Novel Cycloadditions of Isoquinoline Reissert Salts

Andrew W. Bridge,[a] Michael B. Hursthouse,[b] Christian W. Lehmann,[b] David J. Lythgoe*,[a] and Christopher G. Newton[a]

[a] *Dagenham Research Centre, Rhône-Poulenc Rorer Ltd., Rainham Road South, Dagenham, Essex RM10 7XS, UK*

[b] *Department of Chemistry and Applied Chemistry, University of Wales College of Cardiff, PO Box 68, Cardiff, CF1 3TB, UK*

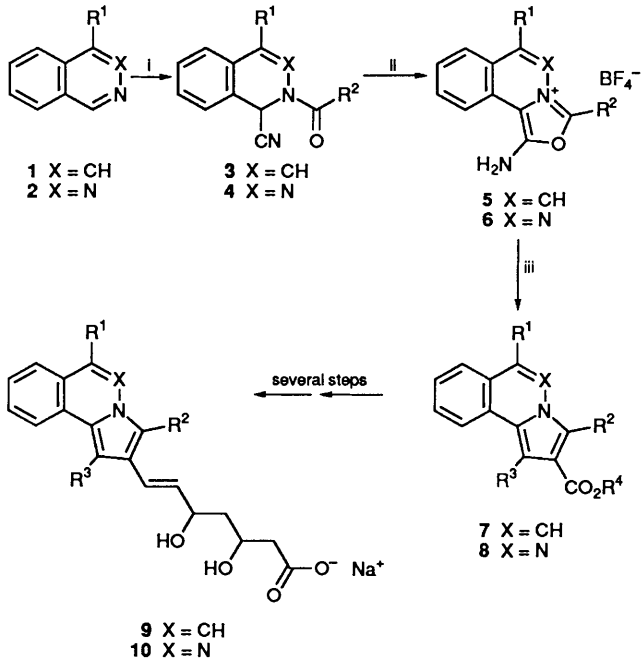
Isoquinoline Reissert salts **5** partake in novel cycloadditions with acetylenic aldehydes **11** giving novel oxazoles **14** which have been characterised by X-ray crystallography. In contrast, closely related phthalazine Reissert salts **6** and phenanthridine Reissert salts **15** react by an alternative pathway giving pyrrolo[2,1-*a*]phthalazines **12** and pyrrolo[1,2-*f*]phenanthridines **16** respectively.

Reissert compounds (*e.g.* **3**, **4**) have been known for many years,[1] and several reviews are available.[2–5] They are traditionally synthesised from appropriate nitrogen heterocycles (*e.g.* **1**, **2**) and acid chlorides in the presence of a cyanide source, but only recently have general and high yielding methods been developed.[6–12] The transformation of Reissert compounds (*e.g.* **3**, **4**) into Reissert salts (*e.g.* **5**, **6**) is known, however, exploitation of these salts in synthesis has received limited attention.[13–21] It was whilst using these compounds (**5**, **6**) during a programme of work in these laboratories that a novel cycloaddition of Reissert salts was discovered.

During a programme of work to synthesise novel HMG CoA reductase inhibitors,[22,23] we utilised the known[13,15,17,18] 1,3-dipolar cycloaddition of Reissert salts (*e.g.* **5**, **6**) with acetylenes to construct pyrrolo[2,1-*a*]isoquinolines **7** (from the Reissert salt **5**) or pyrrolo[2,1-*a*]phthalazines **8** (from the Reissert salt **6**) having the desired functionality. Subsequent modification and elaboration of the cycloadducts **7**, **8** provided the highly active target compounds **9**, **10**[22] (Scheme 1).

Our early syntheses used appropriate acetylenic esters to introduce the ester functionality into the 2-positions of the pyrrolo[2,1-*a*]isoquinoline **7** and pyrrolo[2,1-*a*]phthalazine **8** rings by, in most cases, a regioselective 1,3-dipolar cycloaddition.[22] The ester group then required modification into a carbaldehyde moiety to enable subsequent transformation into the target molecules **9**, **10**. In an effort to increase the synthetic efficiency, we attempted to introduce the carbaldehyde functionality directly by use of an appropriately substituted acetylenic aldehyde **11**. This route proved successful with the phthalazine Reissert salt **6** (R^1 = H, R^2 = Pr^i) and the required product **12** (R^1 = H, R^2 = Pr^i, R^3 = Ph) was obtained in comparable yield to our earlier three-step procedure (Scheme 2). However, when the analogous reaction was applied to an isoquinoline Reissert salt **5** (R^1 = H, R^2 = Pr^i), none of the expected pyrrolo[2,1-*a*]isoquinoline **13** (R^1 = H, R^2 = Pr^i, R^3 = Ph) was obtained. In this case, the only product isolated was shown to be the trisubstituted oxazole[24] derivative **14** (R^1 = H, R^2 = Pr^i, R^3 = Ph) (Scheme 2).

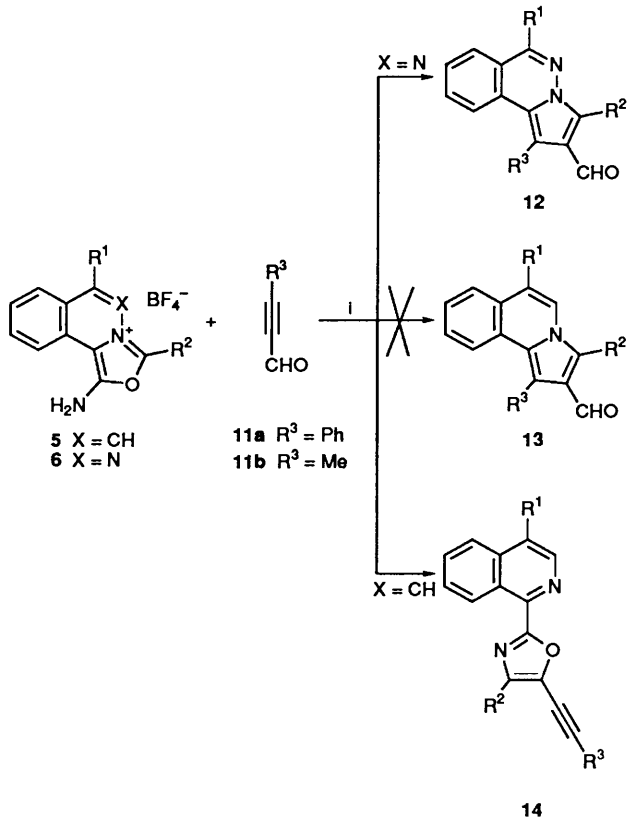
We have explored this reaction using a variety of isoquinoline Reissert salts **5** with either 3-phenylprop-2-ynal **11a** or but-2-ynal **11b**[25] and have found the reaction to be general in giving the oxazoles **14** (yields 10–40%) as isolable products. Although the reactions produce multi-component mixtures and yields are moderate, the conditions have not been optimised and products are isolated in a simple procedure. It is interesting to note that the phenanthridine Reissert salt **15** behaves in a similar manner to the phthalazine salt **6** and gives the pyrrolo[2,1-*a*]phenanthridine **16** (Scheme 3). Since isomeric structures were plausible, the structure of the oxazoles **14** was proven by X-ray crystal structural determination of the representative compound **14h**. The close proximity of the oxazole ring N-atom to the isoquinoline C(8)H (2.368 Å) is clearly seen in the ORTEP[26] representation of the X-ray crystal structure [Fig. 1; these atoms are denoted as N(3) and the proton attached to C(18) respectively in the ORTEP[26]], thus confirming anisotropic deshielding as the reason for the large shift downfield of the isoquinoline C(8)H in the ^{1}H NMR spectrum. The oxazoles **14** were fully supported by analytical and



In formulae 3–6:

a	R^1 = H, R^2 = Me	**i**	R^1 = H, R^2 = 4-BrC_6H_4
b	R^1 = H, R^2 = Et	**j**	R^1 = H, R^2 = 4-$O_2NC_6H_4$
c	R^1 = H, R^2 = Pr^i	**k**	R^1 = H, R^2 = 4-$MeOC_6H_4$
d	R^1 = H, R^2 = Bu^t	**l**	R^1 = Br, R^2 = 4-$MeOC_6H_4$
e	R^1 = H, R^2 = $(CH_2)_{14}Me$	**m**	R^1 = H, R^2 = 4-$Bu^tC_6H_4$
f	R^1 = H, R^2 = Ph	**n**	R^1 = H, R^2 = 3,4,5-$(MeO)_3C_6H_2$
g	R^1 = H, R^2 = 4-FC_6H_4	**o**	R^1 = H, R^2 = 3-$F_3CC_6H_4$
h	R^1 = H, R^2 = 4-ClC_6H_4	**p**	R^1 = H, R^2 = furan-2-yl
		q	R^1 = H, R^2 = CH=CHPh

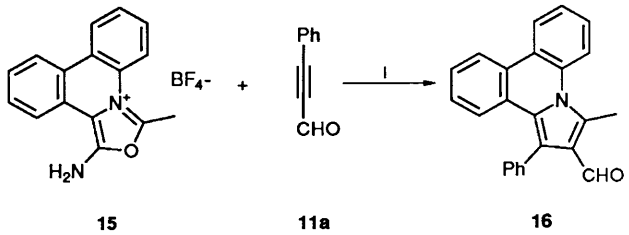
Scheme 1 *Reagents and conditions:* i, R^2COCl, CH_2Cl_2, $AlCl_3$, TMSCN, 30 °C, 12 h; ii, AcOH, HBF_4, 75 °C, 5 min; iii, $R^3{\equiv}CO_2R^4$, DMI, 25–40 °C, 18 h



In formulae **12**–**14**:

a R^1 = H, R^2 = Me, R^3 = Ph
b R^1 = H, R^2 = Et, R^3 = Ph
c R^1 = H, R^2 = Pr^i, R^3 = Ph
d R^1 = H, R^2 = Bu^t, R^3 = Ph
e R^1 = H, R^2 = $(CH_2)_{14}Me$, R^3 = Ph
f R^1 = H, R^2 = R^3 = Ph
g R^1 = H, R^2 = 4-FC_6H_4, R^3 = Ph
h R^1 = H, R^2 = 4-ClC_6H_4, R^3 = Ph
i R^1 = H, R^2 = 4-BrC_6H_4, R^3 = Ph
j R^1 = H, R^2 = 4-$O_2NC_6H_4$, R^3 = Ph
k R^1 = H, R^2 = 4-$MeOC_6H_4$, R^3 = Ph
l R^1 = Br, R^2 = 4-$MeOC_6H_4$, R^3 = Ph
m R^1 = H, R^2 = 4-$Bu^tC_6H_4$, R^3 = Ph
n R^1 = H, R^2 = 3,4,5-$(MeO)_3C_6H_2$, R^3 = Ph
o R^1 = H, R^2 = 3-$F_3CC_6H_4$, R^3 = Ph
p R^1 = H, R^2 = furan-2-yl, R^3 = Ph
q R^1 = H, R^2 = CH=CHPh, R^3 = Ph
r R^1 = H, R^2 = $(CH_2)_{14}Me$, R^3 = Me
s R^1 = H, R^2 = 4-$MeOC_6H_4$, R^3 = Me
t R^1 = H, R^2 = 3,4,5-$(MeO)_3C_6H_2$, R^3 = Me
u R^1 = Bu, R^2 = 4-$Bu^tC_6H_4$, R^3 = Ph

Scheme 2 *Reagent and conditions:* i, DMI, 25–50 °C, 20 h



15 **11a** **16**

Scheme 3 *Reagent and conditions:* i, DMI, 25–40 °C, 20 h

spectroscopic data (Tables 3, 4), and the most significant feature is the presence of a downfield multiplet centred at about δ 9.6 in the ^{1}H NMR spectrum which we attribute to the C(8)H of the isoquinoline ring being in close proximity to the oxazole ring nitrogen atom. The doublet (J 6 Hz) occurring between δ 8.65–8.80 is assigned as the isoquinoline C(3)H owing to coupling with the C(4)H. This signal becomes a singlet when the C(4) position is substituted as in the case of the bromo and butyl derivatives (**141** and **14u** respectively) (Table 3). All compounds **14** displayed high fluorescence when thin layer chromatograms were visualised under UV light, a feature which aided purification by chromatography. This feature is in common with the known scintillation properties (and use as fluorescent whitening agents) of 2,5-diaryloxazoles.[27]

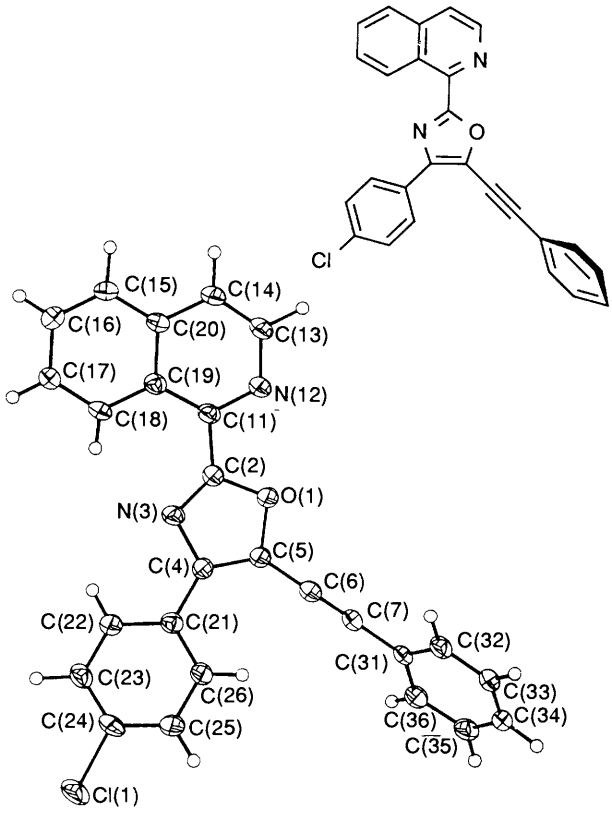


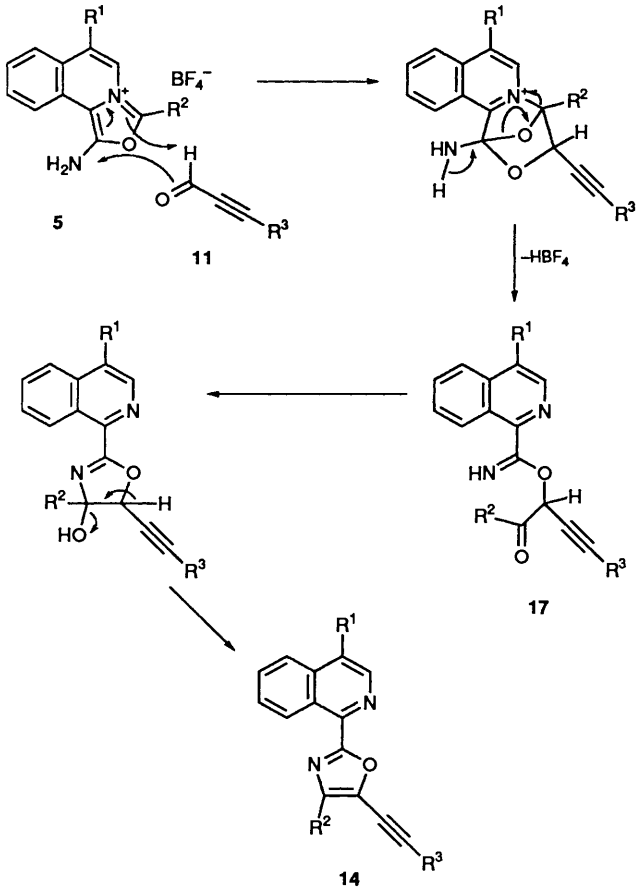
Fig. 1 ORTEP representation of compound **14h**. Hydrogen atom labels follow the numbering scheme of the attached carbon atom and were omitted for clarity.

The products **14** from these novel cycloadditions not only provide new entries to the oxazole ring system, but also represent a new application of Reissert salts **5**.

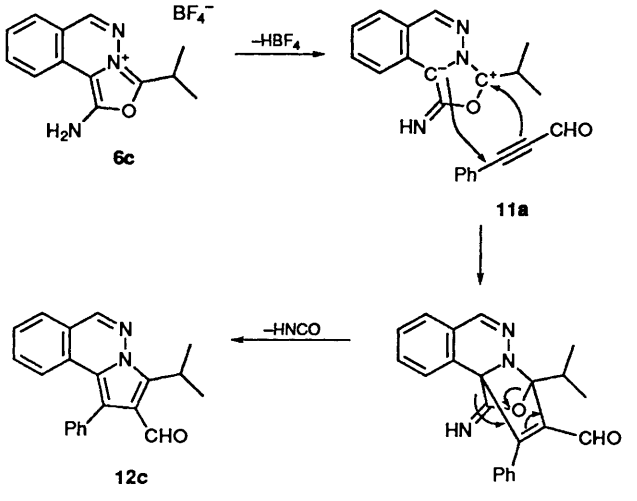
A satisfactory mechanism may involve the initial Diels–Alder cycloaddition of the Reissert salt **5** with the carbonyl group of the acetylenic aldehyde **11** (Scheme 4). Elimination of tetrafluoroboric acid followed by ring opening gives the intermediate **17**. Recyclisation with subsequent dehydration then gives the oxazole **14**. Mechanistically, this is analogous to the Blümlein–Lewy oxazole synthesis[28] and is similar to other known Diels–Alder cycloadditions of Reissert salts which use alkenes as the dienophile.[5,15–17,19,29,30]

An unexpected difference in modes of reaction between different types of Reissert salts and acetylenic aldehydes has been discovered. Thus, Reissert salts **5** derived from isoquinolines **1** react with acetylenic aldehydes **11** at the carbonyl double bond *via* Diels–Alder cycloaddition (Scheme 4) whereas the phthalazine Reissert salt **6c** or the phenanthridine Reissert salt **15** react with acetylenic aldehydes **11** at the acetylene triple bond *via* 1,3-dipolar cycloaddition (*e.g.* Scheme 5).

The electronic and steric factors which are responsible for the different modes of addition are not clear and have not been investigated by theoretical or computational methods, however, it will be appreciated that the factors seem to be finely balanced. Cycloadditions to a carbonyl double bond are often acid



Scheme 4

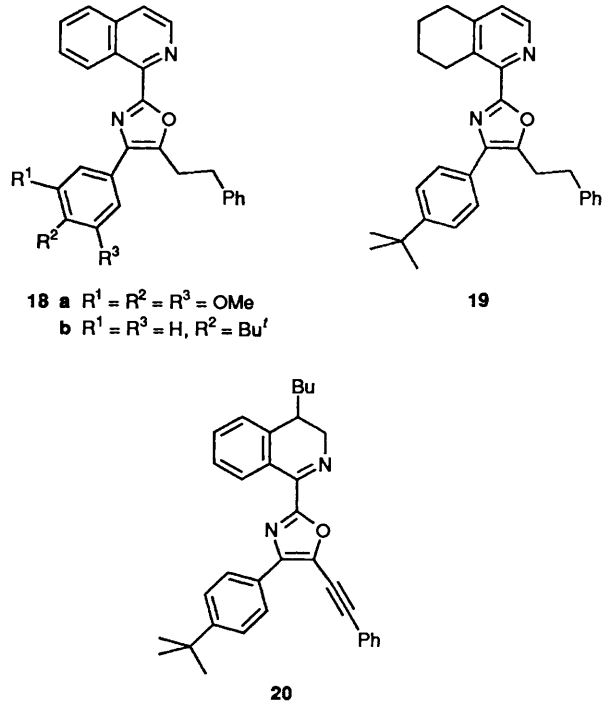


Scheme 5

catalysed and the tetrafluoroboric acid present may be acting as catalyst for this type of addition.[31] Although numerous examples exist of the carbonyl double bond undergoing cycloadditions as dipolarophile or dienophile,[32] examples of reaction at the carbonyl centre are less common when present in an ambident dipolarophile.

The synthetic sequence used to obtain the novel oxazoles **14** involves the use of well known Reissert compounds **3**. The Reissert compounds **3** were prepared from the appropriate isoquinoline **1** by reaction with trimethylsilyl cyanide and an acid chloride using the improved procedure reported by Ruchirawat *et al.*[6] All Reissert compounds **3** gave satisfactory elemental analyses and were obtained in good yield with the exception of the product **3d** which was isolated in only 6.5% yield following the reaction with pivaloyl chloride (which is presumably a consequence of steric congestion) (Table 1). The Reissert compounds **3** were then transformed into the Reissert salts **5** by addition of tetrafluoroboric acid to warm solutions of the compounds **3** in acetic acid according to the known procedure.[13] The crystalline products **5** which separated were collected in good yield (Table 2). Inspection of the ^{1}H NMR data revealed the existence of the NH_2 group confirming the existence of the amino tautomer which is in agreement with previous studies.[14,34] Solutions of the Reissert salts **5** in dimethylimidazolidinone were then treated with the appropriate acetylenic aldehyde **11** and the resulting mixture kept at about 40 °C for 18 h. Alternative solvents such as dimethylformamide or dichloromethane gave inferior results. Subsequent isolation of the corresponding oxazoles **14** was achieved by quenching the reaction mixture with water and extracting the solution with diethyl ether. After evaporation of the solvent, the residue was either subjected to flash chromatography or simply triturated with methanol to give the oxazoles **14** as crystalline solids.

A small number of derivatives were prepared from the oxazoles **14**. Catalytic hydrogenation of ethanolic solutions of compounds **14m** or **14n** using palladium on charcoal as catalyst gave, in both cases, a mixture of products which were purified by flash chromatography. The reductions had proceeded with the complete saturation of the triple bond giving compounds **18**.



However, when the reaction temperature was increased (as in the case of **14m**), reduction of the benzene nucleus of the isoquinoline ring was also observed (in contrast to expectations for the more common saturation of the pyridine nucleus[35]) and compound **19** was also isolated. The proof that saturation of the benzene nucleus had taken place came from inspection of the ^{1}H NMR spectrum. The C(3)H and C(4)H protons of the isoquinoline ring were still present appearing as a pair of doublets at δ 8.48 and 7.07 respectively and the downfield proton [C(8)H] which was present in the starting material **14m** at δ 9.67–9.75 was absent.

Treatment of a solution of compound **14m** in tetrahydrofuran at −50 °C with butyllithium gave an intense purple colouration. Deuterium oxide was added to the solution which was then allowed to warm to ambient temperature before being

diluted with water. The mixture was extracted with diethyl ether, the extract evaporated, and the resulting oil allowed to stand at ambient temperature (18 h). After purification of the extract by flash chromatography, the butyl derivative **14u** was obtained (yield 39%). None of the expected deuterio derivative **14** (R^1 = D, R^2 = 4-Bu^t-C_6H_4, R^3 = Ph) was isolated. The position of substitution was ascertained by comparison of ^{1}H NMR spectra of the product **14u** with the precursor **14m**. The main feature was the disappearance of the signal corresponding to the C(4)H which is normally associated with a multiplet at δ 7.72–7.8 [also containing C(6)H and C(7)H] and the appearance of a singlet at δ 8.59 corresponding to C(3)H [previously seen as a doublet at 8.76 owing to coupling with C(4)H]. Furthermore, examination of the ^{1}H NMR spectral data of closely related isoquinoline derivatives prepared by unambiguous synthesis supports our assignment of 4-(rather than 3-) substitution.[36] Although little is known about nucleophilic addition to the 4-position of isoquinolines, we interpret the formation of compound **14u** as involving the intermediate dihydro derivative **20**. This intermediate **20** arises by nucleophilic addition of the butyl anion to the C-4 position of the isoquinoline ring in compound **14m** and the resulting anion may be stabilised by delocalisation onto the oxazole ring. After quenching the anion, the intermediate **20** then plausibly undergoes aerial oxidation to the observed product **14u**. Evidence for this came by comparison of the thin layer chromatogram of the extract immediately after the reaction, with that after standing for several hours, when a new spot was observed corresponding to the isolated product **14u**.

Experimental

NMR spectra were recorded at ambient temperature on either a Varian CFT-20 spectrometer at 80 MHz, a Varian XL-200 spectrometer at 200 MHz or a Varian VXR 400 spectrometer at 400 MHz. IR spectra were obtained on a Nicolet 20SXB spectrometer. Unless otherwise stated, IR spectra were measured using KBr discs and NMR spectra in deuteriochloroform (tetramethylsilane as internal reference). *J* Values are given in Hz. Only significant bands from IR are quoted. Elemental analyses were determined using a Carlo–Erba elemental analyser model 1106. Mass spectra were recorded on either a VG Micromass 6F or a VG 7070E spectrometer. An ionising potential of 70 eV was used with a source temperature of 250 °C.

Separations by column chromatography were carried out using Merck Kieselgel 60 (230–400 mesh). Concentration and evaporation refer to the removal of volatile materials under reduced pressure (10–15 mmHg at 25–70 °C) on a Buchi Rotavapor. M.p.s were determined using an Electrothermal melting point apparatus and are uncorrected.

Preparation of Reissert Compounds.—*4-Bromo-1-cyano-2-(4-methoxybenzoyl)-1,2-dihydroisoquinoline* **3l**. Anhydrous aluminium trichloride (15 mg) was added to a stirred solution of 4-bromoisoquinoline (9.36 g, 45 mmol) and trimethylsilyl cyanide (TMSCN, 8.9 g, 90 mmol) in dichloromethane (200 cm^3) at ambient temperature. The mixture was then treated by the dropwise addition of 4-methoxybenzoyl chloride (15.35 g, 90 mmol) over a period of 5 min. The mixture was warmed to 30 °C and an exotherm then kept the internal temperature of the homogeneous solution at 30 °C for several minutes before subsiding. After stirring for a further period (4 h), water (200 cm^3) was added and stirring continued (0.5 h). The organic layer was then collected and washed successively with HCl (1 mol dm^{-3}; 1 × 200 cm^3), water (1 × 200 cm^3), NaOH (1 mol dm^{-3}; 1 × 200 cm^3) and finally water (1 × 200 cm^3). The organic solution was dried ($MgSO_4$) and evaporated under reduced pressure to give an oil which was triturated with diethyl ether (100 cm^3) resulting in rapid crystallisation. The solid was then collected, washed with diethyl ether and dried giving the *title compound* **3l** (14.65 g, 88.3%) as a colourless solid, m.p. 141–142 °C (Found: C, 58.7; H, 3.5; N, 7.6. $C_{18}H_{13}BrN_2O_2$ requires C, 58.55; H, 3.55; N, 7.59%); ν_{max}/cm^{-1} 1263, 1323, 1336, 1606, 1623, 1658 and 3452; δ_H($CDCl_3$) 3.9 (s, OCH_3), 6.51 (s, CHCN), 7.00 (d, *J* 8, 2 ArH), 7.07 [s, C(3)H] and 7.3–7.66 (m, 6 ArH); *m/z* 368/370 ($M^{\cdot+}$).

Using the method described above for compound **31**, compounds **3a**–**3k** and **3m**–**3q** were similarly prepared from isoquinoline and the appropriate acid chloride (see Table 1).

1-Cyano-2-isobutyryl-1,2-dihydrophthalazine **4c**.—Anhydrous aluminium trichloride (10 mg) was added to a stirred solution of phthalazine (32.8 g, 252 mmol) and trimethylsilyl cyanide (50 g, 504 mmol) in dichloromethane (500 cm^3) at ambient temperature. The mixture was then treated by the dropwise addition of isobutyryl chloride (53.7 g, 504 mmol) over a period of about 15 min. The exotherm which accompanied the addition was controlled with ice cooling as necessary to maintain the temperature below 33 °C. After stirring for a further period (18 h) at ambient temperature, water (200 cm^3) was added and stirring continued (0.5 h). The organic layer was then collected and washed successively with HCl (1 mol dm^{-3}; 1 × 300 cm^3), water (1 × 300 cm^3), NaOH (1 mol dm^{-3}; 1 × 300 cm^3) and finally water (1 × 300 cm^3). The organic solution was then dried ($MgSO_4$) and evaporated under reduced pressure to give a solid residue which was triturated with diethyl ether (80 cm^3). The solid was then collected and dried giving the *title compound* **4c** (55.1 g, 96.2%) as a colourless solid, m.p. 144–146 °C (Found: C, 68.9; H, 5.6; N, 18.4. $C_{13}H_{13}N_3O$ requires C, 68.7; H, 5.77; N, 18.5%); ν_{max}/cm^{-1} 1224, 1286, 1388, 1453, 1677, 2953, 2971 and 2979; δ_H($CDCl_3$) 1.15 (d, *J* 8, $CHCH_3$), 1.26 (d, *J* 8, $CHCH_3$), 3.55 [sept, *J* 8, $CH(CH_3)_2$], 6.65 (s, CHCN), 7.35–7.45 (m, 2 ArH) and 7.5–7.59 (m, 2 ArH), 7.72 [s, C(4)H]; *m/z* 227 ($M^{\cdot+}$).

Preparation of Reissert Salts.—*1-Amino-6-bromo-3-(4-methoxyphenyl)oxazolo[4,3-a]isoquinolinium tetrafluoroborate* **5l**. A suspension of 4-bromo-1-cyano-2-(4-methoxybenzoyl)-1,2-dihydroisoquinoline **3l** (3.69 g, 10 mmol) in glacial acetic acid (20 cm^3) was warmed to 75 °C giving a pale-yellow homogeneous solution. Aqueous fluoroboric acid (48% w/w; 10 cm^3) was then added with stirring keeping the temperature at 75 °C (for 1 min). The mixture was then allowed to cool to ambient temperature while stirring, chilled to 10 °C and the solid which separated was collected, washed with diethyl ether (5 × 50 cm^3) and dried giving the *title compound* **5l** (4.13 g, 90.4%) as small orange needles, m.p. 210–211 °C (decomp.) (Found: C, 47.2; H, 3.0; N, 6.1. $C_{18}H_{14}BBrF_4N_2O_2$ requires C, 47.3; H, 3.09; N, 6.1%); ν_{max}/cm^{-1} 1272, 1504, 1603, 1668 and 3337; δ_H[$(CD_3)_2SO$] 3.93 (s, OCH_3), 7.3 (d, *J* 8, 2 ArH), 7.6 (dt, *J* 8, 1, 1 ArH), 7.77 (dt, *J* 8, 1, 1 ArH), 7.93 (dd, *J* 8, 1, 1 ArH), 7.96 (d, *J* 8, 2 ArH), 8.07 (br d, *J* 8, 1 ArH), 8.28 (br s, NH_2) and 8.48 (s, 1 ArH).

Using the method described above for compound **5l**, compounds **5a**–**5k** and **5m**–**5q** were similarly prepared from the appropriate Reissert compounds **3a**–**3k** and **3m**–**3q** respectively (see Table 2).

1-Amino-3-isopropyloxazolo[4,3-a]phthalaziniumTetrafluoroborate **6c**.—A suspension of 1-cyano-2-isobutyryl-1,2-dihydrophthalazine **4c** (56.0 g, 247 mmol) in glacial acetic acid (300 cm^3) was warmed to 70 °C giving a pale-yellow homogeneous solution. Aqueous fluoroboric acid (48% w/w; 120 cm^3) was then added with stirring keeping the temperature at 75 °C (for 1 min). The mixture was allowed to cool to ambient temperature while stirring and the mixture then chilled (8 °C). The solid which separated was collected, washed with ethanol (75 cm^3) and dried giving the *title compound* **6c** (61.2 g, 78.7%) as

Table 1 Isoquinoline Reissert compounds **3**

Compound[a]	R^1	R^2	M.p. (°C)	Yield (%)	^{1}H NMR in $CDCl_3$ (for new compounds only)[b]
3a	H	Me	120 (lit.,[33] 119–120)	87.4	
3b	H	Et	111–113 (lit.,[33] 115–117)	78.8	
3c	H	Pr^i	89–91 (lit.,[33] 87–88)	70.4	
3d	H	Bu^t	110–112	6.5	1.36 [s, $C(CH_3)_3$], 6.09 [d, *J* 7, C(3)H], 6.6 [s, C(1)H], 7.06 [dd, *J* 7, C(4)H], 7.14–7.42 (m, 4 ArH)
3e	H	$(CH_2)_{14}Me$	70–72	100.0	0.88 (t, *J* 7, CH_2CH_3), 1.23–1.37 (m, 24 aliphatic H), 1.6–1.76 (m, 2 aliphatic H), 2.4–2.56 (m, 2 aliphatic H), 6.1 [d, *J* 7, C(3)H], 6.67 [br s, C(1)H], 6.76 [br d, *J* 7, C(4)H], 7.18 (d, *J* 7, 1 ArH), 7.28–7.31 (m, 2 ArH), 7.33–7.38 (m, 1 ArH)
3f	H	Ph	124 (lit.,[33] 124–125)	93.6	
3g	H	4-FC_6H_4	180–182 (lit.,[33] 178–179)	92.2	
3h	H	4-ClC_6H_4	154–155 (lit.,[33] 150–151)	93.3	
3i	H	4-BrC_6H_4	158–160	78.7	6.1 [d, *J* 7, C(3)H], 6.53 [br s, C(1)H], 6.59 [br d, *J* 7, C(4)H], 7.23 (d, *J* 7, 1 ArH), 7.34–7.37 (m, 2 ArH), 7.39–7.45 (m, 1 ArH), 7.49 (d, *J* 8, 2 ArH), 7.63 (d, *J* 8, 2 ArH)
3j	H	4-$NO_2C_6H_4$	183–185 (lit.,[33] 177–178)	70.5	
3k	H	4-MeC_6H_4	168–170 (lit.,[33] 173–174)	97.0	
3l	Br	4-$MeOC_6H_4$	141–142	88.3	3.9 (s, OCH_3), 6.5 [br s, C(1)H], 7.0 (d, *J* 8, 2 ArH), 7.07 [s, C(3)H], 7.3–7.58 (m, 4 ArH), 7.62 (d, *J* 8, 2 ArH)
3m	H	4-$Bu^tC_6H_4$	148–150	64.1	1.35 [s, $C(CH_3)_3$], 6.06 [d, *J* 7, C(3)H], 6.54 [br s, C(1)H], 6.7 [br d, *J* 7, C(4)H], 7.22 (d, *J* 8, 1 ArH), 7.32–7.36 (m, 2 ArH), 7.39–7.44 (m, 1 ArH), 7.48 (d, *J* 8, 2 ArH), 7.55 (d, *J* 8, 2 ArH)
3n	H	3,4,5-$(MeO)_3C_6H_2$	175–176	96.8	3.88 (s, 2 × OCH_3), 3.92 (s, OCH_3), 6.09 [d, *J* 7, C(3)H], 6.49 [br s, C(1)H], 6.71 [d, *J* 7, C(4)H], 6.83 (s, 2 ArH), 7.22 (d, *J* 8, 1, 1 ArH), 7.3–7.48 (m, 3 ArH)
3o	H	3-$CF_3C_6H_4$	158–160	37.2	6.14 [d, *J* 7, C(3)H], 6.52–6.6 [m, C(1)H and C(4)H], 7.25 (d, *J* 7, 1 ArH), 7.3–7.48 (m, 3 ArH), 7.64 (t, *J* 7, 1 ArH), 7.83 (dt, *J* 1, 7, 2 ArH), 7.89 (d, *J* 1, 1 ArH)
3p	H	2-furyl	110–111 (lit.,[33] 110–111)	84.6	
3q	H	CH=CHPh	167–169 (lit.,[33] 164–165)	89.9	

[a] All compounds had satisfactory elemental analyses. [b] *J* Values are given in Hz.

tiny yellow needles, m.p. 186 °C (decomp.) (Found: C, 49.2; H, 4.4; N, 13.3. $C_{13}H_{14}BF_4N_3O$ requires C, 49.6; H, 4.48; N, 13.3%); δ_H[$(CD_3)_2SO$] 1.4 [d, *J* 8, $CH(CH_3)_2$], 3.74 [sept, *J* 8, $CH(CH_3)_2$], 7.56 (dt, *J* 1, 7, 1 ArH), 7.84–8.05 (m, 3 ArH), 8.12 (br s, NH_2) and 8.98 [s, C(6)H].

1-*Amino*-3-*methyloxazolo*[4,3-f]*phenanthridinium Tetrafluoroborate* **15**.—A suspension of 5-acetyl-6-cyano-5,6-dihydrophenanthridine[37] (1.0 g, 4 mmol) in glacial acetic acid (15 cm^3) was warmed to 75 °C giving a colourless homogeneous solution. Aqueous fluoroboric acid (48% w/w; 10 cm^3) was then added with stirring keeping the temperature at 75 °C (for 1 min). The mixture was then allowed to cool to ambient temperature while stirring and the solid which separated was collected, washed with diethyl ether (4 × 10 cm^3) and dried giving the *title compound* **15** (1.1 g, 81.8%) as small cream needles, m.p. 224–225 °C (decomp.) [lit.,[37] 217–220 °C (decomp.)] (Found: C, 57.2; H, 3.8; N, 8.3. $C_{16}H_{13}BF_4N_2O$ requires C, 57.2; H, 3.9; N, 8.4%); ν_{max}/cm^{-1} 1673 and 3332; δ_H[$(CD_3)_2SO$] 3.24 (s, CH_3), 7.47–7.85 (m, 4 ArH, NH_2), 8.01 (dd, *J* 8, 1, 1 ArH), 8.22 (dd, *J* 8, 1, 1 ArH), 8.46 (dd, *J* 8, 1, 1 ArH) and 8.61 (dd, *J* 8, 1, 1 ArH).

Cycloadditions with Acetylenic Aldehydes.—3-*Isopropyl*-1-*phenylpyrrolo*[1,2-a]*phthalazine*-2-*carbaldehyde* **12c**. 3-Phenylprop-2-ynal **11a** (2.21 g, 17 mmol) was added to a stirred suspension of 1-amino-3-isopropyloxazolo[4,3-*a*]phthalazinium tetrafluoroborate **6c** (3.15 g, 10 mmol) in *N*,*N*′-dimethylimidazolidinone (DMI, 25 cm^3) at ambient temperature. The resulting mixture was heated at 60 ± 10 °C (1 h), then allowed to stand at ambient temperature (38 h). The dark-brown solution was poured into water (200 cm^3) and extracted with diethyl ether (5 × 100 cm^3). The combined extract was washed with water (2 × 250 cm^3), dried ($MgSO_4$) and evaporated to give a brown oil which was subjected to MPLC (dichloromethane as eluent). The major fraction (R_f 0.44) was collected and the solution concentrated. The resulting concentrated solution was triturated with a 2:1 mixture of light petroleum (b.p. 60–80 °C) and diethyl ether (10 cm^3) and the solid which separated was collected, washed with diethyl ether and dried giving the *title compound* **12c** (0.5 g, 16%) as a yellow solid, m.p. 163–164 °C (Found: C, 80.4; H, 5.8; N, 8.8. $C_{21}H_{18}N_2O$ requires C, 80.2; H, 5.77; N, 8.9%); δ_H($CDCl_3$) 1.56 [d, *J* 8, $CH(CH_3)_2$], 4.42 [sept, *J* 8, $CH(CH_3)_2$], 7.3–7.4 (m, 3 Ar*H*), 7.44–7.55 (m, 5 ArH), 7.58–7.68 (m, 1 ArH), 8.36 (s, 1 ArH) and 9.87 (s, CHO); *m*/*z* 314 ($M^{\cdot+}$).

2-(4-*Bromoisoquinolyl*)-4-(4-*methoxyphenyl*)-5-*phenylethynyloxazole* **14l**.—3-Phenylprop-2-ynal **11a** (2.87 g, 22 mmol), was added to a stirred suspension of 1-amino-6-bromo-3-(4-methoxyphenyl)oxazolo[4,3-*a*]isoquinolinium tetrafluoroborate **5l** (10.14 g, 2 mmol) in *N*,*N*′-dimethylimidazolidinone (100 cm^3) at ambient temperature. The resulting mixture was heated at 55 ± 5 °C (0.5 h) then set aside at ambient temperature (19 h). The dark-brown solution was poured into water (500 cm^3) and extracted with a 1:1 mixture of diethyl ether–ethyl acetate (3 × 250 cm^3). The combined extract was washed with water (3 × 250 cm^3), dried ($MgSO_4$) and evaporated to give a brown oil which was subjected to MPLC (dichloromethane as eluent). The major fraction (R_f 0.27) was collected and the solution concentrated. The resulting concentrated solution was triturated with diethyl ether and the solid which separated was collected, washed with diethyl ether and dried giving the *title compound* **14l** (1.64 g, 15.5%) as a yellow solid, m.p. 182–183 °C (Found: C, 67.3; H, 3.45; N, 5.9. $C_{27}H_{17}BrN_2O_2$ requires C, 67.4; H, 3.56; N, 5.8%); ν_{max}/cm^{-1} 1214, 1251, 1303, 1374, 1509 and 1610; δ_H($CDCl_3$) 3.91 (s, OCH_3), 7.07 (d, *J* 8, 2 ArH), 7.38–

Table 2 Isoquinoline Reissert salts **5**

Compound[a]	R^1	R^2	M.p. (°C) (decomp.)	Yield (%)	Colour	^{1}H NMR [in $(CD_3)_2SO$ unless stated otherwise; new compounds only]
5a	H	Me	176 (lit.,[14] 169–170)	78.0	Yellow	
5b	H	Et	188–190	81.7	Yellow	$(CD_3)_2SO$ + $CDCl_3$ 1.50 (t, *J* 7, CH_2CH_3), 3.33 (q, *J* 7, CH_2CH_3), 3.6 (br s, NH_2), 7.23 (d, *J* 8, 1 ArH), 7.42–7.69 (m, 3 ArH), 7.79 (d, *J* 8, 1 ArH), 8.07 (d, *J* 8, 1 ArH)
5c	H	Pr^i	181–183 (lit.,[15] 170)	81.2	Pale yellow	
5d	H	Bu^t	182–184	68.1	Pale yellow	1.56 [s, $C(CH_3)_3$], 7.34 (d, *J* 8, 1 ArH), 7.47 (dt, *J* 8, 1 ArH), 7.65 (dt, *J* 8, 1, 1 ArH), 7.77 (dd, *J* 8, 1, 1 ArH), 7.88 (br s, NH_2), 8.02 (dd, *J* 8, 1, 1 ArH), 8.16 (d, *J* 8, 1 ArH)
5e	H	$(CH_2)_{14}Me$	96–98	70.9	Cream	$CDCl_3$ 0.87 (t, *J* 8, CH_2CH_3), 1.2–1.42 (m, 24 aliphatic H), 1.8 [quint, *J* 8, $CH_2(CH_2)_{12}CH_3$], 3.13 [t, *J* 8, $CH_2(CH_2)_{13}CH_3$], 5.8 (br s, NH_2), 7.05 (d, *J* 8, 1 ArH), 7.28 (dt, *J* 8, 1 ArH), 7.42 (dd, *J* 8, 1, 1 ArH), 7.45 (d, *J* 8, 1 ArH), 7.5 (dt, *J* 8, 1, 1 ArH), 7.7 (d, *J* 8, 1 ArH)
5f	H	Ph	186 (lit.,[13] 196–198)	79.8	Yellow–orange	
5g	H	4-FC_6H_4		77.0	Yellow	CD_3CN 5.95 (br s, NH_2), 7.36 (t, *J* 8, 2 ArH), 7.49–7.6 (m, 2 ArH), 7.88–7.96 (m, 2 ArH), 7.74–7.94 (m, 2 ArH), 8.12 (d, *J* 8, 1 ArH), 8.17–8.3 (m, 3 ArH)
5h	H	4-ClC_6H_4	188	64.8	Orange	7.44–7.57 (m, 2 ArH), 7.71 (dt, *J* 8, 1, 1 ArH), 7.78–7.86 (m, 3 ArH), 7.97 (d, *J* 8, 2 ArH), 8.12 (d, *J* 8, 1 ArH), 8.22 (d, *J* 8, 1 ArH), 8.33 (br s, NH_2)
5i	H	4-BrC_6H_4	202	77.4	Orange	7.48 (d, *J* 8, 1 ArH), 7.54 (d, *J* 8, 1 ArH), 7.72 (dt, *J* 8, 1, 1 ArH), 7.83 (d, *J* 8, 1 ArH), 7.88 (d, *J* 8, 2 ArH), 7.96 (d, *J* 8, 2 ArH), 8.13 (d, *J* 8, 1 ArH), 8.22 (d, *J* 8, 1 ArH), 8.34 (br s, NH_2)
5j	H	4-$NO_2C_6H_4$	219	70.5	Red	7.56 (dt, *J*, 8, 1, 1 ArH), 7.61 (d, *J* 8, 1 ArH), 7.75 (dt, *J* 8, 1, 1 ArH), 7.88 (d, *J* 8, 1 ArH), 8.19 (d, *J* 8, 3 ArH), 8.38 (d, *J* 8, 1 ArH), 8.51 (d, *J* 8, 2 ArH), 8.63 (br s, NH_2)
5k	H	4-$MeOC_6H_4$	213 (lit.,[13] 210–212)	84.8	Yellow	
5l	Br	4-$MeOC_6H_4$	211	90.4	Orange	3.93 (s, OCH_3), 7.3 (d, *J* 8, 2 ArH), 7.6 (dt, *J* 8, 1, 1 ArH), 7.77 (dt, *J* 8, 1 , 1 ArH), 7.93 (dd, *J* 8, 1, 1 ArH), 7.96 (d, *J* 8, 2 ArH), 8.07 (br d, *J* 8, 1 ArH), 8.28 (br s, NH_2), 8.48 (s, 1 ArH)
5m	H	4-$Bu^tC_6H_4$	224	83.3	Yellow	1.36 [s, $C(CH_3)_3$], 7.42 (d, *J* 8, 1 ArH), 7.5 (dt, *J* 8, 1, 1 ArH), 7.62–7.82 (m, 4 ArH), 7.9 (d, *J* 8, 2 ArH), 8.1 (d, *J* 8, 1 ArH), 8.16–8.28 (m, NH_2, 1 ArH)
5n	H	3,4,5-$(MeO)_3C_6H_2$	214	50.4	Orange	3.82 (s, OCH_3), 3.92 (s, 2 × OCH_3), 7.2 (s, 2 ArH), 7.41 (d, *J* 8, 1 ArH), 7.52 (t, *J* 8, 1 ArH), 7.7 (t, *J* 8, 1 ArH), 7.81 (d, *J* 8, 1 ArH), 8.1 (d, *J* 8, 1 ArH), 8.2–8.29 (m, NH_2, 1 ArH)
5o	H	3-$CF_3C_6H_4$	200	71.1	Yellow–orange	7.48–7.6 (m, 2 ArH), 7.74 (dt, *J* 8, 1, 1 ArH), 7.85 (dd, *J* 8, 1, 1 ArH), 7.97 (t, *J* 8, 1 ArH), 8.07–8.2 (m, 3 ArH), 8.23–8.33 (m, 2 ArH), 8.44 (br s, NH_2)
5p	H	2-Furyl	170	86.2	Orange	7.0–7.05 (m, 1 ArH), 7.46–7.58 (m, 2 ArH), 7.62–7.74 (m, 2 ArH), 7.77–7.84 (m, 1 ArH), 8.09 (d, *J* 8 , 1 ArH), 8.24–8.29 (m, 2 ArH), 8.37 (br s, NH_2)
5q	H	CH=CHPh	226	100.0	Orange	7.44–7.57 (m, 6 ArH), 7.61–7.77 (m, 2 ArH), 7.81–7.95 (m, 3 ArH), 8.07 (d, *J* 8, 1 ArH), 8.38–8.46 (m, 1 ArH, NH_2)

[a] All compounds had satisfactory elemental analyses. [b] *J* Values are given in Hz.

7.46 (m, 3 ArH), 7.55–7.65 (m, 2 ArH), 7.79–7.94 (m, 2 ArH), 8.21–8.30 (m, 3 ArH), 8.91 [s, isoquinoline C(3)H) and 9.72–9.8 (m, 1 ArH); *m/z* 482/480 ($M^{\cdot+}$).

Using the method described above for compound **14l**, compounds **14a–14k** and **14m–14q** were similarly prepared from the appropriate Reissert salts **5a–5k** and **5m–5q** respectively (see Tables 3 and 4).

2-(1-*Isoquinolyl*)-5-(*prop*-1-*ynyl*)-4-(3,4,5-*trimethoxyphenyl*)-*oxazole* **14t**.—But-2-ynal[25] **11b** (3.4 g, 50 mmol), was added to a stirred suspension of 1-amino-3-(3,4,5-trimethoxyphenyl)-oxazolo[4,3-*a*]isoquinolinium tetrafluoroborate **5n** (4.38 g, 10 mmol) in *N*,*N*′-dimethylimidazolidinone (140 cm^3) at ambient temperature. The resulting mixture was then heated at 45 ± 5 °C (18 h). The resulting dark-brown solution was poured into water (500 cm^3) and the mixture then extracted with a 4:1 mixture of diethyl ether–ethyl acetate (3 × 200 cm^3). The combined extract was washed with water (1 × 500 cm^3), dried ($MgSO_4$) and evaporated to give a brown oil which was subjected to MPLC (39:1, dichloromethane methanol as eluent). The major fraction (R_f 0.38) was collected and the solution evaporated. The resulting residue was triturated with cold methanol and the solid was collected, washed with cold methanol and dried giving the *title compound* **14t** (0.94 g, 23.5%) as a yellow–orange solid, m.p. 155–156 °C (Found: C, 72.0; H, 5.0; N, 6.9. $C_{24}H_{20}N_2O_4$ requires C, 72.0; H, 5.03; N, 7.0%); ν_{max}/cm^{-1} 1374, 1394, 1418, 1459, 1502 and 1591; $\delta_H(CDCl_3)$ 2.26 (s, CCH_3), 3.92 (s, OCH_3), 3.99 (s, 2 × OCH_3), 7.55 (s, 2 ArH), 7.74–7.79 (m, 3 ArH), 7.89–7.93 (m, 1 ArH), 8.73 (d, *J* 8, 1 ArH) and 9.54–9.57 (m, 1 ArH); *m/z* 400 ($M^{\cdot+}$).

Using the method described above for compound **14t**, compounds **14r** and **14s** were similarly prepared from the appropriate Reissert salts **5e** and **5n** respectively (see Tables 3 and 4).

3-*Methyl*-1-*phenylpyrrolo*[1,2-f]*phenanthridine*-2-*carbaldehyde* **16**.—3-Phenylprop-2-ynal **11a** (2.7 g, 20.8 mmol) was added to a stirred suspension of 1-amino-3-methyloxazolo[4,3-*f*]phenanthridinium tetrafluoroborate **15** (7.0 g, 20.8 mmol) in *N*,*N*′-dimethylimidazolidinone (90 cm^3) at ambient temperature. The resulting mixture was heated at 60 ± 10 °C (18 h). The

Table 3 Spectral data for oxazoles **14**

Compound[a]	R^1	R^2	R^3	M.p. (°C)	Yield (%)	Colour	^{1}H NMR (in $CDCl_3$ unless stated otherwise)[b]
14a	H	Me	Ph	120–122	9.1	Buff	2.5 (s, CH_3), 7.34–7.43 (m, 3 ArH), 7.51–7.62 (m, 2 ArH), 7.7–7.8 (m, 3 ArH), 7.84–7.93 (m, 1 ArH), 8.7 (d, *J* 6, 1 ArH), 9.45–9.56 (m, 1 ArH)
14b	H	Et	Ph	91–93	14.6	Pale yellow	1.45 (t, *J* 7, CH_2CH_3), 2.87 (q, *J* 7, CH_2CH_3), 7.36–7.41 (m, 3 ArH), 7.54–7.59 (m, 2 ArH), 7.72–7.77 (m, 3 ArH), 7.86–7.92 (m, 1 ArH), 8.71 (d, *J* 6, 1 ArH), 9.52–9.56 (m, 1 ArH)
14c	H	Pr^i	Ph	103–105	14.8	Pale yellow	1.47 [d, *J* 7, $CH(CH_3)_2$], 3.28 [sept, *J* 7, $CH(CH_3)_2$], 7.32–7.44 (m, 3 ArH), 7.52–7.62 (m, 2 ArH), 7.7–7.8 (m, 3 ArH), 7.83–7.92 (m, 1 ArH), 8.7 (d, *J* 6, 1 ArH), 9.5–9.58 (m, 1 ArH)
14d	H	Bu^t	Ph	122–123	9.3	Pale yellow	1.56 [s, $C(CH_3)_3$], 7.3–7.4 (m, 3 ArH), 7.48–7.58 (m, 2 ArH), 7.66–7.75 (m, 3 ArH), 7.79–7.88 (m, 1 ArH), 8.68 (d, *J* 6, 1 ArH), 9.5–9.59 (m, 1 ArH)
14e	H	$(CH_2)_{14}Me$	Ph	54–58	25.9	Pale yellow	0.88 (t, *J* 8, CH_2CH_3), 1.2–1.34 (m, 20 aliphatic H), 1.35–1.5 (m, 4 aliphatic H), 1.87 [quint, *J* 7, $CH_2(CH_2)_{12}CH_3$], 2.82 [t, *J* 7, $CH_2(CH_2)_{13}CH_3$], 7.37–7.4 (m, 3 ArH), 7.54–7.58 (m, 2 ArH), 7.73–7.77 (m, 3 ArH), 7.88–79.2 (m, 1 Ar, H), 8.71 (d, *J* 6, 1 ArH), 9.52–9.56 (m, 1 ArH)
14f	H	Ph	Ph	156–157	11.6	Pale yellow	7.37–7.69 (m, 8 ArH), 7.72–7.83 (m, 3 ArH), 7.84–7.95 (m, 1 ArH), 8.29–8.37 (m, 2 ArH), 8.74 (d, *J* 6, 1 ArH), 9.67–9.75 (m, 1 ArH)
14g	H	$4\text{-}FC_6H_4$	Ph	170–171	15.5	Pale yellow	7.22 (t, *J* 8, 2 ArH), 7.38–7.46 (m, 3 ArH), 7.56–7.64 (m, 2 ArH), 7.72–7.84 (m, 3 ArH), 7.86–7.95 (m, 1 ArH), 8.28–8.36 (m, 2 ArH), 8.74 (d, *J* 6, 1 ArH), 9.62–9.7 (m, 1 ArH)
14h	H	$4\text{-}ClC_6H_4$	Ph	164–165	22.2	Yellow	7.36–7.52 (m, 5 ArH), 7.55–7.63 (m, 2 ArH), 7.71–7.83 (m, 3 ArH), 7.86–7.94 (m, 1 ArH), 8.27 (d, *J* 8, 2 ArH), 8.73 (d, *J* 6, 1 ArH), 9.6–9.7 (m, 1 ArH)
14i	H	$4\text{-}BrC_6H_4$	Ph	163–165	12.1	Pale yellow	7.4–7.46 (m, 3 ArH), 7.6–7.63 (m, 2 ArH), 7.66 (d, *J* 8, 2 ArH), 7.78–7.83 (m, 3 ArH), 7.91–7.94 (m, 1 ArH), 8.22 (d, *J* 8, 2 ArH), 8.75 (d, *J* 6, 1 ArH), 9.66–9.69 (m, 1 ArH)
14j	H	$4\text{-}NO_2C_6H_4$	Ph	233–234	17.0	Yellow–orange	7.40–7.48 (m, 3 ArH), 7.58–7.66 (m, 2 ArH), 7.75–7.85 (m, 3 ArH), 7.89–7.97 (m, 1 ArH), 8.36 (d, *J* 8, 2 ArH), 8.5 (d, *J* 8, 2 ArH), 8.74 (d, *J* 6, 1 ArH), 9.59–9.66 (m, 1 ArH)
14k	H	$4\text{-}MeOC_6H_4$	Ph	166–168	19.4	Yellow	3.92 (s, OCH_3), 7.09 (d, *J* 10, 2 ArH), 7.4–7.48 (m, 3 ArH), 7.58–7.67 (m, 2 ArH), 7.76–7.48 (m, 3 ArH), 7.88–7.96 (m, 1 ArH), 8.31 (d, *J* 10, 2 ArH), 8.75 (d, *J* 6, 1 ArH), 9.69–9.76 (m, 1 ArH)
14l	Br	$4\text{-}MeOC_6H_4$	Ph	182–183	15.5	Yellow	3.91 (s, OCH_3), 7.07 (d, *J* 8, 2 ArH), 7.38–7.46 (m, 3 ArH), 7.55–7.65 (m, 2 ArH), 7.79–7.94 (m, 2 ArH), 8.21–8.3 (m, 3 ArH), 8.91 (s, 1 ArH), 9.72–9.8 (m, 1 ArH)
14m	H	$4\text{-}Bu^tC_6H_4$	Ph	180–181	21.0	Buff	1.38 [s, $C(CH_3)_3$], 7.38–7.44 (m, 3 ArH), 7.56 (d, *J* 8, 2 ArH), 7.58–7.65 (m, 2 ArH), 7.72–7.8 (m, 3 ArH), 7.85–7.93 (m, 1 ArH), 8.27 (d, *J* 8, 2 ArH), 8.72 (d, *J* 6, 1 ArH), 9.67–9.75 (m, 1 ArH)
14n	H	$3,4,5\text{-}(MeO)_3C_6H_2$	Ph	195–197	33.9	Yellow–green	3.93 (s, OCH_3), 4.00 (s, 2 × OCH_3), 7.4–7.45 (m, 3 ArH), 7.56–7.62 (m, 2 ArH), 7.63 (s, 2 ArH), 7.77–7.83 (m, 3 ArH), 7.92–7.96 (m, 1 ArH), 8.76 (d, *J* 6, 1 ArH), 9.6–9.64 (m, 1 ArH)
14o	H	$3\text{-}CF_3C_6H_4$	Ph	205–206	25.5	Cream	7.38–7.47 (m, 3 ArH), 7.58–7.69 (m, 4 ArH), 7.74–7.86 (m, 3 ArH), 7.88–7.96 (m, 1 ArH), 8.46–8.54 (m, 1 ArH), 8.67 (br s, 1 ArH), 8.75 (d, *J* 6, 1 ArH), 9.61–9.69 (m, 1 ArH)
14p	H	2-Furyl	Ph	142–144	10.0	Orange	6.58–6.63 (m, 1 ArH), 7.12 (d, *J* 3, 1 ArH), 7.37–7.46 (m, 3 ArH), 7.58–7.68 (m, 3 ArH), 7.74–7.83 (m, 3 ArH), 7.86–7.95 (m, 1 ArH), 8.72 (d, *J* 6, 1 ArH), 9.56–9.64 (m, 1 ArH)
14q	H	CH=CHPh	Ph	168–169	4.3	Yellow	7.29–7.46 (m, 6 ArH), 7.56–7.68 (m, 5 ArH), 7.72–7.82 (m, 4 ArH), 7.86–7.94 (m, 1 ArH), 8.72 (d, *J* 6, 1 ArH), 9.57–9.65 (m, 1 ArH)
14r	H	$(CH_2)_{14}Me$	Me	77–78	11.0	Buff	0.88 (t, *J* 8, CH_2CH_3), 1.22–1.46 (m, 24 aliphatic H), 1.79 [quint, *J* 7, $CH_2(CH_2)_{12}CH_3$], 2.17 (s, CH_3), 2.76 [t, *J*7, $CH_2(CH_2)_{13}CH_3$], 7.71–7.74 (m, 3 ArH), 7.86–7.89 (m, 1 ArH), 8.68 (d, *J* 6, 1 ArH), 9.46–9.49 (m, 1 ArH)
14s	H	$4\text{-}MeOC_6H_4$	Me	138–139	20.1	Yellow	2.26 (s, CH_3), 3.89 (s, OCH_3), 7.04 (d, *J* 10, 2 ArH), 7.76–7.79 (m, 3 ArH), 7.88–7.92 (m, 1 ArH), 8.21 (d, *J* 10, 2 ArH), 8.71 (d, *J* 6, 1 ArH), 9.65–9.68 (m, 1 ArH)
14t	H	$3,4,5\text{-}(MeO)_3\text{-}C_6H_2$	Me	155–156	23.5	Yellow–orange	2.26 (s, CH_3), 3.92 (s, OCH_3), 3.99 (s, 2 × OCH_3), 7.55 (s, 2 ArH), 7.74–7.79 (m, 3 ArH), 7.89–7.93 (m, 1 ArH), 8.37 (d, *J* 6, 1 ArH), 9.54–9.57 (m, 1 ArH)
14u	Bu^n	$4\text{-}Bu^tC_6H_4$	Ph	134–136	39.3[c]	Pale yellow	0.98 (t, *J* 7, CH_2CH_3), 1.38 [s, $C(CH_3)_3$], 1.48 (q, *J* 7, CH_2CH_3), 1.78 (quint, *J* 7, $CH_2CH_2CH_3$), 3.1 [t, $CH_2(CH_2)_2CH_3$], 7.39–7.43 (m, 3 ArH), 7.56 (d, *J* 10, 2 ArH), 7.61–7.64 (m, 2 ArH), 7.74–7.82 (m, 2 ArH), 8.07–8.11 (m, 1 ArH), 8.28 (d, *J* 10, 2 ArH), 8.59 (s, 1 ArH), 9.75–9.78 (m, 1 ArH)

[a] All compounds had satisfactory elemental analyses (see Table 4). [b] *J* Values are given in Hz. [c] Compound made by different route (direct derivatisation of compound **14m**).

Table 4 Analytical data for oxazoles **14**

Compound (Formula	Found (%) (Required) C	H	N	Molecular ion ($M^{\cdot+}$)[a]
14a	80.9	4.6	8.9	310
($C_{21}H_{14}N_2O$)	(81.3	4.55	9.0)	
14b	81.4	4.9	8.8	324
($C_{22}H_{16}N_2O$)	(81.45	5.0	8.65)	
14c	81.6	5.4	8.4	338
($C_{23}H_{18}N_2O$)	(81.65	5.35	8.3)	
14d	82.0	5.7	7.9	352
($C_{24}H_{20}N_2O$)	(81.8	5.7	7.9)	
14e	82.7	8.35	5.4	506
($C_{35}H_{42}N_2O$)	(82.95	8.35	5.55)	
14f	83.7	4.3	7.5	372
($C_{26}H_{16}N_2O$)	(83.9	4.35	7.5)	
14g	79.6	3.85	7.2	390
($C_{26}H_{15}FN_2O$)	(80.0	3.85	7.2)	
14h	76.9	3.65	6.95	406 (^{35}Cl)
($C_{26}H_{15}ClN_2O$)	(76.75	3.72	6.9)	
14i	68.9	3.25	6.4	450/452
($C_{26}H_{15}BrN_2O$)	(69.2	3.35	6.2)	
14j	74.8	3.6	10.0	417
($C_{26}H_{15}N_3O_3$)	(74.8	3.6	10.05)	
14k	80.3	4.4	6.9	402
($C_{27}H_{18}N_2O_2$)	(80.6	4.5	7.0)	
14l	67.3	3.45	5.9	480/482
($C_{27}H_{17}BrN_2O_2$)	(67.4	3.55	5.8)	
14m	84.0	5.65	6.55	429 (MH^+)[b]
($C_{30}H_{24}N_2O$)	(84.1	5.65	6.55)	
14n	75.1	4.6	5.8	469
($C_{29}H_{22}N_2O_4$)	(75.3	4.8	6.05)	
14o	73.3	3.35	6.4	441 (MH^+)[b]
($C_{27}H_{15}F_3N_2O$)	(73.6	3.45	6.35)	
14p	79.7	3.9	7.8	362
($C_{24}H_{14}N_2O_2$)	(79.5	3.9	7.7)	
14q	84.4	4.5	7.0	398
($C_{28}H_{18}N_2O$)	(84.4	4.55	7.05)	
14r	81.1	9.3	6.0	444
($C_{30}H_{40}N_2O$)	(81.05	9.05	6.3)	
14s	77.5	4.65	8.1	341 (MH^+)[b]
($C_{22}H_{16}N_2O_2$)	(77.65	4.75	8.25)	
14t	72.0	5.0	6.9	400
($C_{24}H_{20}N_2O_4$)	(72.0	5.05	7.0)	
14u	83.9	6.75	5.45	485 (MH^+)[b]
($C_{34}H_{32}N_2O$)	(84.25	6.65	5.8)	

[a] By electron impact. [b] By direct chemical ionisation using ammonia as carrier gas.

dark-brown solution was poured into water (500 cm^3) and extracted with a 2:1 mixture of diethyl ether–dichloromethane (2 × 250 cm^3). The combined extract was washed with water (2 × 250 cm^3), dried ($MgSO_4$) and evaporated to give a brown oil (10.5 g) which was subjected to MPLC (dichloromethane as eluent). The major fraction (R_f 0.35) was collected and the solution concentrated. The resulting concentrated solution was triturated with diethyl ether and the solid which separated was collected, washed with diethyl ether and dried giving the *title compound* **16** (1.0 g, 14.3%) as a yellow solid, m.p. 169–171 °C (Found: C, 85.9; H, 5.0; N, 4.1. $C_{24}H_{17}NO$ requires C, 85.94; H, 5.1; N, 4.18%); ν_{max}/cm^{-1} 1377, 1662 and 1675; $\delta_H(CDCl_3)$ 3.28 (s, CH_3), 7.3 (dt, *J* 8, 1, 1 ArH), 7.24–7.58 (m, 9 ArH), 8.12–8.36 (m, 3 ArH) and 9.74 (s, CHO); *m/z* 335 ($M^{\cdot+}$).

Catalytic Hydrogenation of Compound **14n**.—A suspension of 2-(isoquinolyl)-5-phenylethynyl-4-(3,4,5-trimethoxyphenyl)-oxazole **14n** (1.1 g, 2.38 mmol) and 5% w/w palladium on charcoal (1.1 g) in ethanol (130 cm^3) was shaken under an atmosphere of hydrogen until uptake ceased. The catalyst was removed by filtration and the filtrate evaporated to give a yellow gum which was purified by MPLC (49:1, CH_2Cl_2–MeOH as eluent). The major fraction was collected and the solvent evaporated giving 2-(1-*isoquinolyl*)-5-*phenethyl*-4-(3,4,5-*trimethoxyphenyl*)*oxazole* **18a** (0.33 g, 30%) as a pale yellow solid, m.p. 175–177 °C. $\delta_H(CDCl_3)$ 3.22 (t, *J* 8, CH_2CH_2), 3.36 (t, *J* 8, CH_2CH_2), 3.88 (s, OCH_3), 3.89 (s, 2 × OCH_3), 6.86 (s, 2 ArH), 7.18–7.23 (m, 3 ArH), 7.25–7.3 (m, 2 ArH), 7.71–7.78 (m, 3 ArH), 7.91 (dd, *J* 8, 1, 1 ArH), 8.74 (d, *J* 6, 1 ArH) and 9.58–9.63 (m, 1 ArH); *m/z* 466 ($M^{\cdot+}$).

Catalytic Hydrogenation of Compound **14m**.—A suspension of 4-(4-*tert*-butylphenyl)-2-(1-isoquinolyl)-5-phenylethynyloxazole **14m** (1.43 g, 3.3 mmol) and 5% w/w palladium on charcoal (0.95 g) in ethanol (80 cm^3) was shaken at about 50 °C under an atmosphere of hydrogen until uptake ceased. The catalyst was removed by filtration and was washed with ethanol (2 × 50 cm^3). The combined filtrate was evaporated to give an orange gum. Trituration of the gum with cold methanol (25 cm^3) resulted in the separation of a solid which was collected and purified by MPLC (39:1, CH_2Cl–MeOH as eluent). The minor fraction was collected, the eluent evaporated, and the residue washed with methanol and then dried giving 4-(4-tert-*butylphenyl*)-2-(1-*isoquinolyl*)-5-*phenethyloxazole* **18b** (0.1 g, 7%), as a very pale-yellow solid, m.p. 160–162 °C (Found: C, 83.3; H, 6.4; N, 6.5. $C_{30}H_{28}N_2O$ requires C, 83.3; H, 6.53; N, 6.48%); $\delta_H(CDCl_3)$ 1.38 [s, $C(CH_3)_3$], 3.19 (t, *J* 8, CH_2CH_2), 3.37 (t, *J* 8, CH_2CH_2), 7.2–7.33 (m, 5 ArH), 7.49 (d, *J* 10, 2 ArH), 7.66 (d, *J* 10, 2 ArH), 7.73–7.78 (m, 3 ArH), 7.88–7.92 (m, 1 ArH), 8.72 (d, *J* 6, 1 ArH) and 9.7–9.73 (m, 1 ArH); *m/z* 432 ($M^{\cdot+}$).

The major fraction was collected, the eluent evaporated, and the oil triturated with methanol. The solid which separated was collected and dried giving 4-(4-tert-*butylphenyl*)-5-*phenethyl*-2-(5,6,7,8-*tetrahydro*-1-*isoquinolyl*)*oxazole* **19** (0.59 g, 41.0%) as a colourless solid, m.p. 141–142 °C (Found: C, 82.2; H, 7.3; N, 6.4. $C_{30}H_{32}N_2O$ requires C, 82.5; H, 7.39; N, 6.42%); ν_{max}/cm^{-1} 1363, 1408, 1427, 1455, 1498, 1579, 2866, 2954 and 3436; $\delta_H(CDCl_3)$ 1.35 [s, $C(CH_3)_3$], 1.8–1.92 (m, 4 aliphatic H), 2.85 (t, *J* 8, CH_2CH_2), 3.11–3.17 (m, 2 aliphatic H), 3.27–3.33 (m, 4 aliphatic H), 7.07 (d, *J* 6, 1 ArH), 7.18–7.34 (m, 5 ArH), 7.44 (d, *J* 8, 2 ArH), 7.6 (d, *J* 8, 2 ArH) and 8.48 (d, *J* 6, 1 ArH); *m/z* 437 (MH^+).

Reaction of compound **14m** *with butyllithium*.—A solution of butyllithium in hexanes (2.5 mol dm^{-3}; 0.5 cm^3, 1.2 mmol) was added dropwise to a cold (−50 °C) stirred solution of 4-(4-*tert*-butylphenyl)-2-(1-isoquinolyl)-5-phenylethynyloxazole **14m** (428 mg, 1 mmol) in dry tetrahydrofuran (20 cm^3) under an argon atmosphere resulting in an intense dark-purple colouration. After stirring (10 min), deuterium oxide (0.5 cm^3) was added and the mixture allowed to warm to ambient temperature. Water (30 cm^3) and diethyl ether (70 cm^3) were then added and the organic layer was separated, dried ($MgSO_4$) and the solvent evaporated to give an orange oil. After standing at ambient temperature (18 h), the oil was subjected to MPLC (CH_2Cl_2 as eluent) and the major fraction (R_f 0.66) collected. Evaporation of the eluent gave a residue which was triturated with a little methanol and the solid which separated was collected and dried giving 2-(4-*butyl*-1-*isoquinolyl*)-4-(4-tert-*butylphenyl*)-5-*phenylethynyloxazole* **14u** (190 mg, 39.3%) as a pale-yellow solid, m.p. 134–136 °C (Found: C, 83.9; H, 6.7; N, 5.4. $C_{34}H_{32}N_2O$ requires C, 84.26; H, 6.66; N, 5.78%); $\delta_H(CDCl_3)$ 0.98 (t, *J* 7, CH_2CH_3), 1.38 [s, $C(CH_3)_3$], 1.48 (q, *J* 7, CH_2CH_3), 1.78 (quintet, *J* 7, $CH_2CH_2CH_3$), 3.1 [t, *J* 7, $CH_2(CH_2)_2CH_3$], 7.39–7.43 (m, 3 ArH), 7.56 (d, *J* 10, 2 ArH), 7.61–7.64 (m, 2 ArH), 7.74–7.82 (m, 2 ArH), 8.07–8.11 (m, 1 ArH), 8.28 (d, *J* 10, 2 ArH), 8.59 [s, isoquinoline C(3)H] and 9.75–9.78 (m, 1 ArH); *m/z* 485 (MH^+).

X-Ray Crystal Structure Determination of Oxazole **14h**.—Suitable crystals were grown from cyclohexane and a specimen

Table 5 Crystal data for compound **14h**

Formula	$C_{26}H_{15}ClN_2O$
M	406 (^{35}Cl)
Crystal system	Monoclinic
Space group	$I2/a$
a/Å	16.492(2)
b/Å	12.798(4)
c/Å	19.473(9)
β/°	109.40(2)
V/Å^3	3876.7
Z	8
D_c/g cm^{-1}	1.394
μ/cm^{-1} [Mo-Kα]	2.145
F(000)	1680

was mounted on an Enraf–Nonius FAST-TV area detector diffractometer attached to a rotating anode equipped with a Mo-target [λ(Mo-Kα) = 0.710 69 Å] and a graphite monochromator. Following the known procedure,[38] orienting reflections for indexing and lattice parameter refinement were collected, (Table 5), with the detector positioned at −25° swing angle and 40 mm distance. The crystal was cooled to 150 K using an Oxford Cryostream Cooler. A total of 12 641 intensities were collected in the 2θ range −53 to +2.5°. After merging and averaging, this resulted in 4746 unique reflections (R_{merge} = 0.066). Of these, 1861 had intensities of more than $1.5\sigma(I)$ and were considered observed. The structure was solved by the direct methods program SHELXS-86[39] and subsequently refined using full-matrix least-squares methods based on F_{rel} incorporated into the program SHELX-76,[40] and the weighting scheme $w = 1/\sigma^2(F)$. For non-hydrogen atoms, all positional and anisotropic displacement parameters were refined. Hydrogen atoms were located by Fourier difference synthesis and were restricted to refinement of positional and isotropic displacement parameters. Final R and R_w values are 0.043, 0.036. Tables of atomic coordinates, thermal parameters, bond lengths, bond angles and selected non-bonded distances have been deposited at the Cambridge Crystallographic Data Centre.*

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* For details of the deposition scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1993, issue 1.

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