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THE CONFORMATIONAL BEHAVIOUR OF SOME DIHYDRO-1,4-THIAZINES—III[1]

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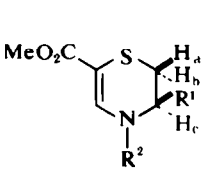
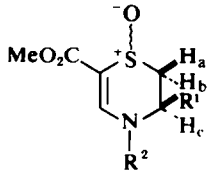
Abstract—Oxidation of **1**, **3**, **5**, **13** and **14** by either *m*-chloroperbenzoic acid or sodium periodate gave single sulphoxides, which are assigned the *R* configuration. The minor sulphoxide formed by sodium periodate oxidation of **4** and the major sulphoxide obtained in the corresponding oxidation of **6** are assigned the *S* configuration. The conformational properties of the above sulphoxides have been examined by the NMR method; the derivatives show an overwhelming preference to adopt the conformation with the oxide function in the axial environment.

In connection with other work, (3R)-2,3-*dihydro*-3-*hydroxymethyl*-6-*methoxycarbonyl*-1,4-*thiazine* 1-*oxide* (**7**) was prepared by *m*-chloroperbenzoic acid oxidation of **1**.[1] The single sulphoxide (isomer *A*), which was isolated (61%), showed in its NMR spectrum (C_5H_5N) a triplet at τ 7·51 ($J_{ab} = J_{ac} =$ 12·8 Hz) for H_a and a double doublet at 6·72 ($J_{ab} =$ 12·8 and $J_{bc} = 2·4$ Hz) for H_b.

In order to determine the value of J_{ac} in an environment where H_a and H_c are expected to possess a dihedral angle of *ca* 180°, (6R)-3-*methoxycarbonyl*-9,9-*dimethyl*-8-*oxa*-4-*thia*-1-*azabicyclo*[4.3.0]*non*-2-*ene* 4-*oxide* (**15**) was prepared (91%) by sodium periodate oxidation of **13**.[1] The sulphoxide was obtained as a single isomer (isomer *A*) and its NMR spectrum ($CDCl_3$) contained a triplet at τ 7·98 ($J_{ab} = J_{ac} = 12·8$ Hz) for H_a and a double doublet at 6·82 ($J_{ab} = 12·8$ and $J_{bc} = 2·6$ Hz) for H_b.

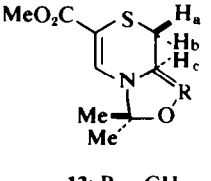
The similar values of J_{ac} strongly suggest that the

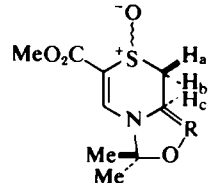




1: $R^1 = CH_2OH$, $R^2 = H$
2: $R^1 = H_d$, $R^2 = H$
3: $R^1 = CO_2H$, $R^2 = H$
4: $R^1 = CH_2OAc$, $R^2 = H$
5: $R^1 = CH_2OMs$, $R^2 = H$
6: $R^1 = CH_2OH$, $R^2 = i$-Pr

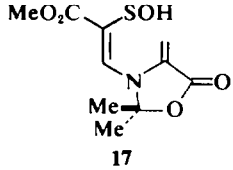
7: $R^1 = CH_2OH$, $R^2 = H$
8: $R^1 = H_d$, $R^2 = H$
9: $R^1 = CO_2H$, $R^2 = H$
10: $R^1 = CH_2OAc$, $R^2 = H$
11: $R^1 = CH_2OMs$, $R^2 = H$
12: $R^1 = CH_2OH$, $R^2 = i$-Pr





13: R = CH_2
14: R = CO

15: R = CH_2
16: R = CO



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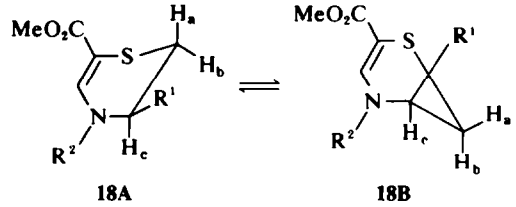
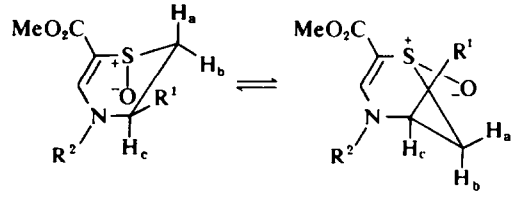
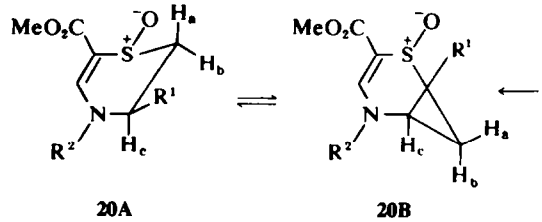


18A **18B**



19A **19B**



20A **20B**

above sulphoxides possess similar geometries. Consequently, the 3-hydroxymethyl group of 7 resides almost exclusively in the equatorial environment.

Previously, we have suggested[2] that atoms 1, 3, 4, 5 and 6 of 3-substituted 2,3-dihydro-6-methoxycarbonyl-1,4-thiazine are *ca* coplanar because of a conjugative interaction between the nitrogen lone-pair electrons and the carbonyl group. Thus, the unsaturated ester CO groups absorbed at *ca* 1680 cm^{-1} (compared to 1710–1720 cm^{-1} for normal $\alpha\beta$-unsaturated esters[3]). The compounds were considered to be represented by the sofa conformers **18A** and **18B**. The ester groups of the corresponding 1-oxides also appear at *ca* 1680 cm^{-1}; conformers **19A**, **19B**, **20A** and **20B** will be assumed to be available to these derivatives. It should be noted, however, that J_{ac} increases by 3·9 Hz from **13** to **15**, which suggests that the geometries of these species are somewhat different.

On the above evidence, **7** (isomer *A*) may be represented by either **19A** ($R^1 = CH_2OH$, $R^2 = H$) or **20A** ($R^1 = CH_2OH$, $R^2 = H$). By contrast, **1** preferentially exists as **18B** ($R^1 = CH_2OH$, $R^2 = H$) in both deuterochloroform and deuteropyridine.[1] The presence of the oxide group, therefore, has a profound effect upon the conformational properties of the system. Before attempting to interpret this behaviour it is necessary to define the configuration of the sulphinyl group.

Several NMR spectroscopic methods are available for determining the configurations of sulphoxides in 6-membered rings.[4] The procedures require that both isomers are available and that the sulphinyl group is axial in one isomer and equatorial in the other. When treated with triethyloxonium fluoroborate followed by sodium hydroxide,[5] **15** (isomer *A*) was converted (84%) into a new sulphoxide (isomer *B*). The NMR spectrum ($CDCl_3$) of **15** (isomer *B*) showed a triplet at τ 7·34 ($J_{ab} = J_{ac} = 12·0$ Hz) for H_a. Since the geminal coupling constant of protons α to the sulphinyl group is larger for an axial sulphoxide than for the equatorial isomer,[6] **15** (isomer *A*) is probably the (*R*)-sulphoxide. The signal for H_c appeared at τ 5·78 in **15** (isomer *A*) and at *ca* 6·1 in **15** (isomer *B*). This deshielding of H_c in isomer *A* is probably the result of a *syn*-axial effect and, although somewhat smaller than usual, it is consistent with the axial orientation of the oxide group.[7]

m-Chloroperbenzoic acid oxidation of **14**[2] yielded (51%) (6R)-3-*methoxycarbonyl*-9,9-*dimethyl*-7-*oxo*-8-*oxa*-4-*thia*-1-*azabicyclo*[4.3.0]*non*-2-*ene* 4-*oxide* (**16**) as a single isomer. Recently, it was shown that this sulphoxide undergoes racemisation when warmed in chloroform. We have suggested that the sulphenic acid **17** is an intermediate in the reaction and that it is formed by a sigmatropic hydrogen shift. This implies that the sulphinyl group and the 6-hydrogen bear a *syn*-axial relationship and, consequently, that **16** is the (*R*)-oxide.[8]

When heated with sulphuric acid in aqueous dioxan, the (*R*)-sulphoxide **15** gave (43%) **7** (isomer *A*) and the (*S*)-sulphoxide **15** afforded (68%) **7** (isomer *B*). Sodium borohydride reduction of the racemate of the (*R*)-oxide **16** yielded (30%) the racemate of **7** (isomer *A*). Consequently, the sulphoxide obtained by *m*-chloroperbenzoic acid oxidation of **1** possesses the *R* configuration and it exists as **19A** ($R^1 = CH_2OH$, $R^2 = H$). The NMR spectrum (D_2O) of the (*S*)-sulphoxide (**7**) showed double doublets at τ 7·00 ($J_{ab} = 15·2$ and $J_{bc} = 5·2$ Hz) for H_b and 6·41 ($J_{ab} = 15·2$ and $J_{ac} = 1·8$ Hz) for H_a. The value of J_{ac} indicates that the derivative exists predominantly as **20B** ($R^1 = CH_2OH$, $R^2 = H$).

The above results show that there is a marked tendency for the (*R*)- and the (*S*)-sulphoxides **7** to exist in the conformation which possesses an axial oxide group. In an attempt to determine the origin of this behaviour we have synthesized a number of dihydro-1,4-thiazines and examined their conformational properties.

Sodium periodate oxidation of **2**[2] produced (84%) (1RS)-2,3-*dihydro*-6-*methoxycarbonyl*-1,4-*thiazine* 1-*oxide* (**8**).

(3R)-2,3-*Dihydro*-3-*carboxy*-6-*methoxycarbonyl*-1,4-*thiazine* (**9**) 1-*oxide* was prepared (70%) as a single isomer by *m*-chloroperbenzoic acid oxidation of **3**.[2] The oxide is assigned the *R* configuration since its racemate was obtained by treating the racemate of the (*R*)-sulphoxide **16** with sodium hydroxide.

Sodium periodate oxidation of **4**[1] afforded a mixture (9:1 by NMR spectroscopy) of (3R)-3-*acetoxymethyl*-2,3-*dihydro*-6-*methoxycarbonyl*-1,4-*thiazine* 1-*oxides* (**10**). The major sulphoxide, which was obtained (69%) by recrystallisation of the mixture from methanol, is assigned the *R* configuration since it was converted (90%) into the (*R*)-sulphoxide **7** by methanolic sodium methoxide. The minor sulphoxide was isolated (10%) by silica gel fractionation of the mother liquor; it yielded (73%) the (*S*)-sulphoxide **7** in the presence of methanolic sodium methoxide.

m-Chloroperbenzoic acid oxidation of **5**[1] gave a mixture of (3R)-2,3-*dihydro*-3-*methanesulphonyloxymethyl*-6-*methoxycarbonyl*-1,4-*thiazine* 1-*oxide* (**11**) and the (*R*)-sulphoxide **7**. The last derivative (12%) almost certainly arises from the (*S*)-sulphoxide **11** by hydrolysis involving participation of the sulphinyl oxygen atom.[9] The isolated (69%) mesylate sulphoxide is assigned the *R* configuration since it was slowly converted (44%) into the (*R*)-sulphoxide **7** in boiling water buffered at pH 7.

(3R)-2,3-*Dihydro*-3-*hydroxymethyl*-4-*isopropyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**6**) was obtained (55%) by diborane reduction of **14**;[2] its NMR spectrum [$(CD_3)_2SO$], which showed double doublets

at τ 7·75 (J_{ab} = 12·8 and J_{ac} = 2·8 Hz) for H_a and at 7·03 (J_{ab} = 12·8 and J_{bc} = 2·4 Hz) for H_b, established[1] that it existed as **18B** ($R^1 = CH_2OH$, R^2 = *i*-Pr). Sodium periodate oxidation of **6** gave (3R)-2,3-*dihydro*-3-*hydroxymethyl*-4-*isopropyl*-6-*methoxycarbonyl*-1,4-*thiazine* 1-*oxide* (**12**) as a mixture (7:3 by NMR spectroscopy) of isomers. The mixture was separated to give the major sulphoxide (44%) and the minor sulphoxide (15%). NMR spectroscopy (see Table 1) left little doubt that the major sulphoxide was the (*S*)-isomer and the minor sulphoxide was the (*R*)-isomer.

The coupling constants and chemical shifts of the ab protons of the above sulphoxides, which were evaluated from 90 MHz spectra by first-order analysis, are summarised in Table 1.

It is clear that the (*R*)-sulphoxides (**7**, **9**, **10**, **11** and **12**), which are characterised by J_{ac} = 12·6–13·6 and J_{bc} = 1·7–2·4 Hz, show a dramatic preference for conformer **19A**. By contrast, the (*S*)-sulphoxides (**7**, **10** and **12**), which possess J_{ac} = 1·8–2·2 and J_{bc} = 4·8–5·2 Hz, exist overwhelmingly as **20B**. It is also interesting to note that J_{ab} is significantly larger in the (*S*)-sulphoxides compared with the (*R*)-sulphoxides. This effect is presumably associated with the presence of the axial 3-substituents in the former derivatives.

The above results illustrate that 2,3-dihydro-6-methoxycarbonyl-1,4-thiazine 1-oxides exist predominantly as the conformer which possesses an axial group. In order to interpret this behaviour it is necessary to compare the major interactions in each conformer.

Conformer **19A** is expected to be destabilised by $A^{(1,2)}$ strain[10] between R^1 and R^2 and **19B** by $A^{(1,2)}$ strain between the oxide and methoxycarbonyl groups. The former interaction is likely to be negligible in **8** and to be small in the (*R*)-sulphoxides (**7**, **9**, **10** and **11**) (the corresponding Me:H interaction in 3-methylcyclohexene is estimated[11] to be *ca* 0·6 kcal mol^{-1}); however, it is expected to be substantial in the (*R*)-sulphoxide **12**. Nevertheless, the last derivative shows an overwhelming preference for **19A** ($R^1 = CH_2OH$, R^2 = i-Pr).

Conformer **20A** is expected to be destabilised by $A^{(1,2)}$ strain between the oxide and methoxycarbonyl groups and between R^1 and R^2; **20B** is likely to experience a 1,3-diaxial interaction between the oxide group and R^1 (the corresponding interaction in 3,3-dimethylthiane 1-oxide is considered[12] to be > 2 kcal mol^{-1}). As the size of R^2 is decreased a larger proportion of **20A** is expected to contribute to the equilibrium mixture. However, this effect is not detectable since the values of J_{ac} and J_{bc} are very similar in the (*S*)-sulphoxides (**7**, **10** and **12**). This finding suggests that values of J_{ac} = 2·0 and J_{bc} = 5·0 Hz are diagnostic of **20B**; evidently, the last conformer is favoured over **20A** by at least 1·5 kcal mol^{-1} in spite of the 1,3-diaxial interaction between the oxide group and R^1. Therefore, the $A^{(1,2)}$ strain between the sulphinyl and methoxycarbonyl groups in conformers **19B** and **20A** is probably > 3·5 kcal mol^{-1}.

In summary, 2,3-dihydro-6-methoxycarbonyl-1,4-thiazine 1-oxides show a marked preference to adopt the conformer which possesses an axial oxide group. The higher free-energy of the conformer with an equatorial oxide formation is ascribed to a severe $A^{(1,2)}$ interaction between the sulphinyl and methoxycarbonyl groups.

Table 1. Coupling constants (in Hz) and chemical shifts of the ab protons† of dihydro-1,4-thiazine 1-oxides

Sulphoxide	Solvent	τ_a	τ_b	J_{ab}	J_{ac}	J_{bc}
15 [(*R*)-isomer]	$CDCl_3$	7·98	6·82	12·8	12·8	2·6
15 [(*S*)-isomer]‡	$CDCl_3$	7·34	6·27	12·0	12·0	2·5
16 [(*R*)-isomer]	$CDCl_3$	7·71	6·56	13·4	13·4	3·0
7 [(*R*)-isomer]	C_5H_5N	7·51	6·72	12·8	12·8	2·4
7 [(*S*)-isomer]	D_2O	6·41	7·00	15·2	1·8	5·2
8 [(*RS*)-isomer]	D_2O	7·67	7·09	13·6	13·6	2·8
9 [(*R*)-isomer]	$(CD_3)_2SO$	7·40	6·77	13·2	13·2	2·4
10 [(*R*)-isomer]	$(CD_3)_2SO$	7·71	7·05	13·6	13·6	2·4
10 [(*S*)-isomer]	D_2O	6·47	7·14	15·2	1·9	5·1
11 [(*R*)-isomer]	$(CD_3)_2SO$	7·69	6·98	13·0	13·0	3·0
12 [(*R*)-isomer]	$CDCl_3$	7·34	6·88	13·6	12·6	1·7
12 [(*S*)-isomer]	$CDCl_3$	6·43	7·29	14·8	2·2	4·8

†The proton at higher field is considered to be the axial proton.

‡Measured at 220 MHz.

EXPERIMENTAL

For general details see Part II.[1]

Reaction of (3R)-2,3-*dihydro*-3-*hydroxymethyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**1**) *with* m-*chloroperbenzoic acid*

A stirred soln of **1**[1] (1·71 g, 9 mmol) in CH_2Cl_2 (40 ml) was treated with *m*-chloroperbenzoic acid (1·56 g, 9 mmol) in CH_2Cl_2 (40 ml) at 0°. After 30 min the mixture was extracted with H_2O and the aqueous layer was evaporated to leave the crude (*R*)-sulphoxide (**7**); the material was chromatographed on silica gel using EtOAc–MeOH (4:1) as eluant to give the pure (*R*)-sulphoxide (1·13 g, 61%); m.p. 175–176° (MeOH–ether); $[\alpha]_D$ + 314° (0·82% in H_2O); ν_{max}^{KBr} 3300 and 2950 (NH and OH), 1690 (unsat C=O) and 1580 cm^{-1} (C=C); λ_{max}^{EtOH} 273 nm (ϵ 14,700); τ (C_5H_5N) 7·51 (1H, t, $J_{ab} = J_{ac}$ = 12·8 Hz, H_a), 6·72 (1H, dd, J_{ab} = 12·8 and J_{bc} = 2·4 Hz, H_b), 6·28 (3H, s, CO_2Me) and 5·72 (4H, superimposed signals, H_c and CH_2OH). (Found: C, 40·7; H, 5·4; N, 6·8%; *M*, 205 (mass spectrum, mol ion). $C_7H_{11}NO_4S$ requires; C, 41·0; H, 5·5; N, 6·9%; *M*, 205).

Reaction of (6R)-3-*methoxycarbonyl*-9,9-*dimethyl*-8-*oxa*-4-*thia*-1-*azabicyclo*[4.3.0]*non*-2-*ene* (**13**) *with sodium periodate*

A stirred soln of **13**[1] (1·03 g, 4·49 mmol) in MeOH (10 ml) was treated with $NaIO_4$ (0·96 g, 4·49 mmol) in H_2O (12 ml). After 25 min the mixture was diluted with H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated to leave the (*R*)-sulphoxide **15** (1·0 g, 91%); m.p. 169–170° ($CHCl_3$–ether); $[\alpha]_D$ + 339° (0·1% in $CHCl_3$); ν_{max}^{KBr} 1685 (unsat C=O) and 1595 cm^{-1} (C=C); λ_{max}^{EtOH} 285 nm (ϵ 15,400); τ

($CDCl_3$) 8·53 and 8·47 (each 3H, s, *gem*-Me_2), 7·98 (1H, t, $J_{ab} = J_{ac} = 12·8$ Hz, H_a), 6·82 (1H, dd, $J_{ab} = 12·8$ and $J_{bc} = 2·6$ Hz, H_b), 6·48 (3H, s, CO_2Me), 6·36 (1H, s, 7-H), 5·78 (1H, m, H_c), 5·75 (1H, t, $J = 6·0$ Hz, 7-H) and 2·15 (1H, s, 2-H). (Found: C, 48·9; H, 6·2; N, 5·7%; *M*, 245 (mass spectrum, mol ion). $C_{10}H_{15}NO_4S$ requires: C, 49·0; H, 6·2; N, 5·7%; *M*, 245).

(4S,6R)-3-*Methoxycarbonyl*-9,9-*dimethyl*-8-*oxa*-4-*thia*-1-*azabicyclo*[4.3.0]-*non*-2-*ene* 4-*oxide* (**15**)

The (*R*)-sulphoxide **15** was converted into the (*S*)-sulphoxide by the procedure of Johnson.[7] A soln of the (*R*)-oxide **15** (0·5 g, 2·04 mmol) in dry CH_2Cl_2 (1 ml) was treated with a soln of Et_3OBF_4 (0·43 g, 2·24 mmol) in CH_2Cl_2 (1 ml). After 12 hr the salt, which crystallised from the mixture, was collected by filtration and washed with ether. The salt (0·7 g, 1·94 mmol) was dissolved in H_2O (80 ml) and treated with NNaOH (1·94 ml). After 5 min the soln was extracted with $CHCl_3$ and the extract was washed with H_2O, dried ($MgSO_4$) and evaporated to leave the (*S*)-sulphoxide **15** (0·42 g, 84%); m.p. 165–172° ($CHCl_3$-ether); $[\alpha]_D$ +72° (0·24% in $CHCl_3$); ν_{max}^{KBr} 1685 (unsat C=O) and 1580 cm^{-1} (C=C); λ_{max}^{EtOH} 235 (ε 4000) and 298 nm (ε 14,000); τ (220 MHz, $CDCl_3$) 8·54 and 8·49 (each 3H, s, *gem*-Me_2), 7·34 (1H, t, $J_{ab} = J_{ac} = 12·0$ Hz, H_a), 6·34–6·2 (2H, m, CH_2O), 6·27 (1H, dd, $J_{ab} = 12·0$ and $J_{bc} = 2·5$ Hz, H_b), 6·23 (3H, s, CO_2Me), *ca* 6·1 (1H, m, H_c) and 2·38 (1H, s, 2-H). (Found: C, 48·8; H, 5·9; N, 5·5%; *M*, 245·072. $C_{10}H_{15}NO_4S$ requires: C, 49·0; H, 6·2; N, 5·7%; *M*, 245·072).

Reaction of (6R)-3-*methoxycarbonyl*-9,9-*dimethyl*-7-*oxo*-8-*oxa*-4-*thia*-1-*azabicyclo*[4.3.0]*non*-2-*ene* (**14**) *with* m-*chloroperbenzoic acid*

A soln of the lactone[2] **14** (1·15 g, 4·73 mmol) in CH_2Cl (20 ml), cooled in acetone-solid CO_2, was treated with *m*-chloroperbenzoic acid (0·9 g, 5·2 mmol) in CH_2Cl_2 (20 ml). After 2 hr the mixture was shaken with $NaHCO_3$ aq and H_2O. The organic layer was dried ($MgSO_4$) and evaporated at room temp to a small volume (*ca* 10 ml). On addition of ether the (*R*)-sulphoxide **16** crystallised (0·72 g, 51%); it was recrystallised *in the cold* from $CHCl_3$-ether, m.p. 189–190° (dec); $[\alpha]_D$ +105° (1·4% in $CHCl_3$); ν_{max}^{KBr} 1790 (γ-lactone C=O), 1695 (unsat C=O) and 1580 cm^{-1} (C=C); λ_{max}^{EtOH} 280 nm (ε 14,300); τ ($CDCl_3$) 8·23 and 8·13 (each 3H, s, *gem*-Me_2), 7·71 (1H, t, $J_{ab} = J_{ac} = 13·4$ Hz, H_a), 6·56 (1H, dd, $J_{ab} = 13·4$ and $J_{bc} = 3·0$ Hz, H_b), 6·16 (3H, s, CO_2Me), 5·25 (1H, dd, $J_{ab} = 13·4$ and $J_{ac} = 3·0$ Hz, H_c) and 1·99 (1H, s, 2-H). (Found: C, 46·1; H, 5·0; N, 5·3; *M*, 259 (mass spectrum, mol ion). $C_{10}H_{13}NO_5S$ requires: C, 46·3; H, 5·1; N, 5·4% *M*, 259).

When the (*R*)-sulphoxide **16** was recrystallised from hot $CHCl_3$-ether the product was a racemate, m.p. 180–185° (dec); $[\alpha]_D$ 0° (1·5% in $CHCl_3$).

Reaction of (6R)-3-*methoxycarbonyl*-9,9-*dimethyl*-8-*oxa*-4-*thia*-1-*azabicyclo*[4.3.0]*non*-2-*ene* 4 *oxides* (**15**) *with sulphuric acid*

(a) A soln of the (*R*)-sulphoxide **15** (0·075 g, 0·306 mmol) in 50% aqueous dioxan (1·2 ml) was heated at 100° for 2 hr with 6N H_2SO_4 (1·2 ml). The mixture was extracted with $CHCl_3$ and the extract evaporated to leave the starting sulphoxide (0·013 g, 17%). The aqueous layer was neutralised with $Ba(CO_3)_2$, treated with cationic-exchange resin [Amberlite IR 120 (H^+)] and evaporated. The residue was fractionated by silica gel chromatography using benzene-MeOH (5:1) as eluant to give the (*R*)-sulphoxide **7** (0·027 g, 43%); m.p. 174–176° (MeOH-ether).

(b) A soln of the (*S*)-sulphoxide **15** (0·127 g, 0·5 mmol) in H_2O (1 ml) was heated at 85° for 1 hr with 6N H_2SO_4 (0·1 ml). The mixture was neutralised with $Ba(CO_3)_2$ and filtered. The filtrate was treated with cationic-exchange resin [Amberlite IR 120 (H^+)] and evaporated to leave the (*S*)-oxide **7** (0·073 g, 68%); m.p. 160–161° (MeOH-ether); $[\alpha]_D$ +70° (0·59% in MeOH); ν_{max}^{KBr} 3300 (NH and OH), 1690 (unsat C=O) and 1595 cm^{-1} (C=C); λ_{max}^{EtOH} 276 nm (ε 14,000); τ (D_2O) 7·0 (1H, dd, $J_{ab} = 15·2$ and $J_{bc} = 5·2$ Hz, H_b), 6·41 (1H, dd, $J_{ab} = 15·2$ and $J_{ac} = 1·8$ Hz, H_a), 6·15 (3H, s, CO_2Me), 6·2–5·77 (3H, superimposed signals, H_c and CH_2O) and 1·81 (1H, s, 2-H). (Found: C, 41·0; H, 5·4; N, 6·9%; *M*, 205·041 (mass spectrum, mol ion). $C_7H_{11}NO_4S$ requires: C, 41·0; H, 5·5; N, 6·9%; *M*, 205·041).

Reaction of the racemate of (4R,6R)-3-*methoxycarbonyl*-9,9-*dimethyl*-7-*oxo*-8-*oxa*-4-*thia*-1-*azabicyclo*[4.3.0]*non*-2-*ene* 4-*oxide* (**16**) *with sodium borohydride*

A soln of the racemate of the (*R*)-oxide **16** (0·207 g, 0·8 mmol) in dry dioxan (8 ml) was stirred overnight with $NaBH_4$ (0·046 g, 1·2 mmol). The mixture was diluted with acetone and H_2O and treated with ion-exchange resin [Amberlite IR 120 (H^-)]. Evaporation of the solvent left a syrup (0·11 g) which was fractionated by silica gel chromatography using MeOH–EtOAc (1:4) as eluant to give the racemate of the (*R*)-sulphoxide **7** (0·05 g, 30%); m.p. 193–197° (dec) (MeOH-ether). The NMR, UV and mass spectra of the material were identical to those of the (*R*)-sulphoxide **7**.

Reaction of 2,3-*dihydro*-6-*methoxycarbonyl*-1,4-*thiazine* (**2**) *with sodium periodate*

A soln of $NaIO_4$ (1·48 g, 6·92 mmol) in H_2O (10 ml) was added to a stirred soln of **2**[2] (1·0 g, 6·29 mmol) in MeOH. After 25 min the mixture was diluted with H_2O and an excess of M $Ba(OAc)_2$ was added. The precipitated salts were removed by filtration and the filtrate was treated with ion-exchange resin [Amberlite IR 120 (H^+)]. Evaporation of the solvent left crude **8** (0·923 g, 84%); m.p. 160–163° (dec) ($CHCl_3$-ether); ν_{max}^{KBr} 3180 (NH), 1685 (unsat C=O) and 1600 cm^{-1} (C=C); λ_{max}^{EtOH} 273 nm (ε 14,900); τ (D_2O) 7·67 (1H, sextet, $J_{ab} = J_{ac} = 13·6$ and $J_{ad} = 4·8$ Hz, H_a), 7·09 (1H, sextet, $J_{ab} = 13·6$ and $J_{bc} = J_{bd} = 2·8$ Hz, H_b), 6·96–6·23 (2H, m, H_c and H_d), 6·47 (3H, s, CO_2Me) and 2·18 (1H, s, 5-H). (Found: C, 40·8; H, 5·1; N, 7·9%; *M*, 175 (mass spectrum, mol ion). $C_6H_9O_3NS$ requires: C, 41·1; H, 5·1; N, 8·0%; *M*, 175).

Reaction of (3R)-2,3-*dihydro*-3-*carboxy*-6-*methoxycarbonyl*-1,4-*thiazine* (**3**) *with* m-*chloroperbenzoic acid*

A stirred soln of **3**[2] (4·06 g, 0·02 mol) in dioxan at 12° was treated dropwise with *m*-chloroperbenzoic acid (3·45 g, 0·02 mol) in dioxan (40 ml). After 35 min the mixture was diluted with H_2O and extracted with $CHCl_3$ (2 times). Evaporation of the aqueous layer left the (*R*)-oxide **9** (3·15 g, 70%); m.p. 158–160° (dec) (MeOH); $[\alpha]_D$ +222° (1·3% in H_2O); ν_{max}^{KBr} 3250 and 3100 (NH and OH), 1730 (CO_2H), 1680 (unsat C=O), 1610 and 1590 cm^{-1} (C=C); λ_{max}^{EtOH} 273 nm (ε 13,700); τ [$(CD_3)_2SO$] 7·4 (1H, t, $J_{ab} = J_{ac} = 13·2$ Hz, H_a), 6·77 (1H, dd, $J_{ab} = 13·2$ and $J_{bc} = 2·4$ Hz, H_b), 6·23 (3H, s, CO_2Me), 5·77 (1H, m, H_c), 2·2 (1H, d, $J = 7·3$ Hz, 5-H) and 0·9br (1H, d, $J = 7·2$ Hz,

NH) (addition of D_2O to the soln caused the signal at τ 2·2 to collapse to a singlet and that at 0·9 to disappear). (Found: C, 38·6; H, 4·1; N, 6·5%. $C_7H_9NO_5S$ requires: C, 38·4; H, 4·2; 6·4%).

Reaction of the racemate of (4R,6R)-3-*methoxycarbonyl*-9,9-*dimethyl*-7-*oxo*-8-*oxa*-4-*thia*-1-*azabicyclo*[4.3.0]*non*-2-*ene* 4-*oxide* (**16**) *with sodium hydroxide*

The racemate of the (*R*)-lactone sulphoxide **16** (0·13 g, 0·5 mmol) was dissolved in 0·1N NaOH (5 ml, 0·5 mmol). After 0·5 hr the soln was diluted with H_2O, washed with $CHCl_3$ and treated with ion-exchange resin [Amberlite IR 120 (H^+)]. Evaporation of the solvent left the racemate of the (*R*)-sulphoxide **9** (0·104 g, 95%); m.p. 157–159° (dec) (MeOH). The NMR and UV spectra of the material were identical to those of the (*R*)-sulphoxide **9**.

Reaction of (3R)-3-*acetoxymethyl*-2,3-*dihydro*-6-*methoxycarbonyl*-1,4-*thiazine* (**4**) *with sodium periodate*

A soln of $NaIO_4$ (1·37 g, 6·4 mmol) in H_2O (25 ml) was added to a stirred soln of **4**[1] (1·34 g, 5·8 mmol) in MeOH (25 ml). After 20 min the mixture was diluted with H_2O, treated with an excess of M $Ba(OAc)_2$ soln and filtered. The filtrate was treated with ion-exchange resin [Amberlite IR 120 (H^+)] and evaporated to leave **10** as a mixture (9:1 by NMR spectroscopy) of isomers. Recrystallisation of the residue from MeOH afforded the major (*R*)-sulphoxide **10** (0·99 g, 69%); m.p. 195–200° (dec); $[\alpha]_D$ +338° (0·29% in H_2O); ν_{max}^{KBr} 2960 (NH), 1735 (acetate C=O), 1665 (unsat C=O) and 1585 cm^{-1} (C=C); λ_{max}^{EtOH} 275 nm (ϵ 15,400); τ [$(CD_3)_2SO$] 7·93 (3H, s, MeCO), 7·71 (1H, t, $J_{ab} = J_{ac} = 13·6$ Hz, H_a), 7·05 (1H, dd, $J_{ab} = 13·6$ and $J_{ac} = 2·4$ Hz, H_b), 6·36 (3H, s, CO_2Me), 6·18 (1H, m, H_c), 5·67 (2H, m, CH_2O), 2·23 (1H, d, J = 7·4 Hz, 5-H) and 1·07br (1H, J = 7·4 Hz, NH) (when D_2O was added to the soln the signal at τ 1·07 disappeared and the doublet at 2·23 collapsed to a singlet). (Found: C, 43·6; H, 5·2; N, 5·6%; *M*, 247 (mass spectrum, mol ion). $C_9H_{13}NO_5S$ requires: C, 43·7; H, 5·3; N, 5·7%; *M*, 247).

The mother liquor (0·35 g) was fractionated by silica gel chromatography using benzene–MeOH (5:1) as eluant (fractions from the column were monitored by NMR spectroscopy). A further quantity of the (*R*)-sulphoxide **10** (0·24 g, 16%) was obtained in addition to the (*S*)-sulphoxide **10** (0·14 g, 10%); m.p. 150–151° (MeOH-ether); $[\alpha]_D$ + 121° (0·7% in H_2O); ν_{max}^{KBr} 3400 (NH), 1745 (acetate C=O), 1655 (unsat C=O) and 1585 cm^{-1} (C=C); λ_{max}^{KBr} 271 nm (ϵ 15,000); τ (D_2O) 7·91 (3H, s, COMe), 7·14 (1H, dd, $J_{ab} = 15·2$ and $J_{bc} = 5·1$ Hz, H_b), 6·47 (1H, dd, $J_{ab} = 15·2$ and $J_{ac} = 1·9$ Hz, H_a), 6·25 (3H, s, CO_2Me), 5·51 – 5·18 (3H, superimposed signals, H_c and CH_2O) and 1·93 (1H, s, 5-H). (Found: C, 43·8; H, 5·0; N, 5·6%; *M*, 247·0515 (mass spectrum, mol ion). $C_9H_{13}NO_5S$ requires: C, 43·7; H, 5·3; N, 5·7%; *M*, 247·0514).

Saponification of (3R)-3-*acetoxymethyl*-2,3-*dihydro*-6-*methoxycarbonyl*-1,4-*thiazine* 1-*oxides* (**10**)

(a) The (*R*)-sulphoxide **10** (0·04 g, 0·162 mmol) was dissolved in MeOH (0·5 ml) and 2·43M NaOMe soln (0·1 ml) was added. After 10 min the soln was diluted with H_2O and treated with ion-exchange resin [Amberlite IR 120 (H^+)]. Evaporation of the solvent left the (*R*)-oxide **7** (0·031 g, 90%); m.p. 176–177° (MeOH-ether).

(b) The (*S*)-sulphoxide **10** (0·076 g, 0·31 mmol) was dissolved in MeOH (0·5 ml) and 2·43M NaOMe soln (0·1 ml) was added. After 10 min the soln was diluted with H_2O and treated with ion-exchange resin [Amberlite IR 120 (H^+)]. Evaporation of the solvent left the (*S*)-sulphoxide **7** (0·046 g, 73%); m.p. 157–159° (MeOH-ether),

Reaction of (3R)-2,3-*dihydro*-3-*methanesulphonyloxymethyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**5**) *with* m-*chloroperbenzoic acid*

A soln of *m*-chloroperbenzoic acid (0·19 g, 1·1 mmol) in CH_2Cl_2 (4 ml) was added to a stirred soln of **5**[1] (0·267 g, 1·0 mmol) in CH_2Cl_2 (4 ml), which was cooled in acetone-solid CO_2. After 1·75 hr the mixture was diluted with CH_2Cl_2 and extracted with H_2O. The aqueous extract was evaporated to leave a residue (0·27 g), which was dissolved in the minimum volume of benzene–MeOH (1:1). On addition of ether the (*R*)-sulphoxide **11** crystallised as white needles (0·164 g, 58%); m.p. 158–160° (dec) (benzene-MeOH-ether); $[\alpha]_D$ + 260° (0·14% in H_2O); ν_{max}^{KBr} 3140 (NH), 1670 (unsat C=O) and 1590 cm^{-1} (C=C); λ_{max}^{EtOH} 270 nm (ϵ 13,900); τ [$(CD_3)_2SO$] 7·69 (1H, t, $J_{ab} = J_{ac} = 13·0$ Hz, H_a), 6·98 (1H, dd, $J_{ab} = 13·0$ and $J_{bc} = 3·0$ Hz, H_b), 6·74 (3H, s, SO_2Me), 6·36 (3H, s, CO_2Me), 6·07 (1H, m, H_c), 5·47 (2H, m, CH_2O), 2·17 (1H, d, J = 7·0 Hz, 5-H) and 0·97br (1H, d, J = 7·0 Hz, NH) (on addition of D_2O to the soln the signal at τ 0·97 disappeared and that at 2·17 collapsed to a singlet). (Found: C, 34·1; H, 4·6; N, 4·9%. $C_8H_{13}NO_6S_2$ requires: C, 33·9; H, 4·6; N, 5·0%).

The mother liquor was evaporated and the residue was dissolved in MeOH. Solid $NaHCO_3$ was added to the soln, which was filtered and concentrated. The derived syrup, which contained two components by TLC, was fractionated by silica gel chromatography using benzene–MeOH (5:1) as eluant. The first-eluted substance (0·032 g, 11%) was the (*R*)-sulphoxide **11**; m.p. 158–160° (dec) (benzene-MeOH-ether). The second-eluted material (0·025 g, 12%) was the (*R*)-sulphoxide **7**; m.p. 169–170° (MeOH-ether).

Hydrolysis of (1R,3R)-2,3-*dihydro*-3-*methanesulphonyloxymethyl*-6-*methoxycarbonyl*-1,4-*thiazine*-1-*oxide* (**11**)

A soln of the (*R*)-sulphoxide **11** (0·05 g, 0·177 mmol) was heated overnight under reflux in pH 7·0 phosphate buffer (1 ml). The soln was evaporated and the residue was fractionated by silica gel chromatography using benzene–MeOH (5:1) as eluant (fractions were monitored by NMR spectroscopy). The first-eluted substance (0·017 g, 34%) was starting material and the second-eluted material (0·016 g, 44%) was the (*R*)-sulphoxide **7**; m.p. 169–171° (MeOH-ether).

(3R)-2,3-*Dihydro*-3-*hydroxymethyl*-4-*isopropyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**6**)

A freshly prepared sample of **14**[2] (5·7 g, 2·35 mmol) was dissolved in dry THF under N_2. Diborane was bubbled through the soln until the material with R_f 0·3 [$CHCl_3$–EtOAc (9:1)] was the major component. The soln was cautiously added to N HCl (200 ml) and extracted (3 times) with $CHCl_3$. The organic layer was washed with $NaHCO_3$ aq and H_2O, dried ($MgSO_4$) and evaporated to leave a syrup. This was fractionated by silica gel chromatography using $CHCl_3$–ether (7:3) as eluant to give **6** (2·98 g, 55%); m.p. 69–70° (ether-light petroleum); $[\alpha]_D$ 0° (0·5% in $CHCl_3$); ν_{max}^{KBr} 3440 (OH), 1660 (unsat C=O) and 1600 cm^{-1} (C=C); λ_{max}^{EtOH} 221 (ϵ 6800), 256 (ϵ 2000) and 315 nm (ϵ 13,500); τ[$(CD_3)_2SO$]8·99 (6H, d, J = 7·0 Hz, $CH\underline{Me}_2$), 7·75 (1H, dd, $J_{ab} = 12·8$ and $J_{bc} = 2·8$ Hz, H_b), 7·03 (1H, dd, $J_{ab} = 12·8$ and $J_{ac} = 2·4$ Hz, H_a), 6·67 – 6·36 (4H, superimposed signals, H_c, CH_2O and $C\underline{H}Me_2$), 6·45 (3H, s, CO_2Me), 5·12 (1H, t, J = 5·0 Hz,

OH) and 2·44 (1H, s, 5-H) (when D_2O was added to the soln the signal at τ 5·12 disappeared). (Found: C, 52·2; H, 7·3; N, 6·1%; *M*, 231·0928 (mass spectrum, mol ion). $C_{10}H_{17}NO_3S$ requires: C, 51·9; H, 7·4; N, 6·1%; *M*, 231·0929).

Reaction of (3R)-2,3-*dihydro*-3-*hydroxymethyl*-4-*isopropyl*-6-*methoxycarbonyl*-1,4-*thiazine* (**6**) *with sodium periodate*

A soln of $NaIO_4$ (2·14 g, 10 mmol) in H_2O (20 ml) was added to a stirred soln of **6** (1·15 g, 5·0 mmol) in MeOH (20 ml). After 15 min the mixture was diluted with H_2O (40 ml) and an excess of M $Ba(OAc)_2$ soln was added. The insoluble salts were removed by filtration and the filtrate was extracted with $CHCl_3$ (3 times). The organic layer was dried ($MgSO_4$) and evaporated to leave a syrup, which afforded the (*S*)-sulphoxide **12** (0·54 g, 44%) on the addition of EtOAc and ether; m.p. 103–104° (EtOAc-ether); $[\alpha]_D - 126°$ (0·15% in $CHCl_3$); ν_{max}^{KBr} 3200 (OH), 1690 (unsat C=O) and 1590 cm^{-1} (C=C); λ_{max}^{KBr} 285 nm (ϵ 18,300); τ ($CDCl_3$) 8·48 and 8·54 (each 3H, d, J = 6·5 Hz, CHMe$_2$), 7·29 (1H, dd, J_{ab} = 14·8 and J_{bc} = 4·8 Hz, H_b), 6·43 (1H, dd, J_{ab} = 14·8 and J_{ac} = 2·2 Hz, H_a), 6·10 (3H, s, CO_2Me), 6·27–5·45 (4H, superimposed signals, CHMe$_2$, H_c and CH_2O), 4·96br (1H, s, OH) and 1·97 (1H, s, 5-H) (when D_2O was added to the soln the signal at τ 4·96 disappeared). (Found: C, 48·6; H, 7·0; N, 5·5%; *M*, 247 (mass spectrum, mol ion). $C_{10}H_{17}NO_4S$ requires: C, 48·6; H, 6·9; N, 5·7%; *M*, 247).

The aqueous layer was treated with ion-exchange resin [Amberlite IR 120 (H^+)] and evaporated to a syrup, which was extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated and the residue was recrystallised from acetone to give the (*R*)-sulphoxide **12** (0·18 g, 15%); m.p. 171–172°; $[\alpha]_D + 185°$ (0·12% in $CHCl_3$); ν_{max}^{KBr} 3200 (OH), 1690 (unsat C=O) and 1600 cm^{-1} (C=C); λ_{max}^{EtOH} 283 nm (ϵ 21,600); τ ($CDCl_3$) 8·62 and 8·51 (each 3H, d, J = 6·8 Hz, CHMe$_2$), 7·34 (1H, dd, J_{ab} = 13·6 and J_{ac} = 12·6 Hz, H_a), 6·88 (1H, dd, J_{ab} = 13·6 and J_{bc} = 1·7 Hz, H_b), 6·13 (3H, s, CO_2Me), 6·13 – 5·34 (5H, superimposed signals, H_c, CHMe$_2$ and CH_2O), 5·29br (1H, s, OH) and 1·93 (1H, s, 5-H) (when D_2O was added to the soln the signal at τ 5·29 disappeared). (Found: C, 48·4; H, 7·1; N, 5·6%; *M*, 247 (mass spectrum, mol ion). $C_{10}H_{17}NO_4S$ requires: C, 48·6; H, 6·9; N, 5·7%; *M*, 247).

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