Transformations of Penicillins. Part IV.[1] On the Trapping of Sulphenic Acids from Penicillins with Thiols

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On heating, penicillin *S*-oxides form equilibrium mixtures with the corresponding sulphenic acids. The sulphenic acids can be trapped intermolecularly with a variety of reagents, including thiols. The disulphides (3) so obtained react with trialkyl phosphites to produce the corresponding sulphides, the alkyl residue arising from the phosphite reagent. Cleavage of the nitrogen-containing substituent from the disulphides or sulphides was effected by addition of diazomethane across the double bond of the unsaturated ester to give an epimeric mixture of pyrazolines, which was then treated with base or reduced. The pyrazolines could also be reduced with *NN'*-dihydrobenzo[*c*]-cinnoline, a new, mild reducing agent.

HEATING penicillin *S*-oxides [*e.g.* (1; R = $CH_2 \cdot CCl_3$)] produces the isomeric sulphenic acids [*e.g.* (2)], which have proved to be versatile species. Thus, modification of penicillins,[2] the incorporation of deuterium by isotopic exchange,[3] reductions,[4] and the inversion of the sulphoxide configuration [5] have all been effected *via* such intermediates. The present paper describes the extension of the synthetic utility of these sulphenic acid intermediates by using intermolecular trapping reactions.

Relatively little is known about the chemistry of alkanesulphenic acids, since these species are often unstable and disproportionate into thiolsulphinates,[6] or disulphides and thiolsulphonates.[7] Sulphenic acids have been invoked as intermediates in the oxidation of thiols into disulphides, the intermediate acid reacting with more thiol to give the disulphide and water.[8] In view of the latter observation it seemed reasonable to attempt the trapping of the penicillin sulphenic acid (2) with a thiol. The resulting disulphides (3) are of interest in that they may be used for the preparation of modified penicillins. The thiol group of the cleaved thiazoline ring is protected as a disulphide system but can be liberated when required, for example by mild reduction or nucleophilic attack.

The sulphoxide (1; R = $CH_2 \cdot CCl_3$) was dissolved in cyclohexanethiol containing a trace of aluminium tribromide and the solution was heated to reflux for 1 min. Chromatography of the products afforded a small amount of the disulphide (3; R = C_6H_{11}). Its ^1H n.m.r. spectrum was fully consistent with the assigned structure and its i.r. spectrum showed that the β-lactam carbonyl absorption had shifted from 1800 in the starting material to 1775 cm^{-1}. The aluminium tribromide reagent was originally added as a buffer to inhibit attack of any free thiolate anion on the β-lactam function of the substrate. However, with either freshly distilled 2-methylpropane-1-thiol or butane-1-thiol such buffers were unnecessary: both thiols gave good yields of the corresponding disulphides (3; R = Bu^i or Bu^n). Dilution of the thiol with added solvents decreased the yield of the disulphides, which were best obtained with the neat thiol as reaction medium.

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[2] 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; R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, 1971, **36**, 1259.

[3] D. H. R. Barton, F. Comer, D. G. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1059; R. D. G. Cooper, *J. Amer. Chem. Soc.*, 1970, **92**, 5010.

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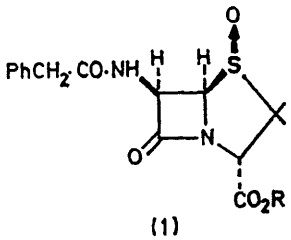
[6] T. Colclough and J. I. Cuneen, *Chem. and Ind.*, 1960, 626; A. Burawoy and A. Chaudhuri, *J. Chem. Soc.*, 1956, 653; J. P. Danehy, *Quart. Reports Sulphur Chem.*, 1971, **6**, 103.

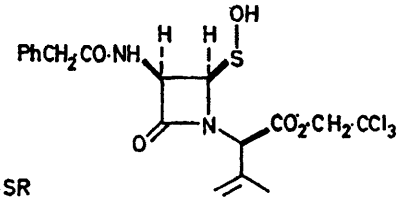
[7] J. R. Shelton and K. E. Davis, *J. Amer. Chem. Soc.*, 1967, **89**, 718.

[8] K. Sirakawa, O. Aki, T. Tsujikawa, and T. Tsuda, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 235; J. P. Danehy and M. Y. Oester, *J. Org. Chem.*, 1967, **32**, 1491.

In each trapping reaction only the conjugated esters were produced; no evidence for the presence of the



(1)



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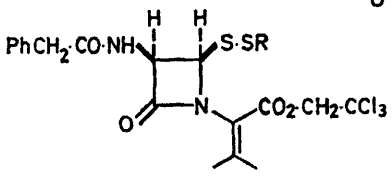

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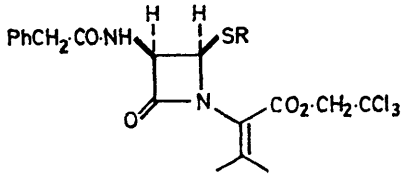
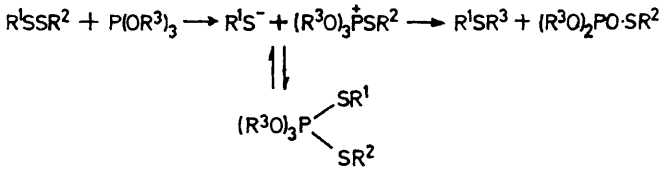


(4)

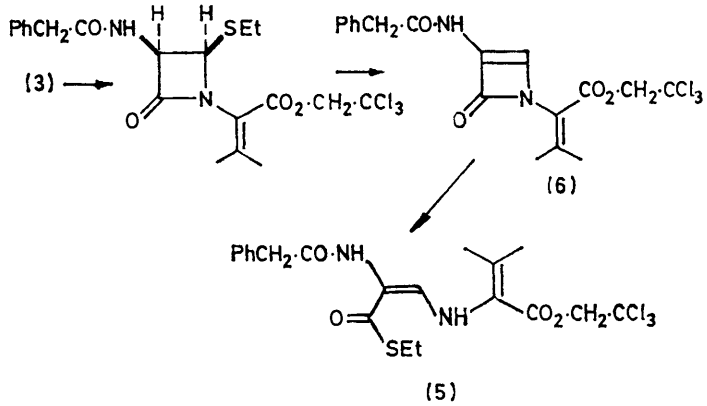
βγ-unsaturated isomers was found. Analogous trapping reactions with the free penicillanic acid *S*-oxide (1; R = H) were abortive, only non-β-lactam-containing products being observed.

Trialkyl phosphites readily react with disulphides.[9] The reaction may be represented as an initial displacement of thiolate anion from the disulphide followed by attack of the thiolate ion on the resulting phosphonium product (Scheme 1) to yield an alkyl sulphide (*cf.* the Michaelis–Arbusov reaction[10]). Treatment of the 2-methylpropyl disulphide (3; R = Bu^i) with 2 equiv. of trimethyl phosphite in refluxing benzene for 30 min gave one major product containing a β-lactam function. This was identified as the expected methylthio-compound



SCHEME 1

(4; R = Me). A similar reaction involving triethyl phosphite produced the analogous ethylthio-derivative (4; R = Et), together with an optically inactive crystalline product, which did not contain a β-lactam group. This side product was isomeric with the ethylthio-derivative (4; R = Et) and had $\nu_{max.}$ 1730 (unsaturated ester) and 1660 cm^{-1}, the latter band being attributed to a thiolester carbonyl absorption. The side product therefore has structure (5). Nucleophilic attack at disulphide bonds usually occurs at the sulphur atom *not* bearing the more electronegative substituent,[11] which is consistent with the observed formation of the sulphides (4). The product (5), however, could be formed by competing attack of the triethyl phosphite on the initial product (4; R = Et), followed by elimination to form the unsaturated lactam (6) and rapid attack at the β-lactam group by the ethyl



SCHEME 2

thiolate anion liberated (Scheme 2). The intermediate formation of quinquecovalent phosphorus derivatives is also possible in these reactions.[12]

[9] A. J. Parker and N. Kharasch, *Chem. Rev.*, 1959, **59**, 583.
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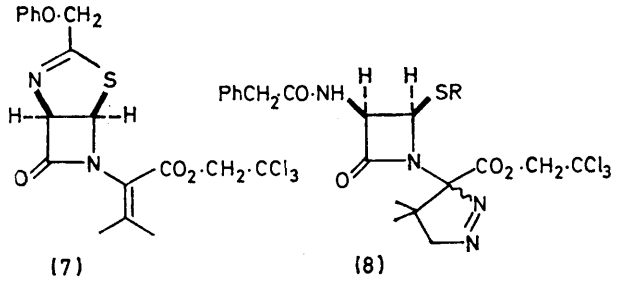
[11] A. J. Parker and N. Kharasch, *J. Amer. Chem. Soc.*, 1960, **82**, 3071.
[12] D. H. R. Barton, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, B. E. Looker, and W. G. E. Underwood, *Chem. Comm.*, 1971, 1137; H. I. Jacobson, R. G. Harvey, and E. V. Jensen, *J. Amer. Chem. Soc.*, 1955, **77**, 6064; A. C. Poshkus and J. E. Herweh, *ibid.*, 1957, **79**, 4245; C. Walling and R. Rabinowitz, *ibid.*, 1959, **81**, 1243; R. G. Harvey, H. I. Jacobson, and E. V. Jensen, *ibid.*, 1963, **85**, 1618; R. S. Davidson, *J. Chem. Soc.* (*C*), 1967, 2131.

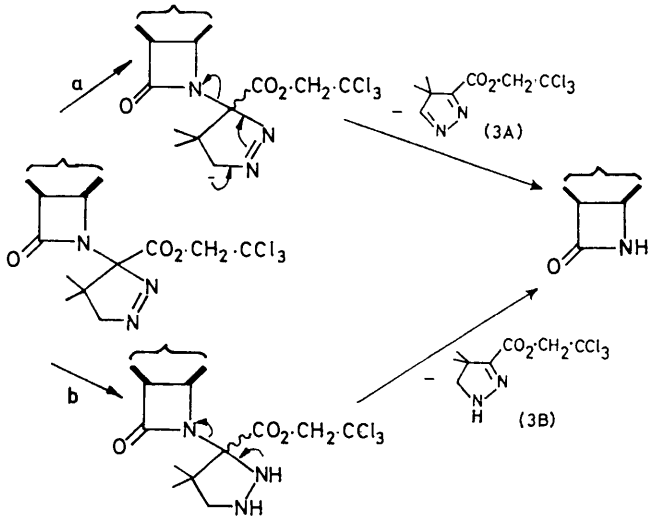
The alkylation of the disulphides with trialkyl phosphites is in contrast to the results obtained in the reduction of the sulphenic acid [*cf.* (2)] derived from



(7) (8)

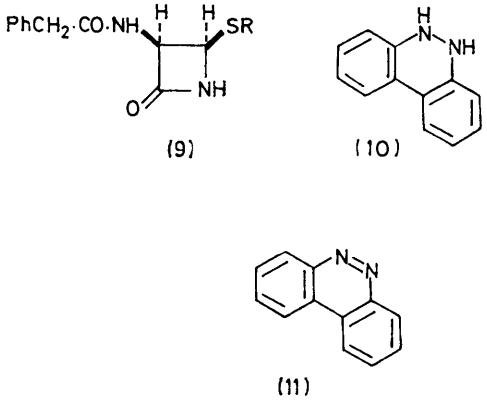
penicillin V *S*-oxide, with trimethyl phosphite. In this case the thiazoline (7) is formed by preferential attack of the thiolate anion on the side chain phenoxyacetamido-group.[4]

In order to extend the synthetic utility of the disulphide (3), isolation of the γ-lactam unit by cleavage of the residual carbon skeleton from the nitrogen atom is required. Recently such removal of the nitrogen substituent has been achieved by oxidation with reagents such as osmium tetroxide or potassium permanganate.[13] In the present instance such oxidative methods are too vigorous, resulting in degradation of the disulphide function, and so an alternative method was



SCHEME 3

developed. In essence this involves the generation of an internal nucleophile which can displace the β-lactam unit.[14] Such an intramolecular nucleophilic centre was introduced by 1,3-dipolar addition of diazomethane across the conjugated ester chromophore[15] of either the disulphide (3) or the sulphide (4). In each case a mixture of two stereoisomeric pyrazolines (8) was formed, which could be used without further purification. Two subsequent procedures for releasing the β-lactam system were possible (Scheme 3). For example, the ethylthio-derivative (8; R = Et) was treated with potassium t-butoxide in t-butyl alcohol for 1 min at room temperature to afford, albeit in low (20%) yield, the required β-lactam derivative (9; R = Et) (Scheme 3, path a). Presumably the pyrazole fragment (3a) was also formed, although this was not isolated. Alternatively, the pyrazoline derivatives could be reduced (Scheme 3, path b). Amongst the successful reducing agents tried were zinc in acetic acid, chromium(II) acetate,[16] and *NN'*-dihydrobenzo[*c*]cinnoline[17] (10). The last reductant, which is an extremely mild reagent,



(9) (10) (11)

is thereby converted into the aromatic benzo[*c*]cinnoline (11). The aromatic species can be removed either by chromatography or by extraction with dilute acid. The dihydro-compound (10) will also reduce azobenzene to hydrazobenzene.

These reductions of the diazomethane adducts liberated both the β-lactam fragment and the corresponding pyrazoline (3b) (Scheme 3), which appeared to resist further mild reduction, *e.g.* with either chromium(II) acetate or the dihydrobenzo[*c*]cinnoline (10). The isolated pyrazoline (3b) was identical with the product obtained by addition of diazomethane across trichloroethyl ββ-dimethylacrylate.

By the application of such reductive methods the disulphide (8; R = SBu^n), which was decomposed by base, afforded the free disulphide (9; R = SBu^n). The isobutyl disulphide (9; R = SBu^i) was also prepared by the pyrazoline route by use of these reducing agents.

The sulphide adducts (8; R = Me or Et) could also be reduced to the corresponding azetidinones. In an alternative route to the latter compound the intermediate disulphide–diazomethane adduct (8; R =

[13] E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1972, 229.
[14] D. H. R. Barton, D. G. T. Greig, P. G. Sammes, and M. V. Taylor, *Chem. Comm.*, 1971, 845.
[15] E. Büchner, *Annalen*, 1893, **273**, 214.
[16] D. H. R. Barton, N. K. Basu, R. H. Hesse, F. S. Morehouse, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1966, **88**, 3016.
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SBu^i) was also treated with triethyl phosphite, to give the same mixture of pyrazolines as obtained by the addition of diazomethane to the *S*-ethyl derivative (4; R = Et).

EXPERIMENTAL

I.r. spectra were recorded on a Unicam SP 200 spectrometer for Nujol mulls, unless otherwise stated. Mass spectra were determined with an A.E.I. MS9 machine, important peaks being assigned by accurate mass measurements. ^{1}H N.m.r. spectra were recorded with a Varian T60 instrument for solutions in deuteriochloroform containing tetramethylsilane as internal reference. Reactions were monitored by t.l.c. on Merck silica gel GF_{254} with acetone–benzene and ethyl acetate–benzene as solvents. Light petroleum refers to the fraction of boiling range 60—80°. M.p.s were determined with a Kofler hot-stage apparatus.

2,2,2-*Trichloroethyl* α-[(2R,3R)-2-*Cyclohexyldithio*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]-α-*isopropylideneacetate* (3; R = C_6H_{11}).—A solution of the penicillin *S*-oxide (1; R = $CH_2{\cdot}CCl_3$) (0·50 g) in cyclohexanethiol (20 ml; redistilled) containing a catalytic amount of aluminium tribromide (*ca.* 5 mg) was rapidly heated to reflux for 1 min. The mixture was evaporated under reduced pressure and the residue chromatographed through silica (20 g), with 1 : 10 ethyl acetate–benzene as eluant, to afford the *disulphide* (0·17 g, 28%), m.p. 108—110° (from ether), $[\alpha]_D^{24}$ +6° (*c* 1·6 in $CHCl_3$), $\nu_{max.}$ 3300 (NH), 1775 (β-lactam), 1735 (unsaturated ester), 1660 (amide), and 1560 cm^{-1} (amide), τ 2·69br (5H, s, Ph), 3·87 (1H, d, *J* 8 Hz, amide NH), 4·62 (1H, d, *J* 4 Hz, 2-H), 4·81 (1H, dd, *J* 4 and 8 Hz, 3-H), 5·23 (2H, AB q, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·37 (2H, s, CH_2Ph), 7·48 (1H, m, $SCHR_2$), 7·68 (3H, s, geminal Me), 7·84 (3H, s, geminal Me), and 8·22 and 8·78 (10H, m, cyclohexyl protons), *m/e* 578 (M^+, 2%), 463 (10), and 431 (100) (Found: C, 49·7; H, 5·3; Cl, 18·3; N, 4·6; S, 11·1, $C_{24}H_{29}Cl_3N_2O_4S_2$ requires C, 49·7; H, 5·0; Cl, 18·3; N, 4·8; S, 11·1%).

2,2,2-*Trichloroethyl* α-*Isopropylidene*-α-[(2R,3R)-2-(2-*methylpropyldithio*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]-*acetate* (3; R = Bu^i).—The penicillin *S*-oxide (1; R = $CH_2{\cdot}CCl_3$) (15·0 g) in freshly distilled 2-methylpropane-1-thiol (300 ml) was heated to reflux for 120 h. The mixture was evaporated under reduced pressure and the solid residue crystallised from ether to give the *disulphide* (11·2 g, 65%), m.p. 103—104°, $[\alpha]_D^{24}$ +3° (*c* 3·6 in $CHCl_3$), $\nu_{max.}$ 3350 (NH), 1770 (β-lactam), (CCl_3) 1735 (unsaturated ester), 1660 (amide), 1560 (amide), and 715 cm^{-1} (CCl_3) τ 2·72br (5H, s, Ph), 3·92 (1H, d, *J* 8 Hz, NH), 4·56 (1H, d, *J* 4 Hz, 2-H), 4·76 (1H, dd, *J* 4 and 8 Hz, 3-H), 5·23 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·32 (2H, s, CH_2Ph), 7·52 (2H, d, *J* 7 Hz, SCH_2), 7·64 (3H, s, geminal Me), 7·84 (3H, s, geminal Me), 8·32 (1H, m, $CH_2{\cdot}CH$), and 9·06 [6H, d, $(CH_3)_2CH$], *m/e* 552 (10%), 463 (100), and 431 (100) (Found: C, 47·8; H, 4·9; Cl, 19·0; N, 5·0; S, 11·8. $C_{22}H_{27}Cl_3N_2O_4S_2$ requires C, 47·8; H, 4·9; Cl, 19·2; N, 5·1; S, 11·6%).

2,2,2-*Trichloroethyl* α-[(2R,3R)-2-*Butyldithio*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]-α-*isopropylideneacetate* (3; R = Bu^n).—In a similar manner, the sulphoxide (1; R = $CH_2{\cdot}CCl_3$) (20 g) in freshly distilled butane-1-thiol (200 ml) was heated to reflux for 96 h. The mixture was worked up to give the *disulphide* (16·1 g, 70%), m.p. 97° (from ether–cyclohexane), $[\alpha]_D^{25}$ +14° (*c* 2·0 in $CHCl_3$), $\nu_{max.}$ 3350 (NH), 1770 (β-lactam), 1735 (unsaturated ester), 1660 (amide), 1560 (amide), and 715 cm^{-1} (CCl_3), τ 2·70 (5H, s, Ph), 3·72 (1H, d, *J* 8 Hz, NH), 4·60 (1H, d, *J* 4 Hz, 2-H), 4·80 (1H, dd, *J* 4 and 8 Hz, 3-H), 5·00 and 5·40 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·36 (2H, s, CH_2Ph), 7·5 (2H, t, $CH_2{\cdot}S$), 7·65 (3H, s, geminal Me), 7·83 (3H, s, geminal Me), and 8·3—9·1 (7H, m) (Found: C, 47·8; H, 5·0; Cl, 19·5; N, 4·9; S, 11·4. $C_{22}H_{27}Cl_3N_2O_4S_2$ requires C, 47·8; H, 4·9; Cl, 19·2; N, 5·1; S, 11·6%).

2,2,2-*Trichloroethyl* α-*Isopropylidene*-α-[(2R,3R)-2-*methylthio*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]*acetate* (4; R = Me).—The disulphide (3; R = Bu^i) (1·0 g) in freshly distilled trimethyl phosphite (0·43 ml) and benzene (50 ml) was heated to reflux for 30 min. The mixture was then evaporated under reduced pressure and the residue triturated with light petroleum (3×) to afford the *sulphide* (0·58 g, 67%) as a foam, $[\alpha]_D^{23}$ −3° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ ($CHBr_3$) 3400 (NH), 1765 (β-lactam), 1735 (unsaturated ester), 1680 (amide), and 1525 cm^{-1} (amide), τ 2·63br (5H, s, Ph), 3·61 (1H, d, *J* 8 Hz, NH), 4·52 (1H, dd, *J* 4 and 8 Hz, 3-H), 4·74 (1H, d, *J* 4 Hz, 2-H), 5·21 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 6·33 (2H, s, CH_2Ph), 7·63 (3H, s, geminal Me), 7·94 (3H, s, geminal Me), 8·09 (3H, s, SMe) (Found: M^+, 478·0297; C, 47·6, H, 4·3; N, 5·8. $C_{19}H_{21}Cl_3N_2O_4S$ requires *M*, 478·0287; C, 47·6; H, 4·4; N, 5·8%)

2,2,2-*Trichloroethyl* α-[(2R,3R)-2-*Ethylthio*-4-*oxo*-3-*phenylacetamidoazetidin*-1-*yl*]-α-*isopropylideneacetate* (4; R = Et).—The disulphide (3; R = Bu^i) (10·0 g) in dry benzene (100 ml) containing freshly distilled triethyl phosphite (6·1 ml) was heated to reflux for 10 min. The mixture was then evaporated to give a gum which was triturated with light petroleum, before chromatography through silica (200 g), with 1 : 10 ethyl acetate–benzene as eluant, to afford the *ethyl sulphide* (2·60 g, 29%) as a foam, $[\alpha]_D^{31}$ −3° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$), 3350 (NH), 1760 (β-lactam), 1735 (unsaturated ester), 1690 (amide), and 1540 cm^{-1} (amide), τ 2·78br (5H, s, Ph), 3·54 (1H, d, *J* 8 Hz, NH), 4·76 (1H, dd, *J* 4 and 8 Hz, 3-H), 4·80 (1H, d, *J* 4 Hz, 2-H), 5·20 (2H, ABq, *J* 12 Hz, $CH_2{\cdot}CCl_3$), 7·86 (2H, q, $S{\cdot}CH_2{\cdot}CH_3$), 8·02 (3H, s, geminal Me), 6·50 (2H, s, CH_2Ph), 7·70 (3H, s, geminal Me), and 8·88 (3H, t, $S{\cdot}CH_2{\cdot}CH_3$) (Found: M^+ 492·0436. $C_{20}H_{23}Cl_3N_2O_4S$ requires *M*, 492·0444).

Further elution of the column with 1 : 4 ethyl acetate–benzene gave 2,2,2-*trichloroethyl* 5-[(*ethylthio*)*carbonyl*]-2-*isopropylidene*-5-*phenylacetamido*-3-*azapent*-4-*enoate* (5) (0·90 g, 10%), m.p. 137—138° (from benzene), $[\alpha]_D^{25}$ 0·00° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ 3200br (amine and amide NH), 1730 (unsaturated ester), 1660 (thiolester), 1650 (amide), and 1600 cm^{-1} (C=C), $\lambda_{max.}$ (EtOH) 284 nm (ε 7800), τ 2·42 (1H, exchanged by D_2O, s, NH), 2·68br (6H, s, Ph and vinylic H), 3·24 (1H, exchanged by D_2O, s, NH), 5·25 (2H, s, $CH_2{\cdot}CCl_3$), 6·32 (2H, s, CH_2Ph), 7·26 (2H, q, $S{\cdot}CH_2{\cdot}CH_3$), 7·80 (3H, s, geminal Me), 8·18 (3H, s, geminal Me), and 8·70 (3H, t, $S{\cdot}CH_2{\cdot}CH_3$) (Found: C, 48·95; H, 4·6; Cl, 21·3; N, 5·5; S, 6·5. $C_{20}H_{23}Cl_3N_2O_4S$ requires C, 48·7; H, 4·7; Cl, 21·6; N, 5·7; S, 6·5%).

Reaction of the Isobutyl Disulphide (3; R = Bu^i) *with Diazomethane*.—The disulphide (0·50 g) in ether (20 ml) was treated with a large excess of diazomethane in ether at 0—5° for 6 days. Evaporation yielded, as a foam, the two epimers of 2,2,2-trichloroethyl 4,4-dimethyl-3ξ-[(2*R*,3*R*)-2-(2-methylpropyldithio)-4-oxo-3-phenylacetamidoazetidin-1-yl]-Δ^1-pyrazoline-3ξ-carboxylate (8; R = SBu^i) (0·54 g, 99%), the more polar epimer constituting

about 80% of the mixture. Chromatography on silica (10 g) with 1 : 10 ethyl acetate–benzene as eluant afforded the *less polar isomer* as a foam, $[\alpha]_D^{24}$ −141° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3350 (NH), 1775 (β-lactam), 1750 (saturated ester), 1670 (amide), and 1540 cm^{-1} (amide), $\lambda_{max.}$ (EtOH) 334 nm (ε 200), τ 2·63br (5H, s, Ph), 3·80 (1H, d, *J* 8 Hz, NH), 4·41 (2H, m, azetidine 2- and 3-H), 5·22 (2H, s, $CH_2{\cdot}CCl_3$), 5·30 (2H, ABq, *J* 16 Hz, pyrazoline protons), 6·30 (2H, s, CH_2Ph), 7·33 (2H, m, $SCH_2{\cdot}CH$), 8·20 (1H, m, $SCH_2{\cdot}CH$), 8·70 (3H, s, geminal Me), 8·92 (3H, s, geminal Me), and 9·03 [6H, d, *J* 6 Hz, $CH(CH_3)_2$] (Found: C, 46·3; H, 4·8; Cl, 17·9; N, 9·5; S, 10·5; $C_{23}H_{29}Cl_3N_4O_4S_2$ requires C, 46·4; H, 4·9; Cl, 17·9; N, 9·4; S, 10·8%).

Further elution with 1 : 10 ethyl acetate–benzene afforded the *more polar epimer* as a foam, $[\alpha]_D^{29}$ −41°, $\nu_{max.}$ ($CHCl_3$) 3350 (NH), 1775 (β-lactam), 1750 (saturated ester), 1670 (amide), and 1540 cm^{-1} (amide), $\lambda_{max.}$ 334 nm (ε 120), τ 2·62br (5H, s, Ph), 3·74 (1H, d, *J* 8 Hz, NH), 4·30 (1H, dd, *J* 4 and 8 Hz, azetidine 3-H), 4·70 (1H, d, *J* 4 Hz, azetidine 2-H), 5·30 (2H, s, $CH_2{\cdot}CCl_3$), 5·36 (2H, ABq, *J* 16 Hz, pyrazoline protons), 6·32 (2H, s, CH_2Ph), 7·40 (2H, m, $SCH_2{\cdot}CH$), 8·30 (1H, m, $SCH_2{\cdot}CH$), 8·62 (3H, s, geminal Me), and 9·05 [9H, m, geminal Me and $S{\cdot}CH_2{\cdot}CH(CH_3)_2$] (Found: C, 46·3; H, 4·8; Cl, 17·9; N, 9·5; S, 10·5%).

Reaction of the Butyl Disulphide (3; R = Bu^n) *with Diazomethane.*—A solution of the disulphide (5 g) in ether (50 ml) was treated with a large excess of diazomethane in ether at 0° for 5 days. Removal of the solvent afforded, as a foam, a mixture of the corresponding pyrazolines (8; R = SBu^n) (5·4 g, 99%): the major epimer of the mixture constituted about 80% of the total. The mixture was used without further purification.

Reaction of the Sulphides (4) *with Diazomethane.*—(a) *Ethyl series.* The ethylthio-compound (4; R = Et) (1·50 g) in ether (60 ml) was treated with an excess of diazomethane at 0—5° for 6 days. Evaporation yielded, as a foam, 2,2,2-trichloroethyl 3ξ-[(2*R*,3*R*)-2-ethylthio-4-oxo-3-phenylacetamidoazetidin-1-yl]-4,4-dimethyl-Δ¹-pyrazoline-3ξ-carboxylate (8; R = Et) (1·62 g, 99%) as a mixture of two epimers. The polar epimer constituted about 80% of the mixture. Chromatography on silica gel (30 g) with 1 : 10 ethyl acetate–benzene as eluant gave the *less polar epimer* as a foam, $[\alpha]_D^{30}$ −142° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3350 (NH), 1775 (β-lactam), 1750 (saturated ester), 1670 (amide), and 1540 cm^{-1} (amide), $\lambda_{max.}$ 330 nm (ε 230), τ 2·68br (5H, s, Ph), 3·76 (1H, d, *J* 8 Hz, NH), 4·50 (2H, m, azetidine 2- and 3-H), 5·22 (2H, s, $CH_2{\cdot}CCl_3$), 5·22 (2H, ABq, *J* 16 Hz, pyrazoline protons), 6·30 (2H, s, CH_2Ph), 7·48 (2H, q, $S{\cdot}CH_2{\cdot}CH_3$), and 8·90 (9H, m, $S{\cdot}CH_2{\cdot}CH_3$ and geminal Me) [Found: *m/e* 506·0594 ($M^+ - N_2$). $C_{21}H_{36}Cl_3N_2O_4S$ requires 506·0601].

Further elution of the column gave the *more polar epimer* as a foam, $[\alpha]_D^{30}$ +33° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3350 (NH), 1775 (β-lactam), 1750 (saturated ester), 1670 (amide), and 1540 cm^{-1} (amide), $\lambda_{max.}$ 330 nm (ε 110), γ 2·68br (5H, s, Ph), 3·74 (1H, d, *J* 8 Hz, NH), 4·26 (1H, dd, *J* 4 and 8 Hz, azetidine 3-H), 4·64 (1H, d, *J* 4 Hz, azetidine 2-H), 5·30 (2H, s, $CH_2{\cdot}CCl_3$), 5·28 and 5·38 (2H, ABq, *J* 16 Hz, pyrazoline protons), 6·34 (2H, s, CH_2Ph), 7·36 (2H, q, $SCH_2{\cdot}CH_3$), and 8·75 (9H, m, $S{\cdot}CH_2{\cdot}CH_3$ and geminal Me) (Found: *m/e* 506·0604).

(b) *Methyl series.* In a similar manner to the ethyl sulphide, the methyl sulphide (4; R = Me) (1·0 g) was treated with an excess of diazomethane. Removal of the solvent ether yielded, as a foam, a mixture of the corresponding pyrazolines (1·0 g, 95%). This material was used without further separation.

Reaction between the Pyrazolines (8; R = SBu^i) *and Triethyl Phosphite.*—A solution of the two pyrazoline epimers (0·50 g; obtained directly from the diazomethane addition reaction) in dry benzene (25 ml) was heated to reflux with triethyl phosphite (0·28 ml) for 1 min. The mixture was then rapidly evaporated to dryness under reduced pressure and the residue subjected to preparative t.l.c. to give, as an amorphous solid, the ethyl sulphides (8; R = Et) (0·045 g, 10%), identical with the material prepared previously.

Cleavage of the Pyrazolines.—(a) *Potassium t-Butoxide.* The ethyl sulphide pyrazolines (8; R = Et) (0·15 g) in anhydrous t-butyl alcohol (5 ml) were added to a solution of potassium t-butoxide (0·03 g) in t-butyl alcohol (5 ml) with vigorous stirring at room temperature. After 1 min the mixture was poured into water (100 ml) and ethyl acetate (100 ml). The organic extract was washed with water (100 ml), aqueous washings being washed with more ethyl acetate (100 ml). The combined organic extracts were dried and evaporated, and the residue was purified by preparative t.l.c. (2 : 1 ethyl acetate–benzene) to give (3*R*,4*R*)-4-ethylthio-3-phenylacetamidoazetidin-2-one (9; R = Et) (0·015 g, 21%), m.p. 168—169° (from benzene), $[\alpha]_D^{28}$ −7° (*c* 1·0 in $CHCl_3$), identical with an authentic sample.[18] This compound was also obtained (90%) by reduction of the pyrazolines (8; R = Et) with zinc–acetic acid.

(b) *Zinc–Acetic acid.* The isobutyl disulphide pyrazoline mixture (8; R = SBu^i) (1·6 g) in 2 : 1 acetic acid–water (120 ml.) at 0° was treated with zinc dust (3·2 g) with vigorous stirring. After 40 min the mixture was filtered, extracted with ethyl acetate, washed with water, dried, and evaporated to dryness to give, after preparative t.l.c., (3R,4R)-4-(2-*methylpropyldithio*)-3-*phenylacetamidoazetidin*-2-*one* (9; R = SBu^i) (0·27 g, 31%) as an amorphous foam, $[\alpha]_D^{20}$ +161° (*c* 1·0 in dioxan), $\nu_{max.}$ ($CHBr_3$) 3420, 3300 (NH), 1780 (β-lactam), 1678 (amide), and 1510 cm^{-1} (amide), τ 2·67br (5H, s, Ph), 3·20 (1H, s, NH), 3·44 (1H, d, *J* 9 Hz, NH), 4·44 (1H, dd, *J* 5 and 9 Hz, 3-H), 5·08 (1H, d, *J* 5 Hz, 4-H), 6·37 (2H, s, CH_2Ph), 7·44 (2H, d, *J* 7 Hz, $S{\cdot}CH_2$), 8·0—8·4 (1H, m, $CHMe_2$), and 9·04 (6H, d, *J* 7 Hz, $CHMe_2$) (Found: C, 55·5; H, 6·2; N, 8·5; S, 19·6. $C_{15}H_{20}N_2O_2S_2$ requires C, 55·55; H, 6·2; N, 8·6; S, 19·7%).

In a similar manner the butyl disulphide (8; R = Bu^n) (1·0 g) was reduced with zinc dust in aqueous acetic acid to yield, after preparative t.l.c., (3R,4R)-4-*butyldithio*-3-*phenylacetamidoazetidin*-2-*one* (9; R = SBu^n) (0·16 g, 30%), m.p. 101—105° (from ether), $[\alpha]_D^{25}$ +228° (*c* 2·0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3420, 3300 (NH), 1780 (β-lactam), 1678 (amide), and 1510 cm^{-1} (amide), τ 2·70 (5H, s, Ph), 3·05 (1H, s, NH), 3·27 (1H, d, *J* 9 Hz, NH), 4·48 (1H, dd, *J* 4 and 9 Hz, 3-H), 5·10 (1H, d, *J* 4 Hz, 4-H), 6·40 (2H, s, CH_2Ph), 7·35 (2H, t, $S{\cdot}CH_2$), and 8·3—9·2 (7H, m). (Found: C, 55·6; H, 6·15; N, 8·6; S, 19·6. $C_{15}H_{20}N_2O_2S_2$ requires C, 55·55; H, 6·2; N, 8·6; S, 19·7%).

The methyl sulphide (8; R = Me) (1·0 g) was treated under similar conditions with zinc dust and aqueous acetic

[18] 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, following paper.

acid to afford the corresponding (3R,4R)-4-*methylthio*-3-*phenylacetamidoazetidin*-2-*one* (9; R = Me) (0·15 g, 30%), m.p. 187—189° (from benzene), $[\alpha]_D^{25}$ −28° (*c* 0·6 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 1765 (β-lactam), 1675 (amide), and 1510 cm^{-1} (amide), τ 1·6 (1H, s, NH), 1·7 (1H, d, *J* 10 Hz, NH), 2·65br (5H, s, Ph), 4·55 (1H, dd, *J* 5 and 10 Hz, 3-H), 5·10 (1H, d, *J* 10 Hz, 4-H), 6·30 (2H, s, CH_2Ph), and 8·02 (3H, s, SCH_3) (Found: C, 57·5; H, 5·7; N, 11·15; S, 12·8. $C_{12}H_{14}N_2O_2S$ requires C, 57·5; H, 5·6; N, 11·2; S, 12·8%).

(c) NN′-*Dihydrobenzo*[c]*cinnoline*. A solution of *NN*′-dihydrobenzo[*c*]cinnoline monohydrochloride (0·20 g) in ethanol (20 ml) was adjusted to pH 7·5 by dropwise addition of triethylamine, the solution being kept under oxygen-free argon. The isobutyl disulphide (8; R = SBu^i) (0·1 g) was added and the solution was stirred for 8 h at room temperature, then evaporated. The residue was extracted with ethyl acetate (25 ml); the extract was washed with water, dried, evaporated, and purified by preparative t.l.c. to give the β-lactam (9; R = SBu^i) (0·02 g, 37%), identical with the specimen prepared previously.

(d) *Chromium*(II) *acetate*. To a solution of the pyrazoline mixture [either (8; R = SBu^n) or (8; R = SBu^i)] (5 g) in ethanol (300 ml) under oxygen-free nitrogen and at room temperature, freshly prepared chromium(II) acetate powder (2·7 mol. equiv.) was added. The mixture was stirred for 3 h, then evaporated to small bulk *in vacuo*, and the residue was extracted with benzene and washed with 5% w/v aqueous tartaric acid. The solution was dried, concentrated, and chromatographed through a column of silica gel (100 g) (1 : 19 ethyl acetate–benzene). The initial product eluted, in both cases, was the pyrazoline (3B), which was followed by the corresponding β-lactams (yields 74 and 70%, respectively), both isolated as crystalline solids. The products were identical with those already described.

Preparation of the Pyrazoline (3B) (by J. Kelly).—An excess of diazomethane in ether was kept with βββ-trichloroethyl ββ-dimethylacrylate for 1 week at 0—5°. Preparative t.l.c. afforded, as the major component, 2,2,2-*trichloroethyl* 4,4-*dimethyl*-Δ²-*pyrazoline*-3-*carboxylate* (3B), as a solid, m.p. 146—148°, $\nu_{max.}$ ($CHCl_3$) 1715, 1550, 1340, and 1105 cm^{-1}, $\lambda_{max.}$ 298 (ε 12,000), τ 5·16 (2H, s), 6·52 (2H, s), and 8·68 (6H, s) (Found: C, 34·95; H, 4·1; N, 10·3. $C_8H_{11}Cl_3N_2O_2$ requires C, 35·1; H, 4·05; N, 10·2%).

Reduction of Azobenzene.—Azobenzene (0·15 g) and *NN*′-dihydrobenzo[*c*]cinnoline monohydrochloride (0·25 g), in ethanol (25 ml) under argon, was adjusted to pH 7·5 with triethylamine. The mixture was stirred at room temperature for 40 min, then poured into water (200 ml) and extracted with ethyl acetate (3 × 20 ml). The extract was washed with 20% v/v phosphoric acid (6 × 20 ml) until the washings were colourless, then with saturated sodium hydrogen carbonate solution (2 × 50 ml) and, finally, with water (50 ml); it was then dried and evaporated to give hydrazobenzene (0·09 g, 60%), identical with an authentic sample.

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