Studies related to Dihydro-1,4-thiazines. Part II.[1] Reduction of Methyl (6*S*)-7-Hydroxy-5,5,9,9-tetramethyl-8-oxa-4-thia-1-azabicyclo[4,3,0]non-2-ene-3-carboxylate and its 4-Oxide [2]

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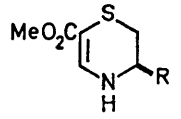
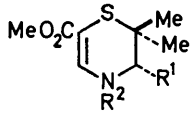
Reduction of methyl (6*S*)-5,5,9,9-tetramethyl-7-oxo-8-oxa-4-thia-1-azabicyclo[4,3,0]non-2-ene-3-carboxylate (12) with sodium aluminium hydride gives the 7-hydroxy-analogue (11). Little stereoselectivity is observed in the conversion of compound (11) into the monodeuteriated alcohol (5) with lithium or sodium borodeuteride, lithium aluminium deuteride, or lithium deuteridotri-t-butoxyaluminate, and of the hemiacetal sulphoxides (13) into the monodeuteriated alcohol sulphoxides (15) with sodium borodeuteride.

The alcohol sulphoxides (14) react with acetyl chloride to give methyl (1*R*,5*S*)-2-chloro-4,4-dimethyl-7-oxa-3-thia-8-azabicyclo[3,2,1]octane-2-carboxylate (16), which affords the amide (17). The derivative (17) is reduced to the alcohol (4) by iron(II) chloride in methanolic hydrochloric acid and to methyl (1*R*,5*S*)-8-acetyl-4,4-dimethyl-7-oxa-3-thia-8-azabicyclo[3,2,1]octane-2-carboxylate (20) by zinc in acetic acid. It also reacts with silver perchlorate in methanol to yield the methoxy-derivative (19).

REARRANGEMENTS involving novel 1,3-sulphur migrations have recently been observed in certain dihydro-1,4-thiazine derivatives.[1] Thus, methyl (3*S*)-3,4-dihydro-3-iodomethyl-2*H*-1,4-thiazine-6-carboxylate (1) underwent racemisation and methyl (3*R*)-3,4-dihydro-3-iodomethyl-2,2-dimethyl-2*H*-1,4-thiazine-6-carboxylate (3) rearranged to methyl (3*R*)-3,4-dihydro-3-isopropenyl-2*H*-1,4-thiazine-6-carboxylate (2) when heated in boiling

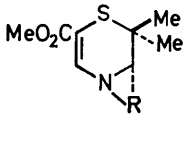


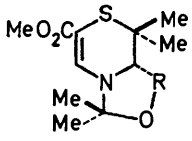


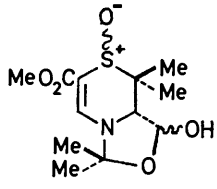
(1) R = CH_2I
(2) R = $CMe{:}CH_2$

(3) $R^1 = CH_2I$, $R^2 = H$
(4) $R^1 = CH_2{\cdot}OH$, $R^2 = H$
(5) $R^1 = CHD{\cdot}OH$, $R^2 = H$
(6) $R^1 = CHO$, $R^2 = H$
(7) $R^1 = CO_2H$, $R^2 = H$
(8) $R^1 = CHO$, $R^2 = CMe_2{\cdot}OH$

ethyl methyl ketone. The derivative (2) was also formed when methyl (6*S*)-5,5-dimethyl-4-thia-1-azabicyclo[4,1,0]hept-2-ene-3-carboxylate (9) was heated in boiling toluene. A study of the rearrangements of the iodides (1) and (3), specifically monodeuteriated in the exocyclic methylene group, and of the aziridine (9), specifically monodeuteriated in the 7-methylene group, is expected to provide insight into the reorganisation mechanisms. This paper describes some attempts to prepare the appropriate monodeuteriated derivatives.







(9) R = CH_2
(10) R = CHD

(11) R = CH·OH
(12) R = CO

(13)

We initially attempted to reduce the aldehyde (6) stereoselectively to the monodeuteriated alcohol (5) by use of a metal deuteride. Since the aldehyde is likely to be a reactive species, a method was required which enables it to be generated and reduced *in situ*. The reaction of the lactol (11) with a metal deuteride was expected to provide such a method. Moreover, there is the possibility that the carbinolamine aldehyde (8) is the intermediate which undergoes reduction; in such an event the *N*-substituent may conceivably increase the selectivity of the reaction.

The lactone (12) was prepared (95%) by stirring the acid [3] (7) in 2,2-dimethoxypropane containing toluene-*p*-sulphonic acid. Reduction [4] of this derivative with sodium aluminium hydride afforded a single hemiacetal (11) (65%), which was reduced to the alcohol (4) by lithium borohydride (99%), by sodium borohydride (49%), by lithium aluminium hydride (17%), and by lithium hydridotri-t-butoxyaluminate (21%).

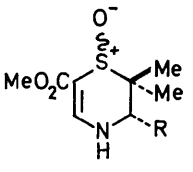
The reduction of the lactol (11) was repeated with the corresponding metal deuterides; in each case the monodeuteriated alcohol (5) was converted into the monodeuteriated aziridine (10) *via* the toluene-*p*-sulphonate.[1] The specificity of the reduction was deduced by comparing the integrated area of the n.m.r. signals due to the 7-*exo*- and 7-*endo*-protons of the aziridine.[1,5] There was no marked difference in the areas of these signals; thus the chiral centre at position 3 of the intermediate [(6) or (8)] can exert little directing influence on the reduction of the adjacent aldehyde group.

In the hope of increasing the stereoselectivity of the reaction, the reduction of the lactol sulphoxides (13) was investigated. The hemiacetal (11) was oxidised to a mixture (6 : 1) of sulphoxides (93%) by sodium periodate. Sodium borohydride reduced this mixture to the alcohol sulphoxides (14). The latter derivatives were also obtained as a mixture (6 : 1) by oxidation of the alcohol [1] (4) with periodate. The major isomer, m.p. 143—145°, $[\alpha]_D$ −276° ($CHCl_3$), was obtained after recrystallisation.

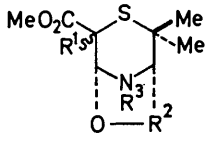
In an attempt to reduce the alcohol sulphoxides (14)

[1] Part I, A. R. Dunn and R. J. Stoodley, *J.C.S. Perkin I*, 1972, 2509.
[2] Preliminary communication, J. Kitchin and R. J. Stoodley, *J.C.S. Chem. Comm.*, 1972, 959.
[3] I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533.
[4] L. I. Zakharkin, V. V. Gaurilenko, D. N. Maslin, and I. M. Khorlina, *Tetrahedron Letters*, 1963, 2087.
[5] A. R. Dunn and R. J. Stoodley, *Tetrahedron Letters*, 1969, 3367.

to the alcohol (4), the mixture was treated with two mol. equiv. of sodium dithionite and acetyl chloride in acetonitrile.[6] However, the reaction gave mainly a substance which moved much faster on t.l.c. than the alcohol (4). A control experiment established that a similar reaction



(14) R = CH_2·OH
(15) R = CHD·OH



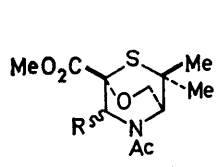
(16) R^1 = Cl, R^2 = CH_2, R^3 = H
(17) R^1 = Cl, R^2 = CH_2, R^3 = Ac
(18) R^1 = Cl, R^2 = CHD, R^3 = Ac
(19) R^1 = OMe, R^2 = CH_2, R^3 = Ac
(20) R^1 = H, R^2 = CH_2, R^3 = Ac

occurred when the sulphoxide mixture was treated with acetyl chloride in acetonitrile. The crystalline product, which was isolated (80%) after silica gel chromatography, is considered to be methyl (1*R*,5*S*)-8-acetyl-2-chloro-4,4-dimethyl-7-oxa-3-thia-8-azabicyclo[3,2,1]-octane-2-carboxylate (17). It was reduced to the alcohol (4) (23%) when heated with iron(II) chloride in hot methanolic hydrochloric acid.

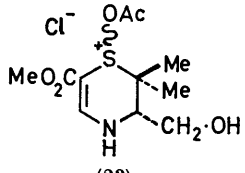
mass spectrometry did provide evidence in favour of the former structure; the prominent peak at *m/e* 155 ($C_8H_{13}NO_2$ by mass measurement), attributable to the loss of MeO_2C·CSCl from the molecular ion, is in accord with cleavage of the 1,2- and 3,4-bonds of compound (17). Unfortunately, there was no metastable peak to indicate that this was a one-step process.

In an attempt to provide further evidence for its structure, the bicyclic derivative was treated with silver perchlorate in methanol. A single methoxy-derivative was obtained (93%), which also contained a prominent peak at *m/e* 155 in its mass spectrum; however, there was still no metastable peak to link this ion with the molecular ion. The n.m.r. spectrum of the product was similar to that of the starting material: the uncoupled proton appeared as a broad signal at τ 4·21 ($CDCl_3$). Consequently, the derivative probably possesses structure (19).

More definitive evidence in favour of structure (17) was provided when the substance was reduced by zinc in acetic acid. Mass spectroscopy showed that the syrupy product (64% after silica gel chromatography) possessed the molecular formula, $C_{11}H_{17}NO_4S$; again a prominent peak at *m/e* 155 was present. The n.m.r. spectrum was consistent with structure (20), but incompatible with



(21) R = Cl
(22) R = H



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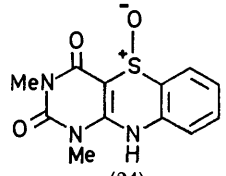

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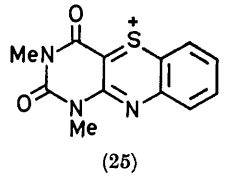

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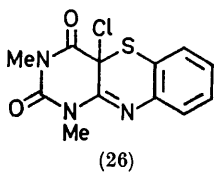

(26)

The reduction of the lactol sulphoxides (13) was repeated with sodium borodeuteride, and the mixture of monodeuteriated alcohol sulphoxides (15) was converted into the monodeuteriated alcohol (5). The alcohol (5) was transformed[1] into the monodeuteriated aziridine (10), which contained equal amounts of deuterium in the 7-*exo*- and 6-*endo*-positions on the basis of n.m.r. spectroscopy. Thus, the presence of the oxide function at position 4 does not influence the stereochemical course of the aldehyde reduction.

The assignment of the structure of the bicyclic derivative derived from the reaction of the alcohol sulphoxides (14) with acetyl chloride is based on the following evidence. Elemental analysis indicated that the compound, $C_{11}H_{16}ClNO_4S$, is formally derived from the sulphoxides by the loss of water and the addition of acetyl chloride. I.r. spectroscopy showed the presence of saturated ester and tertiary amide groups, but absorptions due to NH and OH groups were absent. Since the substance was reduced to the alcohol (4) when heated with iron(II) chloride in methanolic hydrochloric acid, it possesses either structure (17) or (21). N.m.r. spectroscopy did not unambiguously distinguish between these alternatives: the uncoupled proton appeared as a broad (presumably caused by the presence of configurational isomers of the amide) singlet at τ 4·02 ($CDCl_3$). However, structure (22). Thus, it contained doublets at τ 3·98 and 6·54 ($CDCl_3$) for H-1 and H-2; spin decoupling experiments confirmed that these protons were coupled (J 3·0 Hz).

When treated with 1 mol. equiv. of acetyl chloride in acetonitrile, the mixture of sulphoxides (14) was converted into an unstable product. I.r. and n.m.r. spectroscopy left little doubt that the substance was mainly the amine (16), although it decomposed when attempts were made to purify it by chromatography. The crude material was converted into the amide (17) (63%) by acetyl chloride in acetonitrile. Consequently, the amine (16) is an intermediate in the formation of the amide (17).

The conversion of the alcohol sulphoxides (14) into the amine (16) in the presence of acetyl chloride is an unusual reaction, which probably reflects the vinylogous sulphinamide character of the oxides. The reaction is likely to be triggered by the formation of the sulphoxonium salts (23), which afford the bicyclic product (16) by loss of acetic acid. In principle the cyclisation step may precede, follow, or be concerted with the elimination of acetic acid.

[6] G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, *J. Org. Chem.*, 1970, **35**, 2430.

An analogy to the foregoing reaction involves the conversion of the benzothiazine sulphoxide (24) into the chloride (26) in the presence of thionyl chloride.[7] The formation of the stabilised benzothiazinium cation (25) is considered to provide the driving force for the reaction.

EXPERIMENTAL

For general experimental details see Part I.[1] Lithium and sodium borodeuterides were purchased from Koch–Light Ltd. and lithium aluminium deuteride from CIBA (A.R.L.) Ltd.; lithium deuteridotri-t-butoxyaluminate was prepared[8] from lithium aluminium deuteride and t-butyl alcohol.

Reaction of (3R)-3,4-*Dihydro*-6-*methoxycarbonyl*-2,2-*dimethyl*-2*H*-1,4-*thiazine*-3-*carboxylic Acid* (7) *with* 2,2-*Dimethoxypropane*.—The acid[3] (7) (2·31 g, 10 mmol) was stirred in 2,2-dimethoxypropane (50 ml) containing toluene-*p*-sulphonic acid monohydrate (1·90 g, 10 mmol). After 20 min the mixture was diluted with chloroform and washed with sodium hydrogen carbonate solution. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give the *lactone* (12) (2·57 g, 95%), m.p. 140—142° (from chloroform–ether), $[\alpha]_D$ +147° (0·51% in $CHCl_3$), $\nu_{max.}$ (KBr) 1780 (γ-lactone C=O), 1695 (unsat. C=O), and 1605 (C=C) cm^{-1}, $\lambda_{max.}$ 268 (ε 3400) and 321 nm (9700), τ (60 MHz; $CDCl_3$) 8·79 (3H, s), 8·34 (3H, s), and 8·28 (6H, s) (2 *gem*-Me_2), 6·22 (3H, s, OMe), 5·92 (1H, s, 6-H), and 2·39 (1H, s, 2-H) [Found: C, 53·1; H, 6·4; N, 5·2%; *M* (mass spectrum), 271·0876. $C_{12}H_{17}NO_4S$ requires C, 53·1; H, 6·3; N, 5·2%; *M*, 271·0878].

Reaction of Methyl (6S)-5,5,9,9-*Tetramethyl*-7-*oxo*-8-*oxa*-4-*thia*-1-*azabicyclo*[4,3,0]*non*-2-*ene*-3-*carboxylate* (12) *with Sodium Aluminium Hydride*.—The lactone (12) (4·46 g, 0·016 mol) was dissolved in dry tetrahydrofuran (66 ml) and sodium aluminium hydride (1·73 g, 0·032 mol) was added during 3 h to the stirred solution, which was cooled in acetone–solid carbon dioxide. After 7 h the mixture was allowed to warm to −10°, and diluted with dichloromethane (100 ml) followed by 0·5N-hydrochloric acid (200 ml). The organic layer was washed with water (twice), dried ($MgSO_4$). and evaporated to leave a syrup (4·6 g).

The product was purified by silica gel chromatography (using chloroform as eluant) to give the *hemiacetal* (11) (2·92 g, 65%), m.p. 113—115° (decomp.) (from ether–light petroleum), $[\alpha]_D$ +182° (0·2% in $CHCl_3$), $\nu_{max.}$ (KBr) 3400 (OH), 1660 (unsat. C=O), and 1595 (C=C) cm^{-1}, $\lambda_{max.}$ 221 (ε 10,200), 255 (3900), and 322 nm (21,000) τ [90 MHz; $(CD_3)_2SO$] 9·07, 8·67, 8·60, and 8·52 (each 3H, s, 2 *gem*-Me_2), 6·58 (1H, d, *J* 4 Hz, 6-H), 6·43 (3H, s, OMe), 4·79 (1H, dd, *J* 4 and 5·6 Hz, 7-H), 2·98 (1H, d, *J* 5·6 Hz, OH), and 2·47 (1H, s, 2-H) (addition of D_2O to the solution caused the signal at τ 2·98 to disappear and that at 4·79 to collapse to a doublet) [Found: C, 52·8; H, 7·1; N, 5·2%; *M* (mass spectrum), 273. $C_{12}H_{19}NO_4S$ requires C, 52·7; H, 7·0; N, 5·1%; *M*, 273].

Reactions of Methyl (6S)-7-*Hydroxy*-5,5,9,9-*tetramethyl*-8-*oxa*-4-*thia*-1-*azabicyclo*[4,3,0]*non*-2-*ene*-3-*carboxylate* (11) *with Metal Hydrides and Metal Deuterides*.—(*a*) The hemiacetal (11) (0·106 g, 0·4 mmol) was dissolved in dry tetrahydrofuran (3 ml) and lithium borohydride (0·021 g, 1 mmol) was added. The mixture was stirred for 0·5 h, diluted with water, and extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a solid (0·084 g, 99%), which was identical with the alcohol[1] (4) on the basis of t.l.c. and n.m.r. spectroscopy.

Similar reduction of the hemiacetal (11) with lithium borodeuteride afforded the alcohol (5), which was converted[1] into the aziridine (10). The sample was *ca.* 94% monodeuteriated on the basis of mass spectroscopy. N.m.r. spectroscopy indicated that *ca.* 45% of the isotope was contained in the 7-*exo*- and *ca.* 49% in the 7-*endo*-position.

(*b*) The hemiacetal (11) (0·137 g, 0·5 mmol) was dissolved in dry tetrahydrofuran (3 ml) and sodium borohydride (0·042 g, 1·14 mmol) was added. The mixture was left for 0·5 h and worked up as in procedure (*a*) to give the alcohol (4) (0·067 g, 49%).

Reduction of the hemiacetal (11) with sodium borodeuteride afforded the alcohol (5), which was converted[1] into the aziridine (10). The sample was *ca.* 90% monodeuteriated on the basis of mass spectroscopy and n.m.r. spectroscopy indicated that the isotope was *ca.* equally distributed between the 7-*exo*- and 7-*endo*-positions.

(*c*) The hemiacetal (11) (0·682 g, 2·5 mmol) dissolved in dry tetrahydrofuran (20 ml) was cooled in acetone–solid carbon dioxide. Lithium aluminium hydride (0·095 g, 2·5 mmol) was added in small portions to the stirred solution, which was allowed to warm to room temperature after 2·5 h. After a further 5 h, methanol (2 ml), followed by water (10 ml), was added to the mixture, which was extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a syrup which was fractionated by silica gel chromatography (chloroform as eluant) to give the alcohol (4) (0·092 g, 17%).

Similar reduction of the hemiacetal (11) with lithium aluminium deuteride afforded the alcohol (5), which was converted[1] into the aziridine (10). The aziridine was *ca.* 90% monodeuteriated on the basis of mass spectroscopy and n.m.r. spectroscopy indicated that the isotope was *ca.* equally distributed between the 7-*exo*- and 7-*endo*-positions.

(*d*) The hemiacetal (11) (0·136 g, 0·5 mmol) was dissolved in dry tetrahydrofuran (6 ml) and lithium hydridotri-t-butoxyaluminate (0·254 g, 1 mmol) was added. The solution was stirred at room temperature for 1 h, diluted with water, and extracted with chloroform. The organic layer was washed with N-hydrochloric acid and water, dried ($MgSO_4$), and evaporated to leave a syrup, which was fractionated by silica gel chromatography (chloroform as eluant) to give the alcohol (4) (0·023 g, 21%).

Similar reduction of the hemiacetal (11) with lithium deuteridotri-t-butoxyaluminate afforded the alcohol (5), which was converted[1] into the aziridine (10). The sample was shown to be *ca.* 90% monodeuteriated by mass spectroscopy and n.m.r. spectroscopy indicated that the isotope was *ca.* equally distributed between the 7-*exo*- and 7-*endo*-positions.

Reaction of Methyl (6S)-7-*Hydroxy*-5.5,9,9-*tetramethyl*-8-*oxa*-4-*thia*-1-*azabicyclo*[4,3,0]*non*-2-*ene*-3-*carboxylate* (11) *with Sodium Periodiate*.—The hemiacetal (11) (0·7 g, 2·56 mmol) was dissolved in methanol (14 ml) and sodium periodate (1·09 g, 5·1 mmol) in water (14 ml) was added. After 20 min the mixture was diluted with water until the precipitate dissolved. 10M-Barium acetate (5 ml) was then added and the precipitated barium salts were filtered off. The filtrate, after treatment with cationic exchange resin [Amberlite IR-120 (H^+)], was evaporated to leave the hemiacetal

[7] I. M. Goldman and E. G. Andrews, as quoted in *Chem. Eng. News*, 1967, July 10, 44.

[8] H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, 1958, **80**, 5372.

sulphoxide (13) (0·72 g, 93%) as a mixture of isomers (6 : 1 on the basis of n.m.r. spectroscopy), $[\alpha]_D$ −75° (0·19% in $CHCl_3$), $\nu_{max.}$ (film) 3280 (OH), 1700 (unsat. C=O), and 1595 (C=C) cm^{-1}, $\lambda_{max.}$ 286 nm (ε 10,700), τ (60 MHz; $CDCl_3$) major isomer: 9·16, 8·50, 8·46, and 8·39 (each 3H, s, 2 *gem*-Me_2), 6·23 (3H, s, OMe), 6·15 (1H, d, *J* 4·3 Hz, 6-H), 4·56 (1H, d, *J* 4·3 Hz, 7-H), and 2·29 (1H, s, 2-H); minor isomer: 8·99 and 8·32 (each 3H, s, 2 *gem*-Me_2), 6·23 (3H, s, OMe), 6·15 (1H, d, *J* 4·6 Hz, 6-H), 4·19 (1H, d, *J* 4·6 Hz, 7-H), and 2·18 (1H, s, 2-H).

Reactions of Methyl (6S)-7-*Hydroxy*-5,5,9,9-*tetramethyl*-8-*oxa*-4-*thia*-1-*azabicyclo*[4,3,0]*non*-2-*ene*-3-*carboxylate* 4-*Oxide* (13) *with Sodium Borohydride and Sodium Borodeuteride*.—The hemiacetal sulphoxides (13) (0·88 g, 3 mmol) were dissolved in dry dioxan (14 ml) and sodium borohydride (0·114 g, 3 mmol) was added. The mixture was stirred overnight, diluted with water (20 ml), neutralised with cationic exchange resin [Amberlite IR-120 (H^+)], and evaporated. The residue was dissolved in methanol and the solution evaporated (repeated three times) to leave a product (0·46 g, 64%) which, on the basis of i.r., n.m.r., and mass spectroscopy, was identical with the sulphoxide mixture (14) prepared by sodium periodate oxidation of the alcohol (4).

Similar reduction of the hemiacetal sulphoxides (13) with sodium borodeuteride afforded the monodeuteriated sulphoxides (15).

Reaction of Methyl (3S)-3,4-*Dihydro*-3-*hydroxymethyl*-2,2-*dimethyl*-2*H*-1,4-*thiazine*-6-*carboxylate* (4) *with Sodium Periodate*.—The alcohol (4) (0·87 g, 4 mmol) was dissolved in methanol (15 ml) and sodium periodate (0·86 g, 4 mmol) in water (15 ml) was added. The mixture was stirred for 20 min and then diluted with water until the precipitate dissolved. 10M-Barium acetate (10 ml) was added and the precipitate was filtered off. The filtrate was treated with cationic exchange resin [Amberlite IR-120 (H^+)] and evaporated to leave the sulphoxide (14) (0·77 g, 82%) as a mixture of isomers (6 : 1 on the basis of n.m.r. spectroscopy), m.p. 137—140° (from chloroform–ether), $\nu_{max.}$ (KBr) 3220 (NH and OH), 1695 and 1685 (unsat. C=O), and 1590 (C=C) cm^{-1}, τ (60 MHz; D_2O) major isomer: 9·07 and 8·60 (each 3H, s, *gem*-Me_2), 6·19 (3H, s, OMe), 6·60—5·99 (3H, m, 3-H and CH_2·O), and 1·78 (1H, s, 5-H); minor isomer: 8·82 and 8·46 (each 3H, s, *gem*-Me_2), 6·19 (3H, s, OMe), 6·60—5·99 (3H, m, 3-H and CH_2·O), and 1·78 (1H, s, 5-H).

Recrystallisation of the mixture from chloroform–ethyl acetate (twice) afforded the major *sulphoxide* (19%) as white prisms, m.p. 143—145°, $[\alpha]_D$ −276° (0·12% in $CHCl_3$), $\nu_{max.}$ (KBr) 3370 and 3200 (OH and NH), 1695 (unsat. C=O), and 1590 (C=C) cm^{-1}, $\lambda_{max.}$ 275 nm (ε 13,600) [Found: C, 46·1; H, 6·3; N, 6·0%; *M* (mass spectrum), 233. $C_9H_{15}NO_4S$ requires C, 46·3; H, 6·5; N, 6·0%; *M*, 233].

Reaction of Methyl (3S)-3,4-*Dihydro*-3-*hydroxymethyl*-2,2-*dimethyl*-2*H*-1,4-*thiazine*-6-*carboxylate* 1-*Oxides* (14) *with Acetyl Chloride*.—(*a*) The sulphoxides (14) (0·257 g, 1·1 mmol) were suspended in dry acetonitrile (5 ml) and acetyl chloride (0·432 g, 5·5 mmol) in acetonitrile (2 ml) was added. The mixture was stirred at room temperature for 3 h, diluted with water, and extracted with chloroform. The organic layer was washed with sodium hydrogen carbonate solution followed by water, dried ($MgSO_4$), and evaporated to leave a syrup (0·34 g), which was fractionated by silica gel chromatography. The major component (0·26 g, 80%) was the *amide* (17), m.p. 130—131° (from ether–light petroleum), $[\alpha]_D$ +170° (0·48% in $CHCl_3$), $\nu_{max.}$ (KBr) 1750 (ester C=O) and 1675 (amide C=O) cm^{-1}, τ ($CDCl_3$) 8·73 and 8·33 (each 3H, s, *gem*-Me_2), 7·69 (3H, s, MeCO), 6·16 (1H, m, 6-H), 6·13 (3H, s, OMe), 5·70 (1H, d, *J* 8·0 Hz, 6-H), 5·19br (1H, d, *J* 5·5 Hz, 5-H), and 4·02br (1H, s, H-1) [Found: C, 45·1; H, 5·4; N, 4·8%; *M* (mass spectrum), 293. $C_{11}H_{16}ClNO_4S$ requires C, 45·0; H, 5·5; N, 4·8%, *M*, 293].

(*b*) A suspension of the sulphoxides (14) (0·047 g, 0·2 mmol) in dry acetonitrile (1 ml) was cooled to −15°. Acetyl chloride (0·016 g, 0·2 mmol) in acetonitrile (0·5 ml) was added and the mixture was stirred for 30 min and allowed to warm to room temperature. After 1 h the solution was diluted with chloroform, washed with sodium hydrogen carbonate solution followed by water, dried ($MgSO_4$), and evaporated to leave the unstable crude amine (16) (0·044 g), which decomposed when attempts were made to purify it by silica gel and alumina chromtography; $\nu_{max.}$ (film) 3290 (NH), 1740 (ester C=O), and 1600 cm^{-1}, τ ($CDCl_3$) *inter alia* 8·81 and 8·20 (each 3H, s, *gem*-Me_2), 7·45br (1H, s, NH), 6·70—6·20 (2H, m, 5-H and 6-H), 6·14 (3H, s, OMe), 5·69 (1H, d, *J* 7·8 Hz, 6-H), and 4·5br (1H, s, 1-H) (upon addition of D_2O to the solution the signal at τ 4·50 sharpened to a singlet).

Reaction of Methyl (1R,5S)-2-*Chloro*-4,4-*dimethyl*-7-*oxa*-3-*thia*-8-*azabicyclo*[3,2,1]*octane*-2-*carboxylate* (16) *with Acetyl Chloride*.—The amine (16) (0·042 g, 0·17 mmol) was dissolved in acetonitrile (1 ml) and acetyl chloride (0·091 g, 1·2 mmol) in acetonitrile (0·5 ml) was added. After 3 h the solution was diluted with water and extracted with chloroform. The organic layer was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated to leave a syrupy product. Fractionation by silica gel chromatography [chloroform–ether (1 : 1) as eluant] gave the amide (17) (0·31 g, 63%), m.p. 129—130° (from ether–light petroleum), identical (i.r. and n.m.r. spectroscopy) with that obtained from the reaction of the sulphoxides (14) with acetyl chloride.

Reaction of Methyl (1R,5S)-8-*Acetyl*-2-*chloro*-4,4-*dimethyl*-7-*oxa*-3-*thia*-8-*azabicyclo*[3,2,1]*octane*-2-*carboxylate* (17) *with Iron*(II) *Chloride*.—The amide (17) (0·52 g, 2 mmol) was heated under reflux in methanol (20 ml) containing concentrated hydrochloric acid (0·8 ml) and iron(II) chloride tetrahydrate (1·5 g, 8 mmol). After 1·25 h the mixture was diluted with water and extracted (three times) with chloroform. The organic layer was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated to a syrup (0·41 g), which was fractionated by silica gel chromatography. The major product (0·09 g, 23%) was identical with the alcohol (4) on the basis of t.l.c. and n.m.r. spectroscopy.

The monodeuteriated amide (18) was similarly converted into the monodeuteriated alcohol (5). The sample was transformed [1] into the monodeuteriated aziridine (10), which was *ca.* 73% monodeuteriated on the basis of mass spectroscopy. N.m.r. spectroscopy indicated that the isotope was *ca.* equally distributed between the 7-*exo*- and 7-*endo*-positions.

Reaction of Methyl (1R,5S)-8-*Acetyl*-2-*chloro*-4,4-*dimethyl*-7-*oxa*-3-*thia*-8-*azabicyclo*[3,2,1]*octane*-2-*carboxylate* (17) *with Silver Perchlorate in Methanol*.—The amide (17) (0·115 g, 0·4 mmol) was dissolved in methanol (4 ml) and silver perchlorate (0·09 g, 0·43 mmol) in methanol (4 ml) was added. After 15 h the precipitated silver chloride was filtered off and the filtrate was diluted with chloroform and washed with water (twice). The organic layer was dried ($MgSO_4$) and evaporated to leave a syrup (0·126 g), which was purified by silica gel chromatography (chloroform as

eluant) to give the 2-*methoxy-derivative* (19) (0·106 g, 93%), m.p. 88—89° (from chloroform–light petroleum), $[\alpha]_D$ +81° (0·14% in $CHCl_3$), $\nu_{max.}$ (KBr) 1730 (ester C=O) and 1655 (amide C=O) cm^{-1}, τ ($CDCl_3$) 8·79 and 8·49 (each 3H, s, *gem*-Me_2), 7·80 (3H, s, MeCO), 6·64 (3H, s, OMe), 6·17 (4H, superimposed signals, OMe and 6-H), 5·60 (1H, d, *J* 8·7 Hz, 6-H), 5·30br (1H, d, *J* 6·3 Hz, 5-H), and 4·21br (1H, s, 1-H) [Found: C, 49·8; H, 6·7; N, 4·7%; *M* (mass spectrum), 289. $C_{12}H_{19}NO_5S$ requires C, 49·8; H, 6·6; N, 4·9%; *M*, 289].

Reduction of Methyl (1R,5S)-8-*Acetyl*-2-*chloro*-4,4-*dimethyl*-7-*oxa*-3-*thia*-8-*azabicyclo*[3,2,1]*octane*-2-*carboxylate* (17) *by Zinc in Acetic Acid*.—The amide (17) (0·093 g, 0·32 mmol) was dissolved in acetic acid (2 ml) and zinc dust (0·042 g, 0·64 mmol) was added. The vigorously stirred mixture was heated at 80° for 3 h, and then diluted with water. The solution was extracted with chloroform and the extract was washed with sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated. The resulting syrup was fractionated by silica gel chromatography (chloroform as eluant). The major product was *methyl* (1R,5S)-8-*acetyl*-4,4-*dimethyl*-7-*oxa*-3-*thia*-8-*azabicyclo*[3,2,1]*octane*-2-*carboxylate* (20) (0·053 g, 64%), $[\alpha]_D$ +69° (0·84% in $CHCl_3$), $\nu_{max.}$ (film) 1730 (ester C=O), and 1660 (amide C=O) cm^{-1}, τ (90 MHz; $CDCl_3$; measured at +7°) 8·78 and 8·05 (each 3H, s, *gem*-Me_2), 7·78 (3H, s, MeCO), 6·54 (1H, d, *J* 3·0 Hz, 2-H), 6·12 (4H, superimposed signals, OMe and 6-H), 5·6 (1H, d, *J* 7·6 Hz, 6-H), 5·29 (1H, d, *J* 5·5 Hz, 5-H), and 3·98 (1H, d, *J* 3·0 Hz, 1-H) (irradiation at τ 3·98 caused the doublet at 6·54 to collapse to a singlet and irradiation at 6·54 caused the doublet at 3·98 to collapse to a singlet) [Found: *M* (mass spectrum), 259·0869. $C_{11}H_{17}NO_4S$ requires *M*, 259·0878].

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