A Range of Stereoselectivity in the Microbiological Oxidation of Thioethers to Sulphoxides

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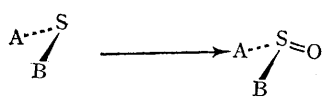
THE oxidations of biotin[1] and some methylthiosteroids[2] provided the first examples of the conversions of thioethers into sulphoxides in the presence of growing aerobic cultures of *Aspergillus niger*. These thioethers are optically active, but Dodson, Newman, and Tsuchiya[3] showed that the optically inactive benzyl phenyl sulphide was converted by the same micro-organism into an active sulphoxide, $[\alpha]_D$ $-20{\cdot}2°$ [18% optically pure based on the rotation $110{\cdot}7°$ found for the (+)-enantiomer (in $CHCl_3$) in the present work]. Examination of the oxidation of various alkyl aryl sulphides has now shown that the stereoselectivity of this microbiological oxidation can range from *ca.* 4 up to 98%. The Table below summarises the results obtained when *A. niger* was grown in the presence of each of the thioethers for four days, the sulphoxides then being isolated by extraction with dichloromethane followed by chromatography. Duplicate experiments were carried out with five of the thioethers, and the results are included in the Table. Figures for the optical purity and yield of each sulphoxide refer to the once crystallised material.

The absolute configurations of the sulphoxides obtained are known, *cf.* references in Table. To facilitate subsequent discussion, the thioethers have been presented in the first column of the Table so that the preferred direction of oxidation of each compound is consonant with the equation:



The high optical purities of some of the sulphoxides produced in this way may be compared with the much lower optical purities (< 6% obtained from the thioethers by a presently available chemical method.[9]

The optical purity of the sulphoxide from t-butyl *p*-tolyl sulphide (*a*) is exceptionally high, and presumably this compound fits especially well into the enzyme system where oxidation occurs. The *p*-tolyl group occupies position A in this oxidation as it does in the reactions of the related *p*-tolyl compounds (*b*), (*c*), and (*e*). In the oxidation of the thioether (*a*), the butyl group occupies position B. The decline in stereoselectivity in proceeding to thioethers (*b*) and (*c*) may be an indication that position B is not as specific for *p*-methylbenzyl and benzyl groups as it is for t-butyl. The oxidation of benzyl t-butyl sulphide (*d*) is in accord with these results; the t-butyl group retains position B and the benzyl group now occupies position A.

Although the selectivity is low, the oxidation of benzyl phenyl sulphide (*f*) provides an example of a thioether in which the *S*-aryl group prefers to occupy position B. Introduction of a *p*-methyl substituent into the *S*-phenyl group of this thioether affords an appreciable directive effect: results (*c*) and (*f*) show that there is a reversal of the preferred direction of oxidation together with a change in the stereoselectivity from 5% to 77%.

4-t-Butylthiacyclohexane was converted by the microbiological procedure into a sulphoxide (11% weight yield) consisting of a 10 : 90 mixture of the *cis*- and *trans*-isomers. Chemical methods in this case give ratios ranging from 10 : 90 to 100 : 0.[10]

Sulphones in up to 5% yield were also obtained from most of the microbiological oxidations. In three cases (*a*), (*c*), and (*d*) the yields of sulphone were sufficiently low (relative to those of sulphoxides) to exclude the possibility that most of the optical activity of the sulphoxides arises *via* the alternative pathway of relatively unselective oxidation of the thioethers followed by partial but highly stereoselective loss of one of the enantiomeric sulphoxides in each pair by oxidation to sulphone. An experiment in which sulphoxide of low optical purity (6%) was recovered from the

partial oxidation (*ca.* 50%) of racemic benzyl *p*-tolyl sulphoxide in the presence of *A. niger* strengthens the conclusion that the optical activity (82 and 71%) of the sulphoxide obtained directly from the thioether (*c*) arises mainly from the asymmetric transfer of oxygen in the initial stage.

TABLE

	Thioether A–S–B	Sulphoxide from *A. niger* % weight yield	% optical purity (sign of rotation)	Reference to absolute configuration
(*a*)	*p*-MeC_6H_4·S·Bu^t	24,20	100,97 (+)	4
(*b*)	*p*-MeC_6H_4·S·CH_2·C_6H_4·Me-*p*	11,11	88,87 (+)	5
(*c*)	*p*-MeC_6H_4·S·CH_2·Ph	19,26	82,71 (+)	6
(*d*)	$PhCH_2$·S·Bu^t	24,61	78,71 (+)	7
(*e*)	*p*-MeC_6H_4·S·Me	48	34 (+)	4
(*f*)	$PhCH_2$·S·Ph	9,35	6,4 (−)	8

(*g*) Phenyl *p*-tolyl sulphide, *o*-tolyl *p*-tolyl sulphide, and mesityl *p*-tolyl sulphide did not give sulphoxides on attempted microbiological oxidation under the present conditions.

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