Photo-reaction of Lipoic Acid and Related Organic Disulphides: Reductive Acylation with Aldehydes

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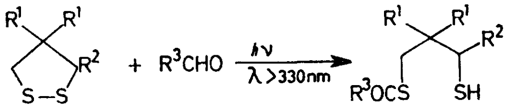
Summary Irradiation of organic disulphides in aldehyde solvents resulted in reductive fission of the S–S linkage giving the corresponding thiol and an equimolar amount of the thiol acylate for linear disulphides and mono *S*-acylated dithiols for cyclic disulphides.

SINCE the early work by Calvin *et al.* the photochemistry of lipoic acid [5-(dithiolan-3-yl)pentanoic acid] (Ia) has been the subject of several investigations.[1] In the course of our studies on the photo-reactions of (Ia) and other 4,4-dialkyl-1,2-dithiolans (Ib—d) we have found that these cyclic disulfides are photo-reduced with aldehydes cleanly to *S*-acyl-1,3-dithiols [equation (1)]. Reactions were carried out for 5 × 10^{-3} M solutions of the disulphide in the aldehyde at <5 °C under nitrogen using liquid-filtered (λ <330 nm removed) radiation from a 100 W immersion type high-pressure mercury lamp. After 1—2 h of irradiation followed by concentration under reduced pressure the residue was purified by column-chromatography on silica gel. The colourless liquid obtained was identified by elemental and spectral analysis. Results are in the Table. The reaction is generally not practicable for substituted aromatic aldehydes since side reactions become serious and product isolation troublesome. Pyruvic acid did not reduce (Ia—d) under our conditions. The product obtained from (Ia) and acetaldehyde was the 8-*S*-acetyldimercapto-octanoic acid (IIIa), as was the case for the preparation from dimercapto-octanoic acid by the conventional acetylation procedure,[2] and not the 6-*S*-acetyl isomer isolated from a natural enzymatic system.[2]



(I) (II) (III)

a; R^1 = H; R^2 = $-[CH_2]_4CO_2H$
b; R^1 = Me; R^2 = H
c; R^1 = Et; R^2 = H
d; R^1,R^1 = $-[CH_2]_5-$, R^2 = H

a; R^1 = H; R^2 = $-[CH_2]_4CO_2H$; R^3 = Me
b; R^1 = Me; R^2 = H; R^3 = Et
c; R^1 = Et; R^2 = H; R^3 = Me
d; R^1 = Et; R^2 = H; R^3 = Et
e; R^1 = Et; R^2 = H; R^3 = Pr^i
f; R^1 = Et; R^2 = H, R^3 = Bu^t
g; R^1 = Et, R^2 = H, R^3 = Ph
h; R^1,R^1 = $-[CH_2]_5-$; R^2 = H; R^3 = Me

The normal method of acylating dithiols, *e.g.*, by acid anhydrides, usually produces a mixture of the desired monoacyl compound, together with the diacyl derivative and the cyclic disulphide produced by oxidation during work-up. The present photochemical procedure gives a clean product and is less sensitive to the presence of other functional groups in the disulphide. The reported yield (< 1%)[6] of (IIIa) from methyl dimercapto-octanoate should be compared with the present yield (78%) from lipoic acid.

This photoreaction was not peculiar to the 1,2-dithiolan ring. Dithian as well as the open chain compound di-n-butyl disulphide in propanal under similar conditions gave an excellent yield of the corresponding thiol propanoate, together with an equimolar amount of butane-1-thiol. Irradiation of L-cystine in acidified aqueous acetaldehyde (80%) gave cysteine in an amount corresponding exactly to the molar amount of cystine which had disappeared; the counterpart product, the *S*-acetyl derivative, was not identified as such, although the *N*-acetyl amino-acid derivative was detected after work-up. Diphenyl disulphide afforded a 60% yield of *S*-phenyl thiopropanoate and benzenethiol. The cyclic compound naphthalene-1,8-diyl disulphide and acetaldehyde similarly produced 1-*S*-acetylnaphthalene-1,8-dithiol† though in much lower yield. The present photo-reaction is a new type of reaction for organic disulphides, though the molecule which accepts the radiation energy in the primary photo-process is probably the solvent aldehyde.

TABLE

Disulphide (I)	Aldehyde (II)	Product (III)	Yield (%)[a]
(Ia)	MeCHO	(IIIa)	78
(Ib)	EtCHO	(IIIb)	42[b]
(Ic)	MeCHO	(IIIc)	73
(Ic)	EtCHO	(IIId)	68
(Ic)	Pr^iCHO	(IIIe)	85
(Ic)	Bu^tCHO	(IIIf)	71
(Ic)	PhCHO	(IIIg)	69
(Id)	MeCHO	(IIIh)	71

[a] Isolated yields are given. [b] The lower yield is caused by polymerization of the starting disulphide before irradiation.

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† This compound was found to be an equilibrium mixture of the ester and its cyclized isomer. It will be discussed elsewhere.

[1] M. Calvin and J. A. Barltrop, *J. Amer. Chem. Soc.*, 1952, **74**, 6153; J. A. Barltrop, P. M. Hayes, and M. Calvin, *ibid.*, 1954, **76**, 4348; R. B. Witney and M. Calvin, *J. Chem. Phys.*, 1955, **23**, 1750; E. E. Smissman and J. R. J. Sorenson, *J. Org. Chem.*, 1965, **30**, 4008; P. R. Brown and J. O. Edwards, *ibid.*, 1969, **34**, 3131; *J. Chromatog.*, 1969, **43**, 512.

[2] I. C. Gunsalus, L. S. Barton, and W. Gruber, *J. Amer. Chem. Soc.*, 1956, **78**, 1763.