Some Studies on Peptide Analogues Involving the Sulphinamide Group

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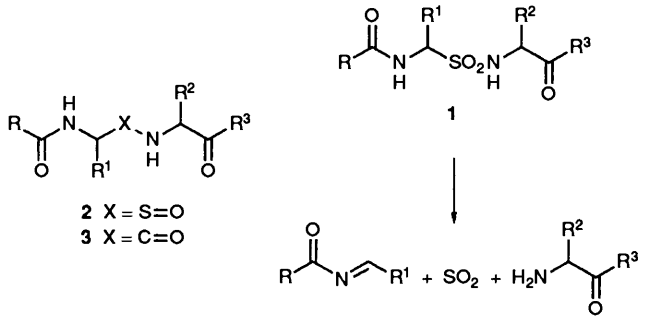
The title compounds are of interest as possible transition state inhibitors of peptidases. A route to *N*-(alkylsulphinyl)amino acids is described. A method for generating α-benzamidosulphinamides is reported; a general route to such systems failed owing to the difficulty of removing the protecting group and the apparent instability of α-amino sulphinamides. A crystal structure on the *N*-phthalimido-protected α-sulphinamide **16a** showed the tetrahedral disposition of substituents around the sulphur atom and the deviation from planarity about the sulphinamide nitrogen atom.

Interest in the synthesis of peptide analogues in which the amide bond is replaced is focused primarily on the development of transition state analogues as potential peptidase inhibitors[1] or as substrates for the development of catalytic antibodies ('abzymes').[2]

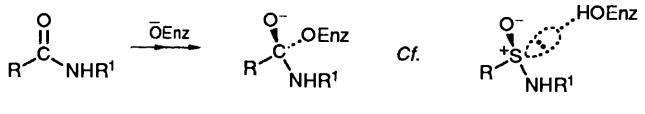
Whilst use of phosphorus analogues, such as the phosphonamide group, is well established, efforts to use sulphur containing systems, such as the sulphonamide group, have been thwarted by their tendency to fragment. Thus systems such as **1** collapse as indicated in Scheme 1,[3] so that such systems are



Scheme 1

unstable. Sulphenamides are also relatively unstable, nucleophilic attack at the weak sulphur–nitrogen bond occurring. By comparison, little work has been carried out on the sulphinamide system **2**. This paper describes our attempts to generate systems such as **2** as analogues of the typical peptide sequence **3**.

Besides its chemical novelty, there were several other reasons for trying to generate the system **2**; first the sulphinamide group



Scheme 2

is expected to be more stable to simple nucleophilic attack than the sulphenamide system and less prone to fragmentation of the type depicted in Scheme 1; second, the structure of the sulphinamide group may closely resemble the transition states adopted during hydrolysis of a normal peptide bond.[4] Enzymatic hydrolysis of the amide bond proceeds *via* chiral orthoamide intermediates (Scheme 2) and the transition states leading to and from these intermediates must involve stretched carbon to oxygen and carbon to nitrogen bonds, as well as considerable sp^3 character on the heteroatoms. Some structural studies on aryl sulphinamide groups[5] have shown that the sulphur atom is not bound in a planar form, the sulphur atom adopting a tetrahedral like configuration, whilst the nitrogen atom is puckered slightly from the sp^2 structure found in the ground state amide atom.

Synthetic requirements to be borne in mind in designing a route to the part structure **2** include: i, a method for formation of the sulphur–nitrogen bond; ii, the labile nature of the sulphinamide group, especially to either heat or acids[6] and iii, the need to select suitable amino acid protecting groups.

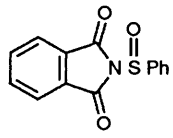
Because of the different reactivity of the sulphinic acid group to that of the carboxylic acid function[7] and because of the unstable nature of the alkanesulphinic acids,[7] it was not expected to form the sulphinamide group by direct coupling of the acid to an amine by use of the usual methods of peptide synthesis; the acid lability of the sulphinamide unit[8] requires use of neutral or slightly basic reaction conditions, thus limiting the choice of protecting groups. For these reasons our approach to dipeptide analogues adopted the use of an ester to protect the *C*-terminal carboxy group and the phthaloyl group to protect the *N*-terminal nitrogen atom.

Simple sulphinamides have previously been synthesised by the treatment of sulphinyl chlorides with amines,[9] reaction of *N*-sulphinylamines with Grignard reagents,[10] reaction of *N*-sulphinylphthalimides with amines,[11] or coupling of a sulphinic acid with an amine using dicyclohexylcarbodiimide (DCC) or 2-chloro-1-methylpyridinium iodide as a coupling reagent.[12] All these routes are unsuitable in the present case, because of the presence of the amine function in an α-position to the sulphinyl group. The unprotected α-aminosulphinic acids **4** are unknown.

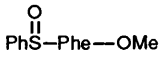
The approach initially adopted was to generate the sulphur–nitrogen bond using an activated sulphinic acid; use of a sulphinyl chloride was discounted because of the known lability of these. The activated sulphinamide derivative **5** was prepared[11] since this is known to react with amines to produce sulphinamides; indeed, reaction of this with L-phenylalanine methyl ester gave the sulphinamide **6** in good yield as a mixture of two diastereoisomers, owing to the chiral nature of the sulphur centre. However, attempts to extend this method to the preparation of α-aminoalkylsulphinamides failed. A second approach was therefore tried in which the sulphur–nitrogen bond was first generated as a sulphenamide[6] followed by oxidation to the sulphinamide. Davis has reviewed the chemistry of the sulphur–nitrogen bond in sulphenamides.[13]

Initially some simple peptide sulphinamides were aimed at,

$H_2NCH_2SO_2H$ (4)

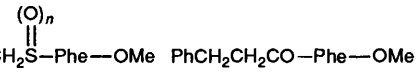


(5)



(6)

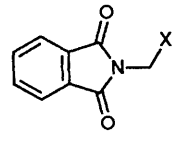
$(PhCH_2CH_2S)_2$ (7)



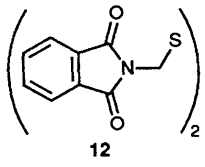
(8 $n = 0$; 9 $n = 1$)

(10)

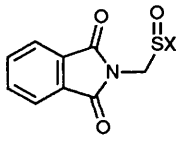
in particular the derivative **9**. Reaction of 1,6-diphenyl-3,4-dithiahexane **7** with L-phenylalanine methyl ester, in the presence of silver acetate and triethylamine in ethyl acetate,[6] afforded the sulphenamide **8** in moderate yield (40%) and this was smoothly oxidised with 1 equiv. of 3-chloroperbenzoic acid (MCPBA) to give the diastereoisomers **9**, which could be separated on silica gel, the least polar isomer being isolated as a crystalline solid and the more polar isomer as a viscous oil. This method for generating alkylsulphinamide derivatives of amino acids and, presumably, peptides should be of general application (*cf.* compounds **9** and **10**). With the route to simple alkyl sulphinamides established, attention was directed to the formation of α-aminoalkylsulphinamides. Reaction of the known bromomethyl derivative of phthalimide **11**[14] with sodium disulphide produced the disulphide **12**. Attempted formation of the corresponding sulphenyl chloride **13**, by reaction of **12** with sulphuryl chloride or chlorine, failed since no reaction with



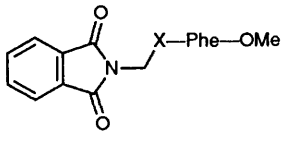
11; X = Br
13; X = SCl
14; X = SN



12



18; X = —Ala—OMe
19; X = —Phe—OBu^t



15; X = S
16; X = SO; **a**, *R*-sulphinamide
b, *S*-sulphinamide
17; X = SO_2

piperidine to form the sulphenamide **14** could be effected. The silver assisted method of Davis *et al.*[6] was therefore employed to form the sulphenamide bond. Reaction of compound **12** with L-phenylalanine methyl ester gave a moderate yield of the sulphenamide **15**. Selective oxidation of the latter with 1 equiv. of MCPBA gave two diastereoisomeric sulphinamides **16** and further oxidation of either of these with a further equivalent of peracid gave the less polar sulphonamide **17**. The protected sulphinamide isomers **16** could be separated by silica gel column chromatography.

The sulphinamide preparation was repeated on two further series of compounds, the methyl alaninate series, leading to the diastereoisomers **18** and the *tert*-butyl phenylalaninate series, giving the diastereoisomers **19**. The last two compounds were isolated as viscous oils, whilst the two phenylalanyl derivatives **16** were crystalline solids.

The less polar isomer **16a**, m.p. 129–131 °C was subjected to single crystal X-ray crystallographic examination. The compound forms triclinic crystals in the chiral space group *P*1. Fig. 1 shows a perspective view of the compound, indicating the crystallographic numbering scheme employed; selected bond lengths and angles are given in Tables 1 and 2, respectively, and the fractional coordinates of the non-hydrogen atoms are given

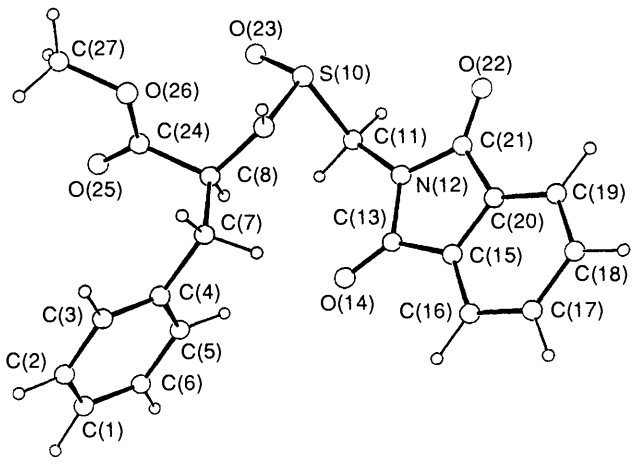


Fig. 1 The molecular structure of **16a** showing the numbering used in the X-ray crystal structure analysis

Table 1 Selected bond lengths (Å) for **16a**

	Bond length		Bond length
C(1)–C(2)	1.356(12)	C(1)–C(6)	1.371(9)
C(2)–C(3)	1.386(12)	C(3)–C(4)	1.373(8)
C(4)–C(5)	1.391(10)	C(4)–C(7)	1.522(10)
C(5)–C(6)	1.396(11)	C(7)–C(8)	1.540(10)
C(8)–N(9)	1.468(8)	C(8)–C(24)	1.512(8)
N(9)–S(10)	1.644(5)	S(10)–C(11)	1.835(6)
S(10)–O(23)	1.493(5)	C(11)–N(12)	1.438(9)
N(12)–C(13)	1.417(9)	N(12)–C(21)	1.405(8)
C(13)–O(14)	1.200(8)	C(13)–C(15)	1.467(10)
C(15)–C(16)	1.402(11)	C(15)–C(20)	1.367(9)
C(16)–C(17)	1.405(11)	C(17)–C(18)	1.390(11)
C(18)–C(19)	1.390(12)	C(19)–C(20)	1.391(10)
C(20)–C(21)	1.476(10)	C(21)–O(22)	1.196(9)
C(24)–O(25)	1.202(9)	C(24)–O(26)	1.333(9)
O(26)–C(27)	1.447(10)	N(9)–H(9n)	0.985

Table 2 Selected interbond angles (°) for **16a**

	Angle (°)		Angle (°)
C(6)–C(1)–C(2)	120.6(8)	C(3)–C(2)–C(1)	121.1(6)
C(4)–C(3)–C(2)	119.4(7)	C(5)–C(4)–C(3)	119.8(7)
C(7)–C(4)–C(3)	120.2(6)	C(7)–C(4)–C(5)	119.9(5)
C(6)–C(5)–C(4)	120.0(6)	C(5)–C(6)–C(1)	119.2(7)
C(8)–C(7)–C(4)	114.0(6)	N(9)–C(8)–C(7)	108.0(5)
C(24)–C(8)–C(7)	109.8(4)	C(24)–C(8)–N(9)	113.5(5)
S(10)–N(9)–C(8)	121.7(4)	C(11)–S(10)–N(9)	99.5(3)
O(23)–S(10)–N(9)	111.8(2)	O(23)–S(10)–C(11)	101.1(3)
N(12)–C(11)–S(10)	111.9(5)	C(13)–N(12)–C(11)	124.6(5)
C(21)–N(12)–C(11)	123.8(6)	C(21)–N(12)–C(13)	111.5(6)
O(14)–C(13)–N(12)	123.7(7)	C(15)–C(13)–N(12)	104.8(6)
C(15)–C(13)–O(14)	131.5(7)	C(16)–C(15)–C(13)	129.2(6)
C(20)–C(15)–C(13)	109.6(6)	C(20)–C(15)–C(16)	121.2(6)
C(17)–C(16)–C(15)	116.6(7)	C(18)–C(17)–C(16)	121.7(8)
C(19)–C(18)–C(17)	120.7(7)	C(20)–C(19)–C(18)	117.5(7)
C(19)–C(20)–C(15)	122.3(7)	C(21)–C(20)–C(15)	108.7(6)
C(21)–C(20)–C(19)	128.9(6)	C(20)–C(21)–N(12)	105.2(6)
O(22)–C(21)–N(12)	124.1(7)	O(22)–C(21)–C(20)	130.7(6)
O(25)–C(24)–C(8)	123.3(6)	O(26)–C(24)–C(8)	112.0(6)
O(26)–C(24)–O(25)	124.4(6)	C(27)–O(26)–C(24)	115.8(7)
H(9n)–N(9)–C(8)	116	H(9n)–N(9)–S(10)	115

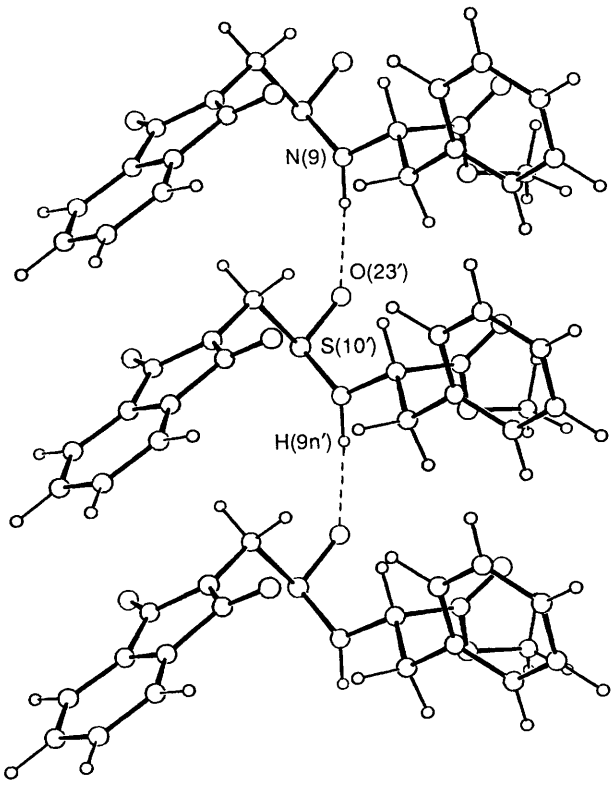


Fig. 2 A view of part of the chain-like structure parallel to the *c* axis, formed in the crystal of **16a** by hydrogen bonding between adjacent molecules, O(23) · · · H(9n) 2.00 Å

Table 3 Fractional atomic coordinates for **16a**

Atom	*x*	*y*	*z*
N(9)	0.699 5(4)	−0.175 0(6)	0.268 8(10)
S(10)	0.809 60	−0.165 60	0.543 40
N(12)	0.866 6(4)	0.155 6(5)	0.631 5(11)
O(14)	0.675 0(4)	0.208 0(5)	0.516 3(12)
O(22)	1.079 5(4)	0.171 1(6)	0.698 0(11)
O(23)	0.755 7(4)	−0.271 7(5)	0.713 4(10)
O(25)	0.399 3(5)	−0.404 2(6)	0.348 7(12)
O(26)	0.521 5(4)	−0.469 9(5)	0.066 3(12)
C(1)	0.138 6(7)	−0.077 3(7)	0.099 4(16)
C(2)	0.149 4(7)	−0.173 7(9)	−0.133 7(18)
C(3)	0.266 2(6)	−0.194 8(8)	−0.153 4(15)
C(4)	0.372 9(6)	−0.116 1(7)	0.066 5(13)
C(5)	0.362 8(6)	−0.015 1(8)	0.304 4(16)
C(6)	0.244 0(7)	0.003 7(8)	0.320 7(16)
C(7)	0.503 1(5)	−0.133 2(7)	0.045 7(13)
C(8)	0.565 4(5)	−0.196 1(6)	0.278 8(13)
C(11)	0.825 8(6)	0.031 0(7)	0.764 2(14)
C(13)	0.785 3(6)	0.232 8(7)	0.508 2(13)
C(15)	0.866 6(5)	0.341 5(7)	0.384 7(13)
C(16)	0.834 3(7)	0.443 3(8)	0.228 7(15)
C(17)	0.932 3(7)	0.531 5(9)	0.129 8(17)
C(18)	1.055 3(7)	0.518 7(8)	0.183 9(16)
C(19)	1.085 5(6)	0.418 0(8)	0.341 1(14)
C(20)	0.988 0(5)	0.330 3(7)	0.437 6(13)
C(21)	0.992 4(6)	0.214 0(7)	0.603 6(14)
C(24)	0.487 6(6)	−0.367 3(8)	0.244 2(14)
C(27)	0.446 7(9)	−0.636 2(11)	0.007 2(22)

in Table 3. Assigning the amino acid centre the known (*S*) configuration requires that, for this less polar isomer the configuration about the sulphur atom is (*R*). Fig. 2 shows part of the crystal structure, indicating an intermolecular hydrogen bond between the NH group and the sulphinyl oxygen atom such that the molecules adopt a linear chain array along the *c*-axis of the crystals. The conformation of the molecule may be described in terms of the selected torsion angles shown in Table 4. Of particular note is the steric arrangement around the sulphinamide group. The sulphinyl group adopts an almost classical tetrahedral shape, whilst the adjacent nitrogen adopts an almost, but not quite planar conformation, the sum of the three binding angles being 352.7°, a value consistent with other literature reports on sulphinamide structures.[5] The N–H bond lies in the same direction as the lone pair on the sulphur atom. Both the sets of aromatic rings from the phthalimide units and those of the phenyl rings of the phenylalanyl units stack along two axes in a similar alignment to that of the hydrogen bonded chains. As expected, the ^{1}H NMR spectrum of the sulphinamide **16a** shows magnetic nonequivalence for the methylene protons adjacent to the asymmetric sulphinamide group, appearing as an AB quartet at δ 4.45 and 4.65 (J/Hz 12).

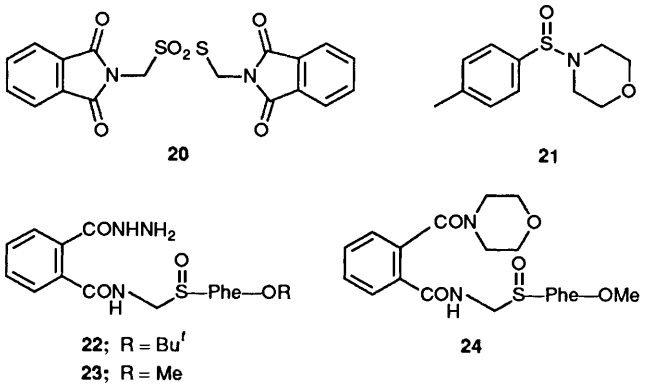
Table 4 Selected torsion angles (°) for **16a**

	Angle (°)
C(7)–C(8)–N(9)–S(10)	157.3
C(7)–C(8)–N(9)–H(9n)	−50.1
H(8)–C(8)–N(9)–S(10)	36.9
H(8)–C(8)–N(9)–H(9n)	−170.4
C(24)–C(8)–N(9)–S(10)	−80.6
C(24)–C(8)–N(9)–H(9n)	72.0
C(8)–N(9)–S(10)–C(11)	−71.1
C(8)–N(9)–S(10)–O(23)	35.0
H(9n)–N(9)–S(10)–C(11)	136.1
H(9n)–N(9)–S(10)–O(23)	−117.9
N(9)–S(10)–C(11)–N(12)	−60.3
O(23)–S(10)–C(11)–N(12)	−174.9

The thermal stability of the diastereoisomers **16** was briefly explored. Both the isomers **16a** and **16b** were stable at ambient temperatures but heating either isomer for a few minutes in refluxing carbon tetrachloride results in reformation of diastereoisomeric mixtures; the mechanism for this epimerisation was not investigated further. More prolonged heating of the diastereoisomeric mixture in refluxing toluene led to decomposition, possibly *via* the formation of sulphenic acid intermediates, the only products isolated from the mixture being the disulphide **12** and the thiosulphonate **20**.

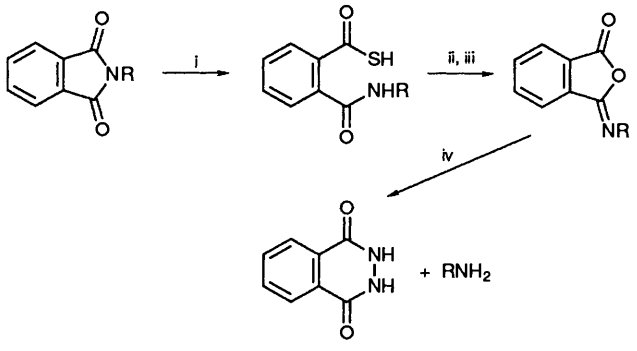
With a route to the substituted sulphinamides established it remained to find ways for removing the phthalimide protecting group in order to connect different peptide units to the *N*-terminus, thus achieving a general synthesis of the target structure **2**. Initially the reaction of the diastereoisomeric *tert*-butyl esters **19** with 1 equiv. of hydrazine hydrate in THF (tetrahydrofuran) according to the method of Kadir *et al.*[15] was studied; in a control study it was found that the sulphinamide **21** was unaffected by treatment with hydrazine under these conditions. A new product was formed and shown to be the expected hydrazide **22**; repetition of the reaction with the methyl esters **16** also formed the monohydrazides **23**, in which the methyl ester had remained intact. The phthalimide group could also be opened with nucleophilic amines such as morpholine, the ester **16** yielding the product **24**.

Having managed to open the phthalimide ring, a neutral or mildly basic method was required to try to cleave the remaining phthalamide bond. Treatment of the *tert*-butyl ester **22** with *N*-acetylimidazole did not lead to cleavage of this bond, reformation of the phthalimide occurring with the release of acetylhydrazide; no acetylation of the amide or sulphinamide nitrogen atoms was observed. Addition of one equivalent of acetic acid, as a mild acid catalyst, did affect the reaction and besides some of the starting phthalimide **19**, TLC indicated the formation of other products, although only one of these was isolated and this proved to be the *N*-acetyl derivative of the phenylalanyl ester **25**, obtained in 9%



yield. We presume that under these mildly acidic conditions some collapse of the phthalamide occurs to liberate the required α-aminosulphinamide **26**, but that this is unstable and immediately collapses to liberate the phenylalanine ester, which is trapped as the *N*-acetyl ester by reaction with the *N*-acetylimidazole present.

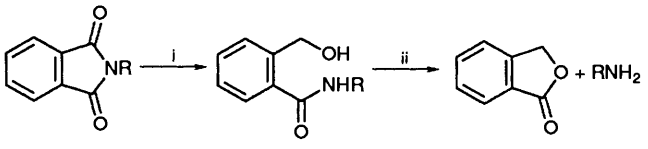
Kukolja[16] has reported a successful modification for the deprotection of phthalimide-protected penicillins and cephalosporins, involving formation of an intermediate isoimide (Scheme 3). When applied to the *tert*-butyl ester **19**, formation



Scheme 3 *Reagents:* i, Na_2S; ii, H_2O; iii, dicyclohexylcarbodiimide (DCC); iv, $N_2H_4 \cdot H_2O$

of the carboxylic acid **27** could be achieved, although the acid was unstable to long term storage. However, treatment with DCC (dicyclohexylcarbodiimide) did not produce the expected isoimide, reformation of the phthalimide being observed. Treatment of the acid **27** with triphenylphosphine and diethyl azodicarboxylate[17] also only afforded the starting phthalimide **19**.

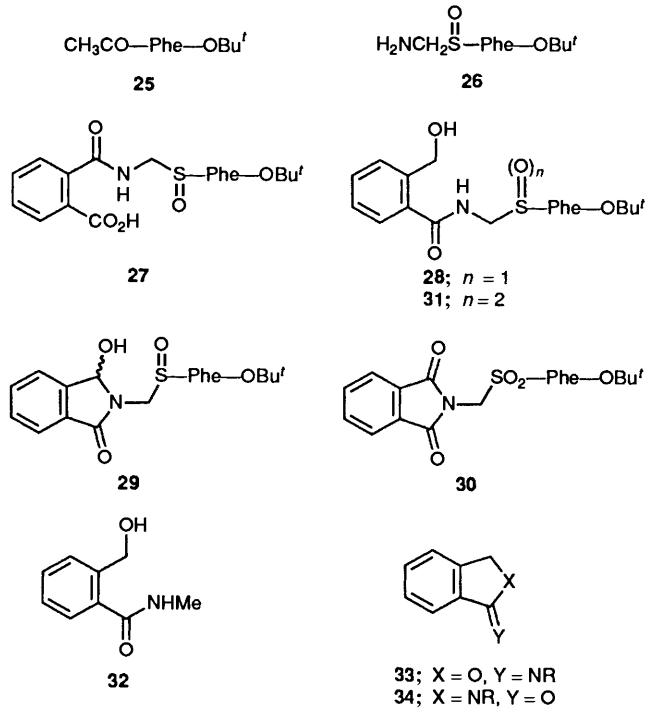
As an alternative deprotection method, the route outlined in Scheme 4 was envisaged. *N*-Substituted phthalimides are



Scheme 4 *Reagents:* i, $NaBH_4$; ii, AcOH

known to react with sodium borohydride to give 2-hydroxymethylbenzamides[18] and, under mild acidic conditions, these cyclise to give phthalide and the free amine.[19] Reduction of the ester **19** with sodium borohydride in aqueous isopropyl alcohol solutions afforded the required hydroxymethyl amide **28** along with some of the partially-reduced carbinolamides **29**; further treatment of the latter with more borohydride under buffered conditions slowly underwent further reduction to the alcohol.

It was of interest to compare the stable sulphinamide **28** with that of the corresponding sulphonamide **31**. Oxidation of the diastereoisomeric mixture **19** with MCPBA afforded the



single sulphonamide **30**. Reduction of the sulphonamide **30** with sodium borohydride did not produce a stable product and, instead of the expected alcohol **31**, two new products were isolated, the *tert*-butyl ester of phenylalanine (isolated in 56% yield), characterised as its *N*-acetyl derivative **25** and the methylamide **32** (59% yield). Thus, in contrast to the sulphinamide series, the *N*-acylated α-sulphonamide itself fragments (see Scheme 1), the intermediate imine being trapped by further reduction with the borohydride to produce the methylamide **32**. This result is consistent with literature reports on attempts to generate such systems.[3] The fact that the *N*-acylated sulphinamide system, *e.g.* compound **28** is stable confirms one of our original assumptions (see discussion above).

Treatment of the alcohol **28** with glacial acetic acid in isopropyl alcohol at room temperature caused little change, although on warming the solution to 60 °C a slow reaction occurred to give the *tert*-butyl ester of phenylalanine, again identified as its *N*-acetyl derivative **25**. Thus although the amide derivative **28** was isolable, liberation of the free amine was thwarted by its fragmentation.

Attempted formation of the imino ether **33** by treatment of the alcohol **28** with triphenylphosphine and diethyl azodicarboxylate also failed, the lactam **34** being formed as the only identifiable product. That compound **34** was the lactam rather than the required imino ether was shown by both its physical and chemical properties. The lactam showed a methylene peak in its NMR spectrum at δ 4.52, as expected for the lactam, rather than at > 5.0 as required for the isomeric cyclic ether; the lactam was also stable to mild acid treatment, conditions under which an imino-ether would be expected to rapidly hydrolyse.

Experimental

M.p.s were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Perkin Elmer 1420 Ratio recording spectrophotometer either on solutions in chloroform, Nujol mulls or, for liquids, as films. ^1H NMR spectra were recorded on a Varian 360A (60 MHz), Perkin Elmer R32 (90 MHz), or JEOL FX90Q (90 MHz) spectrometer and are quoted in ppm relative to tetramethylsilane as internal reference, for solutions in deuteriochloroform; ^{13}C spectra were recorded on

the JEOL instrument using off resonance coupling. All J values are given in Hz. Mass spectra were obtained using a Kratos MS25 instrument and accurate mass determinations were obtained using an AEI-Kratos MS 9/50 instrument. Microanalytical determinations were performed by the University of Leeds Microanalytical Laboratory. UV spectra were recorded on ethanolic solutions. Specific rotations were measured at the sodium D line at 20 °C using an NPL Automatic Polarimeter Type 243, with values quoted in 10^{-1} deg cm^2 g^{-1}.

TLC was carried out on aluminium or glass plates precoated with Merck Kieselgel 60GF$_{254}$. Column chromatography was carried out on either MN Kieselgel 60 (Camlab) or Kieselgel 60G (Merck); columns were generally packed and run under pressure. Solvents were dried and distilled before use using standard methods.[20] Light petroleum refers to the fraction of boiling range 40–60 °C and ether refers to diethyl ether. Solutions of organic compounds from extractions were dried over anhydrous sodium sulphate before being filtered and evaporated under reduced pressure on a rotary evaporator. Dry nitrogen was used as the atmosphere for most reactions.

Preparation of N-(*Phenylsulphinyl*)*phthalimide* **5**.—Chlorine gas was bubbled through a stirred solution of thiophenol (5 g, 45 mmol) in dry dichloromethane (60 cm^3) at 0 °C. After 10 min the red solution was added to a stirred suspension of crushed phthalimide (6.62 g, 45 mmol) and triethylamine (6 g, 59 mmol) in dry dichloromethane (60 cm^3). The mixture was stirred for 1 h at room temperature before pouring into water and the organic layer separated and dried. On removal of the solvent *N*-(phenylsulphenyl)phthalimide separated out as a yellow solid (7.92 g, 69%), m.p. 161–163 °C (lit.,[21] 160–161 °C) (Found: C, 66.0; H, 3.5; N, 5.7; S, 12.5. Calc. for $C_{14}H_9NO_3S$: C, 65.8; H, 3.5; N, 5.5; S, 12.5%).

The *N*-(phenylsulphenyl)phthalimide (3.6 g, 14.1 mmol) was dissolved in dry dichloromethane (90 cm^3) and a solution of 3-chloroperbenzoic acid (MCPBA) (2.84 g, 14.1 mmol) in dichloromethane (40 cm^3) added dropwise over 10 min at 0 °C before stirring the solution for a further 30 min at this temperature and working up. The solid residue was triturated with ether and recrystallised from acetone to afford the title sulphinamide (2.9 g, 76%), m.p. 145–147 °C (lit.,[11] 150–153 °C) (Found: C, 62.0; H, 3.3; N, 5.0; S, 12.0. Calc. for $C_{14}H_9NO_4S$: C, 62.0; H, 3.3; N, 5.2; S, 11.8%).

N-(*Phenylsulphinyl*)-L-*phenylalanine Methyl Ester* **6**.—The sulphinyl compound **5** (0.45 g, 1.7 mmol) was dissolved in dry dichloromethane (15 cm^3) and stirred at room temperature while adding a solution of L-phenylalanine methyl ester (1 equiv.) in dry dichloromethane (15 cm^3). The mixture was stirred overnight and the phthalimide removed by filtration before removing the solvent to produce an oil which was purified by preparative TLC to give the *title diastereoisomers* as an oil (0.35 g, 69.6%); ν_{max}/cm^{-1} 3320 (NH), 3100, 1740, 1445, 1095 and 1062 (Found: C, 63.5; H, 5.9; N, 4.7; S, 10.7. $C_{16}H_{17}NO_3S$ requires C, 63.4; H, 5.6; N, 4.6; S, 10.6%).

N-(*Phenethylsulphinyl*)-L-*phenylalanine Methyl Ester* **9**.—Bis-(phenylethyl)disulphide **7** (1.03 g, 3.76 mmol) was dissolved in ethyl acetate (30 cm^3) before adding silver acetate (1.25 g, 7.5 mmol), triethylamine (1.52 g, 15 mmol) and L-phenylalanine methyl ester (0.72 g, 4 mmol). The mixture was stirred in the dark at room temperature for 15 h before filtering and the filtrate evaporated. The residue was dissolved in ether, washed with water, dried, filtered and evaporated before chromatographing through silica gel, using 1:2 ethyl acetate–light petroleum as eluent, to give *N*-(phenethylsulphenyl)-L-phenylalanine methyl ester **8** [(466 mg, 40%), δ 2.74 (4 H, br s, CH_2CH_2), 3.0 (3 H, m, NH, CH_2), 3.68 (3 H, s, CH_3O), 3.68 (1 H, m, CH) and 7.2 (10 H, m, aromatic H)]. The sulphenamide (0.703 g, 2.23 mmol) was stirred in dichloromethane (10 cm^3) at 0 °C whilst adding a solution of MCPBA (0.453 g, 2.23 mmol) in dichloromethane (10 cm^3). After 1 h the solution was extracted with 5% w/w sodium hydrogen carbonate solution, the organic layer washed with water, separated and dried. After filtering the solvent was removed and the residue chromatographed through silica gel, using 2:1 ethyl acetate–light petroleum as eluent to give the *title compounds* as separate diastereoisomers. The *less polar isomer* (0.31 g, 42%), showed m.p. 105–106 °C acetone), $[\alpha]_D$ −25.4 (*c* 0.13, $CHCl_3$); ν_{max}/cm^{-1} 3270, 1736, 1267 and 1064; δ 2.77 (4 H, br s, CH_2CH_2), 3.07 (2 H, d, *J* 6, $PhCH_2$), 3.7 (3 H, s, CH_3O), 4.3 (1 H, m, CH), 4.95 (1 H, d, *J* 9, NH) and 7.25 (10 H, m, aromatic H) (Found: C, 64.7; H, 6.4; N, 4.2. $C_{18}H_{21}NO_3S$ requires C, 65.2; H, 6.3; N, 4.2%).

The more *polar isomer* (0.28 g, 38%) was isolated as a viscous gum, $[\alpha]_D$ +27.2 (*c* 0.43, $CHCl_3$); δ 2.93 (4 H, br s, CH_2CH_2), 3.05 (2 H, m, $PhCH_2$), 3.72 (3 H, s, CH_3O), 4.3 (1 H, m, CH), 4.95 (1 H, d, *J* 9, NH) and 7.25 (10 H, m, aromatic H) (Found: C, 65.6; H, 6.6; N, 4.2; S, 9.8%. $C_{18}H_{21}NO_3S$ requires C, 65.3; H, 6.3; N, 4.2; S, 9.7%).

Preparation of Bis(*phthalimidomethyl*) *Disulphide* **12**.—Precipitated sulphur (0.416 g, 12.5 mmol) was dissolved in aqueous sodium sulphide solution (3.125 g, 12.5 mmol) in water (30 cm^3) with heating and the solution then cooled to room temperature before adding it to a solution of *N*-bromomethylphthalimide[14] **11** (5 g, 20 mmol) in acetone (80 cm^3) over 5 min. The solution turned yellow and then cleared before formation of a colourless precipitate. After 1 h the precipitate was collected and dried to give the title compound (4.2 g, 86%), m.p. (acetone) 188–191 °C (lit.,[22] 194 °C); ν_{max}(Nujol)/cm^{-1} 1775, 1715, 1305, 1272, 1080 and 915; δ 4.95 (4 H, s, 2 × CH_2) and 7.8 (8 H, m, aromatic H); *m*/*z* 384 (22%), 192 (14), 160 (100) (Found: C, 56.3; H, 3.1; N, 7.2; S, 16.9. Calc. for $C_{18}H_{12}N_2O_4S_2$: C, 56.2; N, 3.1; N, 7.3; S, 16.7%).

Preparation of N-(*Phthalimidomethylthio*)-L-*phenylalanine Methyl Ester* **15**.—A suspension of the disulphide **12** (20 g, 0.052 mol) and silver acetate (16.39 g, 0.104 mol) in ethyl acetate (200 cm^3) was stirred at room temperature in the dark and to it was added triethylamine (15.75 g, 0.156 mol) and a solution of L-phenylalanine methyl ester (3 equiv.) in ethyl acetate (50 cm^3). The mixture was stirred at room temperature under a nitrogen atmosphere overnight and the black precipitate that formed was filtered off and the filtrate evaporated under reduced pressure. The residue was extracted with ether and the ether solution was washed with water, dried, filtered and evaporated. The residue was subjected to column chromatography through silica gel, using 1:1 ethyl acetate–light petroleum as eluent, to give the *title compound* as a pale yellow oil (8.7 g, 45%), δ 3.0 (2 H, d, *J* 7, CH_2Ph), 3.05 (1 H, d, *J*, 7, NH), 3.66 (3 H, s, CH_3), 3.82 (1 H, m, CH), 4.74 (2 H, s, CH_2S), 7.25 (5 H, m, aromatic H) and 7.8 (4 H, m, aromatic H); *m*/*z* 370 (55%), 192 (42), 160 (100) and 91 (58) (Found: M$^+$ 370.094 49. $C_{19}H_{18}N_2O_4S$ requires *M*, 370.094 23).

Preparation of N-(*Phthalimidomethylsulphinyl*)-L-*phenylalanine Methyl Esters* **16a**, **16b**.—The sulphenamide derivative **15** (9.88 g, 26.7 mmol) in dichloromethane (50 cm^3) was oxidised with a solution of MCPBA (5.41 g, 26.7 mmol) in dichloromethane (50 cm^3) at 0 °C for 40 min before washing the solution with 5% w/v sodium hydrogen carbonate solution. The organic layer was separated, dried, and the solvent removed to leave an oil (7.438 g, 73%). The diastereoisomers were separated by column chromatography through silica gel, using 1:1 ethyl acetate–light petroleum as eluent.

The *less polar isomer* **16a** showed m.p. 129–131 °C, $[\alpha]_D$ +42 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3260, 1765, 1705, 1250, 1055 and 1035; δ 3.1 (2 H, d, *J* 7 CH_2Ph), 3.6 (3 H, s, CH_3), 4.4 (1 H, m, $CHCH_2Ph$), 4.55 (2 H, AB q, *J* 12, CH_2SO), 5.02 (1 H, d, *J* 8, NH) and 7.25 and 7.8 (9 H, m, aromatic H) (Found: C, 58.8; H, 4.7; N, 7.3; S, 8.3. $C_{19}H_{18}N_2O_5S$ requires C, 59.1; H, 4.7; N, 7.3; S, 8.3%). This isomer was subjected to X-ray crystallographic examination, see below.

The *more polar isomer* **16b** showed m.p. 96–98 °C; $[\alpha]_D$ +26.8 (*c* 1.0, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3260, 1765, 1705, 1250, 1055 and 1035; δ 3.0 (2 H, m, CH_2Ph), 3.7 (3 H, s, CH_3), 4.2 (1 H, m, CH), 4.65 (2 H, ABq, *J* 12, CH_2SO), 5.1 (1 H, d, *J* 8, NH), 7.0 (5 H, s, aromatic H) and 7.8 (4 H, m, aromatic H) (Found: C, 58.7; H, 4.7; N, 7.3; S, 8.3. $C_{19}H_{18}N_2O_5S$ requires C, 59.0; H, 4.7; N, 7.3; S, 8.3%).

Preparation of N-(*Phthalimidomethylsulphonyl*)-L-*phenylalanine Methyl Ester* **17**.—The diastereoisomeric sulphinamides **16** (200 mg, 0.49 mmol) were dissolved in dichloromethane (5 cm^3) and stirred at room temperature with MCPBA (134 mg, 0.77 mmol) for 30 min before quenching the reaction by pouring it into 5% w/v aqueous sodium hydrogen carbonate, the organic layer separated, was dried and the solvent removed before chromatographing the residue through silica gel, using 1:1 ethyl acetate–light petroleum as eluent. The *title sulphonamide* was obtained as a white solid (170 mg, 81%), m.p. 46–49 °C (decomp.); $[\alpha]_D$ +32.5 (*c* 0.12, $CHCl_3$); ν_{max}/cm^{-1} 3250, 1765, 1705, 1280 and 1135; δ 3.15 (2 H, m, CH_2Ph), 3.7 (3 H, s, CH_3), 4.5 (1 H, m, $CHCH_2Ph$), 4.9 (2 H, s, CH_2SO_2), 5.25 (1 H, d, *J* 7, NH), 7.2 (5 H, m, aromatic H) and 7.8 (4 H, m, aromatic H) (Found: C, 56.6; H, 4.6; N, 6.6; S, 7.7. $C_{19}H_{18}N_2O_6S$ requires C, 56.7; H, 4.5; N, 7.0; S, 8.0%).

Preparation of N-(*Phthalimidomethylsulphinyl*)-L-*alanine Methyl Ester* **18**.—L-Alanine methyl ester (206 mg, 2 mmol) was reacted with the disulphide **12** (760 mg, 2 mmol) under the conditions described above for the phenylalanine ester. After normal work up the intermediate N-(*phthalimidomethylsulphenyl*)-L-*alanine methyl ester* was obtained as a yellow oil (97 mg, 14%), δ 1.35 (3 H, d, *J* 7, CH_3), 3.26 (1 H, d, *J* 7, NH), 3.12 (3 H, s, OCH_3), 3.12 (1 H, m, $CHCH_3$), 4.77 (2 H, s, CH_2S) and 7.8 (4 H, m, aromatic H) (Found: C, 52.8; H, 4.8; N, 9.3; S, 11.0. $C_{13}H_{14}N_2O_4S$ requires C, 53.1; H, 4.8; N, 9.5; S, 10.9%).

The latter sulphenamide was oxidised with 1 equiv. of MCPBA in the manner described above to give the *title sulphinamide* **18** (61%), obtained as a viscous 1:1 mixture of diastereoisomers; ν_{max}/cm^{-1} 3190, 1774, 1745, 1726, 1210, 1146 and 1055; δ 1.40 (3 H, d, *J* 7, CH_3), 1.48 (3 H, d, *J* 7, CH_3), 3.66 and 3.73 (6 H, 2 × s, CH_3O), 4.1 (2 H, m, 2 × $CHCH_3$), 4.77 (2 H, ABq, *J* 12, CH_2SO), 4.82 (2 H, ABq, *J* 12, CH_2SO), 5.0 (1 H, d, *J* 7, NH), 5.18 (1 H, d, *J* 7, NH) and 7.84 (8 H, m, aromatic H) (Found: C, 50.6; H, 4.5; N, 9.0; S, 10.3. $C_{13}H_{14}N_2O_5S$ requires C, 50.3; H, 4.5; N, 9.0; S, 10.3%).

Preparation of N-(*Phthalimidomethylsulphinyl*)-L-*phenylalanine* tert-*Butyl Ester* **19**.—L-Phenylalanine *tert*-butyl ester (21 g, 95 mmol) allowed to react with the disulphide **8** (36 g, 95 mmol) under the conditions described above for the methyl ester. After normal work up the N-*phthalimidomethylsulphenyl*)-L-*phenylalanine* tert-*butyl ester* was obtained (8.92 g, 40%), $[\alpha]_D$ −4.07 (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 3345, 3010, 2985, 1775, 1718, 1408, 1372, 1155, 1082, 914, 843 and 703; δ 1.25 (9 H, s, Bu^t), 2.8 (2 H, d, *J* 7, CH_2Ph), 3.0 (1 H, d, *J* 7, NH), 3.65 (1 H, t, *J* 7, CH), 4.6 (2 H, s, CH_2S), 7.1 (5 H, m, aromatic H) and 7.6 (4 H, m, aromatic H) (Found: *m/z* 412.146 34. $C_{22}H_{24}N_2O_4S$ requires *M*, 412.145 67).

Oxidation of this sulphenamide with MCPBA using the method described above, gave the *title sulphinamide*, as a viscous 1:1 mixture of the diastereoisomers (60%), ν_{max}/cm^{-1} 3300, 1780, 1730, 1532, 1425, 1390 and 1220; δ 1.35 (18 H, s, 2 × Bu^t), 3.0 (4 H, m, 2 × CH_2Ph), 4.2 (2 H, m, 2 × CH), 4.55 (2 H, ABq, *J* 13, CH_2SO), 4.68 (2 H, ABq, *J* 13, CH_2SO), 5.1 (2 H, m, 2 × NH), 7.05 and 7.25 (10 H, m, aromatic H) and 7.8 (8 H, m, aromatic H) (Found: C, 61.5; H, 5.7; H, 6.3; S, 7.5. $C_{22}H_{24}N_2O_5S$ requires C, 61.7; H, 5.6; N, 6.5; S, 7.5%).

N-(p-*Tolylsulphinyl*)*morpholine* **21**.—Toluene-*p*-sulphinic acid (3.5 g, 22 mmol), morpholine (1.95 g, 22 mmol) and *N,N'*-dicyclohexylcarbodiimide (DCC) (4.61 g, 22 mmol) were added together in dichloromethane (150 cm^3) at 0 °C and the mixture left to stand at room temperature overnight. The precipitated urea was removed by filtration and the solvent removed from the filtrate to give the sulphinamide as a white solid (3 g, 60%), m.p. 119–120 °C (benzene) (lit.,[23] 114–115 °C).

A sample of the sulphinamide was stirred with a 1 equiv. of hydrazine hydrate in THF at 50 °C for 2 h, after which time the sulphinamide was recovered unchanged.

Hydrazinolysis Reactions.—To the diastereoisomeric methyl ester **16** (0.5 g, 1.29 mmol) in THF (20 cm^3) stirred at 0 °C was added hydrazine hydrate (77 mg, 1.53 mmol). After 30 min the solvent was removed and the residue purified by column chromatography through silica gel, using 9:1 $CHCl_3$–methanol as eluent, to give *N*-(2-carbazoylbenzamidomethylsulphinyl)-L-phenylalanine methyl ester **23** (0.51 g, 95%). The compound slowly decomposed with time but the freshly obtained material showed ν_{max}/cm^{-1} 3432, 3315, 3245 br, 3010, 1745, 1667, 1635, 1535, 1318, 1054 and 702; δ 3.04 (4 H, m, CH_2Ph), 3.55 (3 H, s, MeO), 3.5–4.7 (complex area of peaks) and 7.1–7.9 (aromatic H); *m/z* 192 (10%), 160 (100), 130 (21), 104 (31) and 76 (30). The compound was too unstable for satisfactory microanalytical data to be obtained.

In a similar fashion the *tert*-butyl ester **19** (0.414 g, 0.97 mmol) was treated with hydrazine hydrate (48 mg, 0.97 mmol) in THF (25 cm^3) for 30 min to give the hydrazide **22**. The latter compound was not isolated but treated, in solution, with acetic acid (0.12 g, 1.9 mmol) and the mixture warmed to 50 °C for 10 min when the solution turned cloudy. After cooling to room temperature, *N*-acetylimidazole (0.11 g, 0.97 mmol) was added and the mixture stirred at room temperature overnight before quenching with water and extracting with ethyl acetate. The organic solvent was removed and the residue chromatographed through silica gel, using 1:1 ethyl acetate–light petroleum as eluent, to give *N*-acetyl-L-phenylalanine *tert*-butyl ester **25** (24 mg, 9%) as the only isolable compound. Compound **25** showed $[\alpha]_D$ +60 (*c* 0.1, $CHCl_3$) {lit.,[24] $[\alpha]_D$ +74 (*c* 1.0, $CHCl_3$)} (Found: M^+ 263.152 23. Calc. for $C_{15}H_{21}NO_3$: *M*, 263.152 13).

N-[2-(N-*Morpholinocarbonyl*)*benzamidomethylsulphinyl*)-L-*phenylalanine Methyl Ester* **24**.—The phthalimide methyl ester **16** (200 mg, 0.52 mmol) was stirred at room temperature with morpholine (0.11 cm^3, 1.5 mmol) in dichloromethane (5 cm^3) for 2 d. The solvent was removed and the residue chromatographed through silica gel, using 9:1 chloroform–methanol as eluent, to give the title *amide* as an oil (200 mg, 82%), δ 2.9 (2 H, d, *J* 7, CH_2Ph), 3.1 (4 H, br m, CH_2NCH_2), 3.6 (4 H, br m, CH_2OCH_2), 3.7 (3 H, s, CH_3O), 4.2 (1 H, m, $CHCH_2Ph$), 4.4 (2 H, m, CH_2SO), 5.7 (1 H, d, *J* 10, NH) and 7.0–7.6 (9 H, m, aromatic H) (Found: M^+ 4.73.161 41. $C_{23}H_{27}N_3O_6S$ requires *M*, 473.162 04).

Hydrolysis of the Phthalimide **19**.—The phthalimide *tert*-butyl ester **19** (200 mg, 0.5 mmol) was dissolved in 1:4 aqueous acetone (5 cm^3) and to the solution was added dropwise, a solution of sodium sulphide nonahydrate (0.11 g, 0.55 mmol) in water (2 cm^3). The solution turned yellow. After 30 min

the solution was quenched with more water (5 cm^3), the pH adjusted to 3 with 1 mol dm^{-3} HCl and the mixture extracted with ethyl acetate, separated and dried. The solvent was removed to leave the diastereoisomers (161 mg, 77%) as an oil, which showed as a single entity on TLC, but which steadily decomposed on standing. The freshly isolated material showed ν_{max}/cm^{-1} 3250, 2980, 1730, 1655, 1525, 1368, 1245, 1150 and 1040; δ 1.3 (9 H, s, Bu^t), 3.1 (2 H, m, CH_2Ph), 4.1 (1 H, m, $CHCH_2Ph$), 4.8 (2 H, m, CH_2SO), 6.6 (3 H, br s, exchanged with D_2O, NH and OH) and 7.0–8.0 (9 H, m aromatic H). The material was too unstable to obtain satisfactory microanalytical data.

A sample of the acid (44 mg, 0.1 mmol) in dichloromethane (2 cm^3), was treated with DCC (22 mg, 0.1 mmol), following the reaction by TLC. The starting phthalimide **19** formed. No evidence for formation of an isoimide could be found. A similar observation was noted using triphenylphosphine and diethyl azodicarboxylate as the coupling reagent. Further attempts to release the phthalimido group were abandoned.

Reduction of the Phthalimide **19**.—The ester (0.97 g, 2.3 mmol) was dissolved in 6:1 isopropyl alcohol–water (28 cm^3) before treating with sodium borohydride (0.35 g, 9 mmol) for 4 h at room temperature. The mixture was poured into water and extracted with ethyl acetate, the organic layer separated, dried and the solvent removed before the residue was chromatographed through silica gel, using 2:1 ethyl acetate–light petroleum as eluent, to give three fractions, each as diastereoisomeric mixtures about the sulphur atom. The first two fractions eluted proved to be the isomeric *N*-[(2,3-dihydro-1-hydroxy-3-oxoisoindol-2-yl)methylsulphinyl]-L-phenylalanine *tert*-butyl esters **29**; the first isomer, isolated as an oil (80 mg, 8%) showed $\nu_{max}(CCl_4)/cm^{-1}$ 3240, 2980, 1720, 1395, 1370, 1250, 1150 and 1065; δ 1.33 (9 H, s, Bu^t), 3.0 (2 H, m, CH_2Ph), 4.12 (1 H, m, $CHCH_2Ph$), 4.63 (2 H, m, CH_2SO), 5.4 (0.5 H, d, *J* 8, NH), 5.9 (1.5 H, m, 0.5 NH and CHOH) and 7.0–7.9 (9 H, m, aromatic H); *m/z* 356 (57%), 281 (59), 162 (65), 133 (100), 120 (76) and 57 (78).

The other carbinolamine (82 mg, 8.4%) showed $\nu_{max}(CCl_4)/cm^{-1}$ 3300, 2990, 1723, 1393, 1370, 1150, 1063 and 695; δ 1.33 (9 H, Bu^t), 3.0 (2 H, CH_2Ph), 4.1 (1 H, m, $CHCH_2Ph$), 4.4–5.2 (2 H, m, CH_2SO), 5.42 (0.5 H, d, *J* 7, NH), 5.8 (1.5 H, m, 0.5 NH and CHOH) and 6.9–7.9 (9 H, m, aromatic H); *m/z* 356 (61%), 311 (57) 162 (100), 133 (93), 120 (66) and 57 (62).

The major, most polar fraction was *N*-[2-(*hydroxymethyl*)-*benzamidomethylsulphinyl*]-L-*phenylalanine* tert-*butyl ester* **28** (363 mg, 37%), ν_{max}/cm^{-1} 3250, 1735, 1660, 1535, 1370, 1255, 1150 and 1045; δ 1.3 (18 H, s, 2 × Bu^t), 3.0 (4 H, d, *J* 8, 2 × CH_2Ph), 4.1 (4 H, m, 2 × $CHCH_2Ph$ and 2 × NH), 4.4 (4 H, m, 2 × CH_2SO), 4.6 (4 H, s, 2 × CH_2OH), 5.18 and 5.6 (2 H, m, 2 × NH) and 7.3 (18 H, m, 2 × aromatic protons) (Found: C, 61.3; H, 6.7; N, 6.8. $C_{22}H_{28}N_2O_5S$ requires C, 61.1; H, 6.5; N, 6.5%).

Further treatment of the carbinolamines **29** with more sodium borohydride under the described reduction conditions slowly transformed these to the alcohol **28**.

Preparation and Reduction of the Sulphonamide **30**.—The phthalimide **26** (0.64 g, 1.4 mmol) was stirred in 6:1 isopropyl alcohol–water (20 cm^3) at room temperature whilst sodium borohydride (0.22 g, 5.6 mmol) was added; it was then stirred for a total of 4 h. The mixture was extracted with ethyl acetate and the extract washed and dried before evaporation. The residue was chromatographed through silica gel, using 1:1 ethyl acetate–light petroleum as eluent, to give two pure fractions. The first was *N*-methyl-2-hydroxymethylbenzamide **32** (140 mg, 59%), m.p. 122–124 °C (lit.,[25] 122–123 °C), ν_{max}/cm^{-1} 3460, 3410, 1648, 1532, 1413 and 1020 (Found: C, 65.5; H, 6.6; N, 8.7. Calc. for $C_9H_{11}NO_2$: C, 65.5, H, 6.6; N, 8.5%).

The other fraction, obtained as an oil was shown to be L-phenylalanine *tert*-butyl ester (179 mg, 56%), δ 1.4 (9 H, s, Bu^t), 1.8 (2 H, br s, NH_2), 2.95 (2 H, m, CH_2Ph), 3.55 (1 H, m, $CHCH_2Ph$) and 7.3 (5 H, m, aromatic H) (Found: *M*, 221.141 97. Calc. for $C_{13}H_{19}NO_2$: M^+ 221.141 57). On treatment with *N*-acetylimidazole, the latter amine produced the amide **25**, identical in its physical properties with the material described above.

Reactions with the Alcohol **28**.—(*a*) *With acetic acid and DCC.* The alcohol (81 mg, 0.19 mmol) was dissolved in isopropyl alcohol (3 cm^3) and 1:1 water–acetic acid added dropwise until the apparent pH reached 3. The mixture was stirred at 60 °C for 2 h after which it was cooled to room temperature and DCC (80 mg, 0.37 mmol) added to it. A white precipitate formed and this was filtered off. The solution was extracted with ethyl acetate and the extract was washed with water, separated, dried, and evaporated. The residue was chromatographed through silica gel, using 2:1 ethyl acetate – light petroleum as eluent, to give as the major compound, *N*-acetyl-L-phenylalanine *tert*-butyl ester **25** (33 mg, 73%), identical with the material described above.

(*b*) *With triphenylphosphine and diethyl azodicarboxylate.* The alcohol (0.55 g, 1.2 mmol) in THF (20 cm^3) at room temperature was stirred with triphenylphosphine (0.36 g, 1.4 mmol) and diethyl azodicarboxylate (0.2 ml, 1.4 mmol) added dropwise over 15 min. Stirring was continued for a further 45 min before removal of solvent and trituration of the residue with ether, to remove the crystalline triphenylphosphine oxide. The ethereal solution was chromatographed through silica gel, using 1:1 ether–ethyl acetate as solvent, to produce the *lactam diastereoisomers* **34** (464 mg, 89%) as an oil. The mixture showed ν_{max}/cm^{-1} 3306, 1730, 1695 and 1455; δ 1.37 (18 H, s, 2 × Bu^t), 3.05 (4 H, m, 2 × CH_2Ph), 4.2 (2 H, m, 2 × $CHCH_2Ph$), 4.52 (4 H, s, 2 × CH_2N), 4.52 (4 H, m, 2 × CH_2SO), 5.27 (2 H, d, *J* 8, 2 × NH), 7.1 (5 H, m, aromatic H), 7.28 (5 H, m, aromatic H), 7.5 (6 H, m, aromatic H) and 7.85 (2 H, m, aromatic H) (Found: C, 63.9; H, 6.3; N, 6.4; S, 7.9. $C_{22}H_{26}N_2O_4S$ requires C, 63.8; H, 6.3; N, 6.8; S, 7.7%).

X-Ray Structure Analysis of **16a**.—*Crystal Data.* [$C_{19}H_{18}N_2O_5S$], *M* = 386.42, Triclinic, space group *P*1, *a* = 11.158(3), *b* = 9.040(3), *c* = 5.033(3) Å, α = 101.86(4), β = 100.54(3), γ = 105.65(3)°, *U* = 462.86 $Å^3$, *F*(000) = 202, μ(Mo-Kα) = 1.64 cm^{-1}, *Z* = 1, D_c = 1.386 g cm^{-3}.

Data were collected on a crystal of dimensions, 0.32 × 0.27 × 0.18 mm. 1954 intensities were recorded ($3.0 < \theta < 25.0°$) on a Philips PW1100 diffractometer, with a scan width of 0.84°. The method of data collection and processing has been described previously.[26] Equivalent reflections were averaged to give 1405 unique observed reflections [$I > 3\sigma(I)$].

The volume of the unit cell was consistent with it containing only one molecule indicating that the very rare non-centrosymmetric space group *P*1 was correct; as the sample was racemic the two enantiomers must be present but in different crystals. The structure was solved using tangent multisolution direct methods and all the non-hydrogen atoms were found from the E-map ranked highest in combined figure of merit.[27] One methyl hydrogen atom and that of the amine were located from difference-Fourier syntheses; the remaining H-atoms were generated at idealised positions (C-H = 1.08 Å) and the thermal parameters of all hydrogen atoms were constrained to be equal to the same free variable. Full-matrix refinement with the S, N and O atoms assigned anisotropic thermal parameters converged at *R* 0.0499 (R_w 0.0496) with $w = 1/\sigma^2(F)$.[27] Refinement of the structure in the opposite

hand gave slightly higher R and R_w of 0.0504 and 0.0501 respectively.

Thermal parameters and fractional coordinates for hydrogen atoms are available from the C.C.D.C.*

* For details of the crystallographic deposition system see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1991, Issue 1.

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