S-Alkylation of Sulphides by an Activated Carbohydrate Epimine under Acidic Catalysis: Formation of α-Acetamido-sulphides. Part 1

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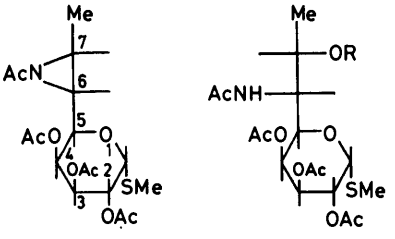
Alkanethiols do not participate in the epimine ring-opening of methyl 2,3,4-tri-*O*-acetyl-6,7-acetylepimino-6,7,8-trideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (I), catalysed by acetic acid, whereas dialkyl sulphides react *via* an α-acetamido-sulphonium salt to give α-acetamido-sulphides. Dialkyl disulphides also are alkylated, giving dialkyl(alkylthio)sulphonium salts, which are cleaved by nucleophilic attack on the sulphenyl sulphur atom to give α-acetamido-sulphides, and offer advantages over dialkyl sulphides in which bulky alkyl groups reduce the nucleophilic reactivity of the sulphide sulphur atom. Exceptions are di-t-butyl disulphide and diallyl disulphide, which yield α-acetamido-disulphides. Diethyl trisulphide is alkylated on the terminal sulphide sulphur atom, giving the ethylthio- and not the ethyldithio-product. The mechanisms of these reactions are discussed.

THE acid-catalysed alcoholysis of the acetylated 6,7-epimino-sugar (I), derived from methyl α-thiolincosaminide,[1] the carbohydrate obtained on hydrazinolysis of the antibiotic lincomycin,† was reported recently,[2] and



(I)

(II) R = alkyl
(III) R = Me
(IV) R = Ac

allowed the synthesis of a series of (7*S*)-7-alkoxy-7-deoxy-amides (II), required for the chemical modification of the antibiotic. Since the reaction was found to require the presence of an acid, it is viewed as resulting from nucleophilic attack of the alcohol at C-7 of the protonated activated epimine.

In an attempt to extend this ring-opening reaction to the introduction of alkylthio-substituents, the analogous reaction of the acetylated epimine (I) with methanethiol was investigated. Use of a large excess of methanethiol in an equal volume of methanol as diluent in the presence of acetic acid at room temperature resulted in a rapid reaction, as indicated by t.l.c., to give an amide, but the product, isolated in quantitative yield, was the methoxy-amide (III), obtained earlier [2] by the reaction in methanol–acetic acid alone. When the reaction between (I) and methanethiol–acetic acid was conducted in a sealed tube at 100 °C in the absence of diluent, the sole product was the acetoxy-amide (IV), which had been isolated from reactions involving less reactive alcohols in which competitive ring-opening by acetate ion had occurred.[2]

Since Pearson [3] has shown that the nucleophilic reactivity of a thiol is *ca.* 10^6 times that of the corresponding alcohol, and 10—10^2 times that of acetate ion, the failure of the thiol to undergo reaction under these conditions is surprising. The initial rationalisation, based on Pearson's theory [3,4] of soft and hard acids and bases, that the protonated *N*-acetylepimine was a hard electrophilic centre, and therefore reacted readily with the hard alcohol but not with the soft thiol, rapidly became untenable (see later).

In an attempt to introduce an alkylthio-substituent at least proximally to C-7, the corresponding reaction with 2-hydroxyethyl methyl sulphide was conducted, using the reagent as solvent, at 100 °C overnight, in the expectation of generating the (7*S*)-7-deoxy-7-[2-(methylthio)ethoxy]-amide (V). T.l.c. of the crude product showed the absence of starting material and the formation of a major and two minor products, which were separated by counter-current distribution. The major product (K‡ 0.97), a colourless crystalline solid, showed an amide II band at 1 550 cm^{-1}, and an unexpectedly complex NH/OH absorption at 3 460, 3 270, and 3 060 cm^{-1}. The ^1H n.m.r. spectrum showed five singlets at δ 2.0—2.25 of area corresponding to five methyl groups instead of the six expected for the *O*- and *N*-acetyl and the two *S*-methyl groups of (V). In addition, signals at δ 2.88 (J 6 Hz) and 3.85br (2 H) were indicative of the presence of $-SCH_2-$ and $-OCH_2-$ groups, respectively; in deuteriated pyridine, the latter broad peak appeared at δ 3.90, and sharpened to a triplet (J 6 Hz) on addition of D_2O, suggesting the presence of a neighbouring hydroxy-group. The mass spectrum contained ions at *m/e* 481 (M^+) [instead of the 495 expected for (V)] 463 ($M^+ - H_2O$), 450 ($M^+ - CH_2OH$), 436 ($M^+ - CH_2CH_2OH$), and 404 ($M^+ - SCH_2CH_2OH$). The substituent introduced, in this major product, was thus $-SCH_2CH_2OH$ and not $-OCH_2-CH_2SMe$; the yield of this product (VI) was 51%.

One minor component (15% yield; K 1.55) was identified as the acetoxy-amide (IV). The other (26%; K 2.90), gave ^1H n.m.r. signals at δ 1.95—2.15, of area equivalent to six methyl groups; the mass spectrum showed *m/e* 451 (M^+), 404 (M^+ — SMe), and 357 (M^+ — 2 SMe). The substituent introduced in this case therefore was –SMe. The crystal structure of this methylthio-derivative was suitable for *X*-ray analysis,

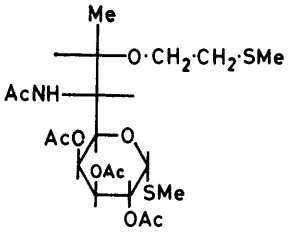
† Lincocin is the trade-mark of The Upjohn Company for lincomycin hydrochloride.

‡ The distribution coefficient K is defined by the expression $K = r/(n - r)$ in which r is the tube no. of the centre of the peak and n is the total no. of transfers.

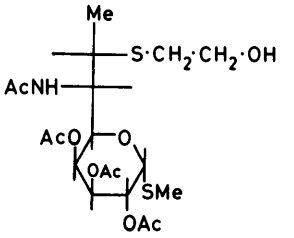
[1] W. Schroeder, B. Bannister, and H. Hoeksema, *J. Amer. Chem. Soc.*, 1967, **89**, 2448.
[2] B. Bannister, *J.C.S. Perkin I*, 1974, 360.
[3] R. G. Pearson, H. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, 1968, **90**, 319.
[4] R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, 1967, **89**, 1827; R. G. Pearson, *J. Chem. Educ.*, 1968, **45**, 581, 643.

which demonstrated the substituent to be at C-7 and to have the *S*-configuration; * the structure is therefore (VII). There was no indication of reaction at the hydroxy-group of the reagent to give the expected (V).

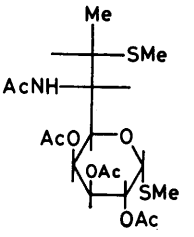
The formation of the sulphides (VI) and (VII) must involve nucleophilic attack of the sulphide sulphur atom of the reagent at C-7 of the protonated epimine † to give a sulphonium salt (1; Scheme 1), which undergoes nucleophilic attack by acetate ion mainly at the methyl group adjacent to the positively charged sulphur atom (route a) to give (VI); attack of acetate ion at the more hindered α-methylene group (route b) gives (VII) as the minor product. No explanation is offered for the alkylation of a sulphide and the failure of the alkylation of a thiol; the two have equivalent softness and nucleophilic reactivity.[3]



(V)

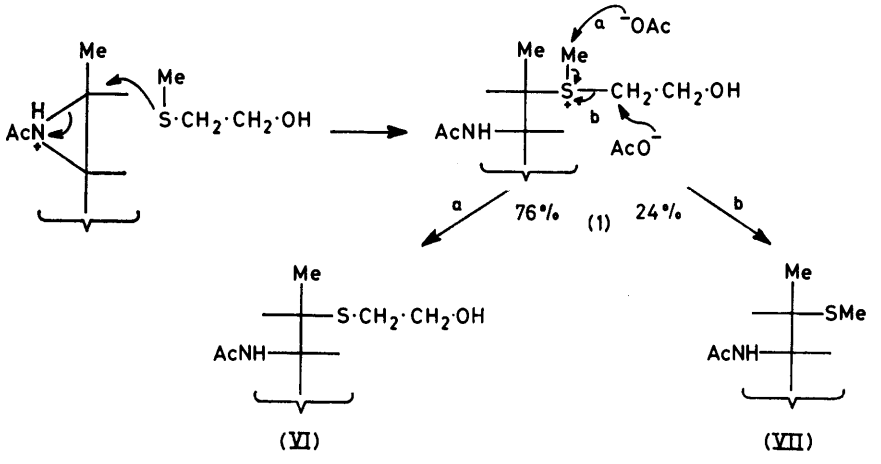


(VI)



(VII)

gave the 7-methylthio-compound (VII) in essentially quantitative yield; with diethyl sulphide, the 7-ethylthio-compound (VIII) was formed in 61% yield (the presence of ethyl acetate in the crude reaction mixture was demonstrated by g.l.c.); with di-n-propyl sulphide, the yield of the 7-n-propylthio-compound (IX) was only 18.5%, and with di-t-butyl sulphide, the yield of the 7-t-butylthio-compound (X) was 2.5%.



SCHEME 1

In all cases in which the 7-acetate (IV) was produced, the acetoxy-group possessed the (7*S*)-configuration, and no (7*R*)-acetate was formed; these acetates can be readily distinguished.[2] The acetate (IV), therefore, is indeed produced by competitive ring-opening of the epimine. The attack of acetate ion on the intermediate sulphonium salt can occur at either of the α-carbon atoms of the original sulphide, but the dialkyl sulphide is not displaced from the intermediate sulphonium salt by nucleophilic attack of acetate ion at C-7, presumably because its approach is too hindered.

Reaction with diallyl sulphide led to two products in addition to some 7-acetate. Counter-current distribution gave materials (A) (*K* 1.76; minor) and (B) (*K* 3.30;

This reaction of sulphides to give sulphonium salts which suffer nucleophilic attack at the carbon atom α to the positively charged sulphur atom, thus collapsing to a

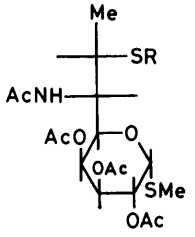
* The *X*-ray crystallographic study was conducted by Dr. D. J. Duchamp and Mrs. C. Wickrema Sinha, Physical and Analytical Chemistry Research, The Upjohn Company, and will be reported elsewhere.

† For comments on the structure of the protonated *N*-acetylepimino-group, see ref. 2.

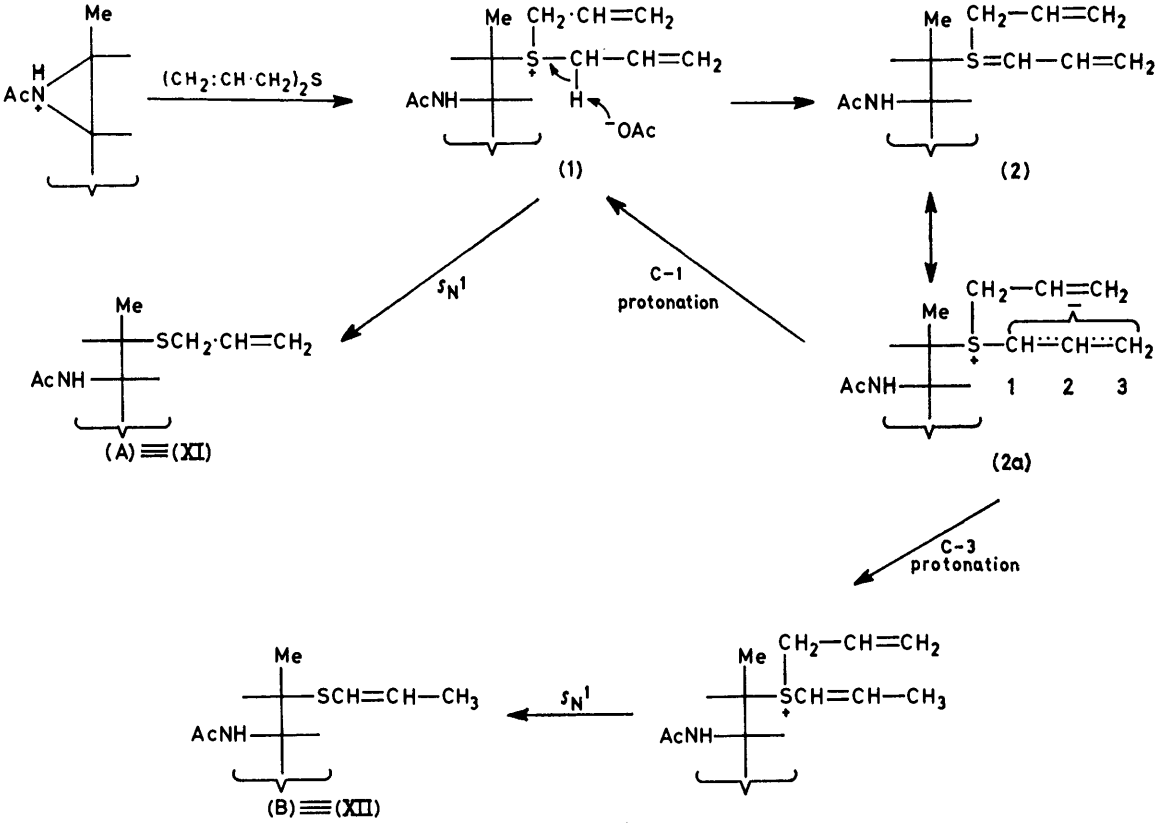
[5] D. H. Ball and F. W. Parrish, *Adv. Carbohydrate Chem.*, 1969, **24**, 139.

major). In agreement with the introduction of the expected allylthio-substituent, each gave satisfactory analytical results, and each showed M^+ in the mass spectra at *m/e* 477, and fragment ions at *m/e* 436 ($M^+ - C_3H_5$) and 404 ($M^+ - SC_3H_5$). However, the minor component (A) showed only end-absorption in the u.v. spectrum, whereas (B) showed end-absorption plus two peaks at $\lambda_{max.}$ 227 (ε 4 550) and 250 nm (4 250). This bathochromic shift from (A) to (B) was indicative of a rearrangement from the allylthio- to the propenylthio-system.[6] Although the i.r. spectra of the two compounds could be differentiated in the 950—1 000 cm^{-1} region, absorptions were too weak and complex for characterising the nature of the double bond in the substituent.[7] In the ^1H n.m.r. spectrum, compound (A) showed a doublet, δ 3.27 (2 H, *J* 6 Hz), assigned to $H_2C{=}CH{\cdot}CH_2S{-}$; in that of (B), this signal was absent, but a doublet, δ 1.75 (3 H, *J* 5 Hz) indicated the presence of an additional methyl group, as $CH_3{\cdot}CH{=}CHS{-}$, indicating (A) to be the 7-allylthio-compound (XI) and (B) the 7-propenylthio-compound (XII).

No interconversion between (XI) and (XII) occurred on heating in acetonitrile in the presence of acetic acid, and the u.v. and ^1H n.m.r. spectra of the reagent recovered by distillation at the end of the original reaction showed no sign of rearrangement of the allyl into the propenyl group, a rearrangement that has been observed to occur on prolonged treatment under strongly basic conditions.[6] The rearrangement must occur at the sulphonium salt stage, therefore. Loss of the allyl group from this ion (1; Scheme 2), reasonably by heterolytic scission to give the stabilised allyl cation, would result in the allylthio-derivative (XI). The allylic methylene



(VIII) R = Et
(IX) R = Pr^n
(X) R = Bu^t
(XI) R = $CH_2{\cdot}CH{:}CH_2$
(XII) R = $CH{:}CH{\cdot}CH_3$
(XIII) R = Pr^i
(XIV) R = cyclopentyl
(XV) R = cyclohexyl
(XVI) R = Ph
(XVII) R = CH_2Ph
(XVIII) R = 2-HO·C_6H_4
(XXI) R = Bu^n



SCHEME 2

[6] D. S. Tarbell and W. E. Lovett, *J. Amer. Chem. Soc.*, 1956, **78**, 2259.
[7] N. Sheppard, *Trans. Faraday Soc.*, 1950, **46**, 429.

group adjacent to the positively charged sulphonium sulphur atom in the ion (1) must be sufficiently acidic that a proton can be removed by acetate ion as base to give the ylide [(2) ⟷ (2a)]; protonation by the acetic acid at C-1 of the ylide would regenerate the original sulphonium salt, but protonation at C-3, favoured as being remote from the positively charged sulphonium sulphur atom, would generate a sulphonium ion bearing a propenyl group (3). Loss of the allyl group by heterolytic bond scission would yield the propenylthio-derivative (XII). There was no evidence of the involvement of the ion (2a) in a Sommelet rearrangement, which would have resulted in the formation of a 7(*S*)-(hexa-1,5-dienyl)thio-substituent.

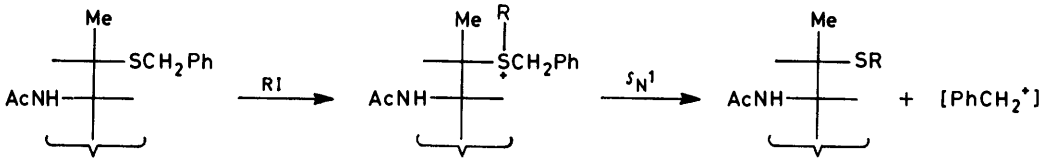
The reduced nucleophilic reactivity of the dialkyl sulphide sulphur atom, noted above, which results in the marked decrease in yield of the 7-alkylthio-amide as the size of the alkyl substituent increases, should be ameliorated by the use of an alkyl methyl sulphide. Methyl n-propyl sulphide gave the n-propylthio-compound (IX) in 29.5% yield, compared with 18.5% from di-n-propyl sulphide, accompanied by an 11.5% yield of the methylthio-compound (VII); the competitive ring-opening by acetate ion was still the major reaction. With methyl isopropyl sulphide, the 7-isopropylthio-compound (XIII) was formed in 27.4% yield. The reaction could be extended to cycloalkyl methyl sulphides. Thus, cyclopentyl and cyclohexyl methyl sulphides gave the 7-cyclopentylthio- (XIV) and 7-cyclohexylthio- (XV) compounds in yields of 32.4 and 30.5%, respectively.

Reaction with t-butyl methyl sulphide gave no 7-t-butylthio-derivative but, instead, a 78.5% yield of the 7-methylthio-compound (VII), the only other product being the 7-acetate. This, together with the results of the diallyl sulphide reaction, indicated that appropriate substituents exerting less steric hindrance about the sulphide sulphur atom than t-butyl, but capable of yielding stabilised carbocations by heterolytic scission of the carbon–sulphonium sulphur bond, could be of utility in the generation of particular thio-substituents in this reaction.

Exemplification of this was provided by the following reactions: benzyl phenyl sulphide gave the 7-phenylthio-compound (XVI) in 69.5% yield, dibenzyl sulphide gave the 7-benzylthio-compound (XVII) in 63.5% yield, and allyl *o*-hydroxyphenyl sulphide gave the 7-(*o*-hydroxyphenyl)thio-compound (XVIII) in 61.8% yield.

In furtherance of the concept of the utilisation of an intermediate sulphonium salt containing a substituent subject to ready heterolytic bond scission, the 7-benzylthio-compound (XVII) appeared to be an attractive starting material. *S*-Alkylation to form a sulphonium salt at C-7, in which the newly introduced substituent would not be capable of carbocation stabilisation, should allow the conversion of the benzylthio- into the desired substituted-thio-compound. It was known [8] that the methyl thioglycosidic group of the penta-acetate of methyl α-thiolincosaminide [1] is not subject to sulphonium salt formation in the presence of alkyl halides or sulphonates and, therefore, should not interfere with *S*-alkylation at C-7 (Scheme 3). However, the benzylthio-compound was recovered quantitatively after prolonged treatment in acetonitrile with an excess of methyl iodide. Further examples of this hindrance to the approach of a reagent experienced by the sulphur atom of a 7-alkylthio-substituent are discussed later.

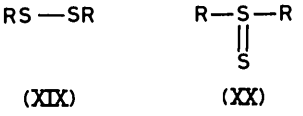
The reduced nucleophilic reactivity of the higher symmetrical dialkyl sulphides, relative to acetate ion, leading to low yields of the bulkier 7-alkylthio-compounds, has been alleviated in part by reducing the steric hindrance about the sulphide sulphur atom by the use of mixed alkyl methyl sulphides; the reaction was



SCHEME 3

complicated by the co-production of the methylthio-derivative, however, which reduced the yield of desired product from the sulphonium salt intermediate. An alternative manner of reducing this steric hindrance about the sulphur atom appeared to be the introduction of a second sulphur atom between the alkyl groups.

Both di- and poly-sulphides are considered to exist in the linear form (XIX), and not in the branched form (XX), on the basis of evidence from physical measurements and radioactive sulphur exchange reactions; this evidence has been reviewed.[9] In order that a symmetrical dialkyl disulphide should react to yield the 7-alkylthio-derivative, it is necessary that (i) the disulphide



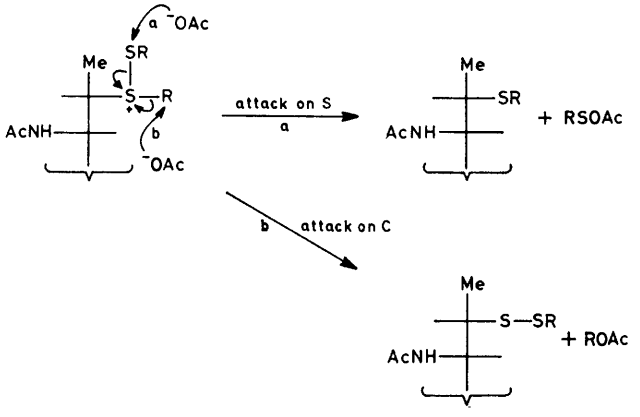
(XIX) (XX)

sulphur atom should be reactive nucleophilically relative to the acetate ion and (ii) the dialkyl(alkylthio)-sulphonium salt formed should collapse because of nucleophilic attack on the sulphenyl sulphur atom (Scheme 4, route a), rather than by attack on the carbon atom α to the sulphonium sulphur atom, which would yield an alkyldithio-derivative (route b).

[8] B. Bannister, unpublished results.

[9] O. Foss, *Acta Chem. Scand.*, 1950, **4**, 404; O. Foss, in 'Organic Sulfur Compounds,' ed. N. Kharasch, Pergamon, New York, 1961, vol. 1, ch. 8, p. 73.

The literature contains some information concerning both these points, but from a mechanistic, rather than a synthetic, aspect. The alkylation of dialkyl disulphides by alkyl halides received little attention after the early work of Hilditch and Smiles,[10] who found the reaction to



SCHEME 4

be slow at room temperature, and to proceed with the ultimate formation of a trialkylsulphonium salt. In the presence of mercury(II) iodide, the reaction rate was increased, and the double salt $Et_2\overset{+}{S}{\cdot}SEt,HgI_3^-$ was isolated from the reaction between ethyl iodide and diethyl disulphide. The reactivity of alkyl halides towards sulphides has been shown to be greater than towards disulphides,[11] and diethyl sulphide is methylated by methyl fluorosulphate one hundred times more rapidly than is diethyl disulphide.[12] However, Helmkamp and his co-workers [13] found that trimethyloxonium trinitrobenzenesulphonate effects the ready alkylation of dimethyl and diethyl disulphides, giving the crystalline dialkyl(alkylthio)sulphonium salts. They also showed that these salts react in solution with iodide ion to give the dialkyl sulphide, dialkyl disulphide, and iodine, and suggested that the sulphur–sulphur bond underwent cleavage as a consequence of nucleophilic attack of iodide ion.[13] From a study of the ^1H n.m.r. spectra of dimethyl sulphide, $MeS–\overset{+}{S}Me_2$, and mixtures of the two, Kice and Favstritsky [14] showed that an exchange reaction between the two takes place extremely rapidly, implying that $Me_2\overset{+}{S}–$ is an excellent leaving group, being expelled as the neutral dimethyl sulphide following nucleophilic attack at the sulphenyl sulphur atom. Furthermore, they calculated that this displacement at the sulphenyl sulphur atom occurs at least 10^9—10^{10} times faster than the analogous displacement on sp^3 carbon in the reaction between methyl iodide and dimethyl sulphide. This implies that, if the dialkyl(alkylthio)sulphonium salt in Scheme 4 is formed in the reaction with the protonated activated epimine, the collapse by route a should be preferred greatly to that by route b.

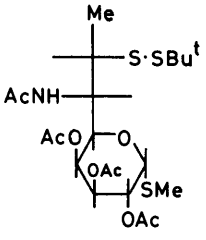
The applicability of disulphides to the introduction of the 7-alkylthio-substituent was investigated by using dimethyl disulphide under the same conditions as used with the tetra-acetylepimine and sulphides. Two products were formed, and were separated by counter-current distribution. The minor product was the 7-acetate, and the second was the desired 7-methylthio-compound (VII), formed in 82% yield; *cf.* the essentially quantitative yield with dimethyl sulphide. With diethyl disulphide, the 7-ethylthio-compound (VIII) was formed in 72% yield; *cf.* 61% from the sulphide. Di-isopropyl disulphide gave the 7-isopropylthio-compound (XIII) in 53% yield; *cf.* 27% from methyl isopropyl sulphide; di-n-butyl disulphide gave the 7-n-butylthio-compound (XXI) in 50% yield, and dibenzyl disulphide gave the 7-benzylthio-compound (XVII) in the same yield (63%) as from dibenzyl sulphide. Thus, disulphides are useful for the introduction of alkylthio-substituents in those cases in which bulky substituents in sulphides reduce their nucleophilic reactivity markedly. In none of these cases was there evidence for the formation of the alkyldithio-compound.

G.l.c. of the crude reaction mixture from the tetra-acetylepimine and diethyl sulphide had demonstrated the presence of ethyl acetate; similar examination of the crude reaction mixture from the diethyl disulphide reaction revealed, as volatile components, only acetic acid and diethyl disulphide, with no indication of ethylsulphenyl acetate. However, it has been shown [15] that sulphenyl carboxylates undergo spontaneous decomposition, generating the radicals $R^1S\cdot$ and $R^2CO_2\cdot$; on heating at 150 °C, anthraquinon-1-ylsulphenyl acetate gave dianthraquinon-1-yl disulphide and acetic acid. In the present case, such decomposition would yield starting materials.

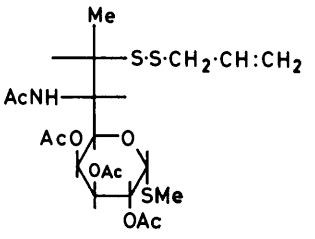
The reaction between the tetra-acetylepimine and di-t-butyl disulphide gave two products, separated by counter-current distribution, the major being the 7-acetate. The second product was not identical with the known 7-t-butylthio-compound (X); its ^1H n.m.r. spectrum was fully consonant with this structure, but the two spectra were not superimposable. The mass spectrum showed ions at *m/e* 525 (M^+) (32 m.u. higher than the 7-t-butylthio-compound), 469 ($M^+ - Bu^t + H$), 436 ($M^+ - SBu^t$), and 404 ($M^+ - S{\cdot}Bu^t$). Elemental analysis and the u.v. spectrum [16] [intense end-absorption and $\lambda_{max.}$ 245sh nm (ε 425)] confirmed the presence of the disulphide linkage, and showed the product to be the 7-t-butyldithio-derivative (XXII). There was no indication of the formation of the t-butylthio-compound.

[10] T. P. Hilditch and S. Smiles, *J. Chem. Soc.*, 1907, **91**, 1394.
[11] M. L. Selker and A. R. Kemp, *Ind. and Eng. Chem.*, 1944, **36**, 16.
[12] R. F. Hudson and F. Filippini, *J.C.S. Chem. Comm.*, 1972, 726.
[13] G. K. Helmkamp, H. N. Cassey, B. A. Olsen, and D. J. Pettitt, *J. Org. Chem.*, 1965, **30**, 933.
[14] K. L. Kice and N. A. Favstritsky, *J. Amer. Chem. Soc.*, 1969, **91**, 1751.
[15] R. E. Putnam and W. H. Sharkey, *J. Amer. Chem. Soc.*, 1957, **79**, 6526.
[16] R. C. Passerini, in 'Organic Sulfur Compounds,' ed. N. Kharasch, Pergamon, New York, 1961, vol. 1, ch. 7, p. 57.

Since the dibenzyl disulphide reaction gave the 7-benzylthio-compound with no indication of disulphide formation, the formation of (XXII) from the intermediate dialkyl(alkylthio)sulphonium salt could not be the consequence simply of the ability of the t-butylsulphonium–sulphur bond to undergo heterolytic scission to



(XXII)



(XXIII)

yield the stabilised t-butyl cation. Construction with space-filling molecular models of the sulphonium salt derived from dibenzyl disulphide revealed no steric problems. However, attempted construction of the corresponding sulphonium salt derived from di-t-butyl disulphide revealed extreme crowding between the carbohydrate side-chain and the t-butyl group. Furthermore, a comparison of the rates of attack of nucleophiles on neopentyl halides and di-t-butyl disulphide has demonstrated that the neopentyl methylene group and the sulphur atom in the t-butylthio-group are subject to similar hindrance to the approach of nucleophiles.[17] The exclusive formation of the t-butyldithio-compound from di-t-butyl disulphide thus appears to be the consequence of the presence concomitantly of three features in the dialkyl(alkylthio)sulphonium salt: (i) a substituent on the sulphonium sulphur atom capable of yielding a stabilised carbocation by heterolytic bond scission, (ii) extreme crowding of this substituent with the side-chain to promote the heterolysis by relief of steric strain, and (iii) a substituent on the sulphenyl sulphur atom which hinders sterically the approach of a nucleophile to this site, thus reducing drastically the proclivity of this sulphur–sulphur bond towards cleavage to sulphide.

The reaction with diallyl disulphide was investigated also. The product was a complex mixture (t.l.c.); three products were isolated by counter-current distribution, but the fate of only 62% of the tetra-acetylepimine was determined, the remainder being an intractable mixture of low polarity. Of highest polarity (K 0.26) was the 7-acetoxy-compound, formed in 29.5% yield; the 7-allylthio-compound (XI) was present (K 2.03) in 13% yield. Redistribution of the ill-separated material of low polarity in a more polar system again left unresolved a broad peak of high K value, but yielded a pure material (K 1.87). The ^{1}H n.m.r. spectrum of this component was similar to that of the allylthio-derivative (XI), but its u.v. spectrum showed high end-absorption with a shoulder at 245 nm (ε 723), indicative of the presence of a disulphide linkage. This was confirmed by elemental analysis and the mass spectrum; no molecular ion was detected, but major fragment ions were present at m/e 468 ($M^+ - CH_2CH{=}CH_2$), 436 ($M^+ - SCH_2CH{=}CH_2$), and 404 ($M^+ - SSCH_2CH{=}CH_2$), showing this product to have the structure (XXIII). This material was formed in 19.7% yield.

Of the three requirements in the intermediate dialkyl(alkylthio)sulphonium salt for disulphide formation discussed in the case of the t-butyldithio-derivative, only that of the stabilisation of a carbocation is present in this instance, for the allyl groups are neither hindered by the carbohydrate side-chain nor hinder the approach of a nucleophile to the sulphenyl sulphur atom. Hence, a totally different cause must be responsible for the formation of the allyldithio-compound which, unlike the t-butyldithio-compound, is not formed to the exclusion of the monothio-derivative.

Höfle and Baldwin[18] have presented evidence that certain α-substituted allylic disulphides rearrange thermally to more stable isomers by a [2,3] sigmatropic shift through an intermediate thiosulphoxide, which can be trapped by desulphurisation. Similar intermediates have been proposed in racemisations and isomerisations of allylic di- and poly-sulphides by Barnard and his co-workers.[19]

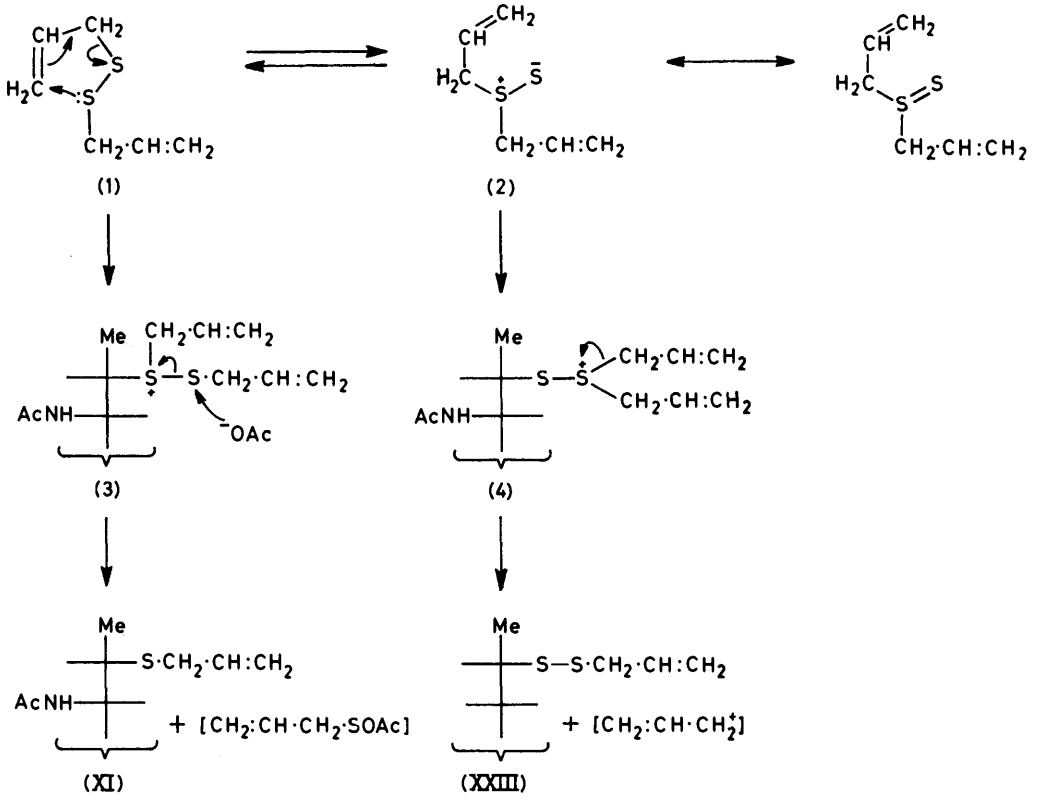
Utilising this concept, an explanation of the results observed with diallyl disulphide is offered (Scheme 5). A [2,3] sigmatropic shift in the reagent (1) would generate an equilibrium involving the thiosulphoxide (2). Reaction of (1) with the protonated activated epimine would yield the alkylallyl(allylthio)sulphonium salt (3), which would generate the 7-allylthio-derivative (XI) by nucleophilic attack on the sulphenyl sulphur atom. The thiosulphoxide (2) would be more nucleophilic (and more reactive nucleophilically) than the linear (1) because of the residence of a negative charge on the terminal branched sulphide sulphur atom in one canonical form. Thus, attack at C-7 of the protonated tetra-acetylepimine would yield the diallyl(alkylthio)sulphonium salt (4). This salt must collapse to the allyldithio-derivative (XXIII) by heterolytic scission of one of the diallylsulphonium bonds; again, nucleophilic attack at the sulphenyl sulphur atom in the salt (4) must be hindered by the carbohydrate side-chain.

In order to investigate further the steric hindrance around the sulphur-substituent at C-7, a simple 7-alkyldithio-derivative of the substrate was required. The desulphurisation of polysulphides by phosphines has been studied extensively by Harpp and his co-workers,[20] *inter alia*, and it has been established that it is accompanied by inversion of configuration of one of the sulphide residues, thus providing information about which disulphide sulphur atom was the electrophile.

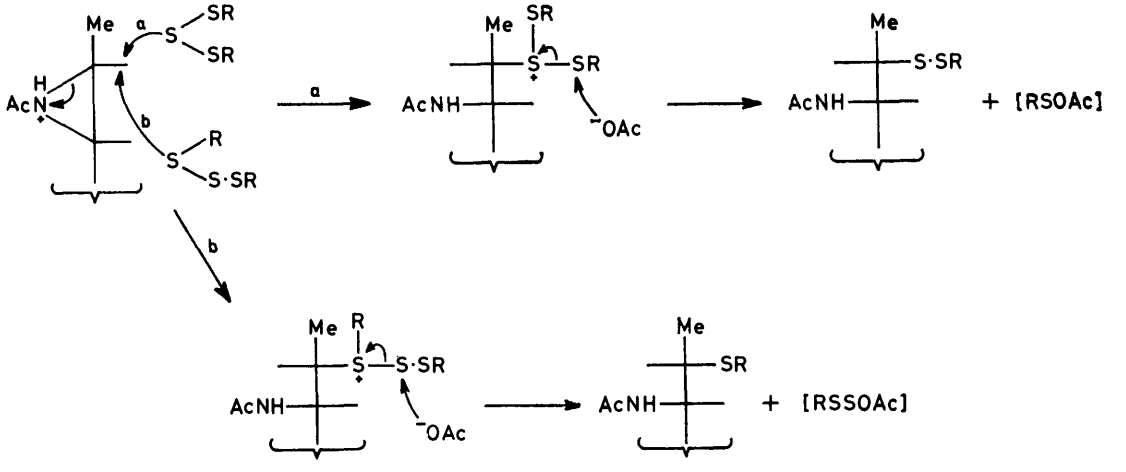
Little is recorded in the literature of the products of *S*-alkylation of a trisulphide but if, in a symmetrical dialkyl trisulphide, the central sulphur atom were the

[17] A. Fava and A. Iliceto, *J. Amer. Chem. Soc.*, 1958, **80**, 3478.
[18] G. Höfle and J. E. Baldwin, *J. Amer. Chem. Soc.*, 1971, **93**, 6307.
[19] D. Barnard, T. H. Houseman, M. Porter, and B. K. Tidd, *J.C.S. Chem. Comm.*, 1969, 371.
[20] D. N. Harpp and T. G. Gleason, *J. Amer. Chem. Soc.*, 1971, **93**, 2437, and references cited therein.

more reactive nucleophilically, then reaction with the protonated tetra-acetylepimine would yield an alkyl-(dialkylthio)sulphonium salt; nucleophilic attack on either of the equivalent sulphenyl sulphur atoms would then yield the 7-alkyldithio-compound (Scheme 6, sulphenyl sulphur atom, to give the 7-alkylthio-derivative (route b). From the reaction with diethyl trisulphide, no ethyldithio-compound was detected; the 7-acetate and 7-ethylthio-compounds were isolated in 37 and 55% yields, respectively, showing the terminal



SCHEME 5



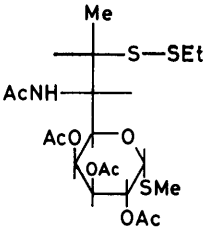
SCHEME 6

route a). However, if the inductive effect of the alkyl substituents were to render the terminal sulphur atoms of the trisulphide the more nucleophilic, the dialkyl-(alkyldithio)sulphonium salt produced would be expected to collapse, following nucleophilic attack on the central sulphur atoms of a trisulphide to be the more reactive nucleophilically.

For the synthesis of the desired 7-ethyldithio-compound, therefore, the reagent ethyl t-butyl disulphide was used. Only a low yield of the ethyldithio-compound

could be expected, owing to both the greater steric hindrance about the t-butyl than the ethyl sulphide sulphur atom in the reagent, and the small degree of hindrance exerted by the ethyl group about the sulphenyl sulphur atom in the desired intermediate dialkyl(alkylthio)-sulphonium salt.

Counter-current distribution of the crude product gave four well-resolved peaks (K 0.23, 1.43, 2.57, and 6.15). Three products were identified as the 7-acetate (K 0.23; 35.8% yield), the 7-ethylthio-compound (VIII) (K 1.43; 36.2% yield), and the 7-t-butyldithio-compound (XXII) (K 6.15; 3.7% yield). These materials, as isolated from the counter-current distribution peaks, were homogeneous by g.l.c.; the material of K 2.57, however, gave two peaks of retention times 9 and 14 min, in the ratio *ca.* 70 : 30. G.l.c.–mass spectrometric examination of this binary mixture gave ions for the major component at m/e 493 (M^+), 436 ($M^+ - Bu^t$), and 404 ($M^+ - SBu^t$), indicating it to be the 7-t-butylthio-derivative (X); co-injection of the material of K 2.57 and authentic (X) gave an increased intensity of the 9 min peak. The minor component gave ions at m/e 497 (M^+), 436 ($M^+ -$ SEt), and 404 ($M^+ -$ SSEt), and appeared, therefore,



(XXIV)

to be the desired 7-ethyldithio-compound (XXIV). In added support of this structure, the mixture of the two components gave a u.v. spectrum of high end-absorption with a shoulder at 245 nm ($E^{1\%}_{1cm}$ cm 3.6). No liquid chromatographic system was found which distinguished between these two compounds, and their separate isolation was not achieved.

Treatment of the mixture of the 7-t-butylthio- and 7-ethyldithio-compounds in benzene solution with an excess of tris(diethylamino)phosphine under reflux overnight gave a mixture of two materials, separable by g.l.c. of retention times 8.5 and 9.0 min, the 14 min peak having disappeared. The area of the 8.5 min peak was enhanced by the co-injection of the 7(*S*)-ethylthio-tetra-acetate, indicating that the desired desulphurisation of the dithio- to the thio-derivative had occurred. After chromatography to remove the excess of reagent and the tris(diethylamino)phosphine sulphide, counter-current distribution gave two materials, K 1.26 and 2.13, identified as the 7-ethylthio-compound (VIII) and the 7-t-butylthio-compound (X), obtained in 1.2 and 4.2% yields from the tetra-acetylepimine.

Since the 7-ethyldithio-compound (XXIV) gave rise to the 7-ethylthio-compound (VIII) of retained configuration [(7*S*)], the sulphide-sulphur atom of the disulphide adjacent to the carbohydrate side-chain must be too hindered to allow the nucleophilic attack of the phosphine, and the desulphurisation reaction must involve the formation of the (7*S*)-7-thiolate anion (Scheme 7).

The course of the reaction between the protonated tetra-acetylepimine and t-butyl ethyl disulphide may be shown as in Scheme 8. The formation of the 7-t-butyldithio-compound (XXII), even in low yield, from the sulphonium ion (1) provides further evidence for the hindrance to the approach of a nucleophile to the sulphenyl sulphur atom occasioned by the t-butyl group. Similarly, the formation of the 7-t-butylthio-compound (X) from the sulphonium ion (2) as the major product of the collapse of this ion, despite the ability of the t-butyl group to generate the t-butyl cation and of the overcrowding of this group in the ion, which leads in part to the formation of the desired 7-ethyldithio-compound (XXIV), is indicative of the proclivity of the sulphonium–sulphenyl sulphur–sulphur bond to undergo cleavage. The formation of the 7-ethylthio-compound (VIII) from the ion (1) as the major product of collapse is surprising, since it does not reflect a sulphenyl sulphur atom in this ion which is highly hindered to the approach of a nucleophile. Instead, it suggests that the sulphonium ion (1) collapses by the heterolytic scission of the sulphonium–sulphenyl sulphur–sulphur bond with formation of the sulphide and of the sulphenium cation Bu^tS^+, a course which is not adopted when the sulphonium sulphur atom also bears a t-butyl substituent.

Sulphenium cations have been postulated as intermediates in a variety of addition reactions of sulphenyl halides, and also in the cleavage of disulphides under acidic conditions.[21,22] Kice,[23] however, considers that the cleavage of the sulphur–sulphur bond of disulphides is the result of sequential electrophilic and nucleophilic attack in general, but gives two examples of sulphur–sulphur bond cleavage in which nucleophilic attack is not involved, and heterolytic bond scission does occur. Although the examples are not of dialkyl(alkylthio)-sulphonium salts but of the conjugate acids of certain arylsulphinyl sulphones and of Bunte salts, they share two features of interest with the sulphonium ion (1; Scheme 8): both allow for the internal stabilisation of a sulphur-containing cation and, in place of the steric hindrance to nucleophilic attack about the sulphenyl sulphur atom in (1), they substitute the feature of the known reduced rate of nucleophilic attack on a tetra-co-ordinate, as compared with a dico-ordinate, sulphur atom.[23]

In the discussions of the collapse of the various sulphonium salt intermediates above, involving nucleophilic

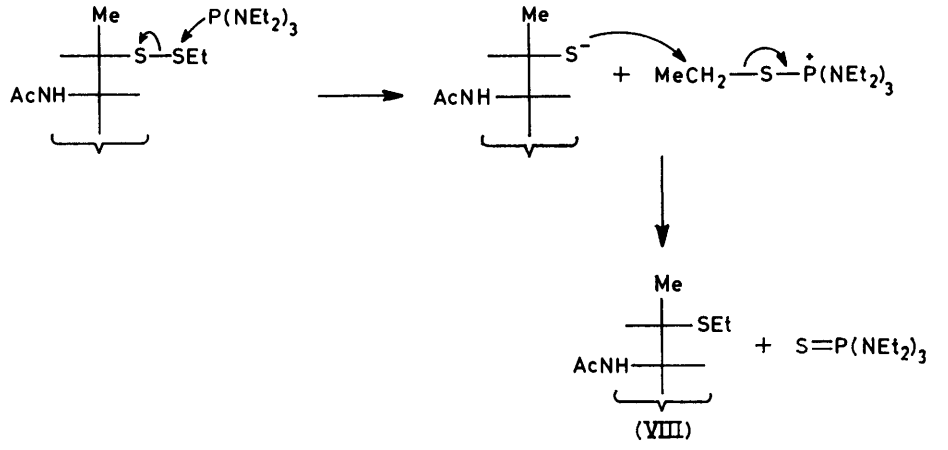
[21] N. Kharasch, in 'Organic Sulfur Compounds,' ed. N. Kharasch, Pergamon, New York, 1961, vol. 1, ch. 32, p. 375, and references cited therein.

[22] G. K. Helmkamp, D. C. Owsley, W. M. Barnes, and H. N. Cassey, *J. Amer. Chem. Soc.*, 1968, **90**, 1635, and references cited therein.

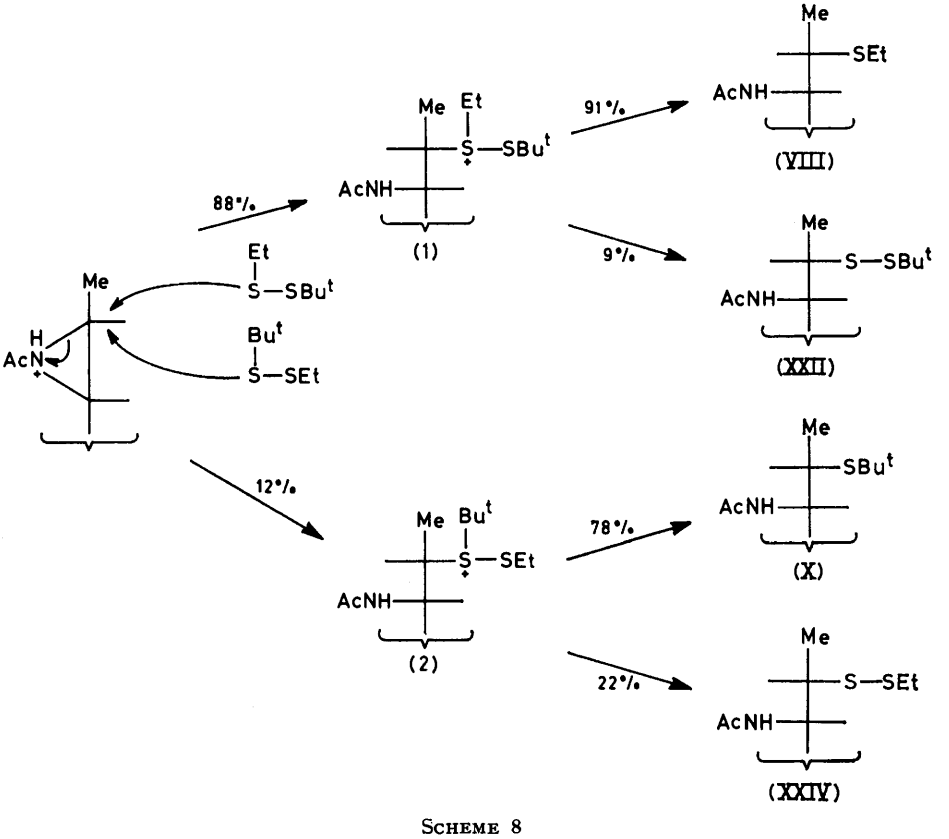
[23] K. L. Kice, *Accounts Chem. Res.*, 1968, **1**, 58.

attack on either a carbon atom or a sulphenyl sulphur atom, the nucleophilic reagent has been indicated to be acetate ion, generated by the protonation of the tetra-acetylepimine, and not the acetic acid itself, present in excess of this requirement. This is based upon the results of sodium acetate to form 2-(methylthio)cyclo-octyl acetate, the salt was recovered unchanged from attempted reaction in the presence of acetic acid.

However, the question of whether the initial nucleophilic attack is by acetate ion, to yield ROAc from the



SCHEME 7



SCHEME 8

of Helmkamp and his co-workers,[24] who found that, whereas *S*-methyl-8-thiabicyclo[6.1.0]nonanium 2,4,6-trinitrobenzenesulphonate underwent reaction in the presence sulphonium salt and RSOAc from the thiosulphonium salt, or by the excess of reagent to yield the secondary salts R_3S^+ from the former and $(RS)_2\overset{+}{S}R$ from the latter, followed by ultimate attack on these salts by acetate ion, has not been answered.

[24] D. C. Owsley, G. K. Helmkamp, and S. N. Spurlock, *J. Amer. Chem. Soc.*, 1969, **91**, 3606.

After the completion of this portion of the investigation of the reactions between sulphides and the tetra-acetylepimine, a report appeared [25] of an analogous *S*-alkylation of methionine and *S*-methylcysteine by reaction in neutral aqueous solution with *N*-ethoxycarbonyl- and *N*-aminocarbonyl-aziridine.

The conversion of the acetylated carbohydrate derivatives described in this paper into the (7*S*)-7-(substituted thio)-7-deoxylincomycins, and the biological properties of these analogues of lincomycin, will be reported elsewhere.

EXPERIMENTAL

General experimental procedures have been described previously.[2] I.r. spectra were obtained with a Perkin-Elmer 421 grating spectrometer, for Nujol mulls. U.v. spectra were measured for solutions in 95% ethanol with a Carey 15 recording spectrometer. ^{1}H N.m.r. spectra were measured at 60 or 100 MHz with a Varian A60A or XL-100-15 spectrometer (tetramethylsilane as internal reference) for solutions in $CDCl_3$, unless stated otherwise. Mass spectra were recorded with an Atlas CH-4 spectrometer (direct inlet) at 70 eV. G.l.c.–mass spectrometric studies were performed with an LKB-9000 instrument. Sulphides were obtained commercially, except where noted otherwise, and were redistilled before use. Commercially available disulphides were washed with base to remove hydrogen iodide and were redistilled before use. Counter-current distribution results were analysed by determination of weights of residues of samples taken from equal volumes of upper and lower phases from every tenth tube of the train, after 500 transfers. If separations were incomplete, the higher number of transfers utilised for separation is indicated. Counter-current systems used were 95% ethanol–water–ethyl acetate–cyclohexane in the proportions (v/v) 1 : 1 : 1 : 0.5 (system A), 1 : 1 : 1 : 2 (system B), 1 : 1 : 1 : 3 (system C), 1 : 1 : 1 : 5 (system D), and 1 : 1 : 0.5 : 3 (system E). 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 Sulphides*

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-[(2-*hydroxyethyl*)*thio*]-1-*thio*-α-*lincosaminide* (VI) *and Methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*methylthio*-1-*thio*-α-*lincosaminide* (VII).—Acetic acid (5.25 g, 86.8 mmol) was added to a solution of the tetra-acetylepimine[2] (5.0 g, 12.4 mmol) in 2-hydroxyethyl methyl sulphide (46 g, 500 mmol) in an oil-bath at 100 °C, and heating was continued under anhydrous conditions for 6 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) demonstrated the absence of the tetra-acetylepimine (R_F 0.68) and the presence of two minor products (R_F 0.53 and 0.45) and a major product (R_F 0.29). Counter-current distribution (system A) gave three well-separated peaks, *K* 0.97, 1.55, and 2.90. Isolation of the major component (*K* 0.97) gave a solid (2.96 g) which separated from ethyl acetate–Skellysolve B as needles, shown to be the 7(S)-[(2-*hydroxyethyl*)*thio*]-*tetra-acetate* (VI), m.p. 226—228°, $[\alpha]_D$ + 185° (*c* 1.01 in $CHCl_3$), δ 1.32 (3 H, d, *J* 7 Hz, 8-H_3), 1.95—2.15 (15 H, 5s, 3 OAc + NAc + SMe), 2.88 (2 H, t, *J* 6 Hz, O·CH_2·CH_2·S), and 3.85br (2 H, O·CH_2·CH_2·S) {in [$^2H_5$]pyridine the broad O·CH_2·CH_2·S signal appeared at δ 3.94, and became a sharp triplet (*J* 6 Hz) on addition of D_2O} (Found: C, 47.2; H, 6.8; N, 2.9; S, 13.2. $C_{19}H_{31}N_2O_9S_2$ requires C, 47.4; H, 6.5; N, 2.9; S, 13.3%).

Isolation of the minor component, *K* 1.55, gave a solid (420 mg) which separated from ethyl acetate as needles, m.p. 312—313°, identified as the 7(*S*)-penta-acetate[2] (IV).

The second minor component (*K* 2.90; 890 mg) separated from ethyl acetate–Skellysolve B as rods, shown to be the 7(S)-*methylthio-tetra-acetate* (VII), m.p. 225—226°, $[\alpha]_D$ +225° (*c* 0.99 in $CHCl_3$), δ 1.32 (3 H, d, *J* 7 Hz, 8-H_3), and 1.95—2.15 (18 H, 6s) (Found: C, 47.9; H, 6.5; N, 3.2; S, 14.3. $C_{18}H_{29}NO_8S_2$ requires C, 47.9; H, 6.5; N, 3.1; S, 14.2%).

From the reaction between the tetra-acetylepimine (5.0 g) and dimethyl sulphide (50 ml) in the presence of acetic acid (5.25 g) in a sealed tube in a steam-bath for 6 h, followed by removal of volatile materials and direct crystallisation from ethyl acetate–Skellysolve B, was isolated an essentially quantitative yield (5.5 g) of the 7(*S*)-methylthio-compound (VII). With the reagent methyl t-butyl sulphide under the same conditions, the 7(*S*)-methylthio-compound resulted in 78.5% yield (4.40 g).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*ethylthio*-1-*thio*-α-*lincosaminide* (VIII).—Reaction under the same conditions with diethyl sulphide gave a solid showing a major zone on t.l.c. in acetone–Skellysolve B (1 : 1), R_F 0.56, and a minor zone (R_F 0.45) coincident with the penta-acetate (IV). Counter-current distribution (system B) gave symmetrical peaks of *K* 0.39 and 1.85. Isolation of the more polar component gave the penta-acetate (IV) (3.5 g); the *K* 1.85 material (3.5 g) separated from ethyl acetate–Skellysolve B in needles, m.p. 236—237°, $[\alpha]_D$ +215° (*c* 0.95 in $CHCl_3$), and was shown to be the 7(S)-7-*ethylthio-tetra-acetate* (VIII), δ 1.23 (2 H, t, *J* 7 Hz, S·CH_2·CH_3), 1.90—2.13 (15 H, 5s, 3 OAc + SMe + NAc), and 2.60 (2 H, q, *J* 7 Hz, S·CH_2·CH_3), *m/e* 465 (M^+), 418 (M^+ − SMe), and 376 (M^+ − MeCHSEt) (Found: C, 49.2; H, 6.5; N, 3.1; S, 13.7. $C_{19}H_{31}NO_8S_2$ requires C, 49.0; H, 6.7; N, 3.0; S, 13.8%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*propylthio*-1-*thio*-α-*lincosaminide* (IX).—Reaction of the tetra-acetylepimine (10.0 g) in di-n-propyl sulphide (100 ml) gave, after counter-current distribution (system B), the penta-acetate (9.25 g) and the 7(S)-7-*propylthio-tetra-acetate* (IX) (*K* 3.10; 2.20 g, 18.5%), needles from ethyl acetate–Skellysolve B, m.p. 259—261°, $[\alpha]_D$ +203° (*c* 0.96 in $CHCl_3$), δ 1.00 (3 H, t, *J* 7 Hz, CH_3·CH_2·CH_2·S), 1.64 (2 H, m, MeCH_2·CH_2·S), and 2.55 (2 H, t, *J* 7 Hz, MeCH_2·CH_2·S), *m/e* 479 (M^+) and 432 (M^+ − SMe) (Found: C, 49.9; H, 7.0; N, 3.0; S, 13.4. $C_{20}H_{33}NO_8S_2$ requires C, 50.1; H, 6.9; N, 2.9; S, 13.4%).

Replacement of the di-n-propyl sulphide by methyl n-propyl sulphide gave the 7(*S*)-propylthio-derivative (3.48 g, 29.5%), together with the 7(*S*)-methylthio-compound (VII) (1.29 g, 11.5%) and the penta-acetate (IV).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*isopropylthio*-1-*thio*-α-*lincosaminide* (XIII).—Reaction of the tetra-acetylepimine (10.0 g) with methyl isopropyl sulphide (100 ml) followed by counter-current distribution (system B) gave the penta-acetate (IV), the 7(*S*)-methylthio-compound (VII) (3.29 g), and the 7(S)-7-*isopropylthio-tetra-*

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

[25] P. A. Capps and A. R. Jones, *J.C.S. Chem. Comm.*, 1974, 320.

acetate (XIII) (3.26 g, 27.4%), needles from ethyl acetate–Skellysolve B, m.p. 274.5—275.5°, $[\alpha]_D$ +200°, δ 1.32 [6 H, d, *J* 7 Hz, $(CH_3)_2CHS$] and 3.20 (1 H, q, *J* 4 Hz, Me_2CHS), *m/e* 479 (M^+), 436 (M^+ — Pr^i), 432 (M^+ — SMe), and 405 (M^+ — SPr^i + H) (Found: C, 49.8; H, 6.95; N, 2.8; S, 13.60%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*t*-*butylthio*-1-*thio*-α-*lincosaminide* (X).—Reaction of the tetra-acetylepimine (10.0 g) with di-t-butyl sulphide (100 ml) followed by counter-current distribution (system C) gave the penta-acetate (IV) (*K* 0.24; 10.8 g) and the 7(S)-7-*t*-*butylthio*-*tetra*-*acetate* (X) (*K* 2.38; 306 mg, 2.5%), needles from ethyl acetate, m.p. 272—273°, $[\alpha]_D$ +187° (*c* 0.64 in $CHCl_3$), δ 1.37 [9 H, s, $(CH_3)_3CS$)], *m/e* 478 (M^+ — Me), 446 (M^+ — SMe), 435 (M^+ — Bu^t), 388 (M^+ — SMe — Bu^t + H), and 346 (M^+ — SMe — SBu^t + H) (Found: C, 51.2; H, 7.3; N, 2.95; S, 13.3. $C_{21}H_{35}NO_8S_2$ requires C, 51.2; H, 7.15; N, 2.8; S, 13.0%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*cyclopentylthio*-7-*deoxy*-1-*thio*-α-*lincosaminide* (XIV).—Reaction of the tetra-acetylepimine (10.0 g) and cyclopentyl methyl sulphide (100 g) followed by counter-current distribution (system C) gave the penta-acetate (*K* 0.25), the 7(*S*)-methylthio-derivative (VII) (*K* 0.92, 1.26 g) and the 7(S)-*cyclopentylthio*-*tetra*-*acetate* (XIV) (*K* 0.92; 4.05 g, 32.4%), needles from ethyl acetate, m.p. 265—265.5°, $[\alpha]_D$ +187° (*c* 0.99 in $CHCl_3$), δ 1.68 (8 H, m, CH_2 of cyclopentyl) and 3.15 (1 H, m, >*CH*S), *m/e* 505 (M^+), 458 (M^+ — SMe), and 328 (M^+ — SMe — $MeCHSC_5H_9$ + H) (Found: C, 52.1; H, 6.9; N, 2.7; S, 12.7. $C_{22}H_{35}NO_8S_2$ requires C, 52.25; H, 7.0; N, 2.8; S, 12.7%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*cyclohexylthio*-7-*deoxy*-1-*thio*-α-*lincosaminide* (XV).—Using cyclohexyl methyl sulphide, the reaction gave, after counter-current distribution (system D), the penta-acetate (*K* 0.15; 2.74 g), the 7(*S*)-methylthio-derivative (VII) (*K* 0.57; 840 mg), and the 7(S)-7-*cyclohexylthio*-*tetra*-*acetate* (XV) (*K* 5.95; 4.04 g, 30.5%), irregular prisms, m.p. 248—250°, $[\alpha]_D$ +184° (*c* 0.86 in $CHCl_3$), δ 1.4 (10 H, m, CH_2 of cyclohexyl), *m/e* 519 (M^+) and 472 (M^+ — SMe) (Found: C, 53.3; H, 7.3; N, 2.8; S, 11.9. $C_{23}H_{37}NO_8S_2$ requires C, 53.15; H, 7.2; N, 2.7; S, 12.3%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*allylthio*-7-*deoxy*-1-*thio*-α-*lincosaminide* (XI) *and Methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*propenylthio*-1-*thio*-α-*lincosaminide* (XII).—Counter-current distribution (system B; 700 transfers) of the crude product from the tetra-acetylepimine (10.0 g) and diallyl sulphide (100 g) gave the penta-acetate (*K* 0.50) and materials (A) (*K* 1.76; 2.13 g) and (B) (*K* 3.30; 3.95 g). Compound (A) separated from ethyl acetate–Skellysolve B as minute needles, m.p. 235—237, $[\alpha]_D$ +194° (*c* 0.63 in $CHCl_3$), shown to be the 7(S)-*allylthio*-*tetra*-*acetate* (XI), δ 3.27 (2 H, d, *J* 6 Hz, H_2C=CH·CH_2·S), *m/e* 477 (M^+), 436 (M^+ — C_3H_5), and 404 (M^+ — SC_3H_5) (Found: C, 50.1; H, 6.7; N, 2.8; S, 13.2. $C_{20}H_{31}NO_8S_2$ requires C, 50.3; H, 6.5; N, 2.9; S, 13.4%).

Compound (B) separated from ethyl acetate–Skellysolve B as needles, m.p. 273—275°, $[\alpha]_D$ +157° (*c* 1.05 in $CHCl_3$), shown to be the 7(S)-7-*propenylthio*-*tetra*-*acetate* (XII), δ 1.75 (3 H, d, *J* 5 Hz, CH_3·CH=CH·S), *m/e* 477 (M^+), 436 (M^+ — C_3H_5), and 404 (M^+ — SC_3H_5), $\lambda_{max.}$ 227 (ε 4 550) and 245 nm (4 250) (Found: C, 50.4; H, 6.45; N, 3.0; S, 13.4%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*phenylthio*-1-*thio*-α-*lincosaminide* (XVI).—From the tetra-acetylepimine (10.0 g) and benzyl phenyl sulphide (100 g), counter-current distribution (system C) gave the penta-acetate (*K* 0.23; 3.10 g) and the 7(S)-*phenylthio*-*tetra*-*acetate* (XVI) (*K* 3.35; 8.95 g, 69.5%), which separated from ethyl acetate in needles, m.p. 275—276°, $[\alpha]_D$ +164° (*c* 0.53 in $CHCl_3$), δ 7.34 (5 H, m, C_6H_5), *m/e* 513 (M^+), 466 (M^+ — SMe), and 404 (M^+ — SC_6H_5), $\lambda_{max.}$ 214sh (ε 10 050), 254 (8 900), and 275sh nm (1 850) (Found: C, 53.9; H, 6.1; N, 2.2; S, 12.5. $C_{23}H_{31}NO_8S_2$ requires C, 53.8; H, 6.1; N, 2.7; S, 12.5%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*benzylthio*-7-*deoxy*-1-*thio*-α-*lincosaminide* (XVII).—Counter-current distribution (system E) of the crude product from the tetra-acetylepimine (10.0 g) and dibenzyl sulphide (100 g) gave the penta-acetate (*K* 0.11) and the 7(S)-*benzylthio*-*tetra*-*acetate* (XVII) (*K* 1.38; 8.30 g, 63.5%) which separated from ethyl acetate–Skellysolve B as flattened prisms, m.p. 216—218°, $[\alpha]_D$ +161° (*c* 1.07 in $CHCl_3$), δ 3.82 (2 H, s, C_6H_5·CH_2·S) and 7.32 (5 H, s, C_6H_5·CH_2·S), *m/e* 527 (M^+), 480 (M^+ — SMe), and 404 (M^+ — $SCH_2C_6H_5$), $\lambda_{max.}$ 253sh (ε 438), 257 (327), and 266 nm (211) (Found: C, 54.7; H, 6.4; N, 2.9; S, 12.2. $C_{24}H_{33}NO_8S_2$ requires C, 54.6; H, 6.3; N, 2.7; S, 12.15%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-[(o-*hydroxyphenyl*)*thio*]-1-*thio*-α-*lincosaminide* (XVIII).—The crude product from the tetra-acetylepimine (10.0 g) and allyl *o*-hydroxyphenyl sulphide * (100 g) was subjected to counter current distribution (system B); the major peak (*K* 1.54) was the 7(S)-(o-*hydroxyphenyl*)*thio*-*tetra*-*acetate* (XVIII) (8.10 g, 61.8%), rods from ethyl acetate, m.p. 240—241°, $[\alpha]_D$ +154° (*c* 0.83 in $CHCl_3$), δ 7.25 (4 H, m, phenyl H), $\lambda_{max.}$ 225sh (ε 8 850), 251 (2 850), and 287 nm (3 800), *m/e* 529 (M^+), 482 (M^+ — SMe), 470 (M^+ — OAc), 422 (M^+ — SMe — HOAc), 404 (M^+ — S·C_6H_4·OH) (Found: C, 52.2; H, 5.9; N, 2.7; S, 12.0. $C_{23}H_{31}NO_9S_2$ requires C, 52.2; H, 5.9; N, 2.65; S, 12.1%).

Reactions of the Tetra-acetylepimine with Disulphides and with Diethyl Trisulphide

For those products which have been described earlier, resulting from the sulphide reagents, the reactions with the various disulphides and with diethyl trisulphide were conducted exactly as with the dialkyl sulphides, again using 3.5—7 mol of acetic acid per mol of tetra-acetylepimine; the products were isolated by counter-current distribution, and were formed in the yields quoted in the Discussion section.

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*butylthio*-7-*deoxy*-1-*thio*-α-*lincosaminide* (XXI).—Counter-current distribution (system C) of the crude product from the tetra-acetylepimine (10.0 g) and di-n-butyl disulphide (100 g) gave the penta-acetate (*K* 0.30; 3.14 g) and the 7(S)-*butylthio*-*tetra*-*acetate* (XXI) (*K* 3.35; 6.13 g, 50.4%), which separated from ethyl acetate as flattened needles, m.p. 234—235°, $[\alpha]_D$ +197° (*c* 0.51 in $CHCl_3$), δ 0.93 (3 H, t, *J* 7 Hz, $CH_3[CH_2]_3S$), 1.42 (4 H, m, $MeCH_2$·CH_2·CH_2·S), and 2.59 (2 H, t, *J* 7 Hz, $Me[CH_2]_2CH_2S$), *m/e* 493 (M^+), 446 (M^+ — SMe), and 434 (M^+ — OAc) (Found: C, 51.05; H, 7.2; N, 2.6; S, 12.8. $C_{21}H_{35}NO_8S_2$ requires C, 51.1; H, 7.15; N, 2.8; S, 13.0%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*t*-*butyldithio*-7-*deoxy*-1-*thio*-α-*lincosaminide* (XXII).—Acetic acid (10.50 g, 173.6 mmol) was added to a solution of the tetra-acetylepimine (10.0 g, 24.8 mmol) in di-t-butyl disulphide (100 g, 560 mmol) in an oil-bath at 100 °C for 6 h. Volatile materials

* The gift of this material by the Dow Chemical Co., Midland, Michigan, U.S.A., is acknowledged gratefully.

were removed by distillation under reduced pressure from the mixture which contained crystalline solid, and the residue was subjected to counter-current distribution (system C). Two components were present in approximately equal amounts; the more polar material (K 0.23) was the penta-acetate (4.71 g). The second component (K 7.35) was shown to be the 7(S)-*t-butyldithio-tetra-acetate* (XXII) (4.97 g, 38.2%), which separated as rods from ethyl acetate–Skellysolve B, m.p. 241—242°, $[\alpha]_D$ +220° (c 0.56 in $CHCl_3$), δ 1.32 [9 H, s, $(CH_3)_3CS$], *m/e* 526 (M^+ + 1), 525 (M^+), 478 (M^+ − SMe), 467 (M^+ − Bu^t + H), 436 (M^+ − SBu^t), 404 (M^+ − $SSBu^t$), $\lambda_{max.}$ 245sh nm (ε 425) (Found: C, 48.0; H, 6.65; N, 2.65; S, 18.65. $C_{21}H_{35}NO_8S_3$ requires C, 48.0; H, 6.7; N, 2.7; S, 18.3%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*allyldithio*-7-*deoxy*-1-*thio*-α-*lincosaminide* (XXIII).—The residue from the removal of volatile materials *in vacuo* from the reaction between acetic acid (10.50 g) and a solution of the tetra-acetylepimine (10.0 g) in diallyl disulphide (100 g) in an oil-bath at 100 °C for 6 h was subjected to counter-current distribution (system C). Two components were separated completely (K 0.26 and 2.03); a third (K 5.66) was separated poorly from material of lower polarity. The most polar material was identified as the penta-acetate (3.38 g), and the second as the 7(*S*)-allylthio-tetra-acetate (XI) (1.54 g, 13.0%).

The material of low polarity was removed from the train and taken to dryness on a rotatory evaporator at 40 °C under reduced pressure to give a syrup (7.12 g). After a further 500 transfers (system E), although the third component (K 1.87) was not separated completely from the material of low polarity, the majority of the peak matched the theoretical curve, and pure material (2.49 g) was isolated from tubes 280—340 (inclusive). This 7(S)-*allyldithio-tetra-acetate* (XXIII) separated from ethyl acetate in stout prisms, m.p. 211—213°, $[\alpha]_D$ +251° (c 1.00 in $CHCl_3$), δ 3.48 (2 H, d, J 7 Hz, H_2C=CH·CH_2·S), $\lambda_{max.}$ 245sh nm (ε 723), *m/e* 509 (M^+), 468 (M^+ − C_3H_5), 462 (M^+ − SMe), 436 (M^+ − SC_3H_5), and 404 (M^+ − SSC_3H_5) (Found: C, 47.0; H, 6.2; N, 2.6; S, 18.7. $C_{20}H_{31}NO_8S_3$ requires C, 47.1; H, 6.1; N, 2.75; S, 18.9%).

Reaction of the Tetra-acetylepimine with Ethyl t-Butyl Disulphide

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*t-butylthio- and* 7-*t-butyldithio*-1-*thio*-α-*lincosaminides* [(X) *and* (XXII)] *and Methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*ethylthio- and* 7-*ethyldithio*-7-*deoxy*-1-*thio*-α-*lincosaminides* [(VII) *and* (XXIV)].—Acetic acid (5.25 g) was added to a solution of the tetra-acetylepimine (10.0 g) in ethyl t-butyl disulphide [26] (50 g) in an oil-bath at 100 °C and heating was continued for 6 h. Volatile materials were removed from the reaction mixture, which contained suspended crystalline solid, and the residue was subjected to counter-current distribution (system C). Four well separated peaks (K 0.23, 1.43, 2.57, and 6.15) resulted, each matching its theoretical curve, and each showing a single zone by t.l.c. The most polar material (K 0.23; 4.11 g) was identified as the penta-acetate (IV) (35.8%); the component with K 1.43 (4.05 g) crystallised from ethyl acetate–Skellysolve B as needles, m.p. 236—237°, and was identified as the 7(*S*)-ethylthio-tetra-acetate (VIII) (36.2%); the least polar material (K 6.15; 470 mg), which crystallised from ethyl acetate–Skellysolve B as rods, m.p. 241—242°, was identified as the 7(*S*)-t-butyldithio-tetra-acetate (XXII) (3.7%). Each material, as isolated directly from the counter-current distribution, showed only a single peak on g.l.c. [Varian 1840 instrument; He carrier gas at a flow rate of 35—40 ml min^{-1}; 90 cm × 3 mm glass column containing 3% OV-17 on Gaschrom Q (100—120 mesh), isothermally at 275°, monitored with a flame-ionisation detector]. The material of K 2.57 (1.06 g) showed two g.l.c. peaks under these conditions, of retention times 9 and 14 min, in the area ratio of 70 : 30. G.l.c.–mass spectrometric examination indicated the major peak to be the 7(*S*)-butylthio-tetra-acetate (X) and the minor to be the ethyldithio-tetra-acetate (XXIV). Co-injection of this mixture and the known (X) caused enhancement of the 9 min peak. No liquid chromatographic system was found which would enable the separation of these two compounds.

The mixture (K 2.57) was dissolved in benzene (60 ml), tris(diethylamino)phosphine [27] (2.75 g) was added, and the solution was heated under gentle reflux in an oil-bath at 100 °C. The reaction was followed by t.l.c. [acetone–Skellysolve B (1 : 1)]; the starting material (R_F 0.60) gradually gave rise to two zones (R_F 0.57 and 0.60). No further change in relative intensities was apparent after 24 h. Examination of the reaction solution by g.l.c. (conditions as earlier) showed the retention of the 9 min peak, the disappearance of the 14 min peak, and the formation of a new peak, t_R 8.5 min, the area of which was enhanced by the co-injection of the 7(*S*)-ethylthio-compound (VIII). Solvent was removed from the reaction mixture, and the residue was chromatographed on silica in ethyl acetate–Skellysolve B (1 : 1) to remove the tris(diethylamino)phosphine sulphide and the excess of reagent, and the column was then eluted with ethyl acetate. Removal of the solvent gave the mixed tetra-acetyl derivatives (1.0 g); counter-current distribution (system C) gave peaks of K 1.41 and 2.55. Isolation of the K 2.55 material (690 mg) gave the 7(*S*)-t-butylthio-compound (X), m.p. 272—273° (needles from ethyl acetate); the material of K 1.41 (300 mg) crystallised from ethyl acetate–Skellysolve B in needles, m.p. 236—237°, and was identified as the 7(*S*)-ethylthio-compound (VIII).

I acknowledge gratefully the analytical data of Dr. A. A. Forist and his associates, the mass spectral results of Drs. M. Grostic and L. Baczynskyj, the n.m.r. results of Dr. G. Slomp and Mr. M. A. Mizsak, the g.l.c. and g.l.c.–mass spectrometric results of Mr. L. E. Reineke, the encouragement of Dr. T. E. Eble, and the valuable technical assistance of Mr. N. E. Barry.

[6/1936 *Received*, 15*th October*, 1976]

[26] D. T. McAllen, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Amer. Chem. Soc.*, 1951, **73**, 3627.

[27] D. M. Harpp and J. G. Gleason, *J. Org. Chem.*, 1970, **35**, 3259.