Pergamon

Tetrahedron, Vol. 53, No. 49, pp. 16859-16866, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10087-4

1,2-Dithia-5-Azacyclooctan-6-one and Related Compounds: Synthesis and Conformation

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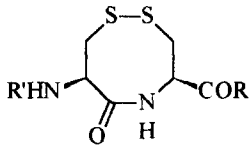
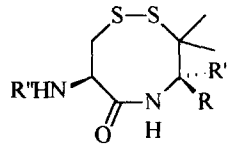
Abstract: The first synthesis of 1,2-dithia-5-azacyclooctan-6-one **11**, the parent member of a heterocyclic ring synthesis is reported. Compound **11** was found by nOe experiments to exist in a conformation with a *trans*-amide bond. The substituted derivatives **12** and **13** were also prepared and compound **12** was found to possess a *trans*-amide bond whilst for compound **13** three conformations were identified with the major conformer possessing a *cis*-amide bond. © 1997 Elsevier Science Ltd.

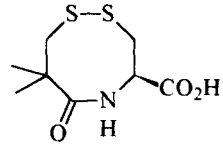
In recent years, we[1] and others[2] have reported the synthesis and conformational analysis of eight-membered ring disulfides **1-9** derived from cysteine and penicillamine. The conformational analysis of these compounds carried out both in solution by NMR techniques and in the solid state by X-ray crystallography revealed that the amide bond in compounds **1-9** could adopt either a *cis* or a *trans*-configuration depending upon the substituents and / or the relative configuration at the two stereocentres. Thus compounds **1-5** exist in conformations containing a *cis*-amide bond, whilst compounds **6-9** were found to possess a *trans*-amide bond. These results are in marked contrast to the situation with simple lactams where it is known that a nine-membered ring is necessary before a *trans*-amide bond can be formed.[3] The synthesis and conformational analysis of all four stereoisomers of the related seven-membered ring monosulfide **10** has also been reported, and in this case it was found that the amide bond always adopted the *cis*-configuration.[4]



1: R= OH, R'= H
2: R= OMe, R'= Boc
3: R= O*t*Bu, R'= Boc



4: R= CO_2Me, R'= H, R"= Boc
5: R= CO_2Me, R'= H, R"= CF_3CO
6: R= H, R'= CO_2Me, R"= Boc
7: R= H, R'= CO_2Me, R"= CF_3CO
8: R= H, R'= CO_2Me, R"= $PhCH_2CO$



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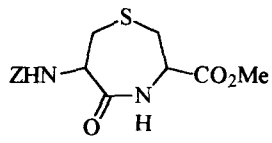

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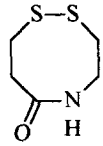
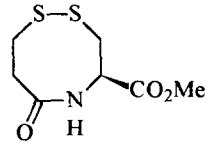
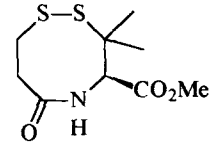


11

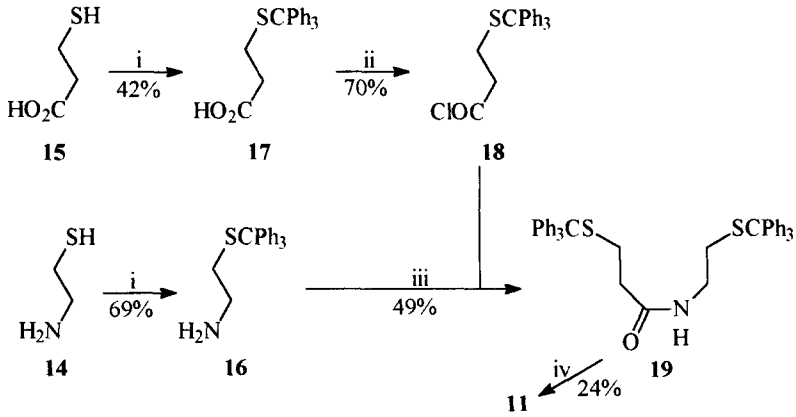


12



13

Cyclic disulfides such as compounds **1-9** are of interest as conformationally constrained building blocks capable of imposing a defined secondary structure on biologically active peptide analogues.[5] This structural unit has also been found in a number of naturally occurring peptides (for example the malformins[6]) and proteins.[7] Despite this interest in these compounds, the synthesis and conformational analysis of the parent compound **11** containing this heterocyclic ring system has not previously been reported. The synthesis of compound **11** is of interest, since a conformational analysis of this compound would enable the 'normal' amide bond geometry of this ring system to be determined, and so aid an understanding as to why the amide bond geometry of compounds **1-9** should be dependent upon the substituents and the relative configuration. This would allow the amide bond geometry of analogues of compounds **1-9** to be predicted in advance of their synthesis, and thus aid their use in conformationally constrained peptides. In this paper, we report the synthesis of compound **11**, and the determination of its amide bond geometry in DMSO solution using NMR techniques. The synthesis of the related derivatives **12** and **13** is also described along with their conformational analysis.



Scheme 1: *Reagents* i) Ph_3CCl; ii) $(COCl)_2$ / DMF (cat.); iii) Et_3N; iv) I_2 / MeOH

The synthesis of compound **11** was achieved as shown in **Scheme 1**. Thus both β-amino ethanethiol **14** and 3-mercaptopropionic acid **15** were reacted with triphenylmethyl chloride to prepare the *S*-protected derivatives **16** and **17** respectively.[8] Acid **17** was then converted to acid chloride **18** using oxalyl chloride and DMF,[9] and reaction of acid chloride **18** with amine **16** in the presence of triethylamine gave cyclization precursor **19**. The deprotection and concomitant cyclization of compound **19** was achieved by the slow addition of a dichloromethane solution of amide **19** to a solution of iodine in methanol.[1,2,10] The standard work-up for this reaction involves the addition of aqueous sodium thiosulfate to destroy excess iodine, followed by evaporation of the methanol and extraction of the product into an organic solvent. In the case of compound **11** however, this failed to produce any product. Eventually, it was discovered that the cyclization reaction was proceeding without difficulty, but that the solubility characteristics of compound **11** were preventing its isolation by this procedure. Therefore, an alternative non-aqueous work-up was developed as detailed in the experimental section, producing compound **11** as an off white amorphous solid. It was

subsequently determined that compound **11** was soluble only in the most polar organic solvents such as DMSO and DMF.

The amorphous nature and poor solubility characteristics of compound **11** have prevented crystals of the compound being obtained, however the eight-membered ring monomeric structure was proven by low and high resolution mass spectrometry, as well as by ^{1}H and ^{13}C nmr. The conformation of compound **11** was determined by nOe experiments in DMSO-d_6, the results of which are shown in **Figure 1**. The observation of an nOe (9% enhancement) between the NH and H_a is particularly characteristic of a *trans*-amide bond, and in the present case is further supported by the nOe seen between the NH and H_b (6% enhancement). A *cis*-amide bond would have been expected to result in a large nOe between H_a and H_c, however no such enhancement was observed. These results clearly indicate that compound **11** possesses a conformation with a *trans*-amide bond.

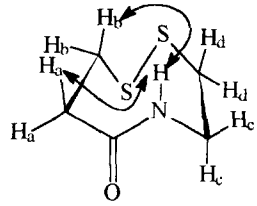
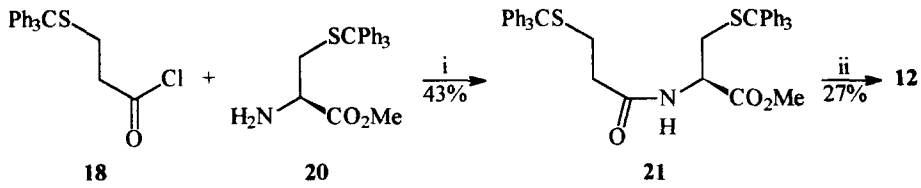


Figure 1: Arrows show important nOe enhancements for compound **11**

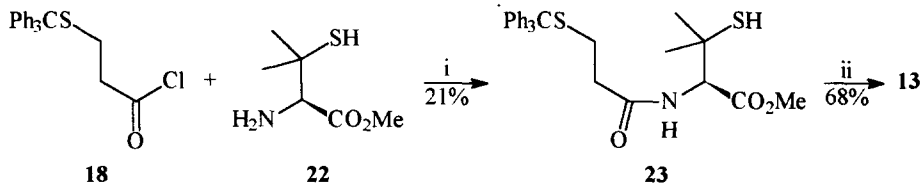
Molecular mechanics calculations also supported the presence of a *trans*-amide bond in compound **11**. A 100 ps molecular dynamics simulation of compound **11** *in vacuo* at 1,000 K with structure sampling every 0.1 ps showed the presence of just four minimum energy conformations after the structures were energy minimized using the MM2 forcefield. Two of these conformations possessed a *trans*-amide bond with the lower energy conformation having the structure shown in **Figure 1**. The other structure with a *trans*-amide bond had the opposite relative configuration of the amide and disulfide bonds. The other two conformations possessed a *cis*-amide bond and were both >10 kCal mol^{-1} higher in energy than the structure shown in **Figure 1**.

A *trans*-amide bond had previously been found in compounds **6-8** which contain two stereocentres of opposite absolute configurations, as well as in compound **9** which contains a single stereocentre but also has two methyl groups adjacent to the amide carbonyl.[1,2] It was therefore of interest to prepare compound **12** to investigate the effect of a single substituent and a single stereocentre on the amide bond geometry. The synthesis of compound **12** was achieved by reaction between acid chloride **18** and methyl (*R*)-*S*-triphenylmethyl-cysteinate[1] **20** to give amide **21** followed by cyclization by treatment with iodine as shown in **Scheme 2**. Compound **12** was again found to be soluble only in highly polar organic solvents, and hence was analyzed by nOe experiments in DMSO. Irradiation of the NH resonance resulted in an enhancement of the signal for one of the hydrogens adjacent to the amide carbonyl, exactly as shown in **Figure 1** for compound **11**. The reverse enhancement of the NH resonance when the CH_2CO protons were irradiated was also observed, and no enhancement of the NCH resonance was observed in this experiment. These results show that compound **12** also exists in DMSO in a conformation with a *trans*-amide bond.



Scheme 2: *Reagents* i) Et_3N; ii) I_2 / MeOH

The influence of substituents adjacent to the disulfide unit was next investigated by the synthesis of compound **13** derived from penicillamine rather than cysteine. Thus reaction of (*R*)-penicillamine methyl ester **22** with acid chloride **18** gave amide **23** which was cyclized by treatment with iodine to give disulfide **13** as shown in **Scheme 3**. Compound **13** was found to be far more soluble in organic solvents than was the case for compounds **11** and **12**, but crystals suitable for X-ray analysis could not be obtained. Hence the conformation of compound **13** was determined by nOe experiments in chloroform. The ^1H NMR spectrum of compound **13** showed three sets of peaks in a ratio of 1 : 4 : 20, thus indicating the presence of three conformations which interconvert slowly on the NMR time scale. Only the conformation of the major diastereomer was determined, however, the minor components were proven to be other conformations of compound **13** since transfer of magnetization to these signals was observed during the nOe experiments. Unlike compounds **11** and **12**, when the NH of compound **13** was irradiated no significant nOe's were observed. However, when H_c (**Figure 2**) was irradiated, enhancements were observed in the signals for both H_a and H_b. These results are characteristic of a conformation possessing a *cis*-amide bond as shown in **Figure 2**. Thus introducing substituents adjacent to the disulfide has a profound effect upon the conformation of the 1,2-dithia-5-azacyclooctan-6-one ring system.



Scheme 3: *Reagents* i) Et_3N; ii) I_2 / MeOH

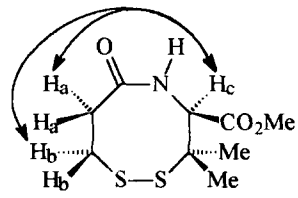


Figure 2: Arrows show important nOe enhancements for compound **13**

CONCLUSIONS

We have prepared 1,2-dithia-5-azacyclooctan-6-one **11**, and have shown that in DMSO solution this compound exists in a single conformation with a *trans*-amide bond. The synthesis of the related heterocycles **12** and **13** has also been achieved. Compound **12** was again found to exist (in DMSO) as a single conformation with a *trans*-amide bond whilst penicillamine derivative **13** was found to exist (in chloroform) as three slowly interconverting conformations, with the major conformation possessing a *cis*-amide bond. Thus it appears that the 'normal' conformation of this ring system possesses a *trans*-amide bond, but that the presence of substituents adjacent to the disulfide can result in a preference for a conformation with a *cis*-amide bond. Our work on the synthesis and applications of this heterocyclic ring system is continuing, and will be reported in due course.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 250 MHz on a Bruker AM250 spectrometer fitted with a ^{1}H-^{13}C dual probe, and were recorded at 293 K in $CDCl_3$ unless otherwise stated. Spectra were internally referenced either to TMS or to the residual solvent peak, and peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), some combination of these, broad (br), or multiplet (m). ^{13}C NMR spectra were recorded at 62.5 MHz on the same spectrometer as ^{1}H NMR spectra, at 293 K and in $CDCl_3$ unless otherwise stated. Spectra were referenced to the solvent peak, and are reported in ppm downfield of TMS. Infra-red spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer, only characteristic absorptions are reported. Mass spectra were recorded by chemical ionization (CI) with ammonia or fast atom bombardment (FAB) on either a VG Autospec spectrometer or a VG Quattro II triple quadrupole spectrometer. Only significant fragment ions are reported, and only molecular ions are assigned. High resolution mass measurements were made on a VG ZAB-E spectrometer. Optical rotations were recorded on an Optical Activity Ltd. Polar 2001 polarimeter, and are reported along with the solvent and concentration in g/100 ml. Melting points are uncorrected.

Flash chromatography[11] was carried out on 40-60 mm mesh silica, thin layer chromatography was carried out on aluminium backed silica plates (0.25 mm depth of silica containing UV254), and the plates were visualized with u.v. light, and/or dodecaphosphomolybdic acid as appropriate. All yields refer to isolated, purified material, and are unoptimized.

N-(2-Triphenylmethylthio)ethyl (3-triphenylmethylthio)propanamide (19)

Acid chloride **18** (10.0 g, 27.3 mmol), amine **16** (8.7 g, 27.3 mmol) and triethylamine (8.3 g, 82.0 mmol) were dissolved in CH_2Cl_2 (200 ml) and the resulting solution stirred at room temperature for 18 hours. The reaction mixture was washed with 10% aqueous sodium carbonate solution (2 x 200 ml), 5% aqueous citric acid solution (2 x 200 ml) and water (2 x 200 ml) after which the organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by washing with cold EtOAc followed by recrystallization from CH_2Cl_2 by the addition of EtOAc, giving amide **19** (8.8 g, 49%) as a white solid. Mp 185-190°C; ν_{max} ($CHCl_3$) 3420 w, 3019 s and 1670cm^{-1} s; δ_H 2.36 (2H, t, *J* 7.4 Hz, CH_2CO), 2.79 (2H, t, *J* 6.3 Hz, CH_2S), 2.89 (2H, t, *J* 7.4 Hz, CH_2S), 3.44 (2H, *pseudo*-q, *J* 6.1 Hz, CH_2N), 5.74 (1H, br, N*H*) and 7.6-7.8 (30H, m,

Ar*H*); δ_C 27.63 (*C*H_2CO), 31.91 (*C*H_2S), 35.62 (*C*H_2S), 38.05 (*C*H_2N), 66.79 (*C*Ph_3), 126.67 (Ar*C*H), 127.92 (Ar*C*H), 129.48 (Ar*C*H), 129.55 (Ar*C*H), 144.97 (Ar*C*) and 170.00 (*C*O); m/z (FAB) 672 (M + Na^+) and 650 (MH^+).

1,2-Dithia-5-azacyclooctan-6-one (11)

Amide **19** (3.0 g, 4.6 mmol) dissolved in CH_2Cl_2 (70 ml) was added over a period of two and a half hours to a solution of iodine (3.5 g, 13.8 mmol) in MeOH (400 ml), after which the solution was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* giving a brown semisolid which was washed thoroughly with EtOAc, CH_2Cl_2, and MeOH, giving compound **11** (0.18 g, 24%) as a beige solid. Mp 110-115°C; ν_{max} (nujol) 3500-3000 br and 1633cm^{-1} m; (Found: C, 36.8; H, 6.0; $C_5H_9NOS_2$ requires: C, 36.8; H, 5.6%); δ_H (DMSO-d_6) 2.4-2.5 (2H, m, CH_2CO), 2.75 (2H, t, *J* 6.6 Hz, CH_2S), 2.88 (2H, t, *J* 6.8 Hz, CH_2S), 3.3-3.4 (2H, m, CH_2N) and 8.16 (1H, t, *J* 5.0 Hz, N*H*); δ_C (DMSO-d_6) 33.77 (*C*H_2CO), 35.02 (*C*H_2S), 37.12 (*C*H_2S), 38.03 (*C*H_2N) and 170.25 (*C*O); m/z (CI, NH_3) 181 (M + NH_4^+), 164 (MH^+) and 132; Found: (CI, NH_3) 181.0469. $C_5H_{13}N_2OS_2$ (M + NH_4^+) requires: 181.0469.

Methyl *N*-(3-triphenylmethylthio)propionoyl-(*R*)-*S*-triphenylmethyl-cysteinate (21)

Acid chloride **18** (1.0 g, 2.7 mmol), methyl (*R*)-*S*-triphenylmethyl-cysteinate **20** (1.1 g, 2.7 mmol) and triethylamine (0.8 g, 8.2 mmol) were dissolved in CH_2Cl_2 (20 ml) and the resulting solution stirred at room temperature for 18 hours. The reaction mixture was washed with 5% aqueous citric acid solution (2 x 20 ml), 10% aqueous sodium hydrogen carbonate solution (2 x 20 ml) and water (2 x 20 ml) after which the organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was subjected to flash chromatography eluting with CH_2Cl_2 / hexane (3 : 1) to give amide **21** (0.8 g, 43%) as a white foaming solid. Mp 70-75°C; $[\alpha]_D^{21}$ +20 (*c* 0.25, $CHCl_3$); ν_{max} ($CHCl_3$) 3418 s, 3060 m, 1742 s, 1676 s and 1215cm^{-1} s; (Found: C, 76.4; H, 5.8; N, 2.0; $C_{45}H_{41}NO_3S_2$ requires: C, 76.8; H, 6.0; N, 2.2%); δ_H 1.9-2.0 (2H, m, CH_2CO), 2.49 (2H, t, *J* 7.4 Hz, CH_2CH_2S), 2.60 (2H, d, *J* 5.1 Hz, CHCH_2S), 3.69 (3H, s, OCH_3), 4.54 (1H, dt, *J* 5.1, 7.7 Hz, NC*H*), 5.73 (1H, d, *J* 7.8 Hz, N*H*) and 7.2-7.5 (30H, m, Ar*H*); δ_C 27.43 (*C*H_2CO), 33.73 (*C*H_2S), 35.38 (*C*H_2S), 50.95 (*C*HN), 52.60 (O*C*H_3), 66.82 (*C*Ph_3), 126.70 (Ar*C*H), 126.88 (Ar*C*H), 126.96 (Ar*C*H), 128.00 (Ar*C*H), 129.46 (Ar*C*H), 129.60 (Ar*C*H), 144.24 (Ar*C*), 144.66 (Ar*C*), 170.49 (*C*O) and 170.73 (*C*O); m/z (FAB) 730 (M + Na^+), 708 (MH^+) and 243.

(*R*)-1,2-Dithia-4-carboxymethyl-5-azacyclooctan-6-one (12)

Amide **21** (1.4 g, 2.0 mmol) dissolved in CH_2Cl_2 (20 ml) was added dropwise to a solution of iodine (1.5 g, 5.9 mmol) in MeOH (300 ml), after which the solution was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* giving a brown semisolid which was washed thoroughly with EtOAc, CH_2Cl_2, and MeOH, giving compound **12** (0.12 g, 27%) as a beige solid. Mp 100-105°C; ν_{max} (nujol) 3300 w, 1735 w and 1641cm^{-1} w; δ_H (DMSO-d_6) 2.5-2.6 (2H, m, CH_2CO), 2.8-2.9 (2H, m, CH_2S), 3.0-3.1 (2H, m, CH_2S), 3.65 (3H, s, OCH_3), 4.56 (1H, dt, *J* 7.6, 5.6 Hz, NCH) and 8.54 (1H, d, *J* 7.6 Hz, N*H*); δ_C (DMSO-d_6) 20.28 (*C*H_2CO), 38.72 (*C*H_2S), 39.91 (*C*H_2S), 56.52 (*C*HN), 57.39 (O*C*H_3), 175.01 (*C*O) and 176.01 (*C*O); m/z (CI, NH_3) 239 (M + NH_4^+), 222 (MH^+) and 123; Found: (CI, NH_3) 222.0259. $C_7H_{12}NO_3S_2$ (M + NH_4^+) requires: 222.0259.

N-(3-Triphenylmethylthio)propionoyl-(*R*)-penicillamine methyl ester (23)

Acid chloride **18** (1.1 g, 3.0 mmol), (*R*)-penicillamine methyl ester **22** (0.5 g, 3.0 mmol) and triethylamine (0.9 g, 9.0 mmol) were dissolved in CH_2Cl_2 (20 ml) and the resulting solution stirred at room temperature for 18 hours. The reaction mixture was washed with 5% aqueous citric acid solution (2 x 20 ml), 10% aqueous sodium hydrogen carbonate solution (2 x 20 ml) and water (2 x 20 ml) after which the organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was subjected to flash chromatography eluting with CH_2Cl_2 / hexane (3 : 1) to give amide **23** (0.3 g, 21%) as a white powder. Mp 45-50°C; ν_{max} ($CHCl_3$) 3415 w, 1736 m, 1677 m and 1215cm^{-1} s; δ_H 1.32 (3H, s, C*H*$_3$), 1.47 (3H, s, C*H*$_3$), 1.61 (1H, br, S*H*), 1.8-2.1 (2H, m, C*H*$_2$CO), 2.4-2.6 (2H, m, C*H*$_2$S), 3.72 (3H, s, OC*H*$_3$), 4.59 (1H, d, *J* 9.4 Hz, NC*H*), 6.19 (1H, d, *J* 9.4 Hz, N*H*) and 7.2-7.4 (15H, m, Ar*H*); δ_C 27.56 (*C*H$_2$CO), 29.43 (*C*H$_3$), 31.00 (*C*H$_3$), 35.60 (*C*H$_2$S), 46.52 (*C*SH), 52.11 (*C*HN), 60.21 (OCH$_3$), 66.87 (*C*Ph$_3$), 126.71 (Ar*C*H), 127.97 (Ar*C*H), 129.58 (Ar*C*H), 144.64 (Ar*C*), 170.76 (*C*O) and 170.83 (*C*O); m/z (FAB) 516 (M + Na$^+$), 493 (M$^+$) and 492.

(*R*)-1,2-Dithia-3,3-dimethyl-4-carboxymethyl-5-azacyclooctan-6-one (13)

Amide **23** (0.4 g, 0.8 mmol) dissolved in MeOH (50 ml) was added dropwise to a solution of iodine (0.6 g, 2.4 mmol) in MeOH (400 ml), after which the solution was stirred at room temperature for 18 hours. Aqueous sodium thiosulfate solution was added until the reaction mixture became colourless, after which the reaction mixture was evaporated *in vacuo*. The residue was redissolved in EtOAc (50 ml) and water (50 ml) and the organic layer was washed with water (50 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by flash chromatography eluting with $CHCl_3$ to give compound **13** (0.13 g, 68%) as a white solid. Mp 90-93°C; $[\alpha]_D^{22}$ +49 (*c* 0.95, $CHCl_3$); ν_{max} (nujol) 3389 w, 1741 m and 1664cm^{-1} m; δ_H 1.16 (3H, s, C*H*$_3$), 1.39 (3H, s, C*H*$_3$), 2.6-2.9 (2H, m, C*H*$_2$), 3.0-3.1 (2H, m, C*H*$_2$), 3.74 (3H, s, OC*H*$_3$), 4.49 (1H, d, *J* 12.0 Hz, NC*H*) and 6.54 (1H, d, *J* 11.9 Hz, N*H*); δ_C 14.55 (*C*H$_3$), 21.64 (*C*H$_3$), 25.12 (*C*H$_2$), 31.03 (*C*H$_2$), 56.01 (OCH$_3$) and 61.96 (*C*HN); m/z (CI, NH_3) 267 (M + NH_4^+) and 250 (MH$^+$); Found: (CI, NH_3) 250.0572. $C_9H_{16}NO_3S_2$ (MH$^+$) requires: 250.0572.

ACKNOWLEDGEMENTS

The authors thank the EU-Erasmus scheme for a grant to SCC, and the EPSRC mass spectrometry service at the University of Wales, Swansea for low and high resolution mass spectra.

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(*Received in UK* 4 *September* 1997; *revised* 15 *September* 1997; *accepted* 18 *September* 1997)