Pergamon

Tetrahedron, Vol. 53, No. 42, pp. 14381-14396, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00922-8

The Functionalisation of Electron Rich Aromatic Compounds with 1,3-Oxazolidines and 1,3-Dimethylimidazolidine

Harry Heaney,* George Papageorgiou and Robert F. Wilkins

Department of Chemistry, Loughborough University, Loughborough, Leicestershire, LE11 3TU, UK

Abstract: *N*-Phenyl- and *N*-alkyl-oxazolidines react with alkyl chlorosilanes in the presence of electron rich aromatic compounds with the formation of the expected Mannich bases: 2-methoxycarbonyl-3-methyloxazolidine also reacts with 2-methylfuran in the presence of thionyl chloride to give an α-amino acid derivative: the iminium salt derived from 1,3-dimethylimidazolidine was also shown to react with 2-methylfuran. © 1997 Elsevier Science Ltd.

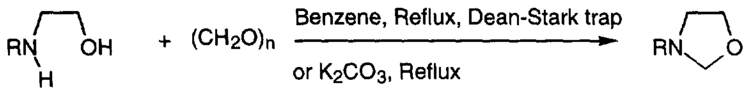
INTRODUCTION

The ring-chain tautomerism of the five- and six-membered 1,3-diaza and 1,3-oxaza heterocycles has been studied by ^{1}H nmr spectroscopy which suggested that under strongly acidic conditions the open-chain form exists as 10-20% of the equilibrium mixture.[1] The hydroxy Schiff base-oxazolidine tautomerism has been further investigated in terms of the apparent breakdown of Baldwin's rules.[2] Although 3-substituted-1,3-oxazolidines have been known for many years,[3] their usage has been concentrated, until recently, mainly on reactions with Grignard reagents.[4] A series of studies by Griengl's group[5] utilised 1,3-oxazolidines in synthetic routes to seven and eight membered heterocyclic compounds. Part of that work involved treatment 1,3-oxazolidines with trifluoroacetic acid in order to generate iminium ions, which were then trapped with cyclic alkenes to give bicyclic 1,4-oxazepines.[5b] A recent report describes the *N*-methylation of serine esters by an acid-catalysed ring opening of 4-methoxycarbonyl-1,3-oxazolidines and *in situ* reduction of the generated iminium species with triethylsilane.[6]

In the course of our investigations involving the development of new protocols in which Mannich reactions were carried out under non aqueous reaction conditions, we prepared a variety of functionalised Mannich bases. Thus, acyclic aminals and aminol ethers, derived from secondary amines, afforded a range of tertiary amines.[7] Bis(aminol) ethers[8] generated from aliphatic primary amines were employed in the synthesis of secondary as well as tertiary amines and those derived from 3,4-dimethoxy-β-phenylethylamine gave access to 2-arylmethyltetrahydroisoquinolines.[9] β-Ketocarbamates were synthesised by diastereoselective reactions of trialkyl silyl ethers with acyliminium ions[10] and the triflic acid catalysed removal of *N-tert*-butyl group from carbamates gave rise to novel carbamate-protected primary amines.[11] It was envisaged that the scope of the Mannich reaction could be increased further by employing a wider range of reagents which could enable the isolation of more functionalised Mannich bases . We reported our preliminary results that involved *in situ* reactions of oxazolidines with a range of nucleophilic aromatic compounds and silyl enol ethers forming a wide range of amino alcohols.[12] The present paper provides a detailed account on the functionalisation of electron rich aromatic compounds using 3-substituted-1,3-oxazolidines and 3-methyl-2-methoxycarbonyl-1,3-oxazolidine as well as 1,3-dimethylimidazolidine.

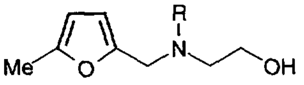
RESULTS AND DISCUSSION

A part of the program of our investigations was dedicated to the *in situ* activation of aminals and aminol ethers by chlorosilanes in reactions with electron rich aromatic compounds.[13] In order to extend this method we prepared a range of 3-substituted-1,3-oxazolidines (**1a-e**) by the literature procedure[1b,14] which involved heating the appropriate *N*-substituted ethanolamine and paraformaldehyde in benzene under Dean-Stark conditions. Although this method worked well for the high-boiling 1,3-oxazolidines the yields of 3-methyl- and 3-ethyl-1,3-oxazolidines (**1a**) and (**1b**) respectively were reduced due to co-distillation of benzene with the product. We improved the method by heating a mixture of the ethanolamine derivative, paraformaldehyde, and anhydrous potassium carbonate in the absence of a solvent.



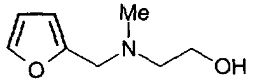
(**1 a**) R = Me
(**1 b**) R = Et
(**1 c**) R = ^{t}Bu
(**1 d**) R = PhCH$_2$
(**1 e**) R = Ph

A series of reactions of 3-substituted-1,3-oxazolidines with 2-methylfuran using chlorosilanes as activating agents allowed the introduction of two functional groups simultaneously into the side chain of the Mannich product. Good yields of 2-hydroxyethanolamines (**2a-e**) were obtained using chlorotrimethylsilane as the activating agent which were further improved when the reactions were carried out in the presence of trichloromethylsilane. Similarly, a reaction of furan with 3-methyl-1,3-oxazolidine (**1a**) and chlorotrimethylsilane gave the amino alcohol (**3**) in 30% yield which was improved to 75% when trichloromethylsilane was used. A smaller disparity between the yields of the reactions involving chlorotrimethylsilane and trichloromethylsilane was observed than with those reactions involving aminals and acyclic aminol ethers.[13] This suggests a higher degree of reactivity for the intermediates involved in reactions of 3-substituted-1,3-oxazolidines.



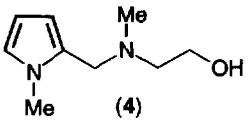
(**2**)

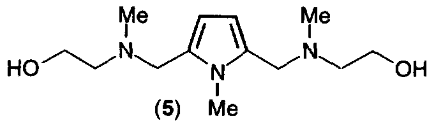
(**2 a**) R = Me
(**2 b**) R = Et
(**2 c**) R = ^{t}Bu
(**2 d**) R = PhCH$_2$
(**2 e**) R = Ph



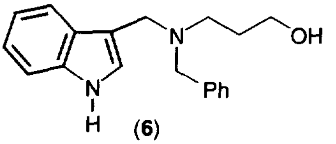
(**3**)

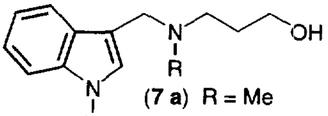
The successful introduction of a side chain containing both tertiary amine and primary alcohol groups into the furan nucleus suggested that further investigation of other electron-rich heterocycles would be profitable. Thus, the reaction of oxazolidine (**1a**) with *N*-methylpyrrole and trichloromethylsilane yielded a mixture of the 2-substituted (**4**) and 2,5-disubstituted (**5**) Mannich bases, in 54% and 12% yield respectively, whereas only the monosubstituted derivative (**4**) was obtained in 73% yield using chlorotrimethylsilane. Although treatment of the oxazolidine (**1a**) with trichloromethylsilane in diethyl ether yielded a white sticky solid, its structure could not be confirmed by low-field ^{1}H nmr spectroscopy. However, subsequent dissolution in acetonitrile and treatment with *N*-methylpyrrole gave the pyrrole derivative (**4**) in 62% yield. It is of interest to note that an attempted reaction in which 3-methyl-1,3-oxazolidine was treated with acetyl chloride failed to yield a Mannich base with *N*-methylpyrrole.


(4)

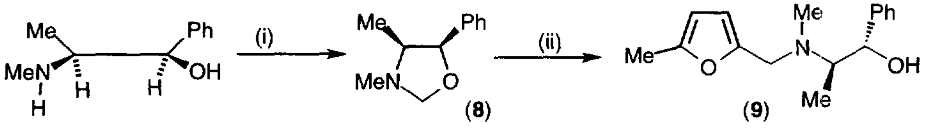

(5)

We also extended this investigation in a number of reactions of indole and *N*-methylindole with 3-substituted-1,3-oxazolidines and chlorosilanes which yielded the expected ethanolamine derivatives (**6**) and (**7a-c**) respectively. In all cases excellent yields were obtained especially when trichloromethylsilane was used as the activating agent. The amino alcohol (**6**) was isolated as a crystalline solid whereas the products of the reactions of *N*-methylindole were homogeneous involatile oils which were characterised after conversion into their respective hydrochloride salts.


(6)


(7 a) R = Me
(7 b) R = Et
(7 c) R = $PhCH_2$

Although numerous 1,3-oxazolidines have been prepared from ephedrine these appear only to have been used synthetically as co-reactants with Grignard reagents.[15] As far as we are aware ephedrine has only been employed previously in a classical Mannich reaction with 1,2-diphenylindolizine and formalin for the preparation of Mannich bases with potential pharmacological activity.[16] In the course of our investigations we prepared 3,4-dimethyl-5-phenyloxazolidine (**8**) from (1R,2S)-ephedrine and paraformaldehyde in an excellent yield. Although this reagent failed to give a product with furan and chlorotrimethylsilane, 2-methylfuran gave the amino alcohol (**9**) in 25% yield using chlorotrimethylsilane but when we used trichloromethylsilane the yield was raised to 80%, as shown in ***Scheme 1***.

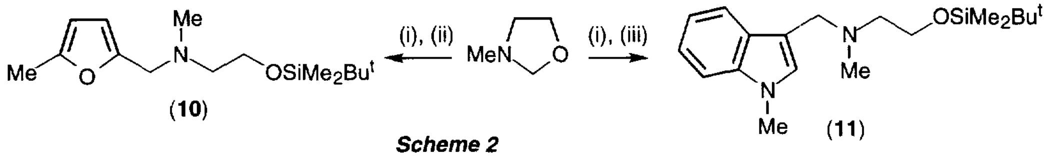


Scheme 1

(i) $(CH_2O)_n$, K_2CO_3, benzene, reflux, Dean-Stark trap; (ii) 2-methylfuran, MeCN, $MeSiCl_3$

The successful activation of oxazolidines with chlorotrimethylsilane and trichloromethylsilane prompted our attention in the use of *t*-butyldimethylsilyl chloride (TBDMSCl). The greater stability of TBDMS ethers as compared with trimethylsilyl ethers suggested that reactions of TBDMSCl with 3-methyl-1,3-oxazolidine (**1a**), in the presence of a suitable aromatic substrate, would permit the isolation of Mannich bases containing an alcohol functionality protected as its silyl ether. An analogy for this type of reaction involves the cleavage of tetrahydrofuran with TBDMSCl in the presence of sodium iodide to yield 1-iodo-4-*t*-butyldimethylsilyloxybutane.[17] Thus, the reaction of 3-methyl-1,3-oxazolidine (**1a**) with 2-methylfuran and TBDMSCl led to the formation of the protected alcohol (**10**) in 32% yield after 48 hours. However, neither the addition of sodium iodide to the reaction mixture nor heating at 55 °C for 16 hours improved the yield of the reaction and only a prolonged reaction time (14 days) gave the product in 66% yield.

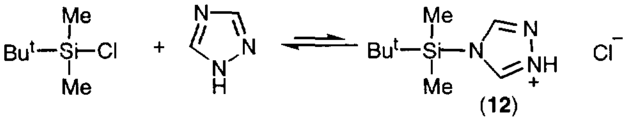
In view of the impractical time scale of this reaction an attempt to improve the efficiency of the reaction was undertaken. A more electrophilic reagent than TBDMSCl was evidently required. Although the rate of formation of TBDMS ethers derived from tertiary alcohols is reported to increase dramatically using TBDMS triflate in the presence of 2,6-lutidine,[18] we found that 2-methylfuran is rapidly destroyed by trialkylsilyl triflates, possibly as a result of the presence of adventitious triflic acid, and we therefore sought an alternative approach. The most frequently employed method of t-butyldimethylsilylation involves the use of TBDMSCl together with a base. The earliest procedure reported used imidazole as a basic catalyst in the protection of hydroxyl groups,[19] though more recent methods recommend the use of 4-*N*,*N*-dimethylaminopyridine (DMAP) in the presence of another base, such as triethylamine.[20] The use of 1,8-diaza-bicyclo[5,4,0]undec-7-ene (DBU) has been recommended,[21] and 1,2,4-triazole is reported to be the reagent of choice in the silylation of tribenzoylated ribofuranose.[22] Although our initial experiments using imidazole and DMAP showed no improvement, the use of one equivalent of 1,2,4-triazole in conjunction with TBDMSCl gave the desired product (**10**) in 61% yield after 72 hours. Similarly a reaction of 1-methylindole without the use of a catalyst gave the derivative (**11**) in 34% yield but the addition of 1,2,4-triazole or DMAP gave the same product in 51% and 53% yields respectively, as shown in ***Scheme 2***. The increased electrophilicity of the silylating agent is thought to be due to the formation of the silylammonium complex (**12**). The higher yields of products obtained using 1,2,4-triazole over imidazole may be due to greater efficiency of positive charge accumulation on the ring as more CH groups are replaced by electronegative nitrogen atoms.[23]



(**10**) (**11**)

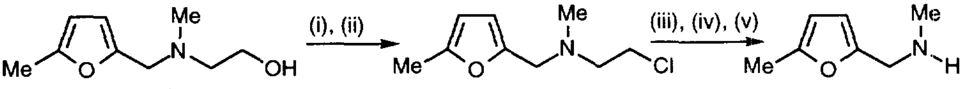
Scheme 2

(i) TBDMSCl, 1,2,4-triazole, MeCN; (ii) 2-methylfuran; (iii) 1-methylindole



(**12**)

In order to extend the synthetic utility of the Mannich reactions of 3-substituted-1,3-oxazolidines we converted the amino alcohol (**2a**) to the corresponding secondary amine. Thus, the alcohol (**2a**) was allowed to react with hexamethylphosphorus triamide (HMPT) in carbon tetrachloride[24] giving the expected chloride in 55% yield. Subsequent treatment of the chloro-derivative (**13**) with zinc in acetic acid in the presence of sodium iodide under reflux, gave the desired secondary amine (**14**)[25] in 61% yield, as shown in ***Scheme 3***. The dehalo-alkylation of 2-haloethyl ethers and 2-dimethylaminomethyl chloride with metals has been reported previously[26] but there is no report of isolation of a secondary amine.



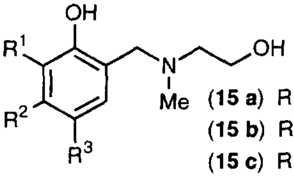
(**2a**) (**13**) (**14**)

Scheme 3

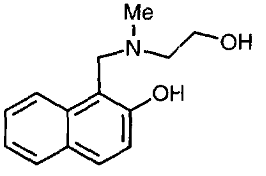
(i)HMPT, CCl$_4$, -40 °C, N$_2$; (ii) 25 °C; (iii) Zn, AcOH, NaI; (iv) ultrasound, 1 h; (v) reflux

It is interesting to speculate whether the reported reactions of phenols with *N*-methylethanolamine[27] and formaldehyde involve the intermediacy of 3-methyl-1,3-oxazolidine. A part of the present investigation included a number of reactions of phenols with 3-methyl-1,3-oxazolidine. Although low yields of the corresponding amino alcohols (**15a-c**) were obtained with moderately nucleophilic phenols, more reactive analogues such as 3-methoxyphenol and 2-naphthol afforded good yields of the Mannich bases (**15d**) and (**16**) respectively in the absence of an activating agent. It is clear that phenols are sufficiently acidic to generate an iminium ion from an oxazolidine. In a different study, 3-substituted-oxazolidines have been employed for the introduction of aminoethanolic moieties onto the nucleus of nucleophilic salicylaldehydes and phenols.[28]

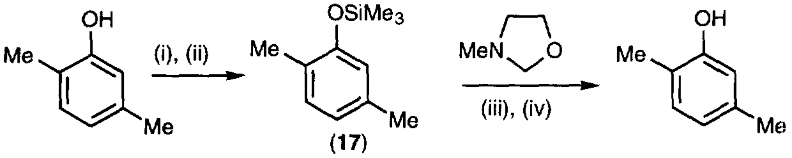
Following the successful use of the cheaper chlorosilanes in the reactions of oxazolidines with aromatic heterocycles an attempt was made to improve the yields of the less reactive phenols. It was found, however, that presence of silicon reagents completely deactivated the phenolic ring. This suggests that the chlorosilane derivative reacts with the phenol forming an aryl silyl ether under the reaction conditions used and that the protection of the phenol by the alkylsilyl group results in the reduction of the nucleophilicity of the phenol. Benzenoid compounds less nucleophilic than *meta*-dimethoxybenzene do not react with the relatively weak electrophiles involved in Mannich reactions.[29] Some evidence for this proposal was obtained from the total inertness of 2,5-(dimethylphenoxy)trimethylsilane (**17**) towards 3-methyl-1,3-oxazolidine (**1a**). Even the presence of fluoride ion did not succeed in reactivating the ring and the only product isolated after hydrolytic work-up was 2,5-dimethylphenol, as shown in ***Scheme 4***. This result supports the view that the presence of free phenolic moiety is essential for the reactions to take place. The acidity of phenols derives from their ability to form the phenoxide anion in neutral or slightly alkaline media. Under acidic conditions phenoxide anion formation is not favoured and the nucleophilicity of the ring is reduced. It is reported that 4-hydroxyacetophenone,[30] for example, reacts at the enolised ketone function under acidic conditions and ring substitution only occurs in a mildly basic medium.



(**15 a**) $R^1 = R^3 = Me, R^2 = H$
(**15 b**) $R^1 = R^2 = H, R^3 = OMe$
(**15 c**) $R^1 = OMe, R^2 = H, R^3 = Me$
(**15 d**) $R^1 = R^3 = H, R^2 = OMe$



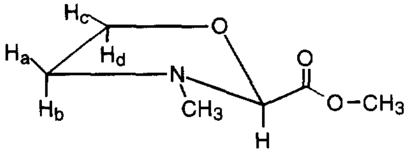
(**16**)



Scheme 4

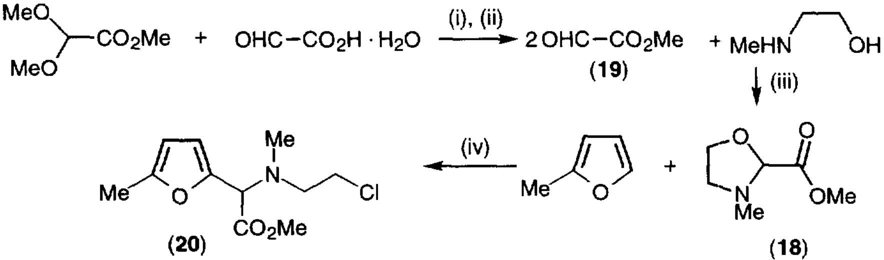
(i) NaH, THF; (ii) Me_3SiCl; (iii) MeCN, KF; (iv) water

In our pursuit of Mannich bases with substituents on the α-carbon to the nucleophile we also synthesised 2-methoxycarbonyl-3-methyl-1,3-oxazolidine (**18**). Methyl glyoxylate (**19**) was prepared by heating methyl dimethoxyacetate and glyoxylic acid monohydrate in the presence of a catalytic amount of *para*-toluenesulphonic acid followed by distillation from phosphorus pentoxide. Condensation with *N*-methylethanolamine in benzene gave the 2-substituted-1,3-oxazolidine (**18**) in 51% yield. The ^{1}H nmr spectrum of compound (**18**) showed resonances at δ_H 2.72 (1H, dt) and 3.17 (1H, dt) for protons H_a and H_b, and 3.69-4.01 (2H, m) which may be assigned to H_c and H_d. The complexity of the spectrum can be attributed to diastereotopicity effects due to the introduction of a stereogenic centre at the 2-position. Thus it can be seen that on each of the methylene carbons, the two protons are in different magnetic environments. The structure of (**18**) was confirmed by high-field ^{1}H-^{1}H and ^{1}H-^{13}C correlation nmr spectra and high resolution electron impact mass spectrometry.



(**18**)

A number of attempted reactions of the oxazolidine (**18**) with 2-methylfuran in the presence of chlorosilanes failed and the use of stronger Lewis acids (boron trifluoride etherate and titanium tetrachloride), or even a protic acid (trifluoroacetic acid) also gave none of the desired product, presumably due to the higher activation energy of formation of the required iminium salt. The known cleavage of tetrahydrofuran by TBDMS-Cl and iodide ion,[17] suggested that S_N2 cleavage of a carbon-oxygen bond on the side remote from the nitrogen and the electron-withdrawing group was possible. It was anticipated that reaction with thionyl chloride, a reagent used for the conversion of alcohols into the related alkyl chlorides, could cause cleavage of the ring in such a manner and simultaneously provide an additional driving force for the generation of an iminium salt by the liberation of sulphur dioxide. Thus, treatment of oxazolidine (**18**) with thionyl chloride in the presence of 2-methylfuran gave the expected *N*-chloroethyl derivative (**20**) , as shown in ***Scheme 5***. This reaction is of synthetic importance since it allows the simultaneous introduction of a number of functional groups into the aminoalkyl residue. Compounds of this type may used as precursors to α-amino acids . However, more significantly, the formation of a new chiral centre provides the possibility of stereoselective Mannich reactions using chiral oxazolidines.

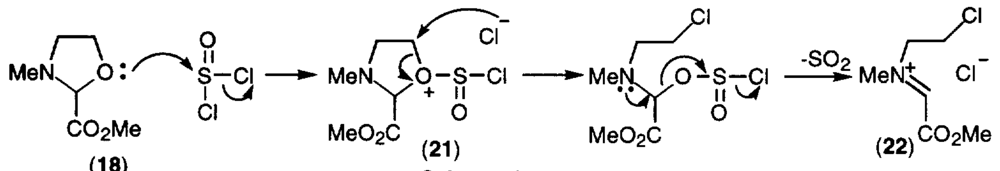


Scheme 5

(i) *p*-TsOH, 80 °C, 18 h; (ii) P_2O_5, 80 °C, 4 h;
(iii) benzene, reflux, Dean-Stark trap; (iv) $SOCl_2$, MeCN

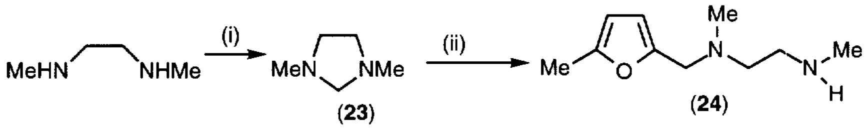
A plausible mechanism for this reaction is outlined in ***Scheme 6***. Thus, reaction of (**18**) with thionyl chloride gives the oxonium species (**21**), which undergoes nucleophilic attack by chloride ion at the 5-position.

Elimination of sulphur dioxide then yields the iminium species (**22**) which interacts with the aromatic ring in the usual way.



Scheme 6

In view of the success that had been achieved using 1,3-oxazolidines, which are nominally cyclic aminol ethers, it was envisaged that cyclic aminals would also prove to be useful reagents. The ^{1}H nmr spectrum of 1,3-dimethylimidazolidine (**23**) has been studied in trifluoroacetic acid and ring-chain tautomerism similar to that reported for 1,3-oxazolidines was observed.[1a] The proportion of the open-chain form was found to be increased from 15-20% to about 28% when the 2-position was substituted by a phenyl group probably due to resonance stabilisation of the cation.[31] In order to test our predictions we prepared 1,3-dimethylimidazolidine (**23**) in a moderate yield by condensation of *N,N'*-dimethylethylenediamine with paraformaldehyde in benzene using potassium carbonate as a dehydrating agent. Although furan failed to give the corresponding Mannich base in a reaction with imidazolidine (**23**) in the presence of trichloromethylsilane, 2-methylfuran gave the diamine (**24**) containing both secondary and tertiary amine functionalities, as shown in ***Scheme 7***.



Scheme 7

(i) $(CH_2O)_n$, K_2CO_3, benzene, reflux; (ii) 2-methylfuran, $MeSiCl_3$, MeCN

Acknowledgements

We thank the University for research training awards (to G.P. and R.F.W.) and Dr D.W. Payling (the former Fisons plc) for help in obtaining elemental analyses and some mass spectra.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer; only selected absorbances are reported. Spectra were recorded as thin films (film), potassium bromide discs (KBr) or nujol mulls (nujol). ^{1}H nmr Spectra were recorded on Varian EM 360 A (60 MHz), Perkin-Elmer R32 (90 MHz), Jeol GSX-270/54 (270 MHz) or Bruker AMX 360 (360 MHz) spectrometers and ^{13}C nmr spectra were recorded on Bruker WP 80 (20.1 MHz) together with off resonance decoupling, Jeol GSX-270/54 (67.8 MHz) or Bruker AMX 360 (90.6 MHz) spectrometers in $CDCl_3$ using TMS as reference unless otherwise stated. Spin-spin coupling constants (*J* values) are given in Hz. Multiplicities are reported as singlet (s), doublet (d), triplet (t), double triplet (dt), quartet (q), multiplet (m). Mass spectra were recorded by electron impact using a Kratos (M.S.80) spectrometer or by fast atom bombardment (FAB) using a V.G.70-250 S spectrometer. Melting Points were recorded using a Kofler hot stage apparatus and are uncorrected. Microanalyses were carried out by the former Fisons plc, (Pharmaceutical Division), Loughborough.

3-Methyl-1,3-oxazolidine (**1a**)

N-Methylethanolamine (15.02g, 0.2 mol), paraformaldehyde (10.01g, 0.33 mol) and anhydrous potassium carbonate (11.06g, 0.08 mol) were heated under reflux for 6 h. The solid was filtered, washed with diethyl ether and the filtrate was dried and fractionally distilled to yield the *title compound* (12.15g, 70%), b.p. 97-100 °C, (lit.[1b], 97-99 °C); δ_H (60 MHz) 2.43 (3H, s, CH_3), 2.94 (2H, t, *J* 7, NCH_2CH_2), 3.78 (2H, t, *J* 7, OCH_2CH_2), and 4.24 (2H, s, NCH_2O) ppm; δ_C (20.1 MHz, CD_2Cl_2) 41.8 (CH_3), 55.1 (NCH_2CH_2), 64.2 (OCH_2CH_2), and 89.3 (NCH_2O) ppm; M^+ measured 87.0672; calc. for C_4H_9NO 87.0684.

3-Ethyl-1,3-oxazolidine (**1b**)

N-Ethylethanolamine (35.6g, 0.4 mol), paraformaldehyde (18.0g, 0.6 mol) and anhydrous potassium carbonate (22.1g, 0.16 mol) were treated as described above for 4.5 h, to yield the *title compound* (25.0g, 62%), b.p. 119-21 °C, (lit.[32], 122 °C), δ_H (60 MHz) 1.12 (3H, t, *J* 8.5, CH_3), 2.58 (2H, q, *J* 8.5, CH_2CH_3), 2.93 (2H, t, *J* 6.5, NCH_2CH_2), 3.79 (2H, t, *J* 6.5, OCH_2CH_2), and 4.28 (2H, s, NCH_2O) ppm; M^+ measured 101.0828; calc. for $C_5H_{11}NO$ 101.0841.

3-t-Butyl-1,3-oxazolidine (**1c**)

N-t-Butylethanolamine (58.6g, 0.5 mol) and paraformaldehyde (16.5g, 0.55 mol) in benzene (250 ml) were heated under reflux using a Dean-Stark trap for 20 h. Concentration in vacuo and fractional distillation gave the *title compound* (51.8g, 80%), b.p. 43 °C/12 mmHg (lit.[33], 63-64 °C/32 mmHg), δ_H (60 MHz) 1.12 (9H, s, CMe_3), 2.92 (2H, t, *J* 6.5, NCH_2CH_2), 3.82 (2H, t, *J* 6.5, OCH_2CH_2), and 4.40 (2H, s, NCH_2O) ppm; δ_C (67.8 MHz) 27.0 (CH_3), 45.2 (NCH_2CH_2), 52.5 ($C\,CH_3$), 66.2 (OCH_2CH_2), and 81.0 (NCH_2O) ppm; M^+ measured 129.1142; calc. for $C_7H_{15}NO$ 129.1154.

3-Benzyl-1,3-oxazolidine (**1d**)

N-Benzylethanolamine (75.6g, 0.5 mol) and paraformaldehyde (16.5g, 0.55 mol) in benzene (250 ml) were treated as described above to give the *title compound* (74.7g, 92%), b.p. 66-69 °C/0.1 mmHg (lit.[34] 90-95 °C/1.5 mmHg), δ_H (60 MHz) 2.89 (2H, t, *J* 7, NCH_2CH_2), 3.67 (2H, s, $PhCH_2$), 3.77 (2H, s, OCH_2CH_2), 4.30 (2H, s, NCH_2O), and 7.35 (5H, s, PhH) ppm; δ_C (67.8 MHz) 51.7 (NCH_2CH_2), 57.8 ($PhCH_2$), 63.1 (OCH_2CH_2), 86.4 (NCH_2O), 127.1 (C-4′), 128.2 (C-2′and C-6′), 128.6 (C-3′and C-5′), and 138.7 (C-1′) ppm; M^+ measured 163.0972; calc. for $C_{10}H_{13}NO$ 163.0997.

3-Phenyl-1,3-oxazolidine (**1e**)

2-Anilinoethanol (68.6g, 0.5 mol) and paraformaldehyde (16.5g, 0.55 mol) in benzene (250 ml) were treated as described above to give the *title compound* (65.0g, 87%), b.p. 68-72 °C/0.1 mmHg (lit.[35], 94 °C/1.5 mmHg), which solidified on cooling, m.p. 28 °C (from pentane) (lit.[34], 28 °C), δ_H (270 MHz) 3.36 (2H, t, *J* 6, NCH_2CH_2), 4.11 (2H, t, *J* 6, OCH_2CH_2), 4.82 (2H, s, NCH_2O), 6.48 (2H, d, J_{AC} 8, 2′-H and 6′-H), 6.75 (1H, t, J_{AB} 8, 4′-H), and 7.22 (2H, m, 3′-H and 5′-H) ppm; δ_C (67.8 MHz) 46.0 (NCH_2CH_2), 67.3 (OCH_2CH_2), 81.1 (NCH_2O), 112.5 (C-2′and C-6′), 117.5 (C-4′), 129.3 (C-3′anf C-5′), and 145.6 (C-1′) ppm; M^+ measured 149.0837; calc. for $C_9H_{11}NO$ 149.0841.

Reactions of 1,3-Oxazolidines with Heterocycles and Chlorosilanes—General Method

A chlorosilane derivative (1.1 equiv.) was added to a mixture of a heterocycle (1.1 equiv.) and 1,3-oxazolidine (1 equiv.) in acetonitrile at 0 °C under dry nitrogen. The reaction mixture was stirred at room temperature for a specified length of time, quenched with water and concentrated *in vacuo* . The residue was acidified to pH2 with 2M HCl when necessary, washed with diethyl ether (3x30 ml) and then basified to pH14 with 4M NaOH and washed with diethyl ether (4x40 ml). The combined organic extracts from the basic solution were dried ($MgSO_4$), concentrated *in vacuo* and the residue was distilled (Kugelrohr) or recrystallised from a suitable solvent.

2-(N-2′-Hydroxyethylmethylaminomethyl)-5-methylfuran (**2a**)

2-Methylfuran (0.90g, 11 mmol), 3-methyl-1,3-oxazolidine (**1a**) (0.87g, 10 mmol) and trichloromethylsilane (1.64g, 11 mmol) in acetonitrile (50 ml) for 48 h, gave the *title compound* (1.47g, 87%), b.p. 63 °C/0.45 mmHg; ν_{max} (film) 3412 (OH) cm^{-1}; δ_H (60 MHz) 2.25 (6H, s, NCH_3 and $ArCH_3$), 2.56 (2H, t, J 6, $\mathrm{NC}H_2\mathrm{CH}_2$), 3.55 (2H, s, $ArCH_2$), 3.63 (2H, t, J 6 , OCH_2), 4.06 (1H, s, D_2O ex., OH), 5.80-5.98 (1H, m, 4-H), and 6.07 (1H, d, J_{AB} 3, 3-H) ppm; M^+ measured 169.1093; $C_9H_{15}NO_2$ requires 169.1103.

2-(N-Ethyl-2′-hydroxyethylaminomethyl)-5-methylfuran (**2b**)

2-Methylfuran (1.35g, 16.5 mmol), 3-ethyl-1,3-oxazolidine (**1b**) (1.52g, 15 mmol) and trichloromethylsilane (2.47g, 16.5 mmol) in acetonitrile (50 ml) for 44 h gave the *title compound* (2.44g, 89%), b.p. 63-64 °C/ 0.1 mmHg. Found: C, 65.15; H, 9.5; N, 7.7. $C_{10}H_{17}NO_2$ requires C, 65.5; H, 9.35; N, 7.6%; ν_{max} (film) 3392 (OH) cm^{-1}; δ_H (60 MHz) 1.03 (3H, t, J 7, $\mathrm{CH_2C}H_3$), 2.29 (3H, s, $ArCH_3$), 2.57 (2H, q, J 7, $\mathrm{C}H_2\mathrm{CH}_3$), 2.65 (2H, t, J 5.5, NCH_2CH_2), 3.49 (1H, s, D_2O ex., OH), 3.58 (2H, t, J 5.5, OCH_2), 3.65 (2H, s, $ArCH_2$), 5.80-5.95 (1H, m, 4-H), and 6.06 (1H, d, J_{AB} 3, 3-H) ppm; M^+ measured 183.1256; requires 183.1259.

2-(N-t-Butyl-2′-hydroxyethylaminomethyl)-5-methylfuran (**2c**)

2-Methylfuran (1.35g, 16.5 mmol), 3-*t*-butyl-1,3-oxazolidine (**1c**) (1.94g, 15 mmol) and trichloromethylsilane (2.47g, 16.5 mmol) in acetonitrile (50 ml) for 44 h, gave the *title compound* (2.70g, 85%), b.p. 75-76 °C/0.1 mmHg. Found: C, 68.0; H, 10.0; N, 6.6. $C_{12}H_{21}NO_2$ requires C, 68.2; H, 10.0; N, 6.6%; ν_{max} (film) 3428 (OH) cm^{-1}; δ_H (60 MHz) 1.16 (9H, s, CMe_3), 2.26 (3H, s, $ArCH_3$), 2.79 (2H, t, J 5.5, $\mathrm{NC}H_2\mathrm{CH}_2$), 3.06 (1H, s, D_2O ex., OH), 3.39 (2H, t, J 5.5, OCH_2), 3.69 (2H, s, $ArCH_2$), 5.83-5.98 (1H, m, 4-H), and 6.07 (1H, d, J_{AB} 3, 3-H), δ_C (20.1 MHz) 13.5 (q, $ArCH_3$), 27.4 (q, $\mathrm{C}C\mathrm{H}_3$), 46.4 (t, $\mathrm{N}C\mathrm{H_2CH_2}$), 51.1 (t, $ArCH_2$), 54.9 (s, $C\mathrm{Me}_3$), 60.3 (t, OCH_2), 106.3 and 108.1 (d, C-3 and d, C-4), and 150.9 and 153.3 (d, C-2 and d, C-5) ppm; M^+ measured 211.1557; requires 211.1572.

2-(N-Benzyl-2′-hydroxyethylaminomethyl)-5-methylfuran (**2d**)

2-Methylfuran (1.35g, 16.5 mmol), 3-benzyl-1,3-oxazolidine (**1d**) (2.45g, 15 mmol) trichloromethylsilane (2.47g, 16.5 mmol) in acetonitrile (50 ml) for 20 h gave the *title compound* (3.02g, 82%), b.p. 115-16 °C/0.05 mmHg; ν_{max} (film) 3420 (OH) cm^{-1}; δ_H (60 MHz) 2.28 (3H, s, CH_3), 2.70 (2H, t, J 5.5, $\mathrm{NC}H_2\mathrm{CH}_2$), 2.93 (1H, s, D_2O ex., OH), 3.59 (2H, t, J 5.5, OCH_2), 3.63 (2H, s, $ArCH_2$), 3.66 (2H, s, $PhCH_2$), 5.85-6.01 (1H, m, 4-H), 6.09 (1H, d, J_{AB} 3, 3-H), and 7.31 (5H, s, PhH) ppm; M^+ measured 245.1412, $C_{15}H_{19}NO_2$ requires 245.1416.

2-(N-2'-Hydroxyethylphenylaminomethyl)-5-methylfuran (**2e**)

2-Methylfuran (1.35g, 16.5 mmol), 3-phenyl-1,3-oxazolidine (**1e**) (2.24g, 15 mmol) and trimethylchlorosilane (1.79g, 16.5 mmol) in acetonitrile (50 ml) for 24 h gave the *title compound* (1.92g, 55%), b.p. 125-28 °C/0.05 mmHg; ν_{max} (film) 3376 (OH) cm^{-1}; δ_H (60 MHz) 2.20 (3H, s, CH_3), 2.68 (1H, s, D_2O ex., OH), 3.29-3.82 (4H, m, CH_2CH_2), 4.39 (2H, s, $ArCH_2$), 5.78-5.96 (1H, m, 4-H), 6.03 (1H, d, J_{AB} 3, 3-H), and 6.54-7.39 (5H, m, PhH) ppm; M$^+$ measured 231.1258, $C_{14}H_{17}NO_2$ requires 231.1259.

2-(N-2'-Hydroxyethylmethylaminomethyl)furan (**3**)

Furan (0.75g, 11 mmol), 3-methyl-1,3-oxazolidine (**1a**) (0.87g, 10 mmol) and trichloromethylsilane (1.64g, 11 mmol) in acetonitrile (50 ml) for 48 h, gave the *title compound* (1.17g, 75%), b.p. 52 °C/0.35 mmHg; δ_H (60 MHz) 2.27 (3H, s, CH_3), 2.57 (2H, t, *J* 6, NCH_2CH_2), 3.63 (2H, s, $ArCH_2$), 3.64 (2H, t, *J* 6, OCH_2), 4.59 (1H, s, D_2O ex., OH), 6.12-6.40 (2H, m, 3-H and 4-H), and 7.30-7.44 (1H, m, 5-H) ppm, δ_C (20.1 MHz) 41.8 (q, CH_3), 53.8 (t, NCH_2CH_2), 58.3 (t, $ArCH_2$), 59.0 (t, OCH_2), 108.1 and 110.1 (d, C-3 and d, C-4), 142.1 (d, C-5), and 152.0 (s, C-2) ppm; M$^+$ measured 155.0947, $C_8H_{13}NO_2$ requires 155.0946.

Reaction of 1-Methylpyrrole with 3-Methyl-1,3-oxazolidine and Trichloromethylsilane

1-Methylpyrrole (1.62g, 22 mmol), 3-methyl-1,3-oxazolidine (**1a**) (1.74g, 20 mmol) and trichloromethylsilane (2.99g, 22 mmol) in acetonitrile (50 ml) for 72 h gave after work-up and Kugelrohr distillation two fractions. First fraction *2-(N-2'-hydroxyethylmethylaminomethyl)-1-methylpyrrole* (**4**) (1.98g, 54%), b.p. 69-70 °C/0.12 mmHg; ν_{max} (film) 3404 (OH) cm^{-1}; δ_H (60 MHz) 2.18 (3H, s, NCH_3) 2.51 (2H, t, *J* 5.5, NCH_2CH_2), 3.02 (1H, br.s, D_2O ex., OH), 3.45 (2H, s, $ArCH_2$), 3.54 (2H, t, *J* 5.5, OCH_2), 3.60 (3H, s, $ArCH_3$), 5.99 (2H, d, J_{AB} 2.5, 3-H and 4-H), and 6.46-6.63 (1H, m, 5-H) ppm, δ_C (20.1 MHz) 33.6 (q, $ArCH_3$), 41.5 (q, NCH_3), 53.9 (t, NCH_2CH_2), 58.4 and 58.9 (t, $ArCH_2$ and t, OCH_2), 106.4 (d, C-4), 109.7 (d, C-3), 122.5 (d, C-5), and 129.0 (s, C-2) ppm; M$^+$ measured 168.1247, $C_9H_{16}N_2O$ requires 168.1263. Second fraction *2,5-di-(N-2'-hydroxyethylmethylaminomethyl)-1-methylpyrrole* (**5**) (0.69g, 12%), b.p. 115-20 °C/0.13 mmHg; ν_{max} (film) 3416 (OH) cm^{-1}; δ_H (60 MHz) 2.21 (6H, s, NCH_3), 2.50 (4H, t, *J* 5.5, NCH_2CH_2), 3.47 (4H, s, $ArCH_2$), 3.55 (4H, t, *J* 5.5, OCH_2), 3.61 (3H, s, $ArCH_3$), and 5.90 (2H, s, 3-H and 4-H) ppm.

3-(N-Benzyl-2'-hydroxyethylaminomethyl)indole (**6**)

Indole (1.93g, 16.5 mmol), 3-benzyl-1,3-oxazolidine (**1d**) (2.45g, 15 mmol) and trichloromethylsilane (2.47g, 16.5 mmol) in acetonitrile (50 ml) for 20 h gave the *title compound* (3.52g, 84%) as colourless plates, m.p. 104-105 °C (from diethyl ether-petroleum ether 40-60 °C). Found: C, 77.5; H, 7.3; N, 9.7. $C_{18}H_{20}N_2O$ requires C, 77.1; H, 7.2; N, 10.0%; ν_{max} (KBr) 3288 (NH), 3412 (OH) cm^{-1}; δ_H (60 MHz) 2.63 (2H, t, *J* 5.3, NCH_2CH_2), 2.65 (1H, s, D_2O ex., OH), 3.55 (2H, t, *J* 5.3, OCH_2), 3.62 (3H, s, $ArCH_2$), 3.78 (2H, s, $PhCH_2$), 6.82-7.38 (4H, m, 2, 5, 6 and 7-H), 7.27 (5H, s, PhH), 7.42-7.70 (1H, m, 4-H), and 8.22 (1H, br.s, D_2O ex., NH) ppm; M$^+$ measured 280.1598, requires 280.1576.

3-(N-2'-Hydroxyethylmethylaminomethyl)-1-methylindole (**7a**)

1-Methylindole (1.44g, 11 mmol), 3-methyl-1,3-oxazolidine (**1a**) (0.87g, 10 mmol) and trichloromethylsilane (4.10g, 27.5 mmol) in acetonitrile (50 ml) for 20 h, gave after column chromatography on alumina (grade 3) with methanol-chloroform (1:9) and Kugelrohr distillation the *title compound* (4.92g, 91%) as a pale yellow oil; ν_{max} (film) 3388 (OH) cm^{-1}; δ_H (60 MHz) 2.22 (3H, s, NCH_3), 2.53 (2H, t, *J* 5.5 , NCH2CH2), 3.38 (1H, s, D_2O ex, OH), 3.58 (2H, t, *J* 5.5, OCH_2), 3.61 (3H, s, $ArCH_3$), 3.69 (2H, s, $ArCH_2$), 6.83 (1H, s, 2-H), 6.95-

7.31 (3H, m, 5, 6 and 7-H), and 7.52-7.82 (1H, m, 4-H) ppm, δ_C (20.1 MHz) 32.0 (q, CH_3), 41.7 (q, NCH_3), 52.6 (t, $N\mathit{C}H_2CH_2$), 58.4 and 58.9 (t, $ArCH_2$ and t, OCH_2), 109.1 (d, C-7), 110.8 (s, C-3), 119.0 (d, C-6), 119.2 (d, C-4), 121.4 (d, C-5), 128.4 (d, C-2), 128.4 (s, C-3a), and 137.0 (s, C-7a) ppm; M^+ measured 218.1408; $C_{13}H_{18}N_2O$ requires 218.1419. A sample of the product (2.00g, 9.2 mmol) was converted to the amine hydrochloride as white crystals (2.28g, 98%) m.p. 126.5-27.5 °C (decomp.) (from dichloromethane-petroleum ether 40-60 °C). Found: C, 61.3; H, 7.7; N, 10.7. $C_{13}H_{19}ClN_2O$ requires C, 61.3; H, 7.7; N, 11.0%.

3-(N-Ethyl-2′-hydroxyethylaminomethyl)-1-methylindole (**7b**)
1-Methylindole (2.16g, 16.5 mmol), 3-ethyl-1,3-oxazolidine (**1b**) (1.52g, 15 mmol) and trichloromethylsilane (2.47g, 16.5 mmol) in acetonitrile (75 ml) for 44 h, gave the *title compound* (3.26g, 94%) as a yellow oil; ν_{max} (film) 3408 (OH) cm^{-1}; δ_H (60 MHz) 1.05 (3H, t, *J* 7.5, $CH_2C\mathit{H}_3$), 2.28-2.78 (4H, m, $C\mathit{H}_2CH_3$ and $NC\mathit{H}_2CH_2$), 3.05 (1H, s, D_2O ex., OH), 3.49 (2H, t, *J* 5.5, OCH_2), 3.63 (3H, s, NCH_3), 3.77 (2H, s, $ArCH_2$), 6.86 (1H, s, 2-H), 6.90-7.47 (3H, m, 5, 6 and 7-H), and 7.51-7.75 (1H, m, 4-H) ppm; M^+ measured 232.1590; $C_{14}H_{20}N_2O$ requires 232.1576. A sample of the product (1.80g, 7.7 mmol) was converted to the amine hydrochloride as white crystals (2.03g, 97%) m.p. 156.5-57.5 °C (from dichloromethane-petroleum ether 40-60 °C). Found: C, 62.5; H, 8.1; N, 10.4. $C_{14}H_{21}ClN_2O$ requires C, 62.5; H, 7.9; N, 10.4%.

3-(N-Benzyl-2′-hydroxyethylaminomethyl)-1-methylindole (**7c**)
1-Methylindole (2.16g, 16.5 mmol), 3-benzyl-1,3-oxazolidine (**1d**) (2.45g, 15 mmol) and chlorotrimethylsilane (1.79g, 16.5 mmol) in acetonitrile (75 ml) for 24 h gave after dry flash chromatography on t.l.c. grade silica with petroleum ether (40-60 °C)-ethyl acetate (0$\rightarrow$100%) the *title compound* (4.21g, 95%) as a viscous colourless oil; ν_{max} (film) 3428 (OH) cm^{-1}; δ_H (60 MHz) 2.56 (2H, t, *J* 5.5, $NC\mathit{H}_2CH_2$), 2.77 (1H, s, D_2O ex., OH), 3.40 (3H, s, NCH_3), 3.49 (2H, t, OCH_2), 3.53 (2H, s, $ArCH_2$), 3.70 (2H, s, $PhCH_2$), 6.75 (1H, m, 2-H), 6.80-7.38 (3H, m, 5, 6 and 7-H), and 7.47-7.68 (1H, m, 2-H) ppm; M^+ measured 294.1726; $C_{19}H_{22}N_2O$ requires 294.1732. A sample of the product (2.37g, 8.05 mmol) was converted to the hydrochloride (2.63g, 99%), white needles, m.p. 135.5-36.5 °C (from dichloromethane-petroleum ether 40-60 °C). Found: C, 68.9; H, 7.2; N, 8.15. $C_{19}H_{23}ClN_2O$ requires C, 68.95; H, 7.0; N, 8.5%.

3,4-Dimethyl-5-phenyloxazolidine (**8**)
(1R,2S)-Ephedrine (125) (33.05g, 0.2 mol), paraformaldehyde (6.61g, 0.22) and potassium carbonate (30.41g, 0.22 mol) in benzene (300 ml) were heated under reflux for 6 hours. The solid was filtered, washed with diethyl ether and the filtrate was concentrated *in vacuo* and distilled to give the *title compound* (33.10g, 93%), b.p. 70 °C/0.1 mmHg (lit.[15], 80 °C/0.5 mmHg); $[\alpha]_D^{27}$ + 10.8° ($CHCl_3$); δ_H (60 MHz) 0.67 (3H, d, *J* 6.5, CH_3), 2.29 (3H, s, NCH_3), 2.53-3.05 (1H, m, $CH_3C\mathit{H}$), 4.01 and 4.81 (1H, d, *J* 3 and 1H, d, *J* 3, NCH_2O), 5.06 (1H, d, *J* 7.5, PhCH), and 7.27 (5H, s, PhH) ppm, δ_C (20.1 MHz) 14.2 (q, CCH_3), 37.5 (q, NCH_3), 63.4 (d, CH_3CH), 82.0 (d, PhCH), 88.2 (t, CH_2), 127.1 (d, C-2′ and C-6′), 127.3 (d, C-4′), 127.9 (d, C-3′and C-5′), and 140.2 (s, C-1′) ppm; M^+ measured 177.1126; $C_{11}H_{15}NO$ requires 177.1153.

2-Methyl-(2-N-aminomethyl-5′-methylfurfuryl)-1-phenylpropan-1-ol (**9**)
2-Methylfuran (0.90g, 11 mmol), 3,4-dimethyl-5-phenyloxazolidine (**8**) (1.77g, 10 mmol) and trichloromethylsilane (1.64g, 11 mmol) in acetonitrile (75 ml) for 48 h gave the *title compound* (2.08g, 80%), b.p. 105-108 °C/0.03 mmHg. Found: C, 74.05; H, 8.0; N, 5.5. $C_{16}H_{21}NO_2$ requires C, 74.1; H, 8.15; N, 5.4%; ν_{max} (film)

3432 (OH) cm^{-1}; $[\alpha]_D^{30}$ - 1.9° ($CHCl_3$); δ_H (60 MHz) 0.89 (3H, d, *J* 6.5, CCH_3), 2.26 (3H, s, $ArCH_3$), 2.28 (3H, s, NCH_3), 2.61-3.12 (1H, m, CH_3CH), 3.64 (2H, s, CH_2), 3.82 (1H, s, D_2O ex., OH), 4.91 (1H, d, *J* 4, PhCH), 5.82-6.00 (1H, m, 4′-H), 6.04 (1H, d, J_{AB} 3, 3′-H), and 7.33 (5H, s, PhH) ppm; δ_C (20.1 MHz) 9.8 (q, CCH_3), 13.5 (q, $ArCH_3$), 39.1 (q, NCH_3), 51.1 (t, CH_2), 62.4 (d, CH_3CH), 72.9 (d, PhCH), 106.0 (d, C-3′), 109.4 (d, C-4′), 126.2 (d, C-2′′ and C-6′′), 126.8 (d, C-4′′), 127.9 (d, C-3′′ and C-5′′), 142.9 (s, C-1′′), and 150.8 and 151.5 (s, C-2′ and s, C-5′) ppm.

2-(N-2′-t-Butyldimethylsilyloxyethylmethylaminomethyl)-5-methylfuran (**10**)
A mixture of 2-methylfuran (0.90g, 11 mmol), 3-methyl-1,3-oxazolidine (**1a**) (0.87g, 10 mmol), 1,2,4-triazole (0.76g, 11 mmol) and t-butylchlorodimethylsilane (1.66g, 11 mmol) in acetonitrile (75 ml) was stirred at room temperature under nitrogen for 72 h. The solvent was removed *in vacuo* and the residue was added to a saturated solution of sodium hydrogencarbonate (50 ml) and extracted into pentane-ether (9:1) (3x50 ml). The combined organic layers were dried, concentrated *in vacuo* and the residue was distilled (Kugelrohr) to give the *title compound* (1.72g, 61%), b.p. 78 °C/0.03 mmHg. Found: C, 63.5; H, 10.0; N, 4.95. $C_{15}H_{29}NO_2Si$ requires C, 63.55; H, 10.0; N, 5.3%; ν_{max} (film) 1106 (SiO) cm^{-1}; δ_H (60 MHz) 0.06 (6H, s, $SiCH_3$), 0.90 (9H, s, CCH_3), 2.26 (3H, s, $ArCH_3$), 2.30 (3H, s, NCH_3), 2.56 (2H, t, *J* 6, NCH_2CH_2), 3.54 (2H, s, $ArCH_2$), 3.76 (2H, t, *J* 6, OCH_2), 5.80-5.98 (1H, m, 4-H), and 6.07 (1H, d, J_{AB} 3, 3-H) ppm; δ_C (20.1 MHz) -5.8 (q, $SiCH_3$), 13.1 (q, $ArCH_3$), 17.8 (s, CCH_3), 25.5 (q, CCH_3), 42.4 (q, NCH_3), 54.1 (t, NCH_2CH_2), 58.2 (t, $ArCH_2$), 61.4 (t, OCH_2), 105.5 (d, C-3), 108.9 (d, C-4), and 150.2 and 151.0 (s, C-2 and s, C-5) ppm; M^+ measured 283.1964; requires 283.1967.

3-(N-2′-t-Butyldimethylsilyloxyethylmethylaminomethyl)-1-methylindole (**11**)
1-Methylindole (1.15g, 8.8 mmol), 3-methyl-1,3-oxazolidine (**1a**) (0.70g, 8 mmol), *t*-butylchlorodimethylsilane (1.33g, 8.8 mmol) and 1,2,4-triazole (0.61g, 8.8 mmol) in acetonitrile (40 ml) for 72 h were treated as described above and gave the *title compound* (1.36g, 51%), b.p. 133-34 °C/0.007 mmHg; ν_{max} (film) 1102 (SiO) cm^{-1}; δ_H (60 MHz) 0.04 (6H, s, $SiCH_3$), 0.90 (9H, s, CCH_3), 2.28 (3H, s, NCH_3), 2.59 (2H, t, *J* 6, NCH_2CH_2), 3.61 (3H, s, $ArCH_3$), 3.73 (2H, s, $ArCH_2$), 3.78 (2H, t, *J* 6, OCH_2), 6.82-7.32 (4H, m, 2, 5, 6, and 7-H), and 7.57-7.90 (1H, m, 4-H) ppm; M^+ measured 332.2295; $C_{19}H_{32}N_2OSi$ requires 332.2284.

2-(N-2′-Chloroethylmethylaminomethyl)-5-methylfuran (**13**)
The alcohol (**2a**) (5.43g, 32 mmol) and carbon tetrachloride (5.38g, 35 mmol) in dry ether (25 ml) were stirred at -40 °C (dry ice-acetone) under nitrogen. Hexamethylphosphorus triamide (6.36 ml, 35 mmol) in dry ether (25 ml) was added dropwise by syringe. The resulting mixture was allowed to warm to room temperature and stirred for 1.5 h during which time two layers separated. Water (25 ml) was added and the ethereal layer was separated, washed with water (25 ml), dried and concentrated *in vacuo*. The resulting yellow liquid was distilled (Kugelrohr) to yield the *title compound* (3.36g, 54%), b.p. 75-76 °C/0.5 mmHg; δ_H (60 MHz) 2.27 (3H, s, $ArCH_3$), 2.33 (3H, s, NCH_3), 2.74 (2H, t, *J* 7, NCH_2CH_2), 3.55 (2H, t, *J* 7, OCH_2), 3.58 (2H, s, $ArCH_2$), 5.82-6.06 (1H, m, 4-H), and 6.13 (1H, d, J_{AB} 3, 3-H) ppm; M^+ measured 187.0738 and 189.0737; $C_9H_{14}ClNO$ requires 187.0734 and 189.0734.

N-(5-Methylfurfuryl)methylamine (**14**)
The β-chloroamine (**13**) (0.62g, 3.3 mmol), anhydrous sodium iodide (0.49g, 3.3 mmol) and zinc powder (0.43g, 0.0066g atom) in glacial acetic acid (10 ml) were subjected to ultrasonication for 1 hour and then heated

under reflux for 1.75 h. The resulting mixture was added to 2M HCl (25 ml) and extracted with ether (2 x 15 ml). The aqueous layer was basified with 4M NaOH, extracted with ether (3 x 30 ml) and the combined ether extracts were washed with water (2 x 30 ml), dried and concentrated *in vacuo* . The residual brown liquid was distilled (Kugelrohr) to yield the *title compound* (0.32g, 61%), b.p. 76-78 °C/13 mmHg (lit.[25] 88 °C); ν_{max} (film) 3328 (NH) cm^{-1}; δ_H (60 MHz) 1.67 (1H, s, D_2O ex., NH), 2.28 (3H, s, $ArCH_3$), 2.43 (3H, s, NCH_3), 3.69 (2H, s, CH_2), 5.83-6.01 (1H, m, 4-H), and 6.09 (1H, d, J_{AB} 3, 3-H) ppm; M^+ measured 125.0836; Calc. for $C_7H_{11}NO$ 125.0841.

Reactions of Phenols with 3-Methyl-1,3-oxazolidine—General Method

A mixture of a phenol (1 equiv.) and 3-methyl-1,3-oxazolidine (1.1 equiv.) in acetonitrile was stirred at room temperature for a specified length of time, quenched with water and concentrated *in vacuo* . The residue was acidified to pH2 with 2M HCl, washed with diethyl ether (3x30 ml) and then basified to pH 9 with 1M NaOH and washed with diethyl ether (4x40 ml). The combined organic extracts from the basic solution were dried ($MgSO_4$), concentrated *in vacuo*, and the residue was distilled (Kugelrohr) .

2,4-Dimethyl-6-(N-2'-hydroxyethylmethylaminomethyl)phenol (**15a**)

2,4-Dimethylphenol (1.83g, 15 mmol) and 3-methyl-1,3-oxazolidine (**1a**) (1.44g, 16.5 mmol) in acetonitrile (45 ml) for 50 h yielded the *title compound* (0.81g, 26%), b.p. 140°C/0.2 mmHg; ν_{max} (film) 3440, 2948, 1664, 1610, 1482 cm^{-1}; δ_H (60 MHz) 2.20 (6H, s, 2-CH_3 and 4-CH_3), 2.27 (3H, s, NCH_3), 2.60 (2H, t, J 7.5, NCH_2), 3.63 (2H, s, $PhCH_2N$), 3.72 (2H, t, J 7.5, CH_2OH), 6.03 (2H, br.s. D_2O ex. 2 OH's), 6.62 (1H, br.s, 3-H), and 6.83 (1H, br.s, 5-H) ppm; δ_C (20.1 MHz) 15.6 (q, 4-CH_3), 20.4 (q, 2-CH_3), 41.5 (q, NCH_3), 58.7 (t, NCH_2), 59.5 (t, $PhCH_2$), 61.3 (t, CH_2CH_2OH), 121.1 (s, C-6), 124.5 (s, C-2), 126.6 (d, C-5), 127.6 (s, C-4), 130.6 (d, C-3), and 153.5 (s, C-1) ppm; (m/z) 209 (M^+, 19.2%), 135 (100), M^+ measured 209.1422; $C_{12}H_{19}NO_2$ requires 209.1416.

2-(N-2'-Hydroxyethylmethylaminomethyl)-4-methoxyphenol (**15b**)

4-Methoxyphenol (1.86g, 15 mmol) and 3-methyl-1,3-oxazolidine (**1a**) (1.44g, 16.5 mmol) in acetonitrile (45 ml) 52 h yielded the *title compound* (0.71g, 22%), b.p. 150°C/0.05 mmHg; ν_{max} (film) 3400, 3032, 2948, 1652, 1616, 1496, 1418 cm^{-1}; δ_H (250 MHz) 2.36 (3H, s, NCH_3), 2.67 (2H, t, J 5.5, NCH_2), 3.74 (2H, s, $PhCH_2$), 3.76 (3H, s, OCH_3), 3.78 (2H, t, J 5.5, CH_2OH), 6.55-6.56 (1H, dd., 3-H), and 6.70-6.78 (2H, m, 5-H and 6-H) ppm; δ_C (62.9 MHz) 41.7 (NCH_3), 55.7 ($PhOCH_3$), 58.8 (NCH_2), 61.4 (CH_2OH), 113.5 (C-5), 114.4 (C-3), 116.5 (C-6), 122.7 (C-2), 151.4 (C-1) and 152.5 (C-4) ppm; (m/z) 211 (M^+, 29.5%), 137 (60), 44 (100), M^+ measured 211.1212; $C_{11}H_{17}NO_3$ requires 211.1208.

2-(N-2'-Hydroxyethylmethylaminomethyl)-6-methoxy-4-methylphenol (**15c**)

2-Methoxy-4-methylphenol (2.76g, 20 mmol) and 3-methyl-1,3-oxazolidine (**1a**) (1.92g, 22 mmol) in acetonitrile (60 ml) for 48 h gave, the *title compound* (1.27g, 28%), b.p. 110°C/0.05 mmHg; ν_{max} (film) 3396, 2944, 2840, 1718, 1600, 1496, 1460, 1400. cm^{-1}; δ_H (250 MHz) 2.25 (3H, s, 4-CH_3), 2.38 (3H, s, NCH_3), 2.66 (2H, t, J 5.5, NCH_2), 3.70 (2H, s, $PhCH_2$), 3.77 (2H, t, J 5.5, CH_2OH), 3.84 (3H, s, OCH_3), 4.20-5.20 (2H, br.s, D_2O ex. OH's), 6.42 (1H, d, J 1.4, 3-H), and 6.62 (1H, d, J 1.4, 5-H) ppm; δ_C (62.9 MHz) 20.9 (4-CH_3), 41.6 (NCH_3), 55.8 (6-OCH_3), 58.7 (NCH_2), 59.4 ($PhCH_2$), 60.8 (CH_2OH), 112.0 (C-5), 121.0 (C-3), 122.0 (C-4), 128.0 (C-2), 144.4 (C-1), and 147.5 (C-6) ppm; (m/z); 225 (M^+, 12.6%), 151 (100), M^+ measured 225.1362; $C_{12}H_{19}NO_3$ requires 225.1365.

2-(N-2′-Hydroxyethylmethylaminomethyl)-5-methoxyphenol (**15d**)

3-Methoxyphenol (1.86g, 15 mmol) and 3-methyl-1,3-oxazolidine (**1a**) (1.44g, 16.5 mmol) in acetonitrile (40 ml) for 46 h gave the *title compound* (2.20g, 69%); ν_{max} (film) 3300, 2940, 1610, 1594, 1508, 1468, 1384 cm^{-1}; δ_H (60 MHz) 2.23 (3H, s, NCH_3), 2.58 (2H, t, *J* 7.5 NCH_2), 3.63 (2H, s, $PhCH_2$), 3.68 (3H, s, 5-OCH_3), 3.70 (2H, t, *J* 7.5, C*H*$_2$OH), 6.20-6.50 (2H, m, 3-H and 4-H), 6.83 (1H, d, *J* 8, 6-H), and 7.27 (2H, s, D_2O ex. OH) ppm; (m/z); 211 (M^+, 51%), 137 (100), M^+ measured 211.1182; $C_{11}H_{17}NO_3$ requires 211.1208.

1-(N-2-hydroxyethyl-N-methylaminomethyl)-2-naphthol (**16**)

2-Naphthol (2.16g, 15 mmol) and 3-methyl-1,3-oxazolidine (**1a**) (1.44g, 16.5 mmol) in acetonitrile (45 ml) a for 50 h afforded the *title compound* as a viscous oil (2.97g, 95%) which was converted to its hydrochloride salt and recrystallised from ethyl acetate/hexane (1:1), m.p. 151-156°C. Found: C, 62.77; H. 6.75; N, 5.21; Cl, 13.24. $C_{14}H_{18}ClNO_2$ requires C, 62.80; H. 6.70; N, 5.23; Cl, 13.21%; ν_{max} (KBr) 3432,3224,3040,1934,1626, 1604, 1580, 1518, 1462 cm^{-1}; δ_H (250 MHz, CD_3OD) 2.88 (3H, s, NCH_3), 3.38 (2H, t, *J* 5.1, NC*H*$_2$CH$_2$), 3.93 (1H, br.s, D_2O ex. OH), 3.99 (2H, t, *J* 5.1, C*H*$_2$OH), 4.81 (2H, s, $ArCH_2$), 7.31 (1H, d, *J* 8.5, 4-H), 7.38-7.86 (4H, m, 5, 6, 7, and 8-H), and 7.96 (1H, d, *J* 8.5, 3-H ppm; δ_C (62.9 MHz, CD_3OD) 41.3 (NCH_3), 52.1 (NCH_2), 56.7 (CH_2OH), 59.3 ($ArCH_2$), 108.6 (C-1), 118.2 (C-3), 122.7 (C-6), 124.4 (C-4a and C-8), 128.9 (C-7-), 129.9 (C-5), 133.4 (C-4), 134.6 (C-8a), 156.7 (C-2) ppm; (FAB). (M^++1) 232.

2,5-(Dimethylphenoxy)trimethylsilane (**17**)

2,5-Dimethylphenol (24.43g, 0.2 mol) was added to a suspension of sodium hydride (5.28g, 0.22 mol) in THF (250 ml) at 0°C under nitrogen. The mixture was stirred at room temperature for 30 min and then cooled to 0 °C, treated with chlorotrimethylsilane (23.90g, 0.22 mol) and stirred at room temperature overnight. The solution was diluted with ether and washed with water. The organic phase was dried and concentrated in vacuo to a yellow oil (33.96g). Fractional distillation gave the *title compound* (33.31g, 86%), b.p. 45°C/5 mmHg; δ_H (60 MHz) 0.23 (9H, s, $OSi[CH_3]_3$), 2.08 (3H, s, 5-CH_3), 2.21 (3H, s, 2-CH_3), and 6.37-7.00 (3H, m, PhH) ppm; δ_C (20.1 MHz) 4.2 (q, $Si[CH_3]_3$), 11.5 (q, 5-CH_3), 16.4 (q, 2-CH_3), 115.2 (d, C-6), 117.5 (d, C-4), 121.1 (s, C-5, 126.2 (d, C-3), 131.6 (s, C-2), and 149.0 (s, C-1) ppm; (m/z); 194 (M^+, 84.6%), 179 (100), M^+ measured 194.1116; $C_{11}H_{18}OSi$ requires 194.1127.

Methylglyoxylate (**19**)

Methyl dimethoxyacetate (31.5g, 236 mmol), glyoxylic acid monohydrate (146) (21.0g, 228 mmol) and para-toluenesulphonic acid monohydrate (0.15g) were heated at 80 °C for 18 h. The resulting syrup was cooled in ice-methanol and phosphorus pentoxide (24g) was added in portions. The mixture was distilled from phosphorus pentoxide to give the *title compound* (25.8g, 64%) as a pale yellow liquid, b.p. 49-51 °C/20 mmHg (lit.[36], 50-59 °C/25 mmHg); δ_H (60 MHz) 4.95 (3H, s, CH_3), and 9.41 (1H, s, CHO) ppm.

2-Methoxycarbonyl-3-methyl-1,3-oxazolidine (**18**)

Freshly distilled methyl glyoxylate (**19**) (21.0g, 238 mmol) and *N*-methylethanolamine (17.9g, 238 mmol) in benzene (250 ml) were treated for 3 h as described for compound (**1c**) to yield the *title compound* (17.6g, 51%), b.p. 38-40 °C/1 mmHg; ν_{max} (film) 1750 (C=O) cm^{-1}; δ_H (360 MHz) 2.45 (3H, s, NCH_3), 2.72 (1H, dt, NCH), 3.17 (1H, dt, NCH), 3.68 (3H, s, CO_2CH_3), 3.69-4.01 (2H, m, OCH_2), and 4.48 (1H, s, CH) ppm;

δ_C (90.6 MHz) 41.2 (NCH_3), 51.9 (CO_2CH_3), 53.3 (NCH_2), 65.5 (OCH_2), 93.5 (CH), and 170.3 (CO_2CH_3) ppm.

Methyl-2-(5′-methylfuryl)-2-(N-2′-chloroethylmethylamino)acetate (**20**)

2-Methylfuran (1.07g, 13 mmol) and 2-methoxycarbonyl-3-methyl-1,3-oxazolidine (**19**) (1.70, 11.7 mmol) in acetonitrile (60 ml) were treated with thionyl chloride (1.55g, 13 mmol) in acetonitrile (20 ml) for 64 h. The black reaction mixture gave a pale yellow liquid on acid-base extraction with ether which was distilled (Kugelrohr) to yield the *title compound* (1.20g, 42%), b.p. 96-98 °C/0.01 mmHg. Found: C, 53.5; H, 6.5; N, 5.7, Cl, 14.7. $C_{11}H_{16}ClNO_3$ requires C, 53.8; H, 6.6; N, 5.7; Cl, 14.4%; ν_{max} 1740 (C=O) cm^{-1}; δ_H (60 MHz) 2.29 (3H, s, $ArCH_3$), 2.44 (3H, s, NCH_3), 2.68-3.12 (2H, m, NCH_2), 3.28-3.67 (2H, m, CH_2Cl), 3.75 (3H, s, CO_2CH_3), 4.52 (1H, s, CH), 5.87-6.05 (1H, m, 4-H), and 6.22 (1H, d, J_{AB} 3, 3-H) ppm; M^+ measured 245.0834 and 247.0836; $C_{11}H_{16}ClNO_3$ requires 245.0819 and 247.0789.

1,3-Dimethylimidazolidine (**23**)

N,N′-Dimethylethylenediamine (16.68g, 0.19 mol), paraformaldehyde (6.25g, 0.21 mol) and anhydrous potassium carbonate (28.76g, 0.21 mol) were heated under reflux in benzene (300 ml) for 6 h. The solid was filtered and most of the benzene was removed by distillation through a 15 cm Vigreux column. The residue was carefully fractionated using a 38 cm Vigreux column to yield the *title compound* (7.17g, 38%), b.p. 108-111 °C (lit.[1b],107-110°C), δ_H (60 MHz) 2.39 (6H, s, N CH_3), 2.79 (4H, NCH_2CH_2), and 3.32 (2H, s, NCH_2N) ppm, δ_C (20.1 MHz) 41.6 (q, NCH_3), 54.9 (t, NCH_2CH_2), and 80.2 (t, NCH_2N) ppm.

N,N′-Dimethyl-N-(5′-methylfurfuryl)ethylene diamine (**24**)

2-Methylfuran (0.72g, 8.8 mmol), 1,3-dimethylimidazolidine (**23**) (0.80g, 8 mmol) and trichloromethylsilane (1.32g, 8.8 mmol) in acetonitrile (60 ml) for 48 h, gave the *title compound* (1.28g, 71%), b.p. 66 °C/0.05 mmHg. Found: C, 65.5; H, 9.7; N, 15.5. $C_{10}H_{18}N_2O$ requires C, 65.8; H, 9.95; N, 15.4%; δ_H (60 MHz) 1.58 (1H, s, D_2O ex., NH), 2.24 (6H, s, $ArCH_3$ and NCH_3), 2.43 (3H, s, $NHCH_3$), 2.46-2.77 (4H, m, CH_2CH_2), 3.48 (2H, s, $ArCH_2$), 5.76-5.95 (1H, m, 4-H), and 6.01 (1H, d, J_{AB} 3, 3-H) ppm; δ_C (20.1 MHz) 13.5 (q, $ArCH_3$), 36.5 (q, $NHCH_3$), 42.1 (q, NCH_3), 49.6 (t, CH_2NCH_2), 54.3 (t, $ArCH_2$), 56.0 (t, $NHCH_2$), 106.6 (d, C-3), 109.3 (d, C-4), and 150.7 and 151.4 (s, C-2 and s, C-5) ppm; M^+ measured 182.1412; requires 182.1419.

REFERENCES

1. (a) Lambert, J.B.; Majchrzak, M.W. *J. Am. Chem. Soc.*, **1979**, *101*, 1048-1049; (b) *ibid.*, **1980**, *102*, 3588-3591.
2. Austudillo, M.E.A.; Chokoto, N.C.J.; Javris, T.C.; Johnson, C.D.; Lewis, C.C.; McDonnell, P.D. *Tetrahedron*, **1985**, *41*, 5919-5928.
3. Senkus, M. *J. Am. Chem. Soc.*, **1945**, *67*, 1515-1519; Goodson, L.H.; Christopher, H. *ibid.*, **1950**, *72*, 358-362.
4. Senkus, M. *J. Am. Chem. Soc.*, **1945**, *67*, 1515-1519; Goodson, L.H.; Christopher, H. *ibid.*, **1950**, *72*, 358-362.
5. (a). Griengl, H.; Bleikolm, A. *Liebigs Ann. Chem.*, **1976**, 1783-1790; 1791-1798; (b) Griengl, H.; Bleikolm, A.; Grubbauer, W.; Sollradl, H. *ibid.*, **1979**, 392-399; (c) Griengl, H.; Prischl, G.; Bleikolm, A. *ibid.*, **1979**, 400-407; **1980**, 1573-; (d) Eichberger, G.; Griengl, H.; Paar, W. *Monatash. Chem.*, **1986**, *117*, 545-551.

6. Beulshausen, T.; Groth, U.; Schöllkopf, U. *Liebigs Ann. Chem.*, **1992**, 523-526.
7. Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron Lett.*, **1988**, *29*, 2377-2380; Eyley, S.C.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *ibid.*, **1988**, *29*, 2997-3000; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *ibid.*, **1988**, *29*, 5801-5804; Cooper, M.S.; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron*, **1989**, *45*, 1155-1166.
8. Earle, M.J.; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron Lett.*, **1990**, *31*, 4229-4232; Heaney, H.; Papageorgiou, G. *Tetrahedron*, **1996**, *52*, 3473-3486.
9. Cooper, M.S.; Earle, M.J.; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Synlett.*, **1990**, 617-618; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron*, **1995**, *51*, 10737-10750.
10. Brown, D.S.; Earle, M.J.; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F.; Eyley, S.C. *Synlett.*, **1990**, 619-621.
11. Earle, M.J.; Fairhurst, R.A.; Heaney, H.; Papageorgiou, G. *Synlett.*, **1990**, 621-623.
12. Fairhurst, R.A.; Heaney, H.; Papageorgiou, G.; Wilkins, R.F.; Eyley, S.C. *Tetrahedron Lett.*, **1989**, *30*, 1433-1436.
13. Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *J. Chem. Soc., Chem. Commun.*, **1988**, 1161-1163; Heaney, H.; Papageorgiou, G.; Wilkins, R.F. *Tetrahedron*, **1997**, *53*, 2941-2958.
14. Jones, R.A.Y.; Katritzky, A.R.; Trepanier, D.L. *J. Chem. Soc. (B)*, **1971**, 1300-1302.
15. Pfanz, H.; Kirchner, G. *Liebigs Ann. Chem.*, **1958**, *614*, 149-158.
16. Harrell, W.B.; Doerge, R.F. *J. Pharm. Sci.*, **1967**, *56*, 225-228; 1200-1202; Harrell, W.B. *ibid.* **1970**, *59*, 275-277; Harrell, W.B.; Kuang, S.-W.; O'Dell, C. *ibid.*, **1970**, *59*, 721-722.
17. Nystorm, J.-E.; McCanna, T.D.; Helquist, P.; Amouroux, R. *Synthesis*, **1988**, 56-58.
18. Corey, E.J.; Cho, H.; Rucker, C.; Hua, D.H. *Tetrahedron Lett.*, **1981**, *22*, 3455-.3458
19. Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.*, **1972**, *94*, 6190-6191.
20. Brooks, D.W.; Woods, K.W. *J. Org. Chem.*, **1987**, *52*, 2036-2039.
21. Aizpurua, J.M.; Palomo, C. *Tetrahedron Lett.*, **1985**, *26*, 475-476.
22. Chavis, C.; Dumont, F.; Wightman, R.H.; Ziegler, J.C.; Imbach, J.L. *J. Org. Chem.*, **1982**, *47*, 202-206.
23. Staab, H.A. *Angew. Chem., Int. Ed. Engl.*, **1962**, *1*, 351-367.
24. Downie, I.M.; Matough, M.F.S.; Lee, J.B. *J. Chem. Soc., Chem. Commun.*, **1968**, 1350-1351.
25. Mertes, M.P.; Borne, R.F.; Hare, L.E. *J. Org. Chem.*, **1968**, *33*, 133-137.
26. Amstutz, E.D. *J. Org. Chem.*, **1944**, *9*, 310-318; Gurien, H. *ibid.*, **1963**, *28*, 878-879.
27. Weatherbee, C.; Temple, R.; Burke, W.J. *J. Org. Chem.*, **1956**, *21*, 1138-1141.
28. Bailey, N.A.; Fenton, D.E.; Papageorgiou, G.; Rodriguez de Barbarin, C.O. *Synlett.*, **1994**, 79-81; Fenton, D.E.; Papageorgiou, G. *Tetrahedron*, **1996**, *52*, 5913-5928.
29. Böhme, H.; Eichler, D. *Arc. Pharm. (Weiheim)*, **1967**, *300*, 679-681.
30. Gautier, J.-A.; Miocque, M.; Quan, D.Q.; *C. R. Hebb. Seances Acad. Sci.*, **1964**, *258*, 3731-3734.
31. Lambert, J.B.; Wang, G.; Huseland, D.E.; Takiff, *J. Org. Chem.*, **1987**, *52*, 68-71.
32. Fernandez, J.E.; Butler, G.B. *J. Org. Chem.*, **1963**, *28*, 3258-3259.
33. Oda, R.; Okano, M.; Tokiura, S.; Miyasu, A. *Bull. Chem. Soc. Jpn.*, **1962**, *35*, 1216-1218.
34. Weinberg, N.L.; Brown, E.A. *J. Org. Chem.*, **1966**, *31*, 4058-4061.
35. Kon, G.A.R.; Roberts, J.J. *J. Chem. Soc.*, **1950**, 978-982.
36. Hook, J.M. *Synth. Commun.*, **1984**, *14*, 83-87.

(*Received in UK* 21 *July* 1997; *revised* 1 *August* 1997; *accepted* 7 *August* 1997)