Studies Related to Dihydro-1,4-thiazines. Part IV.[1] Stereochemical Consequences of 1,3-Sulphur Migrations [2]

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Methyl (6*S*,7*R*)-5,5-dimethyl-4-thia-1-aza[7-^{2}H]bicyclo[4.1.0]hept-2-ene-3-carboxylate (2) is thermally isomerised in boiling toluene to methyl (2*R*,3*R*)-3,4-dihydro-3-isopropenyl-2*H*-[2-^{2}H]1,4-thiazine-6-carboxylate (4), indicating that the new carbon–sulphur bond is formed with retention of configuration. The latter derivative is also produced when methyl (3*R*)-3,4-dihydro-3-{(*S*)-iodo[^{2}H]methyl}-2,2-dimethyl-2*H*-1,4-thiazine-6-carboxylate (15), obtained from the reaction of the aziridine (2) with hydriodic acid, is heated in boiling ethyl methyl ketone; in this case the new carbon–sulphur bond is formed with inversion of configuration.

Derivative (2) was synthesised by way of methyl (3*R*)-3,4-dihydro-3-{(*S*)-hydroxy[^{2}H]methyl}-2,2-dimethyl-2*H*-1,4-thiazine-6-carboxylate (13), obtained from the reaction of 6α-chloro-[(S)-3-*methylene*-^{2}H]penicillanyl alcohol (28) with sodium methoxide. The last-named alcohol is prepared by reduction of 6α-chloro[*formyl*-^{2}H]-penicillanal (23) with actively fermenting yeast. 6α-Chloropenicillanoylmethanol (25), available from the reaction of the diazo-ketone (24) with dilute sulphuric acid, affords the aldehyde (23) by reduction with sodium borodeuteride followed by oxidation with sodium periodate.

REARRANGEMENTS involving novel 1,3-sulphur migrations have recently been observed in certain dihydro-1,4-thiazine derivatives.[3] Thus, methyl (6*S*)-5,5-dimethyl-4-thia-1-azabicyclo[4.1.0]hept-2-ene-3-carboxylate (1) was converted into methyl (3*R*)-3,4-dihydro-3-isopropenyl-2*H*-1,4-thiazine-6-carboxylate (3) when heated in boiling toluene. The latter derivative was also formed from methyl (3*R*)-3,4-dihydro-3-iodomethyl-2,2-dimethyl-2*H*-1,4-thiazine-6-carboxylate (7) in boiling ethyl methyl ketone. A study of the rearrangements of the aziridine (1) and the iodide (7), specifically monodeuteriated at the 7-methylene and the exocyclic methylene groups, is expected to provide information about the reorganization mechanisms.

Previously, we attempted to prepare the monodeuteriated thiazinyl alcohol, *e.g.* (13), by way of the lactol (16).[1,4] However, the approach was unsuccessful.

Since monodeuteriated aldehydes can be reduced enzymically with very high stereoselectivity,[5] an attempt was made to prepare the penicillanal (23). It was hoped that this derivative could be converted into the thiazinyl alcohol, *e.g.* (13), by way of the penicillanyl alcohol, *e.g.* (28).

Although the rearrangement of the acid (17) and the

[1] Part III, J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 1973, 1985.

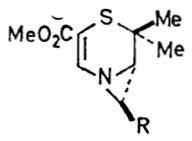
[2] Preliminary communication, J. Kitchin and R. J. Stoodley, *J. Amer. Chem. Soc.*, 1973, **95**, 3439.

[3] A. R. Dunn and R. J. Stoodley, *Chem. Comm.*, 1969, 1169, 1368; *J.C.S. Perkin I*, 1972, 2509.

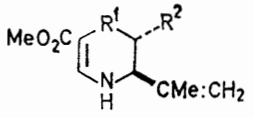
[4] J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 1973, 22.

[5] D. Arigoni and E. L. Eliel, *Topics Stereochem.*, 1969, **4**, 127.

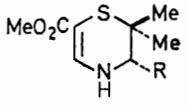
ester (18) to the corresponding thiazine derivatives (11) and (12) is documented,[6] it was necessary to establish that the alcohol (20) reacted in an analogous manner. In the presence of ethyl chloroformate, the triethylamine



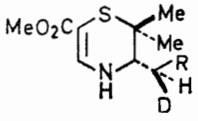
(1) R = H
(2) R = D



(3) R^1 = S, R^2 = H
(4) R^1 = S, R^2 = D
(5) R^1 = SO, R^2 = H
(6) R^1 = SO, R^2 = D

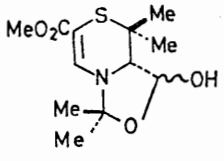


(7) R = CH_2I
(8) R = CH_2·OH
(9) R = CHD·OH



(10) R = CHD·OTs
(11) R = CO_2H
(12) R = CO_2Me

(13) R = OH
(14) R = OTs
(15) R = I



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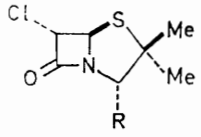


(17) R = CO_2H
(18) R = CO_2Me
(19) R = CO_2·CO_2Et
(20) R = CH_2·OH
(21) R = CHD·OH
(22) R = CHO
(23) R = CDO
(24) R = CO·CHN_2
(25) R = CO·CH_2·OH
(26) R = CH(OH)·CH_2·OH
(27) R = CD(OH)·CH_2·OH

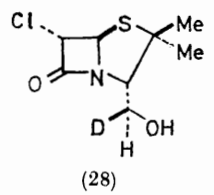
salt of the acid (17) was converted into 6α-chloropenicillanic ethoxyformic anhydride (19), which afforded 6α-chloropenicillanyl alcohol (20) with sodium borohydride in tetrahydrofuran.[7] Methanolic sodium methoxide quantitatively converted the last-named derivative into the thiazinyl alcohol (8).

6α-Chloropenicillanal (22) was obtained in the following manner. The diazo-ketone (24), prepared from the anhydride (19) and diazomethane, was transformed into 6α-chloropenicillanoylmethanol (25) by heating with sulphuric acid. Reduction of the derivative (25) with sodium borohydride yielded a mixture (3 : 2) of 1-(6α-chloro-2,2-dimethylpenam-3-yl)ethane-1,2-diols (26), which was converted into the aldehyde (22) by sodium periodate. Treatment of the ketol (25) with sodium borodeuteride followed by sodium periodate afforded the aldehyde (23), which was 77% monodeuteriated on the basis of mass spectroscopy; the isotope was located at the aldehyde group by n.m.r. spectroscopy.

Actively fermenting yeast converted the aldehyde (22) into the alcohol (20) and the monodeuteriated aldehyde (23) into the monodeuteriated alcohol (21).[8] The monodeuteriated thiazinyl alcohol (9), obtained from the reaction of the derivative (21) with sodium methoxide, was transformed [3] into the monodeuteriated aziridine (2) by way of the toluene-*p*-sulphonate (10). On the basis of mass spectroscopy, the aziridine was 77% monodeuteriated; the isotope was located at the 7-*exo*-position by n.m.r. spectroscopy.

There is ample precedent [9] to expect that the conversion of the toluene-*p*-sulphonate (10) into the aziridine (2) will occur with inversion of configuration at the methylene group. Consequently, the 3-substituents of the toluene-*p*-sulphonate (10), the thiazinyl alcohol (8), and the penicillanyl alcohol (21) are likely to possess the *S*-configuration; the derivatives are therefore represented by structures (14), (13), and (28), respectively. It is reassuring to find that the alcohols obtained in the reduction of monodeuteriated aldehydes by yeast also possess the *S*-configuration.[5]

The monodeuteriated aziridine (2) was heated for 4 days in boiling toluene [3] to give the thiazine (4), without loss of deuterium. Although the 2α- and 2β-hydrogen atoms of the thiazine (3) can be differentiated by n.m.r. spectroscopy, they do possess similar chemical shifts (τ 7·29 and 7·15 respectively). A derivative in which the



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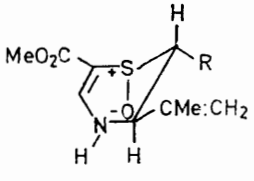
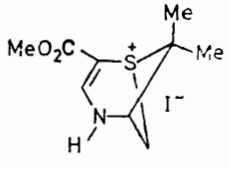


(29) R = H
(30) R = D



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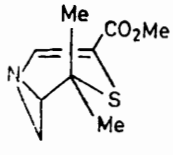

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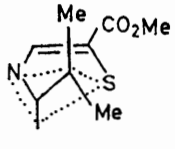

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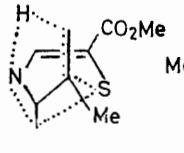

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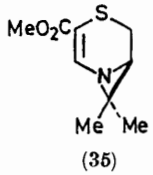

(35)

signals of these protons are further separated was therefore required. The sulphoxide (5), which was obtained

[6] I. McMillan and R. J. Stoodley, *Tetrahedron Letters*, 1966, 1205; *J. Chem. Soc.* (*C*), 1968, 2533.
[7] Y. G. Perron, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, G. T. Holdrege, W. F. Minor, M. E. Neubert, R. A. Partyka, and L. C. Cheney, *J. Medicin. Chem.*, 1964, **7**, 483.
[8] V. E. Althouse, K. Veda, and H. S. Mosher, *J. Amer. Chem. Soc.*, 1960, **82**, 5938.
[9] O. C. Dermer and G. E. Ham, 'Ethylenimine and Other Aziridines: Chemistry and Applications,' Academic Press, London, 1969.

by oxidation of the thiazine (3) with sodium periodate, proved to be satisfactory. Its n.m.r. spectrum ($CDCl_3$) contained a triplet at τ 7·70 ($J_{2\alpha,2\beta}=J_{2\beta,3}=13{\cdot}2$ Hz) for the 2β-proton and a double doublet at 7·00 ($J_{2\alpha,2\beta}$ 13·2, $J_{2\alpha,3}$ 3·0 Hz) for the 2α-proton. On the basis of other work,[10] the sulphoxide is tentatively assigned the *R*-configuration and it is considered to exist predominantly as conformer (29). The n.m.r. spectrum ($CDCl_3$) of the monodeuteriated sulphoxide (30) contained a triplet (0·27H, $J_{2\alpha,2\beta}=J_{2\beta,3}=13{\cdot}2$ Hz) and a doublet (0·73H, $J_{2\beta,3}$ 13·2 Hz) centred at τ 7·70 and a double doublet (0·27H, $J_{2\alpha,2\beta}$ 13·2, $J_{2\alpha,3}$ 3·0 Hz) centred at 7·00, which established that it was 73% monodeuteriated at the 2α-position. Consequently, the rearrangement of the aziridine (2) to the isopropenyl derivative (4) occurs so that the new carbon–sulphur bond is formed with retention of configuration.

The monodeuteriated aziridine (2) was treated with hydriodic acid to give the monodeuteriated iodide (15), which was converted into the isopropenyl derivative (4) in boiling ethyl methyl ketone.[3] Oxidation of compound (4) with sodium periodate afforded the sulphoxide (6), which was 79% monodeuteriated (mass spectroscopy). Its n.m.r. spectrum was virtually identical with that of the sulphoxide obtained from the aziridine rearrangement. Therefore, on the assumption that the ring-opening of the aziridine (2) with hydriodic acid occurs with inversion of configuration,[9] the rearrangement of the iodide (15) to the isopropenyl derivative (4) must proceed so that the new carbon–sulphur bond is formed with inversion of configuration.

Previously we have shown [3] that the aziridine (1) is not an intermediate in the rearrangement of the iodide (7) to the isopropenyl derivative (3). Consequently, the foregoing stereochemical result strongly suggests that the reaction proceeds by way of the ion pair (31).

The isomerisation of the aziridine (1) to the isopropenyl derivative (3) involves a 1,3-sulphur shift, which may either occur after the cleavage of the 1,7- or 4,5-bond or be coupled with the fission of these linkages. Although non-concerted pathways are not excluded, the stereochemical result * is most reasonably accounted for in terms of a concerted reorganization involving the thermodynamically unfavourable conformer (32) [11] of the aziridine. In this conformer the S(4)–C(7) bond distance is *ca.* 2·9 Å according to Dreiding models. Structures (33) and (34) represent possible transition states for the rearrangement. In the former event, the aziridine (35) is an intermediate in the reaction, which represents an example of a [4,4] dyotropic shift.[12]

* A referee has pointed out that this result is also consistent with a bimolecular process, involving cleavage of the 1,7-bond of the aziridine (2) by a second molecule followed by a rearrangement analogous to that proposed for the iodide (15). However, the rates of disappearance of the aziridine (1) and appearance of the isopropenyl derivative (3) were identical (on the basis of t.l.c. and n.m.r. spectroscopy) when 25mM- and 75mM-solutions of the aziridine (1) in toluene were heated under reflux.

[10] J. Kitchin and R. J. Stoodley, *Tetrahedron*, 1973, **29**, 3023.

EXPERIMENTAL

For general experimental details see Part I.[3] Sodium borodeuteride was obtained from Koch–Light Ltd. and baker's yeast from Distillers Company Ltd. The n.m.r. spectra of deuteriated compounds were recorded several times at 90 MHz and stored in the memory of a Fabritek 1074 Signal Averaging System. The spectra were then integrated, after base-line correction, and the heights of the steps corresponding to each signal were read out digitally on an oscilloscope.

Reaction of 6α-*Chloropenicillanic Acid* (17) *with Ethyl Chloroformate*.—Triethylamine (9·3 g, 9·2 mmol) was added to a solution of the acid (17) [6] (21·7 g, 9·2 mmol) in dichloromethane (325 ml). The stirred solution was cooled in acetone–solid carbon dioxide and treated with ethyl chloroformate (29·95 g, 27·6 mmol). After 30 min the mixture was allowed to warm to room temperature and washed with sodium hydrogen carbonate solution followed by water. The dried ($MgSO_4$) organic layer was evaporated to leave 6α-*chloropenicillanic ethoxyformyl anhydride* (19) (21·8 g, 77%), $\nu_{max.}$ (film) 1820 and 1760 (anhydride C=O) and 1790 (β-lactam C=O) cm^{-1}, τ ($CDCl_3$) 8·61 (3H, t, *J* 6·8 Hz, $MeCH_2$), 8·38 and 8·35 (each 3H, s, *gem*-Me_2), 5·60 (2H, q, *J* 6·8 Hz, $MeCH_2$), 5·36 (1H, s, 3-H), 5·19 (1H, d, *J* 1·7 Hz, 6-H), and 4·62 (1H, d, *J* 1·7 Hz, 5-H) (Found: M^+, 307. $C_{11}H_{14}ClNO_5S$ requires *M*, 307).

6α-*Chloropenicillanyl Alcohol* (20).—A stirred solution of the mixed anhydride (19) (5·4 g, 1·76 mmol) in dry tetrahydrofuran (63 ml) was cooled to −8° and sodium borohydride (1·33 g, 3·5 mmol) was added.[7] The mixture was allowed to warm to room temperature and after 2·5 h it was diluted with acetone (30 ml) and dichloromethane (50 ml) and shaken with water (twice). The organic layer was dried ($MgSO_4$) and evaporated to leave a syrup (3·2 g), which was fractionated by silica gel chromatography (chloroform as eluant) to give 6α-*chloropenicillanyl alcohol* (20) (1·1 g, 24%), m.p. 81—82° [from chloroform–light petroleum (b.p. 80—100°)], $[\alpha]_D$ +158° (0·2% in $CHCl_3$), $\nu_{max.}$ (KBr) 3400 (OH) and 1775 (β-lactam C=O) cm^{-1}, τ (90 MHz; $CDCl_3$) 8·50 and 8·44 (each 3H, s, *gem*-Me_2), 7·58br (1H, s, OH), 6·33 (2H, septet, *J* 11·3, *J′* 9·3, *J″* 3·5 Hz, CH_2·O), 5·97 (1H, dd, separation 12·8 Hz, 3-H), 5·22 (1H, d, *J* 1·7 Hz, 6-H), and 4·87 (1H, d, *J* 1·7 Hz, 5-H) (addition of D_2O to the solution caused the signal at τ 7·58 to disappear) (Found: C, 43·2; H, 5·8; Cl, 15·7%; M^+, 221. $C_8H_{12}ClNO_2S$ requires C, 43·4; H, 5·5; Cl, 16·0%; *M*, 221).

Reaction of 6α-*Chloropenicillanyl Alcohol* (20) *with Sodium Methoxide*.—(*a*) The alcohol (20) (0·194 g, 0·874 mmol) was dissolved in dry methanol (0·8 ml) and 2·27M-sodium methoxide solution (0·39 ml, 0·874 mmol) was added. After 3·5 h the solution was diluted with water and extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a crystalline residue (0·19 g, 100%), identical with the thiazinyl alcohol (8) [3] by i.r. and n.m.r. spectroscopy.

(*b*) The monodeuteriated alcohol (21) (1·88 g, 0·85 mmol) was quantitatively converted into the monodeuteriated thiazinyl alcohol (9) by the foregoing procedure.

6α-*Chloropenicillanoyldiazomethane* (24).—An excess of diazomethane in ether was added to a solution of the mixed anhydride (19) (21·8 g, 9·3 mmol) in ether (100 ml) at 0°.

[11] A. R. Dunn and R. J. Stoodley, *Tetrahedron Letters*, 1969, 3367.

[12] M. T. Reetz, *Angew. Chem. Internat. Edn.*, 1972, **11**, 129; *Tetrahedron*, 1973, **29**, 2189.

After 2 h the solution was concentrated to *ca.* 40 ml and refrigerated to give 6α-*chloropenicillanoyldiazomethane* (24) (11·4 g) as yellow prisms. The mother liquor was fractionated by silica gel chromatography (chloroform as eluant) to give a further quantity (2·7 g, total yield 76%) of the diazo-ketone, m.p. 93—95° (decomp.) (from chloroform–ether), $[\alpha]_D$ +400° (0·16% in $CHCl_3$), $\nu_{max.}$ (KBr) 2120 ($C=\overset{+}{N}=\overset{-}{N}$), 1760 (β-lactam C=O), and 1630 (ketone C=O) cm^{-1}, $\lambda_{max.}$ 255 nm (ε 10,800), τ (90 MHz; $CDCl_3$) 8·45 and 8·31 (each 3H, s, *gem*-Me_2), 5·69 (1H, s, 3-H), 5·20 (1H, d, *J* 1·5 Hz, 6-H), 4·74 (1H, d, *J* 1·5 Hz, 5-H), and 4·27 (1H, s, CHN_2) (Found: C, 41·7; H, 3·8; N, 15·9%; M^+, 259. $C_9H_{10}ClN_3O_2S$ requires C, 41·6; H, 3·9; N, 16·2%; *M*, 259).

6α-*Chloropenicillanoylmethanol* (25).—A solution of the diazo-ketone (24) (12·8 g, 5 mmol) in a mixture of dioxan (100 ml), water (30 ml), and 6N-sulphuric acid (20 ml) was heated at 80°. After 2 h the cooled solution was extracted (3 times) with chloroform. The organic layer was washed with sodium hydrogen carbonate solution followed by water, and dried ($MgSO_4$). Evaporation left a syrup, which was purified by silica gel chromatography (ether as eluant) to give 6α-*chloropenicillanoylmethanol* (25) (6·4 g, 52%), $[\alpha]_D$ +235° (0·36% in $CHCl_3$), $\nu_{max.}$ (film) 3460 (OH), 1780 (β-lactam C=O), and 1725 (ketone C=O) cm^{-1}, τ (90 MHz; $CDCl_3$) 8·57 and 8·35 (each 3H, s, *gem*-Me_2) 7·02br (1H, s, OH), 5·56 (2H, d, separation 4 Hz, $CO{\cdot}CH_2$), 5·50 (1H, s, 3-H), 5·18 (1H, d, *J* 1·5 Hz, 6-H), and 4·74 (1H, d, *J* 1·5 Hz, 5-H) (addition of D_2O to the solution caused the signal at τ 7·02 to disappear) (Found: M^+, 249. $C_9H_{12}ClNO_3S$ requires *M*, 249).

Reaction of 6α-*Chloropenicillanoylmethanol* (25) *with Sodium Borohydride.*—(*a*) Sodium borohydride (0·805 g, 2·1 mmol) was added in small portions to a stirred solution of the ketol (25) (10·62 g, 4·2 mmol) in dry tetrahydrofuran (40 ml) at 0°. After 20 min the mixture was diluted with acetone (20 ml) followed by water (30 ml) and extracted (3 times) with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a syrup (5·00 g, 47%), which contained a mixture (3 : 2) of two components (n.m.r. spectroscopy). The mixture was partially fractionated by silica gel chromatography (chloroform as eluant; fractions were monitored by n.m.r. spectroscopy) to give the *major isomer* of 1-(6α-*chloro*-2,2-*dimethylpenam*-3-*yl*)*ethane*-1,2-*diol* (26) (1·35 g, 12%), $[\alpha]_D$ +137° (0·23% in $CHCl_3$), $\nu_{max.}$ (film) 3400 (OH) and 1775 (β-lactam C=O) cm^{-1}, τ (90 MHz; $CDCl_3$) 8·38 (6H, s, *gem*-Me_2), 6·39br (1H, s, OH), 6·33—6·16 (5H, m, 3-H, $CH{\cdot}CH_2{\cdot}O$ and OH), 5·31 (1H, d, *J* 1·4 Hz, 6-H), and 5·00 (1H, d, *J* 1·4 Hz, 5-H) (addition of D_2O to the solution caused the signal at τ 6·39 to disappear and the multiplet centred at 6·25 to sharpen) (Found: M^+, 251. $C_9H_{14}ClNO_3S$ requires *M*, 251).

The *minor isomer* of 1-(6α-*chloro*-2,2-*dimethylpenam*-3-*yl*)-*ethane*-1,2-*diol* (26) (0·93 g, 9%) was obtained in crystalline form, m.p. 76—77° (from chloroform–ether), $[\alpha]_D$ +129° (0·11% in $CHCl_3$), $\nu_{max.}$ (KBr) 3420 (OH) and 1750 (β-lactam C=O) cm^{-1}, τ (90 MHz; $CDCl_3$) 8·51 and 8·40 (each 3H, s, *gem*-Me_2), 7·3br (2H, s, OH), 6·36—5·96 (4H, m, 3-H and $CH{\cdot}CH_2{\cdot}O$), 5·25 (1H, d, *J* 1·4 Hz, 6-H), and 4·80 (1H, d, *J* 1·4 Hz, 5-H) (addition of D_2O to the solution caused the signal at τ 7·27 to disappear) (Found: C, 43·1; H, 5·4; N, 5·6%; M^+, 251. $C_9H_{14}ClNO_3S$ requires C, 42·9; H, 5·6; N, 5·6%; *M*, 251).

(*b*) The ketol (25) (10·21 g, 4·09 mmol) was treated with sodium borodeuteride (0·859 g, 2·05 mmol) as described in procedure (*a*) to give a mixture (3 : 2) of the monodeuteriated diols (27) (6·9 g, 68%). The n.m.r. spectrum was very similar to that of the mixture of undeuteriated diols except for changes in the multiplet centred at τ 6·16.

Reaction of 1-(6α-*Chloro*-2,2-*dimethylpenam*-3-*yl*)*ethane*-1,2-*diols* (26) *with Sodium Periodate.*—(*a*) A mixture (3 : 2) of the diols (26) (0·39 g, 1·55 mmol), stirred in dioxan (10 ml) at 10°, was treated with a solution of sodium periodate (0·332 g, 1·55 mmol) in water (10 ml). After 25 min the mixture was diluted with water and extracted (3 times) with dichloromethane. The organic layer was washed with water and sodium thiosulphate solution, dried ($MgSO_4$), and evaporated to leave 6α-chloropenicillanal (22) (0·24 g, 71%) as a slightly impure syrup, which could not be purified by chromatography, $\nu_{max.}$ (film) 1775 (β-lactam C=O) and 1725 (aldehyde C=O) cm^{-1}, τ ($CDCl_3$) 8·20 (6H, s, *gem*-Me_2), 5·55 (1H, d, *J* 2·4 Hz, 3-H), 5·13 (1H, d, *J* 1·5 Hz, 6-H) and 4·65 (1H, d, *J* 1·5 Hz, 5-H), and 0·3 (1H, d, *J* 2·4 Hz, CHO) (Found: M^+, 219·0123. Calc. for $C_8H_{10}ClNO_2S$: *M*, 219·0121).

(*b*) The mixture of monodeuteriated diols (27) (6·9 g, 2·7 mmol) was converted into the monodeuteriated aldehyde (23) (4·71 g, 78%) by procedure (*a*); τ (90 MHz; $CDCl_3$) as for the aldehyde (22) except 5·55 (1H, s, 3-H) and 0·30 (0·2H, d, *J* 2·4 Hz, CHO). Mass spectroscopy indicated that the sample was 77% mono- and 23% un-deuteriated.

Reaction of 6α-*Chloropenicillanal* (22) *with Baker's Yeast.*—The procedure recommended by Mosher [8] was followed.

(*a*) Baker's yeast (18 g) was made into a paste with water (22 ml) and added to a solution of D-glucose (18 g) in water (56 ml) at 32—33°. The mixture was shaken on a rotary shaker for 20 min and a solution of the aldehyde (22) (0·1 g, 0·457 mmol) in ethanol (0·5 ml) was then added. After shaking for a further 2·25 h, the yeast was removed by filtration over Hiflo and washed with ethanol. The filtrate was extracted with chloroform (3 times) and the organic layer was washed with water (2 times), dried ($MgSO_4$), and evaporated. The derived syrup was fractionated by silica gel chromatography (chloroform as eluant) to give the alcohol (20) (0·029 g, 29%), m.p. 81—82°.

(*b*) The monodeuteriated aldehyde (23) (4·71 g, 2·15 mmol) was converted into the monodeuteriated alcohol (28) (1·88 g, 40%) by procedure (*a*); τ ($CDCl_3$) as for the alcohol (20) except 6·3br (1·2H, d, separation 4·5 Hz, CHD·O) and 5·9br (1H, d, separation 4·5 Hz, 3-H). Mass spectroscopy indicated that the sample was 80% mono- and 20% un-deuteriated.

Methyl (6S,7R)-5,5-*Dimethyl*-4-*thia*-1-*aza*[7-^{2}H]*bicyclo*-[4.1.0]*hept*-2-*ene*-3-*carboxylate* (2).—The monodeuteriated alcohol (13) (1·85 g, 0·85 mmol) was converted [3] into the toluene-*p*-sulphonate (14), m.p. 120—123° (from chloroform–ether), $[\alpha]_D$ −306° (0·26% in $CHCl_3$). Mass spectroscopy indicated that the sample was 78% mono- and 22% un-deuteriated.

A slight modification of the previously described procedure [3] was employed in the conversion of the toluene-*p*-sulphonate (14) into the aziridine. The toluene-*p*-sulphonate (14) (1·86 g, 5·0 mmol) was dissolved in dry tetrahydrofuran (35 ml) and powdered sodamide (0·585 g, 15·0 mmol) was added. After stirring for 1 h, the mixture was diluted with methanol followed by water and extracted with chloroform. The organic layer was washed with water (twice), dried ($MgSO_4$), and evaporated to leave a syrup,

which was fractionated by alumina chromatography (ether as eluant) to give the aziridine (2) (0·60 g, 60%), τ (90 MHz; $CDCl_3$) as for the un-deuteriated aziridine (1) [3,11] except 8·18 (1H, d, $J_{6.7\text{-}endo}$ 3·5 Hz, 7-*endo*-H), 7·70 (0·27H, d, $J_{6.7\text{-}exo}$ 4·6 Hz, 7-*exo*-H), and 7·25 (1H, d, separation 3·4 Hz, 6-H). Mass spectroscopy indicated that the sample was 77% mono- and 23% un-deuteriated.

Thermal Rearrangement of Methyl (6S,7R)-5,5-*Dimethyl*-4-*thia*-1-*aza*[7-^{2}H]*bicyclo*[4.1.0]*hept*-2-*ene*-3-*carboxylate* (2).—The monodeuteriated aziridine (2) (0·26 g, 1·3 mmol) was heated in boiling toluene for 4 days [3] to give the thiazine (4) [0·078 g, 30% (after silica gel chromatography)], which was 80% mono- and 20% un-deuteriated by mass spectroscopy.

Reaction of Methyl (3R)-2,3-*Dihydro*-3-*isopropenyl*-2H-1,4-*thiazine*-6-*carboxylate* (3) *with Sodium Periodate*.—(*a*) A solution of the thiazine [3] (3) (0·058 g, 0·29 mmol) in methanol (3 ml) was treated with sodium periodate (0·068 g, 0·32 mmol) in water (3 ml). After 20 min the mixture was diluted with water and M-barium acetate solution (1 ml) was added. The precipitate was filtered off and the filtrate treated with ion-exchange resin [Amberlite IR 120 (H^+)]. Evaporation left a residue to which chloroform was added. The mixture was filtered and the filtrate evaporated to leave (1R,3R)-2,3-*dihydro*-3-*isopropenyl*-6-*methoxycarbonyl*-2H-1,4-*thiazine* 1-*oxide* (5) (0·058 g, 89%), m.p. 154—156° (decomp.) (from chloroform–ether), $[\alpha]_D$ +291° (0·48% in EtOH), $\nu_{max.}$ (KBr) 3130 (NH), 1675 (unsat. C=O), and 1585 (C=C) cm^{-1}, $\lambda_{max.}$ 274 nm (ε 16,500), τ ($CDCl_3$) 8·11 (3H, s, *Me*C:CH_2), 7·70 (1H, t, $J_{2\alpha\,2\beta} = J_{2\beta.3}$ = 13·2 Hz, 2β-H), 7·00 (1H, dd, $J_{2\alpha.3}$ 3·0 Hz, 2α-H) 6·18 (3H, s, CO_2Me), 5·72 (1H, dd, separation 16·2 Hz, 3-H), 4·89 (2H, m, MeC:CH_2), and 2·05br (1H, s, 5-H) (addition of D_2O to the solution caused the signal at τ 2·05 to change to a sharp singlet) (Found: C, 50·4; H, 6·1; N, 6·4%; M^+, 215. $C_9H_{13}NO_3S$ requires C, 50·2; H, 6·5; N, 6·1%; *M*, 215).

(*b*) The monodeuteriated thiazine (4) (0·078 g, 0·39 mmol), derived from the thermal rearrangement of the monodeuteriated aziridine (2), was converted into the monodeuteriated sulphoxide (6) by the method described in procedure (*a*); τ (90 MHz; $CDCl_3$) as for the sulphoxide (5) except 7·70 (0·73H, d, $J_{2\beta.3}$ 13·2 Hz and 0·27H, t, $J_{2\alpha.2\beta} = J_{2\beta.3}$ = 13·2 Hz, 2β-H), 7·00 (0·27H, dd, $J_{2\alpha.2\beta}$ 13·2, $J_{2\alpha.3}$ 3·0 Hz, 2α-H), and 5·72 (1H, d, $J_{2\beta.3}$ 13·2 Hz, 3-H). The sample was 77% mono- and 23% un-deuteriated on the basis of mass spectroscopy.

(*c*) The monodeuteriated thiazine (4) (0·11 g, 0·55 mmol), derived from the thermal rearrangement of the monodeuteriated iodide (15), was converted into the monodeuteriated sulphoxide (6) by the method described in procedure (*a*). The n.m.r. spectrum of the product was almost identical with that of the sulphoxide obtained by procedure (*b*). Mass spectroscopy indicated that the sample was 79% mono- and 21% un-deuteriated.

Reaction of Methyl (6S,7R)-5,5-*Dimethyl*-4-*thia*-1-*aza*-[7-^{2}H]*bicyclo*[4.1.0]*hept*-2-*ene*-3-*carboxylate* (2) *with Hydriodic Acid*.—The monodeuteriated aziridine (2) (0·26 g, 1·3 mmol) was quantitatively converted into the monodeuteriated iodide (15) by the previously described procedure.[3] The derived iodide was 77% mono- and 23% un-deuteriated (mass spectroscopy).

Thermal Rearrangement of Methyl (3R)-3,4-*Dihydro*-3-{(S)-*iodo*[^{2}H]*methyl*}-2H-1,4-*thiazine*-6-*carboxylate* (15).—The monodeuteriated iodide (15) (0·30 g, 0·92 mmol) was heated in boiling ethyl methyl ketone for 5 days [3] to give the monodeuteriated thiazine (4) [0·11 g, 55% (after silica gel chromatography)]. The sample was 79% mono- and 21% un-deuteriated (mass spectroscopy).

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