Synthesis of 1,3-Disubstituted-pyrrolo[2,1-*a*]isoquinoline-2-carboxylic Acids, Esters and Amides

Andrew W. Bridge,[a,*] Garry Fenton,[a] Frank Halley,[a] Michael B. Hursthouse,[b] Christian W. Lehmann[b] and David J. Lythgoe[a]

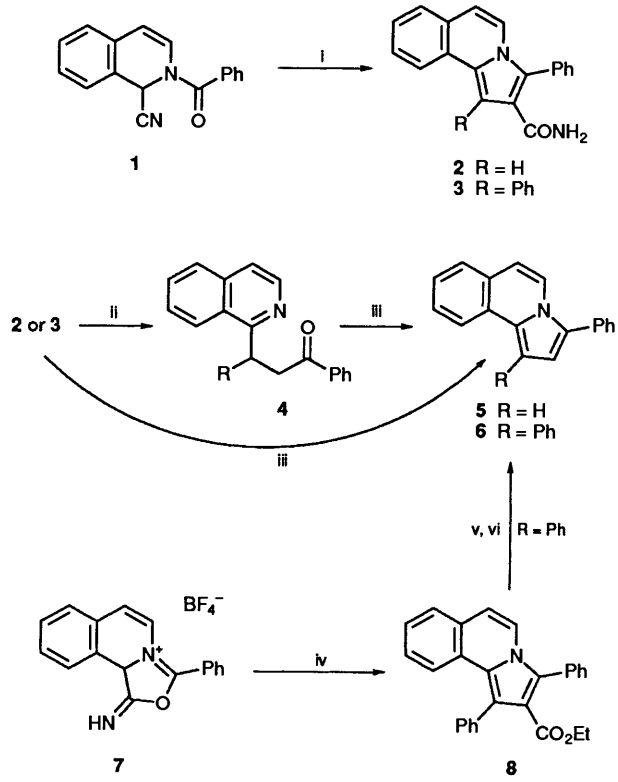
[a] *Dagenham Research Centre, Rhône-Poulenc Rorer Ltd., Rainham Road South, Dagenham, Essex, RM10 7XS, UK*

[b] *School of Chemistry and Applied Chemistry, University of Wales College of Cardiff, PO Box 912, Cardiff, CF1 3TB, UK*

A number of 1,3-disubstituted pyrrolo[2,1-*a*]isoquinoline-2-carboxylic esters have been prepared using a variety of independent routes. The corresponding acids and a range of amides were subsequently synthesised. The primary amides were found to differ significantly from those reported to arise from the reaction between the anion of an isoquinoline Reissert compound and an α,β-unsaturated nitrile. Re-investigation has established that the latter reaction does not produce primary amides. The true nature of the products as 2-acyl-3-aminopyrrolo[2,1-*a*]isoquinolines was established using X-ray crystallography.

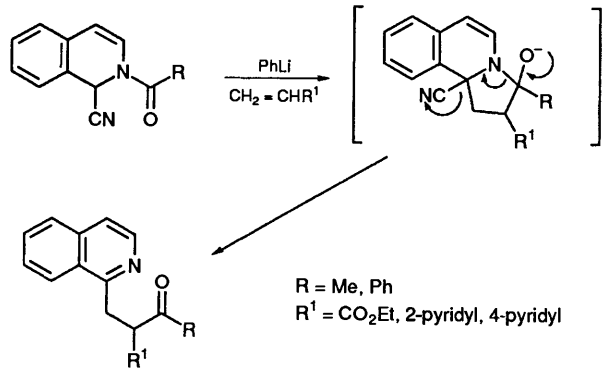
We have recently needed to prepare a number of pyrrolo[2,1-*a*]isoquinoline-2-carboxamides as starting materials for the synthesis of some novel compounds designed to be inhibitors of acyl CoA:cholesterol *O*-acyl transferase (ACAT).[1] In the course of some previous work to make novel HMG CoA reductase inhibitors[2] we had already synthesised a number of pyrrolo[2,1-*a*]isoquinoline-2-carboxylic esters using a variety of independent routes (see below) and were initially able to utilise these to make amides *via* the acids. These acids, esters and amides all exhibited similar, characteristic, spectral properties and were not highly coloured. In seeking a shorter and more efficient source of primary amides, we became aware that Michael addition of the anion derived from 2-benzoyl-1-cyano-1,2-dihydroisoquinoline **1** to acrylonitrile has been reported[3] to yield 3-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide **2** (Scheme 1) and with cinnamonitrile to provide[4,5] the 1,3-diphenyl-2-carboxamide analogue **3**. The reported formation of **2** and **3** required particularly facile hydrolyses of the corresponding nitriles during work-up. These products ('**2**' and '**3**') were 'hydrolysed and decarboxylated' as part of degradative structure determinations[4,5] of the products from the cycloaddition between Reissert salts and phenylpropiolic acid esters. Hydrolysis using hydrochloric acid resulted in isolation of 2-(isoquinolin-1-yl)ethyl phenyl ketones **4**, which were cyclised with phosphoric acid to the 3-phenylpyrrolo[2,1-*a*]isoquinolines **5** and **6**, whereas hydrolysis with phosphoric acid generated the 3-phenylpyrrolo[2,1-*a*]isoquinolines directly[3-5] (Scheme 1). The esters, such as **8**, prepared by cycloaddition of Reissert salts, such as **7**, to phenylpropiolic acid esters were hydrolysed to the corresponding pyrrolo[2,1-*a*]isoquinoline-2-carboxylic acids[3-5] and were then decarboxylated.[4] These acids were not, however, converted into primary amides for direct comparison with those supposed to arise from the Michael addition (Scheme 1). Subsequently, a number of related Michael reactions have been reported, by analogy, to yield carboxamides incorporating quinolines,[6] isoquinolines,[7] phthalazines[7,8] and phenanthridines.[9] These 'amides' are generally bright orange or red solids. In contrast, however, the Michael addition of Reissert-anions to α,β-unsaturated esters or vinylpyridines yields the corresponding β-ketoesters and pyridinyl ketones by rearrangement[3-5,10,11] (Scheme 2).

The properties of the reported[3-5] 'pyrrolo[2,1-*a*]isoquinoline-2-carboxamides', especially the marked colours, differed significantly from those of our authentic samples. Accordingly,



Scheme 1 *Reagents:* i, PhLi, RCH=CHCN; ii, HCl (refs. 3 and 4); iii, H_3PO_4 (refs. 3 and 4); iv, PhC≡CCO_2Et (ref. 4); v, KOH/EtOH; vi, H_3PO_4 (ref. 4).

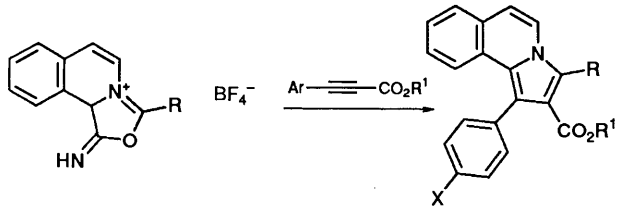
we have re-investigated the reaction of the anion derived from 2-benzoyl-1-cyano-1,2-dihydroisoquinoline with cinnamonitrile. We isolated two products, one of which corresponded with that reported in the literature, and determined that neither was the carboxamide **3**. The true nature of the product purported to be the pyrrolo[2,1-*a*]isoquinoline-2-carboxamide **3** has been established by X-ray crystallography as a 3-amino-2-benzoylpyrrolo[2,1-*a*]isoquinoline **57**. Similarly, we have found that reaction between the anion derived from 2-acetyl-1-cyano-1,2-dihydroisoquinoline with cinnamonitrile produces the corresponding 2-acetyl-3-aminopyrrolo[2,1-*a*]isoquinoline **48**.



Scheme 2

Results and Discussion

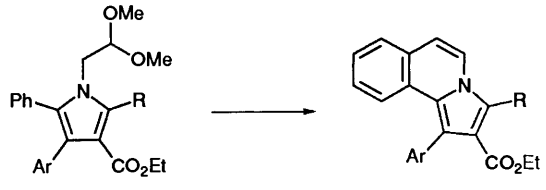
Initial syntheses of pyrroloisoquinoline esters **8**–**12** utilised the known[4] 1,3-dipolar cycloaddition of Reissert salts with arylpropiolates (Scheme 3). Although this is a short and



	X	R	R^1
8	H	Ph	Et
9	H	Me	Et
10	F	Pr^i	Me
11	F	Ph	Me
12	H	Et	Et

Scheme 3

versatile route it suffers from a number of disadvantages: Reissert compounds are cyanide based, the reaction is seldom clean, the products generally require chromatographic purification, and yields of cycloaddition products can be very low, all of which can be inconvenient during large-scale synthesis. To circumvent these difficulties, a new approach was developed based on the concept of building the isoquinoline ring as the final step by intramolecular condensation of 2-alkyl-4-aryl-1-(2,2-dimethoxyethyl)-5-phenylpyrrole-3-carboxylates such as **13** (Scheme 4). Thus, the substitution

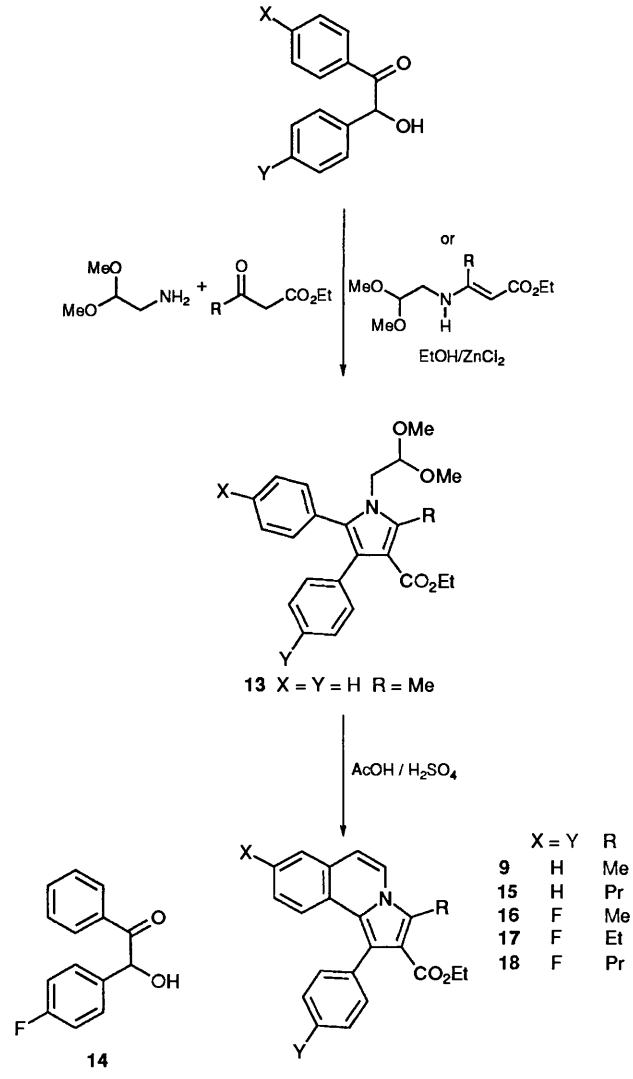


13 R = Me Ar = Ph **9** R = Me Ar = Ph

Scheme 4

patterns of these pyrroloisoquinolines would be unambiguously established during construction of the pyrrole rings.

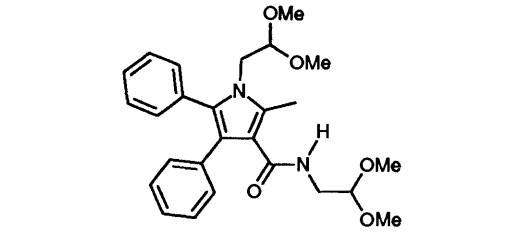
The first and shortest route to pyrroles was based on the Feist reaction of benzoins with β-aminocrotonates.[12] Condensation of aminoacetaldehyde dimethyl acetal with an equivalent of ethyl acetoacetate in boiling toluene and reaction of the crude aminocrotonate with benzoin to form the pyrrole resulted in only a 7% yield of the ester **13** together with a 71% yield (from the acetal) of the derived amide **19**. Amide formation was avoided by forming the aminocrotonate in ethanol rather than toluene, but prior preparation of aminocrotonates was found to be unnecessary: simply treating aminoacetaldehyde dimethyl acetal, a β-keto ester and a benzoin with zinc chloride in ethanol was found to give the pyrrole esters in greatly improved yield in a one-pot synthesis (Scheme 5). Cyclisation of the pyrrole



	X = Y	R
9	H	Me
15	H	Pr
16	F	Me
17	F	Et
18	F	Pr

Scheme 5

intermediates could be achieved using sulfuric or trifluoroacetic acids as reaction media, but was most conveniently effected by adding a solution of the crude 1-(2,2-dimethoxyethyl)pyrrole (*e.g.* **13**) in acetic acid to sulfuric acid. The reaction temperature is not known to be critical and cyclisations were successfully undertaken at temperatures between 0 and 50 °C. Purification of the pyrrole prior to cyclisation was not generally undertaken as the cyclisation product appeared to have fewer by-products by TLC than the crude pyrrole. This is a convenient method for the preparation of pyrroloisoquinolines bearing small alkyl (methyl, ethyl, propyl) substituents at position-3 (**9**, **15**–**18**) starting from 'symmetrically-substituted' benzoins but could not be made to work when the 3-alkyl group was branched (*e.g.* isopropyl). In a typical synthesis of **9** the dimethoxyethylpyrrole intermediate **13** could be obtained in a crude yield of 88% (70 g) (53% after purification), cyclisation could be achieved in 74% yield and an overall yield of 51% **9**, from benzoin, was typically attained when **13** was cyclised without prior purification. When a differentially substituted benzoin **14** was employed, the product after cyclisation, although apparently homogeneous by TLC, was found by NMR to consist of a 50:50 mixture of two pyrroloisoquinolines: isomerisation of the benzoin clearly



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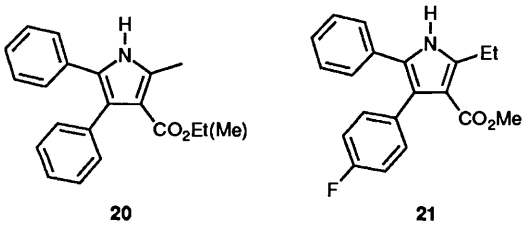

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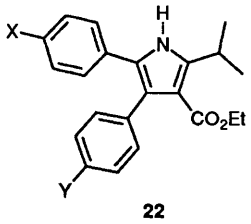

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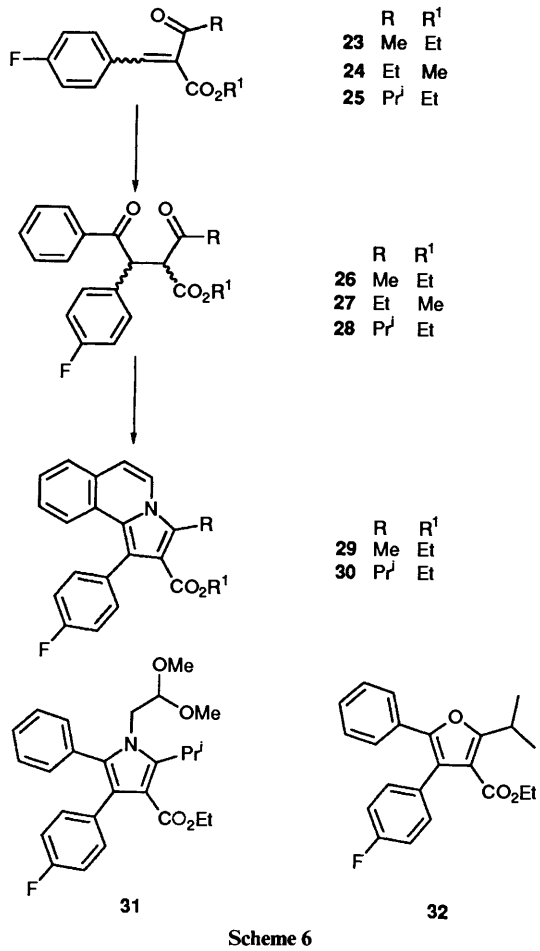
occurs more rapidly than the condensation step between the benzoin and the aminocrotonate limiting this approach in practice to 'symmetrically' derived pyrroloisoquinolines.

To try to overcome the limitation on the 3-alkyl substituent, the method was modified to prepare NH pyrroles with a view to introducing the dimethoxyethyl group as a subsequent step. Benzoin was treated with methyl 3-aminocrotonate in ethanol to generate the *N*-unsubstituted pyrrole **20** (28%) as a mixture of esters (methyl:ethyl, 1:6). Reaction of **20** with potassium *tert*-butoxide and bromoacetaldehyde dimethyl acetal in DMI followed by cyclisation gave **9** (24%), providing no advantage over the aminoacetaldehyde dimethyl acetal method. Reaction of the monofluorobenzoin **14** with ethyl 3-amino-4-methylpent-2-enoate provided a mixture of two pyrroles **22** (X = H, Y = F and X = F, Y = H) in low yield (10%)—highlighting the rapid isomerisation of benzoins—but it was not possible to alkylate **22** with bromoacetaldehyde dimethyl acetal. The reduced yield of **22** and failure to prepare the 3-isopropyl analogue of **9** using either of these methods is probably a consequence of steric congestion.

In order to extend the basic approach to pyrrolo[2,1-*a*]isoquinolines with more diverse substituents in the 1-phenyl and isoquinoline groups, pyrrole intermediates were generated from 1,4-diketones (Scheme 6). The 1,4-diketones **26**–**28** were conveniently prepared by condensing β-keto esters with 4-fluorobenzaldehyde and treating the benzylidene intermediates **23**–**25** with benzaldehyde using the Stetter procedure.[13] Regiochemistry having thus been established, and since stereochemical centres are lost during pyrrole formation, the diastereomeric mixtures of diketones were condensed with aminoacetaldehyde dimethyl acetal in acetic acid and then cyclised without isolation. In this way, compounds such as **29** were prepared with methyl, trifluoromethyl and ethyl groups as 3-substituents* but attempts to obtain the 3-isopropyl analogue **30** by this method failed. The ease of condensation between β-keto esters and aldehydes and the applicability of the Stetter procedure means



	R	R^1
23	Me	Et
24	Et	Me
25	Pr^i	Et

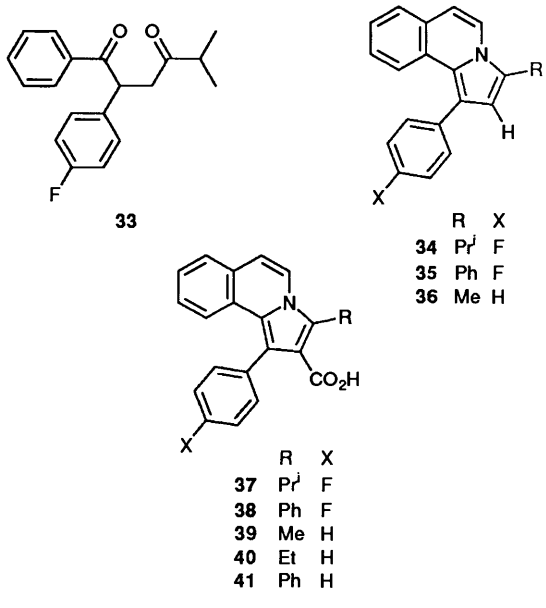
	R	R^1
26	Me	Et
27	Et	Me
28	Pr^i	Et

	R	R^1
29	Me	Et
30	Pr^i	Et

31 32

Scheme 6

that this approach can be used to prepare pyrroloisoquinolines with different substituents in the 1-phenyl and isoquinoline rings and has the potential to be a general source of pyrrolo-fused heterocycles with a wide variety of alkyl, aryl and heterocyclic substituents. A drawback to this route was the concomitant formation of minor impurities (believed to be the corresponding furans, such as **32**) which required careful chromatographic separation. The furans, which were produced in low yield (< 18% during synthesis of **29**) and were not usually isolated except for **32** which was obtained in 5% yield from the



33

	R	X
34	Pr^i	F
35	Ph	F
36	Me	H

	R	X
37	Pr^i	F
38	Ph	F
39	Me	H
40	Et	H
41	Ph	H

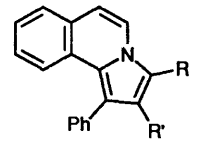
* Compounds analogous to **29** (R = CF_3 or Et) were prepared and used in other work without characterisation and so have not been included in the Experimental section.

preparation of **30** from **28** (see below), are thought to arise by incomplete imine formation and subsequent acid-catalysed cyclisation of the residual 1,4-diketones. Compound **32** was prepared for direct comparison by acidic cyclisation of the 1,4-diketone **28**. Formation of the 2-isopropyl substituted *N*-(2,2-dimethoxyethyl)pyrrole **31** proved to be difficult but was eventually achieved by treating the isopropyl diketone **28** and the aminoacetal for 40 h at 170 °C without additional solvent. The yield, however, was too low (< 10% after cyclisation) to constitute a practical synthesis of **30** or similar analogues. Attempts to improve this reaction by the use of solvents were to no avail. The difficulty in introducing sterically demanding groups into position-3 of pyrrolo[2,1-*a*]isoquinolines was further highlighted when the 1,4-diketone **33** was treated similarly. Here, it was postulated that removal of steric interaction between the ester and the isopropyl groups might permit pyrrole formation to take place effectively, and hence to *provide* a route to **34** which could then be functionalised at position-2 of the pyrroloisoquinoline. In practice, however, **34** was obtained in only 24% yield from **33** emphasising the problem of incorporating sterically demanding groups into position-3 of pyrroloisoquinolines. Pyrroloisoquinolines unsubstituted at position 2, such as **34–36**, are more readily prepared in good yield (50–80%) by decarboxylation of the corresponding 2-carboxylic acids, such as **37–41**.

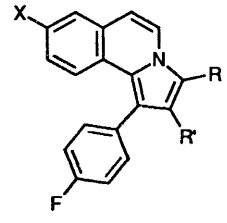
These practical inconveniences were ultimately overcome by the application of a 1,3-dipolar cycloaddition to generate the key pyrrole intermediate **45** (Scheme 7). Condensation of methyl α-bromophenylacetate with aminoacetaldehyde dimethyl acetal and acylation of the derived amine took place almost quantitatively; saponification then afforded the readily purified acid **42** in 72% overall yield after recrystallisation. Cyclisation of **42** with acetic anhydride (in the presence of triethylamine) generated the munchnone **43** which underwent a 1,3-dipolar cycloaddition with methyl 4-fluorophenylpropiolate followed by retro-Diels–Alder elimination of carbon dioxide from the intermediate **44** to provide a one-pot synthesis of pyrroles such as **45**.* Cyclisation of **45** under acidic conditions provided the 3-isopropylpyrroloisoquinoline **4** in 36% yield from **42**. The final stage cycloaddition/cyclisation yield (**42** → **10**: 36%) compared very favourably with those achieved in the Reissert cycloaddition (12%) which always required chromatographic purification. This procedure permits the ready preparation of a range of substituted pyrroloisoquinolines limited only by the availability of the appropriate phenylacetic acids, acylating agents and acetylenes, and constitutes a simple entry into this heterocyclic ring system. The excellent yield of **10** emphasises the potential of this system for the introduction of sterically demanding alkyl groups into position-3 of pyrroloisoquinolines.

The pyrroloisoquinoline-2-esters prepared using the various approaches described above, including the Reissert cycloaddition, gave consistent, characteristic spectral and physical properties; compounds which were synthesised using more than one approach were identical confirming that Reissert cycloaddition affords pyrroloisoquinolines with the reported regiochemistry. As described, the concept of cyclising 2-alkyl-*N*-(2,2-dimethoxyethyl)-5-phenylpyrroles is useful as a route to 3-alkylpyrroloisoquinolines but potential problems may be expected for 3-aryl analogues unless substituents on the aryl groups of the corresponding 2,5-diarylpyrroles can be used to activate or deactivate the rings, and hence to control the direction of cyclisation.

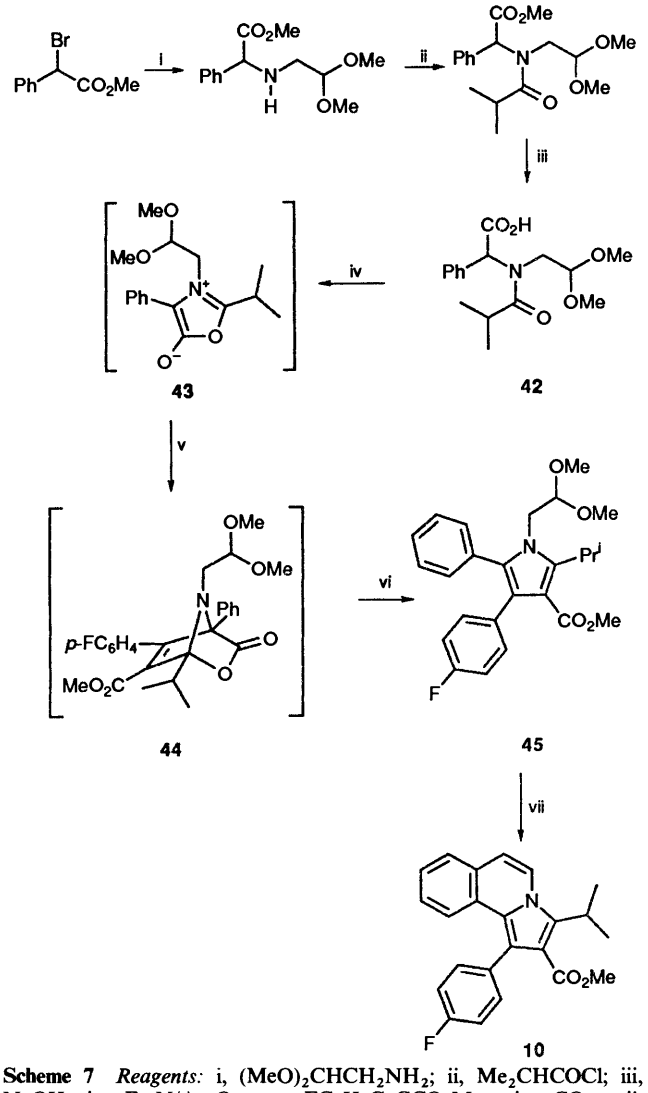
The pyrroloisoquinoline esters, such as **9**, were hydrolysed to



	R	R'
49	Et	$CONH_2$
50	Me	CONHBu
51	Me	CO–N⟨O⟩

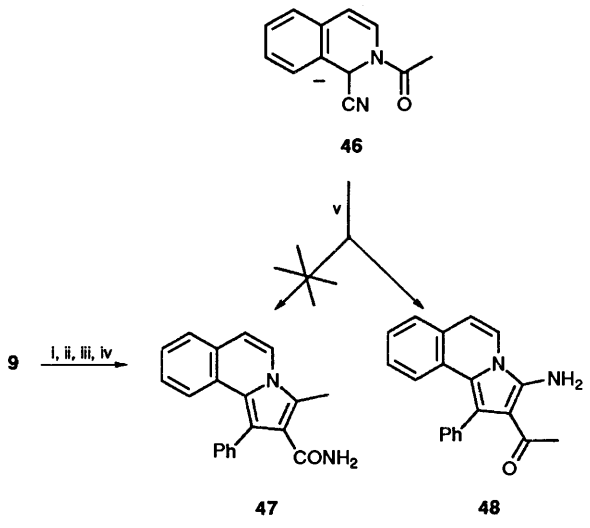


	R	X	R'
52	Me	F	CO–N⟨O⟩
53	Pr^i	H	CO–N⟨NMe⟩



Scheme 7 *Reagents:* i, $(MeO)_2CHCH_2NH_2$; ii, $Me_2CHCOCl$; iii, NaOH; iv, Et_3N/Ac_2O; v, $p\text{-}FC_6H_4C{\equiv}CCO_2Me$; vi, $-CO_2$; vii, $AcOH/H_2SO_4$

* For overviews of the generation, from *N*-acyl-α-amino acids such as **42**, of munchnones such as **43** and their reactions, including 1,3-dipolar cycloadditions to prepare pyrroles such as **45**, see ref. 14.

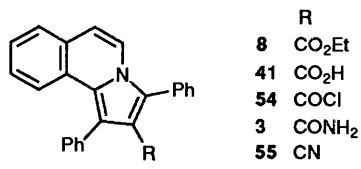


Scheme 8 *Reagents:* i, NaOH/aq. EtOH; ii, HCl; iii, $SOCl_2$; iv, aq. NH_3; v, PhCH=CHCN

the acids (Scheme 8) and converted into a range of primary, secondary and tertiary amides, such as **47**, **49–53**, *via* the acyl chlorides. The acids, and most notably the amides, were all colourless solids—in stark contrast to the highly coloured products that arise from the Reissert-anion synthesis. When the Reissert-anion Michael addition was applied to the synthesis of **47**, by treating the anion from 2-acetyl-1-cyano-1,2-dihydroisoquinoline **46** with cinnamonitrile, we failed to observe **47** and obtained instead a yellow solid **48** (Scheme 8), that melted 43 °C higher than **47**. The IR spectrum of compound **48** contained bands at 3386, 3277, 1649 and 1608 cm^{-1}, consistent with an *ortho*-substituted amino aryl ketone—a vinylogous amide! The ^1H NMR spectra of **48** in $CDCl_3$ and in $(CD_3)_2SO$ solutions were markedly different. The $(CD_3)_2SO$ solution showed a sharp singlet at δ 1.67 for the acetyl methyl and a series of well resolved signals which could be assigned by 2-D NMR as 6-H (d, δ 6.72), 10-H (d, δ 6.83), 9-H (t of d, δ 6.97), 8-H (t of d, δ 7.14) and 5-H (d, δ 7.83). The amino group appeared as a well defined singlet at δ 7.23. The deuteriochloroform spectrum exhibited a sharp singlet at δ 1.82 for the acetyl methyl and a clear doublet (δ 6.65; J 8 Hz) for 6-H. The remainder of the aromatic protons resonated as complex multiplets around δ 7.02 and 7.5. In contrast, the spectrum of the amide **47** in deuteriochloroform contained a singlet at δ 2.85 for the 3-methyl and two broad singlets at δ 5.70 and 5.85 ($CONH_2$). The aromatic hydrogens were located at δ 6.83 (d, 6-H), 7.08 (t of d, 9-H), 7.16 (d, 10-H), 7.25 (t of d, 8-H) and 7.68 (d, 5-H) with the remainder as a multiplet at δ 7.5. The assigned structure of **48** follows from the comparable method of synthesis and spectral similarities with those of **57** (see below).

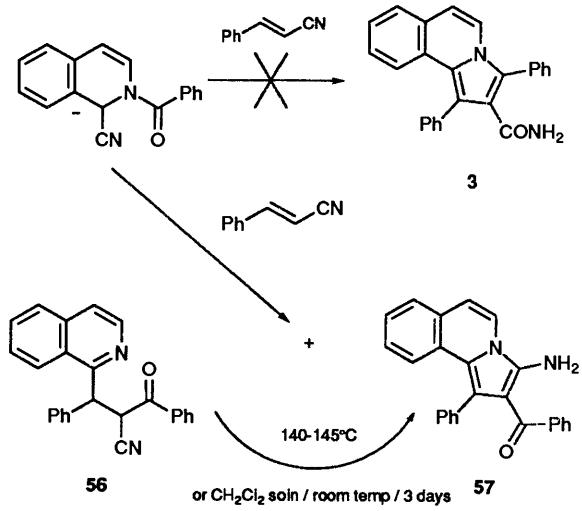
In order to clarify the course of the Reissert-anion Michael addition, we undertook the synthesis of 1,3-diphenylpyrrolo-[2,1-*a*]isoquinoline-2-carboxamide **3**. This was achieved using a Reissert cycloaddition to make the ester **8** as it was expected that the direction of ring closure of an *N*-(2,2-dimethoxyethyl)-2,4,5-triphenylpyrrole-3-carboxylate, using the pyrrole–isoquinoline methodology, could not be controlled and would lead to a mixture of the two possible isomers. Ester **8** was hydrolysed to the acid **41** and converted into the acid chloride **54**, which was treated with aqueous ammonia to afford the primary amide **3** as colourless crystals (m.p. 136 °C). Dehydration of the amide **3** provided the corresponding nitrile **55**, the putative intermediate in the Reissert-anion reaction, which was readily isolated. The ester **8** and the acid **41** corresponded with those described by McEwen *et al.*[4,5]

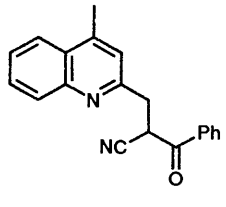
Using the described Reissert-anion method[4,5] (Scheme 9),



we obtained a bright orange compound (**A**; m.p. 223–225 °C) purported to be **3**, although in lower yield, together with a second, colourless compound **B**. Attempts to determine the melting point of **B** resulted in a thermal transformation at 140–145 °C to an orange solid which then melted at 230–232 °C. Further, a colourless dichloromethane solution of **B** (which immediately became bright orange when applied to a silica TLC plate and co-eluted with **A**) turned orange with time and resembled a solution of **A**. The IR spectrum of **B** exhibited C≡N stretching at 2246 cm^{-1} and C=O at 1692 cm^{-1} and the ^1H NMR spectrum accorded with the β-keto nitrile structure **56**. An analogue of **56**, the quinoline **58**, has been described from the reaction of the anion of 1-benzoyl-2-cyano-4-methyl-1,2-dihydroquinoline with acrylonitrile.[6] The ^1H NMR spectrum of **56** changed with time to become identical with that of compound **A**. This conversion, which could be clearly observed in a dichloromethane solution after 6 h and was complete within 3 days, was accelerated by the addition of an acid catalyst. In $(CD_3)_2SO$ isomerisation was more rapid: this isomerisation of compound **56** into **A** clearly occurs very readily and does not favour a primary amide structure for **A**.

The bright orange compound **A** was clearly different by TLC and colour to **3**. The ^1H NMR spectrum of **3** in $CDCl_3$ solution contained a broad singlet at δ 5.19 ($CONH_2$) and signals at δ 6.71 (d, 6-H), 7.13 (t of d, 9-H), 7.28 (t of d, 8-H), 7.34 (d, 10-H) and 7.64 (d, 5-H), whereas the spectrum of **A** in $CDCl_3$ solution exhibited a broad singlet at δ 5.75 (2 H), a doublet at δ 6.65 (1 H), and a series of multiplets between δ 6.95 and 7.4. As observed in the case of compound **48**, the spectrum of **A** was clearer in $(CD_3)_2SO$ and included doublets at δ 6.78 and





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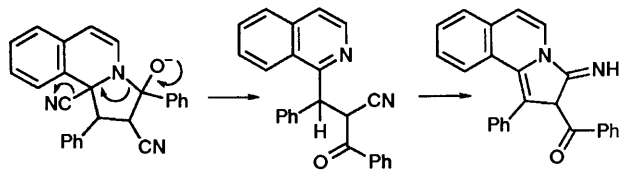
Scheme 9



59 56 57

Scheme 10

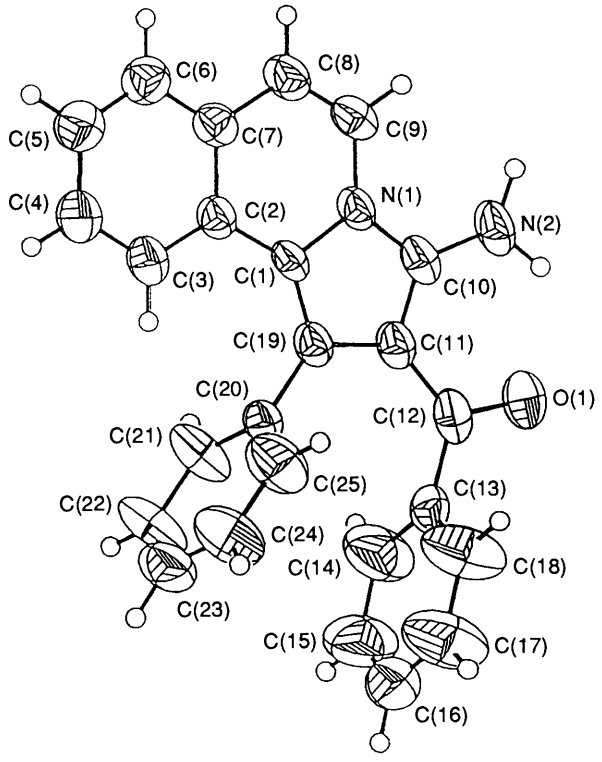
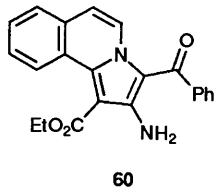


Fig. 1 ORTEP representation of 3-amino-2-benzoyl-1-phenylpyrrolo[2,1-*a*]isoquinoline **57**. Hydrogen atom labels follow the numbering scheme of the attached carbon atom and were omitted for clarity.

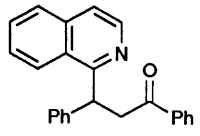
7.91, a broad singlet (2 H) at δ 7.21 and a double doublet at δ 7.45, with the remainder of the resonances as a complex multiplet between δ 6.94 and 7.18.

X-Ray crystallography established the structure of **A** to be the vinylogous amide **57** (Fig. 1). Formation of **57** can be rationalised, as indicated in Scheme 10, by initial addition to generate the dicyano alkoxide **59**. Ring-opening by elimination of cyanide to form **56**, recyclisation to the imine, and tautomerism of the imine provides the amine **57**. The similarity in IR and ^{1}H NMR spectra has led us to assign structure **48** to the acetyl analogue. A related 2-amino-3-benzoylpyrrolo[2,1-*a*]-isoquinoline **60** has been described.[15]

The colourless ketonitrile **56** when heated in phosphoric acid produced 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline **6**. The reaction initially gave an orange solution which paled with time: this colour probably indicates an initial facile cyclisation to give **57**, followed by slow hydrolysis and ring-opening to form the β-keto amide. Subsequent amide hydrolysis and decarboxylation of the resultant β-keto acid would produce 2-(isoquinolin-1-yl)-2-phenylethyl phenyl ketone **61**, the product isolated from hydrochloric acid hydrolysis of **57**.[4] Phosphoric acid cyclodehydrates **61**[4] to generate the observed 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline **6** which is also produced directly when



60



61

phosphoric acid is used to hydrolyse **57**.[4] Treatment of the 2-carboxamide **3** with phosphoric acid under conditions identical with those used with the keto nitrile **56** gave the decarboxylated product **6** in slightly reduced yield, and constitutes the decarboxylation reaction that MeEwen *et al.* believed to be taking place with **57**.[4] Phosphoric acid decarboxylation of pyrrolo[2,1-*a*]isoquinoline-2-carboxylic acids was found to be the most convenient route to pyrrolo[2,1-*a*]isoquinolines unsubstituted at position 2.

In this communication, we have demonstrated the utility of the 2-phenyl-1-(2,2-dimethoxyethyl)pyrrole route to pyrrolo-[2,1-*a*]isoquinolines and have also established that contrary to the claim[4] that the Reissert-anion Michael addition to α,β-unsaturated nitriles provides an 'unambiguous method' of preparing pyrrolo[2,1-*a*]isoquinoline-2-carboxamides and hence pyrrolo[2,1-*a*]isoquinolines, in reality this reaction yields 2-acyl-3-aminopyrrolo[2,1-*a*]isoquinolines. The reported preparations of analogous primary amides by Reissert-anion methodology[6–9] may bear reinterpretation as the corresponding acylamines.

Experimental

Solutions were dried over magnesium sulfate unless otherwise indicated. M.p.s were determined on an electrothermal melting-point apparatus and are uncorrected. IR spectra were recorded in potassium bromide on a Nicolet 20SXB spectrometer. ^{1}H NMR spectra were recorded on a Varian XL 200 or Varian VXR 400 spectrometer in deuteriochloroform (unless otherwise specified) with tetramethylsilane as the internal standard; *J*-values are recorded in Hz. Microanalyses were performed on a Carlo-Erba 1106 microanalyser.

Reissert Synthesis of Pyrrolo[2,1-a]*isoquinolines*

Methyl 1-(4-*Fluorophenyl*)-3-*isopropylpyrrolo*[2,1-a]*isoquinoline-2-carboxylate* **10**.—A mixture of 1-amino-3-isopropyloxazolo[4,3-*a*]isoquinolinium tetrafluoroborate[4] (9.5 g, 30.3 mmol) and methyl (4-fluorophenyl)propiolate (7.2 g, 40 mmol) in 1,3-dimethylimidazolidin-2-one (120 cm^3) was stirred until homogeneous and then left at room temperature for 24 h. The solution was then poured into water (200 cm^3) and the mixture extracted with diethyl ether (4 × 150 cm^3). The combined extracts were dried and evaporated under reduced pressure to leave an oil, chromatography of which on silica gel, eluting with diethyl ether–light petroleum (b.p. 40–60 °C) (1:19, v/v) provided the *title compound* **10** (1.32 g, 12%) as a colourless solid, m.p. 170–172 °C (Found: C, 76.5; H, 5.7; N, 3.9. $C_{23}H_{20}FNO_2$ requires C, 76.4; H, 5.6; N, 3.9%); ν_{max}/cm^{-1} 1699, 1223 and 1151; δ 1.51 [6 H, d, *J* 7, $CH(CH_3)_2$], 3.58 (3 H, s, OCH_3), 4.11 [1 H, septet, *J* 7, $CH(CH_3)_2$], 6.76 (1 H, d, *J* 8, 6-H), 7.03–7.52 (8 H, m, aryl-H) and 7.84 (1 H, d, *J* 8, 5-H). Similarly, the following compounds were made.

Ethyl 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate **8** (25%) as a colourless solid, m.p. 102–104 °C (lit.,[4] m.p. 101–102 °C); δ 0.78 (3 H, t, *J* 7, ester CH_3), 3.92 (2 H, q, *J* 7, ester CH_2), 6.69 (1 H, d, *J* 7, 6-H), 7.10–7.55 (14 H, m, aryl-H) and 7.58 (1 H, d, *J* 7, 5-H).

Ethyl 3-methyl-1-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate **9** (47%), m.p. 117–120 °C (see below).

Methyl 1-(4-fluorophenyl)-3-phenylpyrrolo[2,1-a]*isoquinoline-2-carboxylate* **11** (30%), m.p. 140–142 °C (Found: C, 79.0; H, 4.6; F, 4.7; N, 3.5. $C_{26}H_{18}FNO_2$ requires C, 79.0; H, 4.6; F, 4.8; N, 3.5%); ν_{max}/cm^{-1} 1713, 1703, 1154 and 1150; δ 3.44 (3 H, s, OCH_3), 6.70 (1 H, d, *J* 7, 6-H) and 7.1–7.6 (14 H, m, aryl-H).

Ethyl 3-ethyl-1-phenylpyrrolo[2,1-a]*isoquinoline-2-carboxylate* **12** (44%), m.p. 123–125 °C (Found: C, 80.85; H, 6.2; N, 4.2. $C_{23}H_{21}NO_2$ requires C, 80.45; H, 6.2; N, 4.1%); ν_{max}/cm^{-1} 1694, 1165 and 1156; δ 0.95 (3 H, t, *J* 7, ester CH_3), 1.33 (3 H, t, *J* 8, CH_2CH_3), 3.31 (2 H, q, *J* 8, CH_2CH_3), 4.06 (2 H, q, *J* 7, ester CH_2), 6.80 (1 H, d, *J* 7, 6-H), 7.05–7.50 (9 H, m, aryl-H) and 7.69 (1 H, d, *J* 7, 5-H).

Benzoin Route

N,1-*Bis*(2,2-*dimethoxyethyl*)-2-*methyl*-4,5-*diphenylpyrrole*-3-*carboxamide* **19**.—A solution of aminoacetaldehyde dimethyl acetal (10.5 g, 0.1 mol) and ethyl acetoacetate (13.0 g, 0.1 mol) in toluene (200 cm^3) was stirred at reflux, with azeotropic removal of water, for 4 h. When cool, the solution was evaporated under reduced pressure to leave a yellow oil (19.64 g). A solution of this oil (19.64 g), benzoin (19.19 g, 92.6 mmol) and zinc chloride (26.0 g, 0.191 mol) in ethanol (250 cm^3) was heated at reflux for 2 days, and then evaporated under reduced pressure to a volume of *ca.* 100 cm^3; it was then poured into water (600 cm^3). The solid produced was collected and dissolved in hot isopropyl alcohol. On cooling, the crystallised benzoin was filtered off and the filtrate was evaporated under reduced pressure to leave an oil. This oil was chromatographed on silica gel, eluting first with dichloromethane, and then with a mixture of dichloromethane and methanol (99:1, v/v) to yield *ethyl* 1-(2,2-*dimethoxyethyl*)-2-*methyl*-4,5-*diphenylpyrrole*-3-*carboxylate* **13** [(3.0 g, 7%) see below], and finally with a mixture of dichloromethane and methanol (19:1 v/v) to give the *title compound* **19** (15.5 g, 71% from aminoacetaldehyde dimethyl acetal) as an orange oil (Found: C, 68.8; H, 6.8; N, 6.5. $C_{26}H_{32}N_2O_5$ requires C, 69.0; H, 7.1; N, 6.2%); ν_{max}(neat)/cm^{-1} 1645, 1535 and 1129; δ 2.66 (3 H, s, 2-CH_3), 3.13 (6 H, s, 2 × OCH_3), 3.16 (6 H, s, 2 × OCH_3), 3.33 (2 H, t, *J* 6, $CONHCH_2$), 3.97 (2 H, d, *J* 6, 1-CH_2), 4.16 (2 H, t, *J* 6, 2 × $CHCH_2$), 5.35 (1 H, br t, NH) and 7.1–7.3 (10 H, m, 2 × Ph).

Ethyl 1-(2,2-*dimethoxyethyl*)-2-*methyl*-4,5-*diphenylpyrrole*-3-*carboxylate* **13**.—A solution of methyl acetoacetate (11.6 g, 0.1 mol) and aminoacetaldehyde dimethyl acetal (10.5 g, 0.1 mol) in ethanol (300 cm^3) was refluxed for 16 h with removal of water using a Soxhlet extractor filled with molecular sieves. The solution, evaporated under reduced pressure, provided methyl 3-(2,2-dimethoxyethylamino)crotonate (19.6 g, 96%); δ 1.96 (3 H, s, allyl-CH_3), 3.36 (2 H, m, $NHCH_2$), 3.45 (6 H, s, 2 × OCH_3), 3.65 (3 H, s, ester CH_3), 4.43 (1 H, t, *J* 5, $CHCH_2$), 4.52 (1 H, s, olefinic CH) and 8.63 (1 H, br s, NH).

The oil (19.5 g, 96 mmol), benzoin (18.4 g, 87 mmol) and zinc chloride (27.2 g, 0.2 mol) were heated in ethanol (300 cm^3) at reflux for 40 h and then evaporated under reduced pressure. The residue was taken up in dichloromethane, dried and evaporated under reduced pressure to leave a brown oil which slowly solidified. Recrystallisation of this from methanol provided the *title compound* **13** (17.5 g, 51%) as a white solid, m.p. 117–121 °C (Found: C, 73.3; H, 6.9; N, 3.5. $C_{24}H_{27}NO_4$ requires C, 73.3; H, 6.9; N, 3.6%); ν_{max}/cm^{-1} 1685, 1173, 1153 and 1133; δ 1.00 (3 H, t, *J* 7, ester CH_3), 2.66 (3 H, s, 2-CH_3), 3.13 (6 H, s, 2 × OCH_3), 3.94–4.16 (5 H, m, ester CH_2, $CHCH_2$ and NCH_2) and 7.05–7.35 (10 H, m, 2 × Ph).

Cyclisation in Sulfuric Acid

Ethyl 3-Methyl-1-phenylpyrrolo[2,1-a]*isoquinoline-2-carboxylate* **9**.—The carboxylate **13** (15.30 g, 39 mmol) in acetic acid (75 cm^3) was added dropwise to stirred, ice-cooled sulfuric acid (96%; 75 cm^3) at a rate that kept the temperature < 40 °C. After a further 15 min, the solution was carefully poured onto ice and adjusted to pH 6; the mixture was extracted with dichloromethane and the extract washed with water, dried and evaporated under reduced pressure to leave a solid which was crystallised from methanol to give the *title compound* **9** (9.44 g, 74%), m.p. 118–120 °C (Found: C, 79.9; H, 5.7; N, 4.3. $C_{22}H_{19}NO_2$ requires C, 80.2; H, 5.8; N, 4.25%); ν_{max}/cm^{-1} 1690, 1165, 1155 and 1127; δ 0.94 (3 H, t, *J* 7, ester CH_3), 2.80 (3 H, s, 2-CH_3), 4.06 (2 H, q, *J* 7, ester CH_2), 6.82 (1 H, d, *J* 7, 6-H), 7.04–7.52 (9 H, m, aryl-H) and 7.64 (1 H, d, *J* 7, 5-H).

2-(4-*Fluorophenyl*)-2-*hydroxyacetophenone* **14**.—Freshly distilled phenylglyoxal (18.3 g, 136 mmol) (obtained from the hydrate by azeotropic drying with toluene) in fluorobenzene (75 cm^3) was added over 60 min to a stirred suspension of aluminium chloride (38.5 g, 289 mmol) in fluorobenzene (145 cm^3) at 0 °C. After being stirred at 0 °C for 18 h, the dark green suspension was slowly treated with hydrochloric acid (40 cm^3) in water (175 cm^3) the temperature being kept < 30 °C. The aqueous fraction was extracted with diethyl ether (3 × 150 cm^3) and the combined extracts were washed with brine (500 cm^3), dried and evaporated under reduced pressure to leave a yellow oil. This crystallised from hexane containing a little ethanol to yield the *title compound* **14** (18.1 g, 58%) as a pale yellow powder, m.p. 86–89 °C (Found: C, 72.9; H, 4.8; F, 8.2. $C_{14}H_{11}FO_2$ requires C, 73.0; H, 4.8; F, 8.25%); ν_{max}/cm^{-1} 3415 and 1676; δ 4.55 (1 H, d, *J* 6, exch. D_2O, OH), 5.94 (1 H, d, *J* 6, s on D_2O shake, 2-H), 7.01 (2 H, t, *J* 7, 3′-H and 5′-H), 7.2–7.6 (5 H, m, aryl-H) and 7.89 (2 H, dd, *J* 8 and 2, 2-H and 6-H).

Benzoin Route without Isolation of Intermediates

Ethyl 1-Phenyl-3-propylpyrrolo[2,1-a]*isoquinoline-2-carboxylate* **15**.—A mixture of ethyl 3-oxohexanoate (15.84 g, 0.01 mol), aminoacetaldehyde dimethyl acetal (10.52 g, 0.1 mol), benzoin (21.22 g, 0.1 mol) and zinc chloride (29.7 g, 0.218 mol) was stirred in refluxing ethanol (300 cm^3) for 54 h. The cooled mixture was poured into water and extracted with diethyl ether (3 × 300 cm^3). The combined extracts were washed with brine (2 × 500 cm^3), dried and evaporated under reduced pressure to leave a mobile, orange oil (34.0 g). A solution of this (34.0 g) in acetic acid (50 cm^3) was added over 15 min to ice-cooled, stirred sulfuric acid (96%; 150 cm^3), the temperature being kept < 30 °C. After being stirred for a further 15 min, the brown solution was poured onto crushed ice and extracted with dichloromethane (4 × 250 cm^3). The combined extracts were washed with brine (2 × 800 cm^3), dried and evaporated under reduced pressure to leave a dark red oil (26.25 g). Chromatography of this on silica gel, eluting with dichloromethane, and crystallisation of the resulting product from methanol gave needles of the *title compound* **15** (14.29 g, 40%), m.p. 89–91 °C (Found: C, 80.9; H, 6.5; N, 3.8. $C_{24}H_{23}NO_2$ requires C, 80.6; H, 6.5; N, 3.9%); ν_{max}/cm^{-1} 1696, 1165 and 1153; δ 0.96 (3 H, t, *J* 7, ester CH_3), 1.07 (3 H, t, *J* 7, propyl CH_3), 1.77 (2 H, sextet, *J* 7, $CH_2CH_2CH_3$), 3.28 (2 H, t, *J* 7, $CH_2CH_2CH_3$), 4.07 (2 H, q, *J* 7, ester CH_2), 6.79 (1 H, d, *J* 6, 6-H), 7.02–7.55 (9 H, m, aryl-H)

and 7.69 (1 H, d, *J* 6, 5-H). Similarly, the following compounds were made (overall yield).

Ethyl 3-methyl-1-phenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate **9** (51%), m.p. 119–121 °C (see above).

Ethyl 8-fluoro-1-(4-fluorophenyl)-3-methylpyrrolo[2,1-a]*isoquinoline-2-carboxylate* **16** (30%), m.p. 143–146 °C (Found: C, 72.3; H, 4.7; F, 10.3; N, 4.1. $C_{22}H_{17}F_2NO_2$ requires C, 72.3; H, 4.7; F, 10.4; N, 3.8%); ν_{max}/cm^{-1} 1706, 1220 and 1149; δ 1.00 (3 H, t, *J* 7, ester CH_3), 2.79 (3 H, s, 3-CH_3), 4.08 (2 H, q, *J* 7, ester CH_2), 6.76 (1 H, d, *J* 8, 6-H), 6.85 (1 H, t of d, *J* 9 and 2, 9-H), 7.1–7.4 (6 H, m, aryl-H) and 7.67 (1 H, d, *J* 8, 5-H).

Ethyl 3-ethyl-8-fluoro-1-(4-fluorophenyl)pyrrolo[2,1-a]*isoquinoline-2-carboxylate* **17** (17%), m.p. 115–118 °C (Found: C, 71.9; H, 4.9; F, 10.1; N, 3.75. $C_{23}H_{19}F_2NO_2$ requires C, 72.8; H, 5.05; F, 10.0; N, 3.7%); ν_{max}/cm^{-1} 1701, 1221 and 1149; δ 1.02 (3 H, t, *J* 7, ester CH_3), 1.32 (3 H, t, *J* 7, 3-CH_2CH_3), 3.30 (2 H, q, *J* 7, 3-CH_2CH_3), 4.08 (2 H, q, *J* 7, ester CH_2), 6.74 (1 H, d, *J* 8, 6-H), 6.83 (1 H, t of d, *J* 9 and 2, 9-H), 7.1–7.4 (6 H, m, aryl-H) and 7.70 (1 H, d, *J* 8, 5-H).

Ethyl 8-fluoro-1-(4-fluorophenyl)-3-propylpyrrolo[2,1-a]*isoquinoline-2-carboxylate* **18** (12%), m.p. 118–120 °C (Found: C, 73.1; H, 5.3; N, 3.6. $C_{24}H_{21}F_2NO_2$ requires C, 73.3; H, 5.4; N, 3.6%); ν_{max}/cm^{-1} 1689, 1220 and 1149; δ 0.92–1.12 (6 H, m, 2 × CH_3), 1.72 (2 H, sextet, *J* 7, 3-$CH_2CH_2CH_3$), 3.24 (2 H, q, *J* 7, 3-$CH_2CH_2CH_3$), 4.06 (2 H, q, *J* 7, ester CH_2), 6.73 (1 H, d, *J* 8, 6-H), 6.84 (1 H, t, of d, *J* 9 and 2, 9-H), 7.1–7.4 (6 H, m, aryl-H) and 7.71 (1 H, d, *J* 8, 5-H).

Pyrrole Alkylation

Ethyl and Methyl-2-methyl-4,5-diphenyl-pyrrole-3-carboxylates **20**.—A mixture of benzoin (21.2 g, 0.1 mol), methyl 3-aminocrotonate (11.5 g, 0.1 mol) and zinc chloride (33.6 g, 0.25 mol) in ethanol (150 cm^3) was stirred at reflux for 8 h. When cool, the mixture was poured into water (1500 cm^3) to give a pink solid product. This was collected, suspended in hot ethanol (600 cm^3) and sufficient DMF was added to give a solution. The solution was immediately poured into water (1500 cm^3) and the precipitated solid was collected, dried by suction and crystallised from ethanol to give a mixture of the title compounds **20** (8.45 g, *ca.* 6:1, 28%) as white needles, m.p. 198–200 °C [Found: C, 78.1; H, 6.3; N, 4.3. $C_{20}H_{19}NO_2$ (ethyl ester) requires C, 78.8; H, 6.2; N, 4.6%]; ν_{max}/cm^{-1} 3311, 1678, 1189, 1103, 766 and 697; δ 1.04 (3 H, t, *J* 7, CH_2CH_3), 2.58 (3 H, s, 2-CH_3), 3.60 (3 H, s, CO_2CH_3), 4.16 (2 H, q, *J* 7, CH_2CH_3), 7.1–7.3 (10 H, m, 2 × Ph) and 10.32 (1 H, br s, NH).

Alkylation of Compound **20** *and Cyclisation to Compound* **9**.—2,2-Dimethoxyethyl bromide (1.0 g, 6 mmol) was added to a solution of compound **20** (1.0 g, 3.3 mmol) and potassium *tert*-butoxide (0.65 g, 5.8 mmol) in 1,3-dimethylimidazolidin-2-one (10 cm^3) and THF (5 cm^3). The mixture was heated on a steam-bath for 22 h and then poured into water and the mixture adjusted to pH 1 with hydrochloric acid (2 mol dm^{-3}). The product was extracted into diethyl ether (3 × 150 cm^3) and the combined extracts were washed with brine (200 cm^3), dried and evaporated under reduced pressure. The residue was dissolved in sulfuric acid (96%; 15 cm^3) and the solution kept for 1 h. It was then poured into water (300 cm^3) and extracted with diethyl ether (3 × 80 cm^3). The combined extracts were dried and evaporated under reduced pressure to leave an oil which was chromatographed on silica gel, eluting with dichloromethane, to give compound **9** (260 mg, 24%), m.p. 118–120 °C.

Methyl 2-Ethyl-4-(4-fluorophenyl)-5-phenylpyrrole-3-carboxylate **21**.—A solution of ammonium formate (3.5 g, 56 mmol) and methyl 3-benzoyl-3-(4-fluorophenyl)-2-propionylpropionate **27** (1.7 g, 49.7 mmol) in acetic acid (20 cm^3) was heated at reflux for 2 h and then cooled and poured into water. The precipitated product was taken up into dichloromethane (100 cm^3) and the solution washed with brine, dried and evaporated under reduced pressure to leave a pale brown solid. Recyrstallisation of this from diethyl ether–hexane provided the *title compound* **21** (0.86 g, 54%) as colourless needles, m.p. 136–138 °C (Found: C, 74.1; H, 5.55; N, 4.2. $C_{20}H_{18}FNO_2$ requires C, 74.3; H, 5.6; N, 4.3%); ν_{max}/cm^{-1} 3291, 1675, 1189, 1103, 841, 764 and 693; δ 1.35 (3 H, t, *J* 7, CH_2CH_3), 3.07 (2 H, q, *J* 7, CH_2CH_3), 3.60 (3 H, s, CO_2CH_3), 6.8–7.4 (9 H, m, aryl-H) and 8.35 (1 H, br s, NH).

1,4-Diketone Route

Ethyl 3-(4-Fluorophenyl)-2-(2-methylpropionyl)propenoate **25**.—A mixture of 4-fluorobenzaldehyde (33.4 g, 0.27 mol), ethyl isobutyrylacetate (43.3 g, 0.27 mol), piperidine (4 cm^3) and acetic acid (10 cm^3) in toluene (100 cm^3) was stirred at reflux with azeotropic removal of water for 8 h. The cooled mixture was diluted with diethyl ether, dried and evaporated under reduced pressure. The residual oil was distilled at 130–135 °C/0.2 mmHg to give the *title compound* **25** (53.8 g, 75%) as a 1:1 mixture of *E* and *Z* isomers (Found: C, 68.5; H, 6.7; F, 6.9. $C_{15}H_{17}FO_3$ requires C, 68.2; H, 6.5; F, 7.2%); ν_{max}(neat)/cm^{-1} 1722, 1699, 1672, 1252, 1239, 1229 and 837; δ 1.08 and 1.19 [6 H, 2 × d, *J* 6, $CH(CH_3)_2$], 1.30 (3 H, m, *J* 7, ester CH_3), 2.72 and 3.18 [1 H, 2 × septet, *J* 6, $CH(CH_3)_2$], 4.30 (2 H, m, *J* 7, ester CH_2), 7.00–7.20 (2 H, m, aryl-H), 7.35–7.50 (2 H, m, aryl-H) and 7.56 and 7.73 (1 H, 2 × s, 3-H).

Ethyl 2-acetyl-3-(4-fluorophenyl)propenoate **23** (62%) as a 2:1 mixture of *E* and *Z* isomers, b.p. 125–130 °C/0.2 mmHg (Found: C, 65.5; H, 5.5; F, 7.7. $C_{13}H_{13}FO_3$ requires C, 66.1; H, 5.55; F, 8.0%); δ 1.12 (3 H, m, ester CH_3), 2.37 and 2.42 (3 H, 2 × s, $COCH_3$), 4.33 (2 H, m, ester CH_2), 7.0–7.15 and 7.35–7.68 (5 H, m, aryl-H and 3-H).

Methyl 3-(4-fluorophenyl)-2-propionylpropenoate **24** (73%) as a 1:1 mixture of *E* and *Z* isomers, b.p. 108–112 °C/0.2–0.4 mmHg (Found: C, 65.9; H, 5.6; F, 8.05. $C_{13}H_{13}FO_3$ requires C, 66.1; H, 5.55; F, 8.0%); ν_{max}(neat)/cm^{-1} 1727, 1706, 1672, 1263, 1233, 1231 and 837; δ 1.14 (3 H, m, CH_2CH_3), 2.58 and 2.76 (2 H, 2 × q, *J* 7, CH_2CH_3), 3.83 and 3.85 (3 H, 2 × s, CO_2CH_3), 7.00–7.15 and 7.30–7.50 (4 H, m, aryl-H) and 7.57 and 7.66 (1 H, 2 × s, 3-H).

Ethyl 3-benzoyl-3-(4-fluorophenyl)-2-(2-methylpropionyl)-propionate **28**.—A mixture of the propenoate **25** (5.50 g, 20.8 mmol), benzaldehyde (2.29 g, 21.6 mmol), triethylamine (2.28 g, 22.6 mmol) and 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide (0.98 g, 3.44 mmol) in ethanol (20 cm^3) was heated at reflux under nitrogen for 20 h. When cool, the mixture was diluted with dichloromethane (120 cm^3) and washed sequentially with hydrochloric acid (0.4 mol dm^{-3}; 100 cm^3), aqueous sodium hydrogen carbonate and brine, dried and evaporated under reduced pressure to leave a brown oil. This was chromatographed on silica gel, eluting with dichloromethane, to give a 1:1 mixture of diastereoisomers of the *title compound* **28** (5.61 g, 73%) as a colourless oil (Found: C, 71.3; H, 6.5; F, 5.3. $C_{22}H_{23}FO_4$ requires C, 71.3; H, 6.3; F, 5.1%); ν_{max}(neat)/cm^{-1} 1741, 1714, 1681, 1285 and 1227; δ 0.58 (d, *J* 7) and 0.96–1.30 (9 H, m, 3 × CH_3), 2.42 and 2.89 [1 H, 2 × septet, *J* 7, $CH(CH_3)_2$], 3.97 (q, *J* 7) and 4.00–4.20 (2 H, m, CH_2CH_3), 4.70 (1 H, 2 × d, *J* 11, 2-H), 5.39 (1 H, 2 × d, *J* 11, 3-H), 6.95 (2 H, t, *J* 9, aryl-H), 7.20–7.60 (5 H, m, aryl-H) and 7.93 (2 H, m, aryl-H).

Ethyl 2-acetyl-3-benzoyl-3-(4-fluorophenyl)propanoate **26** (73%) as an oil (*ca.* 2:1 mix of diastereoisomers); δ 1.07 and 1.20 (3 H, 2 × t, *J* 7, CH_2CH_3), 2.03 and 2.46 (3 H, 2 × s, $COCH_3$), 3.92–4.24 (2 H, m, CH_2CH_3), 4.59 and 4.65 (1 H, 2 × d, *J* 11, 2-H), 5.39 (1 H, 2 × d, *J* 11, 3-H), 6.95 (2 H, t, *J*

9, aryl-H) and 7.20–7.60 (5 H, m, aryl-H) and 7.95 (2 H, m, aryl-H).

Methyl 3-benzoyl-3-(4-fluorophenyl)-2-propionylpropanoate **27** (28%) as a white solid (*ca.* 1:1 mix of diastereoisomers), m.p. 104–109 °C (Found: C, 70.1; H, 5.4; F, 5.5. $C_{20}H_{19}FO_4$ requires C, 70.2; H, 5.6; F, 5.55%); ν_{max}/cm^{-1} 1749, 1738, 1716, 1708, 1679, 1225 and 1164; δ 0.91 and 1.08 (3 H, 2 × t, *J* 7, CH_2CH_3), 1.80–2.05 and 2.46–2.80 (2 H, 2 × m, CH_2CH_3), 3.54 and 3.68 (3 H, 2 × s, CO_2CH_3), 4.60 (1 H, 2 × d, *J* 11, 2-H), 5.39 (1 H, 2 × d, *J* 11, 3-H), 6.96 (2 H, t, *J* 9), 7.20–7.55 (5 H, m, aryl-H) and 7.95 (2 H, m, aryl-H).

Ethyl 3-Methyl-1-(4-fluorophenyl)pyrrolo[2,1-a]*isoquinoline-2-carboxylate* **29**.—A solution of the propionate **26** (18.1 g, 52.9 mmol) and aminoacetaldehyde dimethyl acetal (5.52 g, 52.6 mmol) in acetic acid (200 cm^3) was stirred at reflux under nitrogen for 18 h. When cool, the solution was added dropwise to stirred sulfuric acid (96%; 88 cm^3), the temperature being kept < 20 °C. The mixture was then stirred for 1 h and poured onto crushed ice (400 g). The precipitate was collected, washed with saturated aqueous sodium hydrogen carbonate and water and then dried and chromatographed on silica gel, eluting with dichloromethane, to give the *title compound* **29** (8.4 g, 46%) as a white solid, m.p. 134–135 °C (Found: C, 76.3; H, 5.25; N, 3.8. $C_{22}H_{18}FNO_2$ requires C, 76.1; H, 5.2; N, 4.0%); ν_{max}/cm^{-1} 1703, 1227 and 1152; δ 1.01 (3 H, t, *J* 7, CH_2CH_3), 2.82 (3 H, s, 3-CH_3), 4.09 (2 H, q, *J* 7, CH_2CH_3), 6.84 (1 H, d, *J* 8, 6-H), 7.1–7.5 (6 H, m, aryl-H) and 7.66 (1 H, d, *J* 8, 5-H).

Ethyl 4-(4-Fluorophenyl)-2-isopropyl-5-phenylfuran-3-carboxylate **32**.—Sulfuric acid (96%; 1.5 cm^3) was added to a solution of the propionate **28** (0.5 g, 1.35 mmol) in acetic acid (5 cm). After 10 min the solution was poured into water (150 cm^3) and extracted with dichloromethane (100 cm^3). The extract was washed with brine, dried and evaporated under reduced pressure to leave an oil, crystallisation of which from methanol provided the *title compound* **32** (90 mg, 19%) as colourless needles, m.p. 65–67 °C (Found: C, 74.6; H, 6.0; F, 5.4. $C_{22}H_{21}FO_3$ requires C, 75.0; H, 6.0; F, 5.4%); ν_{max}/cm^{-1} 1702, 1234, 1217, 1152 and 851; δ 1.06 (3 H, t, *J* , CH_2CH_3), 1.39 [6 H, d, *J* 8, $CH(CH_3)_2$], 3.80 [1 H, septet, *J* 8, $CH(CH_3)_2$], 4.09 (2 H, q, *J* 7, CH_2CH_3), 7.07 (2 H, t, *J* 7, aryl-H) and 7.14–7.36 (7 H, m, aryl-H).

2-(4-*Fluorophenyl*)-5-*methyl*-1-*phenylhexane*-1,4-*dione* **33**.—A mixture of 1-(4-fluorophenyl)-4-methylpent-1-en-3-one (8.2 g, 42.7 mmol), benzaldehyde (8.6 g, 81 mmol), triethylamine (4.5 g, 44.6 mmol) and 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide (1.99 g, 7 mmol) in ethanol (50 cm^3) was heated at reflux under nitrogen for 40 h. When cool, the mixture was diluted with dichloromethane (250 cm^3) and washed sequentially with hydrochloric acid (0.5 mol dm^{-3}; 100 cm^3), aqueous sodium hydrogen carbonate and brine, dried and evaporated under reduced pressure to leave a brown oil. This was chromatographed on silica gel, eluting with hexane–diethyl ether (2:1), to give the *title compound* **33** (1.25 g, 10%) as a colourless oil (Found: C, 76.5; H, 6.7; F, 6.4. $C_{19}H_{19}FO_2$ requires C, 76.5; H, 6.4; F, 6.4%); ν_{max}(neat)/cm^{-1} 1710 and 1682; δ 1.09 [6 H, 2 × d, *J* 6, $CH(CH_3)_2$], 2.63 (1 H, septet, *J* 6, $CH(CH_3)_2$], 2.78 (1 H, dd, *J* 4 and 18, 3-H), 3.59 (1 H, dd, *J* 9 and 18, 3-H), 5.13 (1 H, dd, *J* 4 and 9, 2-H), 6.98 (2 H, t, *J* 9, aryl-H), 7.15–7.60 (5 H, m, aryl-H) and 7.96 (2 H, m, aryl-H).

1,3-*Dipolar Cycloaddition Route*

2-[N-(2,2-*Dimethoxyethyl*)-2-*methylpropionamido*]*phenylacetic Acid* **42**.—A solution of aminoacetaldehyde dimethyl acetal (36.5 g, 0.348 mol) in acetonitrile (80 cm^3) was added over 15 min to a stirred, ice-cooled solution of methyl α-bromophenylacetate (53.8 g, 0.235 mol) and triethylamine (32.8 g, 0.325 mol) in acetonitrile (450 cm^3), the temperature being kept < 45 °C. The resulting white suspension was stirred at room temperature for 2 h and then left for 2 days. It was then diluted with diethyl ether (800 cm^3) and washed with water (3 × 250 cm^3), dried and evaporated under reduced pressure to leave methyl 2-(2,2-dimethoxyethylamino)phenylacetate (55.5 g, 93%) as a colourless oil; ν_{max}(neat)/cm^{-1} 1739 and 1131; δ 2.16 (1 H, br s, NH), 2.61 (1 H, dd, *J* 5 and 12, NHCH*H*), 2.72 (1 H, dd, *J* 5 and 12, NHC*H*H), 3.33 (3 H, s, OCH_3), 3.36 (3 H, s, OCH_3), 3.69 (3 H, s, CO_2CH_3), 4.41 (1 H, s, 2-H), 4.49 [1 H, t, *J* 5, $CH_2CH(OCH_3)_2$] and 7.35 (5 H, m, Ph).

A solution of isobutyryl chloride (26.39 g, 0.248 mol) in dichloromethane (150 cm^3) was added to a solution of the above described ester (55.0 g, 0.217 mol) and triethylamine (26.35 g, 0.26 mol) in dichloromethane (450 cm^3) at a rate that maintained a gentle reflux. The solution was stirred at room temperature for 2 h and then diluted with dichloromethane (200 cm^3) and washed sequentially with water (250 cm^3), hydrochloric acid (0.5 mol dm^{-3}; 300 cm^3), water (250 cm^3), aqueous sodium hydroxide (0.5 mol dm^{-3}; 300 cm^3) and water (250 cm^3). Drying and evaporation under reduced pressure of the solution afforded methyl 2-[(2,2-dimethoxyethyl)-2-methylpropionamido]phenylacetate as an oil; ν_{max}(neat)/cm^{-1} 1747, 1651 and 1126; δ 1.14 [6 H, d, *J* 7, $CH(CH_3)_2$], 3.1–3.3 [1 H, m, $CH(CH_3)_2$], 3.16 (3 H, s, OCH_3), 3.20 (3 H, s, OCH_3), 3.36–3.44 (2 H, m, CH_2CH), 3.54 [1 H, t, *J* 6, $CH_2CH(OCH_3)_2$], 3.75 (3 H, s, CO_2CH_3), 6.07 (1 H, s, 2-H) and 7.22–7.46 (5 H, m, Ph).

This oil was stirred with sodium hydroxide (30 g, 0.75 mol) in a mixture of methanol (800 cm^3) and water (200 cm^3) for 20 h. The solution was evaporated under reduced pressure to *ca.* 500 cm^3 and then diluted with water (500 cm^3) and washed with diethyl ether (2 × 200 cm^3). The aqueous solution was ice-cooled and acidified with hydrochloric acid (4 mol dm^{-3}), the temperature being kept < 10 °C. The precipitated product was extracted into ethyl acetate (3 × 750 cm^3) and the combined extracts were diluted with methanol (250 cm^3), washed with brine (300 cm^3) and evaporated under reduced pressure to leave an off-white solid: crystallisation of this from ethyl acetate (500 cm^3)–ethanol (35 cm^3) gave the *title compound* **42** (48.37 g, 68% overall) as a white solid, m.p. 147–149 °C (Found: C, 62.3; H, 7.6; N, 4.5. $C_{16}H_{23}NO_5$ requires C, 62.1; H, 7.4; N, 4.5%); ν_{max}/cm^{-1} 1752, 1610 and 1080; δ 1.12 [6 H, m, $CH(CH_3)_2$], 3.11 [1 H, m, $CH(CH_3)_2$], 3.21 (3 H, s, OCH_3), 3.25 (3 H, s, OCH_3), 3.3–3.5 (2 H, m, CH_2CH), 3.76 [1 H, t, *J* 6, $CH_2CH(OCH_3)_2$], 5.86 (1 H, s, 2-H), 7.1 (1 H, br s, exch. D_2O, CO_2H) and 7.37 (5 H, m, Ph).

Methyl 1-(4-Fluorophenyl)-3-isopropylpyrrolo[2,1-a]*isoquinoline-2-carboxylate* **10**.—Triethylamine (11.6 g, 0.115 mol) was added to a stirred suspension of compound **42** (32.14 g, 0.104 mol) and methyl (4-fluorophenyl)propiolate (22.5 g, 0.126 mol) in acetic anhydride (120 cm^3). The resulting amber coloured solution was stirred at room temperature, under an atmosphere of argon, for 24 h and then added over 10 min to stirred, ice-cooled sulfuric acid (96%; 200 cm^3), rinsing-in with acetic acid (120 cm^3). After being stirred for 30 min, the viscous solution was poured onto crushed ice and water (2500 cm^3) and extracted with dichloromethane (3 × 400 cm^3). The combined extracts were washed with water (250 cm^3), and brine (250 cm^3), dried and evaporated under reduced pressure to leave a brown solid. This was recrystallised from methanol to give the *title compound* **10** (13.45 g, 36%), m.p. 171–173 °C, identical (TLC and NMR) with samples prepared using the Reissert route (see above).

Pyrrolo[2,1-a]*isoquinoline-2-carboxylic Acids*

1-(4-*Fluorophenyl*)-3-*isopropylpyrrolo*[2,1-a]*isoquinoline-2-carboxylic Acid* **37**.—After the ester **10** had been hydrolysed with sodium hydroxide in refluxing aqueous ethanol, it was then acidified with 1 mol dm^{-3} hydrochloric acid to give the *title compound* **37** (62%), m.p. 234–235 °C (methanol) (Found: C, 76.2; H, 5.2; F, 5.3; N, 3.9. $C_{22}H_{18}FNO_2$ requires C, 76.1; H, 5.2; F, 5.5; N, 4.0%); ν_{max}/cm^{-1} 3200–2400 and 1673; δ 1.50 [6 H, d, *J* 7, $CH(CH_3)_2$], 4.34 [1 H, septet, *J* 7, $CH(CH_3)_2$], 6.76 (1 H, d, *J* 8, 6-H), 7.00–7.50 (8 H, m, aryl-H) and 7.87 (1 H, d, *J* 8, 5-H).

1-(4-*Fluorophenyl*)-3-*phenylpyrrolo*[2,1-a]*isoquinoline-2-carboxylic acid* **38** (87%) as white crystals from aqueous ethanol, m.p. 238–240 °C (Found: C, 79.4; H, 4.7; F, 4.7; N, 3.5. $C_{25}H_{16}FNO_2$ requires C, 78.7; H, 4.2; F, 5.0; N, 3.7%); ν_{max}/cm^{-1} 3200–2400 and 1671; δ 6.68 (1 H, d, *J* 8, 6-H) and 7.06–7.56 (14 H, m, aryl-H).

3-*Methyl*-1-*phenylpyrrolo*[2,1-a]*isoquinoline-2-carboxylic acid* **39** (52%) as white crystals from ethanol, m.p. 242–244 °C (Found: C, 79.6; H, 5.0; N, 4.7. $C_{20}H_{15}NO_2$ requires C, 79.7; H, 5.0; N, 4.65%); ν_{max}/cm^{-1} 3200–2400 and 1670; δ 2.81 (3 H, s, 3-CH_3), 6.83 (1 H, d, *J* 8, 6-H), 7.00–7.56 (9 H, m, aryl-H) and 7.66 (1 H, d, *J* 8, 5-H).

3-*Ethyl*-1-*phenylpyrrolo*[2,1-a]*isoquinoline-2-carboxylic acid* **40** (98%) as a white solid, m.p. 230–232 °C (Found: C, 80.0; H, 5.4; N, 4.5. $C_{21}H_{17}NO_2$ requires C, 80.0; H, 5.4; N, 4.4%); ν_{max}/cm^{-1} 3200–2400 and 1672; δ[$(CD_3)_2SO$] 1.22 (3 H, t, *J* 7, CH_2CH_3), 3.31 (2 H, q, *J* 7, CH_2CH_3), 6.99 (1 H, d, *J* 8, 6-H), 7.05–7.50 (8 H, m, aryl-H), 7.63 (1 H, d, *J* 8, aryl-H) and 8.09 (1 H, d, *J* 8, 5-H).

1,3-Diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxylic acid **41** (82%) as a white powder from pentyl acetate, m.p. 217–218 °C (lit.,[4] m.p. 214–215.5 °C); δ 6.69 (1 H, d, *J* 7, 6-H), 7.10–7.50 (14 H, m, aryl-H) and 7.52 (1 H, d, *J* 7, 5-H).

1,3-*Diphenylpyrrolo*[2,1-a]*isoquinoline-2-carboxamide* **3**.—A mixture of the acid **41** (5.94 g, 16 mmol), thionyl chloride (12 cm^3, 0.16 mol) and dichloromethane (100 cm^3) was heated at reflux for 2 h, after which the excess of thionyl chloride and solvent were distilled off. The residue was dissolved in 1,4-dioxane (50 cm^3) and poured into a stirred mixture of aqueous ammonia (*d* 0.88; 100 cm^3) and 1,4-dioxane (50 cm^3). After 0.5 h the mixture was diluted with water and the precipitated product was collected, washed with water, and dried. The solid was recrystallised from ethanol and then from toluene, to give the *title compound* **3** (3.77 g, 65%) as colourless crystals, m.p. 135–137 °C (Found: C, 82.8; H, 4.85; N, 7.5. $C_{25}H_{18}N_2O$ requires C, 82.85; H, 5.0; N, 7.7%); ν_{max}/cm^{-1} 3476, 3447, 1683 and 1643; δ 5.2 and 5.3 (2 H, 2 × br s, $CONH_2$), 6.71 (1 H, d, *J* 7.5, 6-H), 7.13 (1 H, t of d, *J* 7.5 and 2, 9-H), 7.28 (1 H, t of d, *J* 7.5 and 2, 8-H), 7.34 (1 H, d, *J* 8, 10-H), 7.45–7.59 (11 H, m, aryl-H) and 7.64 (1 H, d, *J* 7.5, 5-H).

The following compounds were similarly prepared using the appropriate amines and acids.

3-*Methyl*-1-*phenylpyrrolo*[2,1-a]*isoquinoline-2-carboxamide* **47** (66%) as cream coloured crystals, m.p. 216–218 °C (isopropyl alcohol) (Found: C, 79.7; H, 5.3; N, 9.2. $C_{20}H_{16}N_2O$ requires C, 80.0; H, 5.4; N, 9.3%); ν_{max}/cm^{-1} 3458 and 1662; δ 2.85 (3 H, s, 3-CH_3), 5.70 and 5.85 (2 H, 2 × br s, slow exch. D_2O, $CONH_2$), 6.83 (1 H, d, *J* 8, 6-H), 7.08 (1 H, t of d, *J* 7.5 and 2, 9-H), 7.16 (1 H, d, *J* 7.5, 10-H), 7.25 (1 H, t of d, *J* 7.5 and 2, 8-H), 7.46–7.60 (6 H, m, aryl-H) and 7.68 (1 H, d, *J* 8, 5-H).

3-*Ethyl*-1-*phenylpyrrolo*[2,1-a]*isoquinoline-2-carboxamide* **49** (71%) as a cream coloured solid, m.p. 171–173 °C (Found: C, 80.6; H, 5.8; N, 8.9. $C_{21}H_{18}N_2O$ requires C, 80.2; H, 5.8; N, 8.9%); ν_{max}/cm^{-1} 3461 and 1657; δ 1.33 (3 H, t, *J* 8, CH_2CH_3), 3.39 (2 H, q, *J* 8, CH_2CH_3, 3-CH_3), 5.20 (2 H, br s, $CONH_2$), 6.81 (1 H, d, *J* 7, 6-H), 7.05–7.60 (9 H, m, aryl-H) and 7.73 (1 H, d, *J* 7, 5-H).

N-*Butyl*-3-*methyl*-1-*phenylpyrrolo*[2,1-a]*isoquinoline-2-carboxamide* **50** (51%) as a cream coloured solid, m.p. 115–117 °C (Found: C, 81.0; H, 6.8; N, 7.8. $C_{24}H_{24}N_2O$ requires C, 80.9; H, 6.8; N, 7.9%); ν_{max}/cm^{-1} 1619 and 1538; δ 0.77 (3 H, t, *J* 7, butyl-CH_3), 0.95–1.13 (4 H, m, 2 × CH_2), 2.84 (3 H, s, 3-CH_3), 3.13 (2 H, q, *J* 7, $CONHCH_2$), 5.27 (1 H, br t, CONH), 6.81 (1 H, d, *J* 7, 6-H), 7.05–7.60 (9 H, m, aryl-H) and 7.68 (1 H, d, *J* 7, 5-H).

3-*Methyl*-2-(4-*morpholinocarbonyl*)-1-*phenylpyrrolo*[2,1-a]-*isoquinoline* **51** (65%), prepared using oxalyl chloride in place of thionyl chloride, as a white powder, m.p. 174–176 °C (aqueous ethanol) (Found: C, 77.7; H, 6.0; N, 7.4. $C_{24}H_{22}N_2O_2$ requires C, 77.8; H, 5.95; N, 7.6%); ν_{max}/cm^{-1} 1628; δ 2.53 (3 H, s, 3-CH_3), 3.0–3.9 (8 H, br m, morpholine-H's), 6.83 (1 H, d, *J* 7, 6-H), 7.1–7.65 (8 H, m, aryl-H), 7.61 (1 H, d, *J* 7, 5-H) and 7.97 (1 H, d, *J* 8, 7-H).

8-*Fluoro*-1-(4-*fluorophenyl*)-3-*methyl*-2-(4-*morpholinocarbonyl*)*pyrrolo*[2,1-a]*isoquinoline* **52** (84%), prepared using oxalyl chloride in place of thionyl chloride, as cream coloured needles, m.p. 165–167 °C (aqueous ethanol) (Found: C, 70.9; H, 5.0; F, 9.5; N, 6.7. $C_{24}H_{20}F_2N_2O_2$ requires C, 70.9; H, 4.9; F, 9.4; N, 6.9%); ν_{max}/cm^{-1} 1619; δ 2.52 (3 H, s, 3-CH_3), 3.0–3.85 (8 H, br m, morpholine-H's), 6.78 (1 H, d, *J* 7, 6-H), 6.92 (1 H, t of d, *J* 9 and 3, 9-H), 7.05–7.30 (4 H, m, aryl-H), 7.45 (2 H, dd, *J* 6 and 9, 1-Ph 3-H and 5-H), 7.63 (1 H, d, *J* 7, 5-H) and 7.73 (1 H, dd, *J* 5 and 9, 10-H).

1-(4-*Fluorophenyl*)-3-*isopropyl*-2-(4-*methylpiperazin*-1-*ylcarbonyl*)*pyrrolo*[2,1-a]*isoquinoline hemihydrate* **53** (23%), prepared using oxalyl chloride in place of thionyl chloride, as a cream coloured powder, m.p. 90–97 °C (Found: C, 74.0; H, 6.5; F, 4.2; N, 9.5; water, 1.5. $C_{27}H_{28}FN_3O$. 0.5 H_2O requires C, 74.0; H, 6.6; F, 4.3; N, 9.6; water, 2.05%); ν_{max}/cm^{-1} 1628; δ 1.46 [6 H, 2 × d, *J* 7, $CH(CH_3)_2$], 2.15 (3 H, s, NCH_3), 3.39 [1 H, septet, *J* 7, $CH(CH_3)_2$], 1.95–2.2 and 2.25–2.4 and 2.9–3.7 (8 H, m, piperazine-H's), 6.80 (1 H, d, *J* 7, 6-H), 7.0–7.6 (7 H, m, aryl-H) and 7.73 (2 H, br d, *J* 7, 5-H and 7-H).

2-*Cyano*-1,3-*diphenylpyrrolo*[2,1-a]*isoquinoline* **55**.—A solution of 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide **3** (0.2 g, 0.5 mmol) and thionyl chloride (0.13 g, 1.1 mmol) in toluene (20 cm^3) was heated on a steam-bath for 7 h. Methanol (2 cm^3) was added to the solution which was then evaporated under reduced pressure to leave a yellow solid. Recrystallisation of this from acetonitrile and then from acetone provided the *title compound* **55** (60 mg, 33%) as colourless crystals, m.p. 201–202 °C (Found: C, 86.6; H, 4.6; N, 7.9. $C_{25}H_{16}N_2$ requires C, 86.7; H, 4.85; N, 8.4%); ν_{max}/cm^{-1} 2222, 741 and 703; δ 6.83 (1 H, d, *J* 8, 6-H), 7.20–7.78 (14 H, m, aryl-H) and 7.89 (1 H, d, *J* 8, 5-H).

Reaction of Cinnamonitrile with Reissert Anions

(i) *Derived from* 2-*Acetyl*-1-*cyano*-1,2-*dihydroisoquinoline*.—2-*Acetyl*-3-*amino*-1-*phenylpyrrolo*[2,1-a]*isoquinoline* **48**. A solution of phenyllithium in cyclohexane and diethyl ether (1.8 mol dm^{-3}; 7.22 cm^3, 13 mmol) was added dropwise, under nitrogen, to a cold solution of 2-acetyl-1-cyano-1,2-dihydroisoquinoline (1.98 g, 10 mmol) in dry 1,4-dioxane (200 cm^3) and diethyl ether (100 cm^3) the temperature being kept < 0 °C. A solution of cinnamonitrile (1.68 g, 13 mmol) in diethyl ether (7 cm^3) was added to the red solution and the mixture was stirred for 30 min at 0 °C and then for 18 h at room temperature. The mixture was diluted with water (100 cm^3) and extracted with dichloromethane. The extract was dried (Na_2SO_4) and evaporated under reduced pressure to leave an oily residue. Trituration of this with methanol gave the *title compound* **48**

Table 1 Crystal data for 3-amino-2-benzoyl-1-phenylpyrrolo[2,1-*a*]-isoquinoline **57**

Formula	$C_{25}H_{18}N_2O$
M (daltons)	362
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	13.902(2)
b/Å	8.668(1)
c/Å	15.790(6)
β/°	97.09(2)
V/Å^3	1888.19
Z	4
D_c/g cm^{-3}	1.275
μ/cm^{-1} [Mo-Kα]	0.73
F(000)	760

(0.27 g, 10%) as a yellow solid, m.p. 260–263 °C (Found: C, 79.9; H, 5.3; N, 9.5. $C_{20}H_{16}N_2O$ requires C, 80.0; H, 5.4; N, 9.3%); ν_{max}/cm^{-1} 3386, 3277, 1649 and 1608; δ[$(CD_3)_2SO$] 1.67 (3 H, s, $COCH_3$), 6.72 (1 H, d, *J* 7.5, 6-H), 6.83 (1 H, d, *J* 8, 10-H), 6.97 (1 H, t of d, *J* 7.5 and 2, 9-H), 7.14 (1 H, t of d, *J* 7.5 and 2, 8-H), 7.23 (2 H, s, NH_2), 7.40–7.58 (6 H, m, aryl-H) and 7.83 (1 H, d, *J* 7.5, 5-H).

When the reaction was conducted in THF using lithium diisopropylamide in place of phenyllithium and quenching with solid carbon dioxide, **48** was obtained in a yield of 33%.

(ii) *Derived 2-Benzoyl-1-cyano-1,2-dihydroisoquinoline.*—*2-Benzoyl-3-(1-isoquinolyl)-3-phenylpropionitrile* **56** *and 3-amino-2-benzoyl-1-phenylpyrrolo*[2,1-a]*isoquinoline* **57**.—A solution of phenyllithium in cyclohexane and diethyl ether (1.8 mol dm^{-3}; 14.4 cm^3, 26 mmol) was added dropwise, under nitrogen, to a cold solution (−10 °C) of 2-benzoyl-1-cyano-1,2-dihydroisoquinoline (5.2 g, 20 mmol) in dry THF (300 cm^3) the temperature being kept < −10 °C. Cinnamonitrile (3.36 g, 26 mmol) was added to the red solution and the mixture was stirred for 4 h at 0 °C and then for 18 h at room temperature. Solid carbon dixoide (35 g) was added to the mixture, followed by water (35 cm^3). The resultant slurry was diluted with *tert*-butyl methyl ether (350 cm^3) and then washed with brine, dried and evaporated under reduced pressure to leave an orange oil. Trituration of this with dichloromethane–ethanol gave the *title compound* **56** (1.44 g, 20%) as colourless crystals, m.p. 230–232 °C (change to orange solid at 140–145 °C) (Found: C, 82.4; H, 4.9; N, 7.7. $C_{25}H_{18}N_2O$ requires C, 82.85; H, 5.0; N, 7.7%); ν_{max}/cm^{-1} 2246 and 1692; δ($CDCl_3$) 5.79 (1 H, m, 3-H), 5.97 (1 H, d, *J* 10, 2-H), 7.2–7.7 (11 H, m), 7.75 (1 H, br d, *J* 8), 8.08 (2 H, br d, *J* 7), 8.14 (1 H, d, *J* 8) and 8.19 (1 H, d, *J* 5). After 3 days the ^{1}H NMR spectrum of this solution was identical with that described below for compound **57**.

The red filtrate afforded the *title compound* **57** (1.08 g, 15%) as bright orange crystals, m.p. 223–225 °C (Found: C, 82.7; H, 4.9; N, 7.7. $C_{25}H_{18}N_2O$ requires C, 82.85; H, 5.0; N, 7.7%); ν_{max}/cm^{-1} 3417, 3314, 1647, 1600, 746 and 698; δ($CDCl_3$) 5.72 (2 H, br s, NH_2), 6.67 (1 H, d, *J* 8, 6-H), 6.97 (2 H, t, *J* 8, 1-Ph 3-H and 5-H), 7.00–7.14 (7 H, m, aryl-H), 7.17 (1 H, t of d, *J* 7.5 and 2, 2-benzoyl 4-H), 7.23 (2 H, dd, *J* 8 and 2, 1-Ph 2-H and 6-H), 7.37 (1 H, d, *J* 8, 5-H) and 7.39 (2 H, m, 2-benzoyl 2-H and 6-H); δ[$(CD_3)_2SO$] 6.78 (1 H, d, *J* 8, 6-H), 6.97 (3 H, m, aryl-H), 7.07 (5 H, m, aryl-H), 7.09–7.20 (5 H, m, aryl-H), 7.21 (2 H, br s, NH_2), 7.47 (1 H, dd, *J* 2 and 8, 7-H) and 7.91 (1 H, d, *J* 8, 5-H).

1,3-*Diphenylpyrrolo*[2,1-a]*isoquinoline* **6**.—*From 2-benzoyl-3-(1-isoquinolyl)-3-phenylpropionitrile* **56**. A suspension of the propionitrile **56** (0.2 g, 0.55 mmol) in 90% phosphoric acid (4 cm^3) was stirred at 140–160 °C for 2.5 h; the solution first became orange and gradually paled. The solution was cooled and poured onto ice to give a grey solid, recrystallisation of which from ethanol gave the title compound **6** (89 mg, 50%), m.p. 139–141 °C (lit.,[4] m.p. 136–138 °C); δ 6.71 (1 H, d, *J* 8, 6-H), 6.74 (1 H, s, 2-H), 7.18 (1 H, t of d, *J* 8 and 1.5), 7.27 (1 H, t of d, *J* 7 and 1.5), 7.35–7.65 (11 H, m, aryl-H), 7.90 (1 H, br d, *J* 8, 7-H) and 8.03 (1 H, d, *J* 8, 5-H).

From 1,3-*diphenylpyrrolo*[2,1-a]*isoquinoline-2-carboxamide* **3**. A suspension of 1,3-diphenylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide **3** (0.2 g, 0.55 mmol) in 90% phosphoric acid (4 cm^3) was stirred at 140–160 °C for 2.5 h. The solution was cooled and poured onto ice to give a solid which was dissolved in dichloromethane and the solution washed with brine, dried and evaporated under reduced pressure to leave a yellow solid. Recrystallisation of this from aqueous methanol gave the title compound **6** (70 mg, 39%) identical (TLC and ^{1}H NMR) with the material described above.

Decarboxylation of Pyrrolo[2,1-a]*isoquinoline-2-carboxylic Acids*

1-(4-*Fluorophenyl*)-3-*isopropylpyrrolo*[2,1-a]*isoquinoline* **34**.—A suspension of the acid **37** (1.54 g, 4.4 mmol) in orthophosphoric acid (25 cm^3) was stirred and heated to 140 °C. When the temperature reached 120 °C a gentle bubbling commenced. TLC after 5 min at 140 °C indicated complete reaction. The solution was cooled to 80 °C and then poured onto crushed ice. The solid product was taken up in diethyl ether (250 cm^3) and the solution washed with brine, dried and evaporated under reduced pressure to leave a colourless oil. Crystallisation from ethanol provided the *title compound* **34** (0.91 g, 68%) as colourless prisms, m.p. 103–105.5 °C (Found: C, 83.3; H, 6.0; F, 6.2; N, 4.5. $C_{21}H_{18}FN$ requires C, 83.1; H, 6.0; F, 6.3; N, 4.6%); ν_{max}/cm^{-1} 1341, 1217, 783, 768 and 686; δ 1.39 [6 H, d, *J* 7, $CH(CH_3)_2$], 3.22 [1 H, septet, *J* 7, $CH(CH_3)_2$], 6.41 (1 H, s, 2-H), 6.72 (1 H, d, *J* 8, 6-H), 7.0–7.55 (7 H, m, aryl-H), 7.66 (1 H, d, *J* 8, 5-H) and 7.79 (1 H, br d, *J* 8, 7-H).

Reaction of the dione **33** (0.50 g, 1.68 mmol) and toluene-*p*-sulfonic acid (1 crystal) with aminoacetaldehyde dimethyl acetal (0.25 g, 2.4 mmol) at 170 ± 10 °C, under argon, for 18 h, cyclisation of the resulting tar with sulfuric acid (1 cm^3) in acetic acid (1.5 cm^3) and chromatography of the product provided the title compound **34** (0.12 g, 24%), identical (^{1}H NMR) with that described above.

1-(4-*Fluorophenyl*)-3-*phenylpyrrolo*[2,1-a]*isoquinoline* **35** (78%) as pale yellow needles from isopropyl alcohol, m.p. 155–157 °C (Found: C, 85.5; H, 4.8; F, 5.6; N, 4.2. $C_{24}H_{16}FN$ requires C, 85.5; H, 4.75; F, 5.6; N, 4.15%); ν_{max}/cm^{-1} 1334, 1222, 782, 759 and 702; δ 6.70 (1 H, s, 2-H), 6.72 (1 H, d, *J* 8, 6-H), 7.1–7.6 (12 H, m, aryl-H), 7.80 (1 H, br d, *J* 8, 7-H) and 8.01 (1 H, d, *J* 8, 5-H).

3-*Methyl*-1-*phenylpyrrolo*[2,1-a]*isoquinoline* **36** (50%) as cream coloured needles from ethanol, m.p. 107–110 °C (Found: C, 89.0; H, 5.9; N, 5.4. $C_{19}H_{15}N$ requires C, 88.7; H, 5.9; N, 5.4%); ν_{max}/cm^{-1} 1339, 782, 762 and 697; δ 2.52 (3 H, s, 3-CH_3), 6.46 (1 H, s, 2-H), 6.77 (1 H, d, *J* 8, 6-H), 7.1–7.6 (8 H, m, aryl-H), 7.60 (1 H, d, *J* 8, 5-H) and 7.88 (1 H, br d, *J* 8, 7-H).

X-Ray Crystal Structure Determination of Compound **57**.—Suitable crystals were grown from methanol and a specimen 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,[16] orienting reflections for indexing and lattice parameter refinement were collected (Table 1), with the detector positioned at −25 °C swing angle and 40 mm distance. A total of 7484 intensities were collected in the 2θ range 4.6–53.8°. After merging and averaging, this resulted in 3272 unique reflections [*R*(merge) = 0.096]. Of

these, 1265 had intensities of more than 1.5 $\sigma(I)$ and were considered observed. The structure was solved by the direct methods program SHELXS-86[17] and subsequently refined using full-matrix least squares methods based on F(rel) incorporated into the program SHELX-76,[18] 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 one common isotropic displacement parameters, except H(2A) and H(2B) which were given individual isotropic displacement parameters. Final R and R_w values are 0.0615 and 0.0679. Tables of fractional coordinates H-atom coordinates, thermal parameters, bond lengths, bond angles, and some selected non-bonded distances have been deposited as Supplementary Information.*

* For details of the Scheme, see 'Instructions for Authors' in the January issue.

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