Biosynthesis of Porphyrins and Related Macrocycles. Part 29.[1] Synthesis and Chemistry of 2,2-Disubstituted 2*H*-Pyrroles (Pyrrolenines)

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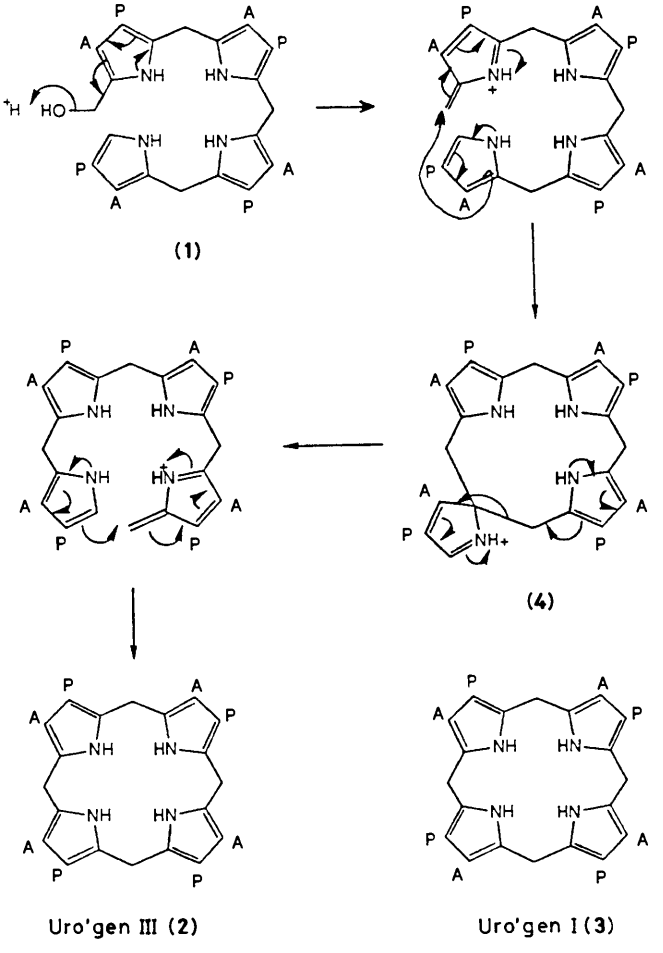
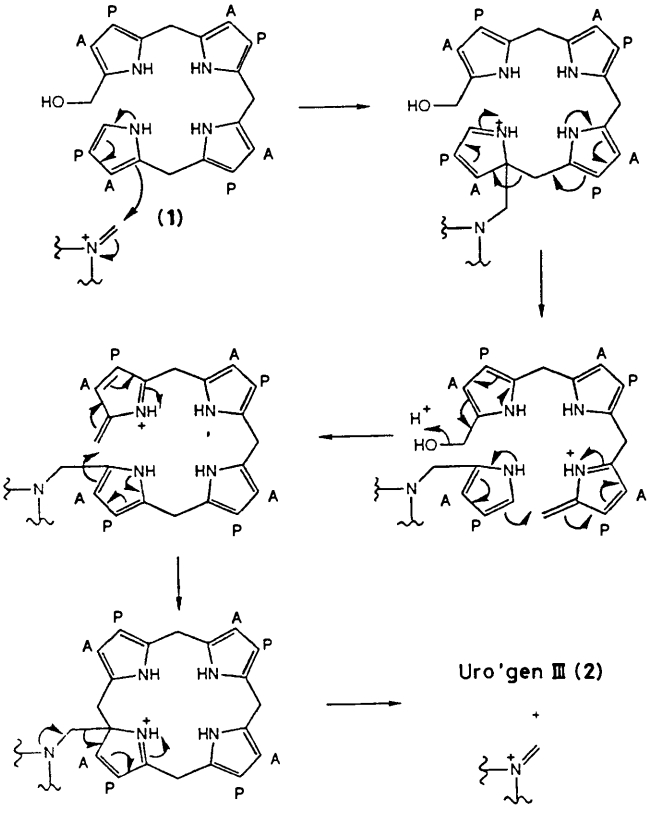
Syntheses are described of three 2*H*-pyrroles (pyrrolenines), (**15**), (**28**), and (**64**), which were designed to test the chemical feasibility of the rearrangements proposed as part of the mechanism of the enzyme cosynthetase (uroporphyrinogen III synthase). All three syntheses create the 2*H*-pyrrole ring by the Michael addition of a nitronate anion to an α,β-unsaturated ester and one introduces an additional substituent by novel alkylations of the dianion of a hydroxamic acid. Some of the intermediates in the syntheses showed unusual n.m.r. properties which reveal strong conformational preferences. The rearrangement of the 2*H*-pyrroles was studied under both thermal and acid-catalysed conditions. The results show that 2,2-disubstituted 2*H*-pyrroles only rearrange easily by [1,5]-sigmatropic shifts if they do not have further substituents on C-3 and C-4. 2-Pyrrolylmethyl-2*H*-pyrroles prefer to rearrange by a fragmentation-recombination mechanism.

In the biosynthesis of porphyrins the key cyclization step from the hydroxymethylbilane (1) to uroporphyrinogen (uro'gen) III (**2**), catalysed by the enzyme cosynthetase (uro'gen III synthase), occurs with inversion of ring D.[2] Non-enzymic cyclization of the hydroxymethylbilane occurs, without any rearrangement, to give uro'gen I (**3**). Two mechanisms have been suggested[3] for the unique enzymic rearrangement: the one shown in Scheme 1 (known as the 'spiro' mechanism) involves cyclization of bilane (1) from the *substituted* α-position of ring D to the hydroxymethyl group to give the spiro intermediate (**4**). This spiro intermediate could rearrange to uro'gen III either by a series of [1,5]-sigmatropic shifts or as shown by a fragmentation followed by recombination. The second suggested mechanism shown in Scheme 2 invokes an enzyme-bound external electrophile such as a methylene-iminium ion to which ring D is attached while it is cleaved from ring C, turned round, and reattached. Ring closure then proceeds normally.



Scheme 1. The 'spiro' mechanism proposed for the biosynthesis of uro'gen III



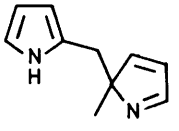
Scheme 2. The 'methylene-iminium ion' mechanism proposed for the biosynthesis of uro'gen III

Both the mechanisms outlined above for the action of co-synthetase involve pyrrolylmethyl-2*H*-pyrroles (pyrrolenines) having the basic skeleton (**5**). The chemistry of such compounds has not been studied before and indeed little is known about 2,2-disubstituted 2*H*-pyrroles in general. We report here the synthesis of some of these types of 2*H*-pyrroles and an investigation of their rearrangement reactions.[4]

Synthesis

Previous methods for the synthesis of 2*H*-pyrroles have relied mainly on either alkylation of 1*H*-pyrroles[5] or on ring-opening reactions of azirines.[6] In general these methods give 2*H*-pyrroles with substituents on C-5, and could not yield a substitution pattern consistent with our eventual aim of synthesizing the 'spiro' intermediate (**4**). Therefore it was decided to develop a new synthesis based on the conjugate addition of nitronate anions to α,β-unsaturated carbonyl compounds. This approach has been used before[7] for the synthesis of 3,4-dihydro-2*H*-pyrroles and the corresponding nitrones, mostly having *gem*-dimethyl substituents at C-2.

2,2-*Dibenzyl*-2H-*pyrrole* (**15**).—The dibenzyl-2*H*-pyrrole (**15**) was chosen as an initial model to test the viability of the synthesis because the benzyl groups may behave in some respects like the pyrrolylmethyl group of the pyrrolenine (**5**).



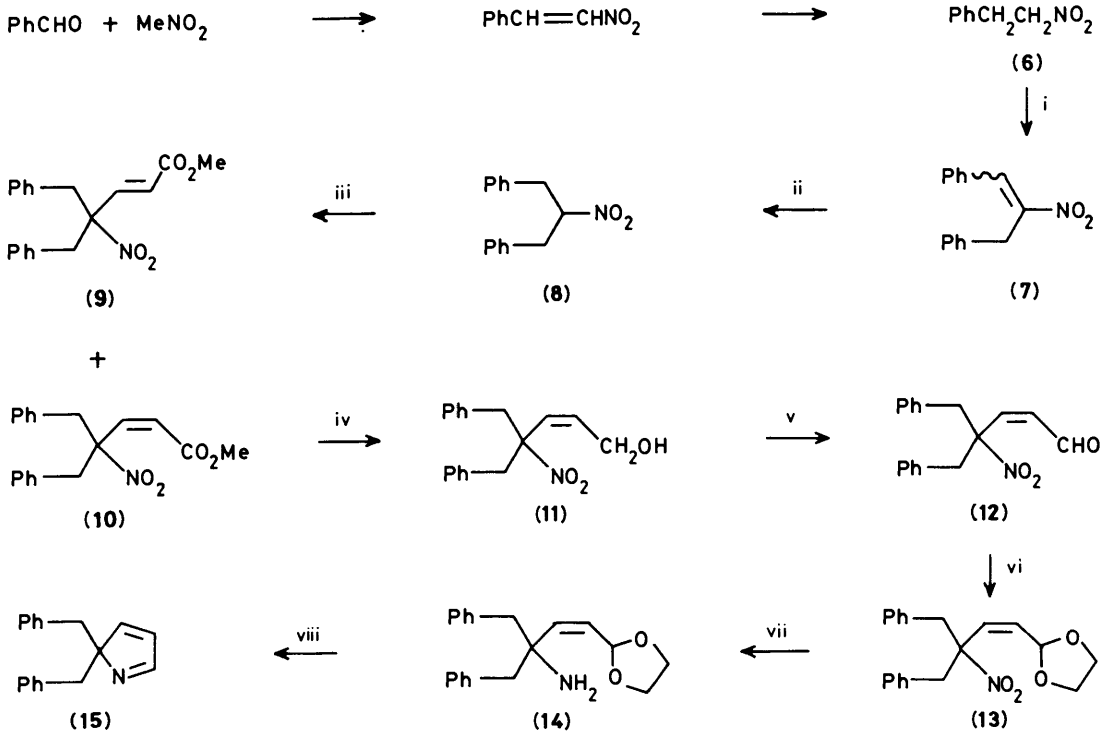
(**5**)

The synthesis of the required nitro compound (**8**) is shown in Scheme 3. Nitroethylbenzene (**6**) was synthesized by base-catalysed condensation of benzaldehyde and nitromethane followed by borohydride reduction of the nitrostyrene.[8] Repetition of this sequence gave the diphenylnitropropane (**8**) without isolation of the intermediate (**7**).

In order to obtain the double bond between C-3 and C-4 of the target 2*H*-pyrrole (**15**), it was decided to employ an acetylenic ester as the Michael acceptor. Reaction of the nitro compound (**8**) with methyl propynoate under basic conditions gave a mixture of the *trans* and *cis* compounds, (**9**) and (**10**), in a ratio of about 6:1. It was hoped that the *cis* alkene (**10**) might be the kinetic product and several different sets of conditions were tried but the best that were found (using fluoride ion as a base under phase-transfer conditions) still gave a *ca.* 4:1 ratio of (**9**) to (**10**). The two isomers were separated by chromatography. Attempted photoisomerization of the *trans* isomer (**9**) did give some *cis* isomer but also gave a large number of by-products and so was not useful preparatively.

Reduction of the ester (**10**) with di-isobutylaluminium hydride (Dibal) at −78 °C did not give the aldehyde (**12**) cleanly but gave a mixture of (**12**) and the alcohol (**11**). Accordingly the reduction was performed at 0 °C to give a virtually quantitative yield of the alcohol (11) which was oxidized with activated manganese dioxide to the aldehyde.

Reduction of the nitro group of (**12**) to an amine would give a compound which would cyclize spontaneously to give the desired 2*H*-pyrrole (**15**). However in similar cases[7] it has been found that protection of the aldehyde is required and in this case too it was found that direct reduction was not a clean reaction. Therefore the aldehyde was converted into its ethylene acetal (**13**). The *trans* isomer of (**13**) was also synthesised, starting from (**9**), and comparison of the n.m.r. spectra showed that no isomerization of the double bond had occurred in either case. Reduction of the nitro group of the acetal (**13**) was effected with zinc in cold acetic acid and deprotection of the aldehyde with



Scheme 3. *Reagents:* i, PhCHO, $MeNH_3^+Cl^-$, KOAc, $HC(OMe)_3$, MeOH; ii, $NaBH_4$, DMSO, HOAc; iii, $HC{\equiv}CCO_2Me$, $Bu_4N^+Cl^-$, $KF{\cdot}2H_2O$, DMF; iv, Dibal, PhMe, 0 °C; v, MnO_2, CH_2Cl_2; vi, $HOCH_2CH_2OH$, TsOH, PhH, reflux; vii, Zn, HOAc; viii, c. HCl, THF

concentrated hydrochloric acid in THF for 5 min afforded the crystalline 2*H*-pyrrole (**15**) in 90% yield.

*2-Methyl-2-pyrrolylmethyl-*2H*-pyrrole* (**28**).—The next target for synthesis was the pyrrolylmethyl-2*H*-pyrrole (**28**) which would mimic more closely the chemistry of systems such as the proposed spiro intermediate (**4**).

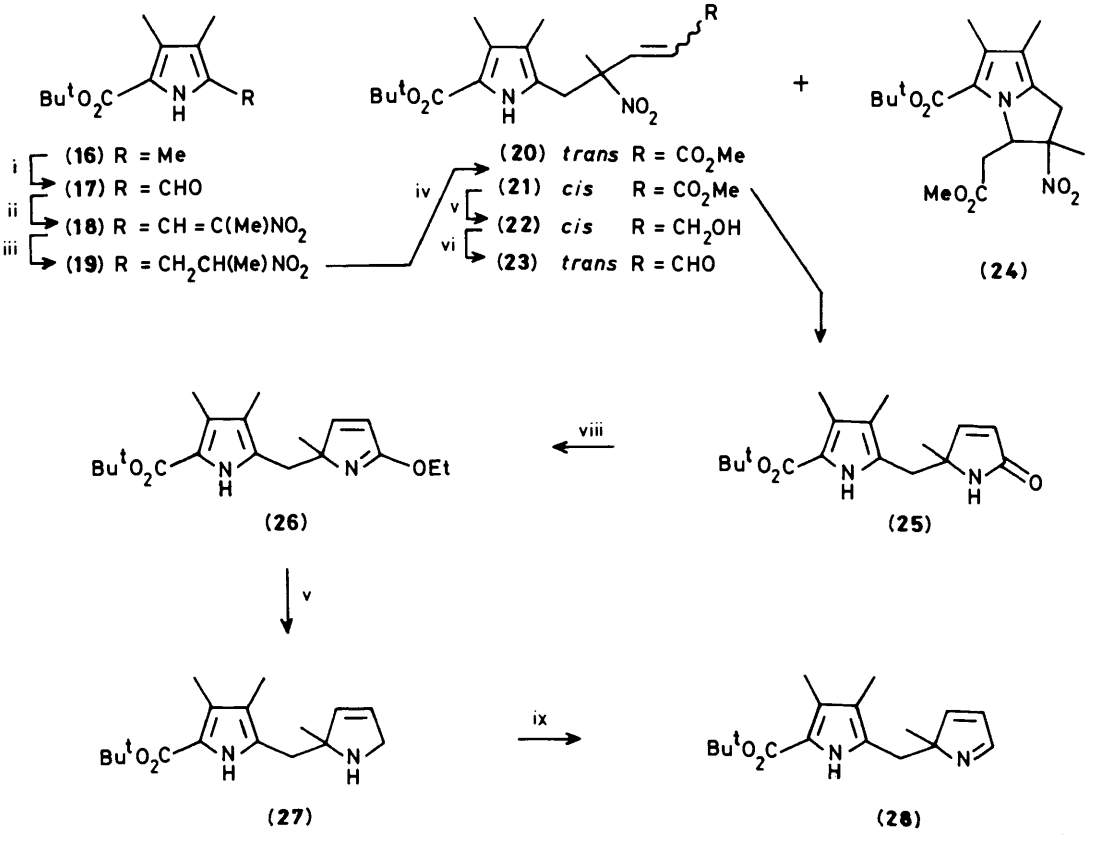
The synthesis of the pyrrolenine (**28**) was planned to follow a similar route to that used for the dibenzyl-2*H*-pyrrole (**15**). Thus, starting from the formylpyrrole (**17**) [obtained by lead tetra-acetate oxidation of the α-methyl pyrrole (**16**)], condensation with nitroethane gave the nitropropenylpyrrole (**18**) and borohydride reduction of this gave the nitropropylpyrrole (**19**) (Scheme 4). The fluoride ion-catalysed addition of this nitro compound to methyl propynoate afforded as the major product, an adduct whose n.m.r. spectrum lacked the expected signals for the vinylic protons and the pyrrolic NH. It is thought that a further intramolecular Michael addition of the initially formed α,β-unsaturated esters, (**20**) or (**21**), produced the bicyclic compound (**24**) as a mixture of diastereoisomers. After some experimentation, it was found that if the nitronate anion formed by the reduction of the nitro olefin (**18**) was not neutralized but was treated directly with methyl propynoate, the unsaturated esters (**20**) and (**21**) were the two main products, isolated in a ratio of about 2:1. Again the desired *cis* isomer was the minor product but nevertheless it proved possible to crystallize it directly from the mixture of products and so reasonable quantities of this isomer were relatively easy to obtain.

Following the previous synthetic plan, the *cis* ester (**21**) was reduced with Dibal to the alcohol (**22**) in over 80% yield. Oxidation of the allylic alcohol with manganese dioxide proved too severe and a number of products were formed. Oxidation with pyridinium chlorochromate caused clean conversion of the alcohol into an aldehyde which proved to be the *trans*-aldehyde (**23**). Similar oxidation of the dibenzyl analogue (**11**) with pyridinium chlorochromate did not cause any isomerization of the double bond and so the pyrrole residue is presumably responsible. Possibly a reversible Michael addition [such as produced by the by-product (**24**)] would explain the isomerization.

In order to avoid any risk of isomerization, it was decided to cyclize the *cis* ester (**21**) immediately. The nitro group of (**21**) was reduced with zinc in acetic acid–tetrahydrofuran at 0 °C and titanium(III) chloride was added to reduce any hydroxamic acid formed to the desired lactam (**25**). In order to obtain selective reduction of the lactam in the presence of the α-pyrrolic ester, the lactam was activated by alkylation with triethyloxonium tetrafluoroborate (Meerwein's reagent) and 1,8-bis(dimethylamino)naphthalene as a base to give the imidate (**26**).

It was hoped that reduction of the imidate with Dibal might lead to the 2*H*-pyrrole directly (in an analogous fashion to the reduction of an ester to an aldehyde); however at −78 °C Dibal was found to have no effect on the imidate (**26**) and at −50 °C the reaction was slow and did not give a clean product. Therefore, the reaction was performed at room temperature to reduce the imidate to the dihydropyrrole (**27**) in near quantitative yield.

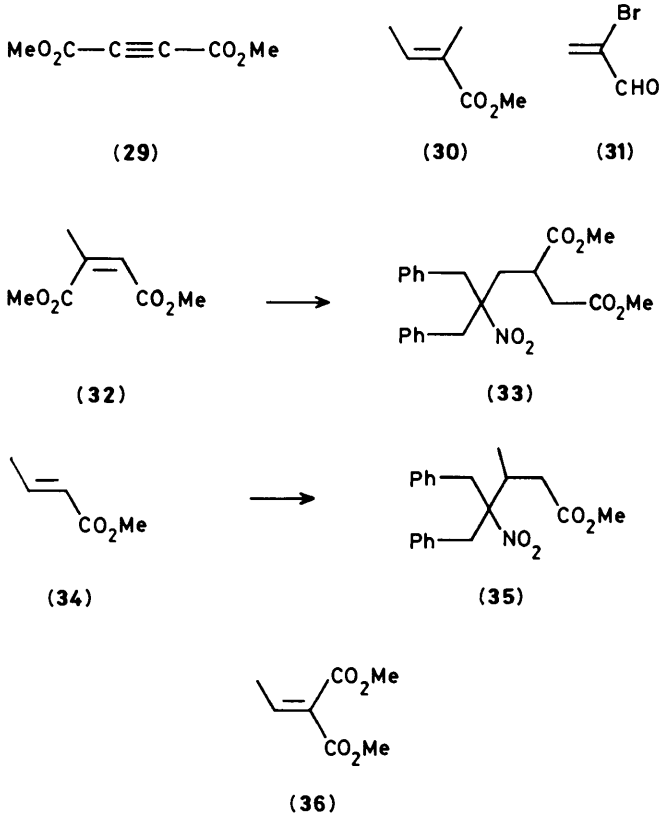
Re-oxidation of the dihydropyrrole (**27**) to the 2*H*-pyrrole (**28**) was achieved by *N*-chlorination with t-butyl hypochlorite and then elimination of HCl with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This reaction worked well with the model dibenzyldihydropyrrole [obtained by borohydride reduction of 2*H*-pyrrole (**15**)] but the pyrrolylmethyl dihydropyrrole (**27**) appeared more sensitive. Treatment of (**27**) with t-butyl



Scheme 4. *Reagents:* i, $Pb(OAc)_4$, HOAc; ii, $EtNO_2$, $MeNH_3^+Cl^-$, KOAc, MeOH; iii, $NaBH_4$, EtOH; iv, as iii then $HC{\equiv}CCO_2Me$; v, Dibal, PhMe; vi, PCC, NaOAc, CH_2Cl_2; vii, Zn, HOAc–THF, 0 °C; viii, $Et_3O^+BF_4^-$, 1,8-$(Me_2N)_2$-naphthalene, CH_2Cl_2; ix, (a) Bu^{t}OCl, CH_2Cl_2, −20 °C, (b) DBU, CH_2Cl_2

hypochlorite in dichloromethane had to be carried out at − 20 °C and the excess of reagent was removed by evaporation to dryness at this temperature. DBU and dichloromethane were then added and the solution was allowed to warm to room temperature. The unstable 2*H*-pyrrole (**28**) was purified by chromatography to give an oil in 20% yield. This compound was extremely acid-sensitive and unstable even in neutral solution. Its n.m.r. spectrum was obtained in the presence of an *equimolar quantity* of t-butylamine which appeared to stabilize it.

Approaches to 2H-*Pyrroles with Substituents at C-3 and C-4.*—Ideally a model for the proposed spiro intermediate should be a 2,2-disubstituted 2*H*-pyrrole having substituents also at C-3 and C-4. To investigate the potential of our synthetic approach to give such substitution patterns, the Michael addition of nitroalkanes (**8**) and (**19**) to various α,β-unsaturated esters was investigated (Scheme 5).



Scheme 5.

The anion from 2-nitro-1,3-diphenylpropane (**8**) failed to react with dimethyl acetylenedicarboxylate (**29**) or methyl (*E*)-2-methylcrotonate (**30**). With 2-bromoacrylaldehyde (**31**) no adduct was formed but the olefin appeared to polymerize. With dimethyl citraconate (**32**) the adduct formed, (**33**), was the product of Michael addition after migration of the double bond. With methyl crotonate (**34**), the adduct (**35**) was formed to a certain extent though the equilibrium mixture was obtained and a competing side-reaction was elimination of nitrous acid from (**8**) to give 1,3-diphenylpropene. As a result, the best conditions found only gave a yield of 40% (over 60% based on unrecovered starting material). With the diester (**36**), the Michael reaction appeared to take place but the resultant anion took part in further Michael reactions and the 1:1 adduct could not be isolated.

With the 1-pyrrolyl-2-nitropropane (**19**), Michael addition to methyl crotonate using tetra-n-butylammonium fluoride as the catalyst gave a 58% yield of the adduct (**37**) as a mixture of diastereoisomers. Reduction of the nitro group of (**37**) with zinc in acetic acid gave the lactams (**38**) and (**39**) which were separable by preparative t.l.c. The higher R_F lactam was shown to be (**38**) and the lower R_F one to be (**39**) by n.O.e. difference spectroscopy. The ^{13}C n.m.r. spectra confirmed this stereochemistry as the methyl and methylene carbons attached to C-5 of the pyrrolidone ring exhibit a marked upfield shift when they are *cis* to the methyl on C-4 due to the γ-gauche effect. A final confirmation of structure (**38**) for the higher R_F lactam was obtained by *X*-ray crystal analysis (see later).

Finally it was demonstrated that this approach could be applied to the synthesis of a 5,5-bis(pyrrolylmethyl)pyrrolidone. The 1,3-dipyrrolyl-2-nitropropane (**40**) was synthesised from (**17**) and nitromethane by the usual sequence of reactions. Michael addition of the anion from (**40**) to methyl acrylate gave the nitro ester (**41**) which yielded the lactam (**42**) on reduction with zinc in acetic acid in the presence of titanium(III) chloride.

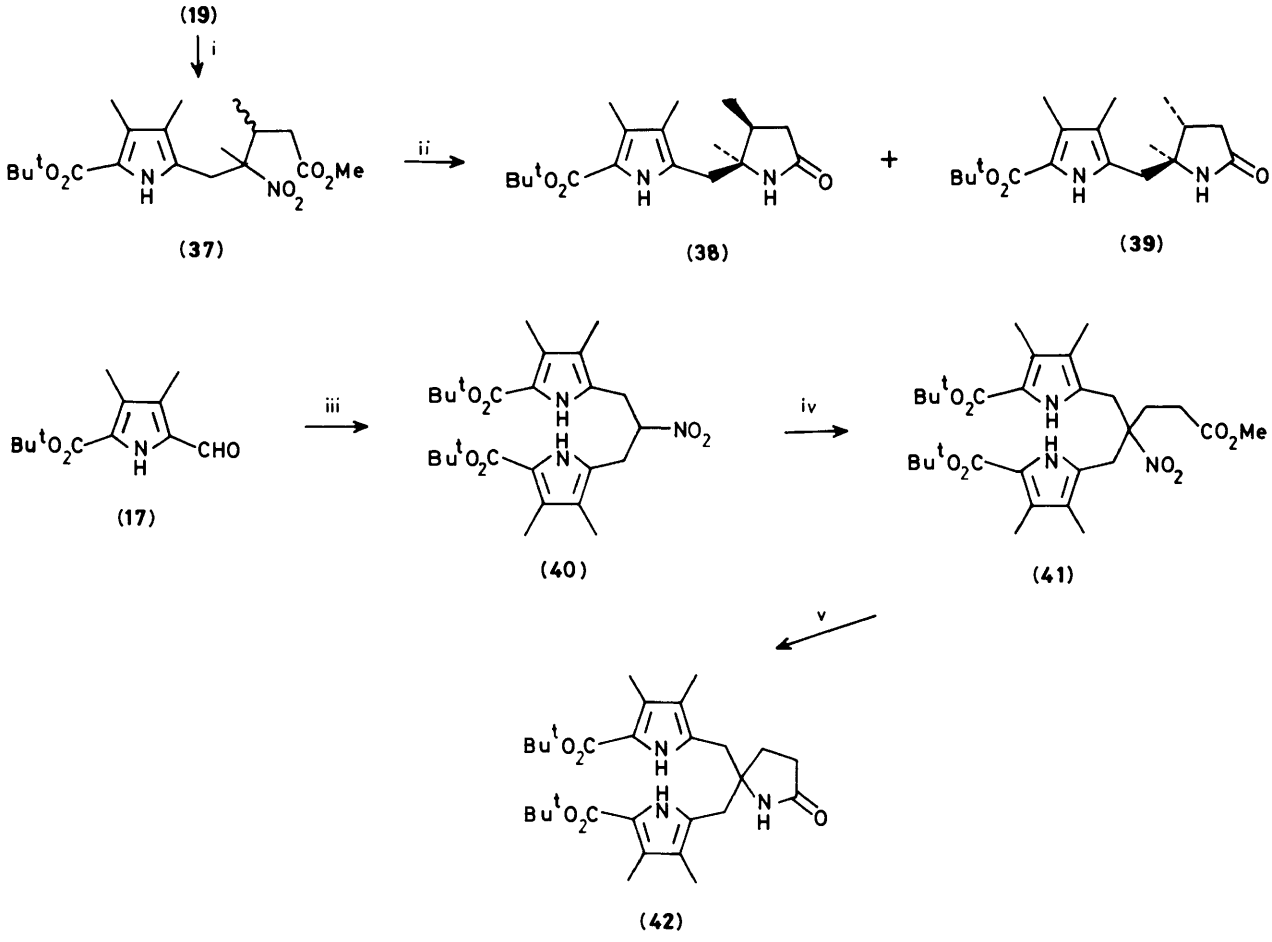
Our experience with these Michael additions of 2-nitropropanes to unsaturated esters is that they are not easy reactions to perform because each different reaction requires a different set of conditions.[9] Furthermore the equilibrium is against formation of the more substituted adducts. As a result we were not able to make 3,4,5,5-tetrasubstituted pyrrolidones by this method. We therefore investigated alkylation of trisubstituted pyrrolidones such as (**38**) and (**39**) (Scheme 6).

Treatment of secondary amides with strong bases causes removal of the N–H which is the most acidic proton. In general[10] it is not possible to achieve a second deprotonation α to the carbonyl with bases such as LDA, but it has been achieved with butyl-lithium. Therefore, we planned to convert each of the lactams (**38**) and (**39**) into an imidate which no longer has an acidic NH.[10] Treatment of the lactam (**38**) with triethyloxonium tetrafluoroborate however, did not give the imidate as expected but instead the *N*-ethyl lactam was the only product detected.

To avoid alkylation on nitrogen, the lactam (**38**) was converted into the thiolactam (**43**) with Lawesson's reagent and this was methylated on sulphur with methyl iodide to give the thioimidate (**44**) (Scheme 7). The thioimidate could be converted into the oxygen analogue, imidate (**45**), by heating in acidic methanol.

In an attempt to introduce an *exo*-methylene group α to the imidate or thioimidate, compounds (**44**) and (**45**) were treated with a variety of bases followed by dimethyl(methylene)-ammonium iodide (Eschenmoser's salt). In no case was any significant reaction observed. The diastereoisomeric imidate (**46**) was synthesised by the same route from the lower R_F lactam (**39**) but with this compound also no *C*-alkylation was observed with lithium di-isopropylamide (LDA) and Eschenmoser's salt. The compound isolated in low yield from this reaction appeared to be the product of dimethylaminomethylation of the *pyrrole* nitrogen. Thus it seems likely that the only deprotonation that occurs, even in the presence of an excess of base, is at the pyrrole N–H and that this prevents a second deprotonation α to the imidate or thioimidate. Evidence will be presented later that there is a close association between the pyrrole and lactam rings in this type of compound and this could explain the failure of the second deprotonation.

2,2-*Dibenzyl*-3,4-*dimethyl*-2H-*pyrrole* (**64**).—It is clear that the introduction of a substituent at C-3 of the lactam ring is not possible by the foregoing approach when there is a pyrrole ring present. Accordingly, we changed our target to 2,2-dibenzyl-3,4-dimethyl-2*H*-pyrrole (**64**) so that we could investigate the necessary chemistry on a more amenable system.



Scheme 6. *Reagents:* i, $Bu_4N^+F^-$, MeCH=CHCO$_2$Me, DMF; ii, Zn, HOAc, 70 °C; iii, (a) PyrroleCH$_2$CH$_2$NO$_2$, piperidine, DMF, 50 °C; (b) NaBH$_4$, EtOH–CH$_2$Cl$_2$; iv, CH$_2$=CHCO$_2$Me, PhCH$_2$NMe$_3^+$OH$^-$, DMF; v, Zn, HOAc. 60 °C, then $TiCl_3$

Reduction of the nitro ester (**35**) under the usual conditions gave the lactam (**47**) (Scheme 8). The nitrogen of this lactam could be methylated with sodium hydride and methyl iodide to give the crystalline *N*-methyl lactam (**48**). Further treatment of (**48**) with LDA followed by methyl iodide in THF produced a mixture of compounds which was judged by n.m.r. and field desorption mass spectrometry to consist of the two α-methyl diastereoisomers and the α,α-dimethyl compound. Obviously it is possible to deprotonate α to the lactam carbonyl provided the NH is protected but the *N*-methyl group cannot readily be removed and therefore other protecting groups were investigated.

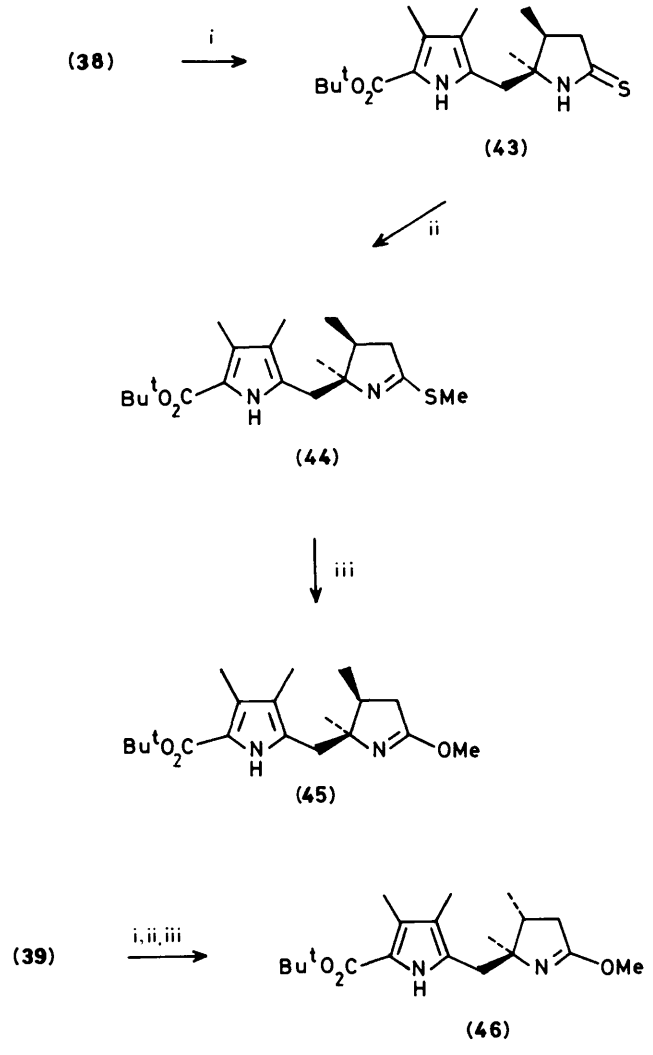
The lactam (**47**) could not be alkylated with benzyl chloromethyl ether and nor could it be acylated with benzoyl chloride (or anhydride), trifluoroacetic anhydride, or pivalic anhydride. Presumably the nitrogen is hindered by the two adjacent benzyl groups. The only successful acylation was with acetic anhydride and a catalytic amount of conc. H_2SO_4 at 110 °C, which probably proceeds *via* an acylium ion. Since the *N*-acetyl product (**49**) has two enolisable sites which would be in competition, its alkylation was not explored.

On the assumption that the nitrogen atom of lactam (**47**) is too hindered, it was reasoned that protection of the hydroxamic acid (**50**) might be easier as the oxygen atom is one bond further from the centre of congestion. The lactam could be regenerated at any stage by reduction of the N–O bond. Hydroxamic acid (**50**) had occasionally been isolated as a by-product of the reduction of the nitro ester (**35**). It is formed when cyclisation of the intermediate hydroxylamine occurs before further reduction to the amine. The hydroxamic acid is not reduced by zinc in acetic acid and it is to effect this step that titanium trichloride is added to the reaction mixture.[11] It was found that by performing the reduction (without added $TiCl_3$) at much higher dilution to slow down the reduction of the intermediate hydroxylamine, an excellent yield of the hydroxamic acid (**50**) could be obtained.

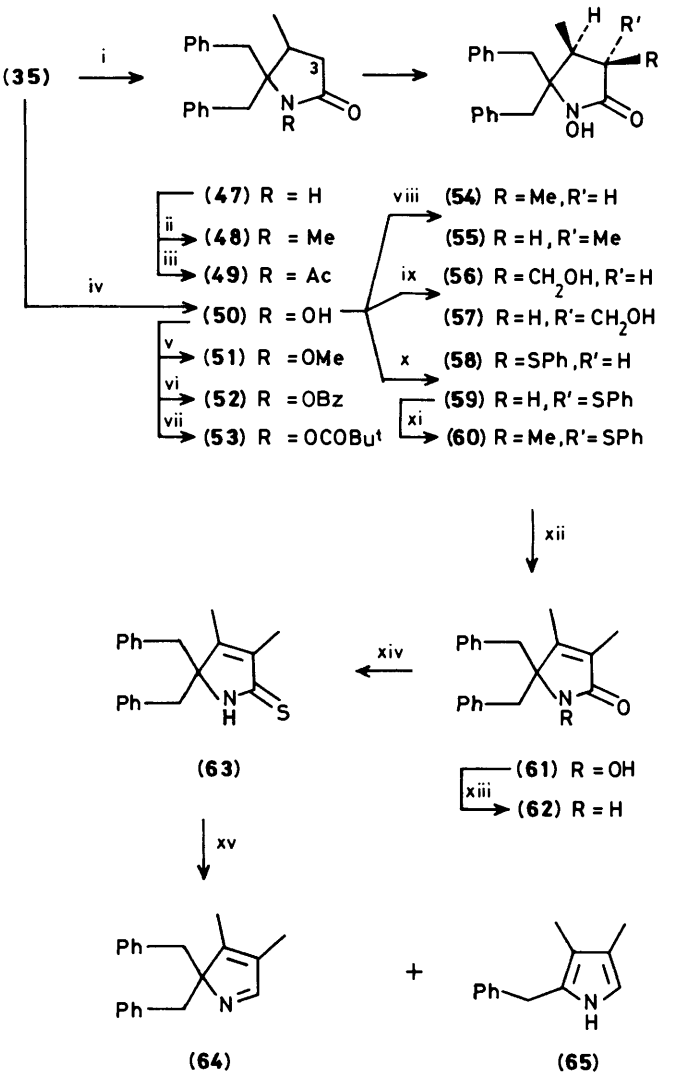
It was indeed found that protection of the hydroxamic acid was much easier than protection of the lactam, and the methyl, benzoyl and pivalyl derivatives, (**51**), (**52**), and (**53**) respectively, were all synthesised. When either of the acyl derivatives, (**52**) or (**53**), was treated with sodium hydride or with LDA followed by an acidic work-up, the only product formed, in near-quantitative yield, was the hydroxamic acid (**50**). This puzzling result was explained when the acidic work-up was omitted for the reaction of lactam (**53**) with LDA. The product in this case was shown by high-field proton n.m.r. and mass spectroscopy to be the enol ester (**66**), presumably formed as shown in Scheme 9. Under acidic work-up conditions, ester (**66**) would be hydrolysed to the hydroxamic acid.

Even more unusual was the observation that treatment of the *O*-methyl derivative (**51**) with strong base gave a quantitative recovery of the lactam (**47**). A possible mechanism for this is shown in Scheme 10.

The fragmentation shown in Scheme 10 may have been prevented at a lower temperature but this was not tried because it was found that the parent hydroxamic acid (**50**) could be



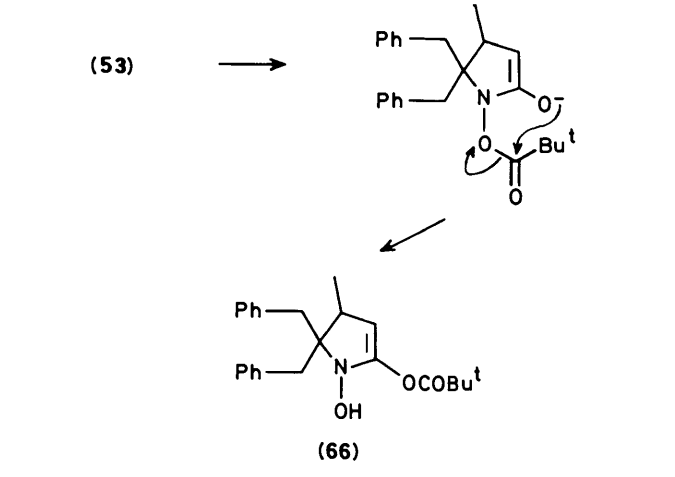
Scheme 7. *Reagents:* i, Lawesson's reagent, PhMe, reflux; ii, MeI, K_2CO_3, THF, 50 °C; iii, MeOH, TsOH, reflux



Scheme 8. *Reagents:* i, Zn, HOAc, 70 °C, then $TiCl_3$; ii, NaH, MeI, THF, reflux; iii, Ac_2O, H_2SO_4, 110 °C; iv, Zn, HOAc, 100 °C; v, Me_2SO_4, K_2CO_3, MeCOEt, reflux; vi, PhCOCl, K_2CO_3; vii, Bu^tCOCl, K_2CO_3; viii, LDA, 4 °C, then MeI; ix, LDA, 4 °C, then $(CH_2O)_n$; x, LDA then PhSSPh; xi, LDA, 4 °C, then MeI; xii, *m*CPBA, CH_2Cl_2, then PhMe, reflux; xiii, Zn, HOAc, NH_4OAc, $TiCl_3$; xiv, Lawesson's reagent, PhH, reflux; xv, Raney Ni, THF–MeOH

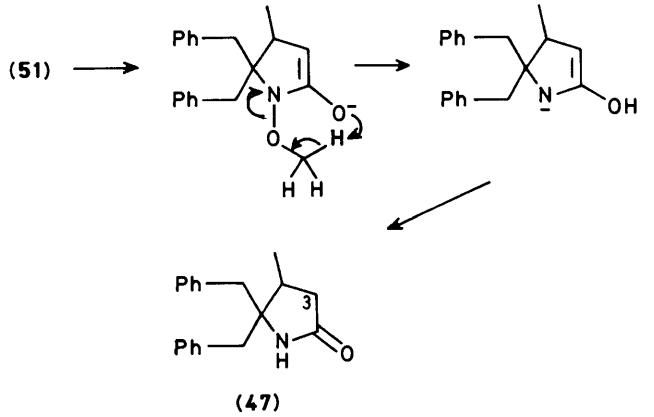
doubly deprotonated. Thus, treatment of acid (**50**) with 6 equiv. of LDA at 4 °C for 3 h produced a deep red solution of the dianion. Addition of methyl iodide then gave a mixture of the two diastereoisomeric monomethylated compounds, (**54**) and (**55**), in a ratio of 8:5 and in excellent overall yield. The two isomers were separated by p.l.c. and their stereochemistry was assigned by n.O.e. difference spectroscopy. For example the major product showed a strong n.O.e. to one of the methyl signals when the other methyl signal was irradiated and is thus the *cis* isomer (**54**). The stereochemical assignment was confirmed by the ^{13}C n.m.r. spectra. Again the *cis* methyl groups of (**54**) are further upfield than the *trans* ones of (**55**) due to the γ-gauche effect. The signals from C-3 and C-4 of the pyrrolidone ring are also further upfield in the *cis* isomer as has been observed for the parent 3,4-dimethylpyrrolidone isomers.[12]

In addition to the introduction of the methyl group α to the carbonyl, it is also necessary to introduce the α,β-double bond. Therefore, the dianion of acid (**50**) was treated with paraformaldehyde to give a 4:3 mixture of the hydroxymethyl compounds (**56**) and (**57**). These isomers could not be separated by t.l.c. or h.p.l.c. but the minor one crystallized from the mixture and so could be obtained pure. The relative stereochemistries were again assigned by n.O.e. difference spectroscopy and again it was found that it was the *cis* compound, (**56**), which predominated.



Scheme 9.

The plan was to eliminate water from the hydroxymethyl compounds to give the *exo* methylene compound. Isomerization to put the double bond in the *endo* position would then give the desired hydroxamic acid (**61**). However, dehydration of the mixture of isomers (**56**) and (**57**) could not be effected either with toluene-*p*-sulphonic acid in toluene at reflux, which gave recovered starting material, or with toluene-*p*-sulphonyl chloride in pyridine, which gave a low yield of the product of tosylation on the NOH among many other products.



(47)

Scheme 10.

An alternative strategy for the introduction of the unsaturation which has been used in the synthesis of butenolides[13] is the introduction of an alkylthio substituent followed by oxidation to the sulphoxide and thermal *syn*-elimination of the alkylsulphenic acid. Using this approach the sulphide (**60**) is the target. In both of the reactions of the dianion of acid (**50**) already described, the major diastereoisomer of the product has resulted from approach of the electrophile from the *same side* as the adjacent methyl group. Thus the methyl group of (**60**) should be put on after the phenylthio group rather than *vice versa*.

Reaction of the dianion of hydroxamic acid (**50**) with diphenyl disulphide gave an 89% yield of a mixture of the diastereoisomeric sulphides (**58**) and (**59**). This mixture could not be readily separated but ^{1}H n.m.r. showed the two compounds in the ratio of 2:11 and n.O.e. experiments on the mixture showed that the major compound in this case was the *trans* isomer (**59**). In view of the previously observed tendency for the *cis* isomer to be the major one, we suspect that, in this case, deprotonation and reprotonation are occurring thus allowing epimerization at the α-position.

The mixture of sulphides (**58**) and (**59**) was deprotonated with LDA at 4 °C and then treated with methyl iodide. The product was apparently a single, crystalline diastereoisomer which n.O.e. experiments suggested was the desired isomer (**60**), although the results in this case were not conclusive. The alternative route to (**60**) by sulphenation of the monomethylated compounds (**54**) and (**55**) was also briefly investigated but t.l.c. showed that no significant reaction had occurred using the standard conditions for anion formation and so this alternative was not pursued.

The sulphide (**60**) was oxidized with *m*-chloroperbenzoic acid to give the two diastereoisomeric sulphoxides due to the new chiral centre at the sulphur atom. These were not separated but were together heated in toluene at reflux to give the α,β-unsaturated hydroxamic acid (**61**) in over 90% yield from the sulphide. The stereochemistry (**60**) for the sulphide was thus confirmed because a *syn* elimination starting from the other diastereoisomer could only have given the *exo* double bond, which was not observed.

It was found that the deoxygenation of hydroxamic acid (**61**) to give lactam (**62**) was best achieved by using titanium(III) chloride in catalytic rather than stoicheiometric amounts in the presence of zinc to regenerate the catalyst.

For the conversion of the lactam (**62**) into the 2*H*-pyrrole (**64**), a new route was investigated instead of the relatively low yielding one used in the synthesis of (**28**); this new route was developed for related studies by Dr. W. M. Stark.[14] The lactam was converted into the thiolactam (**63**) using Lawesson's reagent. Treatment of the thiolactam with Raney nickel in methanol–THF at room temperature resulted in desulphurization to give the desired 2*H*-pyrrole (**64**) as the major product along with a minor amount of the 1*H*-pyrrole (**65**) resulting from loss of a benzyl group. At higher temperatures or longer reaction times (**65**) became the major product. The 2*H*-pyrrole (**64**) could be purified by chromatography but it could not be induced to crystallize and as a result it could not be obtained entirely free of traces of other compounds.

This procedure for the synthesis of a 2*H*-pyrrole from a lactam is a marked improvement over the previous one in both yield and convenience and has the added advantage that the conditions should be compatible with normal ester functionalities.

Conformation of the Lactams and Hydroxamic Acids.—The ^{1}H n.m.r. spectra of the parent lactam (**47**) and its *N*-substituted derivatives, (**48**)—(**53**), showed some very clear trends (Table). The chemical shifts of the two diastereotopic protons at C-3 are very different for most of the derivatives and in each case one of the protons is at abnormally high field compared with the

Table. ^{1}H N.m.r. data of compounds of structure (**67**)

Compound	R	X	3-H_{cis} [b]	3-H_{trans} [b]	4-H	$J_{3,4-cis}$	$J_{3,4-trans}$	4-Me	R
(**47**)	H	H	2.12	2.01	2.40	8.3	11.0	1.13	—
(**48**)	H	Me	2.08	1.61	2.32	8.5	11.9	0.94	—
(**49**)	H	Ac	1.86	1.31	2.34	8.5	13.9	1.26	—
(**50**)	H	OH	1.89	1.12	2.23	8.6	11.0	1.07	—
(**51**)	H	OMe	1.86	0.97	2.42	8.8	9.8	0.87	—
(**52**)	H	OBz	2.15	1.40	2.67	8	10	0.97	—
(**53**)	H	OCOBu^t	2.05	1.32	2.56	9	9	0.97	—
(**54**)	Me	OH	2.06	—	2.49	*a*	—	0.97	0.33
(**55**)	Me	OH	—	1.09	1.63	—	*a*	1.00	0.76
(**56**)	CH_2OH	OH	2.16	—	2.57	*a*	—	1.00	2.63/3.25
(**57**)	CH_2OH	OH	—	1.33	2.07	—	10.9	1.01	3.20/3.55
(**58**)	SPh	OH	3.45	—	2.60	8.6	—	1.23	—
(**59**)	SPh	OH	—	2.34	1.94	—	11.6	1.14	—

[a] Coupling constant not measurable due to multiplicity of signal. [b] *cis* and *trans* Refer to the proton's position in relation to 4-H.

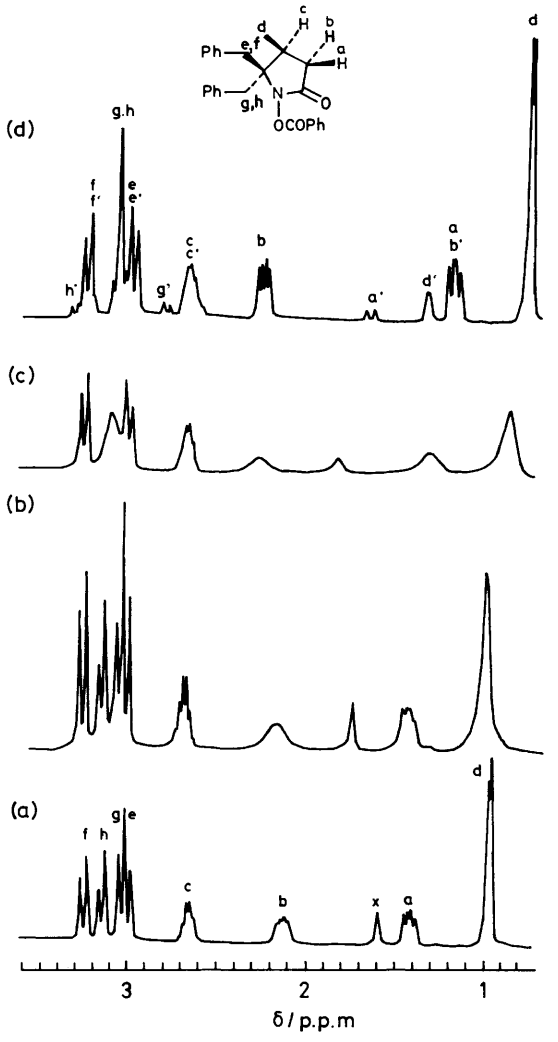


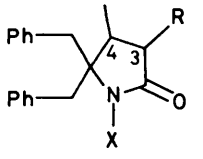
Figure 1. 400 MHz ^{1}H n.m.r. spectra of *O*-benzoylhydroxamic acid (**52**) at (a) 60 °C, (b) 20 °C, (c) 0 °C, and (d) −50 °C. The assignments are indicated on the structure, primed letters in spectrum (d) refer to the minor conformation. The peak marked x is due to water

chemical shifts (δ 2.1 to 2.3) reported [15] for similar compounds lacking the aromatic rings of the benzyl groups. This higher field proton consistently has the larger coupling constant to 4-H. For the hydroxamic acid (**50**), n.O.e. experiments indicated that the higher field proton was the one *trans* to 4-H (*cis* to the methyl group) and the other derivatives have been assigned accordingly. It has been observed in many cases [12,16,17] that protons *cis* to a methyl group on a five-membered ring move upfield but the shifts observed in the present dibenzyl compounds are mostly much larger than those reported.

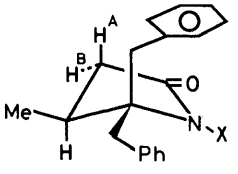
Clearly the aromatic rings of the benzyl groups are affecting the C-3 protons in some way. The clue to what is happening was provided by the *O*-benzoylhydroxamic acid (**52**). At room temperature, some of the signals in its 400 MHz ^{1}H n.m.r. spectrum were strangely broad (Figure 1b) but they were considerably sharper at 60 °C (Figure 1a). On cooling the sample to 0 °C, many of the peaks became very broad indeed (Figure 1c) but at −50 °C, the peaks became well resolved again and now showed two sets of peaks, a major one and a minor one, in a ratio of approximately 9:1 (Figure 1d). This behaviour indicates the existence of two preferred conformations which interconvert rapidly at high temperatures but only slowly at low temperatures thus allowing the spectra of both to be seen separately.

At −43 °C, the slow interconversion of the conformers could be demonstrated by n.m.r.: when a signal from one of the conformers was saturated by irradiation at that frequency, the corresponding signal from the other conformer also became partly saturated because of the interconversion. Using this saturation transfer the peaks due to the two conformers were correlated with one another and this allowed the peaks to be reliably assigned as shown in Figure 1d.

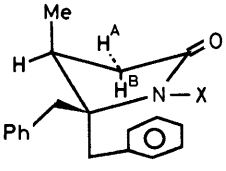
The most notable differences between the spectra of the two conformers are (*i*) the signal for the proton on C-3 which is *cis* to 4-H moves upfield from δ 2.26 in the major conformer to *ca.* δ 1.19 in the minor one; (*ii*) the methyl group on C-4 and the proton *cis* to it on C-3 (*trans* to 4-H) both move downfield by nearly 0.6 p.p.m., from δ 0.77 and 1.19 respectively in the major conformer to δ 1.34 and 1.66 respectively in the minor one; (*iii*) the latter proton changes from a double doublet (*J* 16.5 and 11.5 Hz) in the major conformer to a doublet (*J* 17.3 Hz) in the minor one. This suggests that the angle between 4-H and the 3-H proton *trans* to it approaches 180° in the major conformer and 90° in the minor one. The amide bond of these compounds will have a strong tendency to be planar and this will restrict the conformations of the five-membered ring to the two envelopes (**68**) and (**69**). In conformation (**68**), the methyl group is equatorial and 4-H is axial and has a dihedral angle of almost 180° with the hydrogen atom *trans* to it on C-3 (H^A). This would, therefore, represent the major conformer. In the alternative envelope conformation (**69**) the methyl group is axial and 4-H is equatorial, and models show the dihedral angle with H^A is approximately 90°. This would represent the minor conformer.



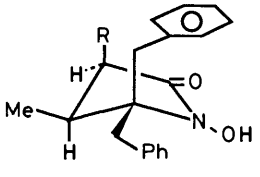
(**67**)



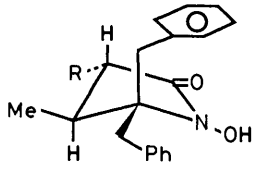
(**68**)



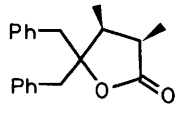
(**69**)



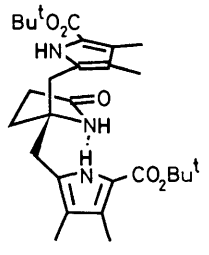
(**70**)



(**71**)



(**72**)



(**73**)

We suggest that in both conformers the aromatic ring of the pseudo-axial benzyl group prefers to lie roughly parallel to the plane of the five-membered ring because of a favourable π–π interaction with the carbonyl group and this has a shielding effect on the other atoms on the same side of the ring. Thus in the major conformer, (**68**), the methyl group and H^A are shielded, whilst in the minor conformer, (**69**), it is H^B which is shielded. At room temperature or above, the time-averaged spectrum is seen and the chemical shifts and coupling constants largely reflect those of the major contributing conformation (**68**).

In order to explain the high free energy of activation (estimated at *ca.* 60 kJ mol^{-1}) required for the interconversion of the conformers, we suggest that there is a further favourable interaction between the other benzyl group (in the pseudo-equatorial position) and the *O*-benzoyl group of (**52**). Both favourable interactions would have to be disrupted for the interconversion to occur. The same conformational argument is equally applicable to the analysis of the n.m.r. spectra of all the compounds (**47**)—(**53**).

In the three pairs of diastereoisomers, (**54**)—(**59**), which have one substituent on C-3, the trends in the chemical shifts and coupling constants are continued. In the *trans* isomers, (**55**), (**57**), and (**59**), (in which 3-H is *trans* to 4-H), 3-H is considerably further upfield than in the corresponding *cis* isomers. Also the coupling constants are within the typical ranges seen for the compounds not substituted at C-3 (*trans* 10—12 Hz; *cis* 8—9 Hz). The same effect is seen on the chemical shifts of the protons on the C-3 substituent. Thus when these are *trans* to 4-H they are at abnormally high field; for example the methyl signal for lactam (**54**) appears at δ 0.33. These observations are consistent with the major contribution being from the envelope conformation in which the methyl group at C-4 is equatorial; *i.e.* conformation (**70**) for the *cis* compounds and (**71**) for the *trans* ones. However, the additional steric effects caused by the substituent at C-3 may cause the preference for these conformations to be reduced.

Shielding effects in the ^1H n.m.r. due to conformations in which a benzyl group has π–π interactions with amide bonds are well-known in dioxopiperazines such as *cyclo*-phenylalanylglycine in which the glycine proton *cis* to the benzyl group is upfield of the *trans* one by 0.58 p.p.m.[18] In this case the energy of the π–π interaction is estimated to be 12 kJ mol^{-1}. A similar conformational effect has been observed for hydantoins of phenylalanine in which the phenyl ring has been shown by n.m.r. and *X*-ray analysis to lie over the carbonyl-containing five-membered ring.[19]

We have synthesised a lactone (**72**), closely related to our lactams, by reaction of 2,3-dimethylsuccinic anhydride with benzylmagnesium bromide. In the *X*-ray crystal structure[20] of this lactone (Figure 2) the conformation is very similar to those described above, (**68**)—(**71**). The ring adopts an envelope conformation and the pseudo-axial benzyl group lies over the carbonyl. It will be evident that for this molecule in the crystal lattice, the methyl group at C-4 is in the unexpected axial position. However, comparison of the n.m.r. spectra of the *cis*-lactone (**72**) and its *trans*-isomer shows that the differences in

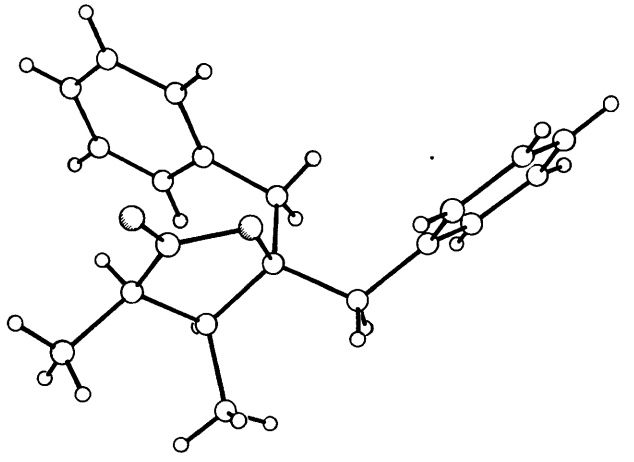


Figure 2. *X*-Ray crystal structure of the lactone (**72**)

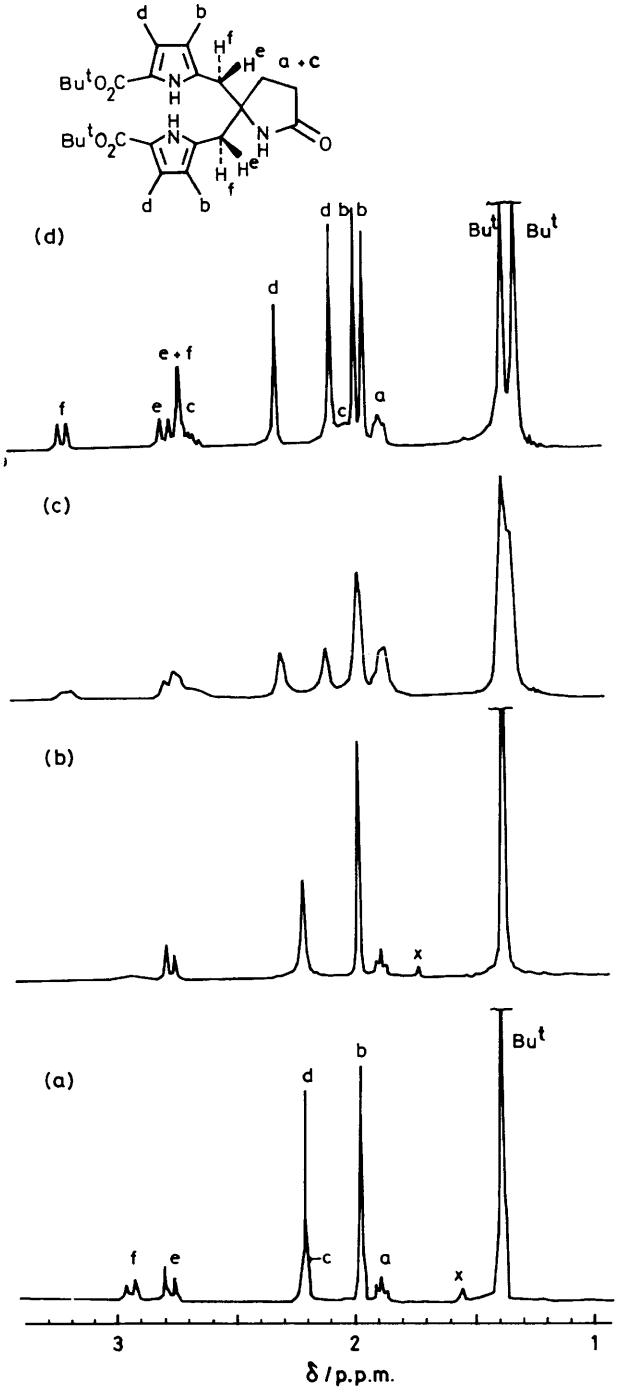


Figure 3. Partial 400 MHz ^1H n.m.r. spectra of bis(pyrrolylmethyl)-lactam (**42**) in $CDCl_3$ at (a) 60 °C, (b) 20 °C, (c) 0 °C, and (d) −30 °C. The assignments are indicated on the structure; the peak marked x is due to water. In addition to the peaks shown, the pyrrole NH's appear as two peaks, δ 9.4 and 11.3, at 0 °C and below, but as a single peak, δ 10.15, at 60 °C; the lactam NH varies from δ 8.25 at −30 °C to δ 7.8 at 60 °C

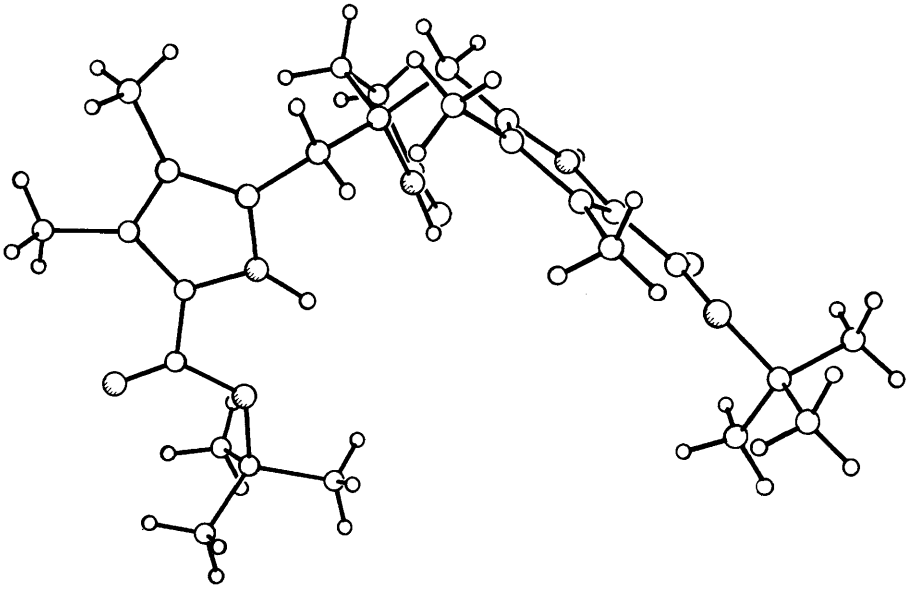


Figure 4. *X*-Ray crystal structure of bis(pyrrolylmethyl)lactam (**42**)

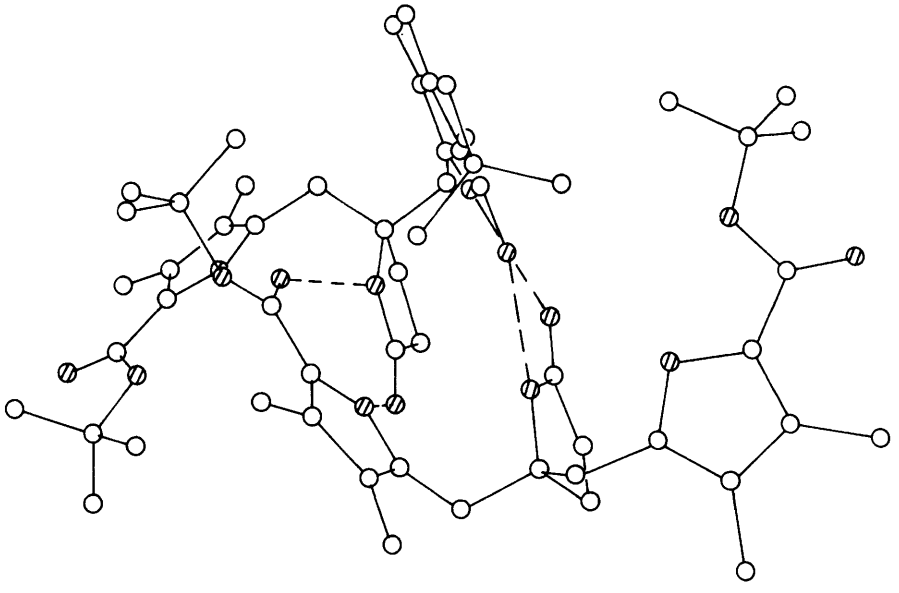


Figure 5. *X*-Ray crystal structure showing the hydrogen-bonded pairs of bis(pyrrolylmethyl)lactam (**42**) molecules

the chemical shifts are considerably smaller than for the hydroxamic acid derivatives (**50**)—(**59**). Therefore the conformational preferences for lactone (**72**) are also presumably smaller and the same probably holds true for the lactam (**47**).

Unusual broadening of the 400 MHz ^{1}H n.m.r. signals was also observed for the bis(pyrrolylmethyl)lactam (**42**) in $CDCl_3$. Again some of the signals were broad at room temperature (Figure 3b) but at 60 °C the spectrum became well resolved and showed the two pyrrole rings to be identical as expected for the symmetrical compound (Figure 3a). At 0 °C most of the peaks became very broad (Figure 3c) but at −30 °C the spectrum sharpened (Figure 3d). At the lowest temperature all the peaks for the pyrrolylmethyl groups were doubled up indicating that the two groups were in different environments. Again these results can be explained by a conformational change which is slow on the n.m.r. timescale at low temperatures. We suggest that a conformation such as (**73**) may be adopted in which the pseudo-axial pyrrolylmethyl group participates in a favourable π–π interaction with the lactam carbonyl (in the same manner as was suggested for the benzyl groups earlier) and the pseudo-equatorial pyrrolylmethyl group is hydrogen bonded to the lactam N–H. Both these interactions would have to be disrupted in order to change to the other envelope conformation which is why there is a considerable barrier to the inversion (also estimated to be *ca.* 60 kJ mol^{-1} at room temperature). In this case also it could be shown that the inversion was still occurring at −30 °C by saturation transfer experiments. These experiments aided the assignment of the peaks, which is indicated in Figure 3d.

When the ^{1}H n.m.r. spectrum of the lactam (**42**) was recorded in $CDCl_3$–CD_3OD (4:1), it was quite normal, with no obvious broadening at room temperature. One would expect the

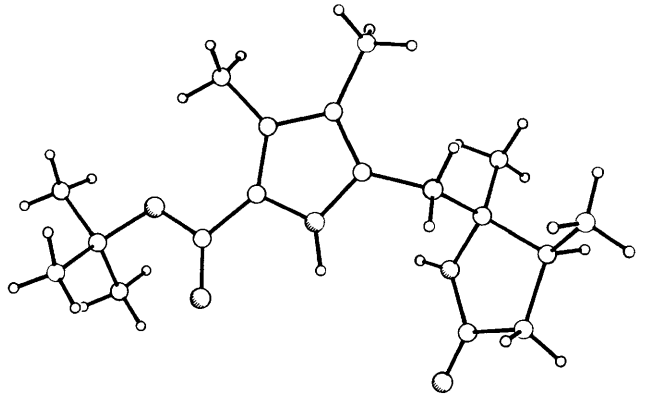


Figure 6. *X*-Ray crystal structure of the pyrrolylmethyl lactam (**38**)

stability conferred on conformation (**73**) by the intramolecular hydrogen bonding to be reduced by the addition of CD_3OD because of competing hydrogen bonding with the solvent.

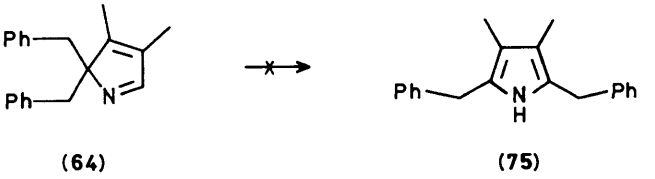
The *X*-ray crystal structure of the lactam (**42**)[20] is shown in Figure 4. It shows the expected puckered lactam ring, and shows that the pseudo-axial pyrrole ring does lie in a plane virtually parallel to that of the lactam carbonyl. However, this pyrrole ring is not directly above the lactam carbonyl but swung out to the side. The reason for this is shown in Figure 5, which shows how the molecules are held together in pairs in the crystal by hydrogen bonding between the lactam of one molecule and the pseudo-axial pyrrole of the other. If this sort of dimerization occurred in solution it could explain our n.m.r. results but on the other hand no change in the spectrum was evident over a range of concentrations down to *ca.* 1 mg ml^{-1} (2 μM) and so dimerization seems unlikely.

The *X*-ray crystal structure[20] of the mono(pyrrolylmethyl)-lactam (**38**) (Figure 6) shows a conformation which is very close to that of the lactam and pseudo-axial pyrrole rings of (**42**). For the lactam (**38**) the n.O.e. measurements indicated a very similar conformation in solution also.

Rearrangement Reactions of 2H-*Pyrroles.*—The crystalline 2*H*-pyrrole (**15**) was quite stable at room temperature. On heating a neat melt of (**15**) to 200 °C, n.m.r. showed that a quantitative conversion into 2,3-dibenzyl-1*H*-pyrrole (**74**) had occurred. This reaction was also acid-catalysed: treatment of the pyrrolenine (**15**) with trifluoroacetic acid (TFA) in dichloromethane gave the same dibenzyl-1*H*-pyrrole isolated in about 30% yield. On following this reaction in CD_2Cl_2 with [$^2H_1$] TFA by n.m.r. it could be seen that 1*H*-pyrrole (**74**) was the only product formed initially but that it started to decompose in the acidic conditions before the 2*H*-pyrrole was consumed.

The mechanism for the rearrangement is presumably a [1,5]-sigmatropic shift of a benzyl group on the 2*H*-pyrrole (which would be protonated in the acid-catalysed reaction) followed by tautomerization to give the 1*H*-pyrrole (Scheme 11).

When the 2,2-dibenzyl-3,4-dimethyl-2*H*-pyrrole (**64**) in CD_2Cl_2 was treated with an excess of TFA, n.m.r. showed complete protonation of the nitrogen (the coupling of the NH with the adjacent proton on C-5 was readily seen) but no rearrangement was observed. Even on heating the sample to 60 °C for 7 h, no rearrangement occurred. After heating the neat pyrrolenine to 130 °C for 15 min, t.l.c. showed a mixture of products as well as the starting material. N.m.r. showed that there could not be a significant amount of the symmetrical 2,5-dibenzyl-3,4-dimethyl-1*H*-pyrrole (**75**) which would be the expected product of a series of three [1,5]-sigmatropic shifts (Scheme 12). It is possible that the decomposition of base (**64**) on heating might be due to the presence of the impurities which it had not been possible to remove.

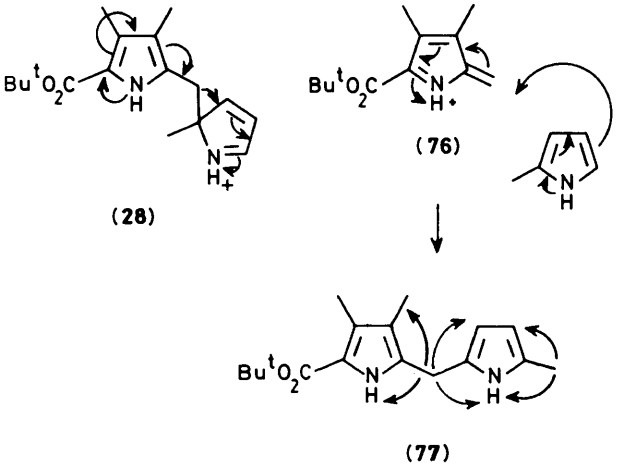


(**64**) (**75**)

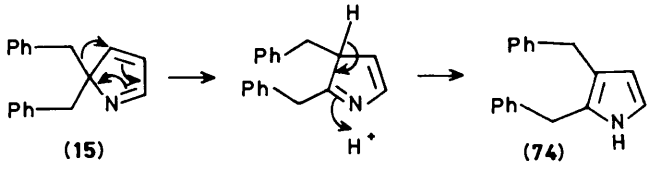
Scheme 12.

The lack of any observable rearrangement of the 2*H*-pyrrole (**64**) by [1,5]-sigmatropic shifts could be caused by two effects: the first is the increased steric hindrance to rearrangement of (**64**) compared to (**15**) and the second is the stabilization of the imine (and iminium ion when protonated) by the electron-donating methyl groups which are present in (**64**) but not (**15**). The conclusion is that while [1,5]-sigmatropic shifts are important in the chemistry of unsubstituted 2*H*-pyrroles such as (**15**), they are much less significant in the chemistry of more substituted 2*H*-pyrroles such as (**64**).

For the pyrrolylmethyl-2*H*-pyrrole (**28**), rearrangement could occur either by a [1,5]-sigmatropic shift like the dibenzyl analogue or by a fragmentation-recombination mechanism such as that shown in Scheme 13. The acid-catalysed rearrangement of (**28**) was effected by addition of 0.05% TFA to a solution in dichloromethane. T.l.c. showed that several air-sensitive products were formed. The reaction and subsequent purification by p.l.c. were performed with the minimum exposure to air and four main products, (**77**)—(**80**), were observed. The structure of these products was based on their n.m.r. and mass spectra and the locations of the substituents were confirmed by the n.O.e.



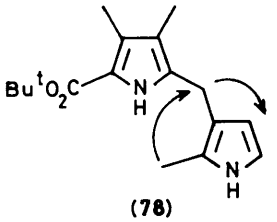
Scheme 13. Rearrangement of pyrrolylmethyl-2*H*-pyrrole (**28**) by a fragmentation–recombination mechanism. The arrows on structures (**77**)—(**80**) indicate the n.O.e.'s observed



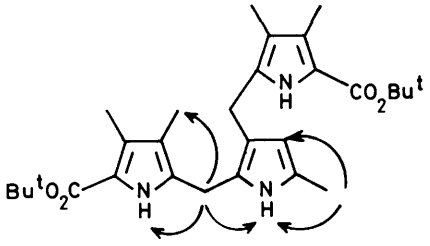
Scheme 11. Rearrangement of 2,2-dibenzyl-2*H*-pyrrole (**15**) by a [1,5]-sigmatropic rearrangement

enhancements which are indicated on the structures by arrows. The molar ratio of these products was estimated as 6:2:1:3.

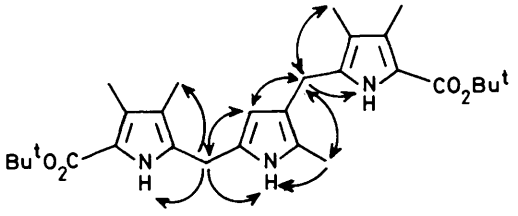
The major product (**77**) is most likely derived by the fragmentation-recombination mechanism (Scheme 13) whereas product (**78**) could be derived in the same way or by a [1,5]-sigmatropic shift. The tripyrrolic products (**79**) and (**80**) are derived by reaction of a dipyrrolic intermediate with the azafulvene (**76**), though in neither case is it certain which pyrrole ring was added last. Thus, for example, (**80**) could be derived from either precursor, (**77**) or (**78**). The thermal rearrangement of pyrrolenine (**28**) was also investigated and n.m.r. indicated that the same products, (**77**)—(**80**), had been formed and the n.m.r. spectrum of the reaction mixture showed that (**77**) and (**80**) predominated.



(**78**)



(**79**)



(**80**)

The evidence is clear that the major rearrangement pathway in this case is fragmentation-recombination as shown in Scheme 13. However, it is less clear whether the [1,5]-sigmatropic shift mechanism also occurs to a lesser extent giving rise to products (**78**) and possibly (**80**). We have seen that in the dibenzyl series, the [1,5]-sigmatropic shift is slowed down by substituents at C-3 and C-4. The 2*H*-pyrroles proposed as intermediates in the mechanism of cosynthetase (Schemes 1 and 2) also have substituents at C-3 and C-4 and therefore are unlikely to rearrange by [1,5]-sigmatropic shifts. The results described here make it much more likely that if the biosynthesis of uro'gen III (**2**) occurs *via* a 2*H*-pyrrole [such as (**4**)], the rearrangement occurs by a fragmentation-recombination mechanism such as illustrated in Schemes 1 and 2.

Experimental

General directions are as in ref. 11 except that ^{1}H n.m.r. spectra were in addition recorded on Bruker WH400 and WM250 spectrometers.

2-*Nitroethylbenzene* (**6**).—Sodium borohydride (17.3 g, 0.46 mol) was added over 30 min to a solution of β-nitrostyrene[21] (97 g, 0.65 mol) and acetic acid (58.5 g, 0.98 mol) in DMSO (325 ml) with the temperature maintained at 25 °C by ice–water cooling. The mixture was stirred at room temperature for 1 h then added to ice–water (600 ml) overlayered with ether (300 ml). The mixture was separated and the aqueous phase was extracted with ether (3 × 150 ml). The combined organic phase was washed with brine (4 × 150 ml), dried (Na_2SO_4), and evaporated. Distillation of the residue yielded 2-nitroethylbenzene (**6**) (68.9 g, 70%), b.p. 94 °C at 0.3 mmHg (lit.,[8] 70—75 °C at 0.1 mmHg) (Found: M^+, 151.0629. Calc. for $C_8H_9NO_2$: *M*, 151.0631); $\nu_{max.}$ 1 550 and 1 380 cm^{-1}; δ_H 3.17 (2 H, t, *J* 8 Hz, $CH_2CH_2NO_2$), 4.47 (2 H, t, *J* 8 Hz, $CH_2CH_2NO_2$), and 7.24 (5 H, s, Ph); *m/z* 151 (1.7%, M^+), 105 (49, $M^+ - NO_2$), 104 (100), 91 (16), 79 (20), and 77 (28).

2-*Nitro*-1,3-*diphenylpropane* (**8**).—A mixture of 2-nitroethylbenzene (**6**) (60.4 g, 0.4 mol), benzaldehyde (46.6 g, 0.44 mol), methylamine hydrochloride (27 g, 0.4 mol), potassium acetate (39.2 g, 0.4 mol) and trimethyl orthoformate (42.4 g, 0.4 mol) in methanol (200 ml) was stirred and heated under reflux for 16 h. The mixture was diluted with ether (1 l) and filtered. The filtrate was washed with water (2 × 400 ml), saturated aqueous sodium metabisulphite (2 × 200 ml), 2M hydrochloric acid (200 ml), saturated aqueous sodium hydrogen carbonate (200 ml), water (200 ml), and brine (2 × 200 ml), dried (Na_2SO_4) and evaporated. The residue was heated under reduced pressure (150 °C at 0.5 mmHg) to remove starting materials, then dissolved in DMSO (150 ml) containing acetic acid (36 g, 0.6 mol) and cooled to 0 °C. A solution of sodium borohydride (15 g, 0.4 mol) in DMSO (50 ml) was added over 15 min keeping the temperature at 20 °C. The mixture was stirred at room temperature for 1 h then added to ice-water (400 ml) overlayered with ether (400 ml). After separation, the organic phase was washed with brine (4 × 100 ml) and water (2 × 100 ml), dried (Na_2SO_4) and evaporated. Crystallization of the residue from dichloromethane–hexane gave 2-*nitro*-1,3-*diphenylpropane* (**8**) [30.8 g, 32% from (**6**)], m.p. 103—104 °C (Found: C, 74.5; H, 6.3; N, 5.9. $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.27; N, 5.80%); $\nu_{max.}$ 1 550 and 1 370 cm^{-1}; δ_H 2.93—3.47 (4 H, m, 2 × $PhCH_2$), 4.90 (1 H, m, $CHNO_2$), and 7.05—7.37 (10 H, m, 2 × Ph); *m/z* 241 (2%, M^+), 194 (71), and 91 (100).

Methyl (*E*) *and* (*Z*)-4-*Benzyl*-4-*nitro*-5-*phenylpent*-2-*enoate* (**9**) *and* (**10**).—A mixture of 2-nitro-1,3-diphenylpropane (**8**) (6.05 g, 25 mmol), tetra-n-butylammonium chloride (85%, 8.21 g, 25 mmol) and potassium fluoride dihydrate (11.75 g, 125 mmol) in dry DMF (30 ml) under nitrogen was stirred for 2.5 h. Methyl propynoate (3.75 ml, 42 mmol) was added and the mixture was stirred for 1.5 h, then diluted with ether (500 ml), washed with water (2 × 150 ml), 1M hydrochloric acid (2 × 100 ml), and brine (2 × 100 ml), dried (Na_2SO_4) and evaporated. The residue was chromatographed (eluant dichloromethane–ether–hexane, 1:0:9 then 1:1:8, and 0:2:8, 0:1:1, and 0:1:0) yielding first the (*Z*)-*ester* (**10**) (1.45 g, 18%), m.p. 108.5—109.5 °C (from dichloromethane–hexane) (Found: C, 70.0; H, 5.95; N, 4.6. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.9; N, 4.30%); $\nu_{max.}$ 1 720, 1 650, and 1 550 cm^{-1}; δ_H 3.72 (2 H, d, *J* 14 Hz, 2 × PhCH*H*), 3.82 (3 H, s, CO_2Me), 3.92 (2 H, d, *J* 14 Hz, 2 × PhC*H*H), 6.00 (1 H, d, *J* 14 Hz, CH=C*H*CO_2Me), 6.52 (1 H, d, *J* 14 Hz, C*H*=$CHCO_2Me$), and 7.18 (10 H, s, 2 × Ph); *m/z* 279 (24%, $M^+ - NO_2$) and 91 (100). This was followed by the (*E*)-*ester* (**9**) (5.71 g, 71%), m.p. 112 °C (from dichloromethane–hexane) (Found: C, 70.00; H, 6.10; N, 4.45); $\nu_{max.}$ 1 720, 1 660, and 1 540 cm^{-1}; δ_H 3.27 (2 H, d, *J* 14 Hz, 2 × PhC*H*H), 3.59 (2 H, d, *J* 14 Hz, 2 × PhCH*H*), 3.74 (3 H, s, CO_2Me), 5.98 (1 H, d, *J* 17 Hz, CH=C*H*CO_2Me), and 7.02—

7.35 (11 H, m, C*H*=CHCO$_2$Me and 2 × Ph); *m/z* 219 (24%) and 91 (100, C_7H_7).

(Z)-4-*Benzyl*-4-*nitro*-5-*phenylpent*-2-*en*-1-*ol* (**11**).—Di-isobutylaluminium hydride (4 ml of a 25% solution in toluene, 6 mmol) was added slowly to a solution of methyl (*Z*)-4-benzyl-4-nitro-5-phenylpent-2-enoate (**10**) (0.98 g, 3 mmol) in dry toluene (30 ml) under argon at 0 °C. The solution was stirred for 2 h at 0 °C then quenched with 1M hydrochloric acid (12 ml) and allowed to warm to room temperature. The mixture was diluted further with 1M hydrochloric acid (30 ml) and separated. The aqueous layer was extracted with ether (3 × 15 ml). The combined organic phase was washed with 5% aqueous sodium hydrogen carbonate (2 × 15 ml) and brine (2 × 15 ml), dried (Na_2SO_4), and evaporated. Crystallization of the residue from dichloromethane–hexane gave the (Z)-*alcohol* (**11**) (0.87 g, 98%), m.p. 98—99 °C (Found: C, 72.9; H, 6.7; N, 4.8. $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.44; N, 4.71%); $\nu_{max.}$ 3 590, 3 430br, 1 540, and 1 350 cm^{-1}; δ_H 1.24 (1 H, br, exchangeable with D_2O, OH), 3.26 (2 H, d, *J* 14 Hz, 2 × PhC*H*H), 3.50 (2 H, d, *J* 14 Hz, 2 × PhCH*H*), 3.57 (2 H, d, *J* 5.4 Hz, CH_2OH), 5.53—5.95 (2 H, m, CH=CH), and 7.21 (10 H, s, 2 × Ph); *m/z* 250 (80%, $M^+ - HNO_2$), 233 (84), 232 (72), and 91 (100).

(Z)-4-*Benzyl*-4-*nitro*-5-*phenylpent*-2-*enal* (**12**).—A mixture of the foregoing (*Z*)-alcohol (11) (735 mg, 2.5 mmol) and manganese dioxide[22] (5.5 g) in dry dichloromethane (200 ml) was stirred for 30 min then filtered through Celite, which was then washed with chloroform. Evaporation of the filtrate gave the (Z)-*aldehyde* (**12**) (591 mg, 81%), which crystallized from dichloromethane–hexane, m.p. 116—118 °C (Found: C, 73.25; H, 5.85; N, 4.65. $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74%); $\nu_{max.}$ 1 680, 1 620, 1 540, and 1 350 cm^{-1}; δ_H 3.54 (2 H, d, *J* 14 Hz, 2 × PhC*H*H), 3.74 (2 H, d, *J* 14 Hz, 2 × PhCH*H*), 6.12 (1 H, dd, *J* 6 and 13 Hz, CH=C*H*CHO), 6.64 (1 H, d, *J* 13 Hz, C*H*=CHCHO), 6.93—7.28 (10 H, m, 2 × Ph), and 9.35 (1 H, d, *J* 6 Hz, CHO); *m/z* 249 (32%, $M^+ - NO_2$), 157 (43), and 91 (100).

(Z)-4-*Benzyl*-4-*nitro*-5-*phenylpent*-2-*enal Ethylene Acetal* (**13**).—A mixture of (*Z*)-4-benzyl-4-nitro-5-phenylpent-2-enal (**12**) (515 mg, 1.75 mmol), toluene-*p*-sulphonic acid monohydrate (50 mg, 0.26 mmol), and ethylene glycol (0.5 ml, 8.9 mmol) in dry benzene (60 ml) was heated under reflux for 17 h with constant azeotropic removal of water. The mixture was diluted with ether (100 ml), washed with 5% aqueous sodium hydrogen carbonate (2 × 25 ml) and brine (2 × 25 ml), dried ($MgSO_4$), and evaporated to give the (Z)-*acetal* (**13**) (471 mg, 79%) which crystallized from dichloromethane–hexane, m.p. 137—138 °C (Found: C, 70.6; H, 6.1; N, 4.05. $C_{20}H_{21}NO_4$ requires C, 70.78; H, 6.24; N, 4.13%); $\nu_{max.}$ 1 607, 1 550, and 1 350 cm^{-1}; δ_H 3.47 (2 H, d, *J* 13.8 Hz, 2 × PhC*H*H), 3.64 (2 H, d, *J* 13.8 Hz, 2 × PhCH*H*), 3.89—4.09 (4 H, m, OCH_2CH_2O), 5.56—6.11 (3 H, m, CH=CHCH), and 7.18 (10 H, s, 2 × Ph); *m/z* 339 (0.06%, M^+), 293 (25, $M^+ - NO_2$), 91 (100), and 73 (64).

(E)-4-*Benzyl*-4-*nitro*-5-*phenylpent*-2-*en*-1-*ol*.—Di-isobutylaluminium hydride (10 ml of a 25% solution in toluene, 15 mmol) was added slowly to a solution of methyl (*E*)-4-benzyl-4-nitro-5-phenylpent-2-enoate (**9**) (1.6 g, 5 mmol) in dry toluene (50 ml) under argon at 0 °C. The mixture was stirred for 3 h, then quenched with 1M hydrochloric acid (30 ml) and allowed to warm to room temperature. 1M Hydrochloric acid was added and the mixture was separated. The aqueous layer was extracted with ether (3 × 30 ml). The combined organic phase was washed with 1M hydrochloric acid (30 ml), 5% aqueous sodium hydrogen carbonate (50 ml), and brine (30 ml), dried ($MgSO_4$), and evaporated. Crystallization of the residue from dichloromethane–hexane gave the (E)-*alcohol* (1.17 g, 79%), m.p. 68—69 °C (Found: C, 72.55; H, 6.4; N, 4.75); $\nu_{max.}$ 3 620, 3 450br, 1 550, and 1 360 cm^{-1}; δ_H 1.64 (1 H, br, exchangeable with D_2O, OH), 3.30 (2 H, d, *J* 14 Hz, 2 × PhC*H*H), 3.52 (2 H, d, *J* 14 Hz, 2 × PhCH*H*), 4.14 (2 H, d, *J* 3.5 Hz, CH_2OH), 5.83—5.95 (2 H, m, CH=CH), and 7.21 (10 H, s, 2 × Ph); *m/z* 233 (8%), 194 (7), and 91 (100).

(E)-4-*Benzyl*-4-*nitro*-5-*phenylpent*-2-*enal*.—A mixture of the foregoing (*E*)-alcohol (190 mg, 0.64 mmol) and manganese dioxide[22] (1.4 g) in dry dichloromethane (50 ml) was stirred for 15 min. The mixture was diluted with chloroform, filtered through Celite and evaporated to give the (E)-*aldehyde* (144 mg, 76%) which crystallized from dichloromethane–hexane, m.p. 98—100 °C (Found: C, 73.25; H, 5.85; N, 4.8); $\nu_{max.}$ 1 690, 1 550, and 1 360 cm^{-1}; δ_H 3.32 (2 H, d, *J* 14 Hz, 2 × PhC*H*H), 3.73 (2 H, d, *J* 14 Hz, 2 × PhCH*H*), 6.28 (1 H, dd, *J* 7.5 and 16.5 Hz, CH=C*H*CHO), 7.04—7.37 (11 H, m, C*H*=CHCHO and 2 × Ph), and 9.47 (1 H, d, *J* 7.5 Hz, CHO); *m/z* 295 (0.06%, M^+), 266 (0.4, $M^+ - CHO$), 157 (38), and 91 (100).

(E)-4-*Benzyl*-4-*nitro*-5-*phenylpent*-2-*enal Ethylene Acetal*.—A mixture of the foregoing (*E*)-4-benzyl-4-nitro-5-phenylpent-2-enal (295 mg, 1 mmol), toluene-*p*-sulphonic acid monohydrate (30 mg, 0.16 mmol), and ethylene glycol (0.3 ml, 5.3 mmol) in dry benzene (30 ml) was heated under reflux for 17 h with constant azeotropic removal of water. The mixture was diluted with ether (20 ml), washed with 5% sodium hydrogen carbonate (2 × 20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated. The residue was crystallized from dichloromethane–hexane to yield the (E)-*acetal* (274 mg, 81%), m.p. 73—75 °C (Found: C, 70.6; H, 6.3; N, 4.0); $\nu_{max.}$ 1 550 and 1 360 cm^{-1}; δ_H 3.29 (2 H, d, *J* 14.4 Hz, 2 × PhC*H*H), 3.55 (2 H, d, *J* 14.4 Hz, 2 × PhCH*H*), 3.90 (4 H, s, OCH_2CH_2O), 5.29 (1 H, d, *J* 5.2 Hz, CH=CHC*H*), 5.74 (1 H, dd, *J* 5.2 and 16.1 Hz, CH=C*H*CH), 6.22 (1 H, d, *J* 16.1 Hz, C*H*=CHCH), and 7.18 (10 H, m, 2 × Ph); *m/z* 293 (16%, $M^+ - NO_2$), 231 (18), and 91 (100).

(Z)-4-*Amino*-4-*benzyl*-5-*phenylpent*-2-*enal Ethylene Acetal* (**14**).—Zinc powder (5 g, 77 mmol) was added over 10 min to a cooled (ice-water) solution of (*Z*)-4-benzyl-4-nitro-5-phenylpent-2-enal ethylene acetal (**13**) (1.02 g, 3 mmol) in acetic acid (50 ml). The mixture was stirred at room temperature for 1.5 h, then filtered through Celite, which was then washed with ether (100 ml). The filtrate was diluted with water (300 ml) and cooled to 0 °C. 10M Sodium hydroxide (110 ml) was added until the aqueous layer was at pH 12. After separation, the aqueous phase was extracted with ether (2 × 50 ml). The combined organic phase was washed with water (50 ml), dried (Na_2SO_4) and evaporated to give the *amine* (**14**) (0.89 g, 96%) which crystallized from hexane, m.p. 89—90 °C (Found: C, 77.55; H, 7.60; N, 4.6. $C_{20}H_{23}NO_2$ requires C, 77.64; H, 7.49; N, 4.53%); $\nu_{max.}$ 3 380, 3 310, and 1 605 cm^{-1}; δ_H 1.45 (2 H, br, NH_2), 2.76 (2 H, d, *J* 12.5 Hz, 2 × PhC*H*H), 2.90 (2 H, d, *J* 12.5 Hz, 2 × PhCH*H*), 3.73—3.87 (4 H, m, OCH_2CH_2O), 5.26—5.79 (3 H, m, CH=CHCH), and 7.25 (10 H, s, 2 × Ph); *m/z* 310 ($M^+ + 1$), 309 (M^+), 247, 218 ($M^+ - C_7H_7$), 174, 156, and 146.

2,2-*Dibenzyl*-2H-*pyrrole* (**15**).—10M Hydrochloric acid (1.2 ml) was added to a solution of the foregoing amine (**14**) (618 mg, 2 mmol) in THF (10 ml). The mixture was stirred for 5 min then diluted with water (40 ml) and ether (20 ml) and neutralized by the addition of potassium carbonate (1.1 g). After a further 5 min the mixture was separated and the aqueous layer was extracted with ether (2 × 10 ml). The combined organic phase was washed with brine (10 ml), dried ($MgSO_4$), and evaporated to give the 2H-*pyrrole* (**15**) (441 mg, 89%), which crystallized

from hexane, m.p. 78—79 °C (Found: C, 87.15; H, 7.15; N, 5.75. $C_{18}H_{17}N$ requires C, 87.41; H, 6.93; N, 5.66%); $\nu_{max.}$ 1 607, 1 598, and 1 500 cm^{-1}; δ_H 3.12 (4 H, s, 2 × PhCH_2), 6.02 (1 H, d, *J* 5 Hz, 4-H), 7.12 (10 H, s, 2 × Ph), 7.25 (1 H, d, *J* 5 Hz, 3-H), and 7.76 (1 H, s, 5-H); δ_C 42.3 (2 × Ph*C*H_2), 86.0 (C-2), 126.3 (2 × *p*-Ph), 127.5 and 130.3 (2 × *o*-, and *m*-Ph), 136.8 (C-4), 157.7 (C-3), and 163.4 (C-5); *m/z* 247 (40%, M^+), 156 (74, $M^+ - C_7H_7$), and 91 (100).

2,2-*Dibenzyl*-1,5-*dihydro*-2H-*pyrrole*.—Sodium borohydride (200 mg, 5.3 mmol) was added to a solution of 2,2-dibenzyl-2*H*-pyrrole (**15**) (96 mg, 0.39 mmol) in dry methanol (4 ml). The mixture was stirred for 15 min then diluted with water (50 ml) and extracted with ether (3 × 10 ml). The combined extracts were washed with brine (20 ml), dried ($MgSO_4$), and evaporated. Preparative t.l.c. (eluant ether containing 1% triethylamine) of the residue gave the *dihydropyrrole* (78 mg, 80%) (Found: $M^+ - C_7H_7$, 158.0971. $C_{11}H_{12}N$ requires *M*, 158.0967); $\nu_{max.}$ 3 400 br and 1 610 cm^{-1}; $\delta_H(CD_2Cl_2)$ 2.34 (1 H, br, NH), 2.87 (2 H, d, *J* 13.2 Hz, 2 × PhC*H*H), 2.94 (2 H, d, *J* 13.2 Hz, 2 × PhCH*H*), 3.23 (2 H, br s, CH_2N), 5.65 (1 H, dt, *J* 5.8 and 1.7 Hz, C*H*=CHCH$_2$), 5.78 (1 H, dt, *J* 5.8 and 2.2 Hz, CH=C*H*CH$_2$), and 7.20—7.37 (10 H, m, 2 × Ph); *m/z* 158 (90%, $M^+ - C_7H_7$) and 91 (100).

t-Butyl 5-*Formyl*-3,4-*dimethylpyrrole*-2-*carboxylate* (**17**).—Lead tetra-acetate (150 g, 0.34 mol) was added over 20 min to a solution of t-butyl 3,4,5-trimethylpyrrole-2-carboxylate[23] (**16**) (31.4 g, 0.15 mol) in acetic acid (150 ml). During the addition the temperature rose to 85 °C and the mixture was kept at 80 °C for a further 30 min then cooled to room temperature. Ethylene glycol (5 ml) was added to destroy excess of oxidant and the mixture was diluted with water (900 ml) and extracted with dichloromethane (3 × 15 ml). The combined extracts were washed with water (150 ml) and evaporated. The residue was dissolved in 50% aqueous THF (450 ml) and heated under reflux for 2 h. The mixture was diluted with ether (225 ml) and separated. The organic layer was washed with saturated aqueous sodium hydrogen carbonate (3 × 150 ml) and brine (150 ml), dried ($MgSO_4$), and evaporated to give the formylpyrrole (**17**) (22.9 g, 68%) which crystallized from hexane, m.p. 102—103 °C (lit.,[23] 100—101 °C) (Found: C, 64.65; H, 7.45; N, 6.2. Calc. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27%); $\nu_{max.}$ 3 450, 1 700, and 1 660 cm^{-1}; δ_H 1.57 (9 H, s, Bu^t), 2.22 (3 H, s, Me), 2.27 (3 H, s, Me), 9.75 (1 H, br, NH), and 9.78 (1 H, s, CHO); *m/z* 223 (M^+), 167 ($M^+ - C_4H_8$), 150 ($M^+ - C_4H_9O$) and 121.

t-Butyl 3,4-*Dimethyl*-5-(2-*nitroprop*-1-*enyl*)*pyrrole*-2-*carboxylate* (**18**).—A mixture of compound (**17**) (20.1 g, 90 mmol), potassium acetate (9.68 g, 99 mmol), methylamine hydrochloride (6.08 g, 90 mmol), and nitroethane (13 ml, 180 mmol) in dry methanol (135 ml) was stirred for 4 h. The mixture was diluted with water (700 ml) and extracted with dichloromethane (3 × 150 ml). The combined extracts were washed with water (150 ml) and evaporated to yield the *nitropropenyl pyrrole* (**18**) (13.7 g, 54%), m.p. 122—124 °C (from methanol) (Found: C, 60.0; H, 7.45; N, 9.85. $C_{14}H_{20}N_2O_4$ requires C, 59.99; H, 7.19; N, 9.99%); $\nu_{max.}$ 3 480, 1 690, 1 640, 1 510, and 1 340 cm^{-1}; δ_H 1.57 (9 H, s, Bu^t), 2.08 and 2.19 (each 3 H, s, Me), 2.49 (3 H, s, Me), 7.99 (1 H, s, C=CH), and 9.00 (1 H, br, NH); *m/z* 280 (M^+), 224 ($M^+ - C_4H_8$), 207 ($M^+ - C_4H_9O$), 177, 167, and 149.

t-Butyl 3,4-*Dimethyl*-5-(2-*nitropropyl*)*pyrrole*-2-*carboxylate* (**19**).—Sodium borohydride (0.38 g, 10 mmol) was added in one portion to a slurry of the foregoing pyrrole (**18**) (1.4 g, 5 mmol) in ethanol (50 ml). The mixture was stirred for 30 min then evaporated. The residue was dissolved in water (20 ml) and neutralized by the addition of acetic acid. The resulting precipitate was collected, washed with water and recrystallized from methanol to give the *nitropropylpyrrole* (**19**) (1.03 g, 73%), m.p. 143—144 °C (Found: C, 59.80; H, 7.85; N, 9.70. $C_{14}H_{22}N_2O_4$ requires C, 59.56; H, 7.85; N, 9.92%); $\nu_{max.}$ 3 450, 1 680, 1 555, and 1 370 cm^{-1}; δ_H 1.46 (3 H, d, *J* 6 Hz, CHMe), 1.53 (9 H, s, Bu^t), 1.87 and 2.17 (each 3 H, s, ArMe), 2.85—3.48 (2 H, m, ArCH_2), 4.68 (1 H, m, *J* 6 Hz, C*H*Me), and 8.90 (1 H, br, NH); *m/z* 282 (M^+), 226 ($M^+ - C_4H_8$), 209 ($M^+ - C_4H_9O$), 180, 179, 162, 154, and 152.

Methyl (Z)-5-(3,4-*Dimethyl*-5-t-*butoxycarbonylpyrrol*-2-*yl*)-4-*methyl*-4-*nitropent*-2-*enoate* (**21**).—Sodium borohydride (5.7 g, 150 mmol) was added over 20 min to a slurry of compound (**18**) (4.2 g, 15 mmol) in dry methanol (150 ml). The mixture was stirred for 15 min and then treated with methyl propynoate (2.7 ml, 30 mmol). After 8 h the mixture was diluted with water (300 ml), neutralized by the addition of acetic acid, and extracted with chloroform (3 × 100 ml). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate (250 ml) and evaporated. The residue was dissolved in methanol (12 ml) and cooled to give the (Z)-α,β-*unsaturated ester* (**21**) (1.69 g, 31%), m.p. 133—134 °C (Found: C, 58.95; H, 7.15; N, 7.6. $C_{18}H_{26}N_2O_6$ requires C, 59.00; H, 7.15; N, 7.65%); $\nu_{max.}$ 3 460, 1 735, 1 680, 1 560, and 1 370 cm^{-1}; δ_H 1.57 (9 H, s, Bu^t), 1.84 (3 H, s, Me), 1.91 and 2.22 (each 3 H, s, ArMe), 3.58 (2 H, s, CH_2), 3.72 (3 H, s, CO_2Me), 5.94 (1 H, d, *J* 13 Hz, CH=C*H*CO$_2$Me), 6.33 (1 H, d, *J* 13 Hz, C*H*=CHCO$_2$Me), and 8.45 (1 H, br, NH); *m/z* 366 (5%, M^+), 152 (100), 134 (18), and 84 (23).

t-Butyl 5-[(Z)-5-*Hydroxy*-2-*methyl*-2-*nitropent*-3-*enyl*]-3,4-*dimethylpyrrole*-2-*carboxylate* (**22**).—Di-isobutylaluminium hydride (5.7 ml of a 25% solution in toluene, 9 mmol) was added slowly to a solution of compound (**21**) (1.1 g, 3 mmol) in dry toluene (50 ml) under argon at 0 °C. The mixture was stirred for 5.5 h at 0 °C then diluted with 1M hydrochloric acid (20 ml) and allowed to warm to room temperature. A further portion of 1M hydrochloric acid (80 ml) was added and the mixture was separated. The aqueous layer was extracted with ether (3 × 50 ml). The combined organic phase was washed with 1M hydrochloric acid (3 × 50 ml), 5% aqueous sodium hydrogen carbonate (100 ml), and brine (50 ml), dried ($MgSO_4$), and evaporated to yield the (Z)-*allylic alcohol* (**22**) (0.82 g, 81%) which crystallized from ether–hexane, m.p. 86—88 °C (Found: C, 60.5; H, 7.7; N, 8.35. $C_{17}H_{26}N_2O_5$ requires C, 60.34; H, 7.74; N, 8.28%); $\nu_{max.}$ 3 625, 3 460, 3 400br, 1 680, 1 550, and 1 370 cm^{-1}; δ_H 1.53 (9 H, s, Bu^t), 1.69 (3 H, s, Me), 1.90 and 2.19 (each 3 H, s, ArMe), 2.61 (1 H, br, OH), 3.37 (2 H, s, ArCH_2), 4.09 (2 H, d, *J* 6 Hz, CH_2OH), 5.70 (1 H, d, *J* 13 Hz, C*H*=CHCH$_2$OH), 5.86 (1 H, dt, *J* 6 and 13 Hz, CH=C*H*CH$_2$OH), and 9.00 (1 H, br, NH); *m/z* 338 (8%, M^+), 208 (13), 154 (23), 152 (100), and 83 (35).

t-Butyl 5-[(E)-2-*Methyl*-2-*nitro*-5-*oxopent*-3-*enyl*]-3,4-*dimethylpyrrole*-2-*carboxylate* (**23**).—A solution of compound (**22**) (2.13 g, 6.25 mmol) in dichloromethane (5 ml) was added to a suspension of pyridinium chlorochromate[24] (2.03 g, 9.52 mmol) and sodium acetate (0.2 g, 2.44 mmol) in dichloromethane (10 ml). The mixture was stirred for 2 h, then diluted with dry ether (75 ml) and filtered through Florisil. The filtrate was evaporated and the residue was dissolved in dichloromethane (20 ml), washed with 5% aqueous sodium carbonate (20 ml), dried ($MgSO_4$), and evaporated to give the (E)-*aldehyde* (**23**) (1.31 g, 62%) which crystallized from ether–hexane, m.p. 105—106 °C (Found: C, 60.6; H, 7.0; N, 8.15. $C_{17}H_{24}N_2O_5$ requires C, 60.70; H, 7.19; N, 8.33%); $\nu_{max.}$ 3 460, 1 700, 1 550, and 1 370 cm^{-1}; δ_H 1.58 (9 H, s, Bu^t), 1.80 (3 H, s, Me), 1.89 and 2.23 (each 3 H, s, ArMe), 3.43 (2 H, s, ArCH_2), 6.28 (1 H, dd, *J* 7.5 and 16.5 Hz, CH=C*H*CHO), 7.15 (1 H, d, *J* 16.5 Hz,

C*H*=CHCHO), 8.97 (1 H, br, NH), and 9.59 (1 H, d, *J* 7.5 Hz, CHO); *m/z* 336 (M^+), 263 (M^+ − CHO), 234, 208, and 152.

t-Butyl 5-(2-*Methyl*-5-*oxo*-2,5-*dihydropyrrol*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**25**).—Zinc powder (6.56 g, 0.1 mol) was added over 10 min to a solution of compound (**21**) (1.84 g, 5 mmol) in acetic acid–THF (1:1, 100 ml) at 0 °C. The mixture was stirred at 0 °C for 1.75 h then allowed to warm to room temperature. Ammonium acetate (0.77 g, 10 mmol) was added, followed by titanium trichloride (3 ml of a 15% aqueous solution, 3 mmol). The mixture was stirred for 3 h, then diluted with dichloromethane (50 ml), neutralized by the addition of saturated aqueous potassium carbonate and filtered through Celite, which was then washed with dichloromethane (50 ml). The filtrate was diluted with water (200 ml) and separated. The aqueous layer was extracted with dichloromethane (2 × 25 ml) and the combined organic phase was washed with 5% aqueous sodium hydrogen carbonate (2 × 150 ml), dried ($MgSO_4$), and evaporated to yield the *lactam* (**25**) (1.26 g, 82%) which crystallized from ethyl acetate–hexane, m.p. 180—181 °C (Found: C, 66.9; H, 7.9; H, 8.95. $C_{17}H_{24}N_2O_3$ requires C, 67.08; H, 7.95; N, 9.20%); $\nu_{max.}$ 3 450, 3 300br, and 1 700 cm^{-1}; δ_H 1.29 (3 H, s, Me), 1.43 (9 H, s, Bu^t), 1.82 and 2.12 (each 3 H, s, ArMe), 2.83 (2 H, s, $ArCH_2$), 5.89 (1 H, dd, *J* 2 and 6 Hz, CH=C*H*CO), 6.94 (1 H, dd, *J* 1.5 and 6 Hz, C*H*=CHCO), 7.58 (1 H, br, lactam NH), and 9.39 (1 H, br, pyrrole NH); *m/z* 304 (M^+), 208, 152, and 134.

t-Butyl 5-(5-*Ethoxy*-2-*methyl*-2H-*pyrrol*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**26**).—A mixture of the foregoing lactam (**25**) (608 mg, 2 mmol), triethyloxonium tetrafluoroborate (380 mg, 2 mmol), and 1,8-bis(dimethylamino)naphthalene (425 mg, 2 mmol) in dry dichloromethane (10 ml) under argon was stirred for 19 h. After evaporation, the residue was dissolved in ether, filtered and evaporated. Preparative t.l.c. (eluant ether containing 1% triethylamine) of the residue gave the *imidate ester* (**26**) (479 mg, 72%) (Found: M^+, 332.2105. $C_{19}H_{28}N_2O_3$ requires *M*, 332.2093); $\nu_{max.}$ 3 470, 3 375br, 1 680, 1 625, and 1 555 cm^{-1}; δ_H 1.26 (3 H, s, Me), 1.38 (3 H, t, *J* 7.5 Hz, CH_2Me), 1.55 (9 H, s, Bu^t), 1.88 and 2.22 (each 3 H, s, ArMe), 2.60 and 3.01 (each 1 H, d, *J* 15 Hz, $ArCH_2$), 4.40 (2 H, q, *J* 7.5 Hz, CH_2Me), 5.99 (1 H, d, *J* 5 Hz, CH=C*H*COEt), 7.16 (1 H, d, *J* 5 Hz, C*H*=CHCOEt), and 9.49 (1 H, br, NH); *m/z* 332 (7%, M^+), 208 (20), 152 (100), 125 (71), and 96 (76).

t-Butyl 5-(2-*Methyl*-1,5-*dihydro*-2H-*pyrrol*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**27**).—Di-isobutylaluminium hydride (10 ml of a 25% solution in toluene, 15 mmol) was added to a solution of the foregoing imidate ester (**26**) (830 mg, 2.5 mmol) in dry toluene (12.5 ml) under argon. The mixture was stirred for 3.5 h then cooled to 0 °C and quenched with methanol (10 ml). A further portion of methanol (140 ml) was added and the mixture was stirred for 1 h then filtered through Celite and evaporated to give the *amine* (**27**) (714 mg, 98%), which was homogeneous by t.l.c. (Found: M^+, 290.1982. $C_{17}H_{26}N_2O_2$ requires *M*, 290.1988); $\nu_{max.}$ 3 460, 3 375br, and 1 680 cm^{-1}; δ_H 1.29 (3 H, s, Me), 1.54 (9 H, s, Bu^t), 1.87 and 2.20 (each 3 H, s, ArMe), 2.72 (2 H, s, $ArCH_2$), 3.41 (1 H, br, amine NH), 3.63 and 3.88 (each 1 H, dt, *J* 15.2 and 1.6 Hz, CH_2N), 5.65—5.84 (2 H, m, CH=CH), and 9.79 (1 H, br, pyrrole NH); *m/z* 291 (0.6%, $M^+ + 1$), 290 (0.14, M^+), 288 (1.4, $M^+ - H_2$), 209 (48), 153 (100), and 152 (82).

t-Butyl 5-(2-*Methyl*-2H-*pyrrol*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**28**).—t-Butyl hypochlorite (33 μl, 0.3 mmol) was added to a solution of the foregoing amine (**27**) (87 mg, 0.3 mmol) in dry dichloromethane (0.5 ml) under argon at −20 °C in the dark. The solution was left at −20 °C for 2 h and then evaporated, first in a stream of argon then by evacuation to 0.5 mmHg while still at −20 °C. DBU (0.15 ml, 0.9 mmol) and then dry dichloromethane (0.5 ml) were added to the residue which was then allowed to warm to room temperature over 4 h. The mixture was evaporated and preparative t.l.c. (eluant ether–hexane, 4:1, containing 0.1% triethylamine) of the residue gave the 2H-*pyrrole* (**28**) (19 mg, 22%) (Found: M^+, 288.1854. $C_{17}H_{24}N_2O_2$ requires *M*, 288.1832); δ_H(CD_2Cl_2 containing t-butylamine) 1.19 (3 H, s, Me), 1.54 (9 H, s, Bu^t), 1.91 and 2.20 (each 3 H, s, ArMe), 2.45 and 3.03 (each 1 H, d, *J* 14.8 Hz, $ArCH_2$) 6.36 (1 H, d, *J* 4.8 Hz, 4-H), 7.35 (1 H, d, *J* 4.8 Hz, 3-H), 8.03 (1 H, s, 5-H), and 9.25 (1 H, br, NH).

Methyl 4-*Benzyl*-3-*methyl*-4-*nitro*-5-*phenylpentanoate* (**35**).—A solution of 2-nitro-1,3-diphenylpropane (**8**) (18.08 g, 75.0 mmol), tetrabutylammonium chloride (24.5 g of Aldrich 85%, 75.0 mmol), potassium fluoride dihydrate (7.05 g, 75.0 mmol), and methyl crotonate (**34**) (39.8 ml, 375 mmol) in dry dimethylformamide (110 ml) was stirred under argon at 60 °C for 50 h. The mixture was cooled, taken up in ether (2 000 ml), washed with water (400 ml) and the aqueous washing extracted with ether (400 ml). The combined organic phase was washed with water (400 ml), 1M hydrochloric acid (2 × 400 ml), and saturated brine (400 ml), then was dried ($MgSO_4$) and evaporated. Portions of toluene were added and the mixture re-evaporated to remove excess of methyl crotonate (**34**). The residue was taken up in hot dichloromethane–ether–hexane and the solution seeded with 2-nitro-1,3-diphenylnitropropane (**8**) and cooled to give crystalline starting material (2.43 g). The mother liquors were evaporated and then the residue separated by column chromatography (70 × 200 mm, eluant dichloromethane–hexane, 1:1 then 1:0) yielding further starting material (**8**) (4.16 g, total 6.59 g) and product, which was crystallized from ether–hexane to yield the *nitro ester* (**35**) (10.307 g, 40.3% or 63.4% based on unrecovered starting material), m.p. 82—83.5 °C (Found: C, 70.4; H, 6.8; N, 4.05. $C_{20}H_{23}NO_4$ requires C, 70.36; H, 6.79; N, 4.10%); $\nu_{max.}$(CCl_4) 1 745, 1 530, 1 500, and 1 490 cm^{-1}; δ_H 1.11 (3 H, d, *J* 6.8 Hz, *Me*CH), 1.98 (1 H, dd, *J* 16.1 and 10.3 Hz, MeCHC*H*H), 2.49 (1 H, dd, *J* 16.1 and 2.5 Hz, MeCHCH*H*), 2.86 (1 H, m, MeC*H*CHH), 3.22 and 3.36 (each 1 H, d, *J* 14.8 Hz, $PhCH_2$), 3.32 and 3.36 (each 1 H, d, *J* 15.0 Hz, $PhCH_2$), 3.63 (3 H, s, OMe), and 7.10—7.32 (10 H, m, 2 × Ph); *m/z* 294 (M^+ − HNO_2, 10%), 262 (2), 193 (22), 143 (17), 129 (20), 115 (15), 91 ($C_7H_7^+$, 100), and 65 (12).

Methyl 5-(3,4-*Dimethyl*-5-*t-butoxycarbonylpyrrol*-2-*yl*)-3,4-*dimethyl*-4-*nitropentanoate* (**37**).—Tetrabutylammonium fluoride (1M solution in THF; 4 ml, 4 mmol) was added to a solution of t-butyl 3,4-dimethyl-5-(2-nitropropyl)pyrrole-2-carboxylate (**19**) (0.56 g, 2 mmol) in dry DMF (5 ml) under nitrogen. After 15 min methyl crotonate (**34**) (1.1 ml, 10 mmol) was added and the mixture was stirred for 18 h, then diluted with water (100 ml) and extracted with dichloromethane (3 × 20 ml). The combined extracts were washed with water (50 ml), dried ($MgSO_4$), and evaporated. Preparative t.l.c. (eluant ether–hexane, 3:2) gave a diastereoisomeric mixture of the *methyl esters* (**37**) (443 mg, 58%) (Found: M^+, 382.2114. $C_{19}H_{30}N_2O_6$ requires *M*, 382.2096); $\nu_{max.}$ 3 460, 1 740, 1 680, 1 550, and 1 370 cm^{-1}; δ_H 1.00 (2.1 H, d, *J* 6.7 Hz, CH*Me*), 1.08 (0.9 H, d, *J* 6.9 Hz, CH*Me*), 1.24 (0.9 H, s, Me), 1.38 (2.1 H, s, Me), 1.54 (9 H, s, Bu^t), 1.87 and 2.19 (each 3 H, s, ArMe), 2.10—2.56 (3 H, m, $CHCH_2CO_2Me$), 2.90 and 3.42 (each 0.7 H, d, *J* 15.2 Hz, $ArCH_2$), 2.94 and 3.39 (each 0.3 H, d, *J* 15.1 Hz, $ArCH_2$), 3.70 (0.9 H, s, CO_2Me), 3.71 (2.1 H, s, CO_2Me), and 8.52 (1 H, br, NH); *m/z* 382 (27%, M^+), 279 (95), 268 (79), 236 (70), and 152 (100).

t-Butyl 5-(2,3-*Dimethyl*-5-oxopyrrolidin-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**38**) *and* (**39**).—Zinc powder (1.7 g, 26 mmol) was added over 5 min to a solution of the foregoing mixture of diastereoisomeric methyl esters (**37**) (495 mg, 1.3 mmol) in acetic acid (25 ml). The mixture was stirred for 20 min then heated at 70 °C for 1 h. After being cooled the mixture was filtered through Celite and evaporated. The residue was dissolved in dichloromethane (20 ml), washed with 5% aqueous sodium hydrogen carbonate (20 ml), dried ($MgSO_4$), and evaporated. Preparative t.l.c. (eluant chloroform–methanol, 9:1) of the residue separated the two lactams. The higher R_F *lactam* (**38**) (204 mg, 49%) crystallized from dichloromethane–pentane, m.p. 228—229 °C (Found: C, 67.5; H, 8.6; N, 8.55. $C_{18}H_{28}N_2O_3$ requires C, 67.47; H, 8.81; N, 8.74%); $\nu_{max.}$ 3 280br and 1 690 cm^{-1}; δ_H 1.15 (3 H, d, *J* 6.3 Hz, CH*Me*), 1.20 (3 H, s, Me), 1.37 (9 H, s, Bu^t), 1.90 and 2.09 (each 3 H, s, ArMe), 2.30—2.38 (1 H, m, C*H*Me), 2.32 (1 H, dd, *J* 7 and 17.9 Hz, C*H*HCO) 2.43 and 2.86 (each 1 H, d, *J* 13.7 Hz, $ArCH_2$), 2.48 (1 H, m, CH*H*CO), 7.78 (1 H, br, lactam NH), and 10.74 (1 H, br, pyrrole NH); δ_C 9.7 and 11.1 (2 × ArMe), 12.7 (3′-Me) 24.8 (2′-Me), 28.4 (CMe_3), 30.9 ($ArCH_2$), 38.2 (CH_2CO), 42.0 (*C*HMe), 62.5 (C-2′), 79.7 (CMe_3), 117.1, 118.9, 125.3, and 130.2 (4 × pyrr-C), 162.4 ($ArCO_2$), 177.4 (CONH); *m/z* 320 (7%, M^+), 247 (7, $M^+ - C_4H_9O$), 153 (48), 152 (71), and 112 (100). The lower R_F *lactam* (**39**) (161 mg, 39%) crystallized from dichloromethane–pentane, m.p. 191—192 °C (Found: C, 67.4; H, 8.65; N, 8.6); $\nu_{max.}$ 3 450sh, 3 300br, and 1 690 cm^{-1}; δ_H 1.03 (3 H, d, *J* 6.9 Hz, CH*Me*), 1.13 (3 H, s, Me), 1.47 (9 H, s, Bu^t), 1.90 and 2.17 (each 3 H, s, ArMe), 2.06 (1 H, dd, *J* 8.2 and 16.2 Hz, C*H*HCO), 2.18—2.28 (1 H, m, C*H*Me), 2.51 (1 H, dd, *J* 7.8 and 16.2 Hz, CH*H*CO), 2.69 and 2.77 (each 1 H, d, *J* 14.7 Hz, $ArCH_2$), 7.26 (1 H, br, lactam NH), and 9.60 (1 H, br, pyrrole NH); δ_C 9.4 and 10.9 (2 × ArMe), 15.2 (3′-Me), 21.9 (2′-Me), 28.5 (CMe_3), 36.2, 37.0, and 38.8 ($ArCH_2$, CH_2CO, and *C*HMe), 62.6 (C-2′), 79.9 (CMe_3), 118.1, 119.4, 125.5, and 128.9 (4 × pyrr-C), 161.8 ($ArCO_2$), and 177.4 (CONH); *m/z* 320 (M^+), 247 ($M^+ - C_4H_9O$), 209, 153, 152, and 112.

(E,Z)-2-*Nitro*-1,3-*bis*(3,4-*dimethyl*-5-*t-butoxycarbonylpyrrol*-2-*yl*)*propene*.—Piperidine (1.022 g, 12.0 mmol) was added to a solution of t-butyl 3,4-dimethyl-5-(2-nitroethyl)pyrrole-2-carboxylate[25] (2.683 g, 10.0 mmol) and t-butyl 5-formyl-3,4-dimethylpyrrole-2-carboxylate[25] (**17**) (2.676 g, 12.0 mmol) in dry dimethylformamide (30 ml) and the mixture was stirred under argon at 50 °C for 2.5 h. After being cooled, the mixture was partitioned between ether (50 ml) and 0.1M hydrochloric acid (300 ml) and the aqueous phase extracted with ether (50, 2 × 25 ml). The combined organic phase was washed with brine (2 × 100 ml), dried ($MgSO_4$), and evaporated. The residue was passed down a flash chromatography column (53 × 150 mm, eluant hexane–ethyl acetate, 7:1) and product containing fractions were combined, evaporated, and rechromatographed (30 × 150 mm, same eluant). Crystallization from methanol yielded a mixture of the bright yellow (E)- and (Z)-*nitropropenes* (1.862 g, 39.3%) comprising a 3:2 mixture of (*E*)- and (*Z*)-isomers, m.p. 170—190 °C (Found: M^+, 473.2548. $C_{25}H_{35}N_3O_6$ requires *M*, 473.2526); $\lambda_{max.}$(MeOH) 276 and 399 nm; $\nu_{max.}$ 3 450, 3 350, 1 695br, 1 630, and 1 370 cm^{-1}; δ_H [for the (*E*) isomer] 1.51 (18 H, s, 2 × Bu^t), 2.05, 2.13, 2.20, and 2.22 (each 3 H, s, 4 × pyrr-Me), 4.17 (2 H, s, pyrr-CH_2), 8.18 (1 H, s, C*H*=C), and 8.51 and 8.68 (each 1 H, br s, 2 × NH); [for the (*Z*) isomer] 1.54 and 1.58 (each 9 H, s, 2 × Bu^t), 1.96, 2.00, 2.23, and 2.24 (each 3 H, s, 4 × pyrr-Me), 3.92 (2 H, s, pyrr-CH_2), 6.59 (1 H, s, C*H*=C), and 8.68 and 11.14 (each 1 H, br s, 2 × NH); *m/z* 473 (M^+, 13%), 455 (58), 400 ($M^+ - C_4H_9O$, 23), 344 (94), 314 (92), and 57 ($C_4H_9^+$, 100).

1,3-*Bis*(3,4-*dimethyl*-5-*t-butoxycarbonylpyrrol*-2-*yl*)-2-*nitropropane* (**40**).—The foregoing mixture of nitropropenes (920 mg, 1.943 mmol) was dissolved in dry dichloromethane (10 ml). The solution was stirred during the rapid sequential additions of dry ethanol (40 ml) followed by sodium borohydride (220 mg, 5.82 mmol). The mixture was stirred at room temperature for 10 min and then poured into aqueous ammonium chloride (300 ml) and extracted with dichloromethane (4 × 30 ml). The combined organic extracts were dried ($MgSO_4$), evaporated, and the residue was crystallized from dichloromethane–ether–hexane yielding the *nitropropane* (**40**) (902 mg, 97.6%), m.p. 180—182 °C (Found: C, 63.05; H, 7.85; N, 8.65. $C_{25}H_{37}N_3O_6$ requires C, 63.14; H, 7.84; N, 8,84%); $\lambda_{max.}$(MeOH) 247sh, 278 nm; $\nu_{max.}$ 3 460, 1 695sh, 1 685, 1 560, and 1 370 cm^{-1}; δ_H 1.55 (18 H, s, 2 × Bu^t), 1.85 (6 H, s, 2 × pyrr-Me), 2.18 (6 H, s, 2 × pyrr-Me), 2.99 (2 H, dd, *J* 15.2 and 5.8 Hz, $(CHH)_2CHNO_2$), 3.23 (2 H, dd, *J* 15.2 and 8.2 Hz, $(CHH)_2CHNO_2$), 4.76 (1 H, tt, *J* 8.2 and 5.8 Hz, $CHNO_2$), and 8.65 (2 H, br s, 2 × NH); *m/z* 475 (M^+, 8%), 402 ($M^+ - C_4H_9O$, 2), 234 (17), and 178 (100).

1,3-*Bis*(3,4-*dimethyl*-5-*t-butoxycarbonylpyrrol*-2-*yl*)-2-(2-*methoxycarbonylethyl*)-2-*nitropropane* (**41**).—A solution of the nitropropane (**40**) (713.4 mg, 1.50 mmol) and methyl acrylate (1.290 g, 15.0 mmol) in dry DMF (10 ml) was stirred at room temperature during the addition of benzyltrimethylammonium hydroxide (40 wt% solution in methanol; 1.25 g, 3.0 mmol). The solution was stirred for 15 min, then poured into 0.02M hydrochloric acid (300 ml). The mixture was extracted with ether (4 × 50 ml) and the combined organic extracts were washed with brine (200 ml), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (20 × 120 mm, eluant dichloromethane–ether, 1:0 then 19:1) to yield the *nitro ester* (**41**) (828 mg, 98.3%) (Found: M^+, 561.3033. $C_{29}H_{43}N_3O_8$ requires *M*, 561.3050); $\lambda_{max.}$(MeOH) 279 nm; $\nu_{max.}$ 3 450, 3 350, 1 740, 1 695sh, 1 685, 1 540, and 1 370 cm^{-1}; δ_H 1.54 (18 H, s, 2 × Bu^t), 1.90 (6 H, s, 2 × pyrr-Me), 2.22 (6 H, s, 2 × pyrr-Me), 2.22—2.36 (4 H, m, CH_2CH_2), 3.15 (4 H, s, 2 × pyrr-CH_2), 3.69 (3 H, s, OMe), and 8.87 (2 H, br s, 2 × NH); *m/z* 561 (M^+, 19%), 514 ($M^+ - HNO_2$, 4), 441 (8), 359 (24), 320 (18), 264 (100), and 220 (24).

5,5-*Bis*(3,4-*Dimethyl*-5-*t-butoxycarbonylpyrrol*-2-*ylmethyl*)-*pyrrolidin*-2-*one* (**42**).—Activated zinc powder (1.17 g, 17.9 mmol) was added to a vigorously stirred solution of the nitro ester (**41**) (393 mg, 0.700 mmol) in acetic acid (10 ml) at room temperature. Stirring was continued without heating for 20 min and then at 60 °C for 70 min. The mixture was cooled to room temperature and titanium trichloride (0.14 ml of a 15 wt% aqueous solution, 0.14 mmol) was added. After being stirred for a further 2 h the mixture was filtered through Celite. The filtrate was evaporated and then the residue was taken up in dichloromethane (20 ml) and stirred with aqueous sodium hydrogen carbonate (50 ml). The resulting suspension was filtered through Celite and then the filtrate layers were separated. The aqueous phase was extracted with dichloromethane (2 × 20 ml) and the combined organic solutions were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (10 × 130 mm, eluant dichloromethane then ethyl acetate) and crystallized from ether–hexane to give the *lactam* (**42**) (322 mg, 92.1%), m.p. 239—240.5 °C (decomp.) (Found: M^+, 499.3027. $C_{28}H_{41}N_3O_5$ requires *M*, 499.3046); $\lambda_{max.}$(MeOH) 282 nm; $\nu_{max.}$ 3 460, 3 270, 1 690, 1 640, and 1 370 cm^{-1}; δ_H (400 MHz; 333 K) 1.41 (18 H, s, 2 × Bu^t), 1.90 (2 H, m, CH_2CH_2), 1.96 and 2.20 (each 6 H, s, each 2 × pyrr-Me), 2.17 (2 H, m, CH_2CH_2), 2.77 and 2.90 (each 2 H, d, *J* 14.5 Hz, 2 × pyrr-CH_2), 7.54 (1 H, br s, lactam NH), and 9.92 (2 H, br s, 2 × pyrr NH); δ_H (400 MHz; 243 K) 1.28 and 1.33 (each 9 H, s, 2 × Bu^t), 1.83 (2 H, m, CH_2CH_2), 1.91, 1.94, 2.04,

and 2.27 (each 3 H, s, 4 × pyrr-Me), 1.99 and 2.63 (each 1 H, m, CH_2CHH), 2.68 (2 H, s, pyrr-CH_2), 2.74 and 3.16 (each 1 H, d, J 14.0 Hz, pyrr-CH_2), 8.23 (1 H, br s, lactam NH), and 9.41 and 11.33 (each 1 H, br s, 2 × pyrr NH); δ_C 9.3 and 10.8 (each q, 2 × pyrr-*Me*), 28.5 (q, 2 × CMe_3), 30.0 and 30.3 (each t, CH_2CH_2CONH), 35.8 (br t, 2 × pyrr-CH_2-lactam), 63.8 (s, lactam quaternary), 80.1 (s, 2 × $OCMe_3$), 118.0, 119.5, and 126.2 (each s, 2 × pyrr-C), 129.2 (br s, 2 × pyrr-C), 162.0 (br s, 2 × pyrr-CO_2), and 178.2 (s, CONH); *m/z* 499 (M^+), 426 ($M^+ - C_4H_9O$), 369, 290, 235, 217, 209, 191, and 152.

t-Butyl 5-(2,3-*Dimethyl*-5-*thioxopyrrolidin*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**43**).—A mixture of the higher R_F diastereoisomer, (**38**), of t-butyl 5-(2,3-dimethyl-5-oxopyrrolidin-2-ylmethyl)-3,4-dimethylpyrrole-2-carboxylate (96 mg, 0.3 mmol), and Lawesson's reagent [26] (60 mg, 0.15 mmol) in dry toluene (3 ml) under argon was heated under reflux with stirring for 2.5 h. After evaporation, preparative t.l.c. (eluant dichloromethane–ether, 9:1) of the residue gave the *thiolactam* (**43**) (97 mg, 96%) which crystallized from dichloromethane–hexane, m.p. 224—226 °C (Found: 64.35; H, 8.3; N, 8.25. $C_{18}H_{28}N_2O_2S$ requires C, 64.25; H, 8.39; N, 8.32%); $\nu_{max.}$ 3 230br, 1 670, 1 520, and 1 280 cm^{-1}; $\delta_H(CD_2Cl_2)$ 1.16 (3 H, d, J 7 Hz, CHMe), 1.31 (3 H, s, Me), 1.39 (9 H, s, Bu^t), 1.92 and 2.14 (each 3 H, s, ArMe), 2.39—2.95 (3 H, m, $CHCH_2CS$), 2.54 and 2.88 (each 1 H, d, J 13.9 Hz, $ArCH_2$), 10.12 (1 H, br, thiolactam NH), and 10.56 (1 H, br, pyrrole NH); *m/z* 336 (M^+), 279 ($M^+ - C_4H_9$), 263 ($M^+ - C_4H_9O$), 209, 153, and 152.

t-Butyl 5-(2,3-*Dimethyl*-5-*methylthio*-3,4-*dihydro*-2H-*pyrrol*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**44**).—A mixture of the foregoing thiolactam (**43**) (0.84 g, 2.5 mmol), anhydrous potassium carbonate (1.04 g, 7.5 mmol), and methyl iodide (0.47 ml, 7.5 mmol) in dry THF (50 ml) under argon was stirred at 50 °C for 3.5 h. After evaporation the residue was dissolved in chloroform (50 ml), washed with 5% aqueous sodium hydrogen carbonate (50 ml), dried ($MgSO_4$), and evaporated to yield the *thioimidate* (**44**) (0.65 g, 74%), m.p. 115 °C (from hexane) (Found: C, 65.2; H, 8.9; N, 7.75. $C_{19}H_{30}N_2O_2S$ requires C, 65.11; H, 8.63; N, 7.99%); $\nu_{max.}$ 3 450sh, 3 380br, 1 680, and 1 590 cm^{-1}; $\delta_H(CD_2Cl_2)$ 1.10 (3 H, d, J 6.8 Hz, CHMe), 1.10 (3 H, s, Me), 1.56 (9 H, s, Bu^t), 1.94 and 2.25 (each 3 H, s, ArMe), 2.24—2.29 (1 H, m, C*H*Me), 2.36 (1 H, dd, J 8.5 and 16 Hz, CHC*H*H), 2.47 and 2.62 (each 1 H, d, J 14.9 Hz, $ArCH_2$), 2.54 (3 H, s, SMe), 2.88 (1 H, dd, J 7.9 and 16 Hz, CHCH*H*), and 9.81 (1 H, br, NH); *m/z* 350 (M^+), 277 ($M^+ - C_4H_9O$), 273, 209, 152, and 142.

t-Butyl 5-(5-*Methoxy*-2,3-*dimethyl*-3,4-*dihydro*-2H-*pyrrol*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**45**).—A solution of the foregoing thioimidate (**44**) (350 mg, 1 mmol) and anhydrous toluene-*p*-sulphonic acid (21 mg, 0.12 mmol) in dry methanol (10 ml) was heated under reflux for 6 h. Triethylamine (0.05 ml) was added and the mixture was evaporated. Preparative t.l.c. (eluant ether–hexane, 2:3, containing 0.1% triethylamine) of the residue gave the *imidate* (**45**) (144 mg, 43%) which crystallized from pentane, m.p. 124—125 °C (Found: C, 68.3; H, 9.3; N, 8.50. $C_{19}H_{30}N_2O_3$ requires C, 68.23; H, 9.04; N, 8.38%); $\nu_{max.}$ 3 460, 3 360br, 1 695, 1 650, and 1 580 cm^{-1}; δ_H 1.08 (3 H, s, Me), 1.11 (3 H, d, J 6.9 Hz, CHMe), 1.55 (9 H, s, Bu^t), 1.94 and 2.25 (each 3 H, s, ArMe), 2.18—2.39 (2 H, m, C*H*C*H*H), 2.48 and 2.59 (each 1 H, d, J 14.9 Hz, $ArCH_2$), 2.66—2.75 (1 H, m, CHCH*H*), 3.88 (3 H, s, OMe), and 9.95 (1 H, br, NH); *m/z* 334 (M^+), 261 ($M^+ - C_4H_9O$), and 152.

t-Butyl 5-(5-*Methoxy*-2,3-*dimethyl*-3,4-*dihydro*-2H-*pyrrol*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**46**).—A mixture of the lower R_F diastereoisomer, (**39**), of t-butyl 5-(2,3-dimethyl-5-oxopyrrolidin-2-ylmethyl)-3,4-dimethylpyrrole-2-carboxylate (801 mg, 2.5 mmol) and Lawesson's reagent [26] (0.5 g, 1.25 mmol) in dry toluene (20 ml) under nitrogen was heated under reflux for 2 h. After evaporation the residue was purified twice by preparative t.l.c. (eluants dichloromethane–ether, 9:1, then ether–hexane, 3:2) then dissolved in dry THF (36 ml) containing anhydrous potassium carbonate (0.75 g, 5.4 mmol) under argon. Methyl iodide (0.34 ml, 5.4 mmol) was added and the mixture was stirred at 50 °C for 3.5 h then evaporated. The residue was partitioned between chloroform (25 ml) and 5% aqueous sodium hydrogen carbonate (25 ml). The organic phase was dried ($MgSO_4$), evaporated, and dissolved in dry methanol (18 ml) containing anhydrous toluene-*p*-sulphonic acid (32 mg, 0.18 mmol) under argon. The mixture was heated under reflux for 8 h then treated with triethylamine (0.5 ml) and evaporated. Preparative t.l.c. (eluant ether–hexane, 3:2, containing 0.1% triethylamine) of the residue yielded the *imidate ester* (**46**) [418 mg, 50% from (**39**)] (Found: M^+, 334.2268. $C_{19}H_{30}N_2O_3$ requires M, 334.2249); $\nu_{max.}$ 3 425, 3 335br, 1 685, 1 640, and 1 580 cm^{-1}; δ_H 0.93 (3 H, s, Me), 1.01 (3 H, d, J 6.5 Hz, CH*Me*), 1.53 (9 H, s, Bu^t), 1.89 and 2.24 each 3 H, s, ArMe), 2.06—2.50 (3 H, m, C*H*C*H*H), 2.57 and 2.79 (each 1 H, d, J 15 Hz, $ArCH_2$), 3.84 (3 H, s, OMe), and 9.54 (1 H, br, NH); *m/z* 334 (25%, M^+), 261 (12, $M^+ - C_4H_9O$), 153 (13), 152 (18), 127 (46), 126 (100), 112 (22), and 69 (37).

5,5-*Dibenzyl*-4-*methylpyrrolidin*-2-*one* (**47**).—Activated zinc powder (24.5 g, 375 mmol) was added to a vigorously stirred solution of the nitro ester (**35**) (5.118 g, 15.0 mmol) in acetic acid (150 ml) at room temperature. The mixture was stirred for 25 min without heating for a further 35 min at 70 °C. The mixture was cooled to room temperature, titanium trichloride (6.0 ml of a 15% aqueous solution, 6.0 mmol) was added and stirring continued for a further 40 min. The mixture was filtered through Celite and the filtrate was evaporated. The residue was taken up in dichloromethane (200 ml) and washed with saturated aqueous sodium hydrogen carbonate (250 ml). The resulting emulsion was filtered through Celite, the layers in the filtrate were separated and the aqueous phase was extracted with dichloromethane (2 × 50 ml). The combined organic solutions were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (45 × 120 mm, eluant dichloromethane–ethyl acetate, 1:0 then 9:1 and 7:3) and then crystallized from ether–hexane yielding the *lactam* (**47**) (3.902 g, 93.1%), m.p. 125—127 °C (Found: C, 81.85; H, 7.55; N, 5.05. $C_{19}H_{21}NO$ requires C, 81.68; H, 7.58; N, 5.01%); $\nu_{max.}$ 3 500, 3 400, 1 750, 1 700, 1 690, 1 645, 1 600, 1 495, and 1 460 cm^{-1}; δ_H 1.13 (3 H, d, J 7.0 Hz *Me*CH), 2.01 (1 H, dd, J 16.7 and 11.0 Hz, MeCHC*H*H), 2.12 (1 H, dd, J 16.7 and 8.3 Hz, MeCHCH*H*), 2.40 (1 H, m, MeC*H*CHH), 2.72 and 2.81 (each 1 H, d, J 14.2 Hz, PhCH_2), 2.72 and 2.87 (each 1 H, d, J 13.2 Hz, PhCH_2), 5.57 (1 H, br s, NH), and 6.99—7.37 (10 H, m, 2 × Ph); δ_C 13.1 (Me), 35.1, 37.7, and 41.5 (2C) (*CH*CH_2 and 2 × PhCH_2), 63.7 (C-5), 126.5 and 126.7 (2 × *p*-Ph), 128.1, 128.3, 130.5, and 130.7 (2 × *o*- and *m*-Ph), 136.0 and 136.1 (2 × Ph C-1), and 176.1 (CONH); *m/z* 188 ($M^+ - C_7H_7$, 70%), 125 (8), 105 (17), 98 (13), and 91 ($C_7H_7^+$, 100).

5,5-*Dibenzyl*-1,4-*dimethylpyrrolidin*-2-*one* (**48**).—A mixture of the lactam (**47**) (1.117 g, 4.00 mmol) and sodium hydride (50% dispersion in mineral oil; 384 mg, 8.00 mmol) was stirred in dry tetrahydrofuran (16 ml) with a trace of ethanol under argon at 60 °C for 2 h and then heated at reflux for 1 h. The mixture was cooled to room temperature, dry methyl iodide (0.62 ml, 10.0 mmol) was added and stirring was continued for 3 h. A solution of methylamine in methanol (2 ml) was added to destroy the excess of methyl iodide and sodium hydride. After 5 min the mixture was poured into 3M hydrochloric acid (40 ml)

and extracted with dichloromethane (40 ml then 2 × 20 ml). The combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$) and then evaporated. The residue was purified by flash chromatography (30 × 150 mm, eluant dichloromethane–ethyl acetate, 1:0 then 4:1 and 3:2) and crystallized from ethyl acetate–ether–hexane yielding the N-*methyl lactam* (**48**) (1.099 g, 93.6%), m.p. 149.5—150.5 °C (Found: C, 81.7; H, 7.9; N, 4.8. $C_{20}H_{23}NO$ requires C, 81.87; H, 7.90; N, 4.77%); $\nu_{max.}$ 1 670, 1 600, 1 580, 1 495, 1 455, and 1 400 cm^{-1}; δ_H 0.94 (3 H, d, *J* 7.0 Hz, *Me*CH), 1.61 (1 H, dd, *J* 16.3 and 11.9 Hz, MeCHC*H*H), 2.08 (1 H, dd, *J* 16.3 and 8.5 Hz, MeCHCH*H*), 2.32 (1 H, ddq, *J* 11.9, 8.5, and 7.0 Hz, MeC*H*CHH), 2.75 (3 H, s, NMe), 2.88 and 2.96 (each 1 H, d, *J* 14.2 Hz, PhCH_2), 2.98 and 3.07 (each 1 H, d, *J* 14.3 Hz, PhCH_2), and 7.14—7.33 (10 H, m, 2 × Ph); *m/z* 202 ($M^+ - C_7H_7$, 91%), 145 (8), 91 ($C_7H_7^+$, 100), and 65 (13).

1-*Acetyl*-5,5-*dibenzyl*-4-*methylpyrrolidin*-2-*one* (**49**).—Concentrated sulphuric acid (6 drops) was added to a solution of the lactam (**47**) (420 mg, 1.50 mmol) in dry acetic anhydride (6 ml). The resulting mixture was protected by a drying tube and then heated to 110 °C for 6.5 h. After being cooled, the solution was poured into dichloromethane (30 ml) and washed with water (20 ml). The aqueous phase was extracted with more dichloromethane (2 × 10 ml) and the combined organic solutions were dried ($MgSO_4$) and evaporated, adding portions of toluene and re-evaporating to remove the excess of acetic anhydride. The residue was purified by flash chromatography (30 × 170 mm, eluant ethyl acetate–30:40 light petroleum, 1:6) and then crystallized from hexane to give the N-*acetyl lactam* (**49**) (431 mg, 89.2%), m.p. 75.6—78 °C (Found: $M^+ - C_7H_7$, 230.1198. $C_{21}H_{23}NO_2$ requires $M - C_7H_7$, 230.1181); $\nu_{max.}$ 1 735, 1 690, 1 600, 1 580, 1 495, 1 460, 1 390, and 1 380 cm^{-1}; δ_H 1.26 (3 H, d, *J* 7.1 Hz, *Me*CH), 1.31 (1 H, dd, *J* 17.2 and 13.9 Hz, MeCHC*H*H), 1.86 (1 H, dd, *J* 17.2 and 8.5 Hz, MeCHCH*H*), 2.34 (1 H, m, MeC*H*CHH), 2.56 (3 H, s, *Me*CO), 2.87 and 3.91 (each 1 H, d, *J* 14.1 Hz, PhCH_2), 2.93 and 3.76 (each 1 H, d, *J* 14.3 Hz, PhCH_2), and 7.06—7.30 (10 H, m, 2 × Ph); *m/z* 230 ($M^+ - C_7H_7$, 19%), 201 (4), 188 (100), 105 (13), 91 ($C_7H_7^+$, 66), and 65 (10).

5,5-*Dibenzyl*-1-*hydroxy*-4-*methylpyrrolidin*-2-*one* (**50**).—Activated zinc powder (17.28 g, 264.3 mmol) was added to a vigorously stirred solution of the nitro ester (**35**) (15.02 g, 44.0 mmol) in acetic acid (900 ml) at room temperature. The mixture was stirred for 20 min without heating then for 3 h at 100 °C. The reaction mixture was cooled, filtered through a sinter, and the filtrate was evaporated. The residue was partitioned between water (100 ml) and dichloromethane (100 ml), the organic phase was separated and the aqueous phase was extracted with more dichloromethane (3 × 50 ml). The combined organic solutions were dried ($MgSO_4$), evaporated, and then the residue was crystallized from ethyl acetate–hexane to yield the *hydroxamic acid* (**50**) (10.67 g, 82.1%), m.p. 162—163 °C (Found: C, 77.35; H, 7.1; N, 4.75. $C_{19}H_{21}NO_2$ requires C, 77.26; H, 7.17; N, 4.74%); $\nu_{max.}$ 3 400—2 500br, 1 675, 1 600, 1 495, and 1 460 cm^{-1}; δ_H 1.07 (3 H, d, *J* 7.2 Hz, *Me*CH), 1.12 (1 H, dd, *J* 15.0 and 11.0 Hz, MeCHC*H*H), 1.89 (1 H, dd, *J* 15.0 and 8.6 Hz, MeCHCH*H*), 2.23 (1 H, ddq, *J* 11.0, 8.6, and 7.2 Hz, CH_3C*H*CHH), 2.89 and 3.32 (each 1 H, d, *J* 14.5 Hz, PhCH_2), 2.94 and 3.29 (each 1 H, d, *J* 14.5 Hz, PhCH_2), 7.21—7.43 (10 H, m, 2 × Ph), and 10.50 (1 H, br s, NOH); δ_C 13.4 (Me), 31.9, 35.3, 39.3, and 43.0 (*C*HCH_2 and 2 × PhCH_2), 70.1 (C-5), 126.7 and 126.8 (2 × *p*-Ph), 128.3 (2C), 130.7, and 130.8 (2 × *o*- and *m*-Ph), 136.2 and 136.5 (2 × Ph C-1), and 170.8 (C=O); *m/z* 204 ($M^+ - C_7H_7$, 100%), 188 (34), 125 (9), 91 ($C_7H_7^+$, 91), 86 (28), 84 (47), 69 (11), and 65 (8); *m/z* (f.d.) 295 (M^+, 100%).

5,5-*Dibenzyl*-1-*methoxy*-4-*methylpyrrolidin*-2-*one* (**51**).—A mixture of the hydroxamic acid (**50**) (590 mg, 2.00 mmol), anhydrous potassium carbonate (5.0 g, 36.2 mmol), and dimethyl sulphate (278 mg, 2.20 mmol) was stirred under reflux in butanone (20 ml) for 40 min. The mixture was cooled, filtered through Celite, and the filtrate was evaporated. The residue was purified by flash chromatography (10 × 100 mm, eluant dichloromethane then ethyl acetate) and then crystallized from ether to yield the N-*methoxy lactam* (**51**) (561 mg, 90.8%), m.p. 120—121.5 °C (Found: C, 77.7; H, 7.45; N, 4.45. $C_{20}H_{23}NO_2$ requires C, 77.64; H, 7.49; N, 4.53%); $\nu_{max.}$(CCl_4) 1 725, 1 605, 1 495, and 1 455 cm^{-1}; δ_H 0.87 (3 H, d, *J* 7.1 Hz, *Me*CH), 0.97 (1 H, dd, *J* 16.6 and 9.8 Hz, MeCHC*H*H), 1.86 (1 H, dd, *J* 16.6 and 8.8 Hz, MeCHCH*H*), 2.42 (1 H, m, MeC*H*CHH), 2.89 and 3.24 (each 1 H, d, *J* 14.5 Hz, PhCH_2), 3.01 and 3.19 (each 1 H, d, *J* 13.2 Hz, PhCH_2), 4.10 (3 H, s, OMe), and 7.18—7.38 (10 H, m, 2 × Ph); *m/z* 218 ($M^+ - C_7H_7$, 100%), 176 (7), 144 (7), and 91 ($C_7H_7^+$, 56).

1-*Benzoyloxy*-5,5-*dibenzyl*-4-*methylpyrrolidin*-2-*one* (**52**).—A mixture of the hydroxamic acid (**50**) (1.182 g, 4.00 mmol) and anhydrous potassium carbonate (6.0 g, 43.4 mmol) protected by a drying tube was stirred in benzoyl chloride (20 ml) at room temperature for 13 h. The mixture was partitioned between ether (150 ml) and water (150 ml), and the aqueous layer extracted with more ether (2 × 75 ml). The combined organic extracts were washed with water (2 × 75 ml), brine (75 ml) and then were dried ($MgSO_4$) and evaporated. A portion of toluene was added, and the mixture evaporated again to remove the last traces of benzoyl chloride. The residue was purified by flash chromatography (150 × 30 mm, eluant dichloromethane–ether, 1:0 then 19:1) and crystallized from dichloromethane–hexane yielding the N-*benzoyloxy lactam* (**52**) (1.318 g, 82.5%), m.p. 186.5—188.5 °C (Found: $M^+ - C_7H_7$, 308.1284. $C_{26}H_{25}NO_3$ requires $M - C_7H_7$, 308.1287); $\nu_{max.}$(CCl_4) 1 785, 1 735, 1 605, 1 495, and 1 455 cm^{-1}; δ_H 0.97 (3 H, d, *J* 7 Hz *Me*CH), 1.40 (1 H, dd, *J* 16 and 10 Hz, MeCHC*H*H), and 2.15 (1 H, dd, *J* 16 and 8 Hz, MeCHCH*H*), 2.67 (1 H, m, MeC*H*CHH), 3.01 and 3.26 (each 1 H, d, *J* 14.5 Hz, PhCH_2), 3.05 and 3.15 (each 1 H, d, *J* 13.6 Hz, PhCH_2), and 7.23—7.99 (15 H, m, 3 × Ph); δ_C 14.63 (br, Me) 34.0, 34.8, 38.7, and 44.3 (br) (*C*HCH_2 and 2 × PhCH_2), 69.4 (C-5), 126.78, 126.84, and 126.96 (3 × *p*-Ph), 128.33, 128.37, 128.45, 129.95, 130.45, and 130.66 (3 × *o*- and *m*-Ph), 133.9, 135.4, and 136.0 (3 × Ph C-1), 163.2 (Ph*C*O), and 169.1 (NCO); *m/z* 308 ($M^+ - C_7H_7$, 28%), 188 (19), 105 ($C_6H_5CO^+$, 100), 91 ($C_7H_7^+$, 83), and 77 ($C_6H_5^+$, 44).

5,5-*Dibenzyl*-1-(2,2-*dimethylpropanoyloxy*)-4-*methylpyrrolidin*-2-*one* (**53**).—A mixture of the hydroxamic acid (**50**) (295 mg, 1.00 mmol) and anhydrous potassium carbonate (2.0 g, 14.5 mmol) was stirred in 2,2-dimethylpropanoyl chloride (10 ml) at room temperature for 85 h protected by a drying tube. The mixture was poured into water (50 ml) and extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. A portion of toluene was added and the mixture re-evaporated to remove residual acid chloride. The residue was purified by flash chromatography (30 × 130 mm, eluant dichloromethane–ethyl acetate 1:0 then 1:1) and crystallized from ether–hexane to yield the N-*trimethylacetoxy lactam* (**53**) (343 mg, 90.5%), m.p. 122—123 °C (Found: C, 75.85; H, 7.55; N, 3.9. $C_{24}H_{29}NO_3$ requires C, 75.95; H, 7.70; N, 3.70%); $\nu_{max.}$ 1 785, 1 710, 1 600, 1 580, 1 495, 1 480, and 1 460 cm^{-1}; δ_H 0.97 (3 H, d, *J* 7 Hz, *Me*CH), 1.31 (9 H, s, Bu^t), 1.32 (1 H, dd, *J* 18 and 9 Hz, MeCHC*H*H), 2.05 (1 H, dd, *J* 18 and 9 Hz, MeCHCH*H*), 2.56 (1 H, m, MeC*H*CHH), 2.92 and 3.13 (each 1 H, d, *J* 14.5 Hz, PhCH_2), 2.94 and 3.00 (each 1 H, d, *J* 13.5 Hz, PhCH_2), and 7.20—7.38 (10 H, m, 2 × Ph); *m/z* 288 ($M^+ - C_7H_7$, 69%), 204 (77), 188

(27), 91 ($C_7H_7^+$, 50), 88 (12), 86 (65), 84 (100), 69 (7), and 57 ($C_4H_9^+$, 23).

Lithium Di-isopropylamide.—The following general method was used to prepare solutions containing *x* mmol of lithium di-isopropylamide in dry tetrahydrofuran. A dry round-bottomed flask containing a magnetic stirrer bar was charged with a solution of dry di-isopropylamine (1.03*x* mmol) in dry tetrahydrofuran (approx. 4 ml/mmol) under an atmosphere of argon. The solution was cooled to −10 °C and freshly titrated[27] n-butyl lithium (approx. 1.6M in hexane; *x* mmol) was added dropwise with stirring over 10 min. The solution was stirred at 0 °C for a further 5 min prior to use.

cis- *and* trans-5,5-*Dibenzyl*-1-*hydroxy*-3,4-*dimethylpyrrolidin*-2-*one* (**54**) *and* (**55**).—A solution of the hydroxamic acid (**50**) (74 mg, 0.25 mmol) in dry tetrahydrofuran (1 ml) under argon was cooled to −78 °C and stirred during the dropwise addition of a solution of lithium di-isopropylamide (1.50 mmol) in dry tetrahydrofuran. The resulting solution was allowed to warm to 4 °C and was stirred at this temperature for a further 3.5 h. Dry methyl iodide (0.15 ml, 2.4 mmol) was added with vigorous stirring and after 5 min the reaction was quenched by the addition of formic acid (0.1 ml). The resulting mixture was poured into dichloromethane (25 ml) and washed with 3M hydrochloric acid (25 ml). The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by p.l.c. (two plates, eluant ethyl acetate) to yield two bands. The higher band gave the trans-*dimethylhydroxamic acid* (**55**) (25 mg, 32.3%), R_F (EtOAc) 0.54—0.59 (Found: $M^+ - C_7H_7$, 218.1184. $C_{20}H_{23}NO_2$ requires $M - C_7H_7$, 218.1181); $\nu_{max.}$ 3 200—2 500br, 1 675, 1 605, 1 495, and 1 460 cm^{-1}; δ_H 0.76 (3 H, d, *J* 7 Hz, *Me*CH), 1.00 (3 H, d, *J* 7 Hz, *Me*CH), 1.09 and 1.63 (each 1 H, m, each MeC*H*), 2.81 and 3.30 (each 1 H, d, *J* 14 Hz, PhCH_2), 2.90 and 3.30 (each 1 H, d, *J* 14 Hz, PhCH_2), 7.19—7.33 (10 H, m, 2 × Ph), and 10.20 (1 H, br s, NOH); δ_C 11.5 and 14.3 (2 × Me), 39.4, 39.8, 40.6, and 43.1 (2 × *C*HMe and 2 × PhCH_2), 69.2 (PhCH_2*C*), 126.6, 126.8, 128.3 (2C), 128.4 (2C), 130.7 (2C), 130.8 (2C), 136.3, and 136.6 (12 × Ph-C), and 172.9 (C=O); *m*/*z* 218 ($M^+ - C_7H_7$, 100%), 202 (23), 190 (6), 91 ($C_7H_7^+$, 53), and 65 (12); *m*/*z* (f.d.) 309 (M^+, 100%). The lower band gave the cis-*dimethylhydroxamic acid* (**54**) (39 mg, 50.4%), R_F (EtOAc) 0.46—0.51 (Found: $M^+ - C_7H_7$, 218.1181. $C_{20}H_{23}NO_2$ requires $M - C_7H_7$, 218.1181); $\nu_{max.}$ 3 200—2 500br, 1 675, 1 605, 1 495, and 1 460 cm^{-1}; δ_H 0.33 (3 H, d, *J* 7 Hz, *Me*CH), 0.97 (3 H, d, *J* 7 Hz, *Me*CH), 2.06 and 2.49 (each 1 H, m, each MeC*H*), 2.90 and 3.27 (each 1 H, d, *J* 13.9 Hz, PhCH_2), 2.93 and 3.29 (each 1 H, d, *J* 14.5 Hz, PhCH_2), 7.19—7.39 (10 H, m, 2 × Ph), and 10.60 (1 H, br s, NOH); δ_C 10.3 and 11.0 (2 × Me), 33.9, 36.5, 40.3, and 43.7 (2 × *C*HMe and 2 × PhCH_2), 69.8 (PhCH_2*C*), 126.6, 126.7, 128.4 (4C), 130.7 (2C), 131.0 (2C), 136.5, and 137.0 (12 × Ph-C), and 172.5 (C=O); *m*/*z* 218 ($M^+ - C_7H_7$, 100%), 202 (33), 190 (8), 91 ($C_7H_7^+$, 73), and 65 (11); *m z* (f.d.) 309 (M^+, 100%).

cis- *and* trans-5,5-*Dibenzyl*-1-*hydroxy*-3-*hydroxymethyl*-4-*methylpyrrolidin*-2-*one* (**56**) *and* (**57**).—A solution of the hydroxamic acid (**50**) (295.5 mg, 1.00 mmol) in dry tetrahydrofuran (4 ml) under argon was cooled to −78 °C and stirred during the dropwise addition of a solution of lithium di-isopropylamide (3.50 mmol) in dry tetrahydrofuran. The solution was allowed to warm to 4 °C and was stirred at this temperature for a further 5 h. Stirring was continued during the addition of solid paraformaldehyde (90 mg, 3.00 mmol), and then the solution was allowed to warm to room temperature. After a further 30 min, the reaction mixture was poured into a mixture of dichloromethane (20 ml), 3M hydrochloric acid (10 ml), and brine (10 ml). The organic phase was separated and the aqueous phase was extracted with more dichloromethane (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (10 × 150 mm, eluant ethyl acetate–methanol, 1:0 then 20:1) to give a 4:3 mixture of the cis and trans *hydroxymethylhydroxamic acids* (245 mg, 75.3%). Repeated crystallization from chloroform gave the pure *trans* isomer (**57**), m.p. 92—94 °C (Found: $M^+ - C_7H_7$, 234.1113. $C_{20}H_{23}NO_3$ requires $M - C_7H_7$, 234.1130); $\nu_{max.}$ 3 500—2 400br, 1 675, 1 600, 1 580, 1 495, and 1 460 cm^{-1}; δ_H 1.01 (3 H, d, *J* 7.1 Hz, *Me*CH), 1.33 (1 H, m, C*H*CH$_2$OH), 1.85—2.25 (1 H, br s, CH$_2$O*H*), 2.07 (1 H, dq, *J* 10.9 and 7.1 Hz, MeC*H*), 2.87 and 3.30 (each 1 H, d, *J* 14.4 Hz, PhCH_2), 2.98 and 3.27 (each 1 H, d, *J* 14.0 Hz, PhCH_2), 3.20 (1 H, dd, *J* 11.3 and 6.5 Hz, C*H*HOH), 3.55 (1 H, dd, *J* 11.3 and 3.8 Hz, CH*H*OH), and 7.20—7.37 (10 H, m, 2 × Ph); *m*/*z* 234 ($M^+ - C_7H_7$, 26%), 216 (15), 200 (11), 91 ($C_7H_7^+$, 100), and 65 (15). From a 400 MHz proton n.m.r. spectrum of the mother liquors after crystallization of the mixture of isomers the following signals were attributed to the *cis* isomer (**56**), δ_H 1.00 (3 H, d, *J* 7.5 Hz, *Me*CH), 2.16 (1 H, m, C*H*CH$_2$OH), 2.57 (1 H, m, MeC*H*), 2.63 (1 H, m, C*H*HOH), 2.82 and 3.30 (each 1 H, d, *J* 14.1 Hz, PhCH_2), 3.02 and 3.24 (each 1 H, d, *J* 14.4 Hz, PhCH_2), 3.25 (1 H, m, CH*H*OH), and 7.21—7.40 (10 H, m, 2 × Ph).

cis- *and* trans-5,5-*Dibenzyl*-1-*hydroxy*-4-*methyl*-3-*phenylthiopyrrolidin*-2-*one* (**58**) *and* (**59**).—A solution of the hydroxamic acid (**50**) (2.954 g, 10.0 mmol) in dry tetrahydrofuran (40 ml) under argon was cooled to −78 °C and stirred during the dropwise addition of a solution of lithium di-isopropylamide (24.0 mmol) in dry tetrahydrofuran. The resulting solution was allowed to warm to room temperature and was stirred for 1 h. The solution was then cooled to 0 °C and stirred vigorously during the rapid addition of a solution of diphenyl disulphide (4.366 g, 20.0 mmol) in dry tetrahydrofuran (5 ml). The mixture was allowed to warm to room temperature over 15 min, then was cooled to −10 °C and the reaction quenched by the addition of 3M hydrochloric acid (15 ml). The resulting emulsion was poured into 3M hydrochloric acid (100 ml) and extracted with dichloromethane (100, 3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (60 × 120 mm, eluant dichloromethane–ethyl acetate, 1:0 then 30:1, 20:1, 10:1, and 4:1) to yield the *sulphide* (3.606 g, 89.4%) as a 2:11 mixture of the *cis* (**58**) and *trans* (**59**) isomers (Found: M^+, 403.1585. $C_{25}H_{25}NO_2S$ requires *M*, 403.1606); $\nu_{max.}$ 3 300—2 400br, 1 685, 1 600, 1 580, 1 495, 1 480, 1 455, and 1 440 cm^{-1}; δ_H [*trans* isomer (**59**)] 1.14 (3 H, d, *J* 7.1 Hz, *Me*CH), 1.94 (1 H, dq, *J* 11.6 and 7.1 Hz, MeC*H*), 2.34 (1 H, d, *J* 11.6 Hz, PhSC*H*), 2.85 and 3.24 (each 1 H, d, *J* 14.2 Hz, PhCH_2), 2.87 and 3.35 (each 1 H, d, *J* 14.4 Hz, PhCH_2), 7.01—7.47 (15 H, m, 3 × Ph), and 9.4—11.2 (1 H, br s, NOH); [signals attributable to the *cis* isomer (**58**)] 1.23 (3 H, d, *J* 7.1 Hz, *Me*CH), 2.60 (1 H, dq, *J* 8.6 and 7.1 Hz, MeC*H*), 2.77 and 3.39 (each 1 H, d, *J* 14.2 Hz, PhCH_2), 3.08 and 3.18 (each 1 H, d, *J* 14.3 Hz, PhCH_2), and 3.45 (1 H, d, *J* 8.6 Hz, PhSC*H*); *m*/*z* 403 (M^+, 1%), 387 (1), 312 ($M^+ - C_7H_7$, 27), 296 (6), 186 (29), 174 (100), and 110 (22).

(±)-(3S,4R)-5,5-*Dibenzyl*-1-*hydroxy*-3,4-*dimethyl*-3-*phenylthiopyrrolidin*-2-*one* (**60**).—A solution of the foregoing mixture of hydroxamic acids (**58**) and (**59**) (3.606 g, 8.94 mmol) in dry tetrahydrofuran (30 ml) under argon was cooled to −78 °C and stirred during the dropwise addition of a solution of lithium di-isopropylamide (26.8 mmol) in dry tetrahydrofuran. The resulting solution was allowed to warm to 4 °C and was stirred at this temperature for a further 3.5 h. Dry methyl iodide (1.95 ml, 31.3 mmol) was added with vigorous stirring and after 15 min the reaction was quenched by the addition of 3M

hydrochloric acid (15 ml). The mixture was taken up in warm ethyl acetate (250 ml) and was washed with 3M hydrochloric acid (250 ml). The aqueous layer was extracted with more ethyl acetate (3 × 100 ml) and the combined organic solutions were dried ($MgSO_4$) and evaporated. The residue was crystallized from ethyl acetate–hexane to give the cis-*dimethylhydroxamic acid* (**60**) (2.931 g, 78.5%) sufficiently pure for the next step. A small sample was recrystallised from dichloromethane–hexane, m.p. 211.5—213 °C (Found: C, 74.95; H, 6.5; N, 3.35; $M^+ - C_7H_7$, 326.1242. $C_{26}H_{27}NO_2S$ requires C, 74.79; H, 6.52; N, 3.35%; $M - C_7H_7$, 326.1215); $\nu_{max.}$ 3 250—2 400br, 1 675, 1 600, 1 495, 1 475, 1 460, and 1 445 cm^{-1}; δ_H 0.38 (3 H, s, MeCSPh), 0.69 (3 H, d, *J* 7.5 Hz, *Me*CH), 2.42 and 3.05 (each 1 H, d, *J* 13.4 Hz, PhCH_2), 2.45 (1 H, q, *J* 7.5 Hz, MeC*H*), 2.80 and 3.31 (each 1 H, d, *J* 14.6 Hz, PhCH_2), and 6.99—7.53 (15 H, m, 3 × Ph); *m/z* 326 ($M^+ - C_7H_7$, 24%), 310 (8), 298 (7), 216 (11), 200 (30), 110 (28), 91 ($C_7H_7^+$, 100), and 65 (16).

5,5-*Dibenzyl*-1-*hydroxy*-3,4-*dimethylpyrrol*-2-(5H)-*one* (**61**).—A solution of the sulphide (**60**) (2.505 g, 6.00 mmol) in dichloromethane (300 ml) at 0 °C was stirred during the addition of solid *m*-chloroperoxybenzoic acid (1.284 g of 90% peracid, 6.6 mmol). The resulting solution was allowed to stand at 0 °C for 17 h and was then evaporated. The residue was taken up in toluene (150 ml) and heated to reflux for 30 min. The resulting solution was again evaporated and the residue was purified by flash chromatography (60 × 120 mm, eluant dichloromethane–ethyl acetate, 1:0 then 19:1, 12:1, 6:1, and 4:1). Impure fractions were rechromatographed (same column and eluant) and then the combined pure fractions from both columns were evaporated. The residue was crystallized from ethyl acetate to yield the *unsaturated hydroxamic acid* (**61**) (1.674 g, 90.8%), m.p. 225—226 °C (Found: C, 78.15; H, 7.1; H, 4.4%; M^+, 307.1581. $C_{20}H_{21}NO_2$ requires C, 78.15; H, 6.89; N, 4.56%; *M*, 307.1573); $\nu_{max.}$ 3 300—2 400br, 1 675, 1 600, 1 495, and 1 460 cm^{-1}; δ_H 1.28 and 1.86 (each 3 H, q, *J* 1.1 Hz, 2 × Me), 2.92 and 3.49 (each 2 H, d, *J* 13.9 Hz, 2 × PhCH_2), 7.07—7.18 (10 H, m, 2 × Ph), and 9.5—13.5 (1 H, br s, NOH); *m/z* 307 (M^+, 4%), 216 ($M^+ - C_7H_7$, 100), 200 (81), 110 (9), 91 ($C_7H_7^+$, 11), and 65 (30).

5,5-*Dibenzyl*-3,4-*dimethylpyrrol*-2(5H)-*one* (**62**).—Activated zinc powder (4.90 g, 75.0 mmol) was added to a vigorously stirred solution of the hydroxamic acid (**61**) (922 mg, 3.00 mmol) in acetic acid (24 ml) at room temperature, and the mixture was stirred for 2 h without heating. Ammonium acetate (578 mg, 7.50 mmol) was added, followed by the addition of titanium trichloride (1.2 ml of a 15% aqueous solution, 1.2 mmol). The mixture was stirred for a further 1.5 h, filtered through Celite, and the filtrate was evaporated. The residue was taken up in 3M hydrochloric acid (120 ml) and the resulting emulsion extracted with dichloromethane (50 ml then 2 × 25 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated, and this was followed by addition of a further portion of toluene (30 ml) and evaporation to remove acetic acid. The residue was crystallized from dichloromethane–ether to yield the *unsaturated lactam* (**62**) (819 mg, 93.7%), m.p. 176.5—178 °C (Found: C, 82.1; H, 7.3; N, 4.6%; M^+, 291.1631. $C_{20}H_{21}NO$ requires C, 82.44; H, 7.26; N, 4.81% *M*, 291.1623); $\nu_{max.}$ 3 430, 1 685, 1 600, 1 495, and 1 455 cm^{-1}; δ_H 1.51 and 2.02 (each 3 H, q, *J* 1.1 Hz, 2 × Me), 2.86 and 2.97 (each 2 H, d, *J* 13.6 Hz, 2 × PhCH_2), 5.96 (1 H, br s, NH), and 7.05—7.24 (10 H, m, 2 × Ph); *m/z* 291 (M^+, 1%), 200 ($M^+ - C_7H_7$, 29), 157 (14), 91 ($C_7H_7^+$, 100), and 65 (31).

5,5-*Dibenzyl*-3,4-*dimethylpyrrole*-2(5H)-*thione* (**63**).—A mixture of the lactam (**62**) (729 mg, 2.50 mmol) and Lawesson's reagent[26] (758 mg, 1.87 mmol) in dry benzene (75 ml) was heated to reflux with stirring under argon for 30 min. The mixture was cooled and then evaporated. The residue was purified by flash chromatography (30 × 150 mm, eluant dichloromethane–ethyl acetate 1:0 then 9:1) and then crystallized from dichloromethane–hexane to give the *thiolactam* (**63**) (737 mg, 96%), m.p. 236—238 °C (Found: C, 78.0; H, 7.0; N, 4.4%; M^+, 307.1382. $C_{20}H_{21}NS$ requires C, 78.13; H, 6.88; N, 4.56%; *M*, 307.1395); $\nu_{max.}$ 3 410, 1 640, 1 600, 1 495, 1 470, and 1 450 cm^{-1}; δ_H 1.68 and 2.03 (each 3 H, q, *J* 1.1 Hz, 2 × Me), 2.89 and 3.05 (each 2 H, d, *J* 13.7 Hz, 2 × PhCH_2), 7.06—7.27 (10 H, m, 2 × Ph), and 7.99 (1 H, br s, NH); *m/z* 307 (M^+, 5%), 216 ($M^+ - C_7H_7$, 100) 135 (90), 128 (90), and 91 ($C_7H_7^+$, 50).

2,2-*Dibenzyl*-3,4-*dimethyl*-2H-*pyrrole* (**64**).—The thiolactam (**63**) (307.5 mg, 1.00 mmol) was dissolved in tetrahydrofuran (25 ml) and then methanol (40 ml) was added. The resulting solution was stirred vigorously at room temperature during the portionwise addition of Raney nickel (prepared by standard literature procedures[28] and stored under water). Between additions the reaction mixture was analysed by t.l.c. (eluant dichloromethane–ethyl acetate, 9:1) and as soon as no starting material (**63**) remained, the mixture was filtered through Celite, washing with methanol (taking care to keep the nickel always under solvent). The filtrate was evaporated. The residue was purified by flash chromatography (20 × 140 mm, eluant dichloromethane–ethyl acetate, 1:0 then 7:1 and 3:1) and then p.l.c. (six plates, eluant dichloromethane–ethyl acetate, 3:1) to give the *pyrrolenine* (**64**) (165 mg, 59.9%) (Found: M^+, 275.1661. $C_{20}H_{21}N$ requires *M*, 275.1674); $\nu_{max.}$ 1 600, 1 580, 1 495, 1 455, and 1 385 cm^{-1}; δ_H 1.46 and 2.02 (each 3 H, q, *J* 1.1 Hz, 2 × pyrr-Me), 2.92 and 3.32 (each 2 H, d, *J* 13.2 Hz, 2 × PhCH_2), 7.02—7.16 (10 H, m, 2 × Ph), and 7.54 (1 H, s, N=CH); δ_C 9.7 and 12.1 (2 × pyrr-Me), 42.2 (2 × PhCH_2), 86.2 (C-2), 126.4 (2C), 127.4 (4C), and 129.9 (4C) (10 × Ph CH), 133.3 (C-4), 136.2 (2C, 2 × Ph C), 158.8 (br, C-3), and 167.1 (C-5); *m/z* 275 (M^+, 43%), 260 (13), 198 (43), 184 ($M^+ - C_7H_7$, 88), 91 ($C_7H_7^+$, 100), and 65 (6). In another experiment the less polar by-product 2-*benzyl*-3,4-*dimethylpyrrole* (**65**) was isolated, δ_H 1.99 and 2.02 (each 3 H, s, 2 × pyrr-Me), 3.89 (2 H, s, PhCH_2), 6.39 (1 H, s, pyrr-H), 7.17—7.34 (5 H, m, Ph), and 7.35 (1 H, br s, NH).

cis-5,5-*Dibenzyl*-3,4-*dimethyldihydrofuran*-2(3H)-*one* (**72**) *and* trans-*Isomer*.—A solution of benzylmagnesium bromide was prepared from dry benzyl bromide (5.0 ml, 42.0 mmol) and magnesium turnings (3.0 g, 123 mmol) using dry ether (40 ml) as the solvent. The solution of Grignard reagent was diluted with dry tetrahydrofuran (50 ml) and stirred under nitrogen at room temperature during the dropwise addition of a solution of a mixture of *cis* and *trans* isomers of 2,3-dimethylsuccinic anhydride (0.876 g, 6.83 mmol) in dry tetrahydrofuran (50 ml). The resulting solution was stirred for 17 h and then poured into 3M hydrochloric acid (150 ml). The organic phase was separated and the aqueous phase extracted with more ether (100 ml). The combined organic solutions were washed with brine (100 ml), and then were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (45 × 150 mm, eluant hexane–dichloromethane–methanol, 1:2:0 then 1:3:0, 0:1:0, and 0:49:1) to give the mixture of diastereoisomeric *lactones* (1.331 g, 66.2%) as a viscous gum which crystallized slowly. Fractional crystallization from ether–hexane gave pure samples of the two isomers for characterisation. The major isomer, obtained by repeated crystallization from ether, was the *trans*-lactone, m.p. 142—144 °C (Found: M^+, 294.1606. $C_{20}H_{22}O_2$ requires *M*, 294.1620); $\nu_{max.}$ 1 760, 1 600, 1 580, 1 495, 1 455, 1 390, and 1 380 cm^{-1}; δ_H 0.99 (3 H, d, *J* 6.8 Hz, *Me*CH), 1.14 (3 H, d, *J* 6.8 Hz, *Me*CH), 1.98 (1 H, dq, *J* 12.5 and 6.8 Hz, MeC*H*), 2.04 (1 H, dq, *J* 12.5 and 6.8 Hz, MeC*H*), 2.80

and 3.07 (each 1 H, d, J 14.4 Hz, $PhCH_2$), 2.88 and 3.01 (each 1 H, d, J 14.3 Hz, $PhCH_2$), and 7.12—7.37 (10 H, m, 2 × Ph); m/z 294 (M^+, 1%), 203 ($M^+ - C_7H_7$, 13), 119 (16), 91 ($C_7H_7^+$, 100), and 65 (10). The minor isomer, obtained by repeated crystallization from ether–hexane, was shown to be the *cis-lactone* (**72**) by *X*-ray crystal structure analysis,[20] m.p. 84.5—86 °C (Found: M^+, 294.1618. $C_{20}H_{22}O_2$ requires M, 294.1620); $\nu_{max.}$ 1 755, 1 600, 1 495, 1 460, 1 390, and 1 380 cm^{-1}; δ_H 1.06 (3 H, d, J 7.7 Hz, *Me*CH), 1.07 (3 H, d, J 7.5 Hz, *Me*CH), 2.16 (1 H, dq, J 9.4 and 7.7 Hz, MeC*H*), 2.65 (1 H, dq, J 9.4 and 7.5 Hz, MeC*H*), 2.71 and 2.97 (each 1 H, d, J 14.2 Hz, $PhCH_2$), 2.85 and 3.17 (each 1 H, d, J 14.4 Hz, $PhCH_2$), and 7.11—7.42 (10 H, m, 2 × Ph); m/z 294 (M^+, 1%), 203 ($M^+ - C_7H_7$, 20), 119 (21), 91 ($C_7H_7^+$, 100), and 65 (11).

Rearrangement of 2,2-*Dibenzyl*-2H-*pyrrole* (**15**).—(*a*) *Thermal.* 2,2-Dibenzyl-2*H*-pyrrole (**15**) was heated under argon at 200 °C for 4 h to yield quantitatively (by n.m.r.) 2,3-*dibenzyl*-1H-*pyrrole* (**74**); δ_H 3.80 and 3.87 (each 2 H, s, 2 × $PhCH_2$), 5.97 (1 H, t, J 3 Hz, 4-H), 6.50 (1 H, t, J 3 Hz, 5-H), 7.19 (10 H, s, 2 × Ph), and 7.55 (1 H, br, NH).

(*b*) *Acid-catalysed.* Trifluoroacetic acid (50 μl) was added to a solution of 2,2-dibenzyl-2*H*-pyrrole (**15**) (10 mg, 0.04 mmol) in dry dichloromethane (2.5 ml) under argon. After 4 h the mixture was diluted with dichloromethane (5 ml), washed with 5% aqueous sodium hydrogen carbonate (10 ml), dried ($MgSO_4$), and evaporated. Preparative t.l.c. (eluant ether–hexane, 3:2) of the residue gave 2,3-dibenzyl-1*H*-pyrrole (**74**) (*ca.* 3 mg).

Rearrangement of t-Butyl 5-(2-*Methyl*-2H-*pyrrol*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**28**).—Trifluoroacetic acid (10% solution in dichloromethane; 0.1 ml) was added to a solution of the 2*H*-pyrrole (**28**) (20 mg) in dry dichloromethane (20 ml) under argon in the dark. The mixture was left for 30 min and then washed with 5% aqueous sodium hydrogen carbonate (50 ml), dried ($MgSO_4$), and evaporated. The isolation of the products was effected in an inert atmosphere. Preparative t.l.c. (eluant ether–hexane, 3:2) gave three bands. The highest R_F band yielded *t-butyl* 5-(5-*methylpyrrol*-2-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**77**) (*ca.* 8 mg); δ_H 1.53 (9 H, s, Bu^t), 1.94 (3 H, s, 4-Me), 2.19 (3 H, s, 5′-Me), 2.22 (3 H, s, 3-Me), 3.84 (2 H, s, CH_2), 5.76 (1 H, dd, J 0.8 and 2.9 Hz, 4′-H), 5.85 (1 H, t, J 2.9 Hz, 3′-H), 7.52 (1 H, br, N′-H), and 8.43 (1 H, br, NH); m/z 288 (M^+). The lowest R_F band yielded *t-butyl* 5-[4-(3,4-*dimethyl*-5-*t-butoxycarbonylpyrrol*-2-*ylmethyl*)-5-*methylpyrrol*-2-*ylmethyl*]-3,4-*dimethylpyrrole*-2-*carboxylate* (**80**) (*ca.* 7 mg); δ_H 1.52 and 1.53 (each 9 H, s, 2 × Bu^t), 1.94 (3 H, s, 4-Me), 1.95 (3 H, s, 3″-Me), 2.08 (3 H, s, 5′-Me), 2.21 and 2.22 (each 3 H, s, 3 and 4″-Me), 3.59 (2 H, s, 4′-CH_2), 3.80 (2 H, s, 5-CH_2), 5.72 (1 H, d, J 2.8 Hz, 3′-H), 7.44 (1 H, br, N′-H), 8.32 (1 H, br, N″-H), and 8.46 (1 H, br, NH); m/z 495 (M^+). The intermediate band contained two products whose molar ratio was determined by n.m.r. These were further separated by preparative t.l.c. (eluant dichloromethane–ether, 85:15). The higher R_F band yielded *t-butyl* 5-(2-*methylpyrrol*-3-*ylmethyl*)-3,4-*dimethylpyrrole*-2-*carboxylate* (**78**) (Found: M^+, 288.1841. $C_{17}H_{24}N_2O_2$ requires M, 288.1832); δ_H 1.51 (9 H, s, Bu^t), 1.97 (3 H, s, 4-Me), 2.15 (3 H, s, 2′-Me), 2.21 (3 H, s, 3-Me), 3.66 (2 H, s, CH_2), 5.97 (1 H, t, J 2.7 Hz, 4′-H), 6.61 (1 H, t, J 2.7 Hz, 5′-H), 7.82 (1 H, br, N′-H), and 8.29 (1 H, br, NH); m/z 288 (M^+). The lower R_F band yielded *t-butyl* 5-[3-(3,4-*dimethyl*-5-*t-butoxycarbonylpyrrol*-2-*ylmethyl*)-5-*methylpyrrol*-2-*ylmethyl*]-3,4-*dimethylpyrrole*-2-*carboxylate* (**79**) (Found: M^+, 495.3084. $C_{29}H_{41}N_3O_4$ requires M, 495.3087); δ_H 1.52 and 1.53 (each 9 H, s, Bu^t), 1.88 (3 H, s, 4-Me), 1.93 (3 H, s, 3″-Me), 2.15 (3 H, s, 5′-Me), 2.20 and 2.21 (each 3 H, s, 3 and 4″-Me), 3.62 (2 H, s, 3′-CH_2), 3.17 (2 H, s, 5-CH_2), 5.66 (1 H, m, 4′-H), 7.41 (1 H, br, N′-H) and 8.35 and 8.38 (each 1 H, br, 2 × NH); m/z 495 (M^+).

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