Unusual Pummerer Reactions of 3,4-Dihydro-3-hydroxymethyl-6-methoxycarbonyl-1,4-2*H*-thiazine 1-Oxides

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Summary (3*S*)-3,4-Dihydro-3-hydroxymethyl-6-methoxycarbonyl-2,2-dimethyl-1,4-2*H*-thiazine 1-oxides (**2**) are converted into (1*R*,5*S*)-8-acetyl-2-chloro-2-methoxycarbonyl-4,4-dimethyl-7-oxa-3-thia-8-azabicyclo[3,2,1]-octane (**9**) by acetyl chloride in acetonitrile; (3*R*)-3,4-dihydro-3-hydroxymethyl-6-methoxycarbonyl-1,4-2*H*-thiazine 1-oxide (**3**) undergoes an analogous reaction to give (**13**).

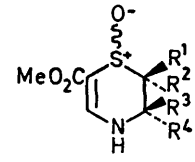
IN connection with other work it was necessary to convert a mixture of the monodeuteriated sulphoxides (**1**) into the monodeuteriated sulphide (**5**). In an exploratory experiment, a crystalline mixture (6:1) of the sulphoxides (**2**), prepared (78%) by sodium metaperiodate oxidation of (3*S*)-3,4-dihydro-3-hydroxymethyl-6-methoxycarbonyl-2,2-dimethyl-1,4-2*H*-thiazine (**6**),[1] was treated with two molar equivalents of sodium dithionite and acetyl chloride in acetonitrile.[2] However, the reaction gave mainly a substance which moved much faster on t.l.c. than the alcohol (**6**). A control experiment established that a similar reaction occurred when the mixture of sulphoxides was treated with acetyl chloride in acetonitrile. The product, m.p. 130—131°, $[\alpha]_D$ +170° ($CHCl_3$), which was isolated (80%) after silica gel chromatography, is considered to be (1*R*,5*S*)-8-acetyl-2-chloro-2-methoxycarbonyl-4,4-dimethyl-7-oxa-3-thia-8-azabicyclo[3,2,1]octane (**9**).

I.r. spectroscopy showed that the compound contained a saturated ester (1745 cm^{-1}) and a tertiary amide (1675 cm^{-1}) group but absorptions due to NH and OH groups were absent. The substance was reduced to the alcohol (**6**) (23%), when heated with ferrous chloride in methanolic hydrochloric acid, indicating that it possessed either structure (**9**) or (**12**). N.m.r. spectroscopy (60 MHz, $CDCl_3$) did not distinguish unambiguously between these alternatives: the uncoupled proton [H-1 of (**9**) or H-7 of (**12**)] appeared as a broad† singlet at τ 4·02. However, the prominent peak at *m/e* 155 ($C_8H_{13}NO_2$ by mass measurement), attributable to the loss of $MeO_2C{\cdot}CSCl$ from the molecular ion, is in accord with cleavage of the 1–2 and 3–4 bonds of (**9**).

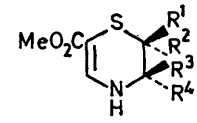
Chemical evidence in support of structure (**9**) was provided by reduction to (**10**) (64% after silica gel chromatography) with zinc in acetic acid. The mass spectrum of the product, $[\alpha]_D$ +69° ($CHCl_3$), showed a molecular ion at *m/e* 259 ($C_{11}H_{17}NO_4S$ by mass measurement) and also a prominent peak at *m/e* 155; its n.m.r. spectrum (90 MHz, $CDCl_3$, measured at +7°) contained doublets at τ 3·98 and 6·54 (each 1H, *J* 3·0 Hz)‡ attributable to H-1 and H-2, respectively, of (**10**).

When treated with one molar equivalent of acetyl chloride in acetonitrile, the mixture of sulphoxides (**2**) was converted into (**11**) (i.r. and n.m.r. spectroscopy), although this decomposed when attempts were made to purify it by chromatography. The crude material was converted into (**9**) by acetyl chloride in acetonitrile. Consequently, (**11**) is an intermediate in the transformation of the sulphoxides (**2**) into (**9**).

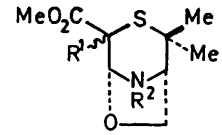
(3*R*)-3,4-Dihydro-3-hydroxymethyl-6-methoxycarbonyl-1,4-2*H*-thiazine 1-oxide (**3**) m.p. 175—176°, $[\alpha]_D$ +295° (EtOH), was prepared (61%) by *m*-chloroperbenzoic acid oxidation of the alcohol (**7**).[3] When treated with acetyl chloride in acetonitrile, it afforded (**13**) (72% after silica gel chromatography), m.p. 112—113°, $[\alpha]_D$ −174° ($CHCl_3$),



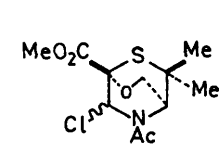
(1) $R^1 = R^2 = Me, R^3 = H, R^4 = CHDOH$
(2) $R^1 = R^2 = Me, R^3 = H, R^4 = CH_2OH$
(3) $R^1 = R^2 = R^4 = H, R^3 = CH_2OH$
(4) $R^1 = R^2 = R^4 = H, R^3 = CH_2OAc$



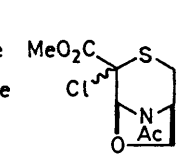
(5) $R^1 = R^2 = Me, R^3 = H, R^4 = CHDOH$
(6) $R^1 = R^2 = Me, R^3 = H, R^4 = CH_2OH$
(7) $R^1 = R^2 = R^4 = H, R^3 = CH_2OH$
(8) $R^1 = R^2 = R^4 = H, R^3 = CH_2OAc$



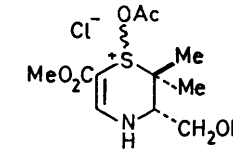
(9) $R^1 = Cl, R^2 = Ac$
(10) $R^1 = H, R^2 = Ac$
(11) $R^1 = Cl, R^2 = H$



(12)



(13)



(14)

τ (90 MHz, $CDCl_3$) 4·03br (1H, H-1). The acetate sulsulphoxide (**4**), m.p. 190—200° (decomp.) $[\alpha]_D$ +338° (H_2O), which was prepared by sodium metaperiodate oxidation of the acetate (**8**),[3] did not give (**13**) under these conditions and, consequently, it is not an intermediate in the transformation.

The unusual reactivity of oxides (**2**) and (**3**) towards acetyl chloride is probably a consequence of their vinylogous sulphinamide character. The reactions are likely to proceed *via* the formation of the sulphoxonium salts, *e.g.* (**14**), which afford the bicyclic products, *e.g.* (**11**), by loss of acetic acid. In principle the cyclisation step may precede,

† The signal is presumably broad due to the presence of configurational isomers of the amide.

‡ The coupling was confirmed by double irradiation.

follow, or be concerted with the elimination of acetic acid. Efforts are being made to distinguish between these mechanistic possibilities.

Satisfactory elemental analyses were obtained for all new compounds.

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[3] A. R. Dunn and R. J. Stoodley, *Tetrahedron*, 1972, **28**, 3315.