The *S*-Alkylation of Sulphides by an Activated Carbohydrate Epimine under Acidic Catalysis: the Formation of α-Acetamido-sulphides. Part 4.[1] Reactions with Dithioacetals and Monothioacetals

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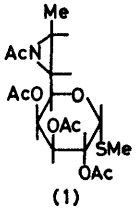
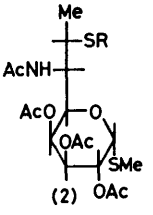
The tetra-acetylepimine (1) has been found to react with dithioacetals and monothioacetals under acidic catalysis to produce monoalkylated sulphonium salts, which collapse *via* methylenesulphonium and methyleneoxonium ions, respectively, to afford sulphides. Cyclic dithioacetals and monothioacetals are efficient reagents for the introduction of ω-mercapto- and -hydroxy-alkylthio-substituents. Although the *N*-acetyl-activating group in (1) permits the stereospecific introduction of such substituents, its replacement by a basic amino-acid activating group leads to a mixture of 7*S*- and 7*R*-epimers. The mechanisms of these reactions are discussed.

PREVIOUS Parts,[1-3] in connection with the modification of the structure of the antibiotic lincomycin,† have described the products obtained by the *S*-alkylation of a variety of types of sulphides by reaction with the tetra-acetylepimine (1) under acidic catalysis, followed by the collapse of the initial sulphonium salts to methyl (7*S*)-7-deoxy-7-(substituted-thio)-1-thiolincosaminides (2). However, certain complications had been encountered. Although the reagent 2-hydroxyethyl methyl sulphide in the presence of acetic acid, permitted the introduction of the 7*S*-(2-hydroxyethylthio)-substituent to give (3),[3] the yield was limited by the alternative collapse of the intermediate sulphonium salt to the methylthio-derivative (4), and by extensive co-formation of the 7*S*-acetate.[4] Cyclic sulphides had been found to provide alternative access to the analogous (ω-acetoxy-alkyl)thio-substituents;[2] however, polymerisation of thiiran made the reaction impracticable for the preparation of (5), and the co-formation of (7) diminished markedly the yield of (6) from thietan.

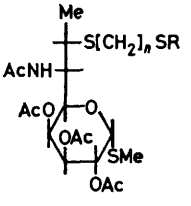


(1)



(2)

(3) R = CH_2CH_2OH
(4) R = Me
(5) R = CH_2CH_2OAc
(6) R = $[CH_2]_3OAc$
(7) R = $[CH_2]_3S[CH_2]_3OAc$



(8) *n* = 2, R = Me (11) *n* = 3, R = H
(9) *n* = 3, R = Me (12) *n* = 2, R = Ac
(10) *n* = 2, R = H (13) *n* = 3, R = Ac

The efficiency of neighbouring group participation had led to difficulties in the introduction of 7*S*-(ω-mercapto-alkyl)thio- and -(ω-methylthioalkyl)thio-substituents.[1,2] Thus, reaction with 1,2-bis(methylthio)ethane gave (4) in high yield, but none of the desired (8), whereas 1,3-bis(methylthio)propane gave the desired (9) as the major product. 2-(Methylthio)ethanethiol gave (4) as the major product with none of the desired thiol (10), and alkylation of the activated thiol sulphur atom [1-3] in the reagent led to the generation of (8) in low yield. 3-(Methylthio)propanethiol gave the thiol (11) in low yield, together with (9) and a small amount of (4). Although the ω-*S*-acetyl compounds (12) and (13) could be obtained using as reagents *S*-acetyl-2-(methylthio)-ethanethiol and -3-(methylthio)propanethiol, respectively,[2] their yields were reduced, and their isolation was complicated, by the co-formation of some methylthio-derivative (4).

A suggestion of a different type of sulphide reagent which might allow the introduction of this type of ω-substituted sulphide was afforded by the conclusions of Hughes and Robson [5] concerning the course of the migration of alkylthio-groups of carbohydrate dialkyl dithioacetals to positions elsewhere in the molecule containing good leaving groups. These authors found that 5-*O*-*p*-tolylsulphonyl-L-arabinose diethyl dithioacetal (14), on heating in aqueous acetone, gave rise to an anomeric mixture of ethyl 1,5-dideoxy-5-ethylthio-1-thio-α- and β-L-arabinofuranosides (15). The rearrangement was explained by the EtS-6 neighbouring group participation of an ethylthio-group in the displacement of the 5-*p*-tolylsulphonyloxy-substituent, with the formation of the thianium ion (16), the opening of which was assisted by the mesomeric effect of the second ethylthio-group to give the acyclic methylenesulphonium ion (17), this ion being quenched by nucleophilic attack of the 4-hydroxy-group to give the anomeric mixture of furanosides [(15), Scheme 1]. Similar migrations of thio-groups to positions 2 and 4 of carbohydrates have been explained along similar lines.[6]

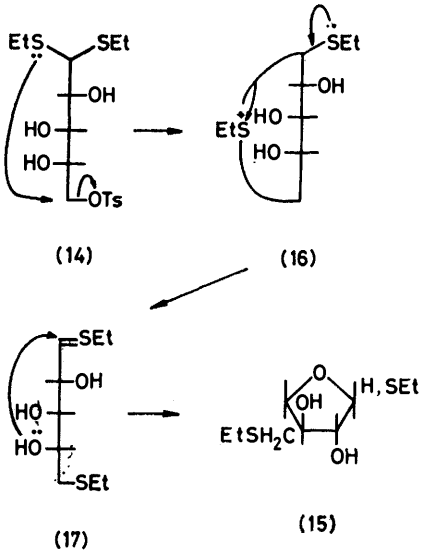
Cyclic dithioacetals (18), if alkylated by the epimine (1) in the presence of an acidic catalyst, thus would be expected to give the cyclic sulphonium ion (19) which, by analogy, should undergo ring-opening to the acyclic sulphonium ion (20); quenching by acetate ion as nucleophile would give the ester of a monothioacetal [(21), Scheme 2].

Although both mono- and di-*S*-alkylation of dithioacetals from both aldehydes [7,8] and ketones [9] are known, in general these alkylations have been conducted with the

† Lincocin is the trade-mark of The Upjohn Company for lincomycin hydrochloride.

highly electrophilic Meerwein trialkyloxonium salts or with methyl fluorosulphate. However, there are two references to the hydrolysis of dithioacetals to the corresponding ketones in which the milder reagent methyl iodide in aqueous solvents suffices to alkylate the dithioacetal sulphur atom(s).[10]

Two observations weighed against the ready *S*-alkylation of a sulphur atom in a dithioacetal or a monothioacetal. Per-*O*-methylation of the hydroxy-groups of



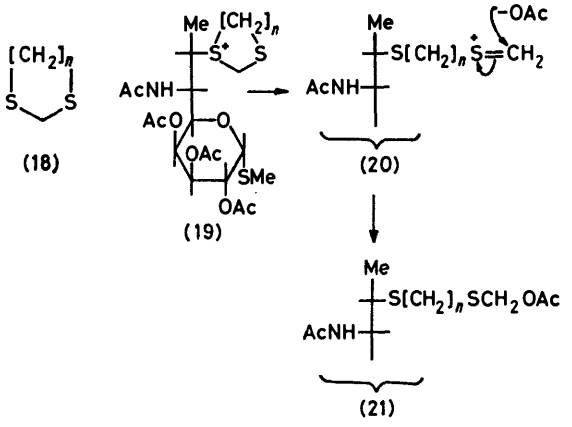
SCHEME 1

carbohydrate dibenzyl dithioacetals standardly is conducted [11] in the presence of a large excess of methyl iodide without the involvement of the dithioacetal sulphur atoms; were *S*-methylation to occur, at least partial replacement of the benzyl groups by methyl should occur. Similarly, the reaction of methyl *N*-acetyl-3,4-*O*-isopropylidene-1-thio-α-lincosaminide under forcing conditions with an excess of methyl iodide in the presence of potassium t-butoxide gives the *N*-methyl-2,7-di-*O*-methyl derivative, with no indication of *S*-alkylation,[12] and methyl *N*-acetyl-2,3,4,7-tetra-*O*-acetyl-1-thio-α-lincosaminide fails to undergo *S*-methylation with methyl iodide.[3]

The reactivity of the methylenesulphonium ion [(20), Scheme 2] was not expected to present problems. Such ions are considered [13] to be intermediates in the Pummerer reaction, in which they are quenched by the nucleophilic attack of acetate ion to give α-acetoxysulphides, and the quenching of the parent ion, $[Me\overset{+}{S}=CH_2]$, by alcohols is accepted as the mechanism of formation of methylthiomethyl ethers as by-products in dimethyl sulphoxide–acetic anhydride oxidations.[14]

Further, Meerwein and his collaborators [7] have shown that methylmethylenesulphonium hexachloroantimonate, $[Me\overset{+}{S}=CH_2]\ SbCl_6^-$, reacts readily with dimethyl sulphide to give the dimethyl(methylthiomethyl)-sulphonium salt, $[MeSCH_2\overset{+}{S}Me_2]\ SbCl_6^-$. Similarly, treatment of 2,3,4-tri-*O*-acetyl-L-arabinose dimethyl dithioacetal with ethanethiol in the presence of zinc chloride gives,[15] after deacetylation, 5-deoxy-5-methylthio-L-arabinose ethyl methyl dithioacetal, demonstrating that the corresponding sulphonium ion is quenched by ethanethiol as nucleophile. However, in all these reactions, except for the dimethyl sulphoxide–acetic anhydride oxidation of alcohols, the nucleophiles which quench the methylenesulphonium ions are the only ones present, and they are present in large excess of the molar requirements. In the case of the oxidation reactions, the formation of acetoxymethyl methyl sulphide, the Pummerer product of the reagent, always occurs; in those instances in which the acetoxymethylthio-ether of the alcohol is formed as a by-product, it is apparent that acetate ion and the alcohol must compete as nucleophiles in the quenching of the methylenesulphonium ion. There remained also, therefore, the question in the projected Scheme 2 of whether the ion (20) would be quenched by the acetate ion present, to give the desired acetoxy-sulphide (21), or by excess of dithioacetal, leading to product(s) useless in the present investigation.

The question of the ability of the epimine (1) to effect alkylation of the sulphur atom of a dithioacetal in the presence of acetic acid was investigated by reaction with the readily available formaldehyde dimethyl dithioacetal. Apart from a trace of the 7*S*-acetoxy-amide, the 7*S*-methylthio-derivative (4) was obtained in almost quantitative yield. There was no indication of the formation of the (methylthio)methylthio-derivative (22), which would have resulted from intermolecular nucleophilic attack at the methyl group of the intermediate

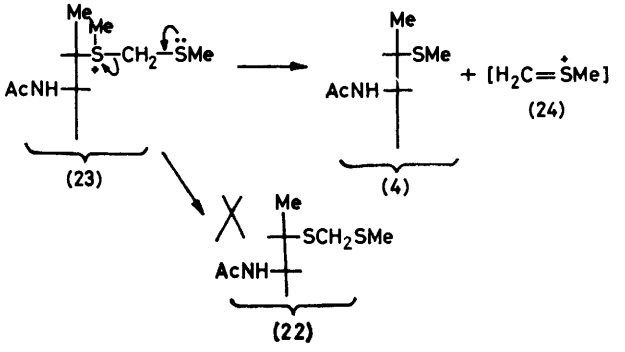


SCHEME 2

sulphonium salt (23), thus substantiating the mode of collapse of this ion by the mesomeric assistance of the heterolysis of the carbon–sulphur bond (Scheme 3), but giving no evidence concerning the fate of the methylenesulphonium salt (24).

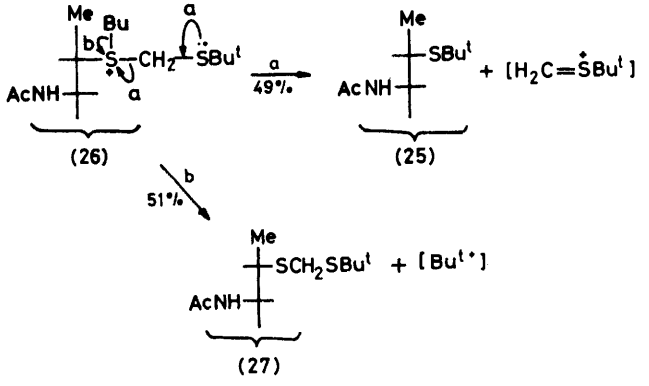
The crude product from the corresponding reaction between the epimine and formaldehyde di-t-butyl dithioacetal showed the presence of two materials by t.l.c., coincident with the 7*S*-acetoxy-amide and the known [3] 7*S*-t-butylthio-derivative (25). Countercurrent

distribution gave three components, however, of which the two more polar were identified as the acetoxy-amide (19%, reflecting the lowered nucleophilic reactivity of the sulphide sulphur atom relative to that of the methyl analogue [3]), and the expected t-butylthio-derivative (25) (38%). The third component showed signals in the ^{1}H n.m.r. spectrum indicative of the presence of both an SCH_2S and an SBu^t group, and this was corroborated



SCHEME 3

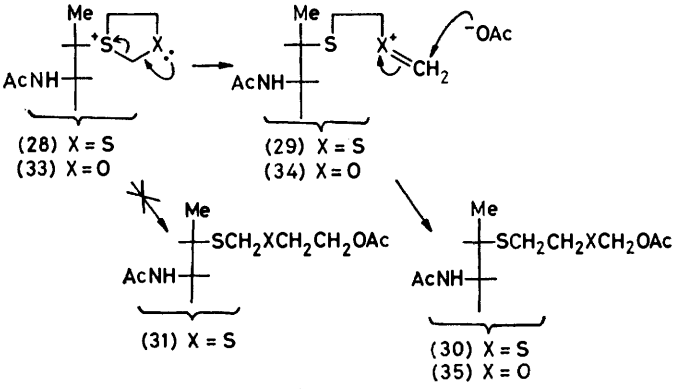
by the mass spectrum, which showed ions at *m/e* 539 (M^+), 492 (M^+ — SMe), 482 (M^+ — Bu^t), 450 (M^+ — SBu^t), 436 (M^+ — CH_2SBu^t), and 404 (M^+ — SCH_2SBu^t), identifying the product as the (t-butylthio)methylthio-derivative (27) (39%). Unlike the intermediate sulphonium ion (23), the ion (26) can collapse by heterolysis of a carbon–sulphur bond either assisted by the mesomeric effect of the sulphide sulphur atom to give (25), or by the alternative generation of a t-butyl carbocation, to give (27) (Scheme 4). These two routes are seen to be essentially equivalent energetically. Despite the operation of these two equally favoured pathways for the collapse of the ion (26), the reaction of



SCHEME 4

the epimine with formaldehyde di-t-butyl dithioacetal constitutes the most efficient method found of introduction of the 7*S*-t-butylthio-substituent; other reagents investigated gave the following yields: di-t-butyl sulphide, 2.5%; [3] di-t-butyl disulphide, 0%,[3] 2-(t-butylthio)ethanethiol, 18%.[1]

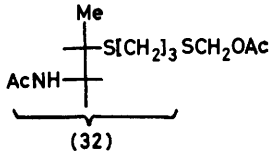
With the knowledge that the reaction conditions were suitable for the alkylation of the sulphur atom of dithioacetals, attention was turned to the crucial case of cyclic dithioacetals. With 1,3-dithiolan, a trace of the acetoxy-amide was formed together with a single product derived from the dithiolan; it showed signals in the ^{1}H n.m.r. spectrum at δ ($CDCl_3$) 1.92—2.17 (18 H, 6s), indicative of the introduction of a new acetate ester group, 2.86 (4 H, s, SCH_2CH_2S), and 5.18 (2 H, s, SCH_2O), which is consistent with the introduction of the desired $SCH_2CH_2SCH_2OAc$ substituent, and was borne out by the presence in the mass spectrum of ions at *m/e* 522 (M^+ — SMe), 464 (M^+ — SCH_2OAc), and 404 (M^+ — $SCH_2CH_2SCH_2OAc$). Therefore, the intermediate sulphonium salt (28) collapses with mesomeric assistance to the acyclic sulphonium salt (29), which is then quenched by attack of acetate ion to yield the desired derivative (30), obtained in 84% yield. There is no quenching observed of the ion (29) by excess of dithiolan. That the collapse of (28) occurs through (29) and not by direct attack of acetate ion is indicated by the failure of the reaction to yield any detectable amount of the isomeric (31) (Scheme 5). Final proof of the



SCHEME 5

structure of this product (30) was obtained *via* Zemplen de-esterification; in view of the existence of a stable aldehydo-D-galactose ethyl monothiohemiacetal penta-acetate,[16] there had been some question of how readily the intermediate $SCH_2CH_2SCH_2OH$ would lose formaldehyde, but the hydrolysis product catalysed the iodine–azide reaction,[17] demonstrating the presence of a thiol group, and acetylation in pyridine–acetic anhydride generated the known [2] *S*-acetyl compound (12).

Similarly, reaction with 1,3-dithian gave the 7*S*-(3-acetoxymethylthio)propylthio-derivative (32) in 83% yield; its structure also was proved by Zemplen de-



esterification, and acetylation to the known [2] *S*-acetyl compound (13). This high yield of (32) from 1,3-dithian is in sharp contrast to the very low yield of the 7*S*-(5-acetoxypentyl)thio-compound obtained from the reaction

with thian, which showed an unexpected diminution of nucleophilic reactivity relative to thiolan.[2] As with thian, 1,3-dithian exists in the chair conformation. However, the flattening of the ring of 1,3-dithian produced by the long carbon–sulphur bonds and the large bond angles [18] and the removal of an axial hydrogen atom by the introduction of the second sulphur atom must enhance the nucleophilic reactivity of the dithian.

Studies of the relative rates of solvolyses of α-halogeno-sulphides and -ethers indicate that the stabilisation of the carbocationic centre by oxygen is 10^2—10^3 times more efficient than by sulphur.[19] Alkylation of the sulphur atom of 1,3-oxathiolan by reaction with the tetra-acetylepimine (1) should give the cyclic sulphonium ion (33), from which the acyclic oxonium ion (34) would thus be expected to be formed even more readily than the acyclic sulphonium ion (29) from the cyclic sulphonium ion (28).

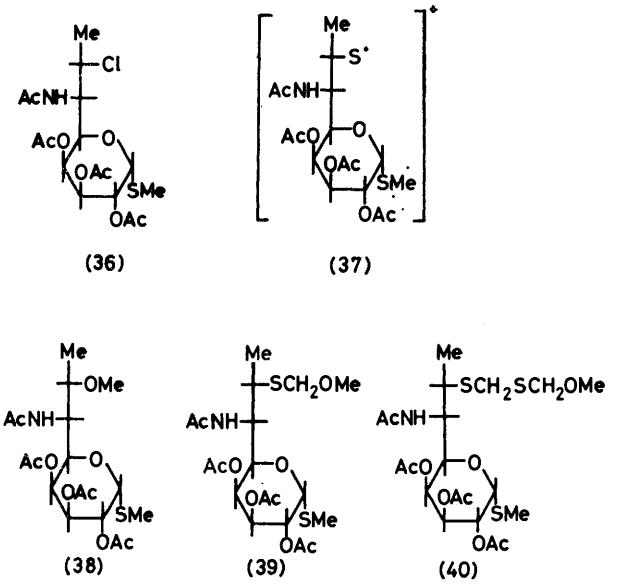
The reaction indeed gave the desired product (35) in 83% yield, together with a small amount of the 7-acetoxy-amide, demonstrating that the oxonium ion (33) was also quenched exclusively by nucleophilic attack of acetate ion. Proof of the structure of (35) was derived from signals in the ^{1}H n.m.r. spectrum at δ ($CDCl_3$) 1.93—2.15 (18 H, 6s, 4 OAc + SMe + NAc), 2.80 (2 H, d, J 6 Hz, SCH_2), 3.80 (2 H, d, J 6 Hz, CH_2O), and 5.25 (2 H, s, OCH_2O); also, Zemplen de-esterification followed by acetylation gave the known [2] 7*S*-(2-acetoxyethylthio)tetra-acetate (5).

The ready collapse of the sulphonium ion (33) by the mesomeric assistance of the acetal oxygen atom suggested that acyclic monothioacetals should provide excellent leaving groups for the collapse of intermediate sulphonium ions to sulphides; thus, the reagent bis-(methoxymethyl) sulphide should allow the introduction of the 7*S*-(methoxymethyl)thio-substituent. However, this reagent is isosteric with dipropyl sulphide, in which steric hindrance reduced the nucleophilic reactivity of the sulphur atom markedly, giving the 7-propylthio-derivative in only 19% yield.[3] The $-I$ inductive effect of the methoxymethyl group might also be expected to reduce the nucleophilicity of the sulphide sulphur atom.

Bis(methoxymethyl) sulphide was prepared from 1,3,5-trithian by the method of Bloch and Höhn,[20] and its reaction with the tetra-acetylepimine was conducted under the standard conditions. Countercurrent distribution of the product yielded four symmetrical peaks on analysis, K 0.24, 0.45, 0.75, and 1.28, the latter being shown to be a mixture of two components by t.l.c.; chromatography gave materials of R_F 0.16 and 0.26. The K 0.24 material was identified as the 7*S*-acetate (21% yield). The mass spectrum of material, R_F 0.26, showed intense fragment ions at m/e 392 and 394 in the correct ratio for ^{35}Cl and ^{37}Cl; an ion of low intensity at m/e 439 was consonant with M^+ (392 + SMe), indicating this component to be the known [21] 7*S*-chloro-tetra-acetate (36), with which it was identified (19% yield).

Each of the products with K 0.45, 0.75, and R_F 0.16, showed ions of significant intensity at m/e 436 in their mass spectra, consistent with the formation of the fragment ion (37), encountered in the mass spectra of 7-thio-substituted derivatives. Peak matching at high resolution of this ion from the K 0.45 material gave m/e 436.1592, consistent only with $C_{18}H_{30}NO_9S$ (calc. 436.1641); a second ion, m/e 388.1607 required $C_{17}H_{26}NO_9$ (calc. 388.1602), and the absence of sulphur in this ion suggested the generation of an oxonium ion by the loss of the anomeric methylthio-group, giving a molecular weight of 435; m/e 436 is therefore $M^+ + 1$, and the 7-substituent must be the methoxy-group. The product was identified as the known [4] 7*S*-methoxy-tetra-acetate (38) (7%). The material, K 0.75, gave ions expected of the desired product of the reaction, the 7*S*-(methoxymethyl)thio-derivative (39), m/e 481 (M^+), 449, (M^+ — MeOH), 436 (M^+ — CH_2OMe), 435 (M^+ — Me_2O), 404 (M^+ — SCH_2OMe), and 403 (M^+ — $HSCH_2$-OMe). The ^{1}H n.m.r. spectrum also was consistent with this structure, showing δ ($CDCl_3$) 3.47 (3 H, s, OMe) and 4.30 and 4.93 (2 H, AB pattern, J_{AB} 13 Hz, SCH_2O). The yield of (39) was 36.5%.

The final product, R_F 0.16, gave ions in the mass

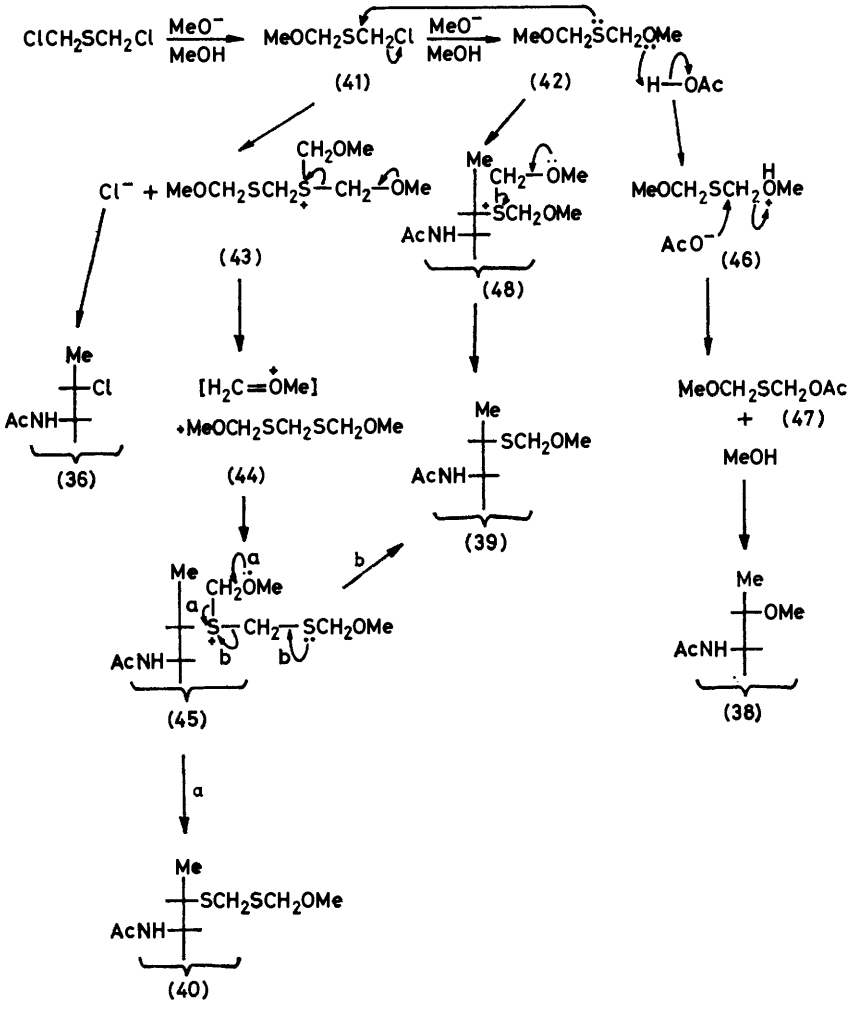


spectrum at m/e 436, 482, and 495, identified by peak matching under high resolution as $C_{17}H_{26}NO_8S_2$ (436.1071, calc. 436.1099) and thus the ion (37), $C_{18}H_{28}NO_8S_3$ (482.0990, calc. 482.0977), giving the 7-substituent as $S(SCH_2)$, and $C_{19}H_{29}NO_8S_3$ (495.1077, calc. 495.1055), expanding this substituent to $S[(SCH_2)(CH)]$. An ion of low intensity at m/e 527 could then be M^+ (495 + MeOH), giving the complete substituent as $S(C_2H_4OSMe)$, suggesting either $SSCH_2CH_2OMe$ or SCH_2SCH_2OMe. The compound showed end absorption only in the u.v. spectrum, denying the disulphide structure, for which $\lambda_{max.}$ 245 nm is expected.[22] The ^{1}H n.m.r. spectrum showed signals at δ($CDCl_3$) 3.41 (3 H, s, OMe), 3.81 (2 H, s, SCH_2S), and 4.70—4.95 (2 H, AB pattern centred at 4.83, J_{AB} 11 Hz, SCH_2O), fully consistent with the

presence of the substituent SCH_2SCH_2OMe, *i.e.* structure (40) (8%.)

Of the four products produced in the reaction, excluding the frequently encountered 7*S*-acetate, the only product resulting from the bis(methoxymethyl) sulphide *is* (39). Alkylation of the bis(methoxymethyl) sulphide evidently proceeds as expected *via* the sulphonium ion bis(methoxymethylthio)methane (44), reaction of which with the epimine would give the observed (40) *via* the ion (45).

The formation of the 7*S*-methoxy-compound (38) demands the generation of methanol during the reaction with the acetylated epimine. This must involve the acetolysis of a methoxymethylthio-substituent, sensibly



SCHEME 6

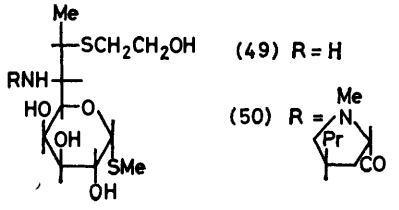
(48) to give the desired 7*S*-methoxymethylthio-compound (39) in 36.4% yield. Re-examination of the reagent and its precursor, the bis(chloromethyl) sulphide, by g.l.c. showed that, under the conditions used, the two had identical retention times and that, therefore, incomplete reaction of the chloro-compound would have escaped detection. The presence of a small amount of *the* intermediate $MeOCH_2SCH_2Cl$ (41) would enable the following rationalisation of the formation of the total products observed (Scheme 6). Alkylation of the bis(methoxymethyl) sulphide (42) by (41) would yield the sulphonium salt (43), providing chloride ion which allows the apparently efficient production of the 7*S*-chloro-compound (36). The salt (43) would be expected to collapse, by loss of methylmethyleneoxonium ion, to the major component (42) *via* (46) to give the acetoxymethyl methoxymethyl sulphide (47) and methanol. Further, the formation of the 7*S*-chloro-derivative (36) demands that the chloromethyl methoxymethyl sulphide (41) be present in the distilled reagent, which requires that the rate of reaction of (41) with methoxide anion to give (42) be slow.

An examination [23] by preparative g.l.c. of the crude product from the reaction between bis(chloromethyl) sulphide and a 4% excess of sodium methoxide in methanol, followed by brief heating, has established the presence of 8.75 molar % of (44) relative to (42). Repetition of the formation of the bis(methoxymethyl) sulphide using a 10% excess of sodium methoxide in methanol followed by lengthy heating under reflux gave,

after distillation, a product which showed a single peak by g.l.c. on a more polar column packing than used earlier, and which was distinguished readily from bis-(chloromethyl) sulphide. There was no indication of the presence of the chloro-methoxy-compound (41), which should have a retention time intermediate between that of the bis(chloromethyl) sulphide and (42).

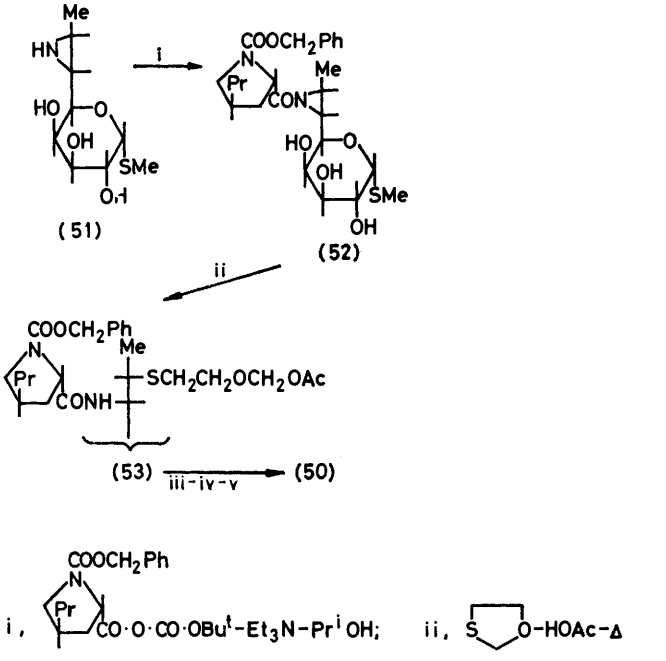
Reaction of the tetra-acetylepimine with the pure reagent (42) gave the 7-acetate (18%), the 7-methoxymethylthio-compound (39) (63%), and the 7-methoxy-compound (38) (12%). Hence, whereas the formation of the 7-chloro- (36) and the 7-(methoxymethylthio)-methylthio-compounds (40) can be avoided by the use of the pure reagent, the formation of methanol, and thus the generation of (38), is a necessary complication of the acidic catalysis of the ring opening of the activated epimine.

Hydrazinolysis of the tetra-acetyl 7*S*-(2-acetoxymethoxy)ethylthio-derivative (35) gave the free amino-sugar (49), identical with that derived from the hydrazinolyses of the corresponding (2-hydroxyethyl)-thio- and 2-(acetoxyethyl)thio-derivatives (3) and (5), respectively, described earlier.[2,3] Condensation of (49) with the mixed anhydride from 1-methyl-4-*trans*-propyl-L-proline [24] and isobutyl chloroformate gave 7*S*-7-deoxy-7-(2-hydroxyethylthio)lincomycin (50), isolated as its crystalline hydrochloride.



The fully acetylated epimine (1) was used in this and earlier investigations [1-4] of ring-opening reactions for the introduction of 7*S*-substituents into the carbohydrate side-chain since (i) activation of the epimine by introduction of an electron-withdrawing substituent at the epimino-nitrogen atom was found to be necessary,[4] (ii) the fully acetylated sugars were found to crystallise more readily than the unesterified amides, (iii) the tetra-acetylepimine is soluble readily in the sulphides, which are used as both reagent and solvent, and (iv) whereas acetylation of the epimine in pyridine–acetic anhydride occurs without complication, selective *N*-acetylation of the epimine with acetic anhydride must be conducted in sterically hindered alcohols to avoid participation of the alcohol in the reaction, which leads to the formation of the α-alkoxy-amide.[4] However, the use of the acetyl group for the activation of the epimino-ring in these reactions, leading to intermediates of interest in the synthesis of analogues of the antibiotic lincomycin, requires that this activating group be cleaved to the free amino-sugar, which must then be condensed with the 1-methyl-*trans*-4-propyl-L-proline, as in the example above.

In order to investigate the use of an activating substituent on the epimino-nitrogen atom that need not be removed in the generation of the lincomycin analogue, the epimine (51) was treated in isopropyl alcohol with the mixed anhydride from the *N*-benzyloxycarbonyl derivative of *trans*-4-propyl-L-proline [25] and isobutyl chloroformate. The syrupy amide (52), $\nu_{max.}$ 1 750 cm^{-1}, no amide II band, in which it was felt that the prolyl substituent would confer adequate solubility upon the triol, was converted under the normal conditions with 1,3-oxathiolan into the ring-opened (53), isolated after chromatography as a syrup. Hydrogenolysis, followed by reductive methylation, gave the acetoxymethoxy-derivative (Scheme 7); base hydrolysis gave the desired



SCHEME 7

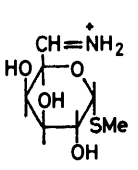
(50) as a chromatographically homogeneous syrup, which gave a crystalline hydrochloride, identical with that obtained from the acylation of the amino-sugar (49).

With the successful use of the protected prolylepimine in the introduction of the (2-hydroxyethyl)thio-substituent, attention was turned to the direct use of the *N*-methyl derivative. Acylation of the epimine with the mixed anhydride from 1-methyl-*trans*-4-propyl-L-proline, and reaction of the crude product with 1,3-oxathiolan and acetic acid, followed by hydrolysis, gave a syrup containing one major component by t.l.c., which was not differentiated from the desired (50). Isolation of this material by chromatography gave a syrup, which showed the signals in the ^1H n.m.r. spectrum (60 MHz) expected of (50), but the hydrochloride of which did not crystallise in the expected yield. Examination of this salt before crystallisation at 100 MHz showed a doubling of the signals of the 8-Me, SMe, SCH_2, OCH_2, and

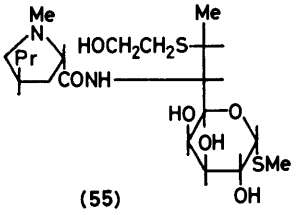
anomeric protons. G.l.c. examination of the pertrifluoroacetylated material showed it to be an 80 : 20 mixture of the required material and a second component, separated incompletely, of longer retention time: both peaks gave identical fragmentation patterns by g.l.c.–m.s. Antibacterial assay *in vitro* of this mixture showed it to be less active than the pure 7*S*-analogue.

The mixture was acetylated in pyridine, and the crude product was subjected to extensive countercurrent distribution. After 2 500 transfers, sufficient separation had occurred to enable the removal of most of each of the pure components. That of K 0.99 was the tetra-acetate of the desired material; the new component, K 0.82, was pure by g.l.c. Zemplen de-esterification gave a syrupy free base, converted into an amorphous hydrochloride, which was found to be significantly less active against gram positive bacteria than (7*S*)-7-deoxy-7-[(2-hydroxyethyl)thio]lincomycin (50), and to be without gram negative antibacterial activity.

Hydrazinolysis of this material was slow, being incomplete after 94 h. Chromatography of the crude product gave the free sugar as an amorphous solid, which showed ions in the mass spectrum at *m/e* 314 ($M^+ + 1$), 266 (M^+ — SMe), 237 (M^+ — SCH_2CH_2OH — H), and 208 [ion (54)]. Since this places the substituent at C-7, the structure of the contaminant must be (7*R*)-7-deoxy-7-[(2-hydroxyethyl)thio]lincomycin (55).



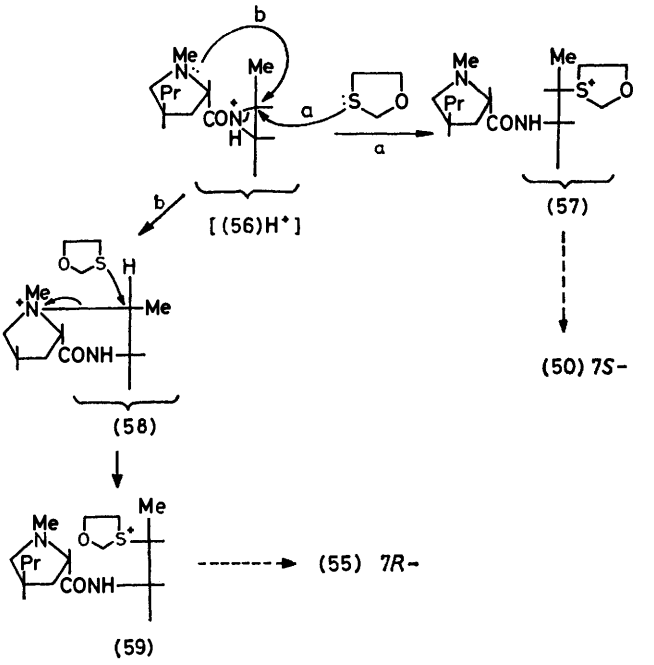
(54)



(55)

No change in reaction conditions existed which might favour a transition from an S_N2 to an S_N1 mechanism, leading to the co-generation of the 7*R*- and 7*S*-epimers. The lack of formation of any 7*R*-epimer in any of the ring-opening reactions of the *N*-acetylated epimine and in the ring-opening of the *N*-(1-benzyloxycarbonyl-*trans*-4-propyl-L-prolyl)epimine (52), implies that the loss of stereospecificity in the ring-opening leading to a mixture of (49) and (55) is occasioned by the presence of the basic nitrogen function in [(56), Scheme 8]. This involvement could be envisaged in two ways. In one, ring-opening of the epimino-ring in (56) by the 1,3-oxathiolan would give the desired sulphonium ion (57) (route a), leading to the formation of the 7*S*-product (50). Competitive ring-opening of the epimine by the basic nitrogen atom of the prolyl fragment, however, would give the quaternary salt (58) (route b); nucleophilic attack by the 1,3-oxathiolan at C-7 of this six-membered cyclic salt would produce the 7*R*-sulphonium salt (59), leading to the formation of the 7*R*-product (55).

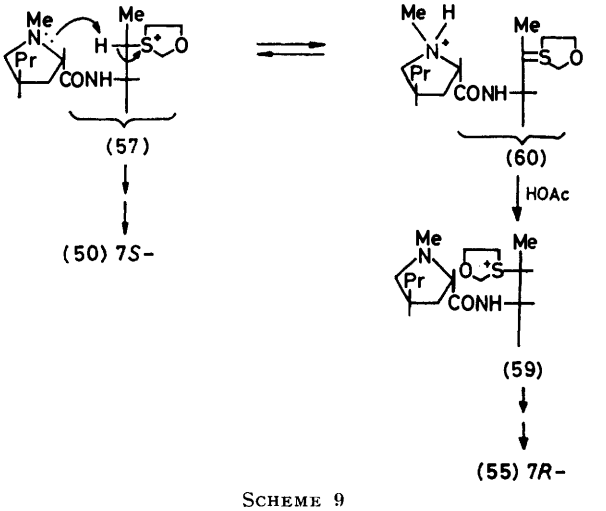
However, the transition state required for the formation of the cyclic quaternary ammonium ion (58), an endocyclic reaction, is five-membered, which is too small



SCHEME 8

to allow the nitrogen atom, C-7, and the epimino-nitrogen atom to be arranged linearly,[26] and is an example of the disfavoured 5- to 7-*endo-tetrahedral* cyclic reaction;[27] this situation has been discussed with reference to an apparent migration of an alkyl substituent in a sulphonium salt.[1,2]

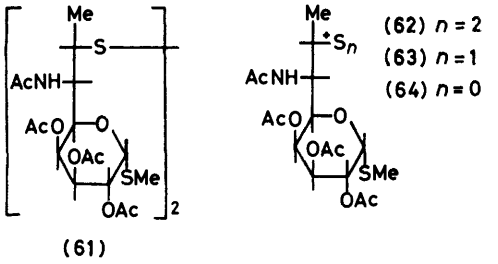
The second, favoured, mechanism invokes the ability of the basic prolyl nitrogen atom to remove the proton at C-7 of the sulphonium salt, (57) to give the ylide (60); re-protonation of this ylide (60) by the acetic acid present can occur from either side of the double bond, to regenerate the salt (57), from which will be derived the 7*S*-product (50), or to give the epimeric sulphonium salt (59), from which will be derived the 7*R*-product (55) (Scheme 9). An attempt is in progress to distinguish between these two possible mechanisms by studies of the

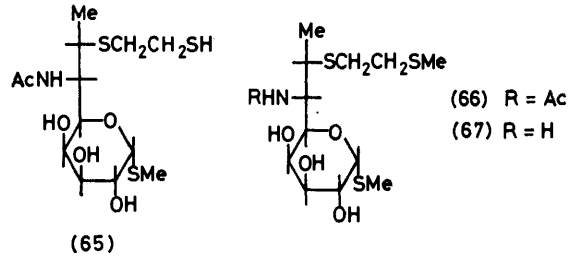


SCHEME 9

incorporation of deuterium when the reaction is conducted in the presence of 1-deuterioacetic acid.

Hydrazinolysis of the 7*S*-(2-acetoxymethylthio)ethylthio-tetra-acetate (30) under the standard conditions gave an unexpectedly polar product, the ^{1}H n.m.r. spectrum of which showed that it lacked the CH_2CH_2S substituent at C-7. Acetylation in pyridine–acetic anhydride gave a material showing $\lambda_{max.}$ 270 nm (ε 326), indicative of a disulphide and not an *S*-acetyl derivative (which would be expected to have ε *ca.* 4 000). The disulphide structure (61) was consistent with the mass spectral ions of *m/e* 872 (M^+), 468 (62), 436 (63), and 404 (64) and with the elemental analysis. Presumably, the oxidation occurs during the isolation of the hydrazinolysis product. This degradation denied access to the 7*S*-(2-mercaptoethyl)thio-amine, and thus to the lincomycin analogue by this route.

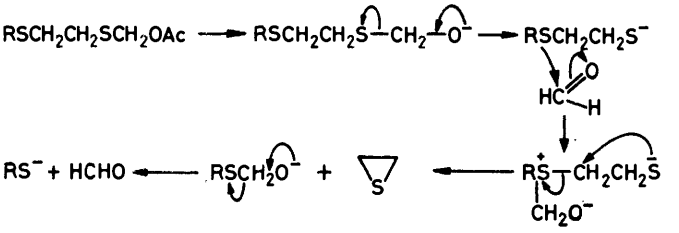




The 7*S*-(2-methylthio)ethylthio-tetra-acetate (8) is available,[2] in low yield only, by the reaction between the tetra-acetylepimine and (2-methylthio)ethanethiol, and the 7*S*-(2-acetoxymethylthio)ethylthio-tetra-acetate (30) appeared to offer ready access to the introduction of this substituent. Hydrolysis of (30) proceeded rapidly in methanolic sodium methoxide to (65); if one equivalent of methoxide were used, and methyl iodide added when starting material was absent by t.l.c., a product of R_F identical with that generated by the microscale de-esterification of (8) was obtained. Isolation gave crystalline (66) in 81% yield, showing signals in the ^{1}H n.m.r. spectrum at δ ($C_5^2H_5N$) 2.08 (6 H, s, 2 SMe), 2.30 (3 H, s, NAc), and 2.7—3.1 (4 H, m, AA'BB' pattern, SCH_2CH_2S), and *m/e* 388 (M^+ — SMe), 311 (M^+ — CH_2CH_2SMe + H), 291 (M^+ — 2 SMe), and 278 (M^+ — SCH_2CH_2SMe). Hydrazinolysis of (66) gave the free amino-sugar (67), identical to that obtained by the hydrazinolysis of (8).

If the reaction of the acetoxymethylthio-derivative (30) in methanolic sodium methoxide were permitted to continue beyond the time required for the disappearance of starting material, a second zone more polar than (65) arose by t.l.c., and became more intense at the expense of that of (65). Isolation of this component by chromatography, followed by acetylation in pyridine–acetic anhydride, gave the octa-acetyl disulphide (61). The cleavage of the 7*S*-sulphur–carbon bond of the substituent occurs under remarkably mildly basic conditions; since the corresponding 7*S*-(2-methylthio)ethylthio-substituent is stable to hydrazinolysis, the participation must be S^--3, in marked contrast to the lack of O^--3 participation during hydrazinolysis of the 7*S*-(2-hydroxyethyl)thio-group.

Since the apparently analogous 2-(methylthio)-,[2,28] 2-(t-butylthio),[2] and 2-(benzylthio)-ethanethiols[2] are not degraded under even strongly basic conditions, the possibility was considered that the formaldehyde, liberated in the early stages of the hydrolysis, might play a role in the cleavage, as indicated in Scheme 10, since



SCHEME 10

the cleavage of a sulphonium salt by S^--3 participation would be expected to occur readily.[1,2] However, no reaction could be detected by g.l.c. between 2-(benzylthio)ethanethiol and methanolic sodium methoxide in the presence of aqueous formaldehyde. Furthermore, the 7*S*-(2-acetylthio)ethylthio-derivative (13) similarly underwent reaction with methanolic sodium methoxide to yield, by t.l.c., a material not distinguished from (65) and, on standing, the disulphide, isolated as the octa-acetate (61).

Since RS-4 participation in general is inefficient, and has proved to be so in the reactions of 1,3-bis(methylthio)propane and 3-(methylthio)propanethiol in this investigation,[2] the cleavage of the side-chain during hydrazinolysis of the 7*S*-(3-acetoxymethylthio)propylthio-tetra-acetate (32) was not expected to be a complication. In this case too, nevertheless, the product was the disulphide, isolated as (61). These cleavage reactions must be associated with some feature of the carbohydrate molecule which has not been recognised to date.

The conversion into the corresponding analogues of lincomycin of 7*S*-thio-substituted sugars described here, other than that with the 2-hydroxyethylthio-substituent already given, together with the biological data, will be described elsewhere.

EXPERIMENTAL

General experimental procedures have been described previously.[3,4] Countercurrent distribution systems used

were 95% ethanol–water–ethyl acetate–cyclohexane in the proportions (v/v) 1 : 1 : 1 : 3 (system A), and 1 : 1 : 1 : 2 (system B), and 95% ethanol–water–acetone–cyclohexane in the proportions (v/v) 1.5 : 3 : 16 : 7 (system C). With compounds of structure ascertained earlier, products were identified by comparison (m.p., mixed m.p., t.l.c., spectrometric examination) with authentic samples.

Reactions of the Tetra-acetylepimine (1) *with Formaldehyde Dialkyl Dithioacetals.—Methyl* (7S)-N-*acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*methylthio*-1-*thio*-α-*lincosaminide* (4). Acetic acid (5.25 g, 86.8 mmol) was added to a solution of the tetra-acetylepimine [4] (5.0 g, 12.4 mmol) in formaldehyde dimethyl dithioacetal [29] [δ($CDCl_3$) 2.15 (6 H, s, 2 SMe) and 3.62 (2 H, s, SCH_2S)] (50 g, 463 mmol) in an oil-bath at 100 °C, and heating was continued under anhydrous conditions for 16 h. Volatile materials were removed as completely as possible by distillation (7 mmHg), and t.l.c. of the solid residue in acetone–Skellysolve B * (1 : 1) showed the absence of the tetra-acetylepimine (R_F 0.68) and the presence of a major product (R_F 0.57) and a minor product (R_F 0.50). Countercurrent distribution (system A) gave two peaks, K 0.25 and 0.92. Isolation of the materials showed the more polar to be the 7*S*-penta-acetate (290 mg, 5%),[4] m.p. 312—313°, and the 7*S*-7-methylthio-tetra-acetate [3] (4) (5.17 g, 92.5%), m.p. 225—226°.

Methyl (7S)-N-*acetyl*-2,3,4-*tri*-O-*acetyl*-7-*t-butylthio*-7-*deoxy*-1-*thio*-α-*lincosaminide* (25) *and methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-(*t-butylthio*)*methylthio*-7-*deoxy*-1-*thio*-α-*lincosaminide* (27). Acetic acid (10.50 g, 173.6 mmol) was added to a solution of the tetra-acetylepimine (10.0 g, 24.8 mmol) in formaldehyde di-t-butyl dithioacetal [30] [δ($CDCl_3$) 1.37 (18 H, s, 2 SC_4H_9) and 3.67 (2 H, s, SCH_2S)] (100 g, 521 mmol) at 100 °C; the reaction was conducted, and the crude product was isolated, as above. T.l.c. in acetone–Skellysolve B (1 : 1) showed a minor zone, R_F 0.50, coincident with that of the penta-acetate, and a zone, R_F 0.70, coincident with that of the 7-t-butylthio-compound (25); [3] g.l.c. (1% OV-17 on 80—100 mesh Gaschrom Q in a 1/4 in × 3 ft stainless steel column, programmed from 200—275° at 8° min^{-1}, then held at 275°) gave peaks of retention time 12.06, 14.79, and 23.22 min, the first two not being differentiated from the penta-acetate and butylthio-compound (25).

Countercurrent distribution (system A) gave peaks of K 0.27, 2.01, and 4.33. The two more polar compounds were identified as the penta-acetate (2.20 g, 19%) and the 7*S*-t-butylthio-tetra-acetate (25), m.p. 272—273° (4.61 g, 37.8%). The third component was shown to be the 7S-7-(*t-butylthio*)*methylthio-tetra-acetate* (27) (5.26 g, 39.3%), prisms from ethyl acetate–Skellysolve B, m.p. 163.5—164.5°, $[\alpha]_D$ +100° (*c* 1.082 in $CHCl_3$), δ($CDCl_3$) 1.34 (3 H, d, *J* 7 Hz, 8-H_3), 1.40 (9 H, s, SC_4H_9), 1.93—2.17 (15 H, 5s, 3 OAc + NAc + SMe), and 3.73 (2 H, s, SCH_2S) (see main text for m.s. data) (Found: C, 49.1; H, 7.0; N, 2.2; S, 18.0. $C_{22}H_{37}NO_8S_3$ requires C, 48.95; H, 6.9; N, 2.6; S, 17.8%).

Reactions of the Tetra-acetylepimine (1) *with* 1,3-*Dithiolan and* 1,3-*Dithian.—Methyl* (7S)-N-*acetyl*-2,3,4-*tri*-O-*acetyl*-7-[(2-*acetoxymethylthio*)*ethylthio*]-7-*deoxy*-1-*thio*-α-*lincosaminide* (30). The reaction of the tetra-acetylepimine (5.0 g) in 1,3-dithiolan [31] (50 g) and acetic acid (5.25 g) was conducted under the standard conditions, and volatile materials were removed by distillation *in vacuo*. The crude product gave a minor zone by t.l.c. in acetone–Skellysolve B (1 : 1) of R_F 0.50, not distinguished from the penta-acetate, and a major zone, R_F 0.55. Countercurrent distribution (system A) gave a small peak, K 0.25, of the penta-acetate (638 mg, 11%), and the major component, K 0.98, shown to be the 7S-7-[(2-*acetoxymethylthio*)*ethylthio*]*tetra-acetate* (30) (5.93 g, 84%), which separated from ethyl acetate–Skellysolve B in needles, m.p. 164—165°, $[\alpha]_D$ +167° (*c* 0.966 in $CHCl_3$) (see main text for spectral data) (Found: C, 46.1; H, 6.2; N, 2.4; S, 16.85. $C_{22}H_{35}NO_{10}S_3$ requires C, 46.4; H, 6.2; N, 2.5; S, 16.9%).

Methyl (7S)-N-*acetyl*-7-*deoxy*-7-[(2-*mercaptoethyl*)*thio*]-1-*thio*-α-*lincosaminide* (65) *and methyl* (7S)-N-*acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-[(2-*acetylthioethyl*)*thio*]-1-*thio*-α-*lincosaminide* (12). The α-acetoxysulphide tetra-acetate (30) (1.0 g), R_F 0.86, underwent rapid de-esterification in methanolic sodium methoxide to the acetamidothiol (65), R_F 0.5, as followed by t.l.c. in methanol–chloroform (1 : 5). The solution was neutralised by the addition of solid carbon dioxide, concentrated to dryness *in vacuo*, and chromatographed on silica in the same solvent system, giving the thiol as an amorphous solid (550 mg), δ($C_5^2H_5N$) 2.25 and 2.28 (6 H, 2s, NAc + SMe) and 3.05 (4 H, s, SCH_2CH_2S); pertrimethylsilylation gave the pentakistrimethylsilyl (TMS) derivative, showing in the mass spectrum *m/e* 731 (M^+), 627 (M^+ — STMS), 613 (M^+ — CH_2STMS), and 599 (M^+ — CH_2CH_2STMS).

Acylation overnight in pyridine–acetic anhydride gave a solid which crystallised from ethyl acetate in needles, m.p. 198—199°, identical with the known [2] (12).

Methyl (7S)-N-*acetyl*-7-*deoxy*-7-[(2-*methylthio*)*ethylthio*]-1-*thio*-α-*lincosaminide* (66) *and methyl* (7S)-7-*deoxy*-7-[(2-*methylthio*)*ethylthio*]-1-*thio*-α-*lincosaminide* (67). The α-acetoxysulphide (30) (8.64 g, 15.2 mmol) in methanol (120 ml) containing sodium methoxide (15.2 mmol) [from sodium metal (351 mg)] was allowed to stand at room temperature; after 1 h, complete conversion to the thiol (65) had resulted [t.l.c., methanol–chloroform (1 : 5)]. Methyl iodide (2.16 g, 15.2 mmol) was added, and the mixture was stirred vigorously. After 30 min, the thiol, R_F 0.50, had disappeared, and a zone, R_F 0.56, coincident with that obtained by the microscale de-esterification of the 7*S*-7-[(2-methylthio)-ethylthio]tetra-acetate (8) was present. The solution was taken to dryness *in vacuo*, and the solid residue was chromatographed on silica in methanol–methylene chloride (1 : 9). Crystallisation from ethyl acetate–Skellysolve B gave the 7S-7-[(2-*methylthio*)*ethylthio*]-*amide* (66) as microscopic rods (4.67 g, 81%), m.p. 111.5—113°, $[\alpha]_D$ +228° (*c* 1.048 in EtOAc) (see main text for spectral data) (Found: C, 43.5; H, 6.9; N, 3.85; S, 24.5. $C_{14}H_{27}NO_5S_3$ requires C, 43.6; H, 7.1; N, 3.6; S, 24.9%).

The amide (66) (11.12 g) was heated under reflux overnight in hydrazine hydrate (100 g) in an oil-bath at 140 °C; volatile materials were then removed by distillation, finally under high vacuum. The residue showed the presence of a trace of the amide, R_F 0.60, by t.l.c. in methanol–benzene (1 : 2), together with a major product, R_F 0.44. Crystallisation of the residue from hot water, followed by recrystallisation from methanol, gave the 7S-7-[(2-*methylthio*)*ethylthio*]-*amine* (67) as rectangular platelets (7.74 g, 78%), m.p. 165—166°, $[\alpha]_D$ +244° (*c* 0.791 in C_5H_5N), δ ($CDCl_3$) 2.0, 2.1 (6 H, 2s, 2 SMe), 2.5—2.8 (4 H, m, SCH_2CH_2S), *m/e* 296 (M^+ — SMe), 236 (M^+ — SCH_2CH_2SMe), 208 (M^+ — $MeCHSCH_2CH_2SMe$), and 160 (M^+ — SMe — SCH_2CH_2-

*A saturated hydrocarbon fraction, b.p. 60—71°, Skelly Oil Co., Kansas City.

SMe + H) (Found: C, 42.3; H, 7.3; N, 4.1; S, 28.35. $C_{12}H_{25}NO_4S_3$ requires C, 41.95; H, 7.3; N, 4.1; S, 28.0%).

Identical material was obtained by the analogous hydrazinolysis of the tetra-acetate (8).

7,7'-Dithio-bis[methyl (7S)-N-*acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-1-*thio*-α-*lincosaminide*] (61).—The α-acetoxysulphide-tetra-acetate (30) (3.0 g) was hydrazinolysed under the usual conditions, and volatile materials were removed by distillation. The solid residue gave a major zone of R_F 0.0 on t.l.c. in methanol–chloroform (1 : 3) and crystallised from aqueous butanol in needles (1.11 g), m.p. 223—226° (decomp.), turning brown at 215°. Acetylation overnight in pyridine–acetic anhydride gave a solid which separated from ethyl acetate in prisms shown to be the *disulphide octa-acetate* (61), m.p. 273—275°, $[\alpha]_D$ +63° (*c* 0.979 in $CHCl_3$), δ ($CDCl_3$) 1.95—2.20 (15 H, 5s, 3 OAc + SMe + NAc) (see main text for m.s. data) (Found: C, 46.6; H, 5.9; N, 2.9; S, 14.2. $C_{34}H_{52}N_2O_{16}S_4$ requires C, 46.8; H, 6.0; N, 3.2; S, 14.7%).

Identical material was obtained on hydrazinolysis of the 7*S*-7-[(3-acetoxymethylthio)propylthio]tetra-acetate (32). When the reaction between the α-acetoxysulphide (30) and methanolic sodium methoxide was allowed to continue beyond the time required for its conversion into the amido-thiol (65), R_F 0.55, as indicated by t.l.c. in methanol–chloroform (1 : 7), a zone of R_F 0.13 became evident. After standing overnight, the two zones were of equivalent intensity. Chromatography in the same solvent system gave the more polar material which, on acetylation and crystallisation from ethyl acetate–Skellysolve B, gave prisms, m.p. 273—275°, identical to the disulphide-octa-acetate (61).

Methyl (7S)-N-*acetyl*-2,3,4-*tri*-O-*acetyl*-7-[(3-*acetoxymethylthio*)*propylthio*]-7-*deoxy*-1-*thio*-α-*lincosaminide* (32). The reaction between the tetra-acetylepimine (5.0 g), 1,3-dithian (50 g), and acetic acid (5.25 g) was conducted as before. The mixture, while still molten, was dissolved in methanol; excess of 1,3-dithian (24.5 g) crystallised, and was removed. The filtrate was taken to dryness, and chromatographed on silica in ethyl acetate–Skellysolve B (1 : 1); when all the 1,3-dithian had been removed, the column was eluted with ethyl acetate, giving a solid (6.33 g) which showed only one zone by t.l.c. Countercurrent distribution (system A) gave a single peak, *K* 1.29, from which was isolated material which crystallised from ethyl acetate–Skellysolve B as prisms (6.15 g, 83%), m.p. 131.5—132.5°, shown to be the 7S-7-(3-*acetoxymethylthio*)*propylthio-tetra-acetate* (32), $[\alpha]_D$ +164° (*c* 0.938 in $CHCl_3$), δ($CDCl_3$) 1.85 (2 H, t, SCH_2CH_2-CH_2S), 1.92—2.15 (18 H, 6s, 4 OAc + SMe + NAc), 2.70 and 2.78 (4 H, 2t, *J* 7 Hz, $SCH_2CH_2CH_2S$), and 5.15 (2 H, s, SCH_2O), *m/e* 583 (M^+), 524 (M^+ — AcO), 510 (M^+ — CH_2OAc), 476 (M^+ — SMe — HOAc), 464 (M^+ — CH_2-SCH_2OAc), 416 (M^+ — SMe — 2 HOAc), and 404 (M^+ — $S[CH_2]_3SCH_2OAc$) (Found: C, 47.5; H, 6.3; N, 2.2; S, 16.2. $C_{23}H_{37}NO_{10}S_3$ requires C, 47.3; H, 6.4; N, 2.4; S, 16.5%).

De-esterification in methanolic sodium methoxide followed by acetylation in pyridine–acetic anhydride gave a product which separated from ethyl acetate–Skellysolve B in needles, m.p. 170—170.5°, identical to the known [2] (13).

Reactions of the Tetra-acetylepimine with Monothioacetals.—*1,3-Oxathiolan.* A mixture of paraformaldehyde (38.5 g, 1.28 mol), benzene (500 ml), 2-hydroxyethanethiol (100 g, 1.28 mol), and toluene-*p*-sulphonic acid monohydrate (500 mg) was stirred and heated in an oil-bath at 100 °C overnight using a Dean–Stark water trap; the theoretical volume of water was formed. Benzene was removed from the reaction mixture by distillation at atmospheric pressure through a 12 in Vigreux column; the product was then distilled, and material of b.p. 88—89° and 195 mmHg was collected (87.0 g, 75.5%), δ($CDCl_3$) 2.98 (2 H, t, *J* 6 Hz, SCH_2CH_2O), 4.08 (2 H, t, *J* 6 Hz, SCH_2CH_2O), and 4.87 (2 H, s, SCH_2O), in agreement with the literature,[31] which gives no experimental details.

Yields of 1,3-oxathiolan were lower, and erratic, if the toluene-*p*-sulphonic acid were removed before distillation by washing with sodium hydrogencarbonate solution.

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-[(2-*acetoxymethoxy*)*ethylthio*]-7-*deoxy*-1-*thio*-α-*lincosaminide* (35).—Under the standard conditions, the tetra-acetylepimine (10.0 g) was heated in 1,3-oxathiolan (100 g) and acetic acid (10.5 g), and volatile materials were removed by distillation *in vacuo*, giving a solid residue. T.l.c. in acetone–Skellysolve B (1 : 1) showed a major zone of R_F 0.45. Countercurrent distribution (system B) gave two peaks, a trace of the penta-acetate (*K* 0.40) and the major product, *K* 0.70, which crystallised from ethyl acetate–Skellysolve B in needles, m.p. 148—149°, and was shown to be the 7S-7(2-*acetoxymethoxy*)*ethylthio-tetra-acetate* (35) (11.30 g, 82.4%), $[\alpha]_D$ +158° (*c* 1.009 in $CHCl_3$) (see main text for ^1H n.m.r. data), *m/e* 506 (M^+ — SMe), 494 (M^+ — OAc), 463 (M^+ — SMe — Ac), 446 (M^+ — SMe — HOAc), 436 (M^+ — OCH_2-OAc), and 404 (M^+ — $SCH_2CH_2OCH_2OAc$) (Found: C, 47.9; H, 6.5; N, 2.4; S, 11.4. $C_{22}H_{35}NO_{11}S_2$ requires C, 47.7; H, 6.4; N, 2.5; S, 11.6%).

The acetoxymethoxy-tetra-acetate (35) (1.0 g) was de-esterified in methanol solution using a catalytic amount of sodium methoxide; after 4 h, t.l.c. in methanol–chloroform (1 : 5) showed a new zone, R_F 0.31, coincident with that obtained by the microscale de-esterification of the (2-hydroxyethyl)thiotetra-acetate (3).[3] Removal of the solvent, and chromatography in methanol–chloroform (1 : 5) gave the *N*-acetyl compound as an amorphous solid, δ(D_2O) 2.04 (3 H, s, NAc), 2.21 (3 H, s, SMe), 2.81 (2 H, t, *J* 6.5 Hz, SCH_2CH_2O), and 3.74 (2 H, t, *J* 6.5 Hz, SCH_2CH_2O). The material gave a pentakistrimethylsilyl derivative, *m/e* 715 (M^+), 700 (M^+ — Me), 668 (M^+ — SMe), and 538 (M^+ — $MeCHSCH_2CH_2OTMS$). Acetylation in pyridine–acetic anhydride gave a solid which separated from ethyl acetate–Skellysolve B in needles, m.p. 206—207°, identical to the known (5).[2]

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-(*methoxymethyl*)*thio*-1-*thio*-α-*lincosaminide* (39), *Methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-[(*methoxymethylthio*)-*methyl*]*thio*-1-*thio*-α-*lincosaminide* (40), *Methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*chloro*-7-*deoxy*-1-*thio*-α-*lincosaminide* (36), *and Methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*methoxy*-1-*thio*-α-*lincosaminide* (38).—The reaction between the tetra-acetylepimine (10.0 g) and bis(methoxymethyl) sulphide [20] (60 g) in the presence of acetic acid (5.25 g) was carried out in the standard manner, and volatile materials were removed *in vacuo*, giving a solid residue. G.l.c. of this residue (UCW-98, 3.8% on a high efficiency Chromosorb W column, 4.6 mm × 122 cm, 255 °C isothermally) showed peaks of retention times 2.0, 2.3, 3.9, and 9.5 min, that of 2.3 min not being distinguished from the 7*S*-penta-acetate derivative.

Countercurrent distribution (system A) gave peaks of *K* 0.24, 0.45, 0.75, and 1.28, the first two being minor, the second two being separated incompletely. The *K* 0.24 and

0.45 materials were removed from the train, and replaced with fresh solvent layers. The *K* 0.24 material (R_t 2.3 min, 2.40 g, 21%) was identified as the 7*S*-penta-acetate; the *K* 0.45 material showed a retention time of 2.0 min by g.l.c. A tube representative of *K* 0.75 showed a major peak by g.l.c. of R_t 3.9 min and a minor peak of 9.5 min, and a tube representative of *K* 1.28 showed 2.0 and 9.5 min peaks. Co-injection of *K* 0.45 and 1.28 materials gave an enhancement of the 2.0 min peak; on programming the temperature of the g.l.c. column from 150 to 260 °C, co-injected *K* 0.45 and 1.28 materials gave a partial separation of the previously 2.0 min peak at 10.2 and 10.4 min.

The *K* 0.75 and 1.28 materials were subjected to an additional 500 transfers (total 1 000 transfers), and the complete separation of the peaks was accomplished. The *K* 0.75 material now showed by g.l.c. a single peak of retention time (255 °C isothermally) 3.9 min, and the *K* 1.28 material still showed peaks of retention times 2.0 and 9.5 min, reflected in zones of R_F 0.16 and 0.26 on t.l.c. in ethyl acetate–Skellysolve B (1 : 1). Column chromatography in the same system yielded the separate compounds.

The product of *K* 0.45 (740 mg) separated from ethyl acetate–Skellysolve B in needles, m.p. 235—236°, and was identified (see main text) as the known [4] 7*S*-7-methoxy-tetra-acetate (38). The product (2.09 g) of R_F 0.26 crystallised from ethyl acetate as needles, m.p. 248—250°, and was identified as the known [21] 7*S*-7-chloro-tetra-acetate (36).

The product of *K* 0.75 (4.35 g) crystallised from ethyl acetate–Skellysolve B in needles, m.p. 216—218°, and was shown to be the desired 7S-7-(*methoxymethyl*)*thio-tetra-acetate* (39) (m.s. and ^{1}H n.m.r. data in main text), $[\alpha]_D$ +111° (*c* 0.844 in $CHCl_3$) (Found: C, 47.4; H, 6.6; N, 2.9; S, 13.1. $C_{19}H_{31}NO_9S_2$ requires C, 47.4; H, 6.5; N, 2.9; S, 13.3%).

The final product (1.04 g), R_F 0.16, crystallised from ethyl acetate–Skellysolve B in needles, m.p. 214.5—215.5°, and was shown to be the 7S-7-(*methoxymethylthio*)*methylthio-tetra-acetate* (40) (m.s. and ^{1}H n.m.r. data in main text), $[\alpha]_D$ +87° (*c* 0.821 in $CHCl_3$) (Found: C, 45.7; H, 6.4; N, 2.7; S, 18.2. $C_{20}H_{33}NO_9S$ requires C, 45.5; H, 6.2; N, 2.7; S, 18.2%).

Preparation of Pure Bis(methoxymethyl) Sulphide.—Bis-(chloromethyl) sulphide [20] (150 g, 1.15 mol) was added during 1 h to a solution of sodium methoxide in methanol [from sodium (57.9 g, 2.5 g-atom) in methanol (500 ml)] heated under gentle reflux; heating was continued for 8 h after the addition was complete. After removal of the majority of methanol by distillation, the reaction mixture was poured into water, extracted with methylene chloride, and the combined extracts were washed with water. The solvent was removed from the dried (Na_2SO_4) solution by distillation, and the residue was fractionated through a 12 in Vigreux column; the main fraction (79.6 g, 57%) had b.p. 45—46° at 15 mmHg, δ($CDCl_3$) 3.40 (6 H, s, OMe), and 4.73 (4 H, s, SCH_2O), g.l.c. (4 ft 3% OV-17 on Chromosorb W, 100 °C isothermally), retention time 0.8 min, retention time of bis(chloromethyl) sulphide 1.0 min; the chloromethyl methoxymethyl sulphide would be expected to be of intermediate retention time. On cooling the column to 80°, the bis(methoxymethyl) sulphide still remained as a symmetrical peak at 1.7 min.

Repetition of the reaction with this pure reagent gave a crude product showing by g.l.c. minor peaks of retention times 2.0 and 2.3 min, and a major peak of 3.9 min, the earlier 9.0 min peak being absent. Countercurrent distribution gave the 7*S*-penta-acetate (*K* 0.23; 2.40 g, 20.9%), the 7*S*-methoxy-tetra-acetate (38) (*K* 0.41; 1.32 g, 12.2%), and the desired 7*S*-(methoxymethyl)thio-tetra-acetate (39) (*K* 0.74; 7.51 g, 62.9%).

Methyl (7S)-7-*Deoxy*-7-(2-*hydroxyethyl*)*thio*-1-*thio*-α-*lincosaminide* (49).—The α-acetoxymethoxy-compound (35) (3.88 g) was heated under gentle reflux with hydrazine hydrate (50 g) in an oil-bath at 140 °C overnight, and volatile material was removed from the solution by distillation *in vacuo*. T.l.c. of the residue in methanol–chloroform (1 : 3) showed a major zone at R_F 0.24, and non-charring zones of hydrazine-related products at R_F 0.05 and 0.44. Chromatography in this system gave a syrup (2.20 g), homogeneous by t.l.c., which crystallised in *platelets* from acetonitrile containing a little ethanol, m.p. 175—176°, $[\alpha]_D$ +234° (*c* 0.521 in H_2O), δ(D_2O) 2.27 (3 H, s, SMe), 2.87 (2 H, t, *J* 6 Hz, SCH_2CH_2O), and 3.83 (2 H, t, *J* 6 Hz, OCH_2CH_2S), *m/e* 314 ($M^+ + 1$), 266 (M^+ — SMe), 237 ($M^+ - SCH_2CH_2OH + H$), and 208 (M^+ — $MeCHSCH_2CH_2OH$) (Found: C, 47.05; H, 7.55; N, 4.4; S, 20.4. $C_{11}H_{23}NO_5S_2$ requires C, 42.15; H, 7.4; N, 4.5; S, 20.5%).

The identical product was obtained in similar yield from the hydrazinolyses of the 7-(2-hydroxyethyl)thio-tetra-acetate (3) and the 7-(2-acetoxyethyl)thio-acetate (5).

(7S)-7-*Deoxy*-7-(2-*hydroxyethyl*)*thiolincomycin* (*Methyl* 6,7,8-*Trideoxy*-7-(2-*hydroxyethyl*)*thio*-6-(1-*methyl*-trans-4-*propyl*-L-*pyrrolidin*-2-*ylcarbonylamino*)-1-*thio*-L-*threo*-α-D-galacto-*octopyranoside* (50).—Triethylamine (995 mg, 9.76 mmol) was added to a stirred suspension of 1-methyl-*trans*-4-propyl-L-proline hydrochloride [24] (930 mg, 4.44 mmol) in acetonitrile (50 ml) under anhydrous conditions. The solution was cooled to −5 °C in ice–methanol, and isobutyl chloroformate (610 mg, 4.44 mmol) was added slowly. After 20 min, a solution of the 7*S*-(2-hydroxyethyl)thio-sugar (49) (700 mg, 2.24 mmol) in water (5 ml) and methanol (5 ml) was added rapidly, and stirring was continued for 1 h without further cooling. T.l.c. in methanol–chloroform (1 : 10) showed the disappearance of free amino-sugar (R_F 0.0) and the appearance of a new zone, R_F 0.29. Solvent was removed from the solution *in vacuo*, water was added, the solution was adjusted to pH 10 by the addition of aqueous sodium hydroxide solution, and was extracted with methylene chloride. Removal of the solvent from the dried (Na_2SO_4) extract gave a syrup (950 mg), which was chromatographed in methanol–chloroform (1 : 10), and yielded a glass (610 mg). The glass was dissolved in water by the addition of aqueous hydrochloric acid till the pH of the resultant solution was 3.5; lyophilisation of this solution gave an amorphous solid, which was dissolved in a small volume of water and diluted with acetone, giving rectangular *plates* of the hydrochloride, m.p. 138—140°, $[\alpha]_D$ +107° (*c* 0.949 in H_2O), δ(D_2O) 1.29 (3 H, d, *J* 6 Hz, 8-H_3), 2.18 (3 H, s, SMe), 2.78 (2 H, t, *J* 6 Hz, SCH_2CH_2O), 2.92 (3 H, s, NMe), 3.71 (2 H, t, *J* 6 Hz, OCH_2CH_2S), 5.33 (1 H, d, *J* 6 Hz, anomeric H), *m/e* 466 (M^+ of free base), 449 (M^+ — OH), 448 ($M^+ - H_2O$), 421 ($M^+ - CH_2CH_2OH$), and 419 (M^+ — SMe) [Found: C, 46.1; H, 8.0; Cl, 6.6; N, 5.0; S, 12.3; H_2O (Karl Fischer titration), 3.4. $C_{20}H_{38}N_2O_6S_2$,-HCl,H_2O requires C, 46.1; H, 7.9; Cl, 6.8; N, 5.4; S, 12.3; H_2O, 3.5%].

Partial Synthesis of (50) via *the* (6R,7R)-(1-*Benzyloxycarbonyl*-trans-4-*propyl*-L-*pyrrolidin*-2-*ylcarbonylamino*)-*epimine* (52).—*trans*-4-Propyl-L-pyrrolidine-2-carboxylic acid [25] (2.93 g, 18.66 mmol) was dissolved in aqueous sodium hydroxide (N, 18.7 ml), benzyloxycarbonyl chloride (3.50 g,

20.71 mmol), and aqueous sodium hydroxide (N, 20.5 ml) were added alternately to the solution during 20 min with vigorous stirring. The pH of the mixture was adjusted from 8 to 10 with N-sodium hydroxide, and stirring was continued for 30 min. The mixture was washed twice with ether, the aqueous solution was made strongly acidic with concentrated hydrochloric acid, and was extracted with ethyl acetate. Removal of the solvent from the combined dried extracts (Na_2SO_4) gave a syrup (5.20 g).

Triethylamine (1.11 g, 11 mmol) was added to a solution of the above benzyloxycarbonyl compound (2.91 g, 10 mmol) in acetonitrile (100 ml), and the solution was cooled to −5 °C in an ice–methanol bath. Isobutyl chloroformate (1.36 g, 10 mmol) was added, and the mixture was stirred at −5 °C for 20 min. To this was added a suspension of the epimine [32] (51) (2.35 g, 10 mmol) in isopropyl alcohol (50 ml). T.l.c. after 1 h in methanol–chloroform (1 : 7) showed the disappearance of epimine (R_F 0.08) and the appearance of a major zone, R_F 0.61. The residue obtained by the removal of the solvent *in vacuo* was dissolved in methylene chloride, washed with water, and dried (Na_2SO_4). Removal of the solvent gave a syrup (5.06 g), $\nu_{max.}$ (neat) 1 700 cm^{-1}, no amide II band.

The benzyloxycarbonylepimine (52) (5.06 g, 10 mmol) was dissolved in 1,3-oxathiolan (37 g, 0.41 mol), heated at 100 °C in an oil-bath, acetic acid (4.2 g, 70 mmol) was added, and heating was continued overnight. Volatile material was removed by distillation *in vacuo*, giving a syrup (10.42 g), showing a major zone, R_F 0.34, in ethyl acetate–Skellysolve B–methanol (3 : 1 : 0.2). Chromatography in this system gave a syrup (53) (4.08 g), homogeneous by t.l.c., $\nu_{max.}$ (neat) 1 750 and 1 680 cm^{-1}. Hydrogenolysis in methanol over palladium on carbon (10%, 3.0 g) under hydrogen (50 lb in^{-2}) resulted in the disappearance of benzyloxycarbonyl compound by t.l.c., a zone of R_F 0.0, which did not quench phosphorescence under u.v. irradiation, being now present (same system). Purification from traces of contaminants was effected by chromatography in methanol–chloroform (1 : 5), giving a syrup (2.90 g).

A solution of this syrup in methanol (100 ml) was reductively methylated over palladium on carbon (10%, 500 mg), in the presence of aqueous formaldehyde (37%, 4 ml) under hydrogen (50 lb in^{-2}), giving by t.l.c. a major product, R_F 0.48 in methanol–methylene chloride (1 : 12). Catalyst was removed by filtration, the solvent was removed *in vacuo*, giving a syrup which was dissolved in methanol and de-esterified by the addition of methanolic sodium methoxide; the new zone, R_F 0.33, was coincident with that of the authentic analogue (50) derived from the amino-sugar (49). The sodium methoxide was neutralised by the addition of solid carbon dioxide, and the residue obtained on the removal of solvent was chromatographed in methanol–chloroform (1 : 10) to give a syrup, converted to the crystalline hydrochloride (1.40 g, 27% from the epimine) as earlier, m.p. 138—140°.

Partial Synthesis of (50) via *the* (6R,7R)-(1-*Methyl*-trans-4-*propyl*-L-*pyrrolidin*-2-*ylcarbonylamino*)*epimine* (56).—Triethylamine (4.3 g, 5.9 ml, 43 mmol) was added to a suspension of 1-methyl-*trans*-4-propyl-L-proline hydrochloride (4.41 g, 21.3 mmol) in acetonitrile (100 ml), and the mixture was cooled to −5 °C in an ice–methanol bath after all the solid had dissolved. Isobutyl chloroformate (2.9 g, 2.8 ml, 21.3 mmol) was added slowly, maintaining the temperature at −5 to −2 °C. A heavy precipitate of triethylammonium chloride was present. After an additional 20 min at −5 °C, a slurry of the epimine (51) (5.0 g, 21.3 mmol) in isopropyl alcohol (120 ml) was added rapidly; no solid remained after 10 min.

Volatile material was removed at 40 °C and 7 mmHg, saturated aqueous sodium hydrogencarbonate was added, and the mixture was extracted thoroughly with chloroform. The combined chloroform extracts were washed with water and dried (Na_2SO_4); removal of solvent *in vacuo* gave a syrup (7.68 g), $\nu_{max.}$ (neat) 1 690 cm^{-1}, no amide II band, as expected of (56), with a major zone (R_F 0.36) in methanol–chloroform (1 : 7).

The acylated epimine (56) (7.68 g, 19.8 mmol) was dissolved in 1,3-oxathiolan (50.4 g, 560 mmol), heated in an oil-bath at 100 °C, and acetic acid (8.33 g, 138.8 mmol) was added. After 16 h, volatile material was removed by distillation *in vacuo*, and the residual syrup was dissolved in methanol (50 ml); t.l.c. in methanol–chloroform (1 : 7) showed a major zone, R_F 0.42. Aqueous sodium hydroxide was added to pH 11, and the solution was left overnight. T.l.c. now showed the disappearance of the R_F 0.42 zone and the generation of a zone, R_F 0.27. The solvent was removed *in vacuo*, the syrup was dissolved in methylene chloride, and extracted twice with N/20-hydrochloric acid. The combined aqueous acidic extracts were washed with methylene chloride, adjusted to pH 10 with aqueous sodium hydroxide (50%), and extracted with methylene chloride; the combined extracts were washed once with water, and dried (Na_2SO_4). T.l.c. in methanol–chloroform (1 : 12) showed a major zone, R_F 0.17, not distinguished from the desired product. Chromatography in the same system of the syrup (4.65 g), obtained on removal of the solvent, gave a chromatographically homogeneous syrup (3.75 g), which was converted into an amorphous hydrochloride by dissolution in water adjusted to pH 3.5, followed by lyophilisation. The ^1H n.m.r. spectrum (D_2O, 60 MHz) was consistent with the signals expected of the desired product, but crystallisation from aqueous acetone occurred in poor yield, and the antimicrobial activity against gram negative bacteria was diminished. On trifluoroacetylation, g.l.c. of this material showed (1% OV-17 on 80—100 mesh Gaschrom Q, 1/4 in × 3 ft stainless steel column, programmed from 225 to 275 °C at 8° min^{-1}, and then held at 275°) a separation into peaks of retention times 5.5 and 5.75 min in a ratio of 4 : 1; co-injection of the pertrifluoroacetate of the authentic compound enhanced the 5.5 min peak. In the g.l.c.–m.s., these two peaks gave identical fragmentation patterns. In the 100 MHz ^1H n.m.r. spectrum, a doubling of the signals due to 8-H_3, SMe, SCH_2CH_2O, and the anomeric protons could be seen.

A sample of the hydrochloride, obtained by this route, was reconverted into the free base (12.93 g) and was acetylated in pyridine–acetic anhydride, giving a syrup (17.60 g); g.l.c.–m.s. (as above, but conducted isothermally at 175 °C) gave peaks of retention times 46.4 and 55.3 min in a ratio of 73 : 27; each peak showed *m/e* 634 (M^+ for a tetra-acetate), and each showed the same fragmentation pattern. Countercurrent distribution (system C) gave a partial separation of the two materials after 500 transfers (K 0.82 and 0.99); essential separation was achieved after 2 500 transfers. Combinations were made on the basis of both theoretical Gaussian curves and g.l.c. and yielded as syrups materials of K 0.99 (11.93 g), of K 0.82 (3.40 g), and of a mixture of the two (2.27 g). The less polar material (K 0.99) was not distinguished from the tetra-acetate of the desired analogue. Zemplen de-esterification gave a syrupy tetra-ol, converted

in aqueous hydrochloric acid, followed by lyophilisation, into an amorphous hydrochloride, which crystallised readily from aqueous acetone giving plates, m.p. 138—140°, identical in physical and biological properties with the authentic (50).

The second syrup (*K* 0.82; 3.4 g) in methanol (100 ml) was treated overnight with sodium methoxide (25% in methanol; 1 ml); t.l.c. in methanol–chloroform (1 : 10) showed the disappearance of tetra-acetate (R_F 0.77) and the appearance of a single new zone, R_F 0.25. The solution was neutralised by the addition of solid carbon dioxide, the solvent was removed *in vacuo*, and the residue was chromatographed in the same solvent system, giving a syrup (2.31 g), converted into its amorphous hydrochloride in aqueous hydrochloric acid followed by lyophilisation. This was shown to be (7R)-7-*deoxy*-7-(2-*hydroxyethyl*)*thiolincomycin* (55), δ(D_2O) 1.37 (3 H, d, *J* 7 Hz, 8-H_3), 2.22 (3 H, s, SMe), 2.83 (2 H, t, *J* 6 Hz, SC$H_2$$CH_2O$), 2.93 (3 H, s, NMe), 3.75 (2 H, t, *J* 6 Hz, OC$H_2$$CH_2S$), and 5.37 (1 H, d, *J* 6 Hz, anomeric H), $[\alpha]_D$ +180° (*c* 0.721 in H_2O) [Found (corrected for 2.27% water): C, 47.5; H, 7.8; Cl, 7.2; N, 5.4; S, 12.8. $C_{20}H_{38}N_2O_6S_2$,HCl requires C, 47.7; H, 7.8; Cl, 7.05; N, 5.6; S, 12.75%].

This material (2.0 g) in hydrazine hydrate (100 g) was heated overnight in an oil-bath at 140 °C; t.l.c. in methanol–chloroform (1 : 3) showed the formation of a small amount of product, R_F 0.19, and the presence of much starting material, R_F 0.63. Hydrazinolysis was still incomplete after 94 h. Removal of volatile materials by distillation *in vacuo* followed by chromatography in the same system gave an amorphous solid (880 mg), which could not be induced to crystallise, but which gave ions in the mass spectrum showing the substituent to be at C-7 (see main text).

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