S-Alkylation of Sulphides by an Activated Carbohydrate Epimine under Acidic Catalysis: Formation of α-Acetamido-sulphides. Part 3.[1] Further Investigation of the Reaction with ω-(Alkylthio)alkanethiols

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The reaction between methyl 2,3,4-tri-*O*-acetyl-6,7-acetylepimino-6,7,8-trideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (1) and ω-(methylthio)alkanethiols, in the presence of acetic acid, gives the 7(*S*)-methylthio-derivative (6) *via* an intermediate sulphonium salt which collapses by neighbouring group participation of the thiol substituent, and the 7(*S*)-[ω-(methylthio)alkyl]thio-derivatives (7). The latter are formed, not by methyl group transference at the sulphonium salt stage, but by direct alkylation of the thiol sulphur atom, due to the enhancement of its nucleophilic reactivity by the methylthio-substituent in the β-, γ-, or δ-position. Similar activation of the thiol group is afforded by an oxygen substituent, but not by a second thiol substituent.

THE reaction between alcohols and methyl 2,3,4-tri-*O*-acetyl-6,7-acetylepimino-6,7,8-trideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (1), catalysed by acetic acid, gives ready access to 7(*S*)-alkoxy-7-deoxy-amides (2).[2] Alkanethiols do not participate in the ring opening of the epimine, the sole product being the 7(*S*)-methoxy-compound (3) if methanol is used as diluent for methanethiol, and the 7(*S*)-acetate if the reaction is conducted in methanethiol in a sealed tube in the absence of a diluent. Dialkyl sulphides, however, react *via* an α-acetamido-sulphonium salt to give α-acetamido-sulphides (Scheme 1).[3]

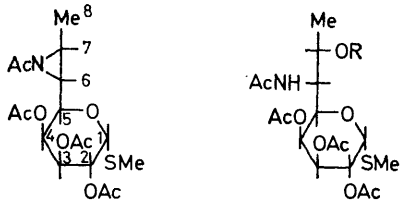
It was shown [1] that the collapse of the sulphonium salt

[1] Part 2, B. Bannister, *J.C.S. Perkin I*, 1978, 274.

[2] B. Bannister, *J.C.S. Perkin I*, 1974, 360.

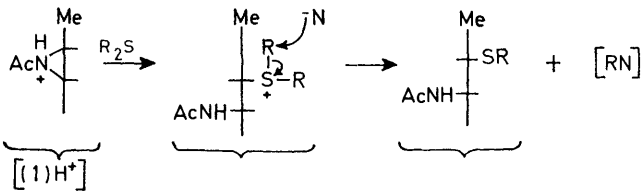
[3] B. Bannister, *J.C.S. Perkin I*, 1977, 1057.

to sulphide could occur by nucleophilic attack on a carbon atom adjacent to the sulphonium atom either by acetate ion or by an excess of sulphide reagent. If the sulphide reagent contains a second sulphide group, in



(1) (2) R = alkyl (3) R = Me (4) R = Ac

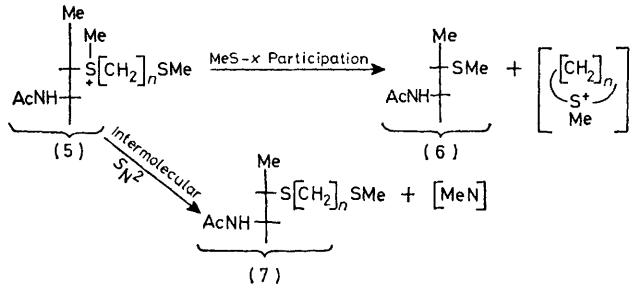
a series of αω-bis(methylthio)alkanes, the mode of collapse of the initial sulphonium salt (5) is controlled by the efficiency of the MeS-*x* participation, this efficiency being high when $x = 3$ or 5, leading to (6) as the sole or major product, but being low when $x = 4$, leading to (7) as the major product (Scheme 2). The same control of the mode of collapse of the initial sulphonium salt (8)



SCHEME 1

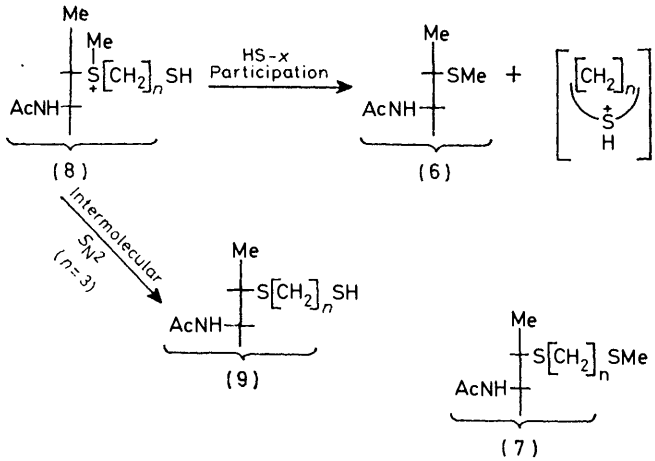
was found using a series of ω-(methylthio)alkanethiols. However, from these latter reagents, additional products were formed in which the 7-substituent was the [ω-(methylthio)alkyl]thio-group (7) (Scheme 3).

Collapse of the sulphonium salts (5) and (8) to the 7-methylthio-derivative (6) by neighbouring group participation involves the assumption of a cyclic transition



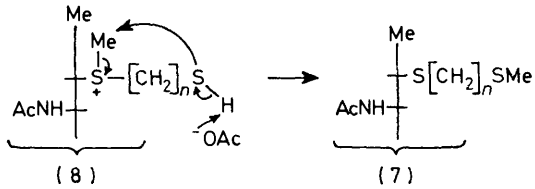
SCHEME 2

state in which the nucleophile, the methylene carbon atom adjacent to the sulphonium sulphur atom, and the leaving group are arranged linearly. This requirement is met in the cases of both MeS- and HS-3, -4, and -5 participation; they fall into the class of favoured 3- to 7-*exo-tetrahedral* processes in the recent Baldwin nomenclature.[4] In view of the demonstrated lack of reactivity of thiols in the ring-opening of the activated epimine (1), it is attractive to consider the formation of the [ω-(methylthio)alkyl]thio-derivatives (7) as arising from the initial sulphonium salt (8) by nucleophilic attack of the thiol group on the methyl substituent attached to the sulphonium sulphur atom, with consequent transference



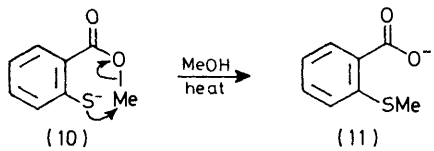
SCHEME 3

of the methyl group from the sulphonium sulphur to the thiol sulphur atom (Scheme 4). [The identity of these products (7; $n = 3$ or 4) with those formed from the 1,3- and 1,4-bis(methylthio)-alkanes showed that a similar displacement by the thiol group had not occurred by rear-side attack at C-7, which would have resulted in inverted stereochemistry at this position.]



SCHEME 4

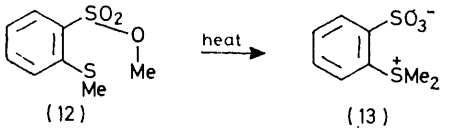
Grivas and Navada[5] have reported a reaction of this type, citing as evidence of its intramolecularity that the yield of the sulphide (11) from the ester (10) is not



diminished greatly on addition to the reaction mixture of sodium benzenethiolate as an intermolecular nucleophile. However, in an investigation of the reaction (12) → (13), Eschenmoser and his collaborators[6] showed that the *S*-methylation occurred by an entirely intermolecular process, and they make the general

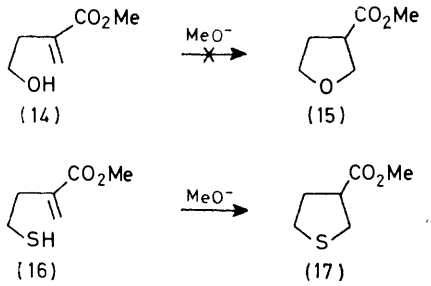
[4] J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734.
[5] J. C. Grivas and K. C. Navada, *J. Org. Chem.*, 1971, **36**, 1520.
[6] L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, 1970, **53**, 2059.

statement that intramolecular reactions in endocyclic displacements involving rings of less than ten atoms are improbable because of the requirement of the tetrahedral carbon atom for back-side attack in S_N2 reactions. Such reactions fall into Baldwin's [4] class of disfavoured 5- to 6-*endo-tetrahedral* processes. On the other hand, Ciuffarin and Guaroldi [7] have pointed out that, although



(12) (13)

the steric requirements in displacement reactions involving sulphur are very similar to those of nucleophilic substitution at the tetrahedral carbon atom, implying that the transition states for carbon and divalent sulphur have a similar geometry, the utilisation of the empty *d* orbitals of sulphur, as a second-row element, could make possible a non-linear transition state. In extension of this concept, Baldwin and his co-workers [8] have reported that, although the disfavoured 5-*endo-trigonal* ring-closure (14) ⟶ (15) does not occur, the cyclisation of the sulphur analogue [(16) ⟶ (17)] does occur, and they ascribe the facilitation of the disfavoured cyclisation to the larger radius and bond lengths allowing the assumption of a conform-

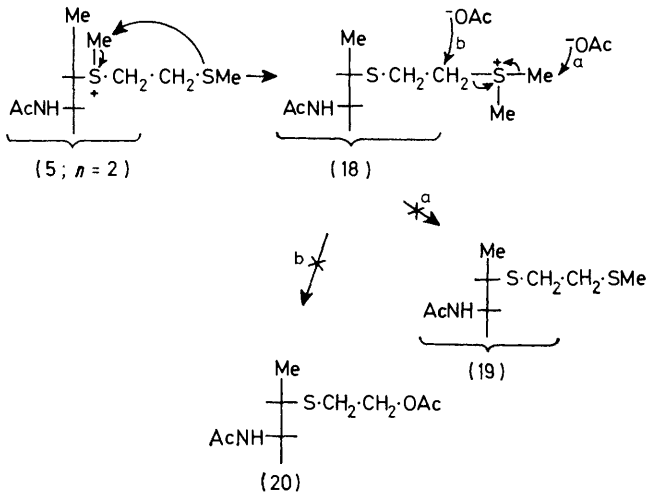


(14) (15) (16) (17)

ation in the transition state which is inadequate for reaction in the case of first-row elements.

Only in the case of the reaction of the epimine (1) with 3-(methylthio)propanethiol was any 7-[ω-(mercapto)-alkylthio]-derivative (9) produced,[2] and a ready explanation for this lies in the inefficiency of HS-4 relative to HS-3 or -5 participation. The possibility of intermolecular *trans*-methylation between two molecules of the intermediate sulphonium salt therefore was implausible as a means of accounting for what would have to be a very efficient *S*-methylation; in the simplest case, it would involve a ten-membered cyclic transition state, and would have to occur to the virtual exclusion of *S*-methylation of the reagent, present in large excess.

The approximate equivalence of efficiency of MeS-5 and HS-5 participation in the collapse of the intermediate sulphonium salts (5) and (8), respectively, to the 7-methylthio-derivative (6), has been demonstrated.[1] If the formation of the 7-[2-(methylthio)ethyl]thio-derivative (7; $n = 2$) were to result from an intramolecular, endocyclic displacement at the sulphonium salt stage (8) (Scheme 4), then it would be expected that a similar participation by the terminal methylthio-group in the salt (5; $n = 2$) would produce the new sulphonium salt (18), which would collapse by intermolecular nucleophilic attack to yield either or both the known derivatives (19) [1] (route a) or (20) [3] (route b) (Scheme 5). Neither



SCHEME 5

was produced in discernible amount, the only product being the 7-methylthio-derivative (6), resulting from the exocyclic displacement.

Reaction of the tetra-acetylepimine (1) with 2-(benzylthio)ethanethiol under the standard conditions gave the known [3] 7-benzylthio-derivative (21) (61%) and the 7-[2-(benzylthio)ethyl]thio-derivative (22) (39%); with 2-(t-butylthio)ethanethiol, the known [3] 7-t-butylthio-derivative (23) (32%) and the 7-[2-(t-butylthio)-ethyl]thio-derivative (24) (67%) were formed. It is unlikely that the proportion of the 7-[2-(substituted thio)ethyl]thio-products would increase in the order Me < CH_2Ph < Bu^t if an intramolecular, endocyclic displacement mechanism were to be operating. Again, ' transfer ' of either substituent following an S_N1 bond scission would not be expected to be an efficient process.

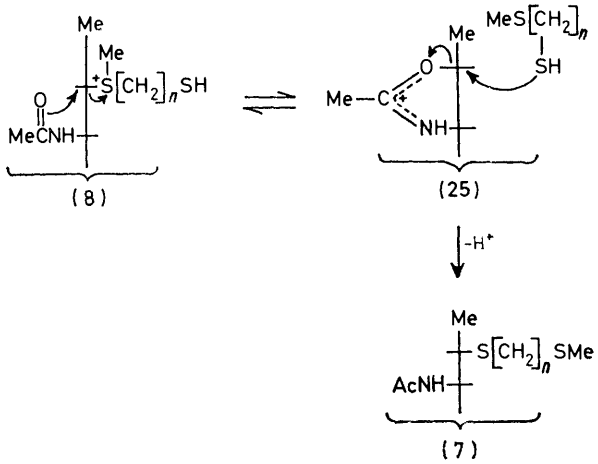
(21) R = CH_2Ph (22) R = CH_2Ph
(23) R = Bu^t (24) R = Bu^t

A totally different mechanism for the formation of the 7-[ω-(methylthio)alkyl]thio-compounds (7) from the sulphonium salt (8), and for the formation of (22) and (24) from the corresponding sulphonium salts, could involve the generation of the oxazolinium ion (25) by

[7] E. Ciuffarin and G. Guaroldi, *J. Amer. Chem. Soc.*, 1969, **91**, 1745.

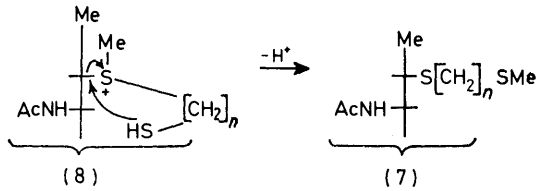
[8] J. F. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, *J.C.S. Chem. Comm.*, 1976, 736.

displacement of the ω-(methylthio)alkanethiol from the 7(*S*)-position by participation of the carbonyl function of the amide group in the 6(*R*)-position, a displacement for which there is precedent.[9] Although the nucleophilic reactivity of a thiol was inadequate to allow its participation in the ring-opening of the epimine itself, it might suffice for the ring-opening of the oxazolinium salt by attack at C-7 to yield the observed (7). Attack by the sulphide sulphur atom would simply regenerate the sulphonium salt (8) (Scheme 6).



SCHEME 6

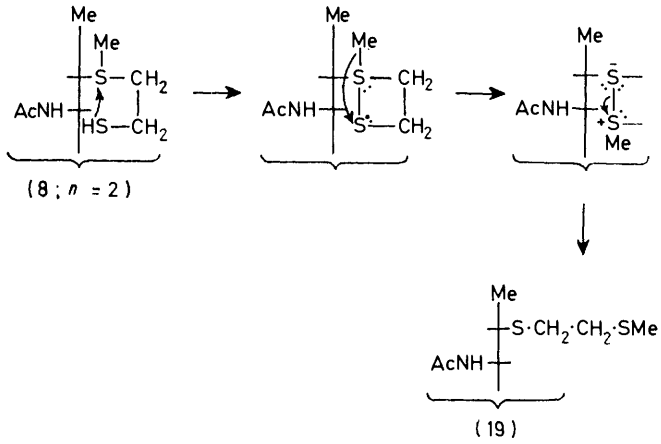
If the oxazolinium ion (25) is an intermediate, then allowing the reaction of the epimine with 2-(methylthio)-ethanethiol to occur in the presence of an equimolar amount of ethane-1,2-dithiol might permit the dithiol to compete in the opening of the oxazolinium ring with the formation of the 7-(2-mercaptoethyl)thio-derivative (9; $n = 2$). In the event, no trace of this product was detected, the same two products, (6) and (7; $n = 2$), being formed in the same ratio as in the absence of the ethane-1,2-dithiol. However, this does not exclude the possibility that the 2-(methylthio)ethanethiol liberated in the formation of (25) is held in a cage, thus preventing competition from the added ethanedithiol.



SCHEME 7

Two other possible reaction mechanisms were considered. An S_Ni mechanism (Scheme 7) would account for the product, but inherently is unlikely, involving in the simplest case, that of 2-(methylthio)ethanethiol, a five-centre transition state. Another, more acceptable, possibility was that intramolecular nucleophilic attack by the thiol sulphur atom occurred on the sulphonium sulphur atom to give a tetracovalent 1,2-dithietan derivative, followed by the migration of the methyl group from the tetracovalent to the dicovalent sulphur atom, and scission of the sulphur–sulphur bond to give product (19) (Scheme 8). The intermediacy of tetracovalent sulphur compounds has been invoked to account for the t-butylation of dimethyl sulphide by di-(t-butyl)methylsulphonium salts.[10]

The endocyclic displacement and the 1,2-dithietan mechanisms (Schemes 4 and 8) require transference of the methyl group from one sulphur atom to the other, whereas no such transference is involved in the oxazolinium cage structure and the S_Ni mechanisms (Schemes 6 and 7). Distinction most simply could be drawn between these pairs of mechanisms by the use of an unsymmetrically branched reagent. Reaction between sodium methanethiolate and 2-methylthiiran would be



SCHEME 8

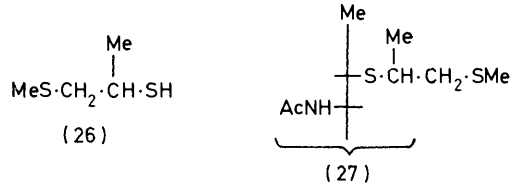
expected to occur at the unsubstituted position; the product, purified by distillation through a spinning-band column, was homogeneous by g.l.c. The ^1H n.m.r. spectrum of this material was as expected for a (methylthio)propanethiol [δ($CDCl_3$) 1.42 (3 H, d, *J* 6 Hz, CH_3·CH–), 2.02 (1 H, d, *J* 5 Hz, –CH·S*H*), 2.17 (3 H, s, CH_3-S–), 2.71 (2 H, d, *J* 7 Hz, –S·CH_2·CH–), and 3.17 (1 H, m, *J* 6 Hz, –CH_2·C*H*·S)]. On addition of D_2O, the doublet at δ 2.02 decreased in area, and this was accompanied by the loss of definition of the multiplet at δ 3.17; the doublet at δ 2.71 (–S·CH_2·CH–) was unaltered, however, thereby identifying the material unambiguously as the expected diastereoisomeric mixture (2*RS*)-1-(methylthio)propane-2-thiol (26).

Reaction of (26) with the tetra-acetylepimine under the usual conditions gave two products, the major being the expected 7-methylthio-derivative (6), and a product corresponding to the introduction at C-7 of the group –S·$\overbrace{\text{CH·CH}}^{\text{H,Me}}$·SMe. It was not possible to determine from the ^1H n.m.r. spectrum which carbon atom in this group bore the methyl substituent; an implication that the

[9] T. Taguchi and M. Kojima, *J. Amer. Chem. Soc.*, 1959, **81**, 4318.

[10] H. Minato, T. Miura, F. Takagi, and M. Kobayashi, *Chem. Letters*, 1975, 211.

branching was not adjacent to the methylthio-function could be found in the presence of an ion, *m/e* 89 ($C_3H_6\dot{S}\overset{+}{M}e$), as the base peak in the mass spectrum. The crystal structure of this material was suitable for *X*-ray analysis,* which showed the substituent to have the 7*S*-configuration, and the methyl substituent to be β to the methylthio-group; the product is the (7*S*)-7-[(1*RS*)-1-methyl-2-(methylthio)ethyl]thio-derivative (27). Its formation, therefore, does not involve a migration of the methyl group, denying the mechanisms of Schemes 4 and 8, but permitting the retention of those of Schemes 6 and 7, both of which seemed doubtful. A reconsideration of the generality of the inability of thiols to participate in this ring-opening reaction was necessary, therefore, since direct alkylation of the thiol sulphur atom could most simply account for the formation of the product (27).



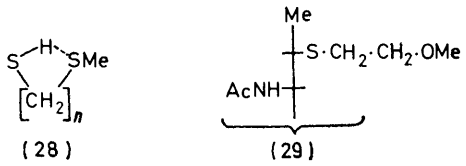
In an investigation of the basic hydrolysis of *O*- and *S*-acetates of hydroxyalkanethiols, Harding and Owen [11] found an unexpectedly high degree of cyclisation to the thiiran with derivatives of 2,3-dimercaptopropanol relative to 2-mercaptoethanol, and to the thiolan with those of 3,4-dimercaptobutanol relative to 4-mercaptobutanol. They postulated that the additional thiol group in the β-position must increase the reactivity of the thiol group involved in the displacement of the leaving acetoxy-group by reinforcement of its electron-donating ability. Although these reactions involved thiolate anions, this example of enhancement of nucleophilic reactivity by an appropriately situated electron donor was of interest in the present work.

Enhancement of the nucleophilicity of the thiol group in an ω-(methylthio)alkanethiol by an inductive effect of the methylthio-substituent must be negligible through two carbon atoms, and cannot be considered to operate through three or four carbon atoms, although an electrostatic field effect acting through space, independently of the intervening bonds, is tenable for such an enhancement. More conventionally, however, the same net effect—of increasing the electron density on the thiol sulphur atom—would result from hydrogen bonding between the thiol and methylthio-groups. Hydrogen bonding between a hydroxy-group and a sulphide sulphur atom has been demonstrated by observations of the generation of a second hydroxy-group stretching band of lower frequency in the i.r. spectrum.[12] In the series of hydroxy-sulphides $HO[CH_2]_nSEt$, hydrogen bonding was demonstrated for $n = 2$ and 3, but not at greater separations; [13] it was found in 2-hydroxyethanethiol also.[14]

Such hydrogen bonding is weak, as expected of protonation of the ' soft ' sulphide sulphur atom. In the series $MeS[CH_2]_nSH$, there is no indication of any shift in the –SH stretching frequency nor, indeed, is there in the compounds $Et_2N[CH_2]_nSH$ ($n = 3$ or 4),[15] in which the basic amino-nitrogen atom would be expected to enhance the ability of the thiol to donate a proton. Nevertheless, some enhancement of the nucleophilicity of the thiol group by the methylthio-substituent by this means [structure (28)] might be sufficient to permit such thiols to participate in the ring opening of the activated epimine.

The plausibility of this explanation was examined using an oxygen substituent as a proton acceptor. From the reaction between 2-methoxyethanethiol and the tetra-acetylepimine, approximately equal amounts of the 7-acetate and the 7-(2-methoxyethyl)thio-derivative (29) were obtained, the latter being identical with the major product of the reaction using 2-methoxyethyl methyl sulphide. The formation of this product from 2-methoxyethanethiol eliminates from consideration the oxazolinium salt-reagent ' cage ' mechanism (Scheme 6); an ether group does not participate in the ring opening of the epimine,[2] so the product must result from the direct alkylation of the thiol sulphur atom by the epimine.

The β-hydroxy-substituent similarly provided the necessary enhancement of nucleophilicity of the thiol group: reaction of 2-hydroxyethanethiol with the tetra-acetylepimine gave the 7-acetate together with two other products, separated by extended counter-current



distribution. The main component derived from the reagent was identified as the known [3] 7-(2-hydroxyethylthio)-tetra-acetate (30) (71%) obtained from 2-hydroxyethyl methyl sulphide. The second product showed signals in the ^1H n.m.r. spectrum at δ($CDCl_3$) 1.53 (1 H, t, *J* 8 Hz, $-CH_2{\cdot}SH$), and 2.68 (2 H, doublet of triplets, J_{OCH_2,CH_2S} 6.5, $J_{CH_2,SH}$ 8.0 Hz, $O{\cdot}CH_2{\cdot}CH_2{\cdot}SH$), and the $O{\cdot}CH_2{\cdot}CH_2{\cdot}SH$ signal appeared as the AB part of an ABM_2 system, A and B each being a doublet of triplets centred at δ 3.68 and 3.38, respectively ($J_{A,B}$ 9.0 Hz); on addition of D_2O, the δ 1.53 signal diminished, and the δ 2.68 signal became simpli-

* Study conducted by Dr. D. J. Duchamp and Mrs. C. Wickrema Sinha, Physical and Analytical Chemistry Research, The Upjohn Company; this will be reported elsewhere.

[11] J. S. Harding and L. N. Owen, *J. Chem. Soc.*, 1954, 1528, 1536.

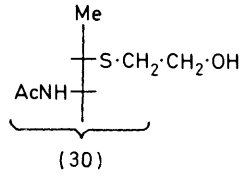
[12] M. Tichý, *Adv. Org. Chem.*, 1965, **5**, 115.

[13] N. Mori, Y. Takahashi, and Y. Tsuzuki, *Bull. Chem. Soc. Japan*, 1967, **40**, 2720.

[14] M. Kuhn, W. Lüttke, and R. Mecke, *Z. analyt. Chem.*, 1959, **170**, 106.

[15] D. Plant, D. S. Tarbell, and C. Whiteman, *J. Amer. Chem. Soc.*, 1955, **77**, 1572.

fied. This second product therefore is the 7-(2-mercaptoethoxy)-derivative (31) (29%). The presence of the thiol group was confirmed by its catalysis of the iodine azide reaction.[16] The presence of the β-hydroxy-substituent has thus made the thiol group 2.5 times as reactive nucleophilically as the hydroxy-group itself; it is interesting that no reaction occurs at the hydroxy-



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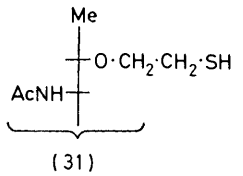
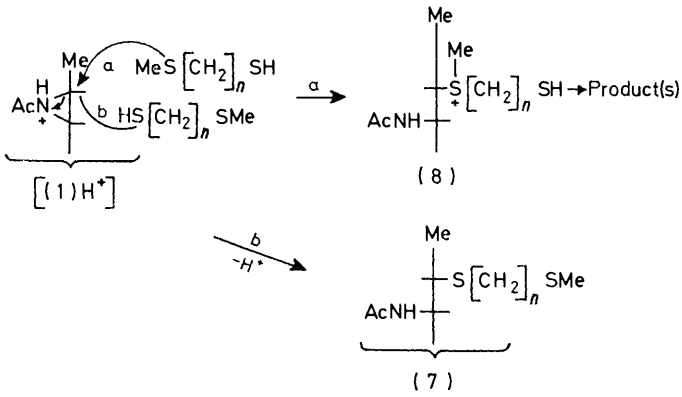


(31)

group with the related sulphide, 2-hydroxyethyl methyl sulphide.[3]

In view of these demonstrations of the enhancement of nucleophilic reactivity of the thiol group in these substituted alkanethiols, further consideration of the inherently unlikely, alternative, S_Ni mechanism (Scheme 7) is unnecessary. The reactions of the activated epimine with the ω-(methylthio)alkanethiols thus involve competitive nucleophilic attack by the sulphide and thiol sulphur atoms, and can be represented as in Scheme 9.

From the relative yield of products, on a molar basis, derived from alkylation of the sulphide group *vs.* the thiol group in the series $MeS[CH_2]_nSH$ (Table 1), it is apparent that the activation of the thiol group is greatest when the methylthio-substituent is in the γ-position, significant when in the β-position, and slight when in the



SCHEME 9

δ-position, indicating that hydrogen bonding is most effective in the case of a six-membered cyclic structure. In the series $RS{\cdot}CH_2{\cdot}CH_2{\cdot}SH$, the extent of alkylation of the thiol group relative to the sulphide group increases in the order R = Me < CH_2Ph < Bu^t (Table 2), and this can be ascribed to the increased electron density on the sulphide sulphur atom, due to the greater inductive effects of the benzyl and t-butyl groups, leading to a greater stabilisation of the hydrogen-bonded structure. In addition, in the case of the t-butyl derivative, the hindrance about the sulphide sulphur atom caused by the bulky alkyl group will render this atom less reactive nucleophilically, and the competitive nucleophilic attack of the thiol group will be favoured.

It must be borne in mind that the lack of participation of simple thiols and 1,2-dithiols in the ring-opening reactions of the activated epimine refers to the conditions under which the reactions were examined—that is, in the presence of acetic acid as a means of generating the protonated species [(1)H^+]. Under these conditions, the nucleophilic reactivity of the acetate ion is such that the thiols are not competitive. It is possible that participation of a thiol in this ring-opening reaction could occur if the acid catalyst were one in which the conjugate base were a much poorer nucleophile than acetate ion. However, this still leaves unresolved the question of why the unactivated thiol group is so poor a nucleophile relative to alcohols, acetate ion, and sulphides under these conditions.

TABLE 1

$MeS[CH_2]_nSH$	MeS : SH attack
n = 2	5.0 : 1
n = 3	1.9 : 1
n = 4	14.9 : 1

TABLE 2

$RS[CH_2]_2SH$	RS : SH attack
R = Me	5.0 : 1
R = CH_2Ph	1.6 : 1
R = Bu^t	0.5 : 1

EXPERIMENTAL

General experimental procedures have been described previously,[3] together with details of spectral determinations, the method of analysis of counter-current distribution results, and the definition of the distribution coefficient K. Counter-current distribution analyses were conducted after 500 transfers. If separations were incomplete, the higher number of transfers utilised for separation is indicated. Solvent systems used were 95% ethanol–water–ethyl acetate–cyclohexane in the proportions (v/v) 1 : 1 : 0.5 : 3 (system A), 1 : 1 : 1 : 3 (B), 1 : 1 : 1 : 2 (C), and 1 : 1 : 1 : 0.5 (D). With compounds of structure ascertained earlier, products were identified by comparison (m.p., mixed m.p., t.l.c., and spectrometric examination) with authentic samples.

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-*benzylthio*-1-*thio*-α-*lincosaminide* (21) *and Methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-[2-(*benzylthio*)*ethylthio*]-1-*thio*-α-*lincosaminide* (22).—2-(Benzylthio)ethanethiol was prepared by the general method of Meade and Woodward [17] from sodium (57.5 g, 1.5 equiv.), ethanol (1 350 ml), toluene-α-thiol (310 g, 1.5 equiv.), and thiiran (100 g, 1 equiv.) at 0 °C. The mixture was neutralised with acetic acid and filtered from sodium acetate, and its solution in chloroform was washed with water, and dried (Na_2SO_4). Removal of the solvent and distillation through a micro-Vigreux column gave the *thiol* as a liquid, b.p. 120—122° at 0.5 mmHg, in 40% yield (122.7 g), δ 1.67 (1 H, t, J 5 Hz, $CH_2{\cdot}SH$), 2.67 (4 H, d, J 4 Hz, $S{\cdot}CH_2{\cdot}CH_2{\cdot}S$), 3.77 (2 H, s, $PhCH_2{\cdot}S$), and 7.37 (5 H, s, $C_6H_5{\cdot}CH_2{\cdot}S$), *m/e* 184 ($M^+$), 137 ($M^+ - CH_2SH$), 123 ($M^+ - CH_2CH_2SH$), and 91 ($M^+ - SCH_2CH_2SH$) (Found: C, 58.4; H, 6.7; S, 34.95. $C_9H_{12}S_2$ requires C, 58.6; H, 6.7; S, 34.8%). To a stirred solution of the tetra-acetylepimine (1) (10 g, 1 equiv.) in 2-(benzylthio)ethanethiol (100 g, 40 equiv.) in an oil-bath at 100 °C was added acetic acid (10.50 g, 7 equiv.), and heating was continued overnight. Removal of volatile

[16] F. Feigl, 'Spot Tests in Organic Analysis,' Elsevier, New York, 1960, p. 242.

[17] E. M. Meade and F. N. Woodward, *J. Chem. Soc.*, 1948, 1894.

materials from the pale yellow solution by distillation under reduced pressure, finally at 0.5 mmHg, gave a solid, which was subjected to counter-current distribution (system A). Three peaks were present: that with K 0.11 was the known [2] 7-acetate, and that with K 1.50 was identified as the known [3] 7-benzylthio-tetra-acetate (21) (5.63 g, 43%), m.p. 216—218° from ethyl acetate–Skellysolve B.* The material with K 4.20 was shown to be the 7-[2-(*benzylthio*)-*ethyl*]*thio-tetra-acetate* (22) (3.97 g, 27.3%), which separated from ethyl acetate–Skellysolve B in prisms, m.p. 145—145.5°, $[\alpha]_D$ +155° (*c* 0.823 in $CHCl_3$), $\lambda_{max.}$ 254 sh (ε 535), 259 (401), and 266 nm (252), δ 1.93—2.14 (15 H, 5s, 3 OAc + NAc + SMe), 2.68 (4 H, m, S·CH_2·CH_2·S), 3.77 (2 H, s, S·CH_2·Ph), and 7.23 (5 H, s, C_6H_5·S), *m/e* 587 (M^+), 540 (M^+ — SMe), 528 (M^+ — OAc), 496 (M^+ — CH_2Ph), 464 (M^+ — SCH_2Ph), and 463 (M^+ — $HSCH_2Ph$) (Found: C, 53.0; H, 6.3; N, 2.4; S, 16.0. $C_{26}H_{37}NO_8S_3$ requires C, 53.1; H, 6.35; N, 2.4; S, 16.4%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-t-*butylthio*-1-*thio*-α-*lincosaminide* (23) and *Methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-[2-(*t-butylthio*)*ethyl*-*thio*]-1-*thio*-α-*lincosaminide* (24).—2-(*t-Butylthio*)*ethanethiol*, prepared by the method mentioned above for the benzyl analogue, was obtained as a liquid, b.p. 83—85° at 20 mmHg (100.1 g, 40%), δ 1.68 (1 H, t, *J* 5 Hz, CH_2·S*H*), 2.07 (9 H, s, SC_4H_9), and 2.71 (4 H, d, *J* 4 Hz, S·CH_2·CH_2·S), *m/e* 150 (M^+), 103 (M^+ — CH_2SH), 89 (M^+ — CH_2CH_2SH), and 57 (M^+ — SCH_2CH_2SH) (Found: C, 48.0; H, 9.5; S, 42.8. $C_6H_{14}S_2$ requires C, 47.9; H, 9.4; S, 42.7%).

Counter-current distribution (system B) of the product of the reaction under the normal conditions between the tetra-acetylepimine (10 g) and the 2-(t-butylthio)ethanethiol (100 g) gave peaks with K 0.24 (the 7-acetate), K 2.38, identified as the known [3] 7-t-butylthio-derivative (23), m.p. 272—273° (from ethyl acetate) (2.18 g, 17.8%), and K 7.95, shown to be the 7-[2-(*t-butylthio*)*ethylthio*]-*tetra-acetate* (24) (5.09 g, 37%), irregular platelets from ethyl acetate–Skellysolve B, m.p. 164—164.5°, $[\alpha]_D$ +164° (*c* 0.583 in $CHCl_3$), δ 1.33 (9 H, s, SC_4H_9), 1.92—2.17 (15 H, 5s, 3 OAc + NAc + SMe), and 2.75 (4 H, s, S·CH_2·CH_2·S), *m/e* 506 (M^+ — SMe), 496 (M^+ — Bu^t), 494 (M^+ — OAc), 463 (M^+ — $HSBu^t$), 437 (M^+ — CH_2=$CHSBu^t$), 416 (M^+ — $HSBu^t$ — SMe), and 404 (M^+ — $SCH_2CH_2SBu^t$) (Found: C, 49.75; H, 7.1; N, 2.3; S, 17.3. $C_{23}H_{39}NO_8S_3$ requires C, 49.9; H, 7.1; N, 2.5; S, 17.4%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-[(1*RS*)-1-*methyl*-2-(*methylthio*)*ethylthio*]-1-*thio*-α-*lincosaminide* (27).—(2*RS*)-1-(Methylthio)propane-2-thiol (26) was obtained by the general method of Meade and Woodward,[17] using 2-methylthiiran. Fractionation through a spinning-band column gave the *thiol* as a liquid, b.p. 123—124° at 43 mmHg (56.5% yield), homogeneous by g.l.c. (10 ft 10% UCW-98 column, programmed from 100 to 275° at 8° min^{-1}; single peak appeared at 144 °C) (see main text for ^1H n.m.r. spectrum), *m/e* 122 (M^+), 107 (M^+ — Me), 88 (M^+ — H_2S), and 74 (M^+ — MeSH) (Found: C, 39.55; H, 8.3; S, 52.5. $C_4H_{10}S_2$ requires C, 39.3; H, 8.25; S, 52.5%).

Counter-current distribution (system B) of the product from the tetra-acetylepimine and 1-(methylthio)propane-2-thiol under the normal conditions gave components with K 0.25 (the 7-acetate; 1.49 g, 13%), K 0.88 [the known [2] 7-methylthio-derivative (6); 7.92 g, 70.8%], and K 2.45, shown to be the (7S)-[(1RS)-1-*methyl*-2-(*methylthio*)*ethylthio*]-*derivative* (27) (1.69 g, 13%), which separated from ethyl acetate in needles, m.p. 219—220.5°, $[\alpha]_D$ +180° (*c* 1.075 in $CHCl_3$), δ 1.39 (3 H, d, *J* 3 Hz, CH·CH_3), 1.93—2.20 (18 H, 6s, 3 OAc + NAc + 2 SMe), and 2.70 (3 H, m, S·C*H*Me·CH_2·S), *m/e* 478 (M^+ — SMe), 404 (M^+ — SC_3H_6-SMe), and 89 (base peak, $C_3H_6\overset{+}{S}Me$) (Found: C, 47.8; H, 6.7; H, 2.5; S, 18.1. $C_{21}H_{35}NO_8S_3$ requires C, 48.0; H, 6.7; N, 2.7; S, 18.3%).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-[2-*methoxyethylthio*]-1-*thio*-α-*lincosaminide* (29).—(a) *From* 2-*methoxyethanethiol*.[18] From reaction between the tetra-acetylepimine (5.0 g, 1 equiv.) and the thiol (29 g, 25.5 equiv.) in the presence of acetic acid (2.61 g, 3.5 equiv.), counter-current distribution (system C) separated two components: K 0.14 (7-acetate; 2.61 g, 45.5%) and K 0.81, shown to be the 7-(2-*methoxyethylthio*)-*tetra-acetate* (29) (2.92 g, 47.6%), rods from ethyl acetate, m.p. 218—220°, $[\alpha]_D$ +171° (*c* 0.899 in $CHCl_3$), δ 1.93—2.16 (15 H, 5s, 3 OAc + NAc + SMe), 2.83 (2 H, t, *J* 6 Hz, S·CH_2·CH_2), 3.46 (3 H, s, OCH_3), and 3.62 (2 H, t, *J* 4 Hz, CH_2·CH_2·O), *m/e* 496 (M^+ + 1), 495 (M^+), 463 (M^+ — MeOH), 436 (M^+ — CH_2CH_2OMe), and 404 (M^+ — SCH_2CH_2OMe) (Found: C, 48.7; H, 6.8; N, 2.8; S, 12.8. $C_{20}H_{33}NO_9S_2$ requires C, 48.5; H, 6.7; N, 2.8; S, 12.9%).

(b) *From* 2-*methoxyethyl methyl sulphide*.[19] From this reaction, conducted under the standard conditions, counter-current distribution (system C; 1 000 transfers) gave peaks of K 0.43 (7-acetate; 26.8%), K 1.27 [the 7-methylthio-derivative (6), 18%], and K 0.88, the 7-(2-methoxyethylthio)-derivative (29) (52%), m.p. 218—220° (from ethyl acetate).

Methyl (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-(2-*hydroxyethylthio*)-1-*thio*-α-*lincosaminide* (30) and *Methyl* (7S)-N-*Acetyl*-2,3,4-*tri*-O-*acetyl*-7-*deoxy*-7-(2-*mercapto-ethoxy*)-1-*thio*-α-*lincosaminide* (31).—The reaction between the tetra-acetylepimine (7.0 g) and 2-hydroxyethanethiol (70 g) in the presence of acetic acid (7.35 g), followed by standard work-up, gave a crude product showing, by t.l.c. [acetone–Skellysolve B (1 : 1)], zones of R_F 0.34, coincident with the 7-(2-hydroxyethyl)thio-derivative (30), and R_F 0.50, coincident with the 7-acetate. Counter-current distribution (system D; 1 000 transfers) gave peaks of K 0.91, identified as the 7-(2-hydroxyethylthio)-derivative [3] (30) (3.50 g, 42%), K 1.27 (the 7-acetate; 2.81 g, 35%), and K 2.12, shown to be the 7-(2-*mercaptoethoxy*)-*tetra-acetate* (31) (1.39 g, 16.7%), which separated from ethyl acetate in needles, m.p. 228.5—230°, $[\alpha]_D$ +176° (*c* 0.889 in $CHCl_3$), δ 1.53 (1 H, t, *J* 8 Hz, CH_2·S*H*), 1.93—2.12 (15 H, 5s, 3 OAc + NAc + SMe), and 2.68 (2 H, q, *J* 8 Hz, CH_2·CH_2·SH), and an AA′B_2X pattern, centred at δ 3.37 and 3.68 (2 H, O·CH_2·CH_2·S), *m/e* 481 (M^+), 434 (M^+ — SMe), 421 (M^+ — HOAc), and 404 (M^+ — OCH_2CH_2SH) (Found: C, 47.55; H, 6.4; N, 3.0; S, 13.2. $C_{19}H_{31}NO_9S_2$ requires C, 47.4; H, 6.5; N, 2.9; S, 13.3%).

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

[18] J. H. Chapman and L. N. Owen, *J. Chem. Soc.*, 1960, 579.
[19] H. T. Clarke, *J. Chem. Soc.*, 1912, **101**, 1788.