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Synthesis and Configurational Assignment of Some Novel Bicyclic Sulphamidites and Sulphamidates†

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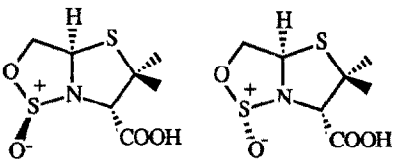
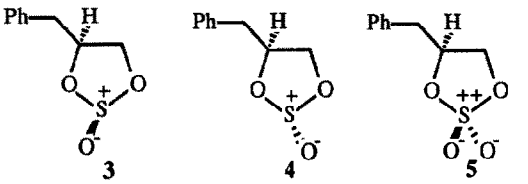
Abstract: (*S*)-Prolinol and 2(*RS*)-piperidine-methanol each react with thionyl chloride to give a pair of diastereoisomeric bicyclic sulphamidites which differ only in their configuration at sulphur. By contrast 2(*RS*)-pyrrolidine-ethanol and 2(*RS*)-piperidine-ethanol each react with thionyl chloride to give single diastereoisomeric products. The configurations of these bicyclic sulphamidites, and the sulphamidates derived from them, have been determined.

Introduction

Synthesis of the diastereoisomeric bicyclic analogues of penicillanic acid (**1** and **2**) has recently been reported, but their instability in aqueous solution effectively ruled out this bicyclic system as the nucleus of a new family of ß-lactam analogues of the penicillins.[1] We have, however, shown that the diastereoisomeric sulphites (**3** and **4**), and the cyclic sulphate diester (**5**) derived from them (by oxidation with ruthenium tetroxide[2]) are sufficiently stable in aqueous solution and are irreversible inhibitors of the serine protease, α-chymotrypsin.[3] This encouraged us to pursue our concept of replacing the ß-lactam ring in the ß-lactam antibiotics by a sulphamidite or sulphamidate ring.



1 **2**



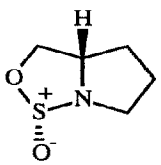
3 **4** **5**

Since monocyclic sulphamidites are also stable in neutral aqueous solution,[4] we decided to investigate the effect of ring size on the stability of bicyclic sulphamidites and report here the synthesis of four new heterocycles, **6** to **9**. Since we first developed a mild and highly efficient method for the oxidation of sulphite diesters to sulphate diesters,[2] and demonstrated how electronic[5] and steric factors[6] could be used to provide complete regiochemical control of ring opening of five and six-membered cyclic sulphate diesters by nucleophiles, the approach has been further developed into a versatile synthetic procedure.[7] Indeed, the cyclic sulphamidate derived from (*S*)-prolinol which we report in this paper has been used to generate homochiral diamines of interest as enantiomeric ligands,[8] while the cyclic sulphamidate derived from N-benzyl-serine *t*-butyl ester has been shown to be a valuable intermediate for the synthesis of novel amino-acids.[9] Both of these contributions are reported in this issue, providing further testimony to this assertion.

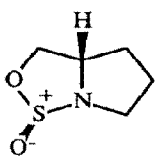
† In this report cyclic sulphamidite will be used to describe a 2-oxo-1,2,3-oxathiazolidine or a 2-oxo-tetrahydro-1,2,3-oxathiazine ring; cyclic sulphamidate will be used to denote the corresponding 2,2-dioxo ring systems.

Results and Discussion

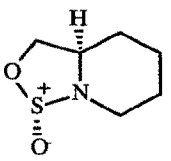
The bicyclic sulphamidites **6** to **9** were synthesised from (*S*)-prolinol, 2(*RS*)-piperidine-methanol, 2(*RS*)-pyrrolidine-ethanol and 2(*RS*)-piperidine-ethanol respectively by reaction with thionyl chloride in the presence of pyridine.[10] After preliminary purification of the diastereoisomers of **6** by fractional distillation, they were separated by gas-liquid chromatography. A good separation was achieved (9 min. difference in the retention times) on an Ov17 column but on scaling up to a preparative column a good deal of decomposition occurred. By lowering the column and injection temperatures, however, the major isomer was isolated. An attempt to separate the diastereoisomers of **7** by gas chromatography was only partially successful, the maximum difference in retention times obtained being only 24 s, but they were successfully separated by HPLC.



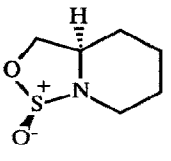
6a



6b



7a



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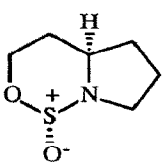

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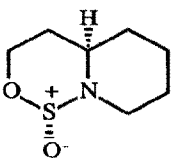

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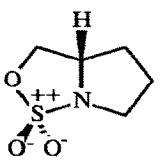

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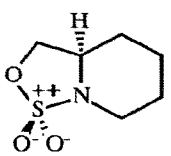

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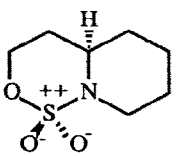

12

In order to determine whether the diastereoisomerism in **6** and **7** was caused by differences of configuration at sulphur or nitrogen (the latter giving rise to *cis* and *trans* ring junctions) the mixture of diastereoisomers of **6** and **7** were oxidised with ruthenium tetroxide (generated *in situ* from ruthenium(IV) oxide hydrate and sodium periodate). The diastereoisomers of **6** were converted into a single product which was shown to have all the properties expected of the bicyclic sulphamidate **10**. Similarly the diastereoisomers of **7** were converted to a single product which was shown to have all the properties expected of the bicyclic sulphamidate **11**. For comparison the single stereoisomer of **9** was oxidised with ruthenium tetroxide and the bicyclic sulphamidate **12** obtained. All three sulphamidates, **10**, **11**, and **12** have a number of properties in common, e.g. all possessed the characteristic $>SO_2$ symmetric and antisymmetric stretching frequencies, which are not of course observed in the cyclic sulphamidites. Clearly the diastereoisomers of **6** and **7** are epimeric at sulphur as depicted in **6a** and **6b**, **7a** and **7b**.

The assignment of the configuration at both sulphur and nitrogen for the diastereoisomers **6a** and **6b**, **7a** and **7b** as well as for the single stereoisomers **8** and **9** was made by a detailed analysis of their ^{1}H nmr spectra, together with double resonance experiments and the application of the shift reagent, Eu(fod)$_3$.

The ^{1}H nmr spectrum of the bicyclic sulphamidite **9** is shown in Fig.1. The assignment of the resonances are shown in the caption in the Figure. The coupling constants and the molar isotropic shifts caused by Eu(fod)$_3$ established that the two rings adopt 'chair' conformations with the S^+-O^- group in an axial position. As expected the data are in accord with the *trans* fused ring system. There is a great deal of evidence to support a stereoelectronic (generalised anomeric) effect in sulphites leading to a marked preference for the conformation with the S^+-O^- group axial.[11] This is perhaps most clearly demonstrated for the parent six-membered cyclic sulphite, trimethylene sulphite, which was shown by X-ray crystallography to adopt a 'chair' conformation with the S^+-O^- bond axial.[12] Under the conditions used for the synthesis of the bicyclic sulphamidites **6** to **9** it seems likely that the presence of pyridine (and/or its hydrochloride generated during the reaction) allows any kinetic product formed to be equilibrated with the thermodynamic product by a ring opening/ring closing mechanism.

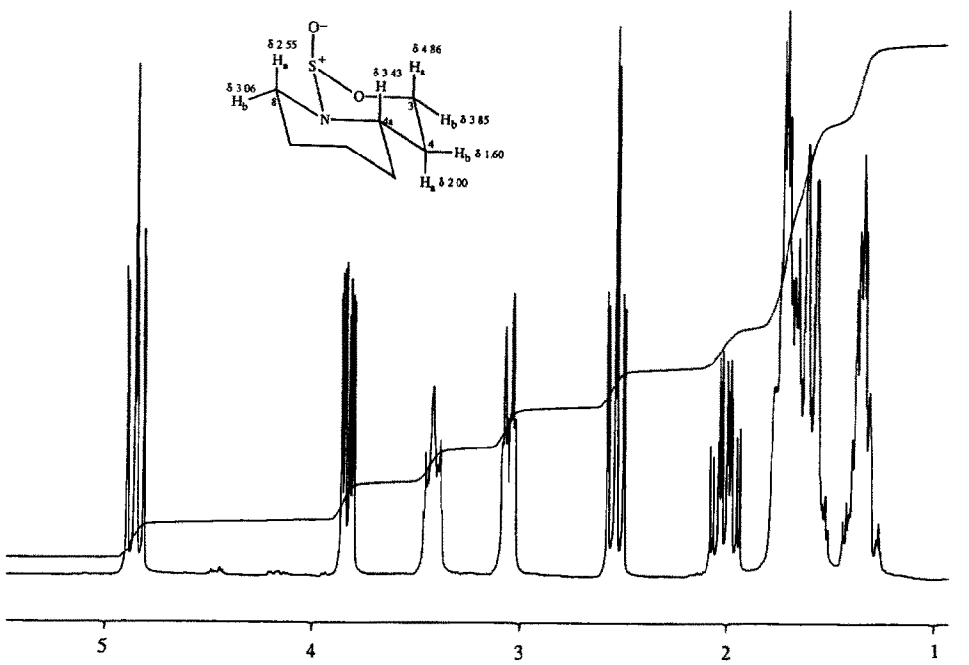

Fig. 1. The ^{1}H nmr spectrum of the bicyclic sulphamidite **9.** The key resonances are assigned in the caption. Coupling constants are given in the experimental section.

The ^{1}H nmr spectrum of the bicyclic sulphamidite **8** is shown in Fig.2. The assignment of the resonances are shown in the caption in Fig.2. The coupling constants together with the effect of the shift reagent Eu(fod)$_3$ established that the six membered ring is in the 'chair' conformation with the S^+-O^- group in an axial position and that the ring junction is *trans* .

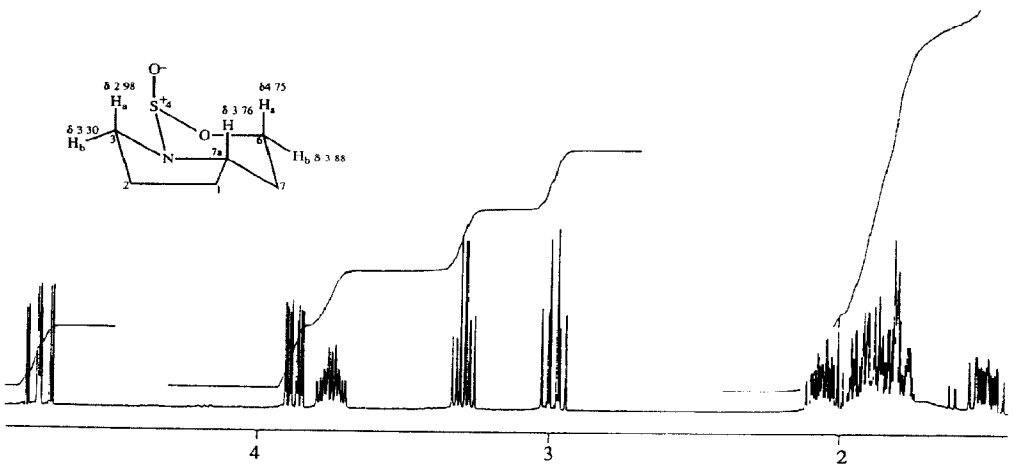

Fig. 2. The ^{1}H nmr spectrum of the bicyclic sulphamidite **8.** The key resonances used for the configurational analysis are shown in the caption. Coupling constants are given in the experimental section.

The ^{1}H nmr spectrum of a mixture of the diastereoisomeric bicyclic sulphamidites **7a** and **7b** is shown in Fig.3. The 17:10 ratio of the diastereoisomers is the normal reaction product ratio, but in a preliminary preparation where the yield was low, a ratio about 11:1 was obtained, probably due to selective decomposition of the minor isomer. This happenstance combined with the knowledge that the two diastereoisomers differed only in the configuration at sulphur, facilitated the analysis of the spectra. The assignment of the key resonances together with the molar isotropic shifts caused by Eu(fod)$_3$ shows the major isomer has the *trans* ring junction and a pseudo-axial S^+-O^- bond, and the minor isomer has the *trans* ring junction with a pseudo-equatorial S^+-O^- bond.

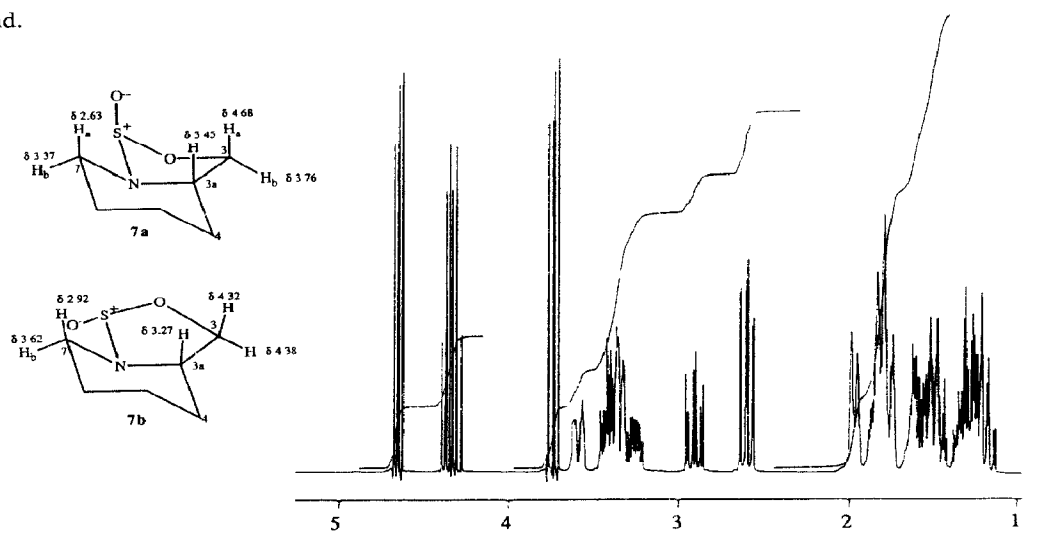

Fig. 3.The ^{1}H nmr spectrum of the bicyclic sulphamidites **7a** and **7b** in the ratio 17:10.The key resonances used for the configurational analysis are shown in the caption. Coupling constants are given in the experimental section.

The ^1H nmr spectrum of a mixture of the diastereoisomeric bicyclic sulphamidites **6a** and **6b** is shown in Fig.4. The proximity of some of the resonances precluded a complete set of double resonance experiments on the mixture, but the major isomer (which had been isolated by gas chromatography) was investigated in this way. Although the diastereoisomers only differ in the configuration at sulphur, the coupling constants did not provide unambiguous evidence for the conformation of the five membered rings and left the stereochemistry at the ring junction in doubt.

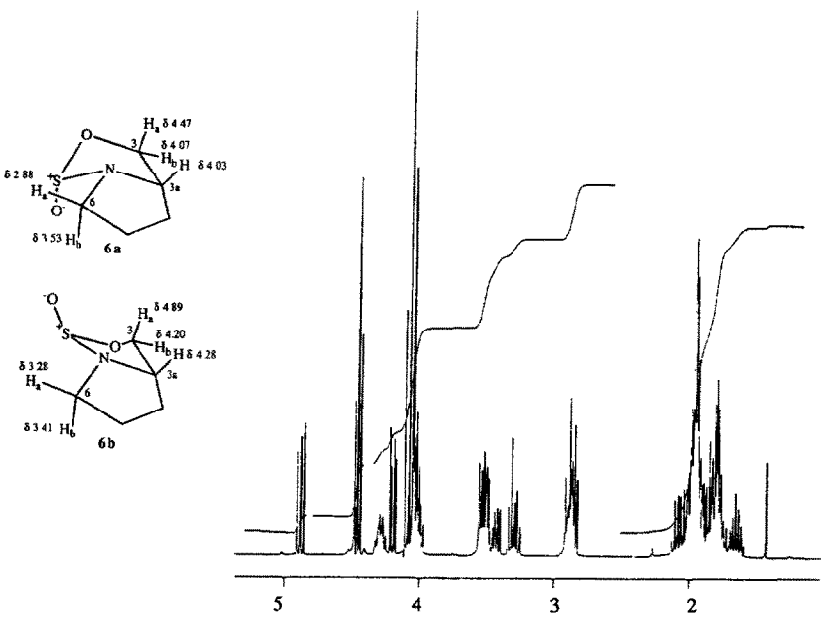

Figure 4. The ^1H nmr spectrum of the bicyclic sulphamidite **6a** and **6b** in the ratio 3:1. The key resonances are shown in the caption. Coupling constants are given in the experimental section.

The ^1H nmr spectrum of the sulphamidate **10** (derived from **6a** and **6b**, *vide supra*) is shown in Fig.5. It was assumed that the sulphamidate ring would take up a twist-envelope like conformation with sulphur as the flap.[13] Although this allowed for some conformational flexibility the restrictions allowed the range of coupling constants to be calculated for 3-H_a and 3-H_b with the ring junction proton 3a-H. The predictions only matched the observed coupling constants if the ring fusion was *cis*. Thus the sulphamidate **10** was assigned the *cis* ring junction and by inference the diastereoisomeric sulphamidites **6a** and **6b** were assigned the *cis* ring junction; this conclusion was supported by the molar isotropic shifts caused by Eu(fod)$_3$. For the major diastereoisomeric sulphamidite, the signals at δ 3.53 and δ 4.07 showed the largest molar isotropic shifts on addition of Eu(fod)$_3$, while the signal at δ 4.03 had the smallest molar isotropic shift. Since Eu(fod)$_3$ ligates the exocyclic oxygen of sulphite diesters,[2] this indicates that the major isomer has the S^+-O^- and ring junction C-H bonds in a *trans* relationship and hence it is assigned the configuration shown in **6a**. On addition of Eu(fod)$_3$ the signals of the minor diastereoisomer at δ 4.89 and δ 4.28 showed the largest molar isotropic shifts indicating that the S^+-O^- and ring junction C-H bonds have a *cis* relationship and hence it is assigned the configuration shown in **6b**.

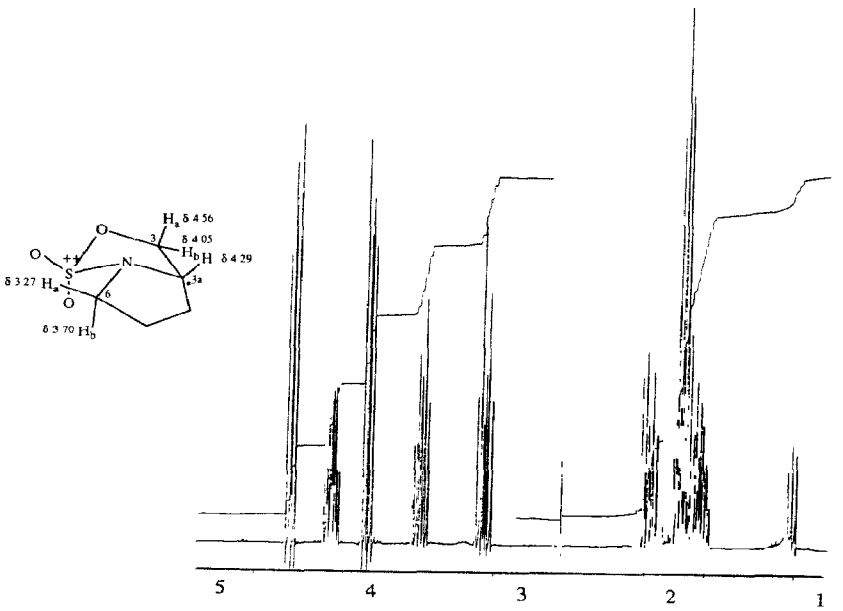

Fig. 5. The ^1H nmr spectrum of the bicyclic sulphamidate **10**. The resonances used for the configurational analysis are shown in the caption. Coupling constants are given in the experimental section.

Conclusions

The configurational analyses of the bicyclic sulphamidites **6** to **9** indicate that when the sulphamidite is part of six-membered ring a single diastereoisomer is formed with the S^+-O^- group in an axial position. When five-membered sulphamidites are prepared, both epimers at sulphur are formed presumably because of the more similar thermodynamic stability. It is pertinent to note, however, that the ring junction only adopts the *cis* configuration in the systems studied when the five-membered sulphamidite is fused to a five-membered ring, as in the diastereoisomers **6a** and **6b**, which is the stereochemistry found at the ring junction in the ß-lactam antibiotics. A preliminary study of the stability of the diastereoisomers **6a** and **6b** has shown that, like the bicyclic sulphamidites **1** and **2**, they are rapidly hydrolysed in aqueous dimethyl sulphoxide at ambient temperatures.

Experimental Procedures

Synthesis of Diastereoismers of (S)-1-Oxo-1-thia-2-oxa-6a-azaperhydropentalene (6a and 6b)

(+)-(2*S*)-pyrrolidine-methanol {(*S*)-prolinol} (4.040g, 40mmol) and dry pyridine (12.8ml, 80mmol) were dissolved in dry benzene (100ml) in a flame dried apparatus. To this was added, dropwise with vigorous stirring for 1h, a solution of freshly distilled thionyl chloride (3ml, 40mmol) in dry benzene (30ml) using an ice/salt bath at 0 to -10°C. The precipitate of pyridine hydrochloride produced was filtered off and the filtrate washed successively with aqueous sodium hydrogen carbonate (200ml), dilute hydrochloric acid (0.1M, 200ml) and water (200ml). The benzene extract was dried (anhydrous magnesium sulphate) and evaporated to yield an

oil, which was purified by distillation under reduced pressure to yield a colourless oil, which was a mixture of isomers in 3:1 ratio of the sulphamidite (**6**) (2.26g, 38%), b.p. 58-60°C (0.7mm Hg) (Found C,40.6; H,6.5; N,9.7. $C_5H_9NO_2S$ requires C,40.8; H,6.2; N,9.5%); $[\alpha]_D^{20}$ -128 (c=0.1 in $CHCl_3$), $\nu_{max.}$(CCl_4) 1165 and 1185cm^{-1} (SO); δ_H (300MHz, $CDCl_3$) Major isomer **6a**: 4.47(1H, dd,J=6.0 and 9.3Hz,3-H_a), 4.07(1H, t,J=9.2Hz, 3-H_b), 4.03(1H, m, 3a-H), 3.53(1H, m, 6-H_b), 2.88(1H, m, 6-H_a), 2.05-1.75(4H, complex, 4-$H_{a,b}$ and 5-$H_{a,b}$) Minor isomer **6b**: 4.89(1H, dd,J=9.6 and 7.5Hz, 3-H_a), 4.28(1H, m, 3a-H) 4.20(1H, dd,J=9.2 and 2.0Hz, 3-H_b), 3.41(1H, m, 6-H_b), 3.28(1H, m, 6-H_a), 2.15-1.60(4H, complex, 4-$H_{a,b}$ and 5-$H_{a,b}$); $^m/_z$ (chemical ionisation, NH_3) 148(M^++1, 100%), 117 (8, M-CH_2O).

*Gas chromatographic Separation of the Diastereoisomeric Sulphamidites (**6a** and **6b**)*

The separation of the mixture of the sulphamidite diastereoisomers (**6**) was investigated using gas chromatography. On analytical columns, injections of 2µl of a 5% solution of substrate in acetone were used. With an Ov17 column (7ft, 10% weight, chromosorb W support), using an injection temperature of 200°C, a column temperature of 160°C and a detector temperature of 200°C two peaks were clearly seen, the first with a retention time of 8min 20s and the second with a retention time of 17min 27s. Initial investigations on the preparative machine used injections of 10µl of a 50% solution of substrate in acetone. Using a Ov17 column (15ft, 15%wt., chromosorb A support) with a column temperature of 230°C one large peak was recorded together with a large "tailing". Using a variety of other columns (Carbowax 20M, Ov225, SE 30) only one peak was obtained. The amount of tailing was reduced on lowering the column and injection temperatures and final preparative chromatography used the Ov17 column with a column temperature of 210°C and an injection temperature of 215°C. The product corresponding to the peak with retention time 8mins 30s was isolated. Analysis by ^{1}H NMR showed it to be the major isomer (**6a**).

Synthesis of the Diastereoisomers of 1-Oxo-1-thia-2-oxa-7a-azaperhydroindene (**7**)

2(*RS*)-piperidine-methanol (4.607g, 40mmol) and dry pyridine (12.8ml, 40mmol) were dissolved in dry benzene (100ml) in flame-dried apparatus. To this was added, dropwise with vigorous stirring for 2h, a solution of freshly distilled thionyl chloride (3ml, 40mmol) in dry benzene (30ml) using an ice/salt bath at 0 to -10°C. The precipitate of pyridine hydrochloride produced was filtered off and the filtrate was washed successively with aqueous sodium hydrogen carbonate (200ml), dilute hydrochloric acid (0.1M, 200ml) and water (200ml). The benzene extract was dried (anhydrous magnesium sulphate) and evaporation of solvent yielded a yellow-brown oil. Flash chromatography on silica gel with dichloromethane + 2% ethyl acetate as eluant gave a very pale yellow oil (R_f=0.37) which was purified further by distillation under reduced pressure to yield a colourless oil, which was a mixture of isomers in 17:10 ratio of the sulphamidite (**7**) (4.38g, 68%), b.p. 68°-70°C (0.7mm Hg) (Found C,44.5; H,7.1; N,8.5. $C_6H_{11}NO_2S$ requires C,44.7; H,6.9; N=8.7%); n_D^{19} 1.5045; υ_{max} (CCl_4) 1165cm^{-1} (SO); δ_H (300MHz , $CDCl_3$) Major isomer **7a**: 4.68(1H, t, J=6.5 and 7.5Hz, 3-H_a), 3.76(1H, dd, J=7.5 and 10.5Hz, 3-H_b), 3.45(1H, m, J=3 and 6.5 and 10.5Hz, 3a-H), 3.37(1H, m, J=2.5 and 13Hz, 7-H_b), 2.63(1H, t of d, J=3 and 11.5Hz, 7-H_a), 1.96-1.26(6H, 4-$H_{a\,b}$, 5-$H_{a\,b}$ and 6-$H_{a\,b}$). Minor isomer **7b**: 4.38(1H, m, J=11.5 and 7.5Hz, 3-H_b), 4.32(1H, m, J=7.5 and 6.5Hz, 3-H_a), 3.62(1H, m, 7-H_b), 3.27(1H, m, J=3 and 6.5 and 11.5Hz, 3a-H), 2.92(1H, t of d, J=4.5 and 12Hz, 7-H_a),1.87-1.22(6H, complex m,4-$H_{a\,b}$, 5-$H_{a\,b}$ and 6-$H_{a\,b}$); $^m/_z$ (electron impact) 161(M^+, 29%), 131(100, M^+-CH_2O); (chemical ionisation, NH_3) 162(M^++1, 100%), 179(26, M^++1+NH_3), 131(4, M^+-CH_2O).

Separation of the Diastereoisomeric Sulphamidites (7a and 7b)

The separation of the isomers of sulphamidite (**7**) was attempted using gas-column chromatography. Analytical investigations using 2μl injections of a 5% solution in acetone. Using a Carbowax 20M column (5ft, 10% wt) and an Ov17 column (5ft, 10%. wt, Chromosorb W support) only one peak was observed. Using a Ov225 column (8ft, 3% wt., chromosorb Q support) with a column temperature of 150°C two partially resolved peaks were observed with a mean retention time of 8mins 12s, with a 24s separation of the two peaks. Increasing the column length and lowering the column temperature gave no improvement in the resolution.

Separation of the isomers was, however, achieved by reverse phase HPLC on a C_{18} ODS 2 column with acetonitrile/water (55:45 v/v) at a flow rate of 1.8ml/min. The major isomer had a retention time of 22.14 min. and the minor isomer 29.38 min. (ratio approximately 3:1). The nmr spectra of the isolated diastereoisomers were as indicated above for the mixture.

Synthesis of 4-Oxo-4-thia-5-oxa-3a-azaperhydroindene (8)

2(*RS*)-pyrrolidine-ethanol (4.607g, 40mmol), prepared by the method of Nikishin *et al.*,[14] and dry pyridine 12.8ml, 80mmol) were dissolved in dry benzene (100ml) in flame-dried apparatus. To this was added, dropwise with vigorous stirring for 1h, a solution of freshly distilled thionyl chloride (3ml, 40mmol) in dry benzene (30ml) using an ice/salt bath at 0 to -10°C. The precipitate of pyridine hydrochloride was filtered off and the filtrate waswashed successively with aqueous sodium hydrogen carbonate (200ml), dilute hydrochloric acid (0.1M, 200ml) and water (200ml). The benzene extract was dried (anhydrous magnesium sulphate) and evaporated to yield a very pale yellow oil. Flash chromatography on silica gel with dichloromethane + 2% ethyl acetate as eluant gave a colourless oil (R_f=0.24) which was purified further by distillation under reduced pressure yielding the sulphamidite (**8**) (2.00g, 31%), b.p. 70-75°C (0.9mm Hg) (Found C,44.7; H,7.1; N, 8.7. $C_6H_{11}NO_2S$ requires C,44.7; H,6.9; N,8.7%); n_D^{19} 1.5045; υ_{max} (CCl_4) 1145cm^{-1} (SO); δ_H (300MHz, $CDCl_3$) 4.75(1H, ddd, J=3 and 12 and 14.5Hz, 6-H_a), 3.88(1H, ddd, J=2 and 5 and 12Hz, 6-H_b) 3.76(1H, m, J=3.5 and 7 and 10.5Hz, 7a-H), 3.30(1H, dt, J=5 and 9Hz, 3-H_b), 2.98(1H, dt, J=6 and 9Hz, 3-H_a), 2.12-2.02(1H, m, 1-H_a), 1.97-1.74(4H, complex m, 2-$H_{a,b}$ and 7-$H_{a,b}$), 1.56-1.43(1H, m, J=7.5 and 10 and 14.5Hz, 1-H_b); $^m/_z$ (chemical ionisation, NH_3) 162(M^++1, 100%).

Synthesis of 1-Oxo-1-thia-2-oxa-8a-azaperhydronaphthalene (9)

2(*RS*)-piperidine-ethanol (5.168g, 40mmol) and dry pyridine (12.8ml, 80mmol) were dissolved in dry benzene (100ml) in a flame-dried apparatus. To this was added, dropwise with vigorous stirring for 1h, a solution of freshly distilled thionyl chloride (3ml, 40mmol) in dry benzene (30ml) using a ice/salt bath at 0 to -10°C. The precipitate of pyridine hydrochloride produced was filtered off and the filtrate was washed successively with aqueous sodium hydrogen carbonate (200ml), dilute hydrochloric acid (0.1M, 200ml) and water (200ml). The benzene extract was dried (anhydrous magnesium sulphate) and evaporation of solvent yielded a brown oil. Flash chromatography on silica gel with dichloromethane + 2% ethyl acetate as eluant gave a very pale yellow oil (R_f=0.32). Further purification by microdistillation under reduced pressure yielded the sulphamidite (**9**) as a colourless oil(2.96g, 42%), b.p. 72°C (1mm Hg), (Found C, 47.9; H, 7.7; N, 7.9. $C_7H_{13}NO_2S$ requires C, 48.0; H, 7.5; N, 8.0%); n_D^{19} 1.5070; υ_{max} (CCl_4) 1135, 1150cm^{-1} (SO); δ_H (300MHz, $CDCl_3$) 4.86 (1H, ddd, J=2.5 and 11.5 and 13Hz, 3-H_a), 3.85(1H, ddd, J=1.5 and 5.0 and 11.5Hz, 3-H_b), 3.43 (1H, m, 4a-H), 3.06 (1H, dt, J=1 and 11.5Hz, 8-H_b), 2.55(1H, dt, J=2.5 and 11.5Hz, 8-H_a), 2.02(1H, m, J=5 and 11.5 and 13.5Hz, 4-H_a), 1.79-1.62 (4H, complex, 7-$H_{a,b}$ and 6-$H_{a,b}$), 1.60 (1H,

m, J=2.5 and 13.5Hz, 4-H_b), 1.43-1.27 (2H, complex, 5-$H_{a,b}$); $^m/_z$ (electron impact) 175(M^+, 6%), 147(7, M^+-C_2H_4); (chemical ionisation, NH_3) 176(M^++1, 100%).

Oxidation of the Diastereoisomers of 1-Oxo-1-thia-2-oxa-6a-azaperhydropentalene (6a and 6b)

To a solution of sodium periodate (0.168g, 0.88mmol) in water (0.1ml) was added ethanol-free chloroform (1.5ml, distilled from phosphorus pentoxide) and ruthenium (IV) oxide hydrate (0.64g, 0.38ml) with rapid stirring. After conversion of the solution from black to pale green (~10min) the solution was cooled with an ice-bath to 0°C. A solution of the isomeric sulphamidites (**6a** and **6b**) (0.048g, 0.33mmol) in chloroform (1ml) was then added rapidly and with stirring. After a reaction time of 10min., propan-2-ol (2ml) was added to quench the reaction mixture which was then diluted with chloroform (20ml). Filtration through celite gave a pale orange solution which was dried (anhydrous magnesium sulphate) and the solvent evaporated to give a viscous oil, which was purified by flash chromatography on silica gel using ether as the eluant to give 1,1-dioxo-1-thia-2-oxa-6a-azaperhydro-pentalene (**10**), (0.026g, 48%) as colourless crystals, m.p.47-48°C(from ether), υ_{max} (CCl_4) 1185(SO_2 symm.), 1390cm^{-1} (SO_2 asymm.); δ_H (250MHz, $CDCl_3$) 4.56(1H, dd, J=7.0 and 8.5Hz, 3-H_a), 4.29(1H, m, J= 7.0 and 6.0 and 4.0Hz, 3a-H), 4.05(1H, dd, J=6.0 and 8.5Hz, 3-H_b), 3.70(1H, m,J=11.2 and 5.6Hz, 6-H_b), 3.27(1H, m,J=11.2 and 7.0Hz, 6-H_a), 2.26-1.77(4H, complex, 5-$H_{a,b}$ and 4-$H_{a,b}$).

Oxidation of the Diastereoisomers of 1-Oxo-1-thia-2-oxa-7a-azaperhydroindene (7a and 7b)

To a solution of sodium periodate (0.186g, 0.88mmol) in water (0.1ml) was added ethanol-free chloroform (1.5ml, distilled from phosphorus pentoxide) and ruthenium(IV) oxide hydrate (0.064g, 0.38mmol) with rapid stirring. The black ruthenium(IV) oxide was converted into a pale green solution of ruthenium tetroxide in 15 to 20 min. after which the solution was cooled with an ice-bath to 0°C. A solution of the isomeric sulphamidites (**7a** and **7b**) (0.052g, 0.32mmol) in chloroform (1ml) was then added rapidly and with stirring. The solution was warmed to room temperature and the reaction was followed by thin-layer chromatography on silica, using dichloromethane + 2% ethyl acetate as eluant. After 1h, propan-2-ol (2ml) was added to quench the reaction mixture which was then diluted with chloroform (20ml); t.l.c. had shown the reaction to be essentially complete after 20min. After filtration through celite the solution was dried (anhydrous magnesium sulphate) and evaporation of solvent gave a viscous oil. This was purified by flash chromatography on silica gel using ether as eluant to give the product 1,1-dioxo-2-oxa-1-thia-7a-azaperhydroindene (**11**) (0.033g, 58%), R_f (CH_2Cl_2 + 2% EtOAc) 0.44; υ_{max} (thin film) 1180(SO_2 symm.), 1340cm^{-1} (SO_2 assym.); δ_H (300MHz, $CDCl_3$) 4.58(1H, dd,J=7.7 and 5.8Hz, 3-H_a), 4.19(1H, dd,J=9.9 and 7.7Hz, 3-H_b), 3.57(1H, br d,J=11.6Hz, 7-H_b), 3.45(1H, complex m, 3a-H), 2.77(1H, dt,J=11.8Hz and 3.1Hz, 7-H_a), 1.97-1.25(6H,complex m, 4-$H_{a,b}$ and 5-$H_{a,b}$ and 6-$H_{a,b}$).

Oxidation of 1-Oxo-1-thia-2-oxa-8a-azaperhydronaphthalene (9)

To a solution of sodium periodate (0.186g, 0.88mmol) in water (0.1ml) was added ethanol-free chloroform (1.5ml) and ruthenium(IV) oxide hydrate (0.064g, 0.38mmol) with rapid stirring. After the solution had changed colour from black to pale green, in approximately 15 min., the solution was cooled to 0°C with an ice-bath. A solution of the sulphamidite (**9**) (0.056g, 0.32mmol) in chloroform (1ml) was added rapidly and with stirring. Following the reaction by t.l.c. on silica gel using dichloromethane + 2% ethyl acetate as eluant showed the reaction to be complete after 18min. The reaction mixture was quenched with propan-2-ol (2ml) and diluted with chloroform (20ml). This was filtered through celite, dried (anhydrous magnesium sulphate) and evaporated. Purification by flash chromatography on silica gel using ether as eluant gave the product 1,1-dioxo-2-oxa-1-thia-8a-azaperhydronaphthalene (**12**) (0.028g, 45%), R_f (CH_2Cl_2 + 2% EtOAc) 0.55; υ_{max} (CCl_4)

1175 (>SO_2 symm.), 1375cm^{-1} (>SO_2 assym.); δ_H (300MHz, $CDCl_3$) 4.73(1H, ddd,J=12.8, 11.5 and 2.8Hz, 3-H_a), 4.47(1H, ddd,J=11.5, 5.0 and 2.0Hz, 3-H_b), 3.60(1H,complex m, 4a-H), 3.47(1H,complex m, 8-H_b), 2.97(1H, ddd,J=11.5, 9.0 and 5.0Hz, 8-H_a), 2.29-2.13(1H, m,J=13.8, 11.3 and 5.0Hz, 4-H_a), 1.90-1.39(7H, complex, 4-H_b and 5-$H_{a,b}$ and 6-$H_{a,b}$ and 7-$H_{a,b}$).

Shift reagent studies on sulphamidites (6) to (9)

Sulphamidites (**6**) (0.0368g, 2.5x10^{-4}mol), (**7**) (0.0403g, 2.5x10^{-4}mol), (**8**) (0.0403g, 2.5x10^{-4}mol), (**9**) (0.0438g, 2.5x10^{-4}mol) were each dissolved in deuterochloroform (5ml) to give the stock solutions A. Identical molar quantities of these sulphamidites together with $Eu(fod)_3$ (0.2593g, 2.5x10^{-4}mol) were dissolved in deuterochloroform (5ml) to give the stock solutions B. For each system the solutions A and B were added together in appropriate proportions to give samples with $Eu(fod)_3$: sulphamidite ratios ranging from 0 to 1.0 in increments of 0.1. Each of these samples was analysed by ^1H NMR (300MHz) and the corresponding peak shifts determined. The results were plotted in graphical form and were subsequently analysed using a least-squares regression of δ versus the $Eu(fod)_3$: sulphamidite ratio; this gave the molar isotropic shifts for each proton in the system.

Qualitative Study of the Stability of Sulphamidites (6 to 9) in water / dimethyl sulphoxide

Each sulphamidite (2.5x10^{-4}mol) was dissolved in d_6-DMSO (0.5ml) and D_2O (3ml) at ambient temperature and kept for 30min. The water was removed *in vacuo* at or below ambient temperature and the resulting sample was analysed by ^1H NMR.

Sulphamidites (**6a** and **6b**) were quantitatively hydrolysed to the amino-alcohol.

Sulphamidite (**7a** and **7b**) were quantitatively recovered, i.e. no hydrolysis was observed.

Sulphamidite (**8**) was about 70% hydrolysed.

Sulphamidite (**9**) was quantitatively hydrolysed.

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