*N*-[2-(hydroxyiminomethyl)phenyl]carbamoyl}acrylate **1a** (100 mg, 0.38 mmol) and phenyl vinyl sulfone (0.064 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a dark yellow oil. Analysis of ^1H NMR spectral data of the impure product suggested a 5:1 mixture of regioisomeric adducts **9a** and **10a**. Purification by flash chromatography (100% Et_2O) afforded the pure products. Isoxazolobenzodiazepinone **9a** was isolated as colourless plates (92 mg, 64%), mp 162–165 °C (from Et_2O–pet. spirit, 3:2) (Found: C, 58.60; H, 5.12; N, 6.51. $C_{21}H_{22}N_2O_6S$ requires C, 58.64; H, 5.14; N, 6.55%); ν_{max}(Nujol mull)/cm^{-1} 3311.2 (NH), 1719.0 (CO_2Et), 1654.3 (NHCO), 1306.0 (SO_2, symmetric) and 1192.2 (SO_2, asymmetric); δ_H(270 MHz; $CDCl_3$) 8.57 (1H, s, NH), 7.76 (2H, d, *J* 8.06, ArH), 7.61 (1H, m, ArH), 7.47 (2H, t, *J* 7.89, ArH), 7.29 (2H, m, ArH), 7.02 (2H, m, ArH), 4.95 (1H, d, *J* 6.59, 7a-H), 4.43 (3H, m, 7-H, 6-H, 6-H′), 4.06 (2H, q, *J* 7.33, OCH_2), 3.98 (1H, dd, *J* 9.53 and 4.58, 3-H), 3.18 (1H, dd, *J* 9.53 and 17.22, 12-H), 2.75 (1H, dd, *J* 4.58 and 17.22, 12-H′), 1.21 (3H, t, *J* 7.33, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 173.97 (NHCO), 171.44 (CO_2Et), 137.46 (SO_2ArC), 136.01 (C-11a), 128.10 (C-7b), 134.30, 132.15, 130.38, 129.55, 128.54, 125.88 and 122.21 (Ar), 71.59 (C-7a), 68.69 (C-7), 67.80 (C-6), 60.84 (OCH_2), 59.32 (C-3), 33.63 (C-12), 14.15 (CH_3). Isoxazolobenzodiazepinone **10a** was isolated as a white solid (39 mg, 24%), mp 175–179 °C (from Et_2O–pet. spirit, 3:2) (Found: C, 58.62; H, 5.09; N, 6.49. $C_{21}H_{22}N_2O_6S$ requires C, 58.64; H, 5.14; N, 6.55%); ν_{max}(Nujol mull)/cm^{-1} 3311.7 (NH), 1720.1 (CO_2Et), 1673.3 (NHCO), 1305.7 (SO_2, symmetric) and 1192.0 (SO_2, asymmetric); δ_H(270 MHz; $CDCl_3$) 8.59 (1H, s, NH), 7.95 (2H, d, *J* 8.80, ArH), 7.71 (1H, m, ArH), 7.61 (2H, m, ArH), 7.37 (2H, m, ArH), 7.37 (1H, m, ArH), 7.03 (1H, d, *J* 8.42, ArH), 5.18 (1H, m, 6-H), 5.01 (1H, dd, *J* 8.42 and 8.42, 7a-H), 4.10 (3H, m, 3-H, OCH_2), 3.08 (3H, m, 7-H, 7-H′, 12-H), 2.68 (1H, dd, *J* 4.98 and 17.64, 12-H′), 1.21 (3H, t, *J* 7.33, CH_3); δ_C(67.5 MHz; $CDCl_3$) 172.20 (NHCO), 171.25 (CO_2Et), 136.13 (SO_2ArC), 136.02 (C-11a), 129.11 (C-7b), 134.30, 131.70, 130.12, 129.55, 125.88 and 122.78 (Ar), 92.04 (C-6), 66.15 (C-7a), 60.71 (OCH_2), 60.52 (C-3), 36.04 (C-7), 34.33 (C-12), 14.08 (CH_3).

5-Ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-8-methyl-1-phenylsulfonylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 9b and 5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-8-methyl-2-phenylsulfonylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 10b

Ethyl {*N*-[2-(hydroxyiminomethyl)-6-methylphenyl]carbamoyl}acrylate **1c** (105 mg, 0.38 mmol) and phenyl vinyl sulfone (0.064 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a dark yellow oil. Analysis of ^1H NMR spectral data of the impure

product suggests a 3:2 mixture of regioisomeric adducts **9b** and **10b**. Purification by flash chromatography (100% Et_2O) afforded the pure products. Isoxazolobenzodiazepinone **9b** was isolated as a white solid (79 mg, 53%), mp 154–156 °C (from Et_2O–pet. spirit, 2:1) (Found: C, 59.42; H, 5.44; N, 6.29. $C_{22}H_{24}N_2O_6S$ requires C, 59.46; H, 5.41; N, 6.31%); δ_H(270 MHz; $CDCl_3$) 8.79 (1H, s, NH), 7.83 (2H, m, ArH), 7.55 (1H, d, *J* 8.49, ArH), 7.34 (4H, m, ArH), 6.90 (1H, d, *J* 8.49, ArH), 5.01 (d, 1H, *J* 6.27, 7a-H), 4.49 (3H, m, 6-H, 6-H′, 7-H), 4.03 (2H, q, *J* 7.32, OCH_2), 3.93 (1H, dd, *J* 9.27 and 5.13, 3-H), 3.31 (1H, dd, *J* 9.27 and 16.85, 12-H), 2.82 (1H, dd, *J* 5.13 and 16.85, 12-H′), 1.93 (3H, s, CH_3), 1.27 (3H, t, *J* 7.32, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 172.13 (NHCO), 170.24 (CO_2Et), 136.89 (SO_2ArC), 135.01 (C-11a), 130.90 (C-7b), 132.45, 128.99, 128.05, 121.98 and 114.23 (Ar), 72.3 (C-7a), 68.56 (C-7), 66.09 (C-6), 60.23 (OCH_2), 59.07 (C-3), 33.37 (C-12), 19.34 (CH_3), 14.21 (CH_2CH_3). NOEDS Results for **9b**: due to problems with overlapping signals NOE data were acquired in both $CDCl_3$ and C_6D_6. Irradiation of H-7a ($CDCl_3$) caused an enhancement on the signals for the following protons H-7 (4.3%) and *o*-ArH (19.3%); irradiation of H-6 caused an enhancement on H-7 (9.4%) and H′-6 (21.8%) and irradiation of H′-6 caused an enhancement on H-6 only (23.1%). Irradiation of H-7a (C_6D_6) caused a 6.2% enhancement on H-7 and 7.2% enhancement on the multiplet representing H-6 and H′-6. Isoxazolobenzodiazepinone **10b** was isolated as a white solid (17 mg, 35%), mp 167–168 °C (from Et_2O–pet. spirit, 1:1) (Found: C, 59.48; H, 5.42; N, 6.33. $C_{22}H_{24}N_2O_6S$ requires C, 59.46; H, 5.41; N, 6.31%); δ_H(270 MHz; $CDCl_3$) 8.51 (1H, s, NH), 7.83 (1H, d, *J* 8.06, ArH), 7.61 (3H, m, ArH), 7.09 (3H, m, ArH), 6.98 (1H, m, ArH), 5.11 (1H, dd, *J* 2.14 and 7.13, 6-H), 5.02 (1H, dd, *J* 8.49 and 8.49, 7a-H), 4.09 (3H, m, 3-H, OCH_2), 3.47 (1H, m, 7-H), 3.26 (1H, dd, *J* 9.21 and 17.22, 12-H), 3.05 (1H, m, 7-H′), 2.34 (1H, dd, *J* 4.99 and 17.22, 12-H′), 1.98 (3H, s, CH_3), 1.27 (3H, t, *J* 7.33, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 172.11 (NHCO), 170.23 (CO_2Et), 136.51 (SO_2ArC), 135.33 (C-11a), 130.41 (C-7b), 133.98, 133.09, 132.42, 130.20, 128.23 and 123.05 (Ar), 92.54 (C-6), 66.85 (C-7a), 61.98 (OCH_2), 60.45 (C-3), 36.78 (C-7), 33.09 (C-12), 18.49 (CH_3), 14.27 (CH_2CH_3). NOEDS Results for **10b**: irradiation of H-7a caused an enhancement on the signals for protons H′-7 (4.7%) and *o*-ArH (15.1%); irradiation of H-6 caused an enhancement on H-7 (6.1%) and irradiation of H-3 caused an enhancement only on the adjacent exocyclic methylene protons.

8-Chloro-3-ethoxycarbonyl-1,3,3a,9b-tetrahydro-1-(3-oxobutyl)-isoxazolo[4,3-*c*]quinolin-4(5*H*)-one 11a

Ethyl {*N*-[4-chloro-2-(hydroxyiminomethyl)phenyl]carbamoyl}acrylate **1b** (112 mg, 0.38 mmol) and methyl vinyl ketone (0.026 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a yellow oil. Analysis of ^1H NMR spectral data shows only one new compound. Purification by flash chromatography (SiO_2, 100% Et_2O) afforded **11a** as a white solid (141 mg, 89%), mp 149–150 °C (Found: C, 55.69; H, 5.18; N, 7.69. $C_{17}H_{19}N_2O_5Cl$ requires C, 55.66; H, 5.18; N, 7.64%); ν_{max}(Nujol mull)/cm^{-1} 3117.1 (NH), 1715.2 (CO_2Et), 1697.1 (CO) and 1647.3, (NHCO); δ_H(270 MHz; $CDCl_3$) 9.57 (1H, s, NH), 7.32 (2H, m, ArH), 6.93 (1H, d, *J* 8.07, ArH), 5.16 (1H, d, *J* 2.24, 3-H), 4.27 (2H, q, *J* 7.33, OCH_2), 3.94 (1H, d, *J* 6.33, 5a-H), 3.62 (1H, dd, *J* 2.24 and 6.33, 2a-H), 3.32 (1H, m, 10-H), 3.09 (1H, m, 10-H′), 2.91 (1H, m, 11-H), 2.79 (1H, m, 11-H′), 2.15 (3H, s, $COCH_3$), 1.36 (3H, t, *J* 7.33, CH_3); δ_C(67.5 MHz; $CDCl_3$) 206.98 (CO), 170.58 (NHCO), 169.01 (CO_2Et), 130.31 (C-9a), 128.92 (C-5b), 123.66, 121.77, 116.92 and 115.43 (Ar), 77.34 (C-5a), 65.90 (C-3), 62.04 (OCH_2), 50.84 (C-10), 50.83 (C-2a), 41.92 (C-11), 30.21 ($COCH_3$), 14.21 (CH_3).

3-Ethoxycarbonyl-1,3,3a,9b-tetrahydro-6-methyl-1-(3-oxobutyl)-isoxazolo[4,3-*c*]quinolin-4(5*H*)-one 11b

Ethyl {*N*-[2-(hydroxyiminomethyl)-6-methylphenyl]carbamoyl}acrylate **1c** (105 mg, 0.38 mmol) and methyl vinyl ketone (0.026 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a yellow oil. Analysis of ^1H NMR spectral data shows only one new compound. Purification by flash chromatography (SiO_2, 100% Et_2O) afforded **11b** as a white solid (90 mg, 72%), mp 148–151 °C (Found: C, 62.44; H, 6.37; N, 8.08. $C_{18}H_{22}N_2O_5$ requires C, 62.43; H, 6.36; N, 8.09%); ν_{max}(Nujol mull)/cm^{-1} 3210.4 (NH), 1723.2 (CO_2Et), 1698.3 (CO) and 1653.1 (NHCO); δ_H(270 MHz; $CDCl_3$) 7.99 (1H, s, NH), 7.24 (2H, m, ArH), 7.09 (1H, d, *J* 8.06, ArH), 5.24 (1H, d, *J* 3.12, 3-H), 4.19 (2H, q, *J* 7.13, OCH_2), 3.92 (1H, d, *J* 6.05, 5a-H), 3.27 (1H, dd, *J* 3.12 and 6.05, 2a-H), 2.97 (1H, m, 10-H), 2.86 (1H, m, 10-H′), 2.69 (1H, m, 11-H), 2.53 (1H, m, 11-H′), 2.19 (3H, s, $COCH_3$), 1.91 (3H, s, CH_3), 1.24 (3H, t, *J* 7.13, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 201.26 ($COCH_3$), 172.68 (NHCO), 165.92 (CO_2Et), 130.29 (C-9a), 122.71 (C-5a), 127.32 (C-6), 125.31, 124.31 and 116.43 (Ar), 78.21 (C-5a), 65.29 (C-3), 62.79 (C-10), 61.21 (OCH_2), 50.93 (C-2a), 41.76 (C-11), 30.29 ($COCH_3$), 19.26 (CH_3), 14.31 (CH_2CH_3).

3-Ethoxycarbonyl-1,3,3a,9b-tetrahydro-1-(3-oxobutyl)isoxazolo-[4,3-*c*]quinolin-4(5*H*)-one 11c and 1-acetyl-5-ethoxycarbonyl-methyl-1,2,7,11b-tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 12

Ethyl {*N*-[2-(hydroxyiminomethyl)phenyl]carbamoyl}acrylate **1a** (100 mg, 0.38 mmol) and methyl vinyl ketone (0.026 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a yellow oil. Analysis of ^1H NMR spectral data of the impure product suggested a 7.7:1 mixture of adducts **11c** and **12**. Purification by flash chromatography (100% Et_2O) afforded the pure products. Isoxazoloquinolinone **11c** was isolated as a white solid (91 mg, 73%), mp 178–180 °C (Found: C, 61.47; H, 6.01; N, 8.40. $C_{17}H_{20}N_2O_5$ requires C, 61.45; H, 6.03; N, 8.43%); ν_{max}(Nujol mull)/cm^{-1} 3113.8 (NH), 1712.4 (CO_2Et), 1695.3 ($COCH_3$) and 1642.1 (NHCO); δ_H(270 MHz; $CDCl_3$) 8.77 (1H, s, NH), 7.32 (2H, m, ArH), 7.10 (1H, m, ArH), 6.90 (1H, d, *J* 8.06, ArH), 5.15 (1H, d, *J* 2.25, 3-H), 4.29 (2H, q, *J* 7.33, OCH_2), 3.95 (1H, d, *J* 6.23, 5a-H), 3.64 (1H, dd, *J* 2.25 and 6.23, 2a-H), 3.29 (1H, m, 10-H), 3.05 (1H, m, 10-H′), 2.88 (1H, m, 11-H), 2.77 (1H, m, 11-H′), 2.11 (3H, s, $COCH_3$), 1.35 (3H, t, *J* 7.33, CH_3); δ_C(67.5 MHz; $CDCl_3$) 206.04 (CO), 170.48 (NHCO), 168.53 (CO_2Et), 130.31 (C-9a), 128.92 (C-5b), 123.66, 121.77, 116.68 and 116.21 (Ar), 77.44 (C-5a), 65.94 (C-3), 62.06 (OCH_2), 50.89 (C-10), 50.87 (C-2a), 41.95 (C-11), 30.24 ($COCH_3$), 14.24 (CH_3). NOEDS Results for **11b**: irradiation of H-3 caused an enhancement on the signals for the following protons H-2a (1.5%) and *o*-ArH (10.5%); irradiation of H-2a caused an enhancement on H-5a (2.5%) and irradiation of H-5a caused an enhancement on H-2a (4.6%). Isoxazolobenzodiazepinone **12** (11 mg, 9%), a white crystalline solid, mp 143–144 °C (from Et_2O–pet. spirit, 3:2) (Found: C, 61.49; H, 6.01; N, 8.46. $C_{17}H_{20}N_2O_5$ requires C, 61.45; H, 6.03; N, 8.43%); δ_H(270 MHz; $CDCl_3$) 8.76 (1H, s, NH), 7.34 (2H, m, ArH), 7.17 (1H, m, ArH), 7.09 (1H, d, *J* 8.25, ArH), 4.85 (1H, d, *J* 7.39, 7a-H), 4.41 (1H, dd, *J* 8.42 and 8.42, 6-H), 4.01 (5H, m, CH_2, 3-H, 6-H′, 7-H), 3.22 (1H, dd, *J* 9.16 and 16.85, 12-H), 2.77 (1H, dd, *J* 5.31 and 16.85, 12-H′), 2.00 (3H, s, $COCH_3$), 1.23 (3H, t, *J* 7.12, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 201.09 ($COCH_3$), 174.26 (NHCO), 171.21 (CO_2Et), 136.13 (C-11a), 129.83 (C-7b), 132.63, 131.13, 125.92 and 122.36 (Ar), 70.12 (C-7a), 68.93 (C-6), 60.61 (OCH_2), 59.79 (C-3), 50.34 (C-7), 34.35 (C-12), 29.21 ($COCH_3$), 14.15 (CH_2CH_3).

1-Acetyl-5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 12 and 2-acetyl-5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydroisoxazolo[2,3-*d*]-[1,4]benzodiazepin-6(5*H*)-one 13

3-Ethoxycarbonylmethyl-1,3-dihydro[1,4]benzodiazepin-2-one *N*-oxide **2a** (100 mg, 0.38 mmol) and methyl vinyl ketone (0.026 mg, 0.38 mmol) were dissolved in THF (30 cm^3) and the resulting solution heated at reflux (66 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a yellow oil. Analysis of ^{1}H NMR spectral data of the impure product suggests a 5:2 mixture of regioisomeric adducts **12** and **13**. Purification by flash chromatography (100% Et_2O) afforded the pure products. Isoxazolobenzodiazepinone **12** was isolated as a white solid (92 mg, 64%), mp 162–165 °C (from Et_2O–pet. spirit, 3:2) analytical data as above. Isoxazolobenzodiazepinone **13** crystallized as a white solid (34 mg, 26%), mp 125–126 °C (from Et_2O–pet. spirit, 3:2) (Found: C, 61.47; H, 6.04; N, 8.47. $C_{17}H_{20}N_2O_5$ requires C, 61.45; H, 6.03; N, 8.43%); δ_H(270 MHz; $CDCl_3$) 8.85 (1H, s, NH), 7.33 (1H, m, ArH), 7.25 (1H, m, ArH), 7.14 (1H, m, ArH), 7.08 (1H, d, *J* 8.06, ArH), 4.58 (2H, m, 6-H, 7a-H), 4.20 (1H, dd, *J* 8.79 and 5.86, 3-H), 4.11 (2H, q, *J* 7.33, OCH_2), 3.19 (1H, dd, *J* 8.79 and 17.58, 12-H), 2.82 (2H, m, 7-H, 12-H′), 2.33 (1H, m, 7-H′), 1.97 (3H, s, $COCH_3$), 1.23 (3H, t, *J* 7.33, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 198.23 ($COCH_3$), 172.80 (NHCO), 171.69 (CO_2Et), 135.91 (C-11a), 129.58 (C-7b), 132.12, 131.01, 125.27 and 122.78 (Ar), 81.53 (C-6), 66.18 (C-7a), 60.71 (C-3), 60.24 (OCH_2), 38.55 (C-7), 34.99 (C-12), 26.04 ($COCH_3$), 14.25 (CH_2CH_3).

3-Ethoxycarbonyl-1,3,3a,9b-tetrahydro-5-methylisoxazolo-[4,3-*c*]quinolin-4(5*H*)-one 14a,[5a] 5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-7-methyl-1-phenylsulfonylisoxazolo[2,3-*d*]-[1,4]benzodiazepin-6(5*H*)-one 15a and 5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-7-methyl-2-phenylsulfonylisoxazolo[2,3-*d*]-[1,4]benzodiazepin-6(5*H*)-one 16a

Ethyl {*N*-[2-(hydroxyiminomethyl)phenyl]-*N*-methylcarbamoyl}acrylate **1d** (105 mg, 0.38 mmol) and phenyl vinyl sulfone (0.064 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a brown oil. ^{1}H NMR Spectral data indicates the crude mixture comprised a (9:5:2) mixture of the 6,6,5-tricyclic adduct **14a**[5a] and the 4- and 5-regioisomeric adducts **15a** and **16a** respectively. Purification by flash chromatography (SiO_2, 100% Et_2O) afforded the pure products. Isoxazoloquinolinone **14a** was isolated as a solid (53 mg, 53%), mp 132–133 °C (from Et_2O–pet. spirit, 2:1).[5a] Isoxazolobenzodiazepinone **15a** was isolated as a white solid (54 mg, 33%), mp 152–153 °C (from Et_2O–pet. spirit, 1:1) (Found: C, 59.49; H, 5.44; N, 6.29. $C_{22}H_{24}N_2O_6S$ requires C, 59.46; H, 5.41; N, 6.31%); δ_H(270 MHz; $CDCl_3$) 7.74 (2H, m, ArH), 7.58 (1H, m, ArH), 7.46 (2H, m, ArH), 7.37 (1H, m, ArH), 7.17 (1H, d, *J* 8.66, ArH), 7.05 (2H, m, ArH), 4.83 (1H, d, *J* 7.33, 7a-H), 4.41 (2H, m, 6-H, 6-H′), 4.05 (3H, m, 7-H, OCH_2), 3.87 (1H, dd, *J* 9.52 and 4.39, 3-H), 3.36 (3H, s, NCH_3), 3.20 (1H, dd, *J* 9.52 and 16.85, 12-H), 2.75 (1H, dd, *J* 4.39 and 16.85, 12-H′), 1.21 (3H, t, *J* 7.32, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 172.98 (NCH_3CO), 171.45 (CO_2Et), 137.52 (SO_2ArC), 136.07 (C-11a), 128.16 (C-7b), 134.33, 132.03, 130.61, 129.58, 128.55, 126.42 and 122.93 (Ar), 71.72 (C-7a), 69.03 (C-7), 67.67 (C-6), 60.79 (OCH_2), 59.21 (C-3), 35.38 (NCH_3), 33.64 (C-12), 14.17 (CH_2CH_3). Isoxazolobenzodiazepinone **16a** was isolated as a white solid (21 mg, 13%), mp 169–170 °C (from Et_2O–pet. spirit, 1:1) (Found: C, 59.43; H, 5.43; N, 6.35. $C_{22}H_{24}N_2O_6S$ requires C, 59.46; H, 5.41; N, 6.31%); δ_H(270 MHz; $CDCl_3$) 7.93 (1H, m, ArH), 7.69 (1H, m, ArH), 7.58 (2H, m, ArH), 7.49 (1H, m, ArH), 7.31 (4H, m, ArH), 5.21 (1H, dd, *J* 2.20 and 7.69, 6-H), 5.01 (1H, dd, *J* 8.12 and 8.27, 7a-H), 4.03 (2H, q, *J* 7.24, OCH_2), 3.98 (1H, dd, *J* 9.90 and 4.03, 3-H), 3.42 (3H, s, NCH_3), 3.10 (2H, m, 12-H, 7-H), 2.75 (1H, m, 7-H′), 2.64 (1H, dd, *J* 4.09 and 17.06, 12-H′), 1.21 (3H, t, *J* 7.24, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 172.91 (NCH_3CO), 171.46 (CO_2Et), 136.34 (SO_2ArC), 135.99 (C-11a), 129.18 (C-7b), 134.41, 131.95, 130.53, 129.58, 125.50 and 123.72 (Ar), 92.38 (C-6), 66.65 (C-7a), 60.71 (OCH_2), 60.39 (C-3), 35.39 (C-7), 35.36 (NCH_3), 34.26 (C-12), 14.17 (CH_2CH_3).

3-Ethoxycarbonyl-1,3,3a,9b-tetrahydro-6,9-dimethylisoxazolo-[4,3-*c*]quinolin-4(5*H*)-one 14b,[5a] 5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-8,11-dimethyl-1-phenylsulfonylisoxazolo-[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 15b and 5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-8,11-dimethyl-2-phenylsulfonylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 16b

Ethyl {*N*-[2-(hydroxyiminomethyl)-3,6-dimethylphenyl]carbamoyl}acrylate **1e** (106 mg, 0.38 mmol) and phenyl vinyl sulfone (0.064 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a brown oil. ^{1}H NMR Spectral data indicates the crude mixture comprised a (8:5:2) mixture of the 6,6,5-tricyclic adduct **14b**[5a] and the 4- and 5-regioisomeric adducts **15b** and **16b**, respectively. Purification by flash chromatography (SiO_2, 100% Et_2O) afforded the pure products. Isoxazoloquinolinone **14b** was isolated as colourless prisms (49 mg, 49%), mp 143–145 °C (from Et_2O–pet. spirit, 2:1).[5a] Isoxazolobenzodiazepinone **15b** was isolated as colourless plates (50 mg, 32%), mp 122–123 °C (from Et_2O–pet. spirit, 1:1) (Found: C, 60.29; H, 5.64; N, 6.09. $C_{23}H_{26}N_2O_6S$ requires C, 60.26; H, 5.67; N, 6.11%); ν_{max}(Nujol mull)/cm^{-1} 3221.89 (NH), 1743.0 (CO_2Et), 1643.8 (NHCO) and 1310.8 (SO_2); δ_H(270 MHz; $CDCl_3$) 8.73 (1H, s, NH), 7.68 (2H, m, ArH), 7.54 (1H, m, ArH), 7.43 (1H, m, ArH), 7.29 (2H, m, ArH), 6.94 (1H, m, ArH), 5.39 (1H, d, *J* 8.06, 7a-H), 4.59 (1H, m, 7-H), 4.22 (2H, m, 6-H, 6-H′), 4.04 (2H, q, *J* 7.33, OCH_2), 3.78 (1H, dd, *J* 9.51 and 4.37, 3-H), 3.09 (1H, dd, *J* 9.52 and 17.59, 12-H), 2.68 (1H, dd, *J* 4.37 and 17.59, 12-H′), 2.48 (3H, s, CH_3), 2.15 (3H, s, CH_3), 1.28 (3H, t, *J* 7.33, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 172.66 (NHCO), 171.56 (CO_2Et), 137.98 (SO_2ArC), 136.32 (C-11a), 130.24 (C-7b), 135.20, 133.09, 128.90, 128.33, 126.01, 121.21 and 114.21 (Ar), 72.01 (C-7a), 67.98 (C-7), 65.32 (C-6), 60.34 (OCH_2), 59.67 (C-3), 33.42 (C-12), 23.21 (CH_3), 18.23 (CH_3), 14.15 (CH_2CH_3). Isoxazolobenzodiazepinone **16b** was isolated as a white solid (17 mg, 12%), mp 157–159 °C (from Et_2O–pet. spirit, 1:1) (Found: C, 60.22; H, 5.62; N, 6.09. $C_{23}H_{26}N_2O_6S$ requires C, 60.26; H, 5.67; N, 6.11%); δ_H(270 MHz; $CDCl_3$) 8.78 (1H, s, NH), 7.75 (1H, d, *J* 8.06, ArH), 7.69 (3H, m, ArH), 7.51 (1H, d, *J* 8.06, ArH), 6.98 (2H, m, ArH), 5.18 (1H, dd, *J* 2.20 and 8.26, 6-H), 5.01 (1H, dd, *J* 8.49 and 8.49, 7a-H), 4.13 (3H, m, 3-H, OCH_2), 3.26 (1H, dd, *J* 9.21 and 16.89, 12-H), 3.11 (2H, m, 7-H, 7-H′), 2.68 (1H, dd, *J* 4.98 and 17.64, 12-H′), 2.39 (3H, s, CH_3), 2.15 (3H, s, CH_3), 1.29 (3H, t, *J* 7.33, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 172.64 (NHCO), 170.93 (CO_2Et), 136.87 (SO_2ArC), 135.93 (C-11a), 129.41 (C-7b), 134.12, 132.08, 130.45, 129.32, 122.12 and 121.66 (Ar), 92.73 (C-6), 66.34 (C-7a), 60.51 (OCH_2), 60.21 (C-3), 36.11 (C-7), 33.98 (C-12), 23.21 (CH_3), 19.21 (CH_3), 14.27 (CH_2CH_3).

3-Ethoxycarbonyl-1,3,3a,9b-tetrahydro-9-methylisoxazolo-[4,3-*c*]quinolin-4(5*H*)-one 14c,[5a] 5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-11-methyl-1-phenylsulfonylisoxazolo-[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 15c and 5-ethoxycarbonylmethyl-1,2,7,11b-tetrahydro-11-methyl-2-phenylsulfonylisoxazolo[2,3-*d*][1,4]benzodiazepin-6(5*H*)-one 16c

Ethyl {*N*-[2-(hydroxyiminomethyl)-3-methylphenyl]carbamoyl}acrylate **1f** (105 mg, 0.38 mmol) and phenyl vinyl sulfone (0.064 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and

heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a brown oil. ^{1}H NMR Spectral data indicates the crude mixture comprised a (4:7:3) mixture of the 6,6,5-tricyclic adduct **14c**[5a] and the 4- and 5-regioisomeric adducts **15c** and **16c**, respectively. Purification by flash chromatography (SiO_2, 100% Et_2O) afforded the pure products. Isoxazoloquinolinone **14c** was isolated as a white solid (23 mg, 23%), mp 119–121 °C (from Et_2O–pet. spirit, 2:1).[5a] Isoxazolobenzodiazepinone **15c** was isolated as a white solid (79 mg, 42%), mp 146–148 °C (from Et_2O–pet. spirit, 2:1) (Found: C, 59.44; H, 5.44; N, 6.29. $C_{22}H_{24}N_2O_6S$ requires C, 59.46; H, 5.41; N, 6.31%); ν_{max}(Nujol mull)/cm^{-1} 3211.9 (NH), 1727.1 (CO_2Et), 1649.2 (NHCO) and 1309.2 (SO_2); δ_H(270 MHz; $CDCl_3$) 8.56 (1H, s, NH), 7.75 (2H, m, ArH), 7.56 (1H, m, ArH), 7.44 (2H, m, ArH), 7.05 (1H, d, *J* 8.06, ArH), 6.83 (1H, d, *J* 8.06, ArH), 6.70 (1H, s, ArH), 4.83 (1H, d, *J* 6.60, 7a-H), 4.46 (3H, m, 6-H, 6-H′, 7-H), 4.05 (2H, q, *J* 7.33, OCH_2), 3.95 (1H, dd, *J* 9.16 and 4.77, 3-H), 3.18 (1H, dd, *J* 9.16 and 17.22, 12-H), 2.74 (1H, dd, *J* 4.77 and 17.22, 12-H′), 2.18 (3H, s, CH_3), 1.28 (3H, t, *J* 7.33, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 174.13 (NHCO), 171.44 (CO_2Et), 135.59 (SO_2ArC), 134.16 (C-11a), 130.84 (C-7b), 132.34, 127.68, 129.34, 128.55 and 122.14 (Ar), 71.64 (C-7a), 68.87 (C-7), 67.68 (C-6), 60.80 (OCH_2), 59.21 (C-3), 33.57 (C-12), 20.66 (CH_3), 14.17 (CH_2CH_3). Isoxazolobenzodiazepinone **16c** was isolated as a white solid (17 mg, 35%), mp 167–168 °C (from Et_2O–pet. spirit, 1:1) (Found: C, 59.48; H, 5.42; N, 6.33. $C_{22}H_{24}N_2O_6S$ requires C, 59.46; H, 5.41; N, 6.31%); ν_{max}(Nujol mull)/cm^{-1} 3218.0 (NH), 1724.5 (CO_2Et), 1647.2 (NHCO) and 1311.3 (SO_2); δ_H(270 MHz; $CDCl_3$) 8.36 (1H, s, NH), 7.95 (1H, d, *J* 7.32, ArH), 7.68 (4H, m, ArH), 7.14 (2H, m, ArH), 6.91 (1H, m, ArH), 5.17 (1H, dd, *J* 2.21 and 7.33, 6-H), 5.04 (1H, dd, *J* 8.43 and 8.43, 7a-H), 4.07 (3H, m, 3-H, OCH_2), 3.47 (1H, m, 7-H), 3.05 (2H, m, 12-H, 7-H′), 2.34 (1H, dd, *J* 5.82 and 16.85, 12-H′), 2.12 (3H, s, CH_3), 1.21 (3H, t, *J* 7.33, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 172.79 (NHCO), 171.84 (CO_2Et), 136.46 (SO_2ArC), 136.30 (C-11a), 130.05 (C-7b), 136.60, 134.01, 134.80, 132.66, 129.57 and 123.34 (Ar), 92.61 (C-6), 66.73 (C-7a), 61.19 (OCH_2), 61.03 (C-3), 36.65 (C-7), 34.33 (C-12), 21.30 (CH_3), 14.25 (CH_2CH_3).

3-Ethoxycarbonyl-1,3,3a,9b-tetrahydro-5-methylisoxazolo-[4,3-*c*]quinolin-4(5*H*)-one 14a[5a] and 3-ethoxycarbonyl-1,3,3a,11b-tetrahydro-5-methyl-1-(3-oxobutyl)isoxazolo-[4,3-*c*]-quinolin-4(5*H*)-one 17a

Ethyl {*N*-[2-(hydroxyiminomethyl)phenyl]-*N*-methylcarbamoyl}acrylate **1d** (105 mg, 0.38 mmol) and methyl vinyl ketone (0.026 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a yellow oil. ^{1}H NMR Spectral data indicates the crude mixture comprised a (5:1) mixture of the 6,6,5-tricyclic adducts **14a** and **17a**, respectively. Purification by flash chromatography (SiO_2, 100% Et_2O) afforded the pure products. Isoxazoloquinolinone **14a** was isolated as a white solid (74 mg, 74%), mp 132–133 °C.[5a] Isoxazoloquinolinone **17a** was isolated as a white solid (18 mg, 15%), mp 149–150 °C (Found: C, 62.48; H, 6.38; N, 8.06. $C_{18}H_{22}N_2O_5$ requires C, 62.43; H, 6.36; N, 8.09%); δ_H(270 MHz, $CDCl_3$) 7.53 (1H, m, ArH), 7.31 (2H, m, ArH), 7.03 (1H, d, *J* 7.73, ArH), 5.23 (1H, d, *J* 2.76, 3-H), 4.35 (2H, q, *J* 7.13, OCH_2), 4.03 (1H, d, *J* 5.98, 5a-H), 3.73 (1H, dd, *J* 2.76 and 5.98, 2a-H), 3.42 (3H, s, NCH_3), 3.29 (1H, m, 10-H), 3.11 (1H, m, 10-H′), 2.96 (1H, m, 11-H), 2.83 (1H, m, 11-H′), 2.19 (3H, s, OCH_3), 1.27 (3H, t, *J* 7.13, CH_3); δ_C(67.5 MHz; $CDCl_3$) 201.34 (CO), 171.32 (NCH_3CO), 170.01 (CO_2Et), 124.32 (C-5b), 130.45 (C-9a), 129.92, 126.56, 117.34 and 116.43 (Ar), 77.34 (C-5a), 67.61 (C-3), 61.94 (OCH_2), 51.14 (C-10), 50.97 (C-2a), 42.50 (C-11), 35.33 (NCH_3), 30.66 ($COCH_3$), 14.31 (CH_3).

3-Ethoxycarbonyl-1,3,3a,11b-tetrahydro-6,9-dimethylisoxazolo-[4,3-*c*]quinolin-4(5*H*)-one 14b[5a] and 3-ethoxycarbonyl-1-(3-oxobutyl)-1,3,3a,11b-tetrahydro-6,9-dimethylisoxazolo[4,3-*c*]quinolin-4(5*H*)-one 17b

Ethyl {*N*-[2-(hydroxyiminomethyl)-3,6-dimethylphenyl]carbamoyl}acrylate **1e** (106 mg, 0.38 mmol) and methyl vinyl ketone (0.026 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a yellow oil. ^{1}H NMR Spectral data indicates the crude mixture comprised a (6:5) mixture of the 6,6,5-tricyclic adducts **14b** and **17b**, respectively. Purification by flash chromatography (SiO_2, 100% Et_2O) afforded the pure products. Isoxazoloquinolinone **14b** was isolated as a white solid (46 mg, 46%), mp 132–133 °C.[5a] Isoxazoloquinolinone **17b** was isolated as a white solid (69 mg, 40%), mp 132–134 °C (Found: C, 63.31; H, 6.68; N, 7.79. $C_{19}H_{24}N_2O_5$ requires C, 63.33; H, 6.66; N, 7.78%); ν_{max}(Nujol mull)/cm^{-1} 3214.6 (NH), 1722.0 (CO_2Et), 1694.3 ($COCH_3$) and 1663.0 (NHCO); δ_H(270 MHz; $CDCl_3$) 7.79 (1H, s, NH), 7.07 (1H, d, *J* 8.06, ArH), 6.86 (1H, d, *J* 7.43, ArH), 5.24 (1H, d, *J* 3.45, 3-H), 4.29 (2H, q, *J* 7.14, OCH_2), 3.88 (1H, d, *J* 5.92, 5a-H), 3.41 (1H, dd, *J* 3.45 and 5.92, 2a-H), 2.81 (1H, m, 10-H), 2.63 (1H, m, 10-H′), 2.49 (1H, m, 11-H), 2.41 (1H, m, 11-H′), 2.39 (3H, s, $COCH_3$), 2.25 (3H, s, CH_3), 2.09 (3H, s, CH_3), 1.34 (3H, t, *J* 7.14, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 207.31 (CO), 172.09 (NHCO), 167.97 (CO_2Et), 136.27, 133.26, 131.56 and 114.32 (Ar), 125.62 (C-9), 120.79 (C-6), 77.26 (C-5a), 65.93 (C-3), 62.93 (C-10), 62.06 (OCH_2), 50.03 (C-2a), 42.11 (C-11), 30.45 ($COCH_3$), 19.24 (CH_3), 16.78 (CH_3), 14.31 (CH_2CH_3).

3-Ethoxycarbonyl-1,3,3a,11b-tetrahydro-9-methylisoxazolo-[4,3-*c*]quinolin-4(5*H*)-one 14c[5a] and 3-ethoxycarbonyl-1,3,3a,11b-tetrahydro-9-methyl-1-(3-oxobutyl)isoxazolo[4,3-*c*]-quinolin-4(5*H*)-one 17c

Ethyl {*N*-[2-(hydroxyiminomethyl)-3-methylphenyl]carbamoyl}acrylate **1f** (105 mg, 0.38 mmol) and methyl vinyl ketone (0.026 mg, 0.38 mmol) were dissolved in toluene (30 cm^3) and heated at reflux (110 °C) under a nitrogen atmosphere for 18 h. Removal of the solvent under reduced pressure afforded a yellow oil. ^{1}H NMR Spectral data indicates the crude mixture comprised a (1:4.8) mixture of the 6,6,5-tricyclic adducts **14c** and **17c**, respectively. Purification by flash chromatography (SiO_2, 100% Et_2O) afforded the pure products. Isoxazoloquinolinone **14c** was isolated as a white solid (13 mg, 13%), mp 119–121 °C (from Et_2O–pet. spirit, 2:1).[5a] Isoxazoloquinolinone **17c** was isolated as a white solid (79 mg, 63%), mp 148–151 °C (Found: C, 62.39; H, 6.36; N, 8.11. $C_{18}H_{22}N_2O_5$ requires C, 62.43; H, 6.36; N, 8.09%); δ_H(270 MHz; $CDCl_3$) 7.74 (1H, s, NH), 7.14 (1H, m, ArH), 6.97 (2H, m, ArH), 5.12 (1H, d, *J* 3.20, 3-H), 4.27 (2H, q, *J* 7.33, OCH_2), 3.88 (1H, d, *J* 5.86, 5a-H), 3.24 (1H, dd, *J* 3.20 and 5.86, 2a-H), 3.20 (1H, m, 10-H), 2.95 (1H, m, 10-H′), 2.71 (1H, m, 11-H), 2.65 (1H, m, 11-H′), 2.24 (3H, s, $COCH_3$), 2.06 (3H, s, CH_3), 1.27 (3H, t, *J* 7.33, CH_2CH_3); δ_C(67.5 MHz; $CDCl_3$) 190.78 (CO), 171.23 (NHCO), 166.52 (CO_2Et), 130.36 (C-9a), 122.76 (C-5a), 128.32 (C-6), 125.32, 121.19 and 116.88 (Ar), 79.31 (C-5a), 67.32 (C-3), 61.91 (OCH_2), 57.79 (C-10), 50.26 (C-2a), 40.21 (C-11), 30.28 ($COCH_3$), 21.34 (CH_3), 14.21 (CH_2CH_3).

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