Iodine Oxidation of 8-Acetylthio-6-mercapto-octanoic Acid and Related *S*-Monoacyl-1,3-dithiols: Oxidative Acyl Transfer

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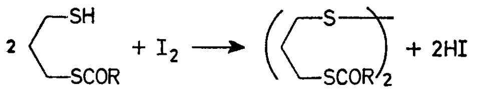
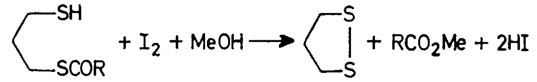
Summary The title compounds when oxidized with iodine in methanol transferred acyl groups to the solvent molecule with the concurrent formation of 1,2-dithiolans.

In apparent contradiction to the behaviour of ordinary thiols iodometry of the title compounds in methanol revealed that 0·5—1·0 mol of iodine was consumed per mol of thiol used, depending on the reaction conditions. Analysis of the reaction mixture indicated the formation of 1,2-dithiolans (u.v. spectroscopy and g.l.c.) and methyl carboxylates (g.l.c.). A detailed study established that in addition to the normal intermolecular oxidation (equation 1) the intramolecular oxidation (equation 2) was also in competition. Since the reaction was instantaneous at room temperature, it was obvious that the acyl group in equation (2) underwent extensive activation through oxidation. A tentative mechanism for reaction (2) is illustrated by equations (3)[†] and (4). It is interesting that this finding in conjunction with the previously reported reductive acylation of 1,2-dithiolans with aldehydes[1] constitutes the total 1,2-dithiolan–1,3-dithiol redox reaction, which can convert aldehydes into potentially active acylating agents.



(1)



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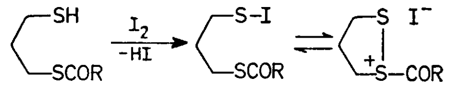

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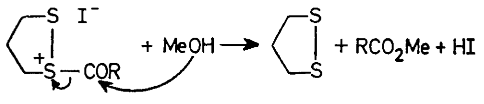

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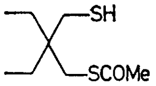
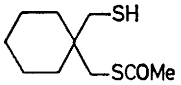


(I)



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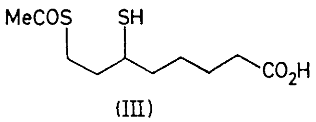

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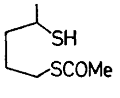

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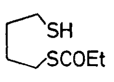

(V)

The substrates were synthesized as previously described[1] and were purified by vacuum distillation. In a typical oxidation study, 0·08 mmol of the substrate and 0·25 mmol of lithium acetate were dissolved in 3 ml of methanol (0·07M AcOH) and the solution was added with stirring to solid iodine (slightly > 1 equiv.). The excess of iodine

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[†] Recently Minato *et al.* (*Chem. Letters*, **1976**, **593**) have suggested the formation of an open chain version of the acylsulphonium intermediate in a different system.

was then back-titrated with a 3% solution of the substrate in n-butanol (Table). The mole fraction, α, of the substrate which reacted *via* equation (2) can be evaluated from any of the three quantities N_D, N_E, or N_I; N_E was found to be the least reliable. The consistency within the data supports the absence of major side reactions. The N_D values are lower than $2N_I - 1$ and this may reflect the instability of 1,2-dithiolans to iodine observed in a control experiment. The oxidation could also be carried out in methanol–acetic acid solvent of various compositions in the absence and in the presence of tertiary amine or lithium acetate. As might be expected from the intramolecular nature of reaction (2), the value of α increases markedly as the concentration of the substrate in the reaction mixture decreases. The effect of the thiol structure on α is uncertain at present, but it is clear that 1,4-dithiol derivatives give lower values than do 1,3-dithiol derivatives.

TABLE. Iodine oxidation of *S*-monoacyldithiols in methanol[a]

Substrate	N_I	N_D[b]	N_E[c]	$2N_I-1$
(I)	0·83	0·56	0·8	0·66
(II)	0·72	0·36	0·7	0·44
(III)	0·65	0·22	0·2	0·30
(IV)	0·58	—	0·5	0·16
(V)	0·57	—	—	0·14

[a] See text for conditions. N_I = no. of mol of I_2 consumed per mol of substrate; N_D and N_E = no. of mol of 1,2-dithiolons and methyl carboxylate esters, respectively, produced per mol of substrate. [b] Determined by u.v. absorption at 360 nm: ϵ for dithiolan related to (I), 84; (II), 76; (III), 91. [c] Determined by g.l.c. The oxidation conditions were different from those in the text. The reaction was carried out in 10 ml MeOH, with I_2 applied as a methanolic solution and $NaHCO_3$ as the base.

Our results are relevant to the enzymic mechanism of pyruvate dehydrogenase. The accepted view[2] is that the acetyl group is transferred from 6-*S*-acetyl-6,8-dimercapto-octanoic acid to CoA and the resultant 6,8-dimercapto-octanoic acid (dihydrolipoic acid) is oxidized by NAD^+ to lipoic acid. The present work, however, indicates that similar reactions could be performed coupled together rather than in a separate series of reactions. Of the numerous oxidants examined (quinones, hydrogen peroxide, *m*-chloroperbenzoic acid, ferrocenium salt, manganese dioxide, Fe^{III} and Mn^{III} salts, bromine, and *N*-bromosuccinimide) only I_2, Br_2, and *N*-bromosuccinimide were effective, and it might be reasonable to expect that such a reaction would occur under favourable unimolecular conditions. The involvement of this coupled oxidation–acyl transfer process has yet to be studied with the pyruvate dehydrogenase complex.

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[1] M. Takagi, S. Goto, and T. Matsuda, *J.C.S. Chem. Comm.*, 1976, 92.

[2] A. L. Fluharty in 'The Chemistry of the Thiol Group, Part 2,' Ed. S. Patai, Interscience, New York, 1974, p. 637; L. J. Reed in 'Comprehensive Biochemistry,' Vol. 14, Eds. M. Florkin and E. H. Stoltz, Elsevier, Amsterdam, 1966, p. 99.