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X=Y-ZH SYSTEMS AS POTENTIAL 1,3-DIPOLES. PART 18.[1] CYCLOADDITION OF 4π-SULPHINYLAMINOMETHAMIDE SPECIES GENERATED FROM α-AMINO ACIDS AND α-AMINO ACID ESTERS BY SULPHONYL GROUP TRANSFER.[2] X-RAY CRYSTAL STRUCTURE OF 4-ISO-PROPYL-7-METHYL-2-THIA-6,8-DIOXO-3,7-DIAZOBICYCLO[3.3.0]OCTANE S-OXIDE.

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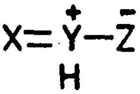
Abstract. Sulphonyl group transfer from N-sulphonyl aniline to α-amino acids followed by decarboxylation affords 4π-sulphinylaminomethamide species with an anti-configuration stereospecifically. Analogous reactions with α-amino acid esters occur at room temperature in toluene and afford carbomethoxy substituted 4π-sulphinylaminomethamide species non-stereoselectively. Both types of 4π-species are trapped in good yield in [3+2]-cycloaddition reactions by N-methylmaleimide. The mechanisms of the reactions are discussed and evidence presented in favour of a 4π-anionic species for the reactions involving α-amino acid esters. A novel cyclic intermediate is invoked to account for the stereospecific formation of anti-4π-sulphinylaminomethamide species from α-amino acids. These latter processes also probably involve 4π-anionic species.

Our recognition of a new type of prototropy, 1,2-prototropy, in X=Y-ZH systems provides a simple entry into a series of nitrogen protonated 1,3-dipoles (1,Y=N) from imines[3,4], hydrazones[5], and oximes[6]. This simple concept of 1,2-prototropy is capable of extension in a number of ways, e.g. to metallo-1,3-dipoles.[7] A potentially direct extension of this idea involves W=X=Y-ZH systems (2). However substrates of type (2), in which W is an electronegative atom, may be less likely to participate in 1,2-prototropy (2)$\rightleftharpoons$(3) owing to the reduced basicity of Y in (2). We have previously demonstrated the effect of imine basicity on the 1,2-prototropy that occurs in arylidene imines of α-amino acid esters (5) where the electronic nature of R influences the rate of 1,2-prototropy.[8] Conversely (2), when W is an electronegative atom, should show an enhanced tendency to form 4π-anions (4) in the presence of a suitable base. Again, such effects have been observed for (5).[7] Similar arguments apply to a decarboxylative route from (6), with (4) possibly being more favoured than (3) if W is an electronegative atom. However, the decarboxylation of (6) might proceed via cyclisation to (7) followed by loss of carbon dioxide in a 1,3-cycloreversion generating (3). We have shown that this latter route, via oxazolidin-5-ones (8), operates in the decarboxylation of arylidene imines of α-amino acids.[9] If, on the other hand, W



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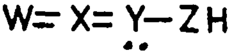

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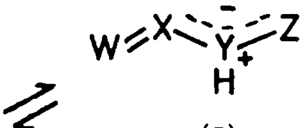

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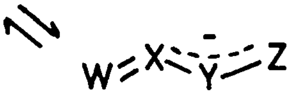

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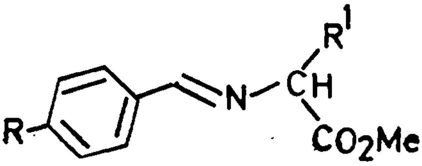

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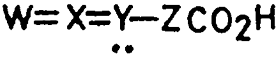

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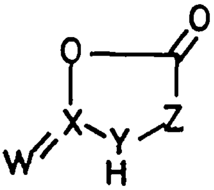

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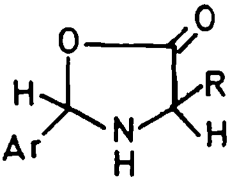

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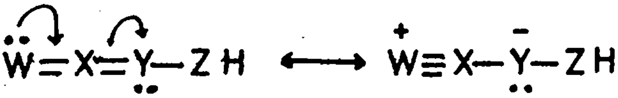

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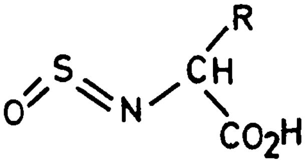

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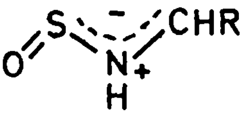

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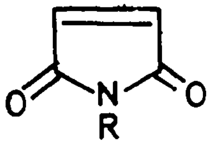
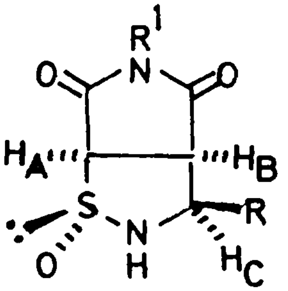


(13) a. R = Me
b. R = $CH_2CH{=}CH_2$



(14) a. R^1 = Me
b. R^1 = $CH_2CH{=}CH_2$

is a donor atom, i.e. (9), it should promote 1,2-prototropy.

Reaction of α-Amino Acids with N-Sulphonylaniline

Our attention focussed initially on a decarboxylative route since it had been reported that N-sulphonylaniline (PhN=S=O) reacts with α-amino acids [$H_2NCH(R)CO_2H$] at 25-80°C in dimethyl sulphoxide to give aldehydes (RCHO).[10] An initial sulphonyl group transfer to give aniline and (10) was proposed but no mechanism was suggested for the subsequent steps leading to aldehyde.[10]. The proposed intermediate (10) was, we believed, potentially a precursor of (11) or (12) upon decarboxylation.

When α-amino acids were heated in DMSO (80°C) with N-sulphonylaniline (PhN=S=O) and a maleimide, (13a) or (13b), decarboxylation occurred and a series of cycloadducts (14) was obtained in good yield (Table 1). These reactions are stereospecific, giving rise to a single cycloadduct in each case. The all cis-stereochemistry of H_A, H_B and H_C in the cycloadducts (14) is readily established by nuclear Overhauser enhancement (n.O.e.) difference spectroscopy. A typical n.O.e. study ($CDCl_3$) on (14a, $R=Bu^i$) illustrates the magnitude of the enhancements that are observed. Irradiation of the signal for H_A (d, δ 4.25) results in enhancement of the signal for H_B (8.5%), whilst irradiation of H_B (t, δ 3.49) causes enhancement of the signals for H_A (9.5%) and H_C (8.5%). The chemical shift of the H_A proton in the cycloadducts (14) spans a narrow range (δ 4.18-4.34) suggesting the stereochemistry at sulphur is the same in all cases. A single crystal X-ray structure of one of the cycloadducts was determined and this showed the S-oxide to be trans to the R substitutent and cis to the ring hydrogen atoms H_A-H_C.

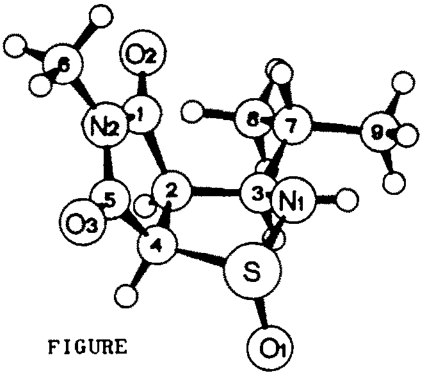
Table 1. Cycloadducts from the reaction of α-amino acids with N-sulphonylaniline and (13) in DMSO at 80°C.

Cycloadduct (14)	Time (h)	Yield (%)
a; R=Ph	4	60
a; $R=CH_2Ph$	2	90
a; $R=Pr^i$	4	74
a; $R=(CH_2)_2SMe$	4	75
a; $R=Bu^s$	4	68
a; $R=Bu^i$	4	72
a; $R=CH_2$-Ind.[b]	4	78
b; $R=CH_2Ph$	1	68
b; $R=Pr^i$	4	68
b; $R=(CH_2)_2SMe$	4	71
b; $R=CH_2$-Ind.[b]	4	70

a. Isolated yields b. Ind. = indol-3-yl.

<u>Crystal data for (14a, $R=Pr^i$):</u> $C_9H_{14}N_2O_3S$. M=230.3. Orthorhombic, space group $Pna2_1$ (no.33), $\underline{a}$ = 7.834(8), $\underline{b}$ = 11.186(11), $\underline{c}$ = 12.240(12)Å, U = 1072.6Å^3, Z = 4, D_x = 1.43g cm^{-3}, F(000) = 488, λ(Mo-K$_\alpha$) = 0.71069Å. Clear, colourless blocks, dimensions 0.3 x 0.4 x 0.9 mm, μ(M$_o$-K$_\alpha$) = 2.4cm^{-1}. Data were recorded on a Stoe STADI2 two-circle diffractometer, using the background-ωscan - background mode with scan width 1.5°, scan speed 1.5 deg min^{-1}, $3 \leq \theta \leq 30°$. 1506 unique data were corrected for Lorentz and polarisation effects and were used in the subsequent analysis. The structure was determined using the direct phasing methods of SHELX[11] and refined by least squares, allowing anisotropic vibrations for non-hydrogen atoms. The hydrogen on the

pyramidal nitrogen (N1) was included at the position determined from a difference Fourier synthesis and was allowed to refine isotropically. All other hydrogens were included in positions calculated from the geometry of the molecule (C-H = 1.08 Å). Common isotropic temperature factors were applied separately to tertiary CH and methyl hydrogens and these refined to final values of $U = 0.05(1)$ and $0.09(1)$ Å^2 respectively. In the final cycles the 1403 data with $F > 6\sigma(F)$ yielded a final R of 0.054. The weighting scheme used was $w = 1/[\sigma^2(F) + 0.0128F^2]$. A projection of the molecule is shown in the Figure.[≠] Bond lengths and angles are listed in tables 3 and 4.[19]



FIGURE

Reaction of α-Amino Acid Esters with N-Sulphonylaniline

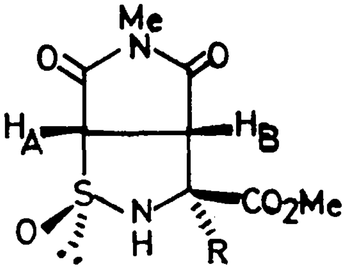
α-Amino acid esters [$H_2NCH(R)CO_2Me$] react with N-sulphonylaniline and (13a) in toluene at room temperature over 1-4h. to give mixtures of two stereoisomeric cycloadducts (15) and (16) (table 2), together with trace amounts (≤ 10% total) of one or two other isomers. Early experiments were performed in boiling toluene[2] and substantial quantities of additional isomers were obtained in one or two cases. Attempts to duplicate these experiments showed the product mixture was sensitive to temperature (see below). However, heating the product mixture produced at room temperature to 110°C for prolonged periods does not result in any noticeable change in product ratio (15):(16) or any increase in the minor isomer(s) suggesting the 1:1 ratio of (15) and (16) may arise from thermodynamic control (see below). As might be expected diethyl aminomalonate gives rise to a single cycloadduct (17) (Table 2).

Table 2. Cycloadducts from the reaction of α-amino acid esters with N-sulphonylaniline and (13a) in toluene at 25°C.[a]

Amino Acid Methyl Ester	Yield (%)[b]
tryptophan	90
alanine	70
phenylglycine	91
methionine	100
aminomalodic[c]	70[d]

a. Reaction time 1-4h. All reactions gave a ca. 1:1 mixture of (15) and (16).
b. Isolated yields; c. Diethyl ester; d. Product (17).

[≠] Tables of atomic coordinates, temperature factors and derived results have been deposited with the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.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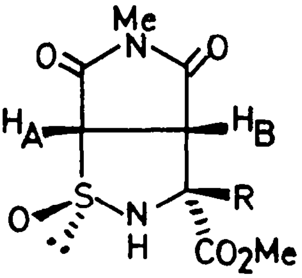
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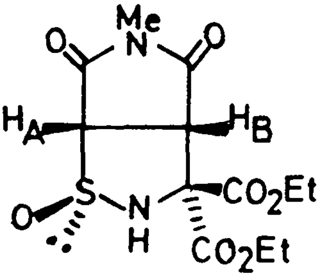
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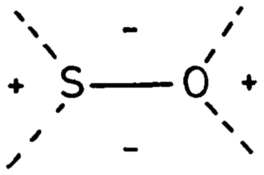
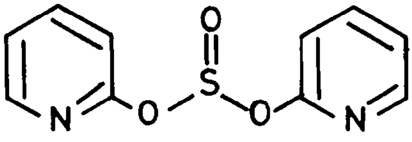

(1') - = deshielding
\+ = shielding

The relative stereochemistry of H_A, H_B and the R substituent in cycloadducts (15) and (16) was readily established by n.O.e. experiments. This technique showed a positive n.O.e. between H_B and R in (16) and a much reduced, or absence of, an n.O.e. between H_B and R in (15) (see experimental section). The stereochemistry at sulphur in these cycloadducts has not been determined. However, we tentatively assign a cis-relationship between the S-oxide and H_A in both isomers. Support for this assignment is provided by the chemical shift of the H_A protons in (14), (15) and (16). In the p.m.r. spectra of cycloadducts (14) in which H_A is cis to the S-oxide H_A gives rise to signal at δ 4.18-4.4. The magnetic anisotropy of the S-oxide bond (18)[12] is analogous to that of an acetylenic bond and results in deshielding of a cis-vicinal proton. The X-ray crystal structure of (14a, $R=Pr^{i}$) shows an H_A-C-S-O torsional angle of 22.3° and H_A --- O and H_A --- S distance of 2.67Å and 2.44Å respectively. The NH group is displaced (0.64Å) out of the plane of the other ring atoms S(O)$CH_ACH_BC(R)H_C$ towards the succinamide moiety. The p.m.r. signals for H_A in (15) (δ4.64-4.98) and (16) (δ4.81-5.01) are deshielded with respect to H_A in (14). This suggests a cis-vicinal relationship between H_A and the S-oxide in both cases accompanied by a reduction of the H_A-C-S-O torsional angle arising from conformational changes consequent on gem-substitution adjacent to the NH group. The seemingly anomalous chemical shift of H_A (δ4.21) in (16, R = indol-3-ylmethyl probably arises from a shielding effect of the indole on H_A and not from a change in stereochemistry at the sulphur atom.

Mechanism of the Cycloaddition Reactions.

The initial products of the sulphonyl group transfer are assumed to be (10) or the corresponding methyl ester, together with aniline. Attempts to utilise (19) as a sulphonyl transfer agent[13] resulted in low yields of cycloadduct (14). The by-product of sulphonyl transfer from (19) is the non-basic 2-pyridone and the low yield when (19) is used as sulphonyl transfer agent thus suggests a possible role for aniline, liberated from N-sulphonylaniline, in the cycloaddition process. Furthermore, we find that (20) reacts with N-sulphonylaniline and (13a) in benzene

($25^{\circ}C$, 24h) in the presence of 1 mol. of triethylamine to give (21) (45%) as a single isomer. The stereochemistry of (21) is assigned on the basis of the chemical shift of the proton H_A (δ 5.1) as discussed above for (15) and (16).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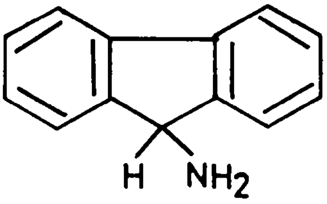
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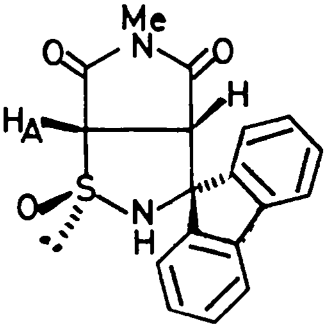
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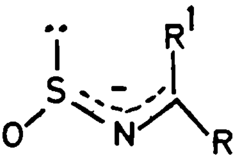
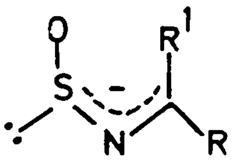

(22)
a. R=H
b. R^1=H
c. R=CO_2Me
d. R^1=CO_2Me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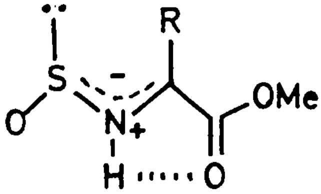
a. R=H
b. R^1=H
c. R=CO_2Me
d. R^1=CO_2Me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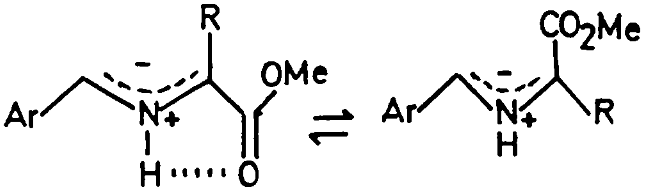
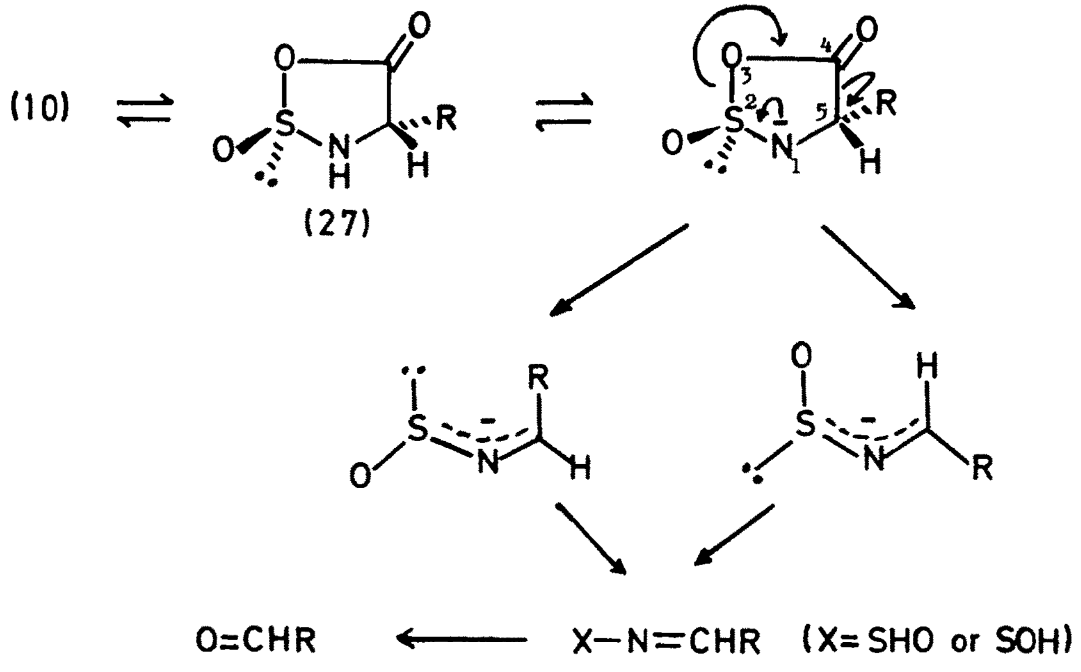

(25) (26)

The stereochemistry of cycloadducts (14) implicates a 4π-species, (22a) or (23b) or the corresponding N-protonated dipoles, with an anti-configuration. Moreover, the absence of cycloadducts derived from the corresponding 4π-syn-species, (22b) or (23b) or the corresponding N-protonated dipoles, suggests either (a) that an equilibration process intervenes, e.g. in the 4π-species prior to cycloaddition or (b) that formation of the 4π-species is rate determining and that either some non-covalent configuration-holding interaction, or an additional intermediate capable of exerting control over the stereochemistry of the 4π-species, is involved. Our previous extensive experience with maleimide dipolarophiles has shown that they trap the kinetically formed 1,3-dipole before any stereomutation (equilibration) can occur.[9] We were unable to detect any cycloadducts derived from (22b) or (23a) (or the corresponding N-protonated dipoles) although such species are readily detected in the corresponding cycloadditions involving α-amino esters (above) suggesting a possible mechanistic role for the free carboxyl group in determining the configuration of the 4π-species. One explanation that accords with our observations is that the initial product of sulphonyl transfer (10) undergoes cyclisation to (27) which, in turn, undergoes a concerted base catalysed cycloreversion giving either (22a) or (23b) (Scheme). A similar cycloreversion without the intervention of base would generate the analogous 1,3-dipolar species. [3+2]-Cycloreversions are known to occur with retention of stereochemistry in the case of 1,3-dipolar cycloreversions[14] and similar orbital symmetry constraints should impose the same outcome on [3+2]-anionic cycloreversions. Thus the configuration of (27) determines the syn- or anti-configuration of the 4π-species (scheme). A distinction between the 4π-anionic and 1,3-dipolar species as the reactive intermediate is not possible on the present evidence. However studies of the analogous reactions of α-amino esters (below) favour the 4π-anionic species.



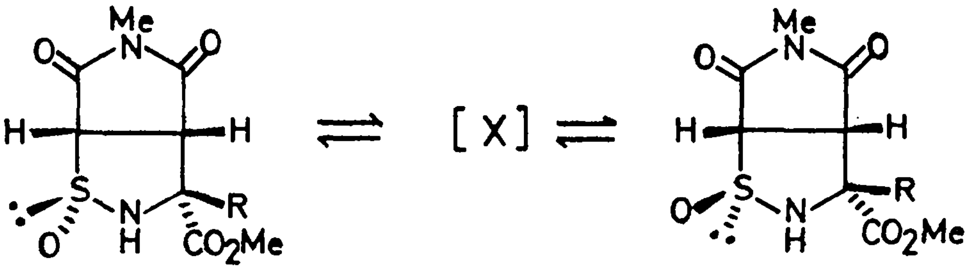
SCHEME

In the cycloreversion step the sp^3 centres at sulphur and C(5) are rehybridising and participating in a disrotatory twisting motion. In this latter process steric interactions between R and the sulphur atom lone pair, and between the oxygen atom and hydrogen atom, and the electronic interactions of these with the developing 4π-anion, manifest their influence over the two alternative disrotatory modes leading to (22a) or (23b). The cycloadducts (14) are either the product of a cycloaddition of (13) and (22a) via an exo-transition state or of cycloaddition of (13) and (23b) via an endo-transition state. N-substituted maleimides are reactive dipolarophiles and tend to give exclusively, or predominantly, endo-adducts and for this reason we favour (23b) as the reactive 4π-species. This analysis parallels that developed by us to explain anti-dipole formation in azomethine ylide formation from α-amino acids and aldehydes.[9] A detailed stereochemical and mechanistic investigation of this latter process provides clear evidence for the intervention of an oxazolidin-5-one (8) and its stereospecific cycloreversion to an azomethine ylide.[9] In the current case, when no dipolarophile is present, the 4π-anions (22a) or (23b) undergo S- or O-protonation giving imines (scheme) which are subsequently hydrolysed to aldehydes (the products observed in the original Japanese work[10]).

The analogous cycloadditions involving α-amino acid esters do not result in stereospecific formation of the corresponding carbomethoxy substituted 4π-sulphinylaminomethamide species. In this case a configuration determining cyclisation cannot occur. However, if the reactive species was a 1,3-dipole configuration controlling intramolecular hydrogen bonding (24) of the type believed to be responsible for stereospecific formation of (25), from imines of α-amino acid esters[15,16], would be expected to operate. In the latter case dipole stereomutation (25)$\rightleftharpoons$(26) does not occur at all when N-methylmaleimide is used as the dipolarophile. When less active dipolarophiles (acrylate, maleate, and fumarate esters etc.) are used, dipole stereomutation is observed for (25, R=Ph) but not to any significant extent for (25, R = alkyl).[15,17]

Monitoring the formation of (15) and (16) by p.m.r. in d_6-DMSO at 25°C indicates the ca. 1:1 mixture arises as a result of thermal equilibration of a mixture of three (or four) isomers during work up. d_6-DMSO was used for these studies because of the tendency of (15) and (16) to precipitate from toluene leading to misleading p.m.r. spectra. The possibility that both 4π-anionic species, e.g. (22c,d) and 1,3-dipolar species, e.g. (24), may be formed in the presence of catalytic amounts of base and acid respectively was considered next. This is analogous to enolate and enol formation from carbonyl compounds.[16] A series of n.m.r. tube experiments was carried out in which solutions of N-sulphonylaniline and alanine methyl ester in d_6-DMSO were allowed to react at room temperature with (i) unrecrystallised NMM (commercial NMM appears to contain some of the maleamic acid precursor[8]), (ii) thrice recrystallised NMM, (iii) recrystallised NMM plus 10 mol % benzoic acid, (iv) recrystallised NMM plus 10 mol.% aniline and (v) recrystallised NMM plus 10 mol.% of both aniline and benzoic acid. Reactions (i) and (ii) were complete in ca. 35 min. whilst reaction (iii) was slowest of all and was incomplete after 4.5h. Reaction (iv) was faster (complete in ca. 4.5h) than both (v) and (iii), but slower than (i) and (ii). The interpretation of these results is difficult at present since two steps, sulphonyl transfer and deprotonation or 1,2-prototropy, are involved. However, the triethylamine catalysed formation of (21) and the non-stereospecific formation of the 4π-species from α-amino acid esters and N-sulphonylaniline suggest configuration determining hydrogen-bonding of the type shown in (24) is not important. We therefore favour 4π-anionic species (22c,d) and (23c,d) as the reactive intermediates.

The observation of thermal equilibration of an initial mixture of three or four isomers to a ca. 1:1 mixture of (15) and (16) could be accommodated by a retro-cycloaddition/cycloaddition sequence or by N-S bond cleavage (ionic or radical)



(28) (29)

followed by cyclisation with inversion of the configuration at sulphur, e.g. (28) $\rightleftharpoons$ (X) $\rightleftharpoons$ (29) (where X=N-S cleaved ionic or radical intermediate). Evidence in favour of the latter explanation is provided by the observation that the pure isomers (15, R=3-indolylmethyl) and (16, R=3-indolylmethyl) are unchanged on heating at 110°C in toluene for 18h.

Experimental. General details were as previously described. Petroleum ether refers to the fraction b.p. 60-80°C. Flash chromatography was performed using Sorbsil C60-40/60 (Crosfields). N-Allyl maleimide was prepared by the literature procedure.[18]

Cycloadditions of α-Amino Acids

General Procedure. A mixture of the α-amino acid (0.02 mol), N-sulphonylaniline (0.02 mol) and dipolarophile (0.02 mol) in DMSO (50 ml) was stirred and heated at 80°C. When all the α-amino acid had dissolved (1-4h.) (Table 1), the reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure. Trituration of the residue with ether-petroleum ether yielded the crude product which was crystallised from an appropriate solvent. Yields are recorded in Table 1.

4-Phenyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14a,R=Ph). Obtained as colourless plates from methanol-petroleum ether, m.p. 178-180°C (Found: C, 54.40; H, 4.45; N, 10.40. $C_{12}H_{12}N_2O_3S$ requires C, 54.55; H, 4.60; N, 10.60%); δ 7.5 (m, 5H, ArH), 5.65 (d, 1H, H_C), 5.0 (br s, 1H, NH), 4.4 (d, 1H, H_A), 3.8 (t, 1H, H_B) and 2.9 (s, 3H, NMe); ^{1}H NOEDS(%) irradiation of H_B effected enhancements in the signals for H_A(11) and H_C(14); ν_{max} 1690, 1430, 1380 and 1280 cm^{-1}; m/z(%) 264 (M^+,7), 153(19), 135(5), 104(8) and 93(100).

4-Benzyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14a, R=CH_2Ph). Obtained as colourless rods from ether-chloroform, m.p. 140-141°C (Found: C, 55.80; H, 5.15; N, 10.35. $C_{13}H_{14}N_2O_3S$ requires C, 56.10; H, 5.05; N, 10.05%); δ 7.31 (m, 5H, ArH), 4.78 (m, 1H, H_C), 4.41 (s, 1H, NH), 4.30 (d, 1H, H_A), 3.5 (m, 2H, H_B + HCHPh), 3.03 (s, 3H, NMe) and 2.72 (dd, 1H, HCHPh); ν_{max} 3400, 3190, 1765, 1690, 1430, 1375, 1280 and 1050 cm^{-1}; m/z(%) 278 (M^+,15), 260(11), 167(100), 112(32), 104(41), and 91(73).

4-iso-Propyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14a, R=Pr^i). Obtained as colourless chunky rhombs from ether-chloroform, m.p. 214-215°C (Found: C, 47.00; H, 6.30; N, 12.30. $C_9H_{14}N_2O_3S$ requires C, 46.95; H, 6.15; N, 12.15%); δ 4.58 (br s, 1H, NH), 4.20 (m, 2H, H_A and H_C), 3.59 (t, 1H, H_B), 2.96 (s, 3H, NMe), 2.2 (m, 1H, $CHMe_2$), and 1.29 and 1.05 (2 x d, 2 x 3H, $CHMe_2$); ν_{max} 3440, 3200, 1765, 1700, 1440, 1380, 1320, 1290 and 1150 cm^{-1}; m/z(%) 244 (M^+,2), 188(89), 133(96) and 112(100).

4-(-Thiomethyl)ethyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14a, R=CH_2CH_2SMe). Obtained as colourless rhombs from methanol, m.p. 151-153°C (Found: C, 41.30; H, 5.35; N, 10.90. $C_9H_{14}N_2O_3S_2$ requires C, 41.20; H, 5.35; N, 10.70%); δ (d_6-DMSO) 6.94 (br s, 1H, NH), 4.28 (m, 1H, H_C), 4.18 (d, 1H, H_A), 3.59 (t, 1H, H_B), 3.23 (s, 3H, NMe), 2.56 (t, 2H, CH_2S), 1.95 (s, 3H, SMe), and 2.04 and 1.63 (2 x m, 2 x 1H, $\underline{CH_2}CH_2S$); ν_{max} 3460, 3140, 1775, 1440 and 1050 cm^{-1}; m/z(%) 262 (M^+,1), 214(64), 198(24), 167(46) and 61(100).

4-sec-Butyl-7-methyl-2-thia--6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14a, R=Bu^s). Obtained as colourless rods from chloroform-ether, m.p. 174-175°C (Found: C, 49.05; H, 6.65; N, 11.55; S, 13.10. $C_{10}H_{16}N_2O_3S$ requires C, 49.15; H, 6.60; N, 11.45; S, 13.10%); δ 4.62 (m, 1H, H_C), 4.52 (s, 1H, NH), 4.20 (d, 1H, H_A), 3.45 (t, 1H, H_B), 2.90 (s, 3H, NMe), 1.92 (m, 2H, $C\underline{H_2}Me$), 1.42 [m, 1H, $C\underline{H}$(Me)Et], 1.02 (t, 3H, CH_2CH_3), 1.01 (d, 3H, $CHCH_3$); ν_{max} 3220, 1770, 1700, 1435 and 1050 cm^{-1}; m/z(%) 244 (M^+,15), 188(95), 187(85) and 123(100).

4-isoButyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14a, R=Bu^i). Obtained as colourless plates from chloroform-ether, m.p. 140-141°C (Found: C, 49.30; H, 6.70; N, 11.25; S, 13.30. $C_{10}H_{16}N_2O_3S$ requires C, 49.15; H, 6.60; N, 11.45; S, 13.10%); δ 4.67 (m, 1H, H_C), 4.25 (d, 1H, H_A), 3.49 (t, 1H, H_B), 1.95 (s, 3H, NMe), 1.8 (m, 2H, CH_2), 1.52 (m, 1H, $\underline{CH}Me_2$) and 1.1 (d, 6H, $CH\underline{Me_2}$); ^{1}H NOEDS (%) irradiation of H_B effected enhancement in the signals for H_A (9.5) and H_C (8.5); ν_{max} 3425, 3125, 1765, 1700, 1430 and 1050 cm^{-1}; m/z(%) 244 (M^+,2), 188(89), 133(96) and 122(100).

4-Indol-3'-ylmethyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14a, R = indol-3-ylmethyl). Obtained as colourless plates from methanol, m.p. 179-181°C (Found: C, 56.70; H, 4.90; N, 13.00. $C_{15}H_{15}N_3O_3S$ requires C, 56.75; H, 4.75; N, 13.25%); δ 8.25 (br s, 1H, NH), 7.1 (m, 5H, ArH), 4.78 (m, 1H, H_C), 4.54 (br s, 1H, NH), 4.12 (dd, 1H, J 1.4 and 7.4Hz, H_A), 3.55 (m, 2H, H_B + HCH-indole), 2.95 (s, 3H, NMe), and 2.87 (m, 1H, HCH-indole); ν_{max} 3590, 3200, 1770, 1690 and 1060 cm^{-1}; m/z(%) 317 (M^+,10), 131(20) and 130(100).

4-Benzyl-7-allyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14b, R=CH_2Ph). Obtained as colourless plates from chloroform-ether, m.p. 140-141°C (Found: C, 59.00; H, 5.35; N, 9.10. $C_{15}H_{16}N_2O_3S$ requires C, 59.20; H, 5.30; N, 9.20%); δ 7.30 (m, 5H, ArH), 5.78 (m, 1H, $C\underline{H}$=CH_2), 5.2

(m, 2H, CH=CH$_2$), 4.81 (m, 1H, H$_C$), 4.35 (br s, 1H, NH), 4.32 (dd, 1H, J 1.8 and 7.4Hz, H$_A$), 4.13 (m, 2H, CH$_2$CH=), 3.60 (m, 2H, H$_B$ + HCHPh), and 2.70 (q, 1H, HCHPh); ν_{max} 3300, 1780, 1799, 1430, 1390 and 1180 cm^{-1}; m/z(%) 304 (M$^+$,71), 213(33), 167(64) and 91(100).

4-iso-Propyl-7-allyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14b, R=Pr^i). Obtained as colourless needles from chloroform-ether, m.p. 100-101°C (Found: C, 51.335; H, 6.15; N, 10.95; S, 12.25. $C_{11}H_{16}N_2O_3S$ requires C, 51.55; H, 6.30; N, 10.90; S, 12.50%); δ 5.72 (m, 1H, CH=CH$_2$), 5.15 (m, 2H, CH=CH$_2$), 4.98 (s, 1H, NH), 4.25 (m, 2H, H$_A$ + H$_C$), 4.07 (d, 2H, CH$_2$CH=), 3.64 (t, 1H, H$_B$), 2.17 (m, 1H, CHMe$_2$), and 1.28 and 1.06 (2 x d, 2 x 3H, CHMe$_2$); ν_{max} 3220, 1770, 1700, 1430 and 1060 cm^{-1}; m/z(%) 256 (M$^+$,4), 213(17), 138(40) and 119(100).

4-(-Thiomethyl)ethyl-7-allyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14b, R=CH$_2$CH$_2$SMe). Obtained as colourless rods from ether-chloroform, m.p. 75-77°C (Found: C, 45.85; H, 5.65; N, 9.65. $C_{11}H_{16}N_2O_3S_2$ requires C, 45.80; H, 5.60; N, 9.70%); δ(d$_6$-DMSO) 7.12 (s, 1H, NH); 5..66 (m, 1H, CH=CH$_2$), 5.04 (m, 2H, CH=CH$_2$), 4.42 (m, 1H, H$_C$), 4.34 (d, 1H, H$_A$), 3.90 (d, 2H, CH$_2$CH=), 3.74 (t, 1H, H$_B$), 2.66 (t, 2H, CH$_2$S), 2.0 and 1.7 (2 x m, 2 x 1H, CH$_2$CH$_2$S), and 2.02 (s, 3H, SMe); ν_{max} 3140, 1775, 1700, 1400 and 1050 cm^{-1}; m/z(%) 288 (M$^+$,1), 240(72), and 61(100).

4-Indol-3'-ylmethyl-7-allyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (14b, R = indol-3-ylmethyl). Obtained as colourless rods from methanol-chloroform, m.p. 208-210°C (Found: N, 12.35. $C_{17}H_{17}N_3O_3S$ requires N, 12.25%); δ (d$_6$-DMSO) 9.4 (br s, 1H, NH), 7.5-6.52 (m, 5H, ArH), 5.65 (m, 1H, CH=CH$_2$), 5.2 (br s, 1H, NH), 5.1 (m, 2H, CH=CH$_2$), 4.85 (m, 1H, H$_C$), 4.1 (dd, 1H, J 1.3 and 7.2Hz, H$_A$), 4.0 (d, 2H, NCH$_2$), 3.58 (m, 2H, H$_B$ + HCH-indole), and 2.92 (m, 1H, HCH-indole); $\nu_{max.}$ 3407, 1777 and 745 cm^{-1}; m/z(%) 343 (M$^+$,1), 341(14) and 130(100).

Cycloadditions of α-Amino Esters

General Procedure. A mixture of the α-amino acid ester (0.02mol), N-sulfonylaniline (0.024mol) and N-methylmaleimide (0.02mol) in toluene (50ml) was stirred at 25°C until the reaction was complete (t.l.c.) (1-4h). The reaction mixture was then washed with water, dried (Na_2SO_4) and evaporated to dryness. Integration of p.m.r. spectrum of the crude product gave the isomer ratio. Isomer mixtures were separated by flash chromatography eluting with 3:7 v/v petroleum ether-ethyl acetate. Note that the room temperature reaction mixture may contain three or four isomers but application of heat during removal of the toluene results in a ca. 1:1 mixture of two isomers with only trace amounts of other isomers.

Methyl 4-indol-3'-ylmethyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane-2-carboxylate S-oxide (15, R = indol-3-ylmethyl). Colourless plates from ether-ethylacetate, m.p. 210-212°C [Found (mixed isomers): C, 54.35; H, 4.45; N, 11.05. $C_{17}H_{17}N_3O_5S$ requires C, 54.40; H, 4.55; N, 11.20%]; δ(d$_6$-DMSO) 10.8 (br s, 1H, NH), 6.98 (m, 5H, ArH), 4.64 (d, 1H, H$_A$), 4.0 (d, 1H, H$_B$), 3.7 and 2.88 (2 x d, 2 x 1H, CH$_2$-Indole), 3.28 (s, 3H, OMe), and 2.64 (s, 3H, NMe); $\nu_{max.}$ 3310, 1700, 1440, 1290 and 750 cm^{-1}; m/z(%) 375 (M$^+$,3), 312(12), 264(41) and 130(100).

(16, R = indol-3-ylmethyl). Colourless plates from benzene, m.p. 227-229°C. δ (d$_6$-DMSO) 11.07 (s, 1H, NH), 7.30 (, 5H, ArH), 4.21 (d, 1H, H$_A$), 3.93 (d, 1H, H$_B$), 3.69 (s, 3H, OMe), 3.33 and 3.27 (2 x d, 2 x 1H, CH$_2$-Indole) and 2.77 (s, 3H, NMe); ^{1}H NOEDS (%) irradiation of CH$_2$-Indole effected enhancement of H$_B$(7); $\nu_{max.}$ 3260, 1700, 1450, 1080, and 760 cm^{-1}; m/z(%) (375 (M$^+$,0.5), 264(6), 131(12) and 130(100).

Methyl 4,7-dimethyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane-2-carboxylate S-oxide

(15, R=Me). Colourless plates from ethyl acetate-petroleum ether, m.p. 155-157°C [Found (mixed isomers): C, 41.45; H, 4.70; N, 10.70. $C_9H_{12}N_2O_5S$ requires C, 41.50; H, 4.65; N, 10.75%]; δ(d$_6$-DMSO) 7.63 (br s, 1H, NH), 4.89 (d, 1H, H$_A$), 4.28 (d, 1H, H$_B$), 3.73 (s, 3H, OMe), 2.85 (s, 3H, NMe), and 2.0 (s, 3H, Me); $\nu_{max.}$ 3320, 1740, 1430, 1290 and 1080 cm^{-1}; m/z(%) 260 (M$^+$,3) 201(81), and 149(100).

(16, R=Me). Colourless plates from ethyl acetate-petroleum ether, m.p. 123-125°C; δ(d$_6$-DMSO) 7.7 (br s, 1H, NH), 5.01 (d, 1H, H$_A$), 3.77 (d, 1H, H$_B$), 3.63 (s, 3H, OMe), and 2.81 (s, 3H, NMe); ^{1}H NOEDS (%) irradiation of C(4)-Me effected enhancement of H$_B$ (26); $\nu_{max.}$ 3150, 1700, 1440, 1250 and 740 cm^{-1}; m/z(%) 260 (M$^+$,2), 202(19), 201(100) and 149(62).

Methyl 4-phenyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane-2-carboxylate S-oxide.

(15, R=Ph). Colourless plates from ethyl acetate-petroleum ether, m.p. 195-197°C [Found (mixed isomers): C, 51.90; H, 4.30; N, 8.40. $C_{14}H_{14}N_2O_5S$ requires C, 52.15; H, 4.35; N, 8.70%]; δ(d$_6$-DMSO) 8.25 (br s, 1H, NH), 7.44 (m, 5H, ArH), 4.98 (d, 1H, H$_A$), 4.82 (d, 1H, H$_B$), 3.73 (s, 3H, OMe), and 2.62 (s, 3H, NMe); ν_{max} 3300, 1700, 1435, 1260 and 1075 cm^{-1}; m/z(%) 322 (M$^+$,21), 279(19) and 263(100).

(16, R=Ph). Colourless plates from ethyl acetate-petroleum ether, m.p. 160-161°C; δ(d$_6$-DMSO) 8.63 (br s, 1H, NH), 7.40 (m, 5H, ArH), 4.81 (d, 1H, H$_A$), 4.29 (d, 1H, H$_B$), 3.61 (s, 3H, OMe), and 2.89 (s, 3H, NMe); ^{1}H NOEDS (%) irradiation of H$_B$ effected enhancement of the ortho-ArH signal (11.5); $\nu_{max.}$ 3300, 1700, 1430, 1250, 1075 and 745 cm^{-1}.

Methyl 4-(β-thiomethyl)ethyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane-2-carboxylate S-oxide.
(15, R=CH_2CH_2SMe). Colourless needles from ethyl acetate-petroleum ether, m.p. 148-150°C [Found (mixed isomers): C, 41.15; H, 5.00; N, 8.90. $C_{11}H_{16}N_2O_5S_2$ requires C, 41.25; H, 5.05; N, 8.75%]; δ(d_6-DMSO) 7.87 (br s, 1H, NH), 4.86 (d, 1H, H_A), 4.21 (d, 1H, H_B), 3.75 (s, 3H, OMe), 2.85 (s, 3H, NMe), 2.81-2.05 (m, 4H, CH_2CH_2S) and 2.01 (s, 3H, SMe); ν_{max} 3200, 1700, 1450 and 1070 cm^{-1}; m/z(%) 320 (M^+,6), 246(24), 111(27) and 61(100).
(16, R=CH_2CH_2SMe). Colourless plates from ethyl acetate-petroleum ether, m.p. 169-171°C; δ(d_6-DMSO) 7.81 (br s, 1H, NH), 5.01 (d, 1H, H_A), 3.92 (d, 1H, H_B), 3.66 (s, 3H, OMe), 2.8 (s, 3H, NMe), 2.24 (m, 4H, CH_2CH_2S), and 2.1 (s, 3H, SMe); ν_{max} 3200, 1700, 1450 and 1070 cm^{-1}; m/z(%) 320 (M^+,0.5), 209(11), 111(37) and 61(100).
Diethyl 7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane-2,2-dicarboxylate S-oxide (17). Colourless plates from chloroform-petroleum ether, m.p. 140-141°C (Found: C, 43.50; H, 4.70; N, 8.25. $C_{12}H_{16}N_2O_7S$ requires C, 43.40; H, 4.85; N, 8.45%); δ 5.57 (br s, 1H, NH), 4.61 (2 x overlapping d, 2 x 1H, H_A and H_B), 4.36 (m, 4H, 2 x CH_2Me), 3.03 (s, 3H, NMe), and 1.34 (2 x overlapping t, 2 x 3H, CH_2Me); ν_{max} 1740, 1700, 1430 and 1380 cm^{-1}; m/z(%) 332 (M^+,0.5), 259(2), 149(10), 148(13), 103(31), and 29(100).
4,4-Spiro-9',9'-fluorenyl-7-methyl-2-thia-6,8-dioxo-3,7-diazobicyclo[3.3.0]octane S-oxide (21). Yellow prisms from chloroform-petroleum ether, m.p. 213-214°C (Found: C, 63.75; H, 4.10; N, 8.35. $C_{18}H_{14}N_2O_3S$ requires C, 63.90; H, 4.15; N, 8.30%); δ 7.72-7.19 (m, 8H, ArH), 5.10 (d, 1H, H_B), 4.97 (br s, 1H, NH), 4.08 (d, 1H, H_A), and 2.93 (s, 3H, NMe); m/z(%) 338 (M^+,1), 227(15), 179(100), 111(19) and 76(8).

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19. Table 3. Bond lengths (Å) for (14a, R=Pr^i)

S1-O1	1.488(3)	S1-N1	1.656(2)
S1-C4	1.852(3)	O2-C1	1.221(3)
O3-C5	1.206(4)	N1-C3	1.489(5)
N2-C1	1.386(4)	N2-C5	1.379(5)
N2-C6	1.462(4)	C1-C2	1.521(4)
C2-C3	1.541(4)	C2-C4	1.536(4)
C3-C7	1.521(4)	C4-C5	1.513(4)
C7-C8	1.532(4)	C7-C9	1.533(4)

Table 4. Bond angles (°) for (14a, R=Pr^i)

N1-S1-O1	113.6(2)	C4-S1-O1	104.7(2)
C4-S1-N1	89.5(1)	C3-N1-S1	112.2(2)
C5-N2-C1	113.8(2)	C6-N2-C1	122.1(3)
C6-N2-C5	123.8(3)	N2-C1-O2	122.9(3)
C2-C1-O2	128.4(3)	C2-C1-N2	108.7(2)
C3-C2-C1	114.9(2)	C4-C2-C1	103.4(2)
C4-C2-C3	107.9(2)	C2-C3-N1	101.4(2)
C7-C3-N1	112.3(2)	C7-C3-C2	116.9(2)
C2-C4-S1	107.8(2)	C5-C4-S1	110.1(2)
C5-C4-C2	106.1(2)	N2-C5-O3	125.8(3)
C4-C5-O3	126.7(3)	C4-C5-N2	107.5(3)
C8-C7-C3	110.2(2)	C9-C7-C3	111.7(2)
C9-C7-C8	109.4(3)		