Inversion of Configuration at C-8 in the Olivanic Acids: Conversion into the Thienamycins and Other Novel Derivatives

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The inversion of stereochemistry at C-8 in the olivanic acids, MM 22383 (7) and MM 22381 (6), is described. The reaction of *p*-nitrobenzyl (5*R*,6*S*)-3-[(*E*)-2-acetamidovinylthio]-6-[(*S*)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8) with diethyl azodicarboxylate, triphenylphosphine, and formic acid afforded the 6-[(*R*)-1-formyloxyethyl] derivative (17), which upon alkaline hydrolysis gave the 6-[(*R*)-1-hydroxyethyl] derivative (18). Hydrogenolysis of the *p*-nitrobenzyl ester (18) furnished the sodium salt of *N*-acetyldehydrothienamycin (15), the (8*R*)-epimer of the olivanic acid MM 22383 (7). The 3-(2-acetamidoethylthio)-analogue, MM 22381 (6), was converted into *N*-acetylthienamycin (14) by performing a similar series of reactions on its *p*-nitrobenzyl ester (10). The transformation of the ester (18) to bis-protected thienamycin (22), *via* the C-3 thiol (21), is also described. Reaction of the olivanic acid esters (8) and (10) with diethyl azodicarboxylate, triphenylphosphine and hydrazoic acid resulted in the formation of the 6-[(*R*)-1-azidoethyl] derivatives (27) and (28). Subsequent hydrogenolysis provided (5*R*,6*R*)-3-[(*E*)-2-acetamidovinylthio]-6-[(*R*)-1-aminoethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (29) and the 3-(2-acetamidoethylthio)-analogue (30).

The olivanic acids constitute a family of β-lactam antibiotics which were isolated from *Streptomyces olivaceus* and are characterised by the presence of the 7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid ring system. The first three metabolites to be discovered were the sulphated derivatives,[1] MM 13902 (1), MM 17880 (2), and MM 4550 (3). Subsequently, four additional compounds, designated MM 22380 (4), MM 22381 (6), MM 22382 (5), and MM 22383 (7), were isolated.[2] Independent of these investigations, the related antibiotic thienamycin [3] (13) was obtained from *Streptomyces cattleya*. The same fermentation broth was later found to produce *N*-acetylthienamycin [4] (14) and *N*-acetyldehydrothienamycin [5] (15). Other related members of this family of antibiotics include PS-5 [6] and the carpetimycins.[7] The exceptional antibacterial activity of this class of compounds has prompted considerable interest in the area.

MM 22381 (6) and MM 22383 (7) differ from *N*-acetylthienamycin (14) and *N*-acetyldehydrothienamycin (15), respectively, by virtue of their stereochemical configuration at C-8, being (*S*) in the olivanic acids and (*R*) in the thienamycins. In order to interrelate the two series, the present work describes the conversion of MM 22381 (6) into *N*-acetylthienamycin (14) and MM 22383 (7) into *N*-acetyldehydrothienamycin (15) by way of inversion of configuration in the hydroxyethyl side-chain. This was achieved by a diethyl azodicarboxylate–triphenylphosphine (DEADCAT [8]) reaction sequence. The combination of this inversion procedure with the utilisation of the previously described C-3 thiol reaction [9] provides a preparation of thienamycin (13) from MM 22383 (7).

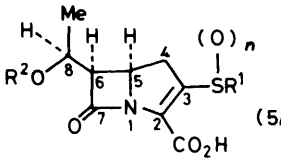
It has been reported previously that the ethylidene derivative (23) may be prepared by reaction of the hydroxy-compound (8) with diethyl azodicarboxylate and triphenylphosphine.[10] Rapid *trans* co-planar *E*2 elimination of triphenylphosphine oxide from the alkoxyphosphonium intermediate (9) afforded the ethylidene derivative (23) which was subsequently converted into an analogue of PS-5.[11] However, it is well documented [12] that in such reactions elimination may be suppressed in favour of S_N2 nucleophilic substitution by addition of an acidic component. Bose *et al.*[13] have reported that the stereospecific esterification of 5α-cholestan-3β-ol could be accomplished by treatment with triphenylphosphine, diethyl azodicarboxylate and an acid, such as benzoic acid or formic acid. Saponification of the ester then afforded the epimeric alcohol. This adaptation of the DEADCAT reaction sequence appeared particularly attractive because such a manipulation on the olivanic acid derivatives (8) and (10) would allow access to the thienamycin family of antibiotics. Indeed, the reaction of the *p*-nitrobenzyl ester of MM 22383 (8) with triphenylphosphine, diethyl azodicarboxylate, and formic acid proceeded with inversion of configuration to yield the formate ester (17) in 39% yield. Competitive elimination accounted for the formation of the ethylidene (23) in 54% yield.

Table. Comparison of ^{1}H n.m.r. data for (8*R*) and (8*S*) diastereoisomers

Compd.	Solvent	Configuration at C-8	δ_{H6} (p.p.m.)	$J_{6,8}$ (Hz)	$J_{5,6}$ (Hz)
(17) [a,b]	[$^2H_7$]-DMF [c]	*R*	3.83	5.9	2.7
(11) [a,b]	[$^2H_7$]-DMF [c]	*S*	3.86	4.0	2.9
(18) [a,b]	[$^2H_7$]-DMF [c]	*R*	3.43	6.3	3.0
(8) [a,d]	[$^2H_7$]-DMF [c]	*S*	3.50	3.5	3.0
(15) [b,e]	D_2O	*R*	3.36	6.0	2.5
(7) [b,e]	D_2O	*S*	3.41	5.0	2.5
(19) [a,b]	[$^2H_7$]-DMF [c]	*R*	3.84	5.9	2.9
(20) [a,c]	[$^2H_7$]-DMF [c]	*R*	3.44	6.1	2.9
(10) [a,d]	[$^2H_7$]-DMF [c]	*S*	3.52	~3.0	~2.5
(14) [b,e]	D_2O	*R*	3.37	6.0	2.5

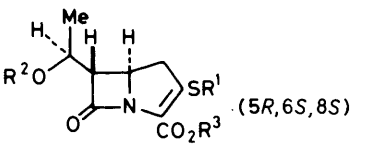
[a] Chemical shifts are reported in p.p.m. downfield from TMS. [b] 250 MHz. [c] [$^2H_7$]Dimethylformamide. [d] 90 MHz. [e] Chemical shifts are quoted in p.p.m. relative to external CH_3CN standard. Accurate coupling constants were determined by scale expansion.

Evidence for the inversion of configuration at C-8 was provided by a direct comparison with the (8*S*)-epimer (11), prepared by treatment of (8) with formic acid and acetic anhydride in pyridine. ^{1}H N.m.r. correlation studies [14] have proved useful as an indication of side-chain stereochemistry for a given pair of C-5, C-6-*trans*, (8*R*)- and (8*S*)-isomers. The C-6 proton usually appears upfield by 0.03—0.15 p.p.m. for that diastereoisomer having the (*R*) configuration at C-8. More significantly, $J_{6,8}$ for the (8*R*)-diastereoisomer is usually 6—8 Hz, whereas $J_{6,8}$ for the corresponding (8*S*)-diastereoisomer is in the region of 3—5 Hz. Observed coupling constants and chemical shifts (see Table) supported the (8*R*)-configuration in (17) and the (8*S*)-configuration in (11). Alkaline hydrolysis of the formate ester (17) furnished the *p*-nitrobenzyl ester of *N*-acetyldehydrothienamycin (18), together with the (*E*)-ethylidene (25), which presumably arose by stereospecific



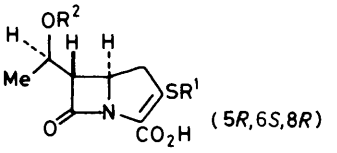
(5*R*,6*R*,8*S*)

(1) MM 13902; n = O, R^1 = CH=CHNHAc, R^2 = SO_3H
(2) MM 17880; n = O R^1 = CH_2CH_2NHAc, R^2 = SO_3H
(3) MM 4550; n = 1, R^1 = CH=CHNHAc, R^2 = SO_3H
(4) MM 22380; n = O, R^1 = CH_2CH_2NHAc, R^2 = H
(5) MM 22382; n = O, R^1 = CH=CHNHAc, R^2 = H



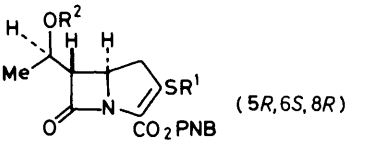
(5*R*,6*S*,8*S*)

(6) MM 22381: R^1 = CH_2CH_2NHAc, R^2 = R^3 = H
(7) MM 22383: R^1 = CH=CHNHAc, R^2 = R^3 = H
(8) R^1 = CH=CHNHAc, R^2 = H, R^3 = PNB
(9) R^1 = CH=CHNHAc, R^2 = $Ph_3\overset{+}{P}$, R^3 = PNB
(10) R^1 = CH_2CH_2NHAc, R^2 = H, R^3 = PNB
(11) R^1 = CH=CHNHAc, R^2 = CHO, R^3 = PNB
(12) R^1 = CH=CHNHAc, R^2 = $MeSO_2$, R^3 = PNB



(5*R*,6*S*,8*R*)

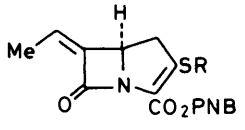
(13) R^1 = $CH_2CH_2NH_2$, R^2 = H
(14) R^1 = CH_2CH_2NHAc, R^2 = H
(15) R^1 = CH=CHNHAc, R^2 = H
(16) R^1 = CH=CHNHAc, R^2 = CHO



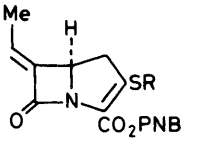
(5*R*,6*S*,8*R*)

(17) R^1 = CH=CHNHAc, R^2 = CHO
(18) R^1 = CH=CHNHAc, R^2 = H
(19) R^1 = CH_2CH_2NHAc, R^2 = CHO
(20) R^1 = CH_2CH_2NHAc, R^2 = H
(21) R^1 = R^2 = H
(22) R^1 = $CH_2CH_2NHCO_2PNB$, R^2 = H

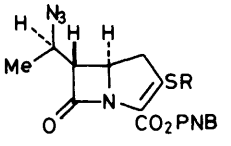
PNB = p-$NO_2C_6H_4CH_2$



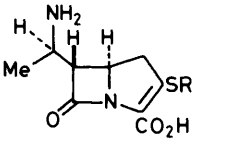
(23) R = CH=CHNHAc
(24) R = CH_2CH_2NHAc



(25) R = CH=CHNHAc
(26) R = CH_2CH_2NHAc



(27) R = CH=CHNHAc
(28) R = CH_2CH_2NHAc



(29) R = CH=CHNHAc
(30) R = CH_2CH_2NHAc

PNB = p-$NO_2C_6H_4CH_2$

*E*2 elimination of formic acid from the ester (17). As these stereospecific elimination reactions are assumed to proceed in a *trans* co-planar manner [10,11] and the configuration at C-6 in (17) is known to be (*S*), then formation of the (*E*)-ethylidene provided additional evidence for the (8*R*)-stereochemistry. As in the case of the formate esters, a comparison of coupling constants for compounds (18) and (8) showed the former to be the (8*R*)-stereoisomer. Hydrogenolysis of the *p*-nitrobenzyl ester (18) afforded the sodium salt of *N*-acetyldehydrothienamycin (15). Spectroscopic data for this sample were in full agreement with those reported.[5] An improved route to compound (15) involved hydrogenolysis of the ester (17) followed by basic hydrolysis of the formate ester in the resulting sodium salt (16). Formation of the ethylidene was thus avoided and the overall yield of compound (15) from the ester (17) was improved considerably. This constitutes the first conversion of an olivanic acid derivative into a member of the thienamycin series.

By performing a similar series of reactions, MM 22381 (6) may be transformed into *N*-acetylthienamycin (14). Treatment of the *p*-nitrobenzyl ester of MM 22381 (10) with diethyl azodicarboxylate, triphenylphosphine, and formic acid furnished the (8*R*)-formate ester (19) together with a substantial quantity of the (*Z*)-ethylidene (24). Basic hydrolysis of the ester (19) afforded compound (20) in 32% yield along with, in this case, the (*E*)-ethylidene (26) (37% yield). Hydrogenolysis of the ester (20) gave the sodium salt of *N*-acetylthienamycin (14),[4,15] which was spectroscopically (Table) and chromatographically (h.p.l.c.) identical with an authentic sample.*

A recent communication from these laboratories described the application of a C-3 thiol intermediate to the preparation of isomers of thienamycin.[9] Utilisation of this methodology, together with the inversion process, permits the elaboration of MM 22383 (7) to thienamycin itself. Reaction of compound (18) with *N*-bromoacetamide in aqueous 1,4-dioxan, followed by alkylation of the resulting thiol (21) with 2-*p*-nitrobenzyloxycarbonylaminoethyl bromide furnished the previously reported bis-protected form of thienamycin (22).[14,16] Spectroscopic data for this compound were in good agreement with those already published. Since the conversion of the bis-protected compound (22) into thienamycin (13) has already been described,[16] this reaction sequence affords a formal synthesis of thienamycin from the olivanic acids.

It is also known that imides and hydrazoic acid may participate in the DEADCAT reaction. Use of phthalimide

* Kindly supplied by Merck, Sharp, and Dohme Research Laboratories.

resulted in quantitative conversion of the MM 22383 ester (8) into the ethylidene (23) whereas incorporation of hydrazoic acid into the DEADCAT reaction proved to be more fruitful, the (8*R*)-azidoethyl derivative (27) being the sole product. A similar reaction on the saturated analogue (10) afforded the azide (28). The azido-derivatives (27) and (28) were readily identified by the characteristic azide i.r. stretching frequency at 2 120 cm^{-1} and could be isolated as stable crystalline solids. In contrast, when the mesylate (12) was treated with either sodium azide or tetramethylguanidinium azide, elimination occurred to yield the ethylidene (23). These results emphasise the critical nature of the leaving group and incoming nucleophile in reactions associated with this system.

Reduction of the azido-function during the course of hydrogenolysis afforded the novel amino-acids (29) and (30), both of which proved to be extremely labile, lyophilisation of an aqueous solution of compound (30) resulting in considerable degradation. The i.r. spectrum of the resulting solid did, however, confirm that the azide group had been fully reduced, although the β-lactam carbonyl absorption was considerably diminished. The presence of the amino-acids in aqueous solution after hydrogenolysis was confirmed by the characteristic olivanic acid u.v. absorption maxima [2] [$\lambda_{max.}$ 307 nm for the unsaturated derivative (29) and $\lambda_{max.}$ 298 nm for the saturated analogue (30)]. Aqueous solutions of the two compounds displayed moderate levels of *in vitro* antibacterial activity.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. U.v. spectra were recorded on a Pye Unicam SP 8000 or a Perkin-Elmer 554 spectrophotometer. I.r. spectra were recorded on a Perkin-Elmer 197 or 457 machine. ^1H N.m.r. spectra were recorded at 90 MHz on a Perkin-Elmer R32, and at 250 MHz on a Bruker WM 250 instrument with tetramethylsilane as internal standard for spectra in $CDCl_3$, [$^2H_7$]-DMF, and [$^2H_6$]acetone and acetonitrile as external standard for spectra in D_2O. The purity of all compounds was tested by t.l.c. on Merck pre-coated silica gel 60 F_{254} plates. Preparative chromatography was carried out on columns of Merck silica gel 60 (1 : 1 mixture of finer than 230 mesh and 230—400 mesh ASTM) using the slightly increased pressure provided by a Medcalf Hy-flo pump. H.p.l.c. was performed on an Altex 110A instrument using a C_{18} μ-Bondapak reversed-phase column with pH 4.7, 0.05M ammonium dihydrogenorthophosphate buffer solution containing acetonitrile as eluant at 2 ml min^{-1}, the compounds being detected by u.v. spectroscopy at λ 300 nm. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Tetrahydrofuran (THF) was dried over sodium hydride and distilled immediately before use. Hydrazoic acid was prepared as a solution in dry toluene and its concentration was determined by titration prior to use. Solutions were dried with anhydrous magnesium sulphate and solvents were removed by evaporation at reduced pressure using a rotary evaporator. The numbering system used for assigning the chemical shifts is that shown in formula (1).

p-*Nitrobenzyl* (5R,6S)-3-[(E)-2-*Acetamidovinylthio*]-6-[(R)-1-*formyloxyethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (17).—A solution of the ester (8) (3.00 g) and triphenylphosphine (3.52 g) in dry tetrahydrofuran (300 ml) was cooled in an ice-bath. Formic acid (98%; 1.26 g; 1.03 ml) and diethyl azodicarboxylate (2.34 g) were added to the stirred solution successively. Stirring was continued at room temperature for 30 min. The solution was partitioned between ethyl acetate (750 ml) and aqueous sodium hydrogencarbonate. The organic phase was separated, washed with water and brine, and dried. The solution was evaporated to small volume at reduced pressure and applied to a column of silica gel (200 g), which was eluted with ethyl acetate to yield two products. The less polar product was obtained as a mixture with triphenylphosphine oxide. This mixture was therefore digested in warm ethyl acetate. Collection of the white crystalline solid afforded the pure *formyloxyethyl derivative* (17) (1.234 g, 39%), m.p. 185—189 °C, $\lambda_{max.}$ (ε) (EtOH) 324 (15 230), 261 (15 250), and 230 nm (15 190); $\nu_{max.}$ 3 250, 1 784, 1 702, 1 673, and 1 623 cm^{-1}; δ_H ([$^2H_7$]-DMF) 1.36 (3 H, d, *J* 6.2 Hz, *Me*CH), 2.02 (3 H, s, COMe), 3.31 (2 H, d, *J* 9.0 Hz, 4-H_2), 3.83 (1 H, dd, *J* 2.7 and 5.9 Hz, 6-H), 4.29 (1 H, dt, *J* 2.7 and 9.0 Hz, 5-H), 5.34 (1 H, m, 8-H), 5.37 and 5.56 (2 H, ABq, CH_2Ar), 5.99 (1 H, d, *J* 13.7 Hz, SCH=C), 7.20 (1 H, dd, *J* 10.2 and 13.7 Hz, NCH=C), 7.82 (2 H, d, *J* 9.0 Hz, Ar), 8.28 (2 H, d, *J* 9.0 Hz, Ar), 8.31 (1 H, s, CHO), and 10.48 (1 H, d, *J* 10.2 Hz, NH) (Found: C, 52.8; H, 4.5; N, 8.65. $C_{21}H_{21}N_3O_8S$ requires C, 53.05; H, 4.45; N, 8.85%); h.p.l.c. (50% CH_3CN) R_t 3.5 min.

The less polar product, the (*Z*)-ethylidene (23), was obtained as a pale yellow solid (1.561 g, 54%), $\nu_{max.}$ (KBr) 3 260, 1 763, 1 694, and 1 620 cm^{-1}; δ_H ([$^2H_7$]-DMF) 2.0 (6 H, d + s, *Me*CHC=C + COMe), 3.0—3.6 (2 H, m, 4-H_2), 4.73 (1 H, broad t, 5-H), 5.33 and 5.57 (2 H, ABq, CH_2Ar), 5.97 (1 H, d, *J* 14 Hz, SCH=C), 6.16 (1 H, q, *J* 8 Hz, MeC*H*=C), 7.19 (1 H, dd, *J* 10 and 14 Hz, NCH=C), 7.84 (2 H, d, *J* 9 Hz, Ar), 8.26 (2 H, d, *J* 9 Hz, Ar), and 10.37 (1 H, d, *J* 10 Hz, NH).

p-*Nitrobenzyl* (5R,6S)-3-[(E)-2-*Acetamidovinylthio*]-6-[(R)-1-*hydroxyethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (18).—The formate ester (17) (0.425 g) was dissolved in 20% aqueous 1,4-dioxan (80 ml) and cooled in an ice-bath. Sodium hydroxide solution (0.1M; 10.75 ml) was added and the solution was stirred at this temperature for 5 min. Ethyl acetate (150 ml) was then added and the organic solution was washed with water and brine, and dried. Removal of the solvent under reduced pressure gave a pale yellow solid, which was chromatographed over silica gel (15 g). Elution with 5% ethanol–chloroform afforded the (*E*)-ethylidene (25) (0.153 g, 40%), $\nu_{max.}$ ($CHCl_3$) 1 761, 1 695, and 1 619 cm^{-1}; δ_H($CDCl_3$) 1.81 (3 H, d, *J* 8 Hz, *Me*CH=C), 2.06 (3 H, s, COMe), 3.06 (2 H m, 4-H_2), 4.70 (1 H, m, 5-H), 5.22 and 5.50 (2 H, ABq, CH_2Ar), 5.90 (1 H, d, *J* 13 Hz, SCH=C), 6.41 (1 H, q, *J* 8 Hz, MeC*H*=C), 7.21 (1 H, dd, *J* 10 and 14 Hz, C=CHN), 7.66 (2 H, d, *J* 9 Hz, Ar), and 8.21 (2 H, d, *J* 9 Hz, Ar). Elution with 10% ethanol–chloroform furnished the (8R)-*hydroxyethyl derivative* (18) (0.10 g, 25%), m.p. 191—192 °C (from ethyl acetate–diethyl ether), $\lambda_{max.}$(ε) (EtOH) 325 (16 880), 263 (17 968), and 225 nm; $\nu_{max.}$ (KBr) 3 420, 3 260, 1 778, 1 700, 1 675, 1 624, and 1 554 cm^{-1}; δ_H([$^2H_7$]-DMF) 1.23 (3 H, d, *J* 6 Hz, *Me*CH), 2.03 (3 H, s, COMe), 3.27 (2 H, *AA'X*, *J* 18.5, 9.0, and 8.7 Hz, 4-H_2), 3.43 (1 H, dd, *J* 3.0 and 6.3 Hz, 6-H), 4.08 (1 H, m, 8-H), 4.28 (1 H, dt, *J* 3.0 and *ca.* 9 Hz, 5-H), 5.37 and 5.57 (2 H, ABq, CH_2Ar), 6.02 (1 H, d, *J* 14 Hz, SCH=C), 7.22 (1 H, dd, *J* 10 and 14 Hz, NCH=C), 7.85 (2 H, d, *J* 9 Hz, Ar), 8.30 (2 H, d, *J* 9 Hz, Ar), and 10.50 (1 H, d, *J* 10 Hz, NH) (Found: C, 53.5; H, 4.7; N, 9.4; S, 7.15. $C_{20}H_{21}N_3O_7S$ requires C, 53.7; H, 4.75; N, 9.4; S, 7.15%); h.p.l.c. (35% CH_3CN) R_t 7.4 min [R_t for (8) 7.0 min].

Sodium Salt of (5R,6S)-3-[(E)-2-*Acetamidovinylthio*]-6-[(R)-1-*hydroxyethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylic Acid* (15).—(*a*) *From the ester* (18). A suspension of 5% palladium-on-carbon catalyst (0.016 g) in 30% aqueous 1,4-dioxan (10 ml) was shaken with hydrogen at ambient temperature and pressure for 20 min. A solution of the ester (18) (0.012 g) in 1,4-dioxan (2 ml) was added and shaking in an atmosphere of hydrogen was continued for a further 3 h. Sodium hydrogencarbonate (0.003 g) was added to the suspension, which was then filtered through Celite, thoroughly

washing with water (25 ml). The filtrate was evaporated under reduced pressure to *ca.* 15 ml and washed with ethyl acetate (3 × 20 ml). The aqueous solution, which was estimated to contain 0.006 g (67%) of the product (15) (based on ε 14 000 at $\lambda_{max.}$ 307 nm) was concentrated further in order to remove any residual organic solvents and lyophilised to yield a pale yellow solid, $\nu_{max.}$(KBr) 3 400br, 1 750, 1 670, 1 618, and 1 510 cm^{-1}.

(*b*) *From the formate ester* (17). 5% Palladium-on-carbon catalyst (0.600 g) was suspended in 30% aqueous 1,4-dioxan (75 ml) and shaken in an atmosphere of hydrogen for 30 min. A suspension of the formate ester (17) (0.400 g) in 30% aqueous 1,4-dioxan (25 ml) was added and shaking continued in the presence of hydrogen at ambient temperature and pressure for 3.5 h. Sodium hydrogencarbonate (0.071 g) was added and the solution filtered through Celite, washing with water (100 ml). The filtrate was evaporated under reduced pressure to *ca.* 100 ml and washed with ethyl acetate (3 × 150 ml). The resulting solution of the sodium salt of (5*R*,6*S*)-3-[(*E*)-2-acetamidovinylthio]-6-[(*R*)-1-formyloxyethyl]-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid (16) was adjusted to pH 8.0 by the addition of aqueous sodium hydrogencarbonate and stirred at room temperature for 16 h. The solution was evaporated to small volume and applied to a column of Diaion HP-20 which was eluted with water. The column fractions were continuously monitored by u.v. spectroscopy. Those possessing the $\lambda_{max.}$ 307 nm absorption maxima were examined by h.p.l.c. (10% CH_3CN). Fractions 10—22 were found to contain the pure *sodium salt* of (5R,6S)-3-[(E)-2-*acetamidovinylthio*]-6-[(R)-1-*hydroxyethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylic acid* (15). They were therefore combined and lyophilised to yield a white fluffy solid (0.089 g), $\lambda_{max.}$(ε) (H_2O) 307 (13 296) and 228 nm (12 570); $\nu_{max.}$(KBr) 3 400br, 1 750, 1 670, and 1 620—1 590 cm^{-1}; $[\alpha]_D^{20}$ +78.3° [*c* (H_2O) 0.59]; δ_H (D_2O) 1.28 (3 H, d, *J* 6 Hz, *Me*CH), 2.06 (3 H, s, COMe), 3.05 (1 H, dd, *J* 8.2 and 18.0 Hz, 4-H_a), 3.19 (1 H, dd, *J* 10.0 and 18.0 Hz, 4-H_b), 3.36 (1 H, dd, *J* 2.5 and 6.0 Hz, 6-H), 4.16 (1 H, dt, *J* 2.5 and *ca.* 9 Hz, 5-H), 4.20 (1 H, m, 8-H), 6.01 (1 H, d, *J* 13 Hz, SCH=C), and 7.14 (1 H, d, *J* 13 Hz, NCH=C). Fractions 23—51 contained a mixture of the 6-[(*R*)-1-hydroxyethyl] compound (15) and the 6-[(*R*)-1-formyloxyethyl] derivative (16), h.p.l.c. (10% CH_3CN) R_t 2.4 and 5.8 min for (15) and (16), respectively. The pH of the combined fractions was therefore adjusted to 8.5 by the addition of sodium hydrogencarbonate and the solution stirred at room temperature for an additional 16 h. H.p.l.c. then indicated that the hydrolysis had proceeded to completion. The solution was concentrated under reduced pressure and subjected to Diaion HP-20 column chromatography, with water as eluant. The relevant fractions were combined and lyophilised to yield an additional quantity of the sodium salt of *N*-acetyldehydrothienamycin (15) as a pale yellow solid (0.029 g) (total yield 0.118 g, 42%), $\lambda_{max.}$(ε) 307 (10 060) and 228 nm (10 080).

p-*Nitrobenzyl* (5R,6S)-3-[(E)-2-*Acetamidovinylthio*]-6-[(S)-1-*formyloxyethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (11).—A solution of formic acid (98%; 0.514 g; 0.42 ml) and acetic anhydride (0.571 g; 0.53 ml) was heated to 50 °C for 15 min with stirring. After the solution had been cooled in an ice-bath, pyridine (1.5 ml) was added, followed by a solution of the ester (8) [2] (0.50 gm) in pyridine (10 ml). Stirring was continued at ambient temperature for 1 h. The solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate and phosphate buffer (0.05M; pH 7.0). The organic solution was washed with water and brine, and dried. Removal of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography (20 g). Elution with 10% ethanol–chloroform provided the *formate-ester* (11) as a white crystalline solid (0.018 g, 3%), m.p. 184—187 °C (from ethyl acetate–diethyl ether), $\lambda_{max.}$(ε) (EtOH) 325 (17 454) and 262 nm (17 275); $\nu_{max.}$(KBr) 3 400, 3 260, 1 778, 1 720, 1 700, 1 619, and 1 550 cm^{-1}; δ_H([$^2H_7$]-DMF) 1.40 (3 H, d, *J* 6.2 Hz, *Me*CH), 2.02 (3 H, s, COMe), 3.28 (2 H, d, *J* 9.0 Hz, 4-H_2), 3.86 (1 H, dd, *J* 4.0 and 2.9 Hz, 6-H), 4.16 (1 H, dt, *J* 2.9 and 9.0 Hz, 5-H), 5.34 (1 H, m, 8-H), 5.37 and 5.58 (2 H, ABq, CH_2Ar), 6.02 (1 H, d, *J* 13.0 Hz, SCH=C), 7.21 (1 H, dd, *J* 10.0 and 13.0 Hz, NCH=C), 7.84 (2 H, d, *J* 9 Hz, Ar), 8.30 (2 H, d, *J* 9 Hz, Ar), 8.35 (1 H, s, CHO), and 10.51 (1 H, d, *J* 10.0 Hz, NH) (Found: C, 52.9; H, 4.45; N, 8.8. $C_{21}H_{21}N_3O_8S$ requires C, 53.05; H, 4.45; N, 8.85%).

p-*Nitrobenzyl* (5R,6S)-3-(2-*Acetamidoethylthio*)-6-[(R)-1-*formyloxyethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (19).—To a cooled solution (ice-bath) of the *p*-nitrobenzyl ester (10) [2] (1.0 g) and triphenylphosphine (1.376 g) in dry tetrahydrofuran (250 ml) was added successively formic acid (98%; 0.494 g) and diethyl azodicarboxylate (0.918 g). The resulting solution was stirred at room temperature for 1 h. The solvent was then evaporated under reduced pressure and the residue partitioned between ethyl acetate and water; the organic phase was washed with brine, dried, and concentrated. Silica gel column chromatography (30 g) gave, after elution with 5% ethanol–chloroform, a white solid. This was digested in hot ethyl acetate and collected by filtration, to give the *formate ester* (19) in pure form (0.180 g, 17%), m.p. 175—178 °C (from ethyl acetate), $\lambda_{max.}$(ε) (CH_3CN) 318 (12 970) and 268 nm (11 175); $\nu_{max.}$($CHBr_3$) 3 270, 1 788, 1 702, and 1 625 cm^{-1}; δ_H([$^2H_7$]-DMF) 1.40 (3 H, d, *J* 6 Hz, *Me*CH), 1.90 (3 H, s, COMe), 3.08 (2 H, m, SCH_2), 3.38—3.50 (3 H, m, NCH_2 + 4-H_a), 3.57 (1 H, dd, *J* 18.5 and 9.5 Hz, 4-H_b), 3.84 (1 H, dd, *J* 2.9 and 5.9 Hz, 6-H), 4.34 (1 H, dt, *J* 2.9 and *ca.* 9 Hz, 5-H), 5.37 (1 H, m, 8-H), 5.36 and 5.56 (2 H, ABq, CH_2Ar), 7.83 (2 H, d, *J* 9 Hz, Ar), 8.21 (1 H, broad t, NH), 8.29 (2 H, d, *J* 9 Hz, Ar), 8.34 (1 H, s, CHO) (Found: C, 52.8; H, 4.9; N, 8.75. $C_{21}H_{23}N_3O_8S$ requires C, 52.8; H, 4.85; N, 8.8%). Although the (*Z*)-ethylidene (24) has been isolated in pure form from other reactions, in this instance the slow careful chromatography essential for the purification of the formate-ester (19) resulted in degradation of the former. T.l.c. investigation of the crude reaction mixture did, however, indicate that the (*Z*)-ethylidene (24) and formate-ester (19) were present in the approximate ratio of 1 : 1.

p-*Nitrobenzyl* (5R,6S)-3-(2-*Acetamidoethylthio*)-6-[(R)-1-*hydroxyethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (20).—A solution of the ester (19) (0.16 g) in 30% aqueous 1,4-dioxan (40 ml) was cooled in an ice-bath with stirring. Sodium hydroxide solution (0.1N; 4.0 ml) was added and stirring continued at this temperature for 5 min. Ethyl acetate (200 ml) was added and the organic phase washed with water and brine, and dried. Removal of the solvent under reduced pressure gave a gum, which was subjected to silica gel column chromatography (5 g). Elution with 5% ethanol–chloroform yielded the (*E*)-ethylidene (26) (0.053 g, 37%), $\nu_{max.}$($CHBr_3$) 3 290, 1 767, 1 698, and 1 628 cm^{-1}; δ_H([$^2H_7$]-DMF) 1.85 (6 H, d + s, 2 × Me), 3.0—3.75 (6 H, m, 4-H_2 + NCH_2CH_2S), 4.85 (1 H, m, 5-H), 5.46 (2 H, q, CH_2Ar), 6.44 (1 H, q, vinylic H), 7.84 (2 H, d, ar), 8.10 (1 H, broad resonance, exchanges with D_2O, NH), 8.27 (2 H, d, Ar).

Elution with 10% ethanol–chloroform afforded the pure (8R)-*hydroxyethyl derivative* (20) (0.048 g, 32%), m.p. 164—167 °C (from ethyl acetate–diethyl ether), $\lambda_{max.}$(ε) (EtOH) 319 (13 265) and 265 nm (11 580); $\nu_{max.}$(KBr) 3 400, 3 290, 1 778, 1 700, 1 641, 1 608, and 1 548 cm^{-1}; δ_H([$^2H_7$]-DMF) 1.24 (3 H,

d, *J* 7 Hz, *Me*CH), 1.88 (3 H, s, COMe), 3.02 (2 H, m, SCH_2), 3.37 (1 H, dd, *J* 8.5 and 18.3 Hz, 4-H_a), 3.43 (2 H, m, NCH_2), 3.44 (1 H, dd, *J* 6.1 and 2.9 Hz, 6-H), 3.53 (1 H, dd, *J* 9.8 and 18.3 Hz, 4-H_b), 4.08 (1 H, m, 8-H), 4.29 (1 H, dt, *J* 2.9 and *ca.* 9 Hz, 5-H), 5.33 and 5.55 (2 H, ABq, CH_2Ar), 7.83 (2 H, d, *J* 8.5 Hz, Ar), 8.19 (1 H, broad t, NH), and 8.28 (2 H, d, *J* 8.5 Hz, Ar) (Found: C, 53.4; H, 5.05; N, 9.35. $C_{20}H_{23}N_3O_7S$ requires C, 53.45; H, 5.15; N, 9.35%).

Sodium Salt of (5R,6S)-3-(2-*Acetamidoethylthio*)-6-[(R)-1-*hydroxyethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylic Acid* (14).—5% Palladium-on-carbon catalyst (0.038 g) was shaken with hydrogen in 30% aqueous 1,4-dioxan (15 ml) at ambient temperature and pressure for 30 min. A solution of the *p*-nitrobenzyl ester (20) (0.025 g) in 1,4-dioxan (5 ml) was added and shaking in the presence of hydrogen continued for an additional 3 h. Sodium hydrogencarbonate (0.006 g) was added and the suspension filtered over Celite, washing well with water (25 ml). The filtrate was concentrated to *ca.* 20 ml and washed with ethyl acetate (3 × 25 ml). The aqueous solution was concentrated to smaller volume and applied to a column of Diaion HP-20. Elution with water and lyophilisation of the aqueous solution furnished the sodium salt of *N*-acetylthienamycin (14) as a white solid (0.016 g, 86%), $\lambda_{max.}$(ε) (H_2O) 299 nm (6 366); $\nu_{max.}$(KBr) 3 400br, 1 750, 1 660—1 610br, 1 588, and 1 555sh; $[\alpha]_D^{20}$ +60° [*c* (H_2O), 0.45]; δ_H(D_2O) 1.27 (3 H, d, *J* 6.5 Hz, *Me*CH), 1.97 (3 H, s, COMe), 2.92 (2 H, tABq, *J* 6.2 and 13.8 Hz, SCH_2), 3.08 (1 H, dd, *J* 8.75 and 17.5 Hz, 4-H_a), 3.25 (1 H, dd, *J* 9.5 and 17.5 Hz, 4-H_b), 3.37 (1 H, dd, *J* 2.5 and 6.0 Hz, 6-H), 3.39 (2 H, t, *J* 6.5 Hz, NCH_2), 3.97 (1 H, dt, *J* 2.5 and *ca.* 9 Hz, 5-H), 4.01 (1 H, m, 8-H); h.p.l.c. (5% CH_3CN) R_t 5.0 min.

p-*Nitrobenzyl* (5R,6S)-3-(2-N-p-*Nitrobenzyloxycarbonyl-aminoethylthio*)-6-[(R)-1-*hydroxyethyl*]-7-*oxo*-1-*azabicyclo*-[3.2.0]*hept*-2-*ene*-2-*carboxylate* (22).—To a stirred solution of the ester (18) (0.130 g) in 1,4-dioxan (10 ml) and water (15 drops) was added a solution of *N*-bromoacetamide (0.041 g) in 1,4-dioxan (5 ml). After the solution had been stirred at ambient temperature for 4.5 min, chloroform (100 ml) was added. The organic phase was washed with phosphate buffer (0.05M; pH 7.0) and brine, dried, and concentrated to yield the crude thiol (21) as a gum, $\nu_{max.}$($CHCl_3$) 1 770, 1 700, and 1 605 cm^{-1}. This gum was dissolved in dry *NN*-dimethylformamide (5 ml) and stirred at room temperature for 25 min with anhydrous potassium carbonate (0.041 g) and 2-*p*-nitrobenzyloxycarbonylaminoethyl bromide (0.177 g). The reaction solution was partitioned between ethyl acetate and water; the organic phase was separated, washed with brine, dried, and evaporated to dryness to yield the crude product, which was chromatographed over silica gel (3 g). Elution with 5% ethanol–chloroform afforded the pure ester (22) as a white solid (0.061 g, 36%), m.p. 181—183 °C (from acetone–diethyl ether) (lit.,[16] 185—187 °C), $\lambda_{max.}$(ε) (EtOH) 317 (12 445) and 266 nm (20 163); $\nu_{max.}$ (Nujol) 3 500, 3 290, 1 769, 1 701sh, 1 691, and 1 608 cm^{-1}; $[\alpha]_D^{20}$ +50° [*c* (DMF) 0.45]; δ_H([$^2H_6$]-acetone) 1.27 (3 H, d, *J* 6.5 Hz, *Me*CH), 3.08 (2 H, m, SCH_2), 3.23—3.39 (2 H, m, 6-H + 4-H_a), 3.39—3.58 (3 H, m, NCH_2 + 4-H_b), 4.13 (1 H, m, 8-H), 4.27 (1 H, dt, *J* 2.6 and *ca.* 8 Hz, 5-H), 5.25 (2 H, s, CH_2Ar), 5.29 and 5.45 (2 H, ABq, CH_2Ar), 6.90 (1 H, broad t, NH), 7.65 (2 H, d, *J* 8.5 Hz, Ar), 7.82 (2 H, d, *J* 8.5 Hz, Ar), and 8.25 (4 H, d, *J* 8.5 Hz, Ar) (Found: C, 52.95; H, 4.4; N, 9.35. Calc. for $C_{26}H_{26}N_4O_{10}S$: C, 53.25; H, 4.45; N, 9.55%).

p-*Nitrobenzyl* (5R,6S)-3-[(E)-2-*Acetamidovinylthio*]-6-[(R)-1-*azidoethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (27).—The ester (8) [2] (1.00 g) and triphenylphosphine (1.17 g) were dissolved in dry tetrahydrofuran (100 ml) and the solution cooled in an ice-bath. Hydrazoic acid (1.59M solution in toluene; 2.8 ml) was added to the stirred solution, followed by diethyl azodicarboxylate (0.78 g). The reaction solution was stirred at room temperature for 20 min. The solvent was evaporated under reduced pressure and the residue partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, dried, and concentrated under reduced pressure. The resulting oil was chromatographed over silica gel (30 g). Elution with ethyl acetate gave the desired product contaminated with triphenylphosphine oxide. Crystallisation of this mixture from ethyl acetate–diethyl ether afforded the pure *azidoethyl derivative* (27) as a white solid (0.28 g), m.p. 182—184 °C (from dichloromethane–hexane), $\lambda_{max.}$(ε) (EtOH) 325 (15 815) and 262 nm (16 600); $\nu_{max.}$($CHCl_3$) 3 430, 2 120, 1 780, 1 700, 1 621, 1 608, and 1 558 cm^{-1}; δ_H($CDCl_3$) 1.45 (3 H, d, *J* 6.7 Hz, *Me*CH), 2.09 (3 H, s, COMe), 3.02 (1 H, dd, *J* 8.5 and 18.2 Hz, 4-H_a), 3.16 (1 H, dd, *J* 8.6 and 2.9 Hz, 6-H), 3.23 (1 H, dd, *J* 9.5 and 18.2 Hz, 4-H_b), 3.93 (1 H, dq, *J* 8.6 and 6.6 Hz, 8-H), 4.13 (1 H, dt, *J ca.* 9 and 2.8 Hz, 5-H), 5.26 and 5.51 (2 H, ABq, CH_2Ar), 5.88 (1 H, d, *J* 13.7 Hz, SCH=C), 7.26 (1 H, dd, *J* 10.5 and 13.5 Hz, NCH=C), 7.53 (1 H, d, *J* 10.8 Hz, NH), 7.65 (2 H, d, *J* 8.9 Hz, Ar), 8.22 (2 H, d, *J* 8.9 Hz, Ar) (Found: C, 50.95; H, 4.35; N, 17.9. $C_{20}H_{20}N_6O_6S$ requires C, 50.85; H, 4.25; N, 17.8%). An additional quantity of the product was obtained by re-chromatographing the mother-liquors over silica gel (20 g), with chloroform as eluant. The resulting solid was recrystallised from ethyl acetate–diethyl ether to yield the pure ester (27) (0.365 g) (total yield 61%).

(5R,6R)-3-[(E)-2-*Acetamidovinylthio*]-6-[(R)-1-*aminoethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylic Acid* (29).—The azidoethyl derivative (27) (0.015 g) was dissolved in 1,4-dioxan (4 ml), water (0.6 ml), ethanol (0.15 ml), and phosphate buffer (0.05M; pH 7.0; 0.75 ml). The solution was shaken in the presence of 5% palladium-on-carbon catalyst (0.025 g) and hydrogen for 2 h. The suspension was filtered over Celite, washing well with water (25 ml). The filtrate was concentrated to *ca.* 20 ml and washed with ethyl acetate (3 × 50 ml). The aqueous solution was further concentrated to a small volume and chromatographed over Biogel P-2, with water as eluant. Fractions containing the amino-acid (29) were identified by the absorption at $\lambda_{max.}$ 307 nm in the u.v. spectrum and combined to yield an aqueous solution of the product (*ca.* 0.002 g based on ε 13 000, 20%).

p-*Nitrobenzyl* (5R,6S)-3-(2-*Acetamidoethylthio*)-6-[(R)-1-*azidoethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (28).—A solution of the ester (10) [2] (0.75 g) and triphenylphosphine (0.878 g) in dry tetrahydrofuran (250 ml) was cooled in an ice-bath with agitation. Hydrazoic acid (1.88M solution in toluene; 2.7 ml) was then added, followed by diethyl azodicarboxylate (0.585 g). The reaction mixture was stirred at ambient temperature for 30 min. The solvent was evaporated to small volume and ethyl acetate (200 ml) added. The organic solution was washed with water and brine, dried, and concentrated. The residual solid was subjected to silica gel column chromatography (22 g). Elution with ethyl acetate gave the pure (8R)-*azidoethyl compound* (28) as a white solid (0.20 g) after digestion in ethyl acetate; m.p. 167—170 °C (from ethyl acetate), $\lambda_{max.}$(ε) (EtOH) 319 (13 591) and 266 nm (11 656); $\nu_{max.}$(KBr) 3 275, 2 120, 1 785, 1 700, 1 630, 1 607, and 1 545 cm^{-1}; δ_H([$^2H_7$]-DMF) 1.39 (3 H, d, *J* 7 Hz, *Me*CH), 1.88 (3 H, s, COMe), 3.08 (2 H, d, *J* 7 Hz, 4-H_2), 3.2—3.6 (m, SCH_2-CH_2N), 3.65 (1 H, dd, *J* 3 and 7 Hz, 6-H), 4.0—4.4 (2 H, m, 5-H + 8-H), 5.32 and 5.58 (2 H, ABq, CH_2Ar), 7.81 (2 H, d, *J* 9 Hz, Ar), 8.10 (broad res., exchanges with D_2O, NH), 8.26

(2 H, d, *J* 9 Hz, Ar) (Found: C, 50.2; H, 4.5; N, 17.4. $C_{20}H_{22}N_6O_6S$ requires C, 50.6; H, 4.65; N, 17.7%). Crystallisation of the mother-liquors from ethyl acetate gave an additional quantity of pure ester (28) (0.177 g) (total yield 48%).

(5R,6R)-3-(2-*Acetamidoethylthio*)-6-[(R)-1-*aminoethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylic Acid* (30).—A solution of the ester (28) (0.05 g) in 1,4-dioxan (12 ml), water (2 ml), ethanol (0.45 ml), and phosphate buffer (0.05M; pH 7.0; 2.25 ml) was shaken for 2 h at ambient temperature and pressure in the presence of hydrogen and 5% palladium-on-carbon catalyst (0.075 g). The suspension was filtered through Celite, washing well with water. The filtrate was concentrated to *ca.* 25 ml and washed with ethyl acetate (3 × 50 ml). The aqueous phase was further concentrated and chromatographed over Biogel P-2. Fractions containing the amino-acid (30), identified by the absorption at $\lambda_{max.}$ 298 nm in the u.v. spectrum, were combined to provide an aqueous solution of the product (*ca.* 0.008 g based on ε 8 500, 24%). Lyophilisation, which was accompanied by decomposition, afforded a pale yellow solid, $\nu_{max.}$(KBr) 3 200br, 1 750, and 1 620 cm^{-1}.

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