Studies Related to Dihydro-1,4-thiazines. Part V.[1] Intramolecular Cyclisations of 3,4-Dihydro-3-hydroxymethyl-6-methoxycarbonyl-2*H*-1,4-thiazines [2]

By **John Kitchin** and **Richard J. Stoodley,*** Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU

(1*R*,3*R*)-3,4-Dihydro-3-hydroxymethyl-6-methoxycarbonyl-2*H*-1,4-thiazine 1-oxide (5) is converted into methyl (1*S*,5*R*)-8-acetyl-2-chloro-7-oxa-3-thia-8-azabicyclo[3.2.1]octane-2-carboxylate (9) by acetyl chloride in acetonitrile. (1*S*,3*R*)-3,4-Dihydro-3-hydroxymethyl-4-isopropyl-6-methoxycarbonyl-2*H*-1,4-thiazine 1-oxide (8) and its (1*R*)-isomer (7) undergo an analogous reaction, *via* a common acetoxysulphonium salt (16), to give methyl (1*S*,5*R*)-2-chloro-8-isopropyl-7-oxa-3-thia-8-azabicyclo[3.2.1]octane-2-carboxylate (11). In the presence of acetic acid the last-named derivative is converted into methyl (1*S*,5*R*)-2-acetoxy-8-isopropyl-7-oxa-3-thia-8-azabicyclo[3.2.1]octane-2-carboxylate (12), which is identical with the product formed in the reaction of methyl (3*R*)-3,4-dihydro-3-hydroxymethyl-4-isopropyl-2*H*-1,4-thiazine-6-carboxylate (25) with lead tetra-acetate.

RECENTLY it was shown that a mixture (6 : 1) of (3*S*)-3,4-dihydro-3-hydroxymethyl-6-methoxycarbonyl-2,2-dimethyl-2*H*-1,4-thiazine 1-oxides (1) was converted into methyl (1*R*,5*S*)-8-acetyl-2-chloro-4,4-dimethyl-7-oxa-3-thia-8-azabicyclo[3.2.1]octane-2-carboxylate (2) by acetyl chloride in acetonitrile.[3] The reaction was considered to involve the intermediacy of the chloro-amine (3), formed by loss of acetic acid from the acetoxysulphonium

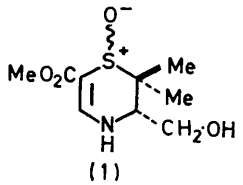
[1] Part IV, J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, preceding paper.

[2] Preliminary communication, J. Kitchin and R. J. Stoodley, *J.C.S. Chem. Comm.*, 1972, 959.

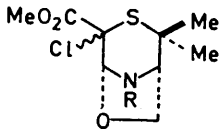
[3] J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 1973, 22.

salt (4). The unusual reactivity of the oxide was ascribed to its vinylogous sulphinamide character.

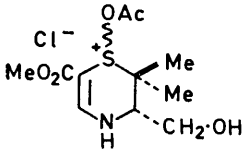
Sulphoxides which contain α-methylene groups usually undergo the Pummerer reaction [4] in the presence of acid halides to give α-chloro-sulphides. Consequently, it was



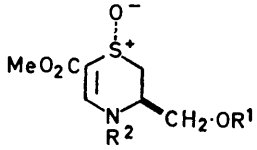
(1)



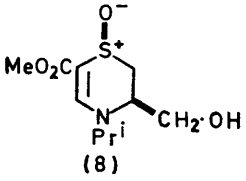
(2) R = Ac
(3) R = H



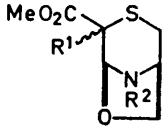
(4)



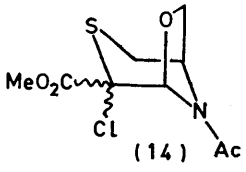
(5) $R^1 = R^2 = H$
(6) $R^1 = Ac, R^2 = H$
(7) $R^1 = H, R^2 = Pr^i$



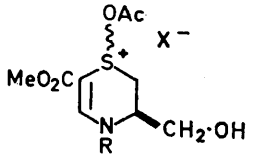
(8)



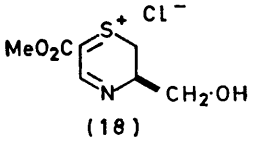
(9) $R^1 = Cl, R^2 = Ac$
(10) $R^1 = Cl, R^2 = H$
(11) $R^1 = Cl, R^2 = Pr^i$
(12) $R^1 = OAc, R^2 = Pr^i$
(13) $R^1 = Pb(OAc)_3, R^2 = Pr^i$



(14)



(15) R = H, X = Cl
(16) R = Pr^i, X = Cl
(17) R = Pr^i, X = OAc



(18)

of interest to examine the reaction of (1*R*,3*R*)-3,4-dihydro-3-hydroxymethyl-6-methoxycarbonyl-2*H*-1,4-thiazine 1-oxide (5) [5] with acetyl chloride in acetonitrile. The reaction afforded the chloro-amide (9) (72%). The structure of the derivative (9) was assigned on the basis of its spectroscopic properties, which were similar to those of the chloro-amide (2); n.m.r. spectroscopy indicated that it existed as conformer (14) in deuteriochloroform solution.

The (*R*)-sulphoxide (6) [5] did not afford the chloro-amide (9) when treated with acetyl chloride in acetonitrile; consequently, it is not an intermediate in the above transformation.

In principle, three processes warrant consideration for the conversions of the sulphoxides (1) and (5) into the chloro-amides (2) and (9). First, the acetoxysulphonium salt, *e.g.* (15), may lose acetic acid to give the sulphonium salt (18), which then affords the chloro-amine (10). Secondly, loss of acetic acid from the acetoxysulphonium salt (15) may be coupled with the cyclisation step, *i.e.* the sulphonium salt (19) is formed by an S_N2' process.[6] Thirdly, the acetoxysulphonium salt (15) may undergo an intramolecular conjugate addition to give the salt (21), which then affords the chloro-amine (10) by a normal Pummerer reaction.

If the first process is involved, a 4-substituted 3,4-dihydro-3-hydroxymethyl-6-methoxycarbonyl-2*H*-1,4-thiazine 1-oxide is unlikely to undergo a comparable reaction since a dication, *e.g.* (23), is required. However, the (*S*)-sulphoxide (8) [5] was readily converted into the chloro-amine (11) (40%) by acetyl chloride in acetonitrile.

If the cyclisation involves an S_N2' process, the reaction may be dependent upon the stereochemistry of the sulphoxide group. Although Pummerer rearrangements are usually insensitive to this effect,[7] stereospecific examples are known.[8] In principle, S_N2' displacements can occur in a *syn*-facial or *apo*-facial manner; the former pathway is preferred in cyclohexene derivatives.[9] Providing that the acetoxysulphonium salts do not interconvert, only the salt derived from the (*S*)-sulphoxide (8) can attain the correct geometry, *i.e.* (24), for the *syn*-facial reaction. However, the (*R*)-sulphoxide (7) was also converted (74%) into the chloro-amine (11). Moreover, when the reactions were carried out in trideuterioacetonitrile at low temperature and followed by n.m.r. spectroscopy, both sulphoxides rapidly afforded the same acetoxysulphonium salt (16), which was slowly transformed into the chloro-amine (11) as the temperature was raised. This result precludes any further discussion of the S_N2' mechanism.

In summary, the conversions of the alcohol sulphoxides (7) and (8) into the chloro-amine (11) involve the rapid formation of a common acetoxysulphonium salt (16), which slowly gives the chloro-amine (11) without the intervention of a detectable intermediate. The slow

[4] G. A. Russell and G. J. Mikol in 'Mechanisms of Molecular Migrations,' vol. 1, ed. B. S. Thyagarajan, Interscience-Wiley, 1968, p. 157; T. Durst, *Adv. Org. Chem.*, 1969, **6**, 285.

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

[6] P. B. D. de la Mare in 'Molecular Rearrangements,' vol. 1, ed. P. de Mayo, Interscience, New York, 1963, p. 27; F. G. Bordwell, *Accounts Chem. Res.*, 1970, **3**, 281.

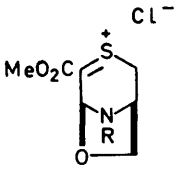
[7] M. Kise and S. Oae, *Bull. Chem. Soc. Japan*, 1970, **43**, 1426; D. N. Jones, E. Helmy, and R. D. Whitehouse, *J.C.S. Perkin I*, 1972, 1329.

[8] S. Glue, I. T. Kay, and M. R. Kipps, *Chem. Comm.*, 1970, 1158.

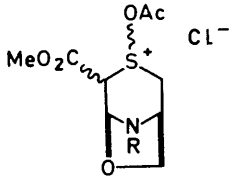
[9] C. W. Jefford, A. Sweeney, D. T. Hill, and F. Delay, *Helv. Chim. Acta*, 1971, **54**, 1691; C. W. Jefford, A. Sweeney, and F. Delay, *ibid.*, 1972, **55**, 2214.

step in the reaction probably involves the formation of the acetoxysulphonium salt (22), although the generation of the sulphonium salt (20) by an S_N2' process is not excluded.

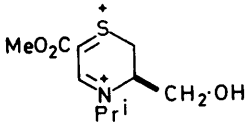
In connection with other work it was necessary to convert the isopropyl derivative (25) into the alcohol (26). Since tertiary amines are often oxidised to iminium salts by lead tetra-acetate,[10] it was hoped that the oxidant would transform the alcohol (25) into the



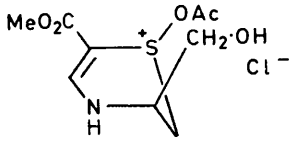
(19) R = H
(20) R = Pr^i



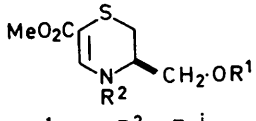
(21) R = H
(22) R = Pr^i



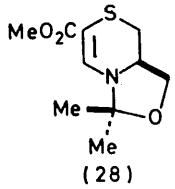
(23)



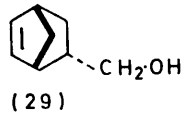
(24)



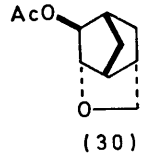
(25) R^1 = H, R^2 = Pr^i
(26) R^1 = R^2 = H
(27) R^1 = Pb(OAc)$_3$, R^2 = Pr^i



(28)



(29)



(30)

bicyclic derivative (28); acidic hydrolysis of compound (28) is known to yield the alcohol (26).[11]

In an exploratory experiment the isopropyl derivative (25) [5] was treated with lead tetra-acetate in acetic acid. The product (83%) was considered to be methyl (1*S*,5*R*)-2-acetoxy-8-isopropyl-7-oxa-3-thia-8-azabicyclo[3.2.1]-octane-2-carboxylate (12), on the basis of elemental analysis and spectroscopic evidence. The derivative (12) was also formed, but in reduced yield (39%), when the oxidation was performed in benzene. The structural relationship between the acetate (12) and the chloro-amine (11) was established when the latter was converted (55%) into the former by acetic acid.

Since lead tetra-acetate can oxidise sulphides to sulphoxides,[12] it is possible that the sulphoxides (7) and (8) are intermediates in the formation of the acetate (12). This possibility was eliminated when the sulphoxides were found to be unchanged under the reaction conditions. However, a mechanism involving the intermediacy of the acetoxysulphonium salt (17), formed directly from the sulphide (25) and lead tetra-acetate, is not excluded. The lead derivatives (13) and (27) also warrant consideration as reaction intermediates.

The formation of cyclic ethers during the lead tetra-acetate oxidation of 5-hydroxyalkenes has precedent in alicyclic chemistry. For example, the alcohol (29) is converted into the acetate (30), probably by addition of lead tetra-acetate in the double bond and nucleophilic participation by the alcohol.[13]

EXPERIMENTAL

For general experimental details see Part I.[14]

Reaction of (1R,3R)-3,4-*Dihydro*-3-*hydroxymethyl*-6-*methoxycarbonyl*-2H-1,4-*thiazine* 1-*Oxide* (5) *with Acetyl Chloride*.—A suspension of the (*R*)-sulphoxide (5) [5] (0·102 g, 0·5 mmol) in dry acetonitrile (2 ml) was treated with acetyl chloride (0·196 g, 2·5 mmol) in dry acetonitrile (0·5 ml). The mixture was stirred overnight, 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, which was fractionated by silica gel chromatography (chloroform as eluant). The major component was *methyl* (1S,5R)-8-*acetyl*-2-*chloro*-7-*oxa*-3-*thia*-8-*azabicyclo*[3.2.0]*octane*-2-*carboxylate* (9) (0·094 g, 71%), m.p. 112—113° [from ether–light petroleum (b.p. 40—60°)], $[\alpha]_D$ −174° (0·21% in $CHCl_3$), $\nu_{max.}$ (KBr) 1750 (ester C=O) and 1660 (amide C=O) cm^{-1}, τ (90 MHz; $CDCl_3$) 7·71 (3H, s, MeCO), 7·44 (1H, dd, *J* 13·2, *J'* 3·6 Hz, 4-H), 6·52 (1H, dd, *J* 13·2, *J'* 2 Hz, 4-H), 6·03 (4H, superimposed signals, CO_2Me and 6-H), 5·90 (1H, d, *J* 7·6 Hz, 6-H), 4·74br (1H, s, 5-H), and 3·9br (1H, s, 1-H) [irradiation at τ 4·74 caused the double doublet at 7·44 to collapse to a doublet (*J* 13·2 Hz)] (Found: C, 40·6; H, 4·7; N, 5·7%; M^+, 265·0185. $C_9H_{12}ClNO_4S$ requires C, 40·7; H, 4·6; N, 5·3%; *M*, 265·0176).

Reaction of (1R,3R)-3-*Acetoxymethyl*-3,4-*dihydro*-6-*methoxycarbonyl*-2H-1,4-*thiazine* 1-*Oxide* (6) *with Acetyl Chloride*.—The (*R*)-sulphoxide (6) [5] (0·069 g, 0·28 mmol), suspended in dry acetonitrile (1 ml), was treated with acetyl chloride (0·11 g, 1·39 mmol) in dry acetonitrile (0·5 ml). The mixture was stirred overnight, 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. The derived syrup (0·058 g) did not contain the chloro-amide (9) (t.l.c. and n.m.r. spectroscopy).

Reaction of (1S,3R)-3,4-*Dihydro*-3-*hydroxymethyl*-4-*isopropyl*-6-*methoxycarbonyl*-2H-1,4-*thiazine* 1-*Oxide* (8) *with Acetyl Chloride*.—(*a*) A stirred solution of the (*S*)-sulphoxide (8) [5] (2·35 g, 9·5 mmol) in dry acetonitrile (48 ml) at −15° was treated slowly with acetyl chloride (1·12 g, 14·2 mmol)

[10] J. B. Aylward, *Quart. Rev.*, 1971, **25**, 407.
[11] A. R. Dunn and R. J. Stoodley, *Tetrahedron*, 1972, **28**, 3315.
[12] B. D. Podolešov, *Croat. Chem. Acta*, 1968, **40**, 201; E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1972, 229.
[13] R. M. Moriarty and K. Kapadia, *Tetrahedron Letters*, 1964, 1165.
[14] A. R. Dunn and R. J. Stoodley, *J.C.S. Perkin I*, 1972, 2509.

in dry acetonitrile (24 ml). After 25 min the mixture was diluted with chloroform and washed with sodium hydrogen carbonate solution and water. The dried ($MgSO_4$) organic layer was evaporated to leave a syrup which, after chromatography on silica gel [benzene–ether (1 : 1) as eluant], gave *methyl* (1S,5R)-2-*chloro*-8-*isopropyl*-7-*oxa*-3-*thia*-8-*azabicyclo*-[3.2.1]*octane*-2-*carboxylate* (11) (1·0 g, 40%) as a mixture (4 : 1 by n.m.r. spectroscopy) of isomers. The major isomer was obtained as white needles, m.p. 82—84° [from benzene–light petroleum (b.p. 40—60°)], $[\alpha]_D$ −217° (0·99% in $CHCl_3$), $\nu_{max.}$ (KBr) 1740 (ester C=O) cm^{-1}, τ ($CDCl_3$) 8·85 (6H, d, *J* 6·5 Hz, $CHMe_2$), 7·56 (1H, dd, *J* 12·0, *J′* 3·4 Hz, 4-H), 7·07 (1H, m, $CHMe_2$), 6·57 (1H, dd, *J* 12·0, *J′* 2 Hz, 4-H), 6·11 (5H, superimposed signals, CO_2Me, 5-H, and 6-H), 5·76 (1H, d, *J* 6·6 Hz, 6-H), and 4·55 (1H, s, 1-H) (Found: C, 45·2; H, 6·2; N, 5·3%; M^+, 265·0544. $C_{10}H_{16}ClNO_3S$ requires C, 45·2; H, 6·1; N, 5·3%; *M*, 265·0539). The n.m.r. spectrum of the minor isomer was similar to that of the major isomer except that it showed signals at τ 9·04 (3H, d, *J* 6·5 Hz) for the isopropyl methyl group and at 4·70 (1H, s) for the 1-proton.

(*b*) A solution of the (*S*)-sulphoxide (8) [5] (0·053 g, 0·213 mmol) in trideuterioacetonitrile (0·4 ml) in an n.m.r. tube was cooled to −40° and acetyl chloride (0·033 g, 0·426 mmol) in trideuterioacetonitrile (0·1 ml) was added. The mixture, which was maintained at −35°, was monitored by 90 MHz n.m.r. spectroscopy; after *ca.* 20 min the starting material had reacted to give the acetoxysulphonium salt (16), τ 8·58 (6H, d, *J* 7·0 Hz, $CHMe_2$), 6·18 (3H, s, CO_2Me), 6·12—5·49 (4H, superimposed signals, probably 3-H, CH_2·O, and $CHMe_2$), 5·00 (1H, dd, *J* 10·0, *J′* 4·0 Hz, 2-H), 4·49 (1H, d, *J* 10·0 Hz, 2-H), 4·78br (1H, s, possibly OH), and 1·58 (1H, s, 5-H). On warming to 0°, the signals corresponding to the acetoxysulphonium salt (16) disappeared and were replaced by those of a mixture (4 : 1) of the chloro-amines (11).

Reaction of Methyl (1R,3R)-3,4-*Dihydro*-3-*hydroxymethyl*-4-*isopropyl*-2H-1,4-*thiazine*-6-*carboxylate* (7) *with Acetyl Chloride.*—(*a*) The (*R*)-sulphoxide (7) [5] (0·04 g, 0·162 mmol) in dry acetonitrile (0·5 ml) was treated with acetyl chloride (0·026 g, 0·324 mmol) in dry acetonitrile (0·5 ml). The mixture was stirred at room temperature for 10 min, diluted with sodium hydrogen carbonate solution, and extracted with chloroform. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a syrup which, after silica gel chromatography, gave the chloro-amine (11) (0·032 g, 74%) as a mixture (4 : 1 by n.m.r. spectroscopy) of isomers.

(*b*) The reaction of the (*R*)-sulphoxide (7) [5] with acetyl chloride in trideuterioacetonitrile was followed by n.m.r. spectroscopy as described for the (*S*)-isomer (8). The acetoxysulphonium salt (16) was again formed at *ca.* −36°; it was converted into a mixture (4 : 1) of the chloro-amines (11) on warming to 0°.

Reaction of Methyl (3R)-3,4-*Dihydro*-3-*hydroxymethyl*-4-*isopropyl*-2H-1,4-*thiazine*-6-*carboxylate* (25) *with Lead Tetra-acetate.*—(*a*) Lead tetra-acetate (0·346 g, 0·78 mmol) was added to a stirred solution of the alcohol (25) [5] (0·09 g, 0·39 mmol) in glacial acetic acid (2 ml). After 30 min the mixture 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. The resultant syrup was chromatographed on silica gel (chloroform as eluant) to give *methyl* (1S,5R)-2-*acetoxy*-8-*isopropyl*-7-*oxa*-3-*thia*-8-*azabicyclo*[3.2.1]*octane*-2-*carboxylate* (12) (0·994 g, 83%), m.p. 75—76° [from ether–light petroleum (b.p. 40—60°)], $[\alpha]_D$ −236° (0·17% in $CHCl_3$), $\nu_{max.}$ (KBr) 1730 (ester C=O) cm^{-1}, τ ($CDCl_3$) 8·90 and 8·87 (each 3H, d, *J* 6·4 Hz, $CHMe_2$), 7·85 (3H, s, MeCO), 7·54 (1H, dd, *J* 11·2, *J′* 3·2 Hz, 4-H), 7·1 (1H, m, $CHMe_2$), 6·65 (1H, dd, *J* 11·2, *J′* 1·8 Hz, 4-H), 6·14 (5H, superimposed signals, CO_2Me, 5-H, and 6-H), 5·74 (1H, d, *J* 6·6 Hz, 6-H), and 4·73 (1H, s, 1-H) (Found: C, 50·1; H, 6·9; N, 4·8%; M^+, 289·0984. $C_{12}H_{19}NO_5S$ requires C, 49·8; H, 6·6; N, 4·9%; *M*, 289·0986).

(*b*) Lead tetra-acetate (0·11 g, 0·25 mmol) was added to a stirred solution of the alcohol (25) [5] (0·057 g, 0·25 mmol) in dry benzene (1 ml). After 2 h the mixture was 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. Fractionation of this material by silica gel chromatography gave the acetate (12) (0·028 g, 39%).

Reaction of Methyl (1S,5R)-2-*Chloro*-8-*isopropyl*-7-*oxa*-3-*thia*-8-*azabicyclo*[3.2.1]*octane*-2-*carboxylate* (11) *with Acetic Acid.*—A solution of the chloro-amine (11) (0·05 g, 0·19 mmol), as a mixture (4 : 1) of isomers, was dissolved in glacial acetic acid (1 ml). After 24 h the solution was diluted with chloroform and washed with sodium hydrogen carbonate solution and water. The dried ($MgSO_4$) organic layer was evaporated to leave a syrup, which was chromatographed on silica gel [benzene–ether (1 : 1) as eluant]. The major component (0·025 g, 55%) was the acetate (12).

Reaction of (3R)-3,4-*Dihydro*-3-*hydroxymethyl*-4-*isopropyl*-6-*methoxycarbonyl*-2H-1,4-*thiazine* 1-*Oxides* (7) *and* (8) *with Lead Tetra-acetate.*—A mixture (3 : 7) of the (*R*)- and (*S*)-sulphoxides (7 and 8) [5] (0·062 g, 0·25 mmol) in glacial acetic acid (1 ml) was treated with lead tetra-acetate (0·111 g, 0·25 mmol). After 2 h the mixture was diluted with water, filtered, and evaporated. The n.m.r. spectrum of the residue (0·057 g) was very similar to that of the starting material.

We thank Mr. P. Kelly for the mass spectral determinations, Dr. N. M. S. Hill for the 90 MHz n.m.r. spectra, and the S.R.C. for a research studentship (to J. K.).

(3/1019 *Received*, 13*th May*, 1973]