Phenol Oxidation and Biosynthesis. Part 26.[1] Isonitriles in the Synthesis of Benzylisoquinoline Derivatives

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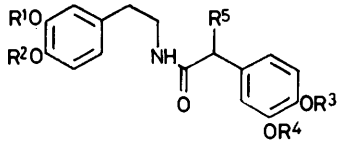
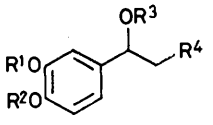
Lithiomethyl and toluene-4-sulphonyl(potassiomethyl)isonitriles have been applied in short high-yield homologations of *O*-benzylvanillin, *O*-benzylisovanillin, and veratraldehyde giving *N*-(2-arylethyl)-2-arylacetamides and subsequently isoquinoline derivatives. These experiments are relevant to the preparation of alkaloids including papaverine and reticuline.

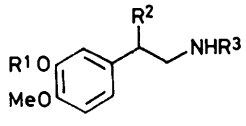
EFFICIENT synthesis of the pharmaceutically useful isoquinoline alkaloids requires a short preparation of the precursor *N*-(2-arylethyl)-2-arylacetamides (1). Prompted by the symmetry of the carbon skeleton in many of these precursors several short syntheses have been directed towards linking two C_6C_1 units to a central CNC moiety.[1] The C_6C_1 units are most conveniently aryl aldehydes. In continuation of this strategy α-metallated isonitriles were examined as CNC units for aldehyde homologation.



(1) a; $R^1 = R^3 = Me$, $R^2 = R^4 = R^5 = H$
b; $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = OMe$



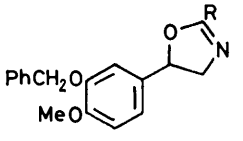
(3) a; $R^1 = PhCH_2$, $R^2 = Me$, $R^3 = H$, $R^4 = NC$
b; $R^1 = PhCH_2$, $R^2 = Me$, $R^3 = Ac$, $R^4 = NC$
c; $R^1 = PhCH_2$, $R^2 = Me$, $R^3 = Li$, $R^4 = NC$
d; $R^1 = PhCH_2$, $R^2 = Me$, $R^3 = H$, $R^4 = NCO$
e; $R^1 = Me$, $R^2 = PhCH_2$, $R^3 = Ac$, $R^4 = NC$



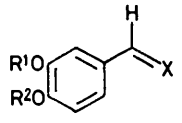
(5) a; $R^1 = PhCH_2$, $R^2 = OH$, $R^3 = Me$
b; $R^1 = R^2 = H$, $R^3 = CHO$
c; $R^1 = PhCH_2$, $R^2 = OH$, $R^3 = CHO$
d; $R^1 = R^2 = R^3 = H$

Efficient synthesis of the pharmaceutically useful isoquinoline alkaloids requires a short preparation of the precursor *N*-(2-arylethyl)-2-arylacetamides (1). Prompted by the symmetry of the carbon skeleton in many of these precursors several short syntheses have been directed towards linking two C_6C_1 units to a central CNC moiety.[1] The C_6C_1 units are most conveniently aryl aldehydes. In continuation of this strategy α-metallated isonitriles were examined as CNC units for aldehyde homologation.

α-Lithiomethyl isonitrile condensed with aromatic aldehydes giving 2-oxazoline (2a) and β-hydroxy- (3a), and β-acetoxy-ethyl isonitriles (3b and e) depending on the method of quenching. Reaction of lithiomethyl isonitrile and *O*-benzylisovanillin (4a) at −78 °C gave, on quenching with methanol, the oxazoline (2a). Spectral data, microanalysis, and literature precedent [2] supported this formulation. The oxazoline (2a) was conveniently converted into the adrenalin derivative (5a) and the *N*-alkylformamide (5b) on reaction with lithium aluminium hydride and on hydrogenolysis, respectively. Spectral data and microanalyses of these and all compounds in the sequel were in agreement with the structures indicated (see Experimental section).



(2) a; R = H
b; R = Li
c; R = D

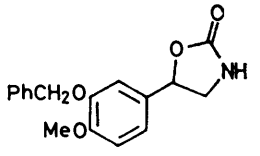


(4) a; $R^1 = PhCH_2$, $R^2 = Me$, X = O
b; $R^1 = Me$, $R^2 = PhCH_2$, X = O
c; $R^1 = R^2 = Me$, X = O
d; $R^1 = PhCH_2$, $R^2 = Me$, X = NPh
e; $R^1 = Me$, $R^2 = PhCH_2$, X = NPh
f; $R^1 = Me$, $R^2 = PhCH_2$, $X = OCH_2CH_2O$
g; $R^1 = Me$, $R^2 = PhCH_2$, $X = (OMe)_2$
h; $R^1 = R^2 = Me$, X = C(Ts)NHCHO *E*
i; $R^1 = R^2 = Me$, X = C(Ts)NC *E*
j; $R^1 = R^2 = Me$, $X = (OMe)_2$
k; $R^1 = R^2 = Me$, X = CHNHCHO *Z*
l; $R^1 = R^2 = Me$, X = H, CH(Ts)NC
m; $R^1 = R^2 = Me$, X = CHNC
n; $R^1 = R^2 = Me$, X = H, CH_2NC
o; $R^1 = Me$, $R^2 = PhCH_2$, X = H, CH_2NH_2

α-Lithiomethyl isonitrile and *O*-benzylisovanillin (4a) at −78 °C gave, on quenching with methanol, the oxazoline (2a). Spectral data, microanalysis, and literature precedent [2] supported this formulation. The oxazoline (2a) was conveniently converted into the adrenalin derivative (5a) and the *N*-alkylformamide (5b) on reaction with lithium aluminium hydride and on hydrogenolysis, respectively. Spectral data and microanalyses of these and all compounds in the sequel were in agreement with the structures indicated (see Experimental section).

The oxazoline (2a) and n-butyl-lithium gave the anion (2b). Although quenching with deuterium oxide gave the deuterio-oxazoline (2c) reaction of anion (2b) with acetic acid or acetic anhydride gave the β-hydroxy- and

β-acetoxy-ethyl isonitrile derivatives (3a and b). The tautomeric equilibration of the oxazoline C-2 (2b) anion with the β-alkoxyethyl isonitrile anion (3c) has previously been described by Schöllkopf.[3,4] The position of equilibrium favours the oxygen anion (3c). Thus, quenching of anion (2b/3c) with acetic acid or acetic anhydride gave the acyclic derivatives (3a and b), respectively. Quenching with methanol, however, reversibly protonated the alkoxide (3c) but irreversibly protonated the C-2 anion (2b). Thus the methanol quench gave the oxazoline (2a). In the acetic acid quench the margin for error was low; too little acetic acid also gave some oxazoline (2a), too much the formamide (5c). The β-hydroxyethyl isonitrile (3a) was oxidised by DMSO and toluene-4-sulphonic acid to the cyanate (3d). This rapidly cyclised giving the oxazolidone (6).



(6)

Electrophilic addition of the second C_6C_1 unit to the β-hydroxyethyl isonitrile, *via* the terminal carbon, required protection of the hydroxy-group. Thus the β-acetoxyethyl isonitrile derivatives (3b) and (3e) from *O*-benzylisovanillin (4a) and *O*-benzylvanillin (4b) were examined. Isonitriles undergo α-addition reactions with acid chlorides[5] to give α-ketoamides. Such a condensation should be applicable in linking the second C_6H_1 unit. As a model, the α-ketoamide (7a),[5] from benzoyl chloride and cyclohexyl isonitrile, was hydrogenated over palladium on charcoal to give the amide (7b). 3-Benzyloxy-4-methoxybenzoyl chloride (8a), being less electrophilic, was slow to react with the isonitrile (3b) in benzene. The ketoamide (9a), isolated after quenching with calcium carbonate–water, was obtained in 54% yield. The yield was comparable in the presence of triethylamine and lower when acetonitrile was used as solvent. Addition of copper(I) chloride prevented condensation, presumably *via* isonitrile co-ordination.[6] Addition of Lewis acids ($AlCl_3$ or $ZnCl_2$) gave only tars. The subsequent catalytic hydrogenation of the ketoamide (9a) was efficient giving the amide (9b) (82%). This completed a formal synthesis[7] of *N*-norprotosinomenine (10a) and may provide a route to the papaveraldine system (10b).[8]

The α-additions of isonitriles with alternative electrophiles are known.[9] In an improvement over acyl chlorides imidoyl chloride analogues and isonitriles are reported[10] to give α-ketoamides. As expected and in contrast to *NN*-diethylbenzimidoyl chloride ($PhCCl{=}\overset{+}{N}Et_2Cl^-$)[9] the iminochloride (8b) and cyclohexyl isonitrile required prolonged reflux for complete reaction to give the ketoamide (7a). Clearly the imidoyl chloride is the preferred C_6C_1 synthon. Condensation of imidoyl chloride (8c) [prepared from amide (8d) and phosgene] and isonitrile (3b) in acetonitrile gave the ketoamide (9a) (35%) and tar.

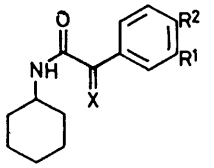
Reaction of isonitrile (3b) and a suitably substituted benzyl halide should provide the required $C_6C_2NC_2C_6$ unit at the correct oxidation state. Alkyl halide–isonitrile condensations, although studied, remain obscure.[11] Catalysis by a silver salt could conceivably give clean alkylation at carbon. However, reaction of isonitrile (3b), the models benzyl bromide or chloride, and silver tetrafluoroborate in THF gave mostly polymeric tar.

Although lithiomethyl isonitrile was an efficient CNC unit, the addition of the second C_6C_1 moiety required improvement. This second C_6C_1 could be most conveniently added as the aldehyde. The α-addition of isonitriles and aldehydes requires a co-electrophile such as a Lewis[12] or mineral acid,[13] acylating agent,[14] or carboxylic acid[15] (Passerini reaction). In contrast to benzaldehyde, the less electrophilic *O*-benzylisovanillin (4a) failed under these conditions to condense with cyclohexyl isonitrile. Clearly a more electrophilic aryl aldehyde derivative was needed. The required activation was found in the condensation of an amine, aldehyde, isonitrile, and carboxylic acid (Ugi reaction or 4-component condensation).[16] Since the rate determining step in the Ugi reaction is the condensation of amine and aldehyde giving Schiff's base[17] this was preformed before the addition of isonitrile and carboxylic acid. Both *O*-benzylisovanillin (4a) and *O*-benzylvanillin (4b) were converted into the derived Schiff's bases (4d and e) with aniline. These derivatives readily condensed with cyclohexyl isonitrile in the presence of one equivalent of trifluoroacetic acid. The initial α-adducts (11a and b) readily underwent intramolecular *O* to *N* acyl transfer even in methanol as solvent giving the bis-amides (7c and d). The isovanillin derivative (7c) was selectively hydrolysed using ethanolic sodium hydroxide to give the amide (7e). Subsequent hydrogenation over palladium–charcoal in perchloric and acetic acids cleaved both the C–O and C–N bonds giving the required amide (7f).

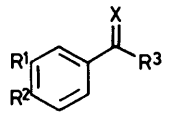
Having completed the model studies, the condensation of the isonitriles (3b or e) and the Schiff's base (4d) was examined. As expected, the trifluoroacetamides (9c and d) were both obtained as mixtures of two diastereoisomers. Both gave microanalytically pure crystalline single (n.m.r.) isomers. Again, hydrolysis with sodium hydroxide gave, respectively, the amines (9e and f) as non-crystalline diastereoisomeric mixtures. Hydrogenolysis of the amino-amide (9f) to the amide (1a) required drastic conditions for reproducible results. The most reliable method involved pretreatment with activated charcoal, di-*N*-ethylation with triethyloxonium tetrafluoroborate, and hydrogenation over palladium–charcoal at 65 °C and 75 atm. Preparation of amide (1a) completed a formal synthesis of reticuline (10c).[18]

Although the amide (1a) could be conveniently prepared from the aryl aldehydes (4a and b) the difficulty

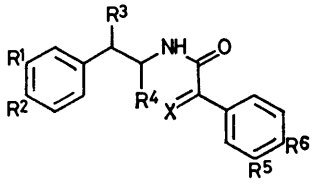
with and the low yield of the hydrogenolysis demanded an alternative route. The benzylic amino-group must be replaced by a function more easily cleaved by hydrogenation; a benzylic alkoxy-function should be suitable. In addition, Bischler–Napieralski cyclisation of the projected product amide (9g) should give papaverine (10d) directly after elimination of methanol. This elimination has some precedent in the Pictet–Gams modification [19]



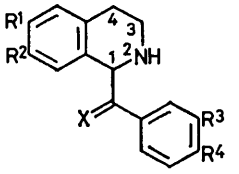
(7) a; $R^1 = R^2 = H$, X = O
b; $R^1 = R^2 = H$, $X = H_2$
c; $R^1 = PhCH_2O$, R = MeO, X = H, N(Ph)$COCF_3$
d; R^1 = MeO, $R^2 = PhCH_2O$, X = H, N(Ph)$COCF_3$
e; $R^1 = PhCH_2O$, R = MeO, X = H, NHPh
f; R^1 = HO, R^2 = MeO, $X = H_2$
g; R^1 = MeO, $R^2 = PhCH_2O$, X = H, OMe
h; R^1 = MeO, R^2 = HO, X = H, OMe
i; R^1 = MeO, R^2 = HO, $X = H_2$



(8) a; $R^1 = PhCH_2O$, R^2 = MeO, R^3 = Cl, X = O
b; $R^1 = R^2 = H$, R^3 = Cl, X = NBu^n
c; $R^1 = PhCH_2O$, R^2 = MeO, R^3 = Cl, X =
d; $R^1 = PhCH_2O$, R^2 = MeO, R^3 = , X = O
e; $R^1 = R^2 = H$, $R^3 = NBu^n$, X = O

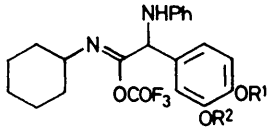


(9) a; $R^1 = R^5 = PhCH_2O$, $R^2 = R^6$ = MeO, R^3 = OAc, R^4 = H, X = O
b; $R^1 = R^5$ = HO, $R^2 = R^6$ = MeO, $R^3 = R^4$ = H, $X = H_2$
c; $R^1 = R^5 = PhCH_2O$, $R^2 = R^6$ = MeO, R^3 = OAc, R^4 = H, X = H, N(Ph)$COCF_3$
d; $R^1 = R^6$ = MeO, $R^2 = R^5 = PhCH_2O$, R^3 = OAc, R^4 = H, X = H, N(Ph)$COCF_3$
e; $R^1 = R^5 = PhCH_2O$, $R^2 = R^6$ = MeO, R^3 = OH, R^4 = H, X = H, NHPh
f; $R^1 = R^6$ = MeO, $R^2 = R^5 = PhCH_2O$, R^3 = OH, R^4 = H, X = H, NHPh
g; $R^1 = R^2 = R^5 = R^6$ = OMe, $R^3 = R^4$ = H, X = H, OMe
h; $R^1 = R^2 = R^5 = R^6$ = OMe, R^3 = H, R^4 = Ts, X = H, OMe
i; R^1 = MeO, $R^2 = PhCH_2O$, $R^3 = R^4 = R^5 = R^6$ = H, X = H, OMe
j; R^1 = MeO, $R^2 = PhCH_2O$, $R^3 = R^4 = R^5 = R^6$ = H, X = H, Cl
k; $R^1 = R^3 = R^4 = R^5$ = H, $R^2 = R^6$ = OMe, X = H, OH



(10) a; $R^1 = R^3$ = HO, $R^2 = R^4$ = MeO, $X = H_2$
b; $R^1 = R^2 = R^3 = R^4$ = OMe, X = O; 1, 2, 3, 4-tetradehydro
c; $R^1 = R^4$ = MeO, $R^2 = R^3$ = HO, $X = H_2$; *N*-methyl
d; $R^1 = R^2 = R^3 = R^4$ = OMe, $X = H_2$; 1, 2, 3, 4-tetradehydro
e; $R^1 = R^2 = R^4 = R^4$ = OMe, X = H,OMe; 1, 2-didehydro
f; R^1 = MeO, $R^2 = PhCH_2O$, $R^3 = R^4$ = H, X = H, OMe; 1, 2-didehydro
g; R^1 = MeO, $R^2 = PhCH_2O$, $R^3 = R^4$ = H, X = H, OMe; *N*-methyl
h; $R^1 = R^2 = R^3 = R^4$ = OMe, X = H, OMe; *N*-methyl
i; $R^1 = R^2 = R^4 = R^5$ = OMe, X = H, OMe; 1, 2, 3, 4-tetradehydro

of the Bischler–Napieralski reaction. Since protonated acetals are in equilibrium with the *O*-alkylated aldehyde cation and alcohol, the acid-catalysed condensation of



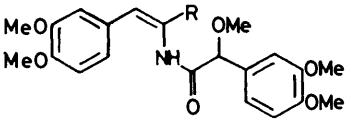
(11) a; R^1 = Me, R^2 = $PhCH_2$
b; R^1 = $PhCH_2$, R^2 = Me

acetals and isonitriles was investigated. While this work was in progress, the titanium tetrachloride condensation of acetals and isonitriles was reported.[20]

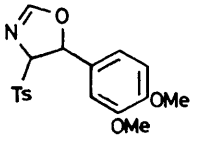
O-Benzylvanillin (4b) was converted into the ethane-1,2-diol acetal (4f). This reacted with cyclohexyl isonitrile and trifluoroacetic acid in methanol to give the major transacetalated product (4g) and amide (7g). In order to avoid acetal exchange, *O*-benzylvanillin dimethylacetal (4g) was condensed with cyclohexyl isonitrile and trifluoroacetic acid in benzene giving the α-methoxyamide (7g) (76%). In order to determine the ease of removal of the methoxy-group, the amide (7g) was hydrogenated. The debenzylated amide (7h) was readily formed and subsequent hydrogenolysis required acetic and perchloric acid as solvent giving the amide (7i).

Model studies complete, the conversion of veratraldehyde (4c) into papaverine (10d) was examined. Toluene-4-sulphonylmethyl isonitrile (12a) was chosen as CNC synthon since the derived anion is readily formed using alkoxide bases.[21] Reaction of veratraldehyde (4c) with one equivalent each of toluene-4-sulphonylmethyl isonitrile (12a) and potassium t-butoxide gave but low

(12) a; R = NC
b; R = NHCHO



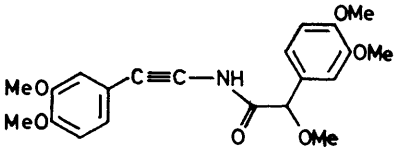
(13) a; R = Ts
b; R = H
c; R = H, *E* stereochemistry



(14)

yields of the expected [22] *N*-formamide (4h). Since veratraldehyde (4c) is of low electrophilicity, the base-catalysed self condensation of toluene-4-sulphonylmethyl isonitrile (12a) [23] was presumably able to compete. Reaction using an excess of potassium t-butoxide gave the formamide (4h) (80%). Subsequent dehydration using phosphoryl chloride and triethylamine gave the expected vinyl isonitrile (4i) (80%). Veratraldehyde dimethylacetal (4j), prepared *in situ*, was condensed with the vinyl isonitrile (4i) and trifluoroacetic acid. Although the product could not be obtained crystalline, all spectral data were consistent with assignment as the acetamide derivative (13a). The intermediates were all obtained as single isomers (n.m.r.). Although the geometry could not be unambiguously assigned, all were determined on the basis of the stereochemistry of the initial formamide (4h). Consideration of steric congestion in the intermediate (14) suggested that the more stable stereochemistry would place the aromatic ring *trans* to the toluene-4-sulphonylmethyl residue. Thus intermediates (4h and i) and (13a) were assigned *E*-stereochemistry.

The projected synthesis of papaverine (10d) required reduction of the double bond and removal of the toluene-4-sulphonyl function in the intermediate (13a). Catalytic hydrogenation of α,β-unsaturated sulphones has been reported to give saturated sulphones, although poisoning of the catalyst was a problem.[24] Hydrogenation of sulphone (13a) in acetic and perchloric acids at 100 atm. over palladium–charcoal resulted in only partial cleavage of the benzylic methoxy-group (n.m.r.). As an alternative, reduction of the sulphone (13a) using sodium borohydride was examined. In boiling ethanol, a mixture of products was obtained. Chromatography gave the *Z*-enamide (13b) (25%), identical with authentic material (see below). Although catalytic hydrogenation of the enamide (13b) should give the required amide (1b) reduction with hydride occurred in low-yield and thus this step required much improvement. Elimination of toluene-4-sulphinic acid from vinyl sulphone (13a) could conceivably give the ynamide (15) which



(15)

could then be easily hydrogenated. Reaction, however, with diazabicyclo[4.3.0]non-5-ene or potassium t-butoxide gave mostly decomposition products.

At this stage, the desirability of removal of either the toluene-4-sulphonyl group or alkene function or both prior to the condensation with the acetal (4j) became obvious. Attempted hydrogenation of the enamide (4h) was again unsuccessful presumably due to poisoning of the catalyst. Reduction of the enamide (4h) with aluminium amalgam,[25] sodium amalgam,[26] or lithium in ammonia gave complex mixtures or little reaction. Reduction with sodium borohydride in ethanol–THF or in DMF gave the *cis*-enamide (4k) (22% and 50% respectively). The predominance of the *Z*-isomer (4k) is difficult to rationalise.

Reduction using sodium borohydride of the vinyl isonitrile (4i) gave the saturated derivative (4l) (75%). This has some precedent in the Michael addition of nucleophiles to α-isocyanoacrylate esters.[27] Elimination of toluene-4-sulphinic acid and subsequent hydrogenation of the isonitrile (4m) should provide the required C_6C_2NC unit (4n). Reaction of isonitrile (4l) with sodium ethoxide, diazabicyclo[5.4.0]undec-5-ene (DBU), or potassium t-butoxide, or attempted reductive cleavage using sodium amalgam or W-2 Raney nickel[28] gave complex mixtures. Removal of the sulphonyl function was left until after the condensation step.

The isonitrile (4l), the acetal (4j) and trifluoroacetic acid gave the expected amide (9h) (93%) as a mixture of diastereoisomers. Crystallisation gave the analytically pure major isomer. In subsequent transformations the crude diastereoisomeric mixture was used. The amide (9h) was converted in low yield into the detosylated derivative (9g) by prolonged boiling with W-2 Raney nickel in ethanol and THF. Reaction, however, of the amide (9h) and DBU in benzene gave a 1 : 1 mixture of the *E*- and *Z*-enamides (13c and b). Assignment of the *Z*-stereochemistry to the less polar isomer (13b) was based on the n.m.r. spectrum ($J_{\text{vinyl-H}}$ 10 Hz). The *E*-isomer (13c) (J 16 Hz) was obtained crystalline and microanalytically pure. Subsequent hydrogenation of the mixture of *E,Z* enamides (13c and b) was extremely slow using platinum-black or palladium–charcoal. This was presumably due to poisoning by the catalyst and was avoided using 50% by weight of W-2 Raney nickel. The preparation of the amide (1b) (34% overall) is comparable in convenience and yield to aryl aldehyde homologation using methoxyacetonitrile.[1]

The last step in the planned synthesis of papaverine (10d) required Bischler–Napieralski cyclisation to give the dihydroisoquinoline (10e) followed by acid-catalysed elimination of methanol. As a model for the cyclisation, the amide (9i) was prepared. Condensation of the amine (4o)[29] and 2-chloro-2-phenylacetyl chloride in benzene–triethylamine gave the expected amide (9j). The benzylic chloride was readily displaced by sodium methoxide giving the α-methoxy-amide (9i) (76%). Reaction of amide (9i) and phosphoryl chloride in dry acetonitrile at room temperature[30] gave the expected dihydroisoquinoline derivative (10f). This unstable compound was characterised by methylation and subsequent reduction using sodium borohydride[31] to give the tetrahydroisoquinoline derivative (10g) as a mixture of diastereoisomers. Thus the α-methoxy-group was shown to be stable to the Bischler–Napieralski reaction conditions. The same sequence of reactions on the amide (1b) gave the analogue (10h). Having established the feasibility of the cyclisation, elimination of methanol from the intermediate dihydroisoquinolines (10e and f) was examined. The model intermediate (10f) gave only the derived salts (n.m.r.) on prolonged reaction with trifluoroacetic acid in chloroform (reflux) or with hydrogen chloride in chloroform (room temperature). Reaction with boron trifluoride–ether at 60 °C in benzene gave a complex mixture. Clearly the anticipated elimination of methanol was not taking place (cleanly). Oxidation of the dihydroisoquinoline (10f) with DDQ in an attempt to prepare methoxypapaverine (10i) also gave a complex mixture. The reactions herein described provide a convenient synthesis of alkoxytetrahydroisoquinolines less readily available by benzylic oxidation.[32]

Both lithiomethyl isonitrile and the potassium salt of toluene-4-sulphonylmethyl isonitrile are useful CNC synthons in the homologation of aryl aldehydes. The derived *N*-(2-arylethyl)-2-arylacetamides and thence tetrahydroisoquinolines are important intermediates in the synthesis of pharmaceutically important alkaloids.

EXPERIMENTAL

M.p.s were determined using a Kofler hot stage. I.r. spectra were recorded using nujol mulls, and u.v. and n.m.r. spectra were recorded for solutions in ethanol and deuteriochloroform (tetramethylsilane reference), respectively, unless otherwise stated. All solvents were dried and purified according to standard procedures.[33] Light petroleum refers to the redistilled fraction with b.p. 40—60°. Transfer of water and/or air-sensitive compounds was by syringe or double-tipped needle. Reactions carried out under nitrogen or argon are designated by (N_2) or (Ar). 'Work-up' refers to partition between the solvents given in parentheses, drying of the organic extract over magnesium sulphate, and evaporation under reduced pressure. Silica and alumina refer, respectively, to Hopkin and Williams MFC (100—200 mesh) and BDH Brockman neutral grade III materials. Analytical and preparative (p.l.c.) thin layer chromatography was performed on Merck Kieselgel GF_{254} silica films (0.25 and 1 mm, respectively).

5-(3-*Benzyloxy*-4-*methoxyphenyl*)-2-*oxazoline* (2a).—Methyl isocyanide (4.51 g) in dry THF (30 ml) was added dropwise over 15 min with stirring to n-butyl-lithium (1.3M; 80 ml) in THF (300 ml) at −78 °C (N_2). After 15 min, 3-benzyloxy-4-methoxybenzaldehyde (4a) (25.19 g) in THF (70 ml) was added dropwise whilst the temperature was kept at ⩽ −60 °C. After 10 min, methanol (5 ml) was added dropwise. At room temperature work-up (benzene–brine) and crystallisation from ethanol gave the *oxazoline* (2a) (24.7 g, 84%, 2 crops), m.p. 85—86°, $\nu_{max.}$ 1 630 cm^{-1}, δ 3.4—4.38 (2 H, m, CH_2), 3.85 (3 H, s, OMe), 5.02 (2 H, s, $ArCH_2$), 5.14, 5.3 (1 H, overlapping dd, J 8 Hz, 5-H), 6.86 (4 H, s, ArH, 2-H), and 7.33 (5 H, s, Ph) (Found: C, 72.15; H, 6.0; N, 4.9. $C_{17}H_{17}NO_3$ requires C, 72.05; H, 6.05; N, 4.95%).

Reaction of the Anion (2b) *and Deuterium Oxide.*—n-Butyl-lithium in ether (1.5M; 2.3 ml) was added with stirring to the oxazoline (2a) (1.0 g) in THF (25 ml) at −78 °C (N_2). After 20 min, excess of deuterium oxide was added and this was followed by work-up (benzene–brine) and crystallisation from ethanol to give the deuteriated oxazoline (2c) (0.87 g, 87%), m.p. 84—85°. The n.m.r. spectrum showed the absence of long-range coupling ($J_{2,4}$ *ca.* 2 Hz) indicating completed deuteriation at C-2.

1-(3-*Benzyloxy*-4-*methoxyphenyl*)-1-*hydroxy*-2-*methylaminoethane* (5a).—The oxazoline (2a) (261 mg) was added slowly to lithium aluminium hydride (136 mg) in THF (30 ml) (N_2). After refluxing for 2 h, the excess of hydride was destroyed by alternate addition of wet diethyl ether and 3N-sodium hydroxide. The mixture was filtered, the solids

leached with ether, and the combined organic phase dried and evaporated. The residue was crystallised from diethyl ether to give the *methylaminoethane derivative* (5a) [102 and 72 mg (1st and 2nd crop), 68%] as microneedles, m.p. 70—71°, δ 2.37 (3 H, s, NMe), 2.64 (2 H, d, *J* 6 Hz, CH_2), 2.75br (2 H, s, OH and NH), 3.84 (3 H, s, OMe), 4.6 (1 H, t, *J* 6 Hz, CH), 5.16 (2 H, s, $ArCH_2$), 6.8—7.06 (3 H, m, ArH), and 7.38br (5 H, s, Ph), *m/e* 287 (M^+), 269, 242 (100%), 196, 178, and 153 (Found: C, 70.85; H, 7.55; N, 4.85. $C_{17}H_{21}NO_3$ requires C, 71.05; H, 7.35; N, 4.85%).

N-(3-*Hydroxy*-4-*methoxyphenethyl*)*formamide* (5b).—The oxazoline (2a) (200 mg) was hydrogenated using 10% palladium–charcoal (30 mg) in ethanol (30 ml) at atmospheric pressure (8 h). Filtration, evaporation, and crystallisation from ethyl acetate gave the *formamide* (5b) (124 mg, 90%) as needles, m.p. 98.5—100° (from chloroform), $\nu_{max.}$ 3 340 and 1 660 cm^{-1}, δ 2.68 (2 H, t, *J* 6 Hz, $ArCH_2$), 3.4, 3.48 (2 H, dt $J_{1,2}$ 6 Hz, NCH_2), 3.8 (3 H, s, OMe), 5.4br (1 H, s, OH), 6.55—6.82 (3 H, m, ArH), and 8.0 (1 H, NCHO) (Found: C, 61.45; H, 6.65; N, 7.25. $C_{10}H_{13}NO_3$ requires C, 61.55; H, 6.7; N, 7.15%).

1-(3-*Benzyloxy*-4-*methoxyphenyl*)-1-*hydroxy*-2-*isocyanoethane* (3a).—The oxazoline anion (2b) was prepared from n-butyl-lithium in ether (1.3M; 12.7 ml) in THF (200 ml) (N_2), methyl isocyanide (0.693 g) in THF (6 ml), and 3-benzyloxy-4-methoxybenzaldehyde (4a) (4.0 g) in THF (10 ml). Glacial acetic acid (1.22 g) was added at −78 °C and after stirring for 30 min and leaving for 1 h at room temperature, work-up (benzene–brine) and crystallisation from benzene gave the *isonitrile* (3a) (3.83 g, 2 crops, 82%), m.p. 67—68°, $\nu_{max.}$ 3 420 and 2 190 cm^{-1}, δ 2.51br (1 H, s, OH), 3.46 (2 H, d, *J* 6 Hz, CH_2), 3.83 (3 H, s, OMe), 4.78 (1 H, t, *J* 6 Hz, CH), 5.08 (2 H, s, $ArCH_2$), 6.83 (3 H, s, ArH), and 7.29 (5 H, s, Ph) (Found: C, 71.95; H, 6.1; N, 4.8. $C_{17}H_{17}NO_3$ requires C, 72.05; H, 6.05; N, 4.95%).

5-(3-*Benzyloxy*-4-*methoxyphenyl*)-2-*oxazolidone* (6).—Dry DMSO (0.6 g) and, in portions, anhydrous toluene-4-sulphonic acid (0.12 g) were added to the isonitrile (3a) (1.98 g) in benzene (4 ml) and dioxan (4 ml) (N_2). After 39 h, work-up (water–ethyl acetate) and p.l.c. (benzene–ethyl acetate 3 : 2) gave the *oxazolidone* (6) (1.06 g, 51%) as an oil, $\nu_{max.}$ 3 260, 1 760, and 1 720 cm^{-1}, δ 3.26—4.02 (2 H, m, CH_2), 3.88 (3 H, s, OMe), 5.1 (2 H, s, $ArCH_2$), 5.4, 5.54 (1 H, dd, *J* 8 Hz, CH), 6.3br (1 H, s, NH), 6.89 (3 H, s, ArH), and 7.34 (5 H, s, Ph) (Found: C, 68.35; H, 5.75; N, 4.65. $C_{17}H_{17}NO_4$ requires C, 68.2; H, 5.7; N, 4.7%).

1-*Acetoxy*-1-(3-*benzyloxy*-4-*methoxyphenyl*)-2-*isocyanoethane* (3b).—Acetic anhydride (18.4 g) was added dropwise over 10 min with stirring at −78 °C to the anion (2b) [from methyl isocyanide (6.0 g), n-butyl-lithium in hexane (2.1M; 69.5 ml), and 3-benzyloxy-4-methoxybenzaldehyde (4a) (30 g)] in THF (290 ml) (N_2). After stirring for 3 h at room temperature work-up (benzene–brine) and crystallisation gave the *isonitrile* (3b) (37.5 g, 93%) as rosettes, m.p. 74—75° (from ethanol), $\nu_{max.}$ 2 160 and 1 735 cm^{-1}, δ 2.06 (3 H, s, OAc), 3.62 (2 H, d, *J* 6 Hz, CH_2), 3.82 (3 H, s, OMe), 5.08 (2 H, s, $ArCH_2$), 5.77 (1 H, t, *J* 6 Hz, CH), 6.83 (3 H, s, ArH), and 7.3br (3 H, s, Ph) (Found: C, 70.05; H, 5.7; N, 4.25. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.9; N, 4.3%).

1-*Acetoxy*-1-(4-*benzyloxy*-3-*methoxyphenyl*)-2-*isocyanoethane* (3e).—By the same procedure 4-benzyloxy-3-methoxybenzaldehyde (4b) gave the *isonitrile* (3e) (89%) as spindles, m.p. 92—93° (from EtOH), $\nu_{max.}$ 2 160 and 1 745 cm^{-1}, n.m.r. spectrum superimposable with the isomer (3b) (Found: C, 70.15; H, 5.9; N, 4.15%).

Hydrogenolysis of N-*Cyclohexyl*-2-*oxo*-2-*phenylacetamide* (7a).—The amide (7a) (846 mg) and 10% palladium on charcoal (75 mg) in ethanol (20 ml) containing 3N-hydrochloric acid (1 drop) was hydrogenated at 1 atm. Filtration, evaporation, and recrystallisation from ethyl acetate gave the acetamide derivative (7b), m.p. 136° (lit.,[34] 137—139°).

2-(3-*Benzyloxy*-4-*methoxyphenyl*)-N-[2-(3-*benzyloxy*-4-*methoxyphenyl*)-2-*acetoxyethyl*]-2-*oxoacetamide* (9a).—The isonitrile (3b) (3.25 g) and 3-benzyloxy-4-methoxybenzoyl chloride (8a) (2.76 g) were heated to reflux in benzene (13 ml) for 46.5 h (N_2). After evaporation, calcium carbonate (1.5 g) and water (10 ml) were added to the residue in acetone (5 ml). After 1 h at 50 °C brine (20 ml) and benzene (20 ml) were added. The organic phase was washed with 5% aqueous sodium hydrogen carbonate, dried (K_2CO_3), filtered through Celite, evaporated, and chromatographed on silica (benzene–ethyl acetate (1 : 1) to leave the α-*ketoamide* (9a) (3.22 g, 54%). Recrystallisation from ethyl acetate gave spheres, m.p. 129—130°, $\nu_{max.}$ 3 375, 1 735, and 1 665 cm^{-1}, δ 2.03 (3 H, s, OAc), 3.62 (2 H, d, *J* 6 Hz, CH_2), 3.82 (3 H, s, OMe), 3.95 (3 H, s, OMe), 5.14 (4 H, s, $ArCH_2$), 5.84 (1 H, t, *J* 6 Hz, CH), 6.7—7.02 (4 H, m, ArH), 7.34br (10 H, s, 2× Ph), and 7.85—8.34 (3 H, m, ArH, NH) (Found: C, 70.1; H, 5.85; N, 2.2. $C_{34}H_{33}NO_8$ requires C, 69.95; H, 5.65; N, 2.4%).

Hydrogenation of α-*Ketoamide* (9a).—The α-ketoamide (9a) (500 mg) and 10% palladium–charcoal (100 mg) in ethanol–ethyl acetate (1 : 1; 75 ml) containing 6N-hydrochloric acid (1 drop) were hydrogenated at 1 atm for 112 h. Filtration, evaporation, and crystallisation from chloroform–benzene (1 : 3) gave the *acetamide* (9b) (244 mg, 86%), m.p. 120—121.5° (lit.,[7] 120—121°). Hydrogenation for a shorter time gave also the more polar α-hydroxyamide (9k) isolated by p.l.c. (methanol–chloroform 1 : 19) as an oil, δ 2.65 (2 H, t, *J* 7 Hz, CH_2), 3.34 (2 H, t, *J* 7 Hz, CH_2), 3.8 (6 H, s, 2× OMe), 4.82 (1 H, s, CH), and 6.36—6.95 (6 H, m, ArH), *m/e* 347 (M^+), 329, 153, and 150 (100%).

Reaction of the Iminochloride (8b) *and Cyclohexyl Isocyanide.*—*N*-n-Butylbenzamide (8e) (1.77 g), thionyl chloride (3.0 g), and benzene (20 ml) were heated to reflux for 7 h (N_2). Evaporation and distillation gave the iminochloride (8b) (1.54 g, 79%), b.p. 85—90° at 45 mmHg, $\nu_{max.}$ (film) 1 670 cm^{-1}. The iminochloride (8b) (1.5 g), cyclohexyl isocyanide (912 mg), and benzene (4 ml) were heated to reflux for 2 days. After evaporation the residue was stirred with 1N-hydrochloric acid for 1 h at 35 °C, extracted with benzene, and crystallised with seeding from ethanol–water (1 : 1) to give the α-ketoamide (7a) [5] (584 mg, 33%), m.p. 115°.

α-*Ketoamide* (9a).—The acid chloride (8a) (4.1 g), piperidine (3.15 g), and dry benzene (10 ml) were heated to reflux for 3 h (N_2), cooled, washed with water, 1N-hydrochloric acid, 5% aqueous sodium hydrogen carbonate, and water, and then dried, evaporated, and crystallised from diethyl ether–ethyl acetate (3 : 1) to give the *amide* (8d) (4.18 g, 87%) as needles, m.p. 98°, $\nu_{max.}$ 1 635 cm^{-1} (Found: C, 73.65; H, 7.05; N, 4.15. $C_{20}H_{23}NO_3$ requires C, 73.8; H, 7.1; N, 4.3%). Reaction of the amide (8d) (3.25 g) with an excess of phosgene in dry toluene (100 ml) at room temperature gave a bright yellow precipitate of the imidoyl

chloride (8c) (3.65 g, >95%), m.p. 111—115°. To the imidoyl chloride (8c) (1.9 g) in dry acetonitrile (60 ml) (dissolved with warming) at 0 °C was added the isonitrile (3b) (1.62 g) in dry acetonitrile (10 ml). After stirring overnight at room temperature, work-up (ice–water, 1 h, benzene) followed by chromatography gave the α-keto-amide (9a) (1.02 g, 35%), m.p. 126—128°, together with much tar.

Imine (4d).—3-Benzyloxy-4-methoxybenzaldehyde (4a) (58.1 g), redistilled aniline (22.3 g), and benzene (250 ml) were heated to reflux for 2 h (Dean–Stark apparatus) (N_2). Evaporation and crystallisation from benzene–diethyl ether (1 : 4) gave the *imine* (4d) (73.3 g, 96%), m.p. 112—113°, $\nu_{max.}$ 1 645 cm^{-1} (Found: C, 79.55; H, 6.0; N, 4.4. $C_{21}H_{19}NO_2$ requires C, 79.45; H, 6.05; N, 4.4%).

2-(3-*Benzyloxy*-4-*methoxyphenyl*)-N-*cyclohexyl*-2-(N-*phenyltrifluoroacetamido*)*acetamide* (7c).—Cyclohexyl isocyanide (5.0 g) was added with stirring to the imine (4d) (12.69 g) and trifluoroacetic acid (4.56 g) in benzene (30 ml) at 0 °C (N_2). After 1 h at room temperature, the *acetamide* (7c) (18.4 g, 85%) was filtered off, m.p. 167—168°, $\nu_{max.}$ 3 280, 1 690, and 1 655 cm^{-1}, δ 0.5—2.29 (10 H, m), 3.45—4.02br (1 H, m, cyclohexyl-CH), 3.83 (3 H, s, OMe), 4.85 (2 H, s, $ArCH_2$), 5.44br (1 H, s, NH), 5.8 (1 H, s, ArCH), and 6.48—7.45 (13 H, m, ArH) (Found: C, 66.65; H, 5.8; N, 5.2. $C_{30}H_{31}F_3N_2O_4$ requires C, 66.7; H, 5.8; N, 5.2%).

Hydrolysis of the Acetamide Derivative (7c).—Sodium hydroxide (4.0 g) in water (50 ml) was added to the acetamide derivative (7c) (18.0 g) in acetone (900 ml) and ethanol (50 ml) (N_2). After stirring overnight, the mixture was filtered. Work-up of the filtrate (benzene–water) and crystallisation from ethanol gave the *amide* (7e) (12.06 g, 81%), m.p. 156—157.5°, $\nu_{max.}$ 3 400, 3 320, and 1 655 cm^{-1}, δ 0.64—2.17 (10 H, m), 3.43—4.05 (1 H, m, cyclohexyl-CH), 3.84 (3 H, s, OMe), 4.55br (2 H, s, ArCH, NH), 5.08 (2 H, s, $ArCH_2$), and 6.02—7.48 (14 H, m, ArH, NH) (Found: C, 75.35; H, 7.1; N, 6.35. $C_{28}H_{32}N_2O_3$ requires C, 75.65; H, 7.25; N, 6.3%).

Hydrogenolysis of Amide (7e).—The amide (7e) (400 mg) and 10% palladium–charcoal (40 mg) in glacial acetic acid (35 ml) and 60% aqueous perchloric acid (1 ml) were hydrogenated at 1 atm. The mixture was filtered through Celite, evaporated to half-volume, diluted with water (100 ml), and extracted with benzene. The organic extract was washed with 5% hydrochloric acid and water, dried, evaporated, and crystallised from ethyl acetate to give the *amide* (7f) (171 mg, 72%) as needles, m.p. 156.5—159°, $\nu_{max.}$ 3 340, 3 180, and 1 640 cm^{-1}, δ 0.74—2.17 (10 H, m), 3.42 (2 H, s, CH_2), 3.6—4.02 (1 H, m, cyclohexyl-CH), 3.89 (3 H, s, OMe), 5.38br (2 H, s, NH, OH), and 6.65—6.9 (3 H, m, ArH) (Found: C, 68.25; H, 7.85; N, 5.35. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.05; N, 5.3%).

2-(4-*Benzyloxy*-3-*methoxyphenyl*)-N-*cyclohexyl*-2-(N-*phenyltrifluoroacetamido*)*acetamide* (7d).—The *imine* (4e) [80% from aniline and 4-benzyloxy-3-methoxybenzaldehyde (4b), m.p. 113—114° (from ethanol) (Found: C, 79.5; H, 6.05; N, 4.3. $C_{21}H_{19}NO_2$ requires C, 79.45; H, 6.05; N, 4.4%)] was converted into the *acetamide derivative* (7d) (75%), m.p. 176—177°, $\nu_{max.}$ 3 280, 1 695, and 1 655 cm^{-1} (Found: C, 66.6; H, 5.75; F, 10.25; N, 5.05. $C_{30}H_{31}F_3N_2O_4$ requires C, 66.65; H, 5.8; F, 10.55; N, 5.2%).

2-(3-*Benzyloxy*-4-*methoxyphenyl*)-N-[2-(3-*benzyloxy*-4-*methoxyphenyl*)-2-*acetoxyethyl*]-2-(N-*phenyltrifluoroacetamido*)*acetamide* (9c).—Trifluoroacetic acid (114 mg) and the isonitrile (3b) (325 mg) in dry benzene (2 ml) were added in sequence over 3 min to the imine (4d) (317 mg) in benzene at 0 °C (N_2). After stirring overnight at room temperature, evaporation, work-up (benzene–water), and p.l.c. (ethyl acetate–benzene 1 : 5) gave the *amide* (9c) (650 mg, 86%) as an oil, δ 1.96 and 2.0 (2s, OAc). Crystallisation from diethyl ether and then ethanol gave one diastereoisomer, m.p. 142—143°, $\nu_{max.}$ 3 330, 1 730, and 1 675 cm^{-1}, δ 1.96 (3 H, s, OAc), 3.37—3.74 (2 H, m, CH_2), 3.79 (3 H, s, OMe), 3.82 (3 H, s, OMe), 4.82 (2 H, s, $ArCH_2$), 5.02 (2 H, s, $ArCH_2$), 5.5—5.86 (3 H, m, 2CH, NH), and 6.44—7.47 (21 H, m, ArH), *m/e* 756 (M^+), 696 (100%), 605, 508, 414, 318, and 298 (Found: C, 66.5; H, 5.35; N, 3.75. $C_{42}H_{39}F_3N_2O_8$ requires C, 66.65, H, 5.2; N, 3.7%).

Hydrolysis of the Acetamide Derivative (9c).—Sodium hydroxide (0.494 g) in water (50 ml) was added to the mixture of diastereoisomers (9c) (1.0 g) in ethanol (200 ml) and the mixture stirred overnight. Filtration, evaporation, work-up (benzene–water), and p.l.c. (benzene–ethyl acetate 3 : 1) gave the amine (9e) (653 mg, 80%) as a foam $\nu_{max.}$ (neat) 3 360 and 1 660 cm^{-1}, δ 3.1—3.62 (2 H, m, CH_2), 3.8 (6 H, s, 2× OMe), 4.44—4.78 (4 H, m, NH, OH, and 2× CH), 4.96 (2 H, s, $ArCH_2$), 5.0 (2 H, s, $ArCH_2$), and 6.42—7.61 (21 H, m, ArH).

Vanillin Analogue (9d).—The isonitrile (3e), imine (4d), and trifluoroacetic acid (N_2) gave the *bis-amide* (9d) (100% crude yield) as a mixture of diastereoisomers. Crystallisation from diethyl ether and then ethanol gave one diastereoisomer, m.p. 148—150°, $\nu_{max.}$ 3 340, 1 735, and 1 680 cm^{-1}, n.m.r. spectrum superimposable with analogue (9c) (Found: C, 66.65; H, 5.15; N, 3.45).

Hydrolysis and Hydrogenation of the Acetamide Derivative (9d).—Hydrolysis of the acetamide (9d) using ethanol–sodium hydroxide and chromatography on silica (benzene–ethyl acetate gradient) gave the amine (9f) (74%) as a mixture of diastereoisomers, $\nu_{max.}$ (film) 3 360 and 1 655 cm^{-1}, δ 3.12—3.48 (2 H, m, CH_2), 3.73 (3 H, s, OMe), 3.77 (3 H, s, OMe), 4.6br (4 H, s, OH, NH, and 2× CH), 5.06 (4 H, s, $ArCH_2$), and 6.4—7.42 (21 H, m, ArH). The amine (9f) (1.0 g) and charcoal (300 mg) in ethanol were heated (steam-bath) for 3 min, filtered hot through Celite, and the filtrate evaporated to dryness under vacuum. The residue was dissolved in dry dichloromethane (20 ml) and triethyloxonium tetrafluoroborate (0.614 g) was added in portions with stirring over 5 min. Excess of ethanol was added and the solvent evaporated off. The residue in glacial acetic acid (10 ml) and 60% aqueous perchloric acid (0.2 ml) was hydrogenated over 10% palladium–charcoal (200 mg) at 65 °C and 75 atm overnight. After cooling and evaporation to half-volume, work-up (dichloromethane–5% aqueous hydrochloric acid, water) and crystallisation from benzene–chloroform (3 : 1) gave the amide (1a) (134 mg, 25%). Recrystallisation gave cubes, m.p. 122—124° (lit.,[18] 124—126°), $\nu_{max.}$ 1 645 cm^{-1}, δ([$^2H_6$]acetone–$CDCl_3$), 2.66 (2 H, t, *J* 7 Hz, CH_2), 3.24—3.6 (4 H, m, $ArCH_2$ and ethylene-CH_2), 3.78 (3 H, s, OMe), 3.81 (3 H, s, OMe), and 6.49—7.0 (9 H, m, ArH, OH, and NH).

2-(4-*Benzyloxy*-3-*methoxyphenyl*)-1,3-*dioxolan* (4f).—4-Benzyloxy-3-methoxybenzaldehyde (4b) (12.1 g), ethane-1,2-diol (2.8 ml), and toluene-4-sulphonic acid (90 mg) in benzene (50 ml) were heated to reflux (Dean–Stark

apparatus). Work-up (benzene–saturated aqueous sodium hydrogen carbonate) and crystallisation from diethyl ether gave the *dioxolan* (4f) (8.6 g, 61%) as needles, m.p. 79—81°, δ 3.85 (3 H, s, OMe), 3.92—4.17 (4 H, m, CH_2CH_2), 5.1 (2 H, s, $ArCH_2$), 5.7 (1 H, s, ArCH), 6.87—7.04 (3 H, m, ArH), and 7.14—7.6br (5 H, s, Ph) (Found: C, 71.3; H, 6.35. $C_{17}H_{18}O_4$ requires C, 71.25; H, 6.2%).

Reaction of the Dioxolan Derivative (4f) *with Cyclohexyl Isocyanide*.—The dioxolan (4f) (715 mg), cyclohexyl isocyanide (278 mg), and trifluoroacetic acid (186 μl) in methanol–benzene (2 : 1; 6 ml) were stood at room temperature for 1 h. Work-up (benzene–saturated aqueous sodium hydrogen carbonate) and chromatography on alumina gave (i) (eluant benzene) the dimethoxyacetal (4g) (0.53 g, 74%) (see below) and (ii) (eluant benzene–ethyl acetate 9 : 1) 2-(4-*benzyloxy*-3-*methoxyphenyl*)-N-*cyclohexyl*-2-*methoxyacetamide* (7g) (0.22 g, 23%) as needles, m.p. 133—134° (from ethyl acetate), $\nu_{max.}$ 3 320 and 1 655 cm^{-1}, δ 1.0—2.1 (10 H, m), 3.34 (3 H, s, OMe), 3.7—3.9 (1 H, m, NCH), 3.84 (3 H, s, OMe), 4.35 (1 H, s, ArCH), 5.0 (2 H, s, $ArCH_2$), 6.74br (3 H, s, ArH), and 7.34br (5 H, s, Ph) (Found: C, 72.05; H, 7.6; N, 3.65. $C_{23}H_{29}NO_4$ requires C, 72.05; H, 7.4; N, 3.55%).

Amide (7g).—4-Benzyloxy-3-methoxybenzaldehyde (4b) (0.3 g), dry hydrogen chloride (catalyst), and methanol (5 ml) were allowed to react for 2.5 h at room temperature. The solution was poured into an excess of aqueous sodium hydrogen carbonate and the precipitate was filtered off, washed with water, and dried to yield the acetal (4g) (0.33 g, 92%), δ 3.32 (6 H, s, OMe), 3.83 (3 H, s, OMe), 5.1 (2 H, s, $ArCH_2$), 5.32 (1 H, s, ArCH), 6.9—7.06 (3 H, m, ArH), and 7.35br (5 H, s, Ph). Reaction of the acetal (4g) (0.37 g), trifluoroacetic acid (97 μl), and cyclohexyl isocyanide (165 μl) for 1 day at room temperature (N_2) gave, on work-up (benzene–saturated aqueous sodium hydrogen carbonate), the amide (7g) (0.37 g, 76%), identical with that previously obtained.

Hydrogenation of Amide (7g).—The amide (7g) (1.0 g) and 10% palladium on charcoal (0.1 g) in methanol (20 ml) were hydrogenated at 1 atm for 2 h. Filtration, evaporation, and crystallisation from aqueous methanol gave the *amide* (7h) (0.75 g, 98%) as needles, m.p. 119—120°, $\nu_{max.}$ 3 400, 3 300, and 1 645 cm^{-1}, δ 1.0—2.2 (10 H, m), 3.35 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.64—4.0 (1 H, m, NCH). 4.5 (1 H, s, ArCH), 5.9br (1 H, m, NHCO), 6.6br (1 H, s, ArOH), and 6.86 (3 H, s, ArH) (Found: C, 65.55; H, 7.9; N, 4.75. $C_{16}H_{23}NO_4$ requires C, 65.5; H, 7.9; N, 4.75%). Further hydrogenation of the amide (7h) (0.1 g) using 10% palladium–carbon (10 mg), 60% aqueous perchloric acid (50 μl), and glacial acetic acid (5 ml) for 6 days at 1 atm gave, on work-up (diethyl ether–saturated aqueous sodium hydrogen carbonate) and crystallisation from ethyl acetate, the *acetamide derivative* (7i) (64 mg, 71%) as plates, m.p. 151—153°, $\nu_{max.}$ 3 370, 3 310, 3 250, 1 650, and 1 630 cm^{-1}, δ 0.85—2.0 (10 H, m), 3.46 (2 H, s, $ArCH_2$), 3.6—4.0 (1 H, m, NCH), 3.84 (3 H, s, OMe), 5.8br (1 H, NH), and 6.6—7.0 (4 H, m, Ar-H and $^-$OH) (Found: C, 68.1; H, 7.7; N, 5.05. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.05; N, 5.3%).

Toluene-4-*sulphonylmethyl Isocyanide* (12a).—To *N*-(toluene-4-sulphonylmethyl)formamide (12b) (1.2 g) in triethylamine (14.5 ml) and dichloromethane (10 ml) was added, with vigorous stirring over 45 min (N_2), phosphoryl chloride (0.9 ml). After warming to room temperature the mixture was added to an excess of ice–saturated aqueous sodium hydrogen carbonate. The aqueous phase was extracted with dichloromethane and the combined organic layers were washed with water, dried, and evaporated. Chromatography on alumina (benzene) and recrystallisation (ethyl acetate–light petroleum) gave the isonitrile (12a), identical with authentic [35] material.

1-(3,4-*Dimethoxyphenyl*)-2-*formamido*-2-(4-*tolylsulphonyl*)*ethene* (4h).—The isonitrile (12a) (2.7 g) in dry THF (13 ml) was added with stirring (< 3 min) (Ar) to potassium t-butoxide (7.6 g) in THF (130 ml). Immediately, the mixture was cooled to −20 °C and an argon-degassed solution of 3,4-dimethoxybenzaldehyde (4c) (2.27 g) in THF (14 ml) was added followed by glacial acetic acid (3.9 ml). The mixture was allowed to warm to room temperature and the THF to evaporate. Work-up (water–dichloromethane) and crystallisation from acetone–hexane gave the *ethylene derivative* (4h) (3.93 g, 80%) as plates, m.p. 171—172°, $\nu_{max.}$ 3 260, 1 700, 1 635, 1 315, and 1 150 cm^{-1}, $\lambda_{max.}$ 235 (ε 22 000), 295 (18 000), and 324 nm (25 000), δ 2.4 (3 H, s, ArMe), 3.78 (3 H, s, OMe), 3.84 (3 H, s, OMe), and 6.64—8.18 (10 H, m, ArH, ArCH=, and NHCHO) (Found: C, 59.8; H, 5.3; N, 3.9; S, 8.85. $C_{18}H_{19}NO_5S$ requires C, 60.05; H, 5.25; N, 3.95; S, 8.95%).

1-(3,4-*Dimethoxyphenyl*)-2-*isocyano*-2-(4-*tolylsulphonyl*)-*ethene* (4i).—Phosphoryl chloride (0.6 ml) was added over 45 min to the formamide derivative (4h) (1.3 g) in triethylamine and dichloromethane (5 : 8; 26 ml) at −30 °C (N_2). The mixture was stirred overnight at room temperature. Work-up (dichloromethane–saturated aqueous sodium hydrogen carbonate, water), chromatography on alumina (benzene) and crystallisation from benzene–light petroleum gave the *isonitrile* (4i) (0.99 g, 80%) as pale yellow needles, m.p. 119—121°, $\nu_{max.}$ 2 108, 1 615, 1 330, and 1 155 cm^{-1}, $\lambda_{max.}$ 239 (ε 12 000), 324 (12 000), and 338 nm (15 000), δ 2.44 (3 H, s, ArMe), 3.86 (3 H, s, OMe), 3.92 (3 H, s, OMe), and 6.86—8.1 (8 H, ArH and ArCH=) (Found: C, 62.95; H, 5.0; N, 4.1; S, 9.35. $C_{18}H_{17}NO_4S$ requires C, 63.0; H, 5.1; N, 3.95; S, 9.4%).

2-(3,4-*Dimethoxyphenyl*)-1-{N-[2-(3,4-*dimethoxyphenyl*)-2-*methoxyacetamido*]}-1-(4-*tolylsulphonyl*)*ethene* (13a).—3,4-Dimethoxybenzaldehyde (4c) (0.33 g), trimethyl orthoformate (0.64 g), and trifluoroacetic acid (15 μl) in methanol (1 ml) were allowed to stand at room temperature for 15 h. Evaporation gave the acetal (4j) (100%), δ 3.2 (6 H, s, OMe), 3.78 (3 H, s, OMe), 3.8 (3 H, s, OMe), 5.2 (1 H, s, ArCH), and 6.78—6.9 (3 H, ArH). Trifluoroacetic acid (0.15 ml) and then the isonitrile (4i) (0.7 g) in benzene (8 ml) were added (Ar). After 4 h, work-up (benzene–saturated aqueous sodium hydrogen carbonate, water) gave the acetamide derivative (13a) (0.75 g, 70%) as a foam, $\nu_{max.}$ 3 250, 1 700, and 1 640 cm^{-1}, δ 2.5 (3 H, s, ArMe), 3.55, 3.8, 3.95, 4.0, 4.05 (15 H, 5s, 5× OMe), 4.67 (1 H, s, ArCH), 6.4—8.0 (1 H, m, ArH, ArCH=H), and 8.4br (1 H, s, NHCO).

2Z-(3,4-*Dimethoxyphenyl*)-1-{N-[2-(3,4-*dimethoxyphenyl*)-2-*methoxyacetamido*]}*ethene* (13b).—Amide (13a) (0.12 g) and sodium borohydride (60 mg) in ethanol (10 ml) were heated to reflux for 3.5 h. At 0 °C dilute hydrochloric acid was added and the solution extracted with dichloromethane. Work-up (dichloromethane–saturated aqueous sodium hydrogen carbonate, water) and p.l.c. (ethyl acetate–benzene 1 : 9) gave the *cis*-acetamide (13a) (24 mg, 25%), identical with authentic material (see below).

1-(3,4-*Dimethoxyphenyl*)-2-*formamidoethene* (4k).—(*a*) The amide (4h) (90 mg), sodium borohydride (60 mg) in THF (3 ml), and ethanol (10 ml) were heated to 60 °C for 2 h. Work-up as for compound (13b) gave the formamide (4k) (13 mg, 22%). (*b*) Reaction in DMF at 60 °C for 0.5 h gave on normal work-up (chloroform–water) the formamide (4k) (50%) as a gum, $\nu_{max.}$ 3 400, 1 695, and 1 655 cm^{-1}, $\lambda_{max.}$ 212 (ε 12 000), 225 (12 500), 278 (15 200), and 292sh nm (11 400), δ 3.9 (6 H, s, OMe), 5.8 (1 H, d, *J* 8 Hz, ArCH=), 6.7—7.0 (4 H, m, ArH and ArCH=), and 8.25br (1 H, s, NHCO).

1-(3,4-*Dimethoxyphenyl*)-2-*isocyano*-2-(4-*tolylsulphonyl*)-*ethane* (4l).—The isonitrile (4i) (0.86 g) in THF (15 ml) was added slowly to sodium borohydride (0.33 g) in ethanol (15 ml) (N_2). The mixture was heated slowly to 40 °C, cooled to room temperature, and then evaporated. Work-up (dichloromethane–water), chromatography on alumina (benzene) and crystallisation (benzene–light petroleum) gave the *isonitrile* (4l) (0.65 g, 75%) as needles, m.p. 159—160°, $\nu_{max.}$ 2 140, 1 330, and 1 135 cm^{-1}, δ 2.55 (3 H, s, ArMe), 2.95—3.6 (2 H, m, $ArCH_2$), 3.9 (6 H, s, OMe), 4.5—4.8 (1 H, dd, *J* 12, 3 Hz), 6.7—6.85 (3 H, m, ArH), and 7.4 and 7.9 (4 H, ABq, *J* 9 Hz, ArH) (Found: 62.6; H, 5.55; N, 4.05; S, 9.3. $C_{18}H_{19}NO_4S$ requires C, 62.7; H, 5.7; N, 4.0; S, 9.3%).

2-(3,4-*Dimethoxyphenyl*)-N-{[2-(3,4-*dimethoxyphenyl*)-1-(4-*tolylsulphonyl*)]*ethyl*}-2-*methoxyacetamide* (9h).—The isonitrile (4l) (2.17 g) in benzene (100 ml) and trifluoroacetic acid (0.54 ml) were added in sequence with stirring (Ar) to the dimethylacetal (4j) [from 3,4-dimethoxybenzaldehyde (4c) (1.15 g)]. After 2 h, work-up (benzene–saturated aqueous sodium hydrogen carbonate, water) gave a gum. This was mixed with dichloromethane (5ml) and stirred overnight with ethanolic aqueous sodium metabisulphite [36] (300 ml) and glacial acetic acid (0.5 ml). Work-up (dichloromethane–water) and crystallisation (benzene–light petroleum) gave the *acetamide derivative* (9h) (3 g, 88%) as plates, m.p. 140—141°, $\nu_{max.}$ 3 330, 1 690, 1 310, and 1 140 cm^{-1}, δ 2.44 (3 H, s, ArMe), 3.1 (2 H, dd, *J* 5 and 3 Hz, $ArCH_2$), 3.26, 3.68, 3.71, 3.82, 3.84 (15 H, 5s, 5 × OMe), 4.22 (1 H, s, ArCH), 5.6 (1 H, m, CHTs), 6.5—6.8 (6 H, m, ArH), and 7.37 and 7.9 (4 H, ABq, *J* 9 Hz, ArH) (Found: C, 61.85; H, 6.15; N, 2.6; S, 5.9. $C_{28}H_{33}NO_8S$ requires C, 61.55; H, 6.15; N, 2.4; S, 6.15%).

2-(3,4-*Dimethoxyphenyl*)-1-{N-[2-(3,4-*dimethoxyphenyl*)-2-*methoxyacetamido*]}*ethene* (13b,c).—1,5-Diazabicyclo-[5.4.0]undec-5-ene (0.82 ml) was added with stirring to the amide (9h) (3g) in benzene (50 ml). After 1.5 days, evaporation and rapid chromatography on alumina (benzene–ethyl acetate 3 : 2) gave the enamide (13b, c) (2g, 90%). P.l.c. (benzene–ethyl acetate 1 : 1) gave the trans-*isomer* (13c) as needles, m.p. 74—77° (from benzene–light petroleum), $\nu_{max.}$ 3 260, 1 665, and 1 645 cm^{-1}, $\lambda_{max.}$ 218 (ε 13 400), 285 (15 800), 292 (16 400), 308 (13 600), and 324sh nm (8 800), δ 3.4 (3 H, s, OMe), 3.84br (12 H, s, OMe), 4.64 (1 H, s, ArCH), 6.2 (1 H, d, *J* 16 Hz, ArCH=), 6.7—7.0 (7 H, m, ArH, NHCO), and 7.3 (1 H, d, *J* 16 Hz, ArCH=), *m/e* 387 (M^+), 355, 181 (100%), 166, and 151 (Found: C, 65.35; H, 6.45; N, 3.55. $C_{21}H_{25}NO_6$ requires C, 65.1; H, 6.5; N, 3.6%), and the *cis*-isomer (13b) a gum, $\nu_{max.}$ 3 380, 1 680, and 1 650 cm^{-1}, $\lambda_{max.}$ 227 (ε 17 900), 280 (19 500), and 294sh nm (13 300), δ 3.34 (3 H, s, OMe), 3.9, 3.95 (12 H, 2s, OMe), 4.6 (1 H, s, ArH), 5.8 (1 H, d, *J* 10 Hz, ArCH=), 6.95br (6 H, s, ArH), 6.7—7.0 (1 H, m, NHCO), and 7.05 (1 H, d, *J* 10 Hz, ArCH=), mass spectrum superimposable with that from the *trans*-isomer (13c).

2-(3,4-*Dimethoxyphenyl*)-N-[2-(3,4-*dimethoxyphenyl*)-*ethyl*]-2-*methoxyacetamide* (1b).—The enamide isomers (13b,c) (1.9 g) and W-2 Raney nickel (0.6 g) in methanol (100 ml) and ethyl acetate (100 ml) were hydrogenated at 1 atm for 2 days. T.l.c. indicated that only the *cis*-isomer (13b) was completely hydrogenated. Additional Raney Nickel (0.40 g) was added and the mixture further hydrogenated for 2 days. Filtration, evaporation, and crystallisation (ethyl acetate–light petroleum) gave the *amide* (1b) (1.6 g, 85%), m.p. 91—92°, $\nu_{max.}$ 3 300 and 1 650 cm^{-1}, δ 2.76 (2 H, t, *J* 7 Hz, $ArCH_2$), 3.32 (3 H, s, OMe), 3.4—3.76 (2 H, m, NCH_2), 3.84 (12 H, s, OMe), 4.56 (1 H, s, ArCH), and 6.74—6.86 (7 H, m, ArH, NHCO), *m/e* 389 (M^+), 181 (100%), 164, and 151 (Found: C, 64.65; H, 6.85; N, 3.55. $C_{21}H_{27}NO_6$ requires C, 64.75; H, 7.0; N, 3.6%).

N-[2-(4-*Benzyloxy*-3-*methoxyphenyl*)*ethyl*]-2-*chloro*-2-*phenylacetamide* (9j).—Phenethylamine (4o) (9.5 g) and triethylamine (6 ml) in benzene (74 ml) were added over 0.5 h with stirring to 2-chloro-2-phenylacetyl chloride (6 ml) in benzene (74 ml). After 2 h the mixture was filtered, the solid triethylammonium chloride washed with benzene, and the combined benzene solutions were evaporated. Crystallisation from ethyl acetate–light petroleum gave the *acetamide derivative* (9j) (11.6 g, 75%) as needles, m.p. 106—107°, $\nu_{max.}$ 3 340 and 1 650 cm^{-1}, δ 2.76 (2 H, m, $ArCH_2$), 3.48 (2 H, m, NCH_2), 3.83 (3 H, s, OMe), 5.16 (2 H, s, $ArCH_2$), 5.36 (1 H, s, ArCH), 6.6—6.96 (3 H, m, ArH), and 7.37—7.7 (10 H, m, 2 × Ph) (Found: C, 70.25; H, 5.95; Cl, 8.65; N, 3.35. $C_{24}H_{24}ClNO_3$ requires C, 70.3; H, 5.9; Cl, 8.65; N, 3.4%).

N-[2-(4-*Benzyloxy*-3-*methoxy*)*ethyl*]-2-*methoxy*-2-*phenyl-acetamide* (9i).—Sodium methoxide (from sodium, 0.16 g) in methanol (2.3 ml) was added dropwise to the amide (9j) (2.0 g) in THF (48 ml). After 2 days glacial acetic acid was added to neutrality and the mixture evaporated. Work-up (dichloromethane–water) gave the crude amide (9i) (1.82 g, 92%). Crystallisation from diethyl ether gave the *amide* (9i) (1.5 g, 76%) as needles, m.p. 70—72°, $\nu_{max.}$ 3 290 and 1 645 cm^{-1}, δ 2.7 (2 H, m, $ArCH_2$), 3.23 (3 H, s, OMe), 3.4 (2 H, m, NCH_2), 3.84 (3 H, s, OMe), 4.6 (1 H, s, ArCH), 5.16 (2 H, s, $ArCH_2$), 6.6—6.9br (3 H, m, ArH), 7.2—7.5 (10 H, m, 2 × Ph) (Found: C, 74.0; H, 6.55; N, 3.4. $C_{25}H_{27}NO_4$ requires C, 74.05; H, 6.7; N, 3.45%).

Bischler–Napieralski Cyclisation of the Amide (9i).—The amide (9i) (0.48 g) and phosphoryl chloride (1.2 ml) in acetonitrile (4.8 ml) were allowed to stand for 3 days (N_2). After evaporation the residual red gum was washed with diethyl ether and dissolved in water. The aqueous solution was filtered, made alkaline with 5% aqueous ammonia (N_2), and rapidly extracted with diethyl ether. After drying, evaporation gave the crude air-sensitive dihydroisoquinoline (10f) (0.39 g, 85%), δ 2.7 (2 H, m, $ArCH_2$), 3.38 (3 H, s, OMe), 3.7—4.0 (2 H, m, NCH_2), 3.84 (3 H, s, OMe), 4.98 (2 H, s, $ArCH_2$), 5.24 (1 H, s, ArCH), 6.6 (1 H, s, ArH), and 7.2—7.5 (11 H, m, ArH and 2 × Ph). The product (10f) (0.39 g) and iodomethane (3 ml) in ethanol (4.5 ml) were refluxed (N_2) overnight. After evaporation, sodium borohydride (1g) was added in portions to the residual red gum in methanol (15 ml). After 2 h at 40 °C, the mixture was evaporated. Work-up (diethyl ether—5% aqueous ammonia) and p.l.c. (ethyl acetate–cyclohexane–

triethylamine (20 : 3 : 1) gave the tetrahydroisoquinoline (10g) (0.21 g, 44%) as a mixture (5 : 2) of diastereoisomers, δ 2.3—3.1 (4 H, m, $ArCH_2$ and NCH_2), 2.46, 2.55 (3 H, 2s, NMe), 3.17 (3 H, s, OMe), 3.6—3.9 (1 H, m, ArCHN), 3.77, 3.8 (3 H, 2s, OMe), 4.2—4.4 (1 H, m, ArCH), 4.65, 4.95 (2 H, 2s, $ArCH_2$), 6.18, 6.42, 6.54 (2 H, 3s, ArH), and 6.8—7.5 (10 H, m, 2 × Ph) (Found: C, 77.15; H, 7.3; N, 3.55. $C_{26}H_{29}NO_3$ requires C, 77.4; H, 7.25; N, 3.45%).

Bischler-Napieralski Cyclisation of the Amide (9g).—Similar reactions with the amide (9g) gave the dihydroisoquinoline (10e) (90%) and the *tetrahydroisoquinoline* (10i) (50%) as a mixture (1 : 1) of diastereoisomers, δ 2.4—3.2 (4 H, m, $ArCH_2$, NCH_2), 2.47, 2.57 (3 H, 2s, NMe), 3.24br (3 H, s, OMe), 3.58—3.9 (12 H, 6s, 6 × OMe), 4.0—4.6 (2 H, m, 2 × ArCH), and 6.2—6.9 (5 H, m, ArH) (Found: C, 68.0; H, 7.55; N, 3.45. $C_{22}H_{29}NO_5$ requires C, 68.2; H, 7.55; N, 3.6%).

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