Thermal Rearrangement of 2,2,4,4-Tetramethylthietan-3-one 1-Oxide; a Reaction related to the Ring Expansion of the Penicillin *S*-Oxides

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When the title compound (4) is heated for 1½ h in refluxing benzene a mixture of ring-expanded products, (6a) (25%) and (7) (67%), is obtained. In acetic anhydride, compound (4) gives the acetate (6b) 77% as the only significant product, and in norbornene, dinorbornyl sulphoxide (12a) 35% is formed. In the presence of a silylating agent the sulphenic acid intermediate (5a) can be trapped as the trimethylsilyl derivative (5b) but this, in turn, undergoes a thermal rearrangement to give the enol ether (13).

It is known that penicillin *S*-oxides can rearrange by opening of the five-membered ring as shown in formula (1).[1] This generates a sulphenic acid group and a double bond, but the initial product (2a) is usually unstable. Among other reactions, it may recyclise in one of two ways: the sulphenic acid (RSOH) may add back to the double bond either in the ' RSO + H ' sense or in the ' RS + OH ' sense (' RS + OAc ' in the case of the Ac_2O-catalysed reaction). The first reaction normally regenerates a five-membered ring [*i.e.* (1) is re-formed] and requires no catalyst. The second often proceeds with ring expansion [to give (3) or a derivative thereof]; it normally requires an acid, a Lewis acid, or acetic anhydride as catalyst, and is often formulated as involving a thiiranium ion intermediate.

During attempts to oxidise 2,2,4,4-tetramethylthietan-3-one [2] it was discovered that the sulphoxide (4) is thermally unstable and undergoes rearrangements very similar to those of the penicillin *S*-oxides.[3] In this case, however, even in the absence of a catalyst, the intermediate sulphenic acid (5a) cyclises both in the ' RSO + H ' and in the ' RS + OH ' sense, and both reactions involve ring expansion.

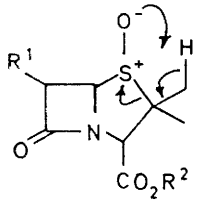
When the sulphoxide (4) is heated in refluxing benzene for 1½ h and the resultant material chromatographed on

[1] R. J. Stoodley, *Tetrahedron*, 1975, **31**, 2321; P. G. Sammes, *Chem. Rev.*, 1976, **76**, 113, and references therein.

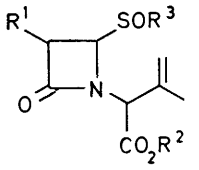
[2] R. J. Bushby, *J.C.S. Perkin I*, 1975, 2513.

[3] Some other rearrangements of cyclic sulphoxides have been reported which are also related to the penicillin *S*-oxide rearrangements: R. B. Morin, D. O. Spry, and R. A. Mueller, *Tetrahedron Letters*, 1969, 849; J. E. Baldwin, G. Hofle, and Se Chun Choi, *J. Amer. Chem. Soc.*, 1971, **93**, 2810; D. O. Spry, *J.C.S. Chem. Comm.*, 1973, 259; A. G. W. Baxter, J. Kitchin, R. J. Stoodley, and R. B. Wilkins, *ibid.*, 1973, 285; R. J. Stoodley and R. B. Wilkins, *J.C.S. Perkin I*, 1974, 1572; A. G. W. Baxter and R. J. Stoodley, *J.C.S. Chem. Comm.*, 1976, 366.

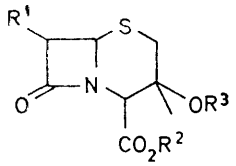
silica, two major products, (6a) (25%) and (7) * (67%), are obtained. The structure of the first of these products (6a) follows unambiguously from its spectra and



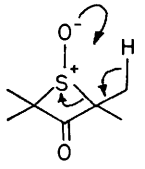
(1)



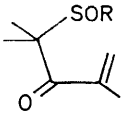
(2) a; R^3 = H
b; R^3 = $SiMe_3$



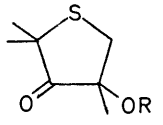
(3) a; R^3 = H
b; R^3 = Ac



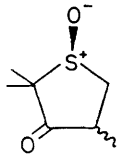
(4)



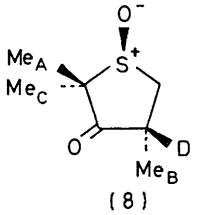
(5) a; R = H
b; R = $SiMe_3$



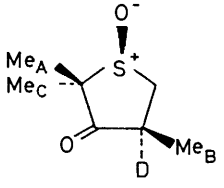
(6) a; R = H
b; R = Ac



(7)



(8)



(9)

those of its acetate (6b). The structure of the second product (7) was more difficult to establish. The i.r. spectrum shows the presence of a carbonyl group in a five-membered ring and of a sulphoxide grouping, but the proton n.m.r. spectrum (in $CDCl_3$) is very complex. It consists, in part, of an $ABCX_3$ spectrum or two overlapping $ABCX_3$ spectra,* and shows one series of many sharp peaks at τ 6.4—7.5 (total 3 H) and another at τ 8.50—8.85 (total 9 H). When, however, the sample in the n.m.r. tube is shaken with D_2O–potassium carbonate the spectrum is greatly simplified. This is a result of exchange of the hydrogen α to the carbonyl group for deuterium giving, eventually, a 3 : 1 mixture of deuterio-derivatives (8) and (9). The complex series of peaks in the methylene region is then replaced by two overlapping AB quartets. The sulphoxide (7) can be oxidised by peracetic acid to the sulphone (10a). This also shows a complex series of peaks in the methylene region of the proton n.m.r. spectrum. The position α to the carbonyl group can be deuteriated in the same manner to give (10b), in the spectrum of which the low-field end is simplified to a single AB quartet.

In the penicillin series recyclisation of the sulphenic acid with cleavage of the sulphur–oxygen bond is catalysed by acetic anhydride [4] and, among other products, (3b) may be formed. It was, therefore, not surprising to find that, when the sulphoxide (4) was heated in refluxing acetic anhydride for 1 h, the acetate (6b) was the only significant product.

Also, in the penicillin series, several methods have been developed for trapping the sulphenic acid intermediate (2a).[1] Barton [5] has shown that, in the presence of a suitable olefin, the sulphenic acid (2a) can be induced to undergo an intermolecular rather than an intramolecular double-bond addition. In an attempt to trap the supposed intermediate (5a) in the rearrangement of the sulphoxide (4), it was heated in norbornene. However, the only product isolated was not the expected adduct (11) but dinorbornyl sulphoxide (12a). Presumably the initial adduct (11) undergoes an elimination reaction as shown, giving norbornanesulphenic acid, which then adds to a second molecule of norbornene. This double elimination–addition is similar to that invoked in order to explain the reaction of di-t-butyl sulphoxide with methyl propiolate [6] or with cycloocta-1,5-diene.[7]

An alternative way of trapping the sulphenic acid intermediate in these reactions is to use a silylating agent; normally a mixture of trimethylsilyl chloride and hexamethyldisilazane.[8] The reaction of the sulphoxide (4) with silylating agent is most conveniently

* G.l.c. or t.l.c. conditions could not be found for separating the *cis*- and *trans*-isomers of (7), and the spectra did not make it clear whether the product was one pure isomer or a mixture of the two.

[4] R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1401; D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.

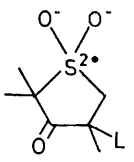
[5] D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1683; I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *J.C.S. Perkin I*, 1973, 1187.

[6] J. R. Shelton and K. E. Davis, *J. Amer. Chem. Soc.*, 1967, **89**, 718; see also E. Block and J. O'Connor, *ibid.*, 1974, **96**, 3929.

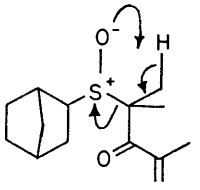
[7] D. N. Jones and D. A. Lewton, *J.C.S. Chem. Comm.*, 1975, 451.

[8] T. S. Chou, *Tetrahedron Letters*, 1974, 725; T. S. Chou, J. R. Burgtorf, A. L. Ellis, S. R. Lammert, and S. P. Kukolja, *J. Amer. Chem. Soc.*, 1974, **96**, 1609.

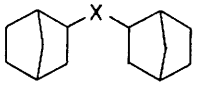
followed by n.m.r. spectroscopy. When a mixture of (4) and an excess of silylating agent in deuteriochloroform, in a sealed n.m.r. tube, is heated at 100 °C, the spectrum of the sulphoxide (singlets at τ 8.40 and 8.50) is rapidly replaced (*ca.* 5 min) by signals at τ 4.22 and 4.56 (multiplets, each 1 H), 8.14 (broadened singlet, 3 H), 8.60 (sharp singlet, 6 H), and 9.88 (singlet, 9 H). This corresponds to the spectrum expected for the trimethylsilyl derivative (5b). Before the formation of (5b) is



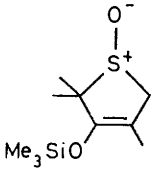
(10) a; L = H
b; L = D



(11)



(12) a; X = SO
b; X = SO_2



(13)

complete, however, a second set of signals starts to appear: τ 6.51 and 6.99 (AB quartet, 2 H), 8.50 (singlet, 3 H), 8.77 and 8.82 (singlets, each 3 H), and 9.85 (singlet, 9 H), which eventually (*ca.* ½ h) totally replaces those for (5b). These signals are assigned to the enol ether (13). The same sequence of reactions (4) ⟶ (5b) ⟶ (13), is observed when benzene is used as solvent instead of deuteriochloroform. However, whereas the rate of the first step (4) ⟶ (5b) appears to be unaltered the second step (5b) ⟶ (13) is quite a lot slower and, by using this solvent, it is possible to stop the reaction at the (5b) stage and obtain a sample virtually uncontaminated by either (4) or (13). The trimethylsilyl derivative (5b) is very unstable and attempts to distil it, even at very low pressure, result only in recovery of (13). Similarly, an attempt to obtain a mass spectrum of (5b) produced one almost identical with the mass spectrum of (13). Presumably, in this case, rearrangement was initiated by the heat of the probe. Hydrolysis of either (5b) or (13) by shaking a chloroform solution with water at room temperature produces mainly (7) and a trace of (6a). Hydrolysis of (13) with D_2O can be followed by n.m.r. spectroscopy. It gives initially a 1 : 1 mixture of (8) and (9), which on treatment with D_2O–potassium carbonate is converted into the equilibrium 3 : 1 mixture. It was also shown that the enol ether (13) can be formed by heating the ring-expanded sulphoxide (7) with silylating agent. The reaction is, however, rather slow (4—6 h at 120 °C), and some by-products are formed.

EXPERIMENTAL

2,2,4,4-Tetramethylthietan-3-one 1-Oxide (4).—Peracetic acid (40% w/v; 0.92 cm³, 4.8 mmol) was added to a stirred, cooled solution of 2,2,4,4-tetramethylthietan-3-one [2] (1.32 g, 9.1 mmol) in benzene (25 cm³). The mixture was allowed to warm to room temperature. After 20 h ether was added and the solution was washed with aqueous sodium carbonate, dried, and evaporated at room temperature under reduced pressure. The residue was chromatographed on silica (elution with ether) to yield first unchanged thietanone (493 mg) and then the *sulphoxide* (630 mg, 69% based on thietanone consumed) as white crystals; m.p. 106—109 °C (decomp.), unchanged by low temperature recrystallisation from ether (Found: C, 52.7; H, 7.6; S, 19.9. $C_7H_{12}SO_2$ requires C, 52.5; H, 7.6; S, 20.0%), $\nu_{max.}$ ($CHCl_3$) 1 765 (C=O) and 1 070 cm^{-1} (SO), τ ($CDCl_3$) 8.40 and 8.51 (each 6 H, s, *cis*- and *trans*-Me). The sulphoxide could be stored unchanged at 0 °C for several days but eventually became sticky and contaminated with rearrangement products.

Thermal Rearrangement of the Sulphoxide (4) *in Benzene.*—A solution of the sulphoxide (600 mg) in benzene (25 cm³) was refluxed for 1½ h, then evaporated, and the residue was chromatographed on silica (elution with ether and then 10% methanol–ether) to yield in elution order, *4-hydroxy-2,2,4-trimethylthiolan-3-one* (6a) (148 mg, 25%) as a semi-solid, giving, after further chromatography and bulb distillation, white crystals, m.p. 48—49.5 °C (Found: C, 52.7; H, 7.3; S, 20.0. $C_7H_{12}SO_2$ requires C, 52.5; H, 7.6; S, 20.0%), $\nu_{max.}$ (film) 3 450 (OH) and 1 750 cm^{-1} (C=O), τ ($CDCl_3$) 6.97 and 7.03 (2 H, AB q, *J* 11.5 Hz, CH_2), 7.12 (1 H, s, removed by exchange with D_2O, OH), and 8.49, 8.52, and 8.53 (3 × 3 H, 3 Me); and *2,2,4-trimethylthiolan-3-one 1-oxide* (7) (404 mg, 67%), as white needles, m.p. 57—62 °C (from petroleum) (Found: C, 52.2; H, 7.6; S, 20.2%; M^+, 142.045 4. $C_7H_{12}SO_2$ requires C, 52.5; H, 7.6; S, 20.0%; *M*, 142.045 2), $\nu_{max.}$ ($CHCl_3$) 1 740 (C=O) and 1 070 cm^{-1} (SO), τ ($CDCl_3$) 6.4—7.5 (3 H, m, CH_2·CH) and 8.5—8.85 (9 H, m, 3 Me), τ ($CDCl_3$; after shaking with D_2O–K_2CO_3) 6.53 and 7.32, also 6.47 and 7.19 (2 H, two overlapping AB quartets, *J* 13.5 Hz, CH_2), 8.52, 8.70, and 8.80 (3 × 3 H, s, 3 Me) (the centre signal is broadened and shows some fine structure, presumably the result of deuterium coupling), δ_C (from Me_4Si) 15.0, 17.0, and 20.0 (methyls), 38.4 (CH), 49.5 (CH_2), 67.0 (CMe_2), and 214.6 (C=O).

Although overlap of signals makes a definite assignment difficult the solvent effect [9] for the proton n.m.r. of the deuterium-exchanged material suggests that the major component of the mixture is the *trans*-isomer (8). In particular, on changing the solvent from CCl_4 to C_6H_6, two of its methyl resonances are shifted markedly to high field. According to Strom's model for solvation of sulphoxides [9] this implies that both methyl groups are *trans* to the sulphur–oxygen bond. The tentative assignments of signals are: for the major isomer (8) (assignment, τ in CCl_4, τ in C_6H_6, difference), (Me_A 8.62, 8.68, 0.06), (Me_B 8.73, 9.18, 0.45, broadened, probably by deuterium coupling), and (Me_C 8.85, 9.39, 0.54); for the minor isomer (9) (Me_A 8.62,

[9] E. T. Strom, B. S. Snowden, and P. A. Toldan, *Chem. Comm.*, 1969, 50.

8.68, 0.06), (Me_B 8.75, 8.87, 0.15, broadened, probably by deuterium coupling), and (Me_C 8.85, 9.35, 0.50).*

Acetylation of the Thiolanone (6a).—The thiolanone (140 mg) was treated with acetic anhydride (3 cm³) and pyridine (3 cm³). After 3 days the mixture was poured into water (100 cm³), and extracted with ether. The extracts were washed with 2N-sulphuric acid and aqueous sodium carbonate, dried, and evaporated under reduced pressure to yield the *acetate* (6b) (166 mg, 83% crude), which was purified by chromatography on silica (elution with ether–petroleum and then ether) and bulb distillation (bath 80 °C; 15 mmHg), after which it solidified to give white needles, m.p. 56—59 °C (Found: C, 53.3; H, 7.2%; M^+, 202.066 3. $C_9H_{14}SO_3$ requires C, 53.4; H, 7.0; M, 202.066 4), $\nu_{max.}$ (film) 1 745 cm^{-1} (C=O), τ ($CDCl_3$) 6.37 and 7.24 (2 H, ABq, J 11 Hz, CH_2), 7.93 (3 H, s, Ac), 8.37 (6 H, s, Me_2C), and 8.57 (3 H, s, Me), *m/e* 202 (M^+, 1%), 143 (21), 142 ($M^+ - CH_3CO_2H$, 21), 115 (22), 74 (? Me_2CS^+, 36), 71 (24), 59 (? $MeCS^+$, 27), 43 (? $MeCO^+$, 100), and 41 (61).

Oxidation of the Sulphoxide (7).—The sulphoxide (112 mg, 0.8 mmol) in benzene (5 cm³) was treated with peracetic acid (40% w/v; 0.2 cm³, 1 mmol). After 7 days the mixture was poured into ether. The ethereal solution was washed with aqueous sodium carbonate, dried, and evaporated under reduced pressure to yield the *sulphone* (10a) (73 mg, 58%), which was purified by chromatography on silica (elution with chloroform) and recrystallisation from chloroform–petroleum, giving white needles, m.p. 45—49 °C (Found: C, 47.5; H, 6.8; S, 18.2. $C_7H_{12}SO_3$ requires C, 47.7; H, 6.9; S, 18.2%), $\nu_{max.}$ ($CHCl_3$) 1 755 (C=O), 1 128 (SO_2 sym.), and 1 325 (SO_2 asym.), τ ($CDCl_3$) 6.0—7.0 (3 H, m, CH_2·CH) and 8.5—8.75 (9 H, m, 3 Me), τ ($CDCl_3$; after shaking with D_2O–K_2CO_3) 6.29 and 6.83 (2 H, ABq, J 13 Hz, CH_2), 8.59 and 8.60 (2 × 3 H, s, 2 Me), and 8.64br (3 H, probably $CDCH_3$).

Thermal Rearrangement of the Sulphoxide (4) *in Acetic Anhydride.*—A solution of the sulphoxide (385 mg) in acetic anhydride (3 cm³) was refluxed for 1 h, poured into water, and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated under reduced pressure. The n.m.r. spectrum of the crude product (387 mg, 77%) showed only peaks attributable to 3,5,5-trimethyl-4-oxothiolan-3-yl acetate (6b), and after purification the product (226 mg) was shown to be identical with the material obtained previously (m.p., i.r. and n.m.r. spectra, and t.l.c.).

Reaction of the Sulphoxide (4) *with Norbornene.*—A stirred solution of the sulphoxide (300 mg) in norbornene (3 g) was heated at 115 °C for 1 h. The mixture was chromatographed on silica (elution first with 25% ether–petroleum and then with ether) to yield *di-(2-norbornyl) sulphoxide* (12a) (173 mg, 35%), which was recrystallised from petroleum to give white plates, m.p. 101—102 °C (Found: C, 70.7; H, 8.9; S, 13.5%; M^+, 238.139 1. $C_{14}H_{20}SO$ requires C, 71.1; H, 8.5; S, 13.5%; M, 238.138 5), $\nu_{max.}$ ($CHCl_3$) 1 030 cm^{-1} (SO), τ ($CDCl_3$) 7.2—9.0 (m, CH_2 and CH), *m/e* 238 (M^+, 7%), 222 ($M^+ - O$, 7), 127 (57), 95 (norbornyl, 100), and 67 (62). The product (100 mg, 0.42 mmol) in benzene (5 cm³) was treated with peracetic acid (40% w/v; 0.5 cm³, 2.5 mmol); after 15 h, work-up and chromatography as before gave the *sulphone* (12b) (100 mg, 94%) as stout white needles, m.p. 85—91 °C (Found: C, 66.5; H, 8.5; S, 12.3%; M^+, 254.133 8. $C_{14}H_{22}SO_2$ requires C, 66.1; H, 8.7; S, 12.6%; M, 254.134 0), $\nu_{max.}$ ($CHCl_3$) 1 140 and 1 314 cm^{-1} (SO_2), τ ($CDCl_3$) 7.2—9.0 (m, CH_2 and CH), *m/e* 254 (M^+, < 1%), 95 (norbornyl, 100), and 67 (22).

Reaction of the Sulphoxide (4) *with Trimethylsilyl Chloride–Hexamethyldisilazane.*—The sulphoxide (160 mg), trimethylsilyl chloride (306 mg), and hexamethyldisilazane (176 mg) in benzene (10 cm³) were heated under reflux for 1¼ h under dry nitrogen. The solvent was removed under reduced pressure; the yellow oil which remained (260 mg) was mainly 2,4-dimethyl-4-(trimethylsilylsulphinyl)pent-1-en-3-one (5b), contaminated with *ca.* 10% of the normal sulphoxide rearrangement products; $\nu_{max.}$ (film) 1 695 cm^{-1} (αβ-unsaturated C=O), τ ($CDCl_3$) 4.22 and 4.56 (2 H, multiplets, C=CH_2), 8.14 (3 H, m, allylic coupling, CH_3·C=C), 8.60 (6 H, s, CMe_2), and 9.88 (9 H, s, $SiMe_3$). If this product was bulb distilled (bath 80 °C; 10^{-3} mmHg) or the reaction time was increased to several hours, then *2,2,4-trimethyl-3-(trimethylsilyloxy)-Δ³-thiolen 1-oxide* (13) was obtained as a water-white liquid (Found: M^+, 232.095 7. $C_{10}H_{20}SSiO_2$ requires M, 232.0953), $\nu_{max.}$ (film), 1 070 (SO) and 1 698 cm^{-1} (C=C);[11] τ ($CDCl_3$) 6.51 and 6.99 (2 H, ABq, J 15 Hz, CH_2), 8.50 (3 H, s, CH_3·C=C), 8.77 and 8.82 (2 × 3 H, s, CMe_2), and 9.85 (9 H, s, $SiMe_3$), *m/e* 232 (M^+, 14%), 216 ($M^+ - O$, 5), 201 (17), 184 ($M^+ - SO$, 53), 169 (24), 75 (60), and 73 (100).

[6/1422 *Received*, 20*th July*, 1976]

* The α-methyl group *trans* to the S–O bond is assigned the signal at higher field; *cf.* refs. 9 and 10.

[10] R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 1408; D. H. R. Barton, F. Comer, D. G. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1059.

[11] H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, 1969, **34**, 2324.