Influence of the *N*-Sulphonyl and *N*-Alkyl Groups on Stereochemical Features of the Peroxy-acid–Imine Reaction

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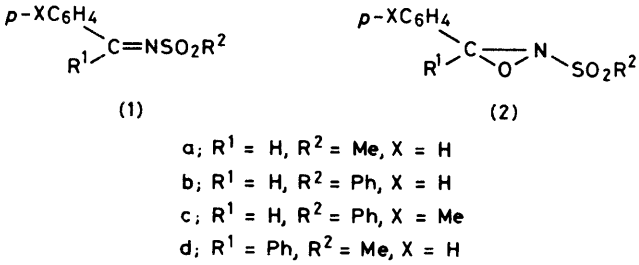
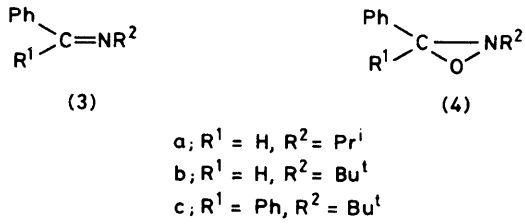
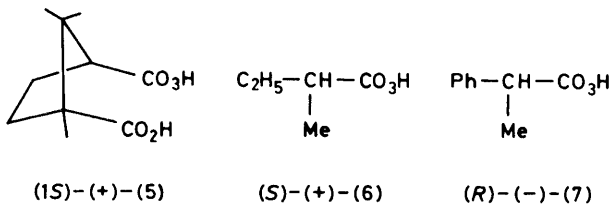
Asymmetric oxidation of prochiral sulphonylimines and *N*-alkylimines has been performed with several chiral peroxy-acids and under the same reaction conditions. The differences in the diastereoselectivity and in the enantioselectivity of the two reactions are discussed in terms of the influence of the sulphonyl and alkyl substituents at nitrogen on the stereochemical features of the peroxy-acid–imine reaction.

Studies carried out by Davis and his co-workers have shown that *m*-chloroperbenzoic acid oxidation of rapidly equilibrating *cis–trans* mixtures of *N*-benzylidenearenesulphonamides [1] affords only the *E*-diastereoisomeric form of the corresponding 2-arylsulphonyl-3-phenyloxaziridines.[2] These compounds represent an interesting new class of stable oxaziridines with a powerful electron-attracting group attached to the nitrogen of the three-membered ring. More recently, we have found that (+)-peroxycamphoric acid oxidation of prochiral *N*-sulphonylimines of types (1a—c) gives optically active *E*-*N*-sulphonyloxaziridines (2a—c).[3] Moreover, fractional crystallization of the crude products allows the separation of highly optically pure enantiomers (2a—c) from the corresponding racemic forms.[3] The easy availability of these new chiral and stable oxaziridines prompted us to study the relative influence of the sulphonyl and alkyl groups on the stereochemical properties of the oxaziridine ring and of the peroxy-acid–imine reaction, by comparing the results of asymmetric oxidations of sulphonylimines and alkylimines of types (1) and (3), respectively, carried out under the same reaction conditions.







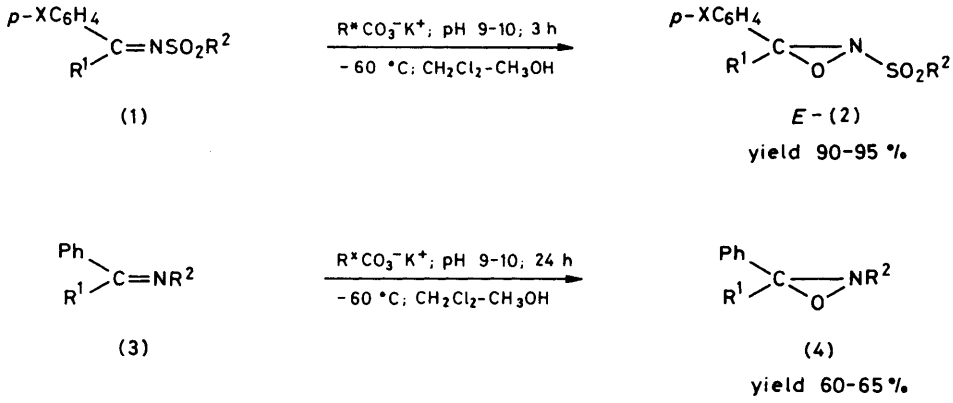
Results

The asymmetric oxidations of (1) and (3) were effected at −60 °C, in basic CH_2Cl_2–CH_3OH solution as summarized in Scheme 1, or in CH_2Cl_2 solution, and by using (1*S*)-(+)-peroxycamphoric acid (5), (*S*)-(+)-2-methylperoxybutyric acid (6), and (*R*)-(−)-2-phenylperoxypropionic acid (7) as chiral oxidative agents (*e.g.*, the chiral peroxy-acids which are known to be of great usefulness in studies regarding the stereochemical properties of the asymmetric oxidation of prochiral sulphides, olefins, or *N*-alkylimines, to the corresponding optically active sulphoxides,[4] epoxides,[5] and *N*-alkyloxaziridines,[6] respectively).

In basic CH_2Cl_2–CH_3OH solution, the oxidation of sulphonylimines (1) affords the corresponding *N*-sulphonyloxaziridines (2) in 90–95% yield, whereas the oxidation of *N*-alkylimines (3) proceeds more slowly and with lower yields of the *N*-alkyloxaziridine derivatives (4). The opposite behaviour is observed when the reaction is carried out in neutral CH_2Cl_2 solution. In this case, the *N*-sulphonyl derivatives (1) undergo attack by peroxy-acids only very slowly, or not at all, whereas compounds (3) are oxidized quite easily (5 h; 80—90% yield) to oxaziridines (4). The stereochemical results of the asymmetric oxidation of prochiral substrates (1) and (3) with optically active peroxy-acids (5)—(7) are summarized in Tables 1 and 2, respectively.

The oxidation by reagents (5)—(7) of *N*-benzylidenemethanesulphonamide (1a) and of *N*-benzylidenearenesulphonamides (1b and c) provided in every case *only* *E*-2-methylsulphonyl-3-phenyloxaziridine (2a) and *E*-2-arylsulphonyl-3-phenyloxaziridines (2b and c); these compounds show negative optical activity. On the other hand, attempts to obtain an enantiomeric excess of 2-methylsulphonyl-3,3-diphenyloxaziridine (2d), *i.e.* of a chiral compound whose molecular asymmetry is due solely to the asymmetric nitrogen atom, by oxidation of *N*-diphenylmethylenemethanesulphonamide (1d) with (+)-(5) or (−)-(7), have failed: in every case, racemic (2d) was recovered (Table 1). The sign of the optical activity of (2a—c) is not correlated with the absolute configuration of the chiral peroxy-acids: (−)-oxaziridines are obtained independently of whether (*S*)-(5), (*S*)-(6), or (*R*)-(7) is used as chiral percxidant. The oxidation of (1) by (*S*)-(5), when carried out in CH_2Cl_2 solution, provided 5—7% yield of optically active oxaziridine only in the case of the *E*-*N*-methylsulphonyl derivative (2a) (Table 1, footnote *c*). The enantiomeric excess of this compound, which still shows negative optical activity, is very low (1.1%), if compared with the 16—20% optical yields of the reactions carried out under the basic conditions of Scheme 1.

Oxidation of *N*-isopropylbenzylideneamine (3a) by (*S*)-(5)



Scheme 1.

Table 1. Asymmetric synthesis of *N*-sulphonyloxaziridines (2) under the reaction conditions of Scheme 1

Peroxy-acid	Oxaziridine	$[\alpha]_D^{20}$ (°) [a]	Optical yield (%) [b]
(*S*)-(+)-(5) [c]	(2a)	−32.0 [d]	16.7
(*S*)-(+)-(6)	(2a)	−2.0	1.0
(*R*)-(−)-(7)	(2a)	−13.8	7.2
(*S*)-(+)-(5) [e]	(2b)	−25.4 [d]	19.4
(*S*)-(+)-(6)	(2b)	−2.6	2.0
(*R*)-(−)-(7)	(2b)	−10.9	8.3
(*S*)-(+)-(5)	(2c)	−19.1 [d]	16.3
(*R*)-(−)-(7)	(2c)	−12.7	10.8
(*S*)-(+)-(5) [f]	(2d)	0.0	
(*R*)-(−)-(7)	(2d)	0.0	

[a] Optical activity of the crude products recorded in $CHCl_3$; values corrected for optically pure peroxy-acids. [b] Calculated on the basis of the highest optical activities of (2a—c) reported in ref. 3. [c] (*S*)-(5) oxidation of (1a), carried out for 65 h in CH_2Cl_2, gave 5—7% of (2a), $[\alpha]_D^{20}$ −3.0° ($CHCl_3$). [d] Value from ref. 3. [e] (*S*)-(5) oxidation of (1b), carried out for 65 h in CH_2Cl_2, gave no detectable amount of (2b). [f] (*S*)-(5) oxidation of (1d), carried out for 10 days in CH_2Cl_2, gave <5% of (2d), $[\alpha]_D$ 0.0°.

gives, in every case, *both* optically active *E*- and *Z*-2-isopropyl-3-aryloxaziridine diastereoisomers (4a) (Table 2). Similarly, oxidations by (*S*)-(5) and (*R*)-(7) of *N*-t-butylbenzylideneamine (3b) and of *N*-(diphenylmethylene)-t-butylamine (3c) provides optically active *E*-2-t-butyl-3-phenyloxaziridine (4b), as well as optically active 2-t-butyl-3,3-diphenyloxaziridine (4c). The oxidation of (3) with (*S*)-(+)-(5), when carried out in CH_2Cl_2 solution, shows a uniform bias in favour of oxaziridines (4) all having the (−)-(*S*) configuration at nitrogen. With the exception of the *Z*-oxaziridine (4a), this behaviour is reversed in favour of *E*-(4a), *E*-(4b), and (4c) having the (+)-(*R*) configuration at nitrogen when the reaction is carried out with (*S*)-(5) and in basic CH_2Cl_2–CH_3OH solution. Under the reaction conditions of Scheme 1, no correlation is observed between the chirality of (*S*)-(5) and (*R*)-(7) peroxy-acids and the configuration of the *N*-t-butyl derivatives (4b and c). In fact, (*R*)-(+)-(4b) and (*R*)-(+)-(4c) have been obtained both from the (*S*)-(5) and the (*R*)-(7) oxidations of (3b and c), respectively. Quite surprisingly, a lack of configurational correlation has also been found between the chirality of the optically active peroxy-acids and the chirality of oxaziridine (4b), as obtained by asymmetric oxidation of the *N*-t-butylimine (3b) in CH_2Cl_2 solution (Table 2). This behaviour strongly contrasts with the correlation observed in the asymmetric oxidations of the *N*-t-butylimine (3c), when carried out in $CHCl_3$ solution with (*S*)-(5) and (*R*)-(7).[7] Finally, in the case of the asymmetric oxidations of *N*-alkylimines (3), and still in contrast with the results for the oxidations of sulphonylimines (1), the reactions carried out in CH_2Cl_2 solution give higher optical yields than the reactions performed in basic CH_2Cl_2–CH_3OH solution.

Discussion

The contrasting results observed in the diastereoselectivity or in the enantioselectivity of derivatives (2) and (4) should depend on the relative effects of the sulphonyl and alkyl groups which, in principle, may operate (i) on the pyramidal stability of the oxaziridine nitrogen, as observed for aziridine systems [8] or (ii) on the stereochemical behaviour of the peroxy-acid–imine reaction.

^{1}H N.m.r. studies [2] seem to indicate that the sulphonyl substituent does not significantly lower the high values (27—34 kcal mol^{-1}) of the nitrogen inversion barrier observed for *N*-alkyloxaziridines.[7] Further evidence of the stereochemical stability of (2) has been obtained by recording the n.m.r. spectrum of (2d) in the presence and absence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato]europium(III), Eu(fhc)$_3$. As reported in the Figure, under achiral conditions and in $CDCl_3$ solution, the enantiotopic CH_3 protons of the *N*-methyl substituent of (2d) show a singlet at δ 3.10, whereas in the presence of Eu(fhc)$_3$ the resonances of the CH_3 protons are well separated (9.6 Hz at 20 °C), of nearly equal area, and remain clearly distinct in the 20—55 °C temperature range, thus supporting an enantiomeric structure for (2d), stable at the pyramidal nitrogen atom at room temperature.*

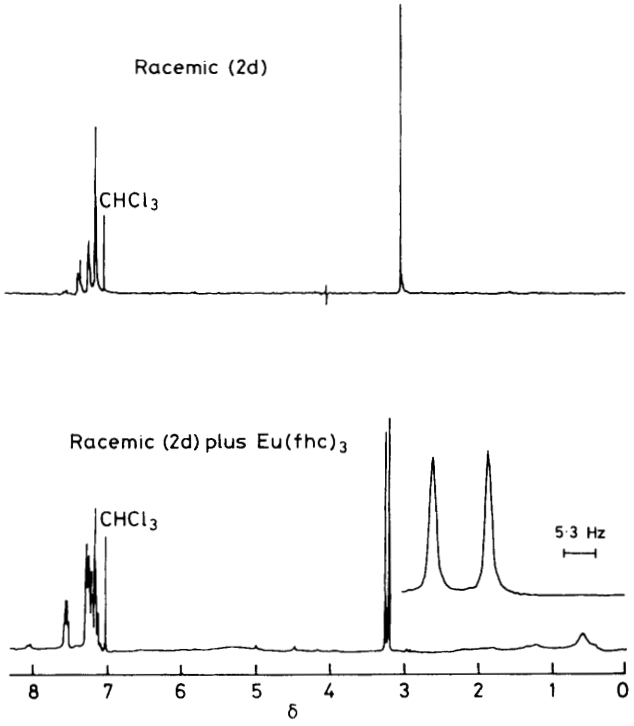
Taking into account this evidence, we can analyse the results of Tables 1 and 2 in the light of the (1) ⟶ (2) and (3) ⟶ (4) oxidation routes in alkaline media. Davis and his co-workers have proposed a two-step process for the oxidation of sulphonylimines which involves attack of the peroxy-acid anion on the electron-deficient C=N bond of the sulphonylimine substrate. This mechanism is similar to that proposed for peroxy-acid oxidation of *N*-alkylimines to oxaziridines under neutral conditions,[6,9,10] and closely resembles the epoxidation process of αβ-unsaturated sulphones [11] and αβ-unsaturated carbonyl compounds.[12] Our previous [3] and

* *X*-Ray crystal spectra clearly indicate pyramidal geometry at the nitrogen atom of (2d) in the solid state (A. Forni, I. Moretti, P. Sgarabotto, and G. Torre, unpublished work).

Table 2. Asymmetric synthesis of *N*-alkyloxaziridines (4)

Peroxy-acid	Oxaziridine		$[\alpha]_D^{20}$ (°) (i) [a]	$[\alpha]_D^{20}$ (°) (ii) [b]	Absolute configuration (i) [a]	Absolute configuration (ii) [b]	Optical yield (%) (i) [a]	Optical yield (%) (ii) [b]
(*S*)-(+)-(5)	(4a)	*E*	+0.7 [c,d]	−24.1 [c,e]	(2*R*,3*R*) [f]	(2*S*,3*S*) [f]		
		Z	−3.9 [c,d]	−11.7 [c,e]	(2*S*,3*R*) [f]	(2*S*,3*R*) [f]	5.4 [g]	16.2 [g]
(*S*)-(+)-(5)	(4b)	*E*	+7.7 [c]	−30.5 [c]	(2*R*,3*R*) [f]	(2*S*,3*S*) [f]	9.0 [h]	35.6 [h]
(*R*)-(−)-(7)	(4b)	*E*	+0.4 [c]	−12.2 [c]	(2*R*,3*R*) [f]	(2*S*,3*S*) [f]	0.5 [h]	14.2 [h]
(*S*)-(+)-(5)	(4c)		+11.2 [i]	−28.2 [i]	(*R*) [m]	(*S*) [m]	4.3 [n]	10.9 [n]
(*R*)-(−)-(7)	(4c)		+9.5 [i]	+26.7 [i]	(*R*) [m]	(*R*) [m]	3.6 [n]	10.4 [n]

[a] Results from the reactions carried out according to Scheme 1. [b] Results from the reactions carried out in CH_2Cl_2. [c] Optical activity in CCl_4 (*c* 3%) of pure isomers obtained by chromatography on silica of the crude product with diethyl ether–light petroleum (b.p. 40—60 °C) as eluant; values corrected for optically pure peroxy-acids. [d] *E*- and *Z*-isomers obtained as a 9 : 1 mixture. [e] *E*- and *Z*-isomers obtained as a 2 : 1 mixture. [f] Absolute configuration assigned according to W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.*, 1978, **43**, 4475. [g] Optical yield determined by n.m.r. spectroscopy carried out in the presence of $Eu(fhc)_3$; attempts to obtain the optical yield of the *E*-diastereoisomer by this way failed. [h] Optical yield calculated according to the maximum optical value reported by Pirkle and Rinaldi. [i] In $CHCl_3$ (*c* 3%). [l] Value from ref. 7. [m] Absolute configuration assigned according to ref. 6. [n] Optical yield calculated on the basis of the maximum optical activity reported in ref. 7.



200 MHz N.m.r. spectrum of the SO_2CH_3 protons of racemic (2d) (0.1M in $CDCl_3$) in the absence (top) and presence (bottom) of *ca.* 0.04M-$Eu(fhc)_3$

present results suggest that resemblances between the oxidations of imines and olefins in basic solution also exist in the stereochemical aspects of the two processes. The stereochemistry of nucleophilic epoxidation of electrophilic olefins has been studied experimentally [11,12] and, very recently, by theoretical calculations.[13] These studies suggest that the stereoselectivity and the stereospecificity of the epoxidation strongly depend on the activation energies for the cyclization process and for rotation around the C^-C^- bond of the intermediate carbanions in the two-step route to epoxides. Accordingly, we may rationalize our results by assuming that the nature of the substituents at the nitrogen atom of the imine substrate essentially acts on the lifetime of intermediate adducts of types (A) and (A′) depicted in Scheme 2, and on the relative energies of the ring-closure transition states. In particular, the results of Table 2 should indicate that, in the case of oxidation of *N*-alkylimines, equilibration of (A) and (A′) is slower than cyclization; on the other hand, the results in Table 1 can be accounted for by considering that the powerful electron-withdrawing sulphonyl substituent should contribute to the formation of long-lived intermediate adducts, so that equilibration of (A) and (A′) by rotation about the C−N bond and/or inversion at nitrogen proceeds faster than ring closure, thus yielding racemic (2d) and the thermodynamically more stable optically active *E*-(2a—c) diastereoisomers.

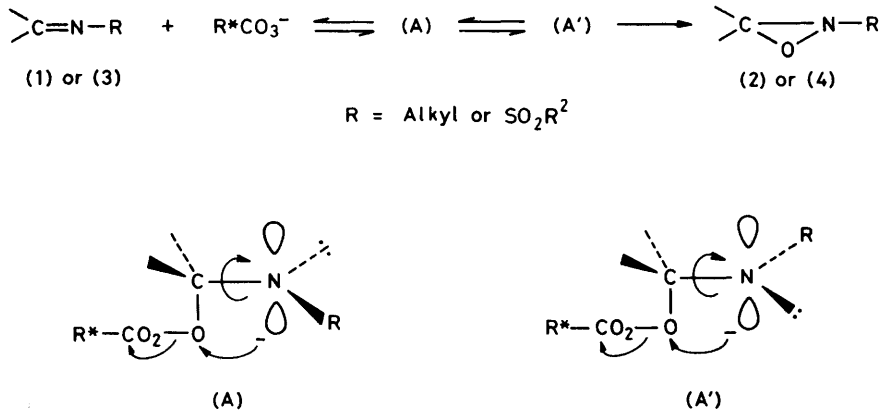
Another interesting aspect of the present work is relevant to the absolute stereochemistry of the chiral peroxy-acid–prochiral imine interaction and, in particular, to the unknown absolute configuration of optically active *N*-sulphonyloxaziridines of types (2a—c). The results of Table 2 indicate that the absolute stereochemistry of the oxidation of imines depends not only on the nature of the solvent, as already reported,[6,7,14] but even on the *cis–trans* and on the aldimine–ketimine structure of the starting material. Such complex behaviour prevents, at present, a confident correlation of the (−)-sign of the optical activity of the *N*-sulphonyloxaziridines *E*-(2a—c) with the (*R*)-configuration at nitrogen observed for the corresponding oxaziridines *E*-(+)-(4a) and -(+)-(4b), when obtained in the basic medium of Scheme 1.

Experimental

Optical rotations were measured with a Perkin-Elmer 141 polarimeter with cells of 1 or 10 cm path length. N.m.r. spectra were recorded for $CDCl_3$ solutions, with a Varian XL-200 instrument. Mass spectra were determined with a Varian MAT-112 instrument.

Starting Materials.—Optically active peroxy-acids (*S*)-5,[15] (*S*)-(6),[4] and (*R*)-(7)[4] were prepared according to the literature.

N-Alkylaldimines (3a and b),[16] and *N*-t-butylketimine (1c),[17] were obtained by condensation of the appropriate carbonyl compound and amine. *N*-Sulphonylaldimines (1a—c) were prepared as previously described.[2,3] *N*-Diphenylmethylenemethanesulphonamide (1d) was prepared by reaction at 0—5 °C of diphenylmethyleneamine in diethyl ether containing a 50% molar excess of triethylamine with a 10% excess of methanesulphonyl chloride. Evaporation of the solvent gave a solid which was twice recrystallized from ethyl acetate–$CHCl_3$ (2 : 1) to give (1d) in 70% yield, m.p. 141—142 °C; *m/e* 259 (M^+); δ ($CDCl_3$) 3.2 (3 H, s) and 7.6 (10 H, s).



Scheme 2.

General Synthesis of Oxaziridines.—In the case of the reactions carried out in basic medium, the following general procedure was used. In a three-necked flask (250 ml), equipped with mechanical stirrer and dropping funnel, were placed the imine (10 mmol) in CH_2Cl_2 (30 ml) and CH_3OH (30 ml). This solution was cooled to −60 °C and added over a few minutes to a solution of the chiral peroxy-acid (11 mmol) in CH_2Cl_2 (10 ml) and CH_3OH (20 ml), made alkaline (pH 9—10) with methanolic KOH. At the end of the reaction, the basic solution was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with aqueous $NaHCO_3$ and water and dried (Na_2SO_4). After the solution was dried, the solvent was removed on a rotatory evaporator keeping the bath temperature at 20—25 °C, to give the crude oxaziridine product. The asymmetric oxidations in CH_2Cl_2 were carried out at −60 °C and according to the procedure described for the corresponding reactions in $CHCl_3$.[7] In every case the end of the oxidation was monitored by t.l.c. on silica with diethyl ether–light petroleum (b.p. 40—60 °C) (1 : 1) as eluant.

Acknowledgement

We thank the C.N.R., Rome, for financial support.

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Received 16*th July* 1982; *Paper* 2/1217