Olivanic Acid Analogues. Part 7.[1] Lead Tetra-acetate Oxidation of 3-Alkylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylates

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Lead tetra-acetate oxidation of alkylthiocarbapenams (**2**)–(**4**) gave α-acetoxy sulphides (**5**)–(**7**) with inversion of stereochemistry. Iodosobenzene diacetate was also an effective oxidant. Oxidation to sulphone and elimination of alkanesulphinic acid provided the 3-acetoxy-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate system (13). Alternatively, elimination of acetic acid from compounds (**5**) or (**6**) with DBU furnished a new route to alkylthiocarbapenems.

As part of our programme leading to the total synthesis of analogues of the olivanic acid antibacterial natural products, we described an iodobenzene dichloride-mediated transformation of alkylthiocarbapenams to the corresponding carbapenems. We succeeded thereby in obtaining a biomimetic synthesis of some representative olivanic acids.[1] We have also studied an alternative oxidative functionalisation based on a Pummerer-type strategy. To this end we investigated the 3-acetoxylation of 3-alkylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylates [(**2**)–(**4**)†] with lead tetra-acetate (LTA).[2]

Other reported syntheses of carbapenems and carbacephems containing oxygen substituents on the azabicycloheptene or azabicyclo-octene ring system include hydroxy,[3–6] alkoxy,[7–9] and acyloxy[10,11] derivatives. The latter category includes our own 4-acetoxy- and 4-benzyloxy-olivanic acid derivatives.[12] We also anticipated that α-acetoxylation reactions of sulphides (**2**)–(**4**) might provide access to Δ^2-3-acetoxy derivatives [e.g. compounds (**13**)]. These are carbacyclic analogues related to known 2-alkoxypenems.[13,14]

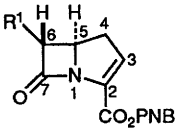
Previously, we have described[15] Michael addition reactions of a series of thiols to the unsubstituted carbapenem (**1a**).[16] The use of ethanethiol provided three adducts (**2a**)–(**4a**) with stereochemistry as indicated. Oxidation of isomers (**2a**) and (**3a**) with LTA (2 mol equiv.) in refluxing benzene (2 h) provided a single isomer (**5a**), (**6a**), respectively, of the corresponding 3-acetoxy-3-ethylthio derivative in good yield. When a mixture of sulphides (**2a**) and (**3a**) (3:2 ratio) was oxidised with LTA in benzene at room temperature under tungsten irradiation (24 h), a comparable yield of acetates (**5a**) and (**6a**) was also obtained (76%; 3:2 ratio). The remaining 2β,3β-sulphide isomer (**4a**) gave compound (**7a**) as the only product (43%).

Isomer (**7a**) was epimerised to (**6a**) by the action of a catalytic amount of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), indicating that these two compounds have the same stereochemistry at C-3.

The structures of the non-crystalline 3-acetoxy-3-ethylthio isomers (**5a**), (**6a**), and (**7a**) were supported by their ^{1}H NMR spectra; all possessed signals corresponding to *S*-ethyl and acetate protons. Their mass spectra did not exhibit molecular ions. However, characteristic $M - C_2H_2O$ ions were evident in their mass spectra, indicating rapid loss of ketene upon electron impact. In each case, precise mass measurements were obtained for this ion.

The regiochemistry of acetoxylation is as predicted from considerations of the formation and stability of the possible sulphenium cationic species; we were unable to detect products arising from substitution at the ethyl group.

Insight into the C-3 stereoselectivity was obtained from a lanthanide-induced shift (LIS) ^{1}H NMR study. This was carried out using Eu([$^2H_9$]fod)$_3$‡ according to principles established in these laboratories in an investigation of 1-oxadethiapenam



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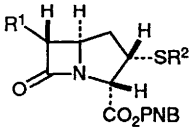

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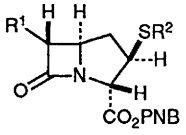

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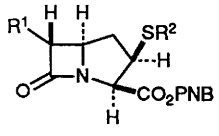

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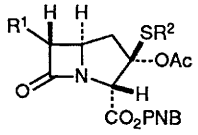

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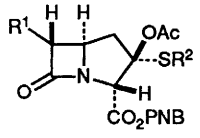

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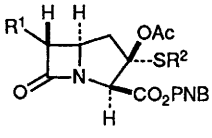
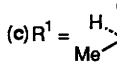


(7)

(**a**) R^1 = H, R^2 = Et
(**b**) R^1 = H, R^2 = $CH_2CH_2CONH_2$
(**c**) R^1 = 

, R^2 = Et

PNB = $CH_2C_6H_4NO_2$-*p*

† This paper employs systematic numbering based on the azabicyclo-[3.2.0]hept-2-ene system throughout. Trivial numbering in respect of the terms 'carbapenem' and 'carbapenam' does not apply.
‡ Eu([$^2H_9$]fod)$_3$ = tris-{6,6,7,7,8,8,8-heptafluoro-2,2-di([$^2H_3$]methyl)-[$^2H_3$]octane-3,5-dionato}europium.

Table. LIS Study of acetoxysulphides (**5a**) and (**6a**). Ratios of absolute shifts relative to 5-H$^{\alpha}$ (= 1.00)[a]

H	(**5a**; β-SEt)	(**6a**; α-SEt)
6α	1.14	1.14
6β	1.58	1.75
4α	1.70	1.09
4β	1.70	1.44
2β	2.26	2.39
$CO_2CH_2C_6H_4NO_2$	0.52	0.47
PNB 2′-, 6′-	0.31	0.27
PNB 3′-, 5′-	0.14	0.14
3-SCH_2Me	1.16	0.72
3-SCH$_2$*Me*	0.45	0.30
3-OAc	1.08	0.87

[a] Spectra were recorded in $CDCl_3$ on a Perkin-Elmer R32 instrument with Me_4Si as an internal standard. Chemical shifts of each proton were plotted against successive increments (0.1 ⟶ 0.9 mol equiv.) of Eu([$^2H_9$]fod)$_3$. For the linear region (*ca.* 0.3–0.9 mol), slope H/slope 5-H$^{\alpha}$ provided the relative shift ratios.

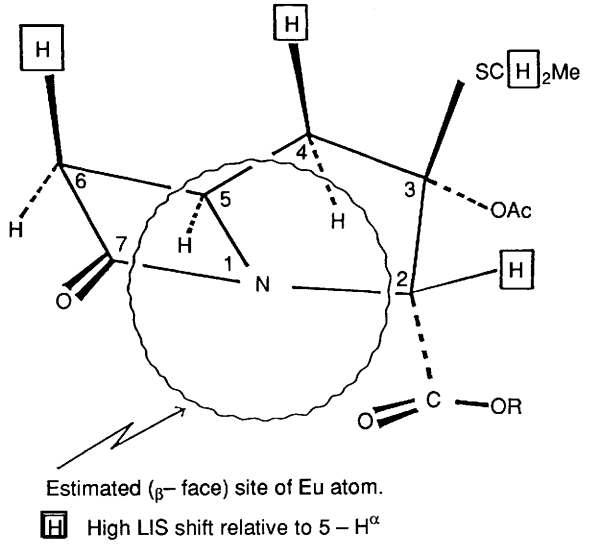
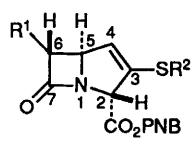


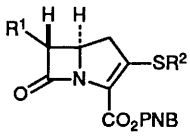
Figure. Estimated europium binding site for isomer (**5a**). Eu([$^2H_9$]fod)$_3$ LIS studies show inversion of configuration at C-3.

('penam' numbering scheme) isomers.[17] The Table lists the ratios of absolute LIS shifts relative to those of 5-H$^{\alpha}$ for the α-acetoxy sulphide isomers (**5a**) and (**6a**). The magnitude of the relative shifts of the 2β, 4β, and 6β-proton in comparison with those of the 5α- and 6α-proton led us to conclude that, for both isomers, the major site of complexation must lie on the β-face of the molecule. Our estimate of the position of the europium binding site is indicated in the Figure for isomer (**5a**). The magnitude of the LIS shifts of the methylene protons of the 3-ethylthio groups (Table) implies a 3β-configuration for isomer (**5a**) (1.16) and a 3α-configuration in the case of isomer (**6a**) (0.72). Thus, whereas in the related iodobenzene dichloride α-chlorosulphoxidations retention of C-3 stereochemistry is favoured,[15] the LTA reaction is seen to proceed with inversion. In inferring these assignments, we note, however, unexpectedly high shifts of the 4-H$^{\alpha}$ (1.70) and acetate (1.08) protons of isomer (**5a**). We interpret these in terms of a secondary binding site involving the accessible α-face acetoxy group of this isomer.

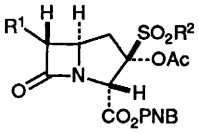
The transformation (**2a**) ⟶ (**5a**) was also effected (60%) by using iodosobenzene diacetate [(diacetoxyiodo)benzene] and pyridine. In contrast, lead tetrakis(trifluoroacetate) (LTTFA), [$Pb(OCOCF_3)_4$],[18] a reagent which we anticipated would provide a highly nucleofugal ring substituent, proved to be destructive to the β-lactam ring. However, phenyl iodoso-bis(trichloroacetate) {[bis(trichloroacetoxy)iodo]benzene} [$PhI(OCOCCl_3)_2$], a new reagent, which we prepared from iodosobenzene diacetate and trichloroacetic acid, gave Δ^3-ester (**8a**)[15] directly but in low yield (14%). We believe that this product arises by elimination of trichloroacetic acid from an intermediate α-trichloroacetyl sulphide.



(**8**)



(**9**)



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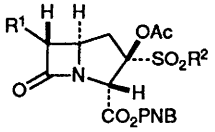

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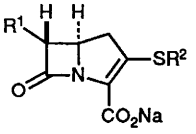
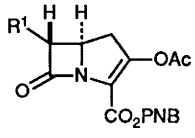
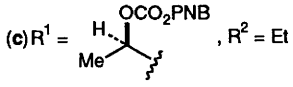


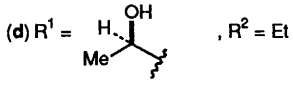
(**12**)



(**13**)

(**a**) R^1 = H, R^2 = Et
(**b**) R^1 = H, R^2 = $CH_2CH_2CONH_2$





Elimination of acetic acid from a mixture of 3-acetoxy-3-ethylthio isomers (**5a**) and (**6a**) by treatment with DBU (1 mol equiv.) at room temperature provided our previously described[15] equilibrium mixture of Δ^3-ester (**8a**) and Δ^2-ester (**9a**). This constitutes an alternative route to Δ^2-3-alkylthio derivatives (**12**) related to the olivanic acids. We were also able to achieve this elimination in the presence of silica gel in methylene dichloride (48 h). Isomers (**5a**) and (**6a**) were converted solely into Δ^3-ester (**8a**) (35%).

On replacing ethanethiol by 2-carbamoylethanethiol(3-mercaptopropionamide) in the Michael addition, we obtained a mixture of adducts (**2b**)–(**4b**). Reaction of isomers (**2b**) and (**3b**) with LTA gave α-acetoxy sulphides (**5b**) and (**6b**). In this case DBU elimination of acetic acid gave the Δ^2-isomer (**9b**) directly.

Oxidation of acetoxy derivatives (**5a**) or (**6a**) with *m*-chloroperbenzoic acid (MCPBA) (2.2 mol equiv.) gave the respective sulphones (**10a**) (78%) and (**11a**) (60%). Exposure of sulphone

isomer (**10a**) to a stoicheiometric amount of DBU rapidly caused elimination of ethanesulphinic acid, providing crude enol acetate (**13a**). Even flash chromatography of this product led to extensive decomposition, although we succeeded thereby in obtaining a crystalline sample [λ_{max}(EtOH) 270 nm (ε 13 100 dm^3 mol^{-1} cm^{-1}); ν_{max}($CHCl_3$) 1 790 and 1 730 cm^{-1}]. In a subsequent experiment using the 3α-sulphone (**11a**), we obtained compound (**13a**) in high yield (90%) by crystallisation of the crude material.

Starting from the carbapenem derivative (**1c**),[19] containing a protected 6-(1-hydroxyethyl) substituent (thienamycin C-5, -6, -8 relative stereochemistry), we obtained a mixture of ethanethiol adducts (**2c**)–(**4c**). Upon using isomers (**2c**) and (**3c**), successive LTA and MCPBA oxidations provided acetoxy sulphones (**10c**) and (**11c**) *via* acetates (**5c**) and (**6c**). DBU elimination then gave the 6-substituted enol acetate (**13c**), which was closely similar in its spectral properties to its unsubstituted counterpart (**13a**). The resulting 3-acetoxy-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate may be envisaged as an olivanic acid analogue of the synthetic 3-acetoxycephalosporin series.[20]

Attempts to isolate sodium salts corresponding to esters (**13a**) or (**13d**) after hydrogenolysis of the *p*-nitrobenzyl esters, using our established conditions,[16] resulted in degradation. Aqueous solutions of the sodium salts derived from carbapenam esters (**5a**) and (**6a**) were antibacterially inactive.

Experimental

The experimental techniques, materials, solvents, and spectroscopic instrumentation employed in this work were as described in Parts 2[21] and 4[19] of the series. Unless stated otherwise, IR spectra were recorded for chloroform solutions and NMR spectra were obtained in $CDCl_3$. Benzene was sodium-dried. Biogel® P2 refers to 200–400 mesh grade.

All compounds prepared are racemic; NMR stereochemical assignments refer to that enantiomer which is depicted.

p-*Nitrobenzyl* 3-*Acetoxy*-3-*ethylthio*-7-*oxo*-1-*azabicyclo*-[3.2.0]*heptane*-2-*carboxylate*; (2RS,3SR,5RS)-*Isomer* (**5a**) *and* (2RS,3RS,5RS)-*Isomer* (**6a**). (i) *Use of LTA*.—(*a*) *p*-Nitrobenzyl 3-ethylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate[15] (0.150 g), a mixture of C-3 epimers (**2a**) and (**3a**), was dissolved in benzene (5 ml) and the solution was treated with LTA (0.398 g) and irradiated (tungsten lamp) for 24 h. The reaction mixture was filtered and evaporated to give a gum. This was chromatographed on silica gel, and eluted with ethyl acetate–light petroleum (1:1). The least polar acetoxy sulphide (**5a**) was a gum (0.067 g, 38%) (Found: $M^+ - C_2H_2O$, 366.0875. $C_{16}H_{18}N_2O_6S$ requires *m/z*, 366.0885); λ_{max}(EtOH) 264 nm (ε 11 600 dm^3 mol^{-1} cm^{-1}); ν_{max} 1 770, 1 750, 1 610, 1 525, and 1 350 cm^{-1}; δ_H(90 MHz) 1.14 (3 H, t, *J* 7 Hz, CH_2Me), 1.85 (3 H, s, OAc), 2.76 (2 H, q, *J* 7 Hz, CH_2Me; and 2 H, m, 4-H_2), 3.05 (1 H, dd, *J* 16 and 4 Hz, 6-H^β), 3.38 (1 H, dd, *J* 16 and 6 Hz, 6-H^α), 4.13 (1 H, m, 5-H^α), 4.98 (1 H, s, 2-H^β), 5.28 (2 H, s, CH_2Ar), and 7.56 (2 H, d, *J* 9 Hz) and 8.24 (2 H, d, *J* 9 Hz) (AA′BB′).

The more polar isomer (**6a**) was obtained also as a gum (0.042 g, 24%) (Found: $M^+ - C_2H_2O$, 366.0880); ν_{max} 1 770, 1 750, 1 610, 1 525, and 1 350 cm^{-1}; δ_H(90 MHz) 1.16 (3 H, t, *J* 7 Hz, CH_2Me), 2.00 (3 H, s, OAc), 2.74 (4 H, m, CH_2Me and 4-H_2), 2.89 (1 H, dd, *J* 16 and 3 Hz, 6-H^β), 3.38 (1 H, dd, *J* 16 and 6 Hz, 6-H^α), 4.18 (1 H, m, 5-H^α), 5.26 (2 H, s, CH_2Ar), 5.39 (1 H, s, 2-H^β), and 7.86 (2 H, d, *J* 9 Hz) and 8.22 (2 H, d, *J* 9 Hz) (AA′BB′).

Intermediate fractions contained a mixture of isomers (**5a**) and (**6a**) (0.024 g, 14%).

(*b*) Similar experiments using LTA (2.2 mol equiv.) under irradiation (24 h), or in refluxing benzene (2 h), showed that pure isomer (**2a**) gave exclusively compound (**5a**) and that pure isomer (**3a**) gave only product (**6a**) in comparable yields (*ca.* 75%).

(ii) *Use of Iodosobenzene Diacetate*.—A solution of ethyl sulphide isomer (**2a**) (0.050 g) in dry methylene dichloride (10 ml) was treated with pyridine (0.027 g, 2.4 mol equiv.) and iodosobenzene diacetate (0.055 g, 1.2 mol equiv.) and heated under reflux for 4 h. Isolation and purification as described for (i) (*a*) gave the pure isomer (**5a**) (0.035 g, 60%).

p-*Nitrobenzyl* (2RS,3SR,5SR)-3-*Acetoxy*-3-*ethylthio*-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**7a**).—Ethyl sulphide isomer (**4a**)[15] (0.100 g) and LTA (0.531 g) were heated in dry benzene under reflux for 1.5 h. Isolation of the product as for products (**5a**) and (**6a**) gave acetoxy sulphide isomer (**7a**) as a gum (0.100 g, 43%) (Found: $M^+ - C_2H_2O$, 366.0907. $C_{16}H_{18}N_2O_6S$ requires *m/z*, 366.0885); ν_{max} 1 750br, 1 710, 1 610, 1 525, and 1 350 cm^{-1}; δ_H 1.28 (3 H, t, *J* 7 Hz, CH_2Me), 1.86 (3 H, s, OAc), 2.79 (2 H, q, *J* 7 Hz, CH_2Me; and 3 H, m, 6-H^β and 4-H_2), 3.31 (1 H, dd, *J* 16 and 5 Hz, 6-H^α), 3.95 (1 H, m, 5-H^α), 4.40 (1 H, s, 2-H^α), 5.31 (2 H, s, CH_2Ar), and 7.63 (2 H, d, *J* 9 Hz) and 8.28 (2 H, d, *J* 9 Hz) (AA′BB′).

Epimerisation of (2RS,3SR,5SR)-*Isomer* (**7a**) *to* (2RS,3RS,5RS)-*Isomer* (**6a**).—Acetoxy sulphide isomer (**7a**) (0.048 g) was dissolved in dry methylene dichloride (5 ml) and the solution was treated with a catalytic quantity of DBU (0.0018 g) at room temperature overnight. Removal of the solvent afforded a gum, which was identical (^{1}H NMR spectroscopy) with isomer (**6a**) (*vide supra*).

Reaction of Sulphides (**2a**) *and* (**3a**) *with LTTFA*.—The reagent was prepared[18] as a mixture with lead bis(trifluoroacetate) containing 44% w/w of the desired material. A solution of *p*-nitrobenzyl 3-ethylthio-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (0.150 g), a mixture of (2*RS*,3*RS*,5*RS*)- and (2*RS*,3*SR*,5*RS*)-isomer (**2a**) and (**3a**), in dry methylene dichloride (10 ml) containing crude LTTFA (1.605 g) was irradiated (W-lamp) at room temperature for 3 h. Starting materials were consumed (TLC analysis). No β-lactam product was obtained (IR spectrum).

Iodosobenzene Bis(*trichloroacetate*) {[*Bis*(*trichloroacetoxy*)-*iodo*]*benzene*}.—Iodosobenzene diacetate (1.61 g) and trichloroacetic acid (0.82 g) were stirred together in chloroform (2 ml) and the mixture was then heated under reduced pressure (water-pump) to 80–100 °C for 30 min. The resulting pale yellow oil was cooled, then dissolved in chloroform (20 ml), and the solution was filtered and concentrated. Trituration of the residue with diethyl ether afforded the bis(trichloroacetate) as a crystalline solid (1.177 g, 44%), m.p. 134 °C (from ethyl acetate–light petroleum); ν_{max} 1 665, 1 295, 1 260, 1 090br, and 1 020 cm^{-1}; δ_H(60 MHz) 7.56 (3 H, m) and 8.01 (2 H, m).

p-*Nitrobenzyl* (2RS,5RS)-3-*Ethylthio*-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-3-*ene*-2-*carboxylate* (**8a**).[15]—(*a*) A solution of ethyl sulphide isomer (**2a**) (0.100 g) and pyridine (0.054 g, 56 μl) in dry methylene dichloride (5 ml) was treated with iodosobenzene bis(trichloroacetate) (0.181 g) and heated under reflux for 1 h. The solution was concentrated and chromotographed on silica gel with ethyl acetate–light petroleum (1:1) as eluant to give Δ^3-ester (**8a**) as a gum (0.014 g, 14%), identical (TLC, IR, ^{1}H NMR) with an authentic sample.[15]

(*b*) A solution of acetoxy sulphide (**6a**) (0.028 g) in dry methylene dichloride (2 ml) was stirred vigorously with a large excess of silica gel at room temperature overnight. Filtration and evaporation gave Δ^3-ester (**8a**) (^{1}H NMR) (0.008 g, 33%).

(*c*) A similar procedure with the (2*RS*,3*SR*,5*RS*)-isomer (**5a**) gave (24 h) a mixture of unchanged starting material and Δ^3-ester (**8a**) (*ca.* 2:1 ratio) (^{1}H NMR).

(*d*) A mixture of isomers (**5a**) and (**6a**) and DBU (1 mol equiv.) in methylene dichloride at room temperature, gave (6 h) our previously described[15] equilibrium mixture of the Δ^2- and Δ^3-ester (**8a**) and (**9a**) (TLC, ^{1}H NMR).

p-*Nitrobenzyl* (2RS,3SR,5RS)-3-*Acetoxy*-3-*ethylsulphonyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**10a**).—A solution of acetoxy sulphide isomer (**5a**) (0.050 g) in dry methylene dichloride (10 ml) was cooled to 0 °C and treated with a solution of MCPBA (0.045 g) in methylene dichloride (5 ml) dropwise during 30 min, and maintained at 0 °C overnight. The solution was concentrated and chromatographed on silica gel, with ethyl acetate–light petroleum (1:1–3:1) as eluant. The sulphone (**10a**) was obtained as a foam (0.042 g, 78%) (Found: $M^+ - C_2H_2O$, 398.0784. $C_{16}H_{18}N_2O_8S$ requires *m*/*z*, 398.0784); ν_{max} 1 780, 1 735sh, 1 610, 1 530, 1 350, and 1 330 cm^{-1}; δ_H(250 MHz) 1.51 (3 H, t, *J* 7.5 Hz, Me), 2.01 (3 H, s, OAc), 2.72 (2 H, d, *J* 7 Hz, 4-H$_2$), 2.88 (1 H, dd, *J* 16 and 2 Hz, 6-H$^\beta$), 3.22–3.54 (3 H, m, SO_2CH_2 and 6-H$^\alpha$), 4.42 (1 H, m, 5-H), 5.17 and 5.23 (each 1 H, *J* 13 Hz) (ABq, C*H*$_2$Ar), 5.25 (1 H, s, 2-H$^\beta$), and 7.56 (2 H, d, *J* 9 Hz) and 8.24 (2 H, d, *J* 9 Hz) (AA′BB′).

p-*Nitrobenzyl* (2RS,3RS,5RS)-3-*Acetoxy*-3-*ethylsulphonyl*-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**11a**).—A solution of the acetoxy sulphide (**6a**) (0.220 g) in dry methylene dichloride (40 ml) was treated with a solution of MCPBA (0.195 g) in methylene dichloride (20 ml) as described for isomer (**10a**). Following purification by silica gel column chromatography [ethyl acetate–light petroleum (1:1 and 3:1)], the sulphone (**11a**) was obtained as a foam (0.101 g, 43%) (Found: $M^+ - C_2H_2O$, 398.0782. $C_{16}H_{18}N_2O_8S$ requires *m*/*z*, 398.0784); ν_{max} 1 765, 1 610, 1 525, 1 355, 1 330, 1 190, and 1 150 cm^{-1}; δ_H(250 MHz) 1.32 (3 H, t, *J* 7.5 Hz, Me), 2.13 (3 H, s, OAc), 2.69 (1 H, dd, *J* 15 and 2 Hz, 4-H), 3.03 (1 H, dd, *J* 16 and 3 Hz, 6-H$^\beta$), 3.23 (1 H, dd, *J* 15 and 9 Hz, 4-H), 3.29 (1 H, dq, *J* 14 and 7.5 Hz), and 3.39 (1 H, dq, *J* 14 and 7.5 Hz) (SO_2CH_2), 3.48 (1 H, dd, *J* 16 and 7.5 Hz, 6-H$^\alpha$), 4.24 (1 H, m, 5-H), 5.19 and 5.28 (2 H, ABq, *J* 16 Hz, C*H*$_2$Ar), 5.66 (1 H, s, 2-H$^\beta$), and 7.55 (2 H, d, *J* 9 Hz) and 8.24 (2 H, d, *J* 9 Hz) (AA′BB′).

p-*Nitrobenzyl* 3-*Acetoxy*-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**13a**).—A solution of sulphone isomer (**10a**) (0.40 g) in methylene dichloride was stirred with DBU (0.014 g) at room temperature for 5 min. The solution was concentrated and chromatographed on silica gel (Art. 9385), with ethyl acetate–light petroleum (1:1) as eluant. The *enol acetate* (**13a**) was obtained as a solid (6 mg, 19%) (Found: M^+, 346.0797. $C_{16}H_{14}N_2O_7$ requires *M*, 346.0794); ν_{max}(EtOH) 270 nm (13 100); ν_{max} 1 790, 1 730, 1 640, 1 610, 1 525, 1 350, and 1 290 cm^{-1}; δ_H(250 MHz) 2.20 (3 H, s, OAc), 3.10 (3 H, m, 6-H$^\beta$ and 4-H$_2$), 3.57 (1 H, dd, *J* 17 and 5.5 Hz, 6-H$^\alpha$), 4.26 (1 H, m, 5-H), 5.25 and 5.42 (2 H, ABq, *J* 14 Hz, C*H*$_2$Ar), and 7.60 (2 H, d, *J* 9 Hz) and 8.23 (2 H, d, *J* 9 Hz) (AA′BB′).

A similar reaction with the (2*RS*,3*RS*,5*RS*)-sulphone isomer (**11a**) (0.060 g) gave, after washing of the eluate with brine, the pure acetate (**13a**) (0.042 g, 90%) without recourse to chromatographic purification.

p-*Nitrobenzyl* 3-*Acetoxy*-3-(2-*carbamoylethylthio*)-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate*; (2RS,3SR,5RS)-*Isomer* (**5b**) *and* (2RS,3RS,5RS)-*Isomer* (**6b**).—A mixture of the C-3 ethyl sulphide isomers (**2b**) and (**3b**), (0.189 g) in a mixture of benzene (5 ml) and methylene dichloride (5 ml) was treated with LTA (0.426 g, 2 mol equiv.) at room temperature under irradiation (W-lamp) for 5 h. After filtration of the reaction mixture the solvent was evaporated off. The residue was chromatographed on silica gel with ethanol–ethyl acetate (1:9) as eluant. Acetoxy sulphide isomer (**5b**) was obtained as a foam (0.074 g, 34%) (Found: $M^+ - C_3H_6NOS$, 347.0873. $C_{16}H_{15}N_2O_7$ requires *m*/*z*, 347.0877); λ_{max}(EtOH) 264 nm (4 300); ν_{max} 1 770sh, 1 750, 1 680, 1 610, 1 525, and 1 350 cm^{-1}; δ_H(60 MHz) 1.90 (3 H, s, OAc), 2.30–3.60 (8 H, m, S[CH_2]$_2$, 4- and 6-H$_2$), 4.18 (1 H, m, 5-H), 5.00 (1 H, s, 2-H$^\beta$), 5.33 (2 H, s, C*H*$_2$Ar), 6.05 (2 H, br s, $CONH_2$) and 7.64 (2 H, d, *J* 9 Hz) and 8.30 (2 H, d, *J* 9 Hz) (AA′BB′).

The more polar acetoxy sulphide isomer (**6b**) was also obtained as a foam (0.033 g, 15%); ν_{max} 1 770sh, 1 750, 1 680, 1 610, 1 525, and 1 350 cm^{-1}; δ_H(90 MHz) 2.01 (3 H, s, OAc), 2.30–3.10 (7 H, m, S[CH_2]$_2$, 4-H$_2$ and 6-H$^\beta$), 3.40 (1 H, dd, *J* 16 and 5 Hz, 6-H$^\alpha$), 4.18 (1 H, m, 5-H), 5.27 (2 H, s, C*H*$_2$Ar), 5.38 (1 H, s, 2-H$^\beta$), 5.90 (2 H, br s, $CONH_2$), and 7.56 (2 H, d, *J* 9 Hz) and 8.22 (2 H, d, *J* 9 Hz) (AA′BB′).

p-*Nitrobenzyl* 3-(2-*Carbamoylethylthio*)-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**9b**).—A mixture of 3-acetoxy-3-(2-carbamoylethyl)sulphide epimers (**5b**) and (**6b**) (*ca.* 2:1) (0.048 g) in dry methylene dichloride (5 ml) was treated with DBU (0.016 g) at room temperature for 20 min. Concentration, followed by silica gel chromatography [elution with ethanol–ethyl acetate (1:9)], afforded a residue which, on trituration with diethyl ether, gave the Δ^2-*ester* (**9b**) as a solid (0.007 g, 17%), m.p. 145–146 °C (from EtOH) (Found: C, 52.2; H, 4.6; N, 10.4; S, 8.15. $C_{17}H_{17}N_3O_6S$ requires C, 52.17; H, 4.38; N, 10.74; S, 8.19%; Found: $M^+ - C_2H_2O$, 349.0726. $C_{15}H_{15}N_3O_5S$ requires *m*/*z* 349.0732); ν_{max}(Nujol) 3 375, 3 180, 1 800, 1 700, and 1 650 cm^{-1}; δ_H[$(CD_3)_2CO$] (250 MHz) 2.40 (2 H, t, *J* 7 Hz, CH_2CO), 2.99–3.10 (2 H, m, 4-H$_2$), 3.10 (1 H, dd, *J* 16 and 3 Hz, 6-H$^\beta$), 3.19–3.38 (2 H, m, SCH_2), 3.46 (1 H, dd, *J* 16 and 5 Hz, 6-H$^\alpha$), 4.17 (1 H, m, 5-H), 5.28 and 5.41 (2 H, ABq, *J* 14 Hz, C*H*$_2$Ar), 6.95–7.40 (2 H, br s, D_2O exch, $CONH_2$), and 7.68 (2 H, d, *J* 9 Hz) and 8.23 (2 H, d, *J* 9 Hz) (AA′BB′).

p-*Nitrobenzyl* 3-*Acetoxy*-3-*ethylthio*-6-[(1RS)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]-7-oxo-1-*azabicyclo*[3.2.0]-*heptane*-2-*carboxylate*; (2RS,3SR,5SR,6RS)-*Isomer* (**5c**) *and* (2RS,3RS,5SR,6RS)-*Isomer* (**6c**).—A mixture of ethyl sulphide epimers (**2c**) and (**3c**) (*ca.* 1:2) (0.245 g) and LTA (0.379 g) in benzene (10 ml) was heated under reflux for 2 h. The reaction mixture was filtered and the solvent was evaporated off. Chromatography on silica gel with ethyl acetate–hexane (1:2) gave acetoxy sulphide isomer (**5c**) as a yellow foam (0.072 g, 27%); ν_{max} 1 780, 1 750, 1 610, 1 525, and 1 350 cm^{-1}; δ_H(250 MHz) 1.25 (3 H, t, *J* 7 Hz, SCH_2*Me*), 1.44 (3 H, d, *J* 7 Hz, CH*Me*), 1.86 (3 H, s, OAc), 2.75 (2 H, q, *J* 7 Hz, S*CH*$_2$Me; and m, 2 H, 4-H$_2$), 3.52 (1 H, dd, *J* 7 and 3 Hz, 6-H$^\beta$), 4.09 (1 H, m, 5-H), 5.13 [1 H, m, MeC*H*(OH)], 5.27 (2 H, s, CO_2CH_2Ar), 5.24 and 5.32 (2 H, ABq, *J* 15 Hz, OCO_2CH_2Ar), and 7.56 (4 H, d, *J* 9 Hz), 8.23 (2 H, d, *J* 9 Hz), and 8.25 (2 H, d, *J* 9 Hz) (2 × AA′BB′); *m*/*z* 571 $(M - AcOH)^+$, 435, 374, and 306.

A more polar product, isomer (**6c**), was also obtained as a foam (0.066 g, 24%); ν_{max} 1 775, 1 750, 1 610, 1 525, and 1 350 cm^{-1}; δ_H(250 MHz) 1.28 (3 H, t, *J* 7 Hz, SCH_2*Me*), 1.46 (3 H, d, *J* 7 Hz, CH*Me*), 1.98 (3 H, s, OAc), 2.42 (1 H, dd, *J* 13 and 10 Hz, 4-H$^\alpha$), 2.76 (2 H, q, *J* 7 Hz, S*CH*$_2$Me), 2.97 (1 H, dd, *J* 13 and 5 Hz, 4-H$^\beta$), 3.33 (1 H, dd, *J* 7 and 2.5 Hz, 6-H$^\beta$), 3.89 (1 H, ddd, *J* 10, 5, and 2.5 Hz, 5-H), 4.39 (1 H, s, 2-H$^\beta$), 5.11 [1 H, m, MeC*H*(OH)], 5.27 (2 H, s, CO_2CH_2Ar), 5.25 and 5.33 (2 H, ABq, *J* 15 Hz, OCO_2CH_2Ar), and 7.55 and 7.58 (4 H, 2 d, *J* 9 Hz), 8.25 and 8.26 (4 H, 2 d, *J* 9 Hz) (2 × AA′,BB′); *m*/*z* 571 $(M - AcOH)^+$, 435, 374, and 306.

p-*Nitrobenzyl* (2RS,3SR,5SR,6RS)-3-*Acetoxy*-3-*ethylsulphonyl*-6-[(1RS)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]-7-

oxo-1-azabicyclo[3.2.0]*heptane-2-carboxylate* (**10c**).—A solution of acetoxy sulphide isomer (**5c**) (0.038 g) in dry methylene dichloride (5 ml) at 0 °C was treated with a solution of MCPBA (0.023 g) in methylene dichloride (5 ml) during 30 min. The mixture was kept at 0 °C overnight and was then concentrated and chromatographed on silica gel, with ethyl acetate–hexane (1:1) as eluant, to give the sulphone (**10c**) as a foam (0.018 g, 40%); ν_{max} 1 790, 1 755, 1 610, 1 525, 1 350, and 1 325 cm^{-1}; δ_H(250 MHz) 1.34 (3 H, t, *J* 7 Hz, SCH_2Me), 1.48 (3 H, d, *J* 7 Hz, $CHMe$), 2.02 (3 H, s, OAc), 2.74 and 2.78 (2 H, each dd, *J* 16 and 7 Hz, 4-H_2), 3.12 (2 H, q, *J* 7 Hz, SCH_2Me), 3.32 (1 H, dd, *J* 8 and 2 Hz, 6-H^{β}), 4.35 (1 H, dt, *J* 7 and 2 Hz, 5-H^{α}), 5.19 [1 H, s, 2-H^{β}; and 1 H, m, $MeCH(OH)$], 5.29 (4 H, m, CO_2CH_2Ar and OCO_2CH_2Ar), and 7.55 (4 H, d, *J* 9 Hz) and 8.24 and 8.26 (4 H, 2 d, *J* 9 Hz) (2 × AA′BB′).

p-*Nitrobenzyl* (2RS,3RS,5SR,6RS)-3-*Acetoxy*-3-*ethylsulphonyl*-6-[(1RS)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (**11c**).—The acetoxy sulphide epimer (**6c**) (0.026 g) was oxidised similarly with a solution of MCPBA (0.016 g) in methylene dichloride (5 ml) to give the sulphone (**11c**). After silica gel purification with ethyl acetate–hexane (1:1) the product was isolated as a foam (0.015 g, 55%); ν_{max} 1 780, 1 755, 1 610, 1 525, 1 350, and 1 325 cm^{-1}; δ_H(250 MHz) 1.45 (3 H, d, *J* 7 Hz, $CHMe$), 1.48 (3 H, t, *J* 7 Hz, CH_2Me), 1.96 (3 H, s, OAc), 2.54 (1 H, dd, *J* 15 and 10 Hz, 4-H^{α}), 3.19 (2 H, dq, *J* 7 and 1.5 Hz, SO_2CH_2Me), 3.33 (1 H, dd, *J* 8 and 2 Hz, 6-H^{β}), 3.36 (1 H, dd, *J* 15 and 6 Hz, 4-H^{β}), 4.02 (1 H, ddd, *J* 10, 6, and 2 Hz, 5-H), 4.78 (1 H, s, 2-H^{β}), 5.09 [1 H, m, $MeCH(OH)$], 5.25 (2 H, s, CO_2CH_2Ar), 5.36 and 5.46 (2 H, ABq, *J* 14 Hz, OCO_2CH_2Ar), and 7.57 and 7.60 (4 H, 2 d, *J* 9 Hz), and 8.24 (4 H, d, *J* 9 Hz) (2 × AA′BB′).

p-*Nitrobenzyl* (5RS,6SR)-3-*Acetoxy*-6-[(1RS)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]-7-oxo-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (**13c**).—A solution of 3-ethyl sulphone epimers (**10c**) and (**11c**) (0.308 g) in dry methylene dichloride (10 ml) at 0 °C was treated with DBU (0.070 g). After 5 min the solution was concentrated and chromatographed on silica gel (Art. 9385) and eluted rapidly with ethyl acetate–hexane (3:2). Subsequent rechromatography provided the enol acetate (**13c**) as a gum (0.044 g, 20%); ν_{max}(EtOH) 266 nm (21 340); ν_{max} 1 790, 1 750, 1 640, 1 610, 1 525, and 1 350 cm^{-1}; δ_H(250 MHz) 1.49 (3 H, d, *J* 7 Hz, $CHMe$), 2.21 (3 H, s, OAc), 3.03 (1 H, dd, *J* 18 and 10 Hz, 4-H^{α}), 3.16 (1 H, dd, *J* 18 and 8 Hz, 4-H^{β}), 3.46 (1 H, dd, *J* 8 and 3 Hz, 6-H^{β}), 4.23 (1 H, ddd, *J* 10, 8, and 3 Hz, 5-H), 5.17 [1 H, m, $MeCH(OH)$], 5.26 (2 H, s, CO_2CH_2Ar), 5.26 and 5.44 (2 H, ABq, *J* 14 Hz, OCO_2CH_2Ar), and 7.55 and 7.61 (4 H, 2 d, *J* 9 Hz), and 8.24 and 8.25 (4 H, d, *J* 9 Hz) (2 × AA′BB′).

Hydrogenolysis of Esters (**5a**) *and* (**6a**).—Solutions of the esters (**5a**) and (**6a**) (0.030 g) in 1,4-dioxane (2 ml) were each added to a suspension of 5% Pd–C catalyst (0.030 g) in 1,4-dioxane (2 ml)–water (2 ml), which had been prehydrogenated for 20 min. Solid sodium hydrogen carbonate (6.2 mg) was added and hydrogenolysis was continued for 1.5 h. The solutions were filtered through Celite, washed with water, and the dioxane was removed under reduced pressure. The aq. filtrates were extracted once with ethyl acetate and concentrated to 3 ml. Chromatography on Biogel P2, and elution with water, gave the required sodium salts, which were stored in aq. solution.

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