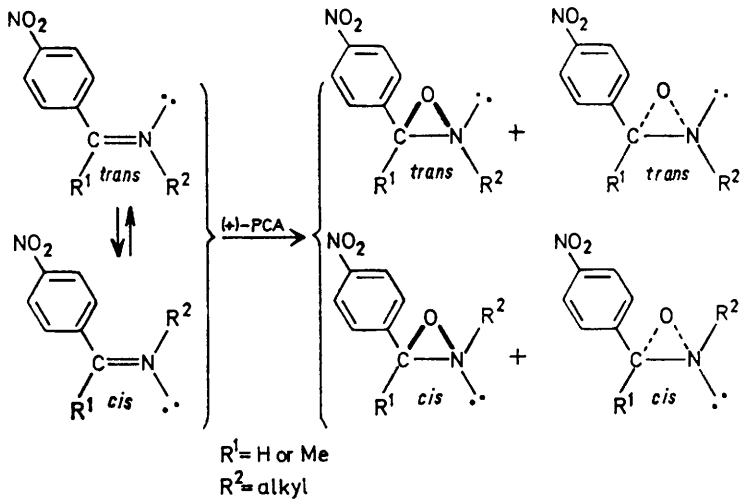
Dynamic Stereochemistry of Imines and Derivatives. Part VII.[1] Thermal Epimerization of Chiral Oxaziridines

By **Johannes Bjørgo, Derek R. Boyd,* Rose M. Campbell,** and **Norris J. Thompson,** Department of Chemistry, Queen's University of Belfast, Belfast BT9 5AG
W. Brian Jennings, Department of Chemistry, University of Birmingham, Birmingham B15 2TJ

An enantiomeric preference in both *cis*- and *trans*-oxaziridine isomers is produced by asymmetric oxygen atom transfer from (+)-peroxycamphoric acid to imines. A favourable selection of reaction conditions followed by fractional crystallization and thermal epimerization is used to obtain enantiomerically homogeneous *cis*- and *trans*-oxaziridines. Optical activity was totally retained in the thermal isomerization cycle (*cis* → *trans* → *cis* or *trans* → *cis* → *trans*) indicating that oxaziridines isomerize by nitrogen inversion rather than by bond cleavage. The barriers to pyramidal nitrogen inversion ($\Delta G^{\ddagger}$) in thermally stable *cis*- and *trans*-oxaziridines were measured by both n.m.r. and polarimetric methods.

PYRAMIDAL nitrogen stability in non-bridgehead positions was first demonstrated in 1968 by the physical separation of *cis*- and *trans*-isomers of *N*-chloroaziridines [2] and *N*-alkyloxaziridines.[3] The latter report also provided the earliest example of asymmetric synthesis at nitrogen since the optically active oxaziridines were formed from the reaction of the chiral oxidant, (+)-peroxycamphoric acid (PCA), with a range of imines. Subsequent studies of the imine–(+)-PCA synthesis of oxaziridines showed that enantioselectivity could be increased to give an optimum of *ca.* 50% optical purity.[4-7] This relatively high optical yield associated with the imine–(+)-PCA reaction is in marked contrast with the low optical purity consistently observed in olefin–(+)-PCA epoxidation (<8%)[8-10] and in sulphide–(+)-PCA sulphoxidation (<12%).[11] Thus in terms of enantioselectivity the imine–(+)-PCA reaction currently represents the closest stereochemical analogy to the chiral oxygen atom transfer enzymes (mono-oxygenases) ubiquitous in nature.[12,13]



SCHEME 1 Stereochemistry of oxidation of *trans–cis*-imines

Earlier studies [3,4] of the imine–(+)-PCA reaction revealed a marked effect of solvent and of temperature on the optical yield of oxaziridines. The present study concerns the effect of imine structure on stereoselectivity. (+)-PCA Oxidation of the equilibrating *trans–cis*-imines shown in Scheme 1 generally gives both *cis*- and *trans*-oxaziridines each with a predominance of one enantiomeric form (enantioselectivity).

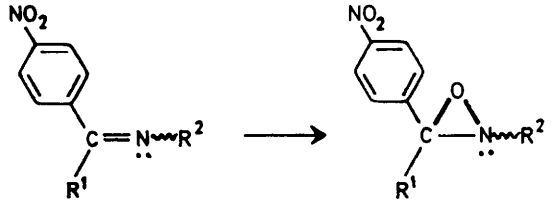
[1] Part VI, D. R. Boyd, D. C. Neill, C. G. Watson, and W. B. Jennings, *J.C.S. Perkin II*, 1975, 1813.
[2] D. Felix and A. Eschenmoser, *Angew. Chem. Internat. Edn.*, 1968, **7**, 224.
[3] D. R. Boyd, *Tetrahedron Letters*, 1968, 4561.
[4] D. R. Boyd and R. Graham, *J. Chem. Soc.* (*C*), 1969, 2648.
[5] D. R. Boyd, R. Spratt, and D. M. Jerina, *J. Chem. Soc.* (*C*), 1969, 2650.
[6] F. Montanari, I. Moretti, and G. Torre, *Chem. Comm.*, 1968, 1694; 1969, 1086.
[7] F. Montanari, I. Moretti, and G. Torre, *Gazzetta*, 1973, **103**, 681.
[8] R. C. Ewins, H. B. Henbest, and M. A. McKervey, *Chem. Comm.*, 1967, 1085.
[9] F. Montanari, I. Moretti, and G. Torre, *Chem. Comm.*, 1969, 135.
[10] D. R. Boyd, D. M. Jerina, and J. W. Daly, *J. Org. Chem.*, 1970, **35**, 3170.
[11] U. Folli, D. Iarossi, F. Montanari, and G. Torre, *J. Chem. Soc.* (*C*), 1968, 1317.
[12] G. S. Fonken and R. A. Johnson, in 'Chemical Oxidations with Microorganisms,' Marcel Dekker, New York, 1972.
[13] B. J. Auret, D. R. Boyd, H. B. Henbest, C. G. Watson, K. Balenović, V. Polak, V. Johanides, and S. Divjak, *Phytochemistry*, 1974, **13**, 65.

The results of (+)-PCA oxidation of imines of the type shown in Scheme 1 are summarized in Table 1. The optical rotations were found to be negative for both the *cis*- and *trans*-epimers as found for previous oxidations of imines with (+)-PCA.[3-7] In order to investigate the optical purity and relative configuration, the separated *cis*- and *trans*-oxaziridine isomers were heating, both isomers of the other oxaziridines (5) and (6) were easily isomerized.

It is clear from the results in Table 2 that thermal epimerization at nitrogen involves a change in sign of the optical rotation. Thus the predominant enantiomers of each of the *cis*- and *trans*-oxaziridines produced simultaneously on oxidation are opposite in absolute

TABLE 1

Stereochemical relationships between *trans–cis*-imines and product *trans–cis*-oxaziridines



Oxaziridine	Imine	R^1	R^2	*cis*-Imine (%) *†	*cis*-Oxaziridine (%) †‡	$[\alpha]_D$ (°) oxaziridine § *trans*	$[\alpha]_D$ (°) oxaziridine § *cis*
(1)	(7)	H	Me	<1	34	−10.5	−0.7
(2)	(8)	H	Pr^i	<1	45	−10.0	+5.7
(3)	(9)	H	Bu^t	<1	1	−11.2	
(4)	(10)	Me	Me	3	80	−5.4	−9.6
(5)	(11)	Me	Pr^i	5	80	−17.0	−12.5
(6)	(12)	Me	Bu^t	2	73	−2.2	−41.0

* % *cis*-Isomer in equilibrium with the *trans*-isomer, determined by n.m.r. in $CDCl_3$ solution at room temperature. † Product oxaziridines were separated and purified by column chromatography prior to optical rotation measurement in chloroform solution at room temperature. ‡ Initial % *cis*-oxaziridine after oxidation in CH_2Cl_2 at *ca.* 0°, determined by n.m.r. in $CDCl_3$ solution at room temperature. § *cis*-Nomenclature is used to relate the *p*-nitrophenyl and R^2 groups.

thermally epimerized in tetrachloroethylene solution (Table 2). The *cis*- and *trans*-isomers were isolated and purified by chromatography and identified by n.m.r. (Table 3) prior to specific rotation measurement. It

TABLE 2

Specific rotations from thermal epimerization of *cis–trans*-oxaziridines

Oxaziridine	$[\alpha]_D$ (°) of oxaziridine *before* attempted epimerization: *trans*	*cis*	$[\alpha]_D$ (°) of oxaziridine *after* attempted epimerization * : *trans*	*cis*
(1)	−10.5		−10.5	
		−0.7	+0.9	−0.7 †
(2)	−10.0		−10.0	
		−5.7	+5.4	−5.7 †
(3)	−11.2		−11.2	
(4)	−5.4		‡	‡
		−9.6		
(5)	−17.0		−17.0	+23.1
		−12.5	+11.0	−12.5
(6)	−2.2		−2.2	+4.1
		−41.0	+19.0	−41.0

* Epimerizations were carried out in C_2Cl_4. † Epimerization terminated at *ca.* 50% interconversion. ‡ Decomposition and low yields of *trans*-isomer prevented the isolation of an adequate quantity of pure product.

was not possible to isomerize the *trans*-oxaziridines (1)—(3), whereas the corresponding *cis*-oxaziridines could be isomerized before decomposition became appreciable. With exception of the oxaziridines *cis*- and *trans*-(4) which were very rapidly decomposed on configuration at the ring carbon atoms. The stereoselectivity of attack at the enantiotopic faces of the

TABLE 3

N.m.r. [$\delta(CDCl_3)$] data for *cis*- and *trans*-oxaziridines

Oxaziridine	NR^2: *trans*	*cis*	CR^1: *trans*	*cis*
(1)	2.95 (s)	2.49 (s)	4.57 (s)	5.33 (s)
(2)	2.47 (sp)	2.30 (sp)	4.69 (s)	5.42 (s)
	1.34 (d)	1.28 (d)		
	1.21 (d)	0.79 (d)		
(3)	1.17 (s)		4.70 (s)	
(4)	2.95 (s)	2.40 (s)	2.02 (s)	1.81 (s)
(5)	1.90 (sp)	1.90 (sp)	1.96 (s)	1.83 (s)
	1.31 (d)	1.20 (d)		
	1.18 (d)	0.83 (d)		
(6)	1.31 (s)	0.91 (s)	2.06 (s)	1.72 (s)

sp = Septuplet.

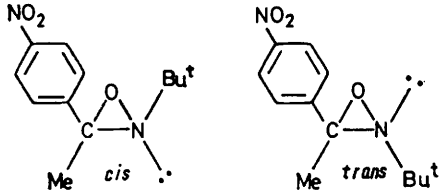
imines during asymmetric synthesis resulted in a higher optical purity for the *trans*-isomer of oxaziridines (1), (2), and (5) but in a lower value for *trans*-(6). It is difficult to detect any definite trend in enantioselectivity with steric size from the results in Table 2 since only oxaziridines *trans*-(3), *trans*-(6), and *cis*-(6) have been resolved (see later).

Optically active oxaziridine *trans*-(3) obtained after (+)-PCA oxidation at −70° in dichloromethane was previously [4] reported to have a maximum $[\alpha]_D$ of −95° ($CHCl_3$), after multiple recrystallization from pentane.†

† Subsequent experiments showed that the maximum rotation was in fact $[\alpha]_D$ −99° ($CHCl_3$) and the latter sample is now considered to be enantiomerically homogeneous.

With similar treatment of oxaziridine *cis*-(6) a constant optical rotation was again observed after multiple recrystallization from pentane, $[\alpha]_D$ −160° ($CHCl_3$). Thermal interconversion of *cis*-(6), $[\alpha]_D$ −160° ($CHCl_3$) produced *trans*-(6), $[\alpha]_D$ +82° ($CHCl_3$). This total resolution was repeated on a larger scale but the maximum optical rotation observed after recrystallization to constant rotation was identical to that recorded above and is thus considered to represent 100% optical purity.

The thermal isomerization of geometric and optical isomers of aziridines [14] and oxirans [15] proceeds *via* conrotatory ring opening to the isoelectronic azomethine ylide and carbonyl ylide intermediates respectively. The complete retention of optical activity which was observed after the thermal isomerization cycle of *trans*-(6) ⟶ *cis*-(6) ⟶ *trans*-(6) or *cis*-(6) ⟶ *trans*-(6) ⟶ *cis*-(6) (Scheme 2) indicates that isomerization did not involve any measurable degree of bond



SCHEME 2 Thermal epimerization cycles

cleavage (*e.g.* nitrone formation) analogous to that found in aziridines and oxirans. Thus, thermal isomerization of oxaziridines *trans*- and *cis*-(6), as suggested previously [6,16] for other oxaziridines, is now shown to proceed exclusively by a nitrogen inversion mechanism.

The barrier to pyramidal nitrogen inversion for *trans*- and *cis*-(6) was determined after following the progress of epimerization by (a) n.m.r. (in tetrachloroethylene) or (b) polarimetry (using the n.m.r. method to determine the equilibrium constant K). Both methods gave approximately the same $\Delta G^{\ddagger}$ values, however the standard deviation was larger by the n.m.r. method:

(a) T 333 K, % *trans* at equilibrium 34 ± 1

$k_{trans \rightarrow cis} + k_{cis \rightarrow trans}$ (2.1 ± 0.3) × 10^{-4} s^{-1}

$k_{trans \rightarrow cis}$ (1.38 ± 0.42) × 10^{-4} s^{-1},
$\Delta G^{\ddagger}_{trans \rightarrow cis}$ 25.40 ± 0.25 kcal mol^{-1}

$k_{cis \rightarrow trans}$ (0.72 ± 0.13) × 10^{-4} s^{-1},
$\Delta G^{\ddagger}_{cis \rightarrow trans}$ 25.85 ± 0.15 kcal mol^{-1}

(b) T 333 K, % *trans* at equilibrium 34 ± 1

$k_{trans \rightarrow cis} + k_{cis \rightarrow trans}$ (2.3 ± 0.1) × 10^{-4} s^{-1}

$k_{trans \rightarrow cis}$ (1.51 ± 0.17) × 10^{-4} s^{-1},
$\Delta G^{\ddagger}_{trans \rightarrow cis}$ 25.35 ± 0.1 kcal mol^{-1}

$k_{cis \rightarrow trans}$ (0.79 ± 0.07) × 10^{-4} s^{-1},
$\Delta G^{\ddagger}_{cis \rightarrow trans}$ 25.80 ± 0.1 kcal mol^{-1}

These isomerization barriers agree well with previous measurements for 2-t-butyl substituted oxaziridines in tetrachloroethylene solvent [16] and are, as anticipated for an inversion mechanism, much lower than those found from thermal epimerization of N-methyloxaziridines (*ca.* 32 kcal mol^{-1}).[17] While thermal decomposition of the N-methyloxaziridines used in the latter work occurs readily, little evidence of decomposition of oxaziridines *trans*- and *cis*-(6) during the course of the kinetic experiments (333 K in tetrachloroethylene) could be found. As expected the $\Delta G^{\ddagger}$ values for 3-alkyl-3-aryloxaziridines *trans*- and *cis*-(6) lie between those for the diaryloxaziridine (13) (26.2 kcal mol^{-1}),[16] and the dialkyloxaziridine (14) (24.9 kcal mol^{-1}).[16]

The mechanism of the imine–peroxyacid reaction is of current interest in view of the conflicting interpre-

TABLE 4

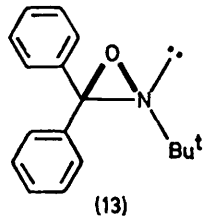
Physical properties and microanalytical data for imines (7)—(12) and oxaziridines (1)—(6)

Imine*	
(7)	M.p. 106—108° (lit.,[19] 107°)
(8)	M.p. 49—50° (lit.,[20] 54—55°)
(9)	M.p. 73—75° (lit.,[20] 73—75°)
(10)	M.p. 71—73° (Found: C, 60.5; H, 5;5, N, 15.5. $C_9H_{10}N_2O_2$ requires C, 60.7; H, 5.6; N, 15.7%)
(11)	B.p. 95° at 0.05 mmHg (Found: C, 64.0; H, 6.8; N, 13.5. $C_{11}H_{14}N_2O_2$ requires C, 64.1; H, 6.8; N, 13.6%)
(12)	B.p. 100° at 0.1 mmHg (Found: C, 65.2; H, 7.3; N, 12.7. $C_{12}H_{16}N_2O_2$ requires C, 65.5; H, 7.3; N, 12.7%)
Oxaziridine*	
trans-(1)	M.p. 83—84°, $[\alpha]_D$ −10.5° (lit.,[1] 80—81°)
cis-(1)	M.p. 93—94°, $[\alpha]_D$ −0.7° (lit.,[1] 94—96°)
trans-(2)	M.p. 46—47°, $[\alpha]_D$ −10.0° (lit.,[1] 47—48°)
cis-(2)	M.p. 103—104°, $[\alpha]_D$ −5.7° (lit.,[1] 102—103°)
trans-(3)	M.p. 61—62°, $[\alpha]_D$ −11.2°; m.p. 83—84°, $[\alpha]_D$ ±99° ($CHCl_3$) (lit.,[20] 65—66°)
trans-(4)	M.p. 87—88°, $[\alpha]_D$ −5.4° (Found: C, 55.9; H, 5.2; N, 14.3. $C_9H_{10}N_2O_3$ requires C, 55.7; H, 5.2; N, 14.4%)
cis-(4)	M.p. 89—90°, $[\alpha]_D$ −9.6° (Found: C, 55.6; H, 5.2; N. 14.6%)
trans-(5)	M.p. 49—50°, $[\alpha]_D$ −17.0° (Found, C, 59.0; H, 6.6; N, 12.4. $C_{11}H_{14}N_2O_3$ requires C, 59.45; H, 6.3; N, 12.6%)
cis-(5)	M.p. 81—83°, $[\alpha]_D$ −12.5° (Found: C, 59.2; H, 6.4; N, 12.5%)
trans-(6)	M.p. 57—58°, $[\alpha]_D$ −2.2° † (Found: C, 60.9; H, 6.8; N, 11.9. $C_{12}H_{16}NO$ requires C, 61.0; H, 6.8; N, 11.9%)
cis-(6)	M.p. 84—85°, $[\alpha]_D$ −40° ‡ (Found: C, 60.6; H, 6.6; N, 11.8%)

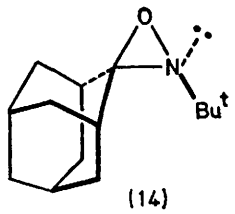
* All taken in $CHCl_3$. † Maximum rotation found from epimerization of *cis*-(6) ($[\alpha]_D$ ±160°) was $[\alpha]_D$ +82°. ‡ Maximum rotation obtained after oxidation in CH_2Cl_2 at −70° and recrystallization to constant rotation was $[\alpha]_D$ ±160°.

[14] R. Huisgen and H. Mader, *J. Amer. Chem. Soc.*, 1971, **93**, 1777.
[15] H. H. J. MacDonald and R. J. Crawford, *Canad. J. Chem.*, 1972, **50**, 428.
[16] J. Bjørgo and D. R. Boyd, *J.C.S. Perkin II*, 1973, 1575.
[17] A. Mannschreck, J. Lins, and W. Seitz, *Annalen*, 1969, **727**, 224.

tations of kinetic studies,[18,19] however it is obviously not possible to distinguish between the concerted and stepwise mechanisms from the differing degrees of enantioselectivity shown by the product *trans*- and



(13)



(14)

cis-oxaziridines. It is however also of interest to speculate on the reasons for the considerably higher optical yields of the imine–(+)-PCA reaction relative to olefin– or the sulphide–(+)-PCA reactions. The much faster rate of imine oxidation (and thus lower temperatures at which oxidation will occur) will favour a higher degree of asymmetric induction. An additional or alternative explanation could be that the mechanism is stepwise, in contrast to the concerted mechanism which has been established for olefin– and sulphide–peroxyacid oxidations.[1] It is also possible that hydrogen bonding between the nitrogen lone pair of the imine and the free carboxy-group in (+)-PCA may increase the rigidity of the transition state and lead to a higher degree of enantioselectivity.

The value of this enantioselective procedure over the analogous epoxidation and sulphoxidation reactions is evident from the range of oxaziridines [(3), (6), (13), and 2-isopropyl-3,3-diphenyloxaziridine] which have to date been isolated in optically pure form after a combination of asymmetric synthesis and fractional crystallization.

[18] V. Madan and L. B. Clapp, *J. Amer. Chem. Soc.*, 1969, **91**, 6078.

EXPERIMENTAL

The methods of synthesis and of stereochemistry determination of imines and of oxaziridines are as previously reported.[1,4,5,16] The separation of *cis*–*trans*-oxaziridine mixtures was achieved by silica-gel column chromatography eluting with either dichloromethane (100%) or ether–light petroleum (5 : 95). Separation of *trans*- and *cis*-(4) proved difficult under the latter conditions and a total separation was obtained by repeated preparative t.l.c. using silica gel plates and dichloromethane as eluant. The physical properties and microanalytical data for all new compounds are included in Table 4.

Kinetic studies were conducted under thermostatically controlled conditions (±0.1 K) using purified tetrachloroethylene. A Varian A-60 n.m.r. instrument and a Perkin-Elmer 141 automatic polarimeter were used to monitor the progress of the epimerization. The n.m.r. kinetic studies were carried out in the usual manner using direct multiple integration which gave both $k_{trans \rightarrow cis} + k_{cis \rightarrow trans}$ and $K_{\text{equil.}}$. The treatment of kinetic data was as reported previously.[16]

We thank Messrs. W. J. Swindall and H. B. McKnight for microanalytical data, the Northern Ireland Ministry of Education for a Studentship (to R. M. C.), and the Queen's University of Belfast for a Demonstratorship (J. B.).

[5/1092 *Received*, 5*th June*, 1975]

[19] Y. Ogata and Y. Sawaki, *J. Amer. Chem. Soc.*, 1973, **95**, 4687.

[20] W. D. Emmons, *J. Amer. Chem. Soc.*, 1957, **79**, 5739.