Reaction of Dimethyl Imidazole-4,5-Dicarboxylate with Styrene Oxide

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The reaction between the potassium salt of dimethyl imidazole-4,5-dicarboxylate and styrene oxide is shown to produce 4-methoxycarbonyl-1-styrylimidazole-5-carboxylic acid or methyl 5,6-dihydro-8-oxo-6-phenyl-8*H*-imidazo[5,1-*c*][1,4]oxazin-1-carboxylate. The subsequent cleavage of this lactone and the use of styrene [^{18}O]oxide indicate the intermediacy of the lactone in the formation of the styryl acid.

We have previously described [1-3] methods for the preparation of *N*-hydroxyethyl- and *N*-vinyl-pyrroles under mild conditions *via* reaction with epoxides. Our interest in cyclic derivatives of β-amino-alcohols [4,5] and the importance of *N*-hydroxyethyl and *N*-vinyl substituents in therapeutic imidazoles [6] has led us to study the reaction of imidazoles with epoxides. Known reactions of this type are generally limited to simple epoxides such as ethylene and propylene oxides and, in contrast to pyrroles,[7] imidazoles undergo solely *N*-alkylation [8] although 4(5)-monosubstituted compounds give rise to isomeric products.[9]

In several studies the reactivity of the bidentate nucleophile 1-chloro-2,3-epoxypropane (epichlorohydrin) [10] has been examined and fused oxazolidines have been isolated [11] from either one- or two-stage reactions. Two examples of the interaction of an *N*-hydroxyalkyl

[1] W. J. Irwin and D. L. Wheeler, *Tetrahedron*, 1972, **28**, 1113.
[2] G. Cooper, W. J. Irwin, and D. L. Wheeler, *Tetrahedron Letters*, 1971, 4321.
[3] G. Cooper and W. J. Irwin, *J.C.S. Perkin I*, 1973, 911.
[4] W. J. Irwin and D. L. Wheeler, *J. Chem. Soc.* (*C*), 1971, 3166.
[5] W. J. Irwin, D. L. Wheeler, and N. J. Harper, *J. Medicin. Chem.*, 1972, **15**, 445.
[6] C. Cosar, C. Crisnan, R. Horclois, R. M. Jacob, J. Robert, S. Tcheletcheff, and R. Vaufre, *Arzneim.-Forsch.*, 1966, **16**, 23; B. Cavalleri, R. Ballotta, V. Arioli, and G. Lancini, *J. Medicin. Chem.*, 1973, **16**, 557.
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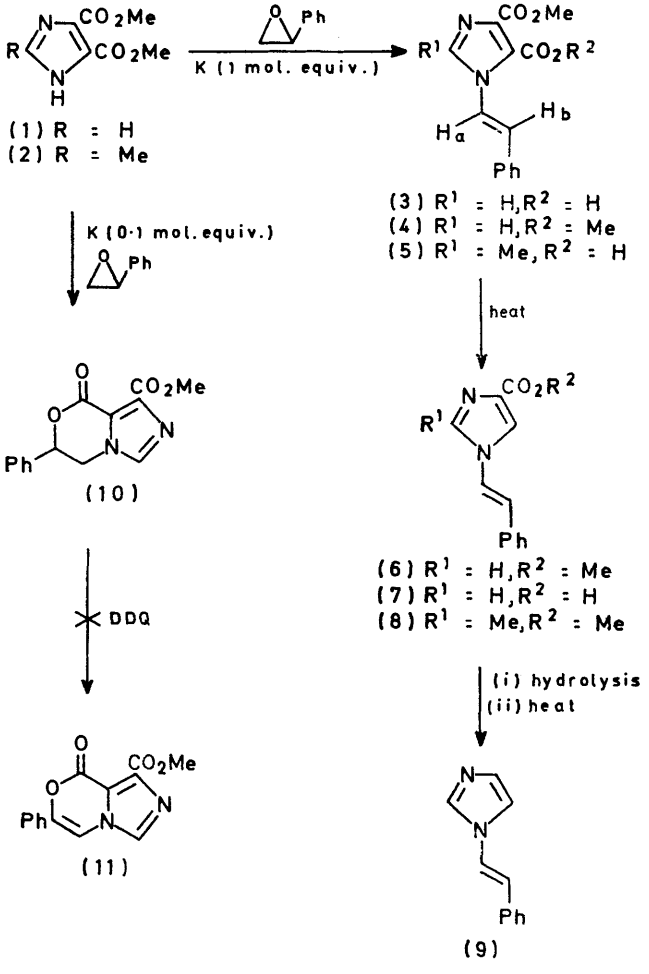
[8] K. Hoffman, 'Imidazole and its Derivatives,' in 'The Chemistry of Heterocyclic Compounds,' Interscience, New York and London, 1953; A. F. Pozharskii, A. D. Gornovskii, and A. M. Simonov, *Russ. Chem. Rev.*, 1966, **35**, 122; M. R. Grimmett, *Adv. Heterocyclic Chem.*, 1970, **12**, 103.
[9] D. E. Welch and R. D. Vatne, *J. Medicin. Chem.*, 1968, **11**, 370; Rhone-Poulenc S.A., Neth. Pat., 6,411,717/1965 (*Chem. Abs.*, 1965, **63**, 148,733); C. S. Rooney, U.S. Pat., 3,349,096/1967 (*Chem. Abs.*, 1968, **68**, 105,201).
[10] F. Hoffmann–La Roche Co., Neth. Pat., 6,606,853/1966 (*Chem. Abs.*, 1968, **68**, 21,933).
[11] G. Serchi and G. Bichi, *Farmaco, Ed. Sci.*, 1957, **12**, 594 (*Chem. Abs.*, 1959, **53**, 18957); M. Echstein, *Diss. Pharm.*, 1962, **14**, 425 (*Chem. Abs.*, 1964, **60**, 8030); K. H. Kleine and R. Haller, *Monatsh.*, 1969, **100**, 1797.

substituent with a 2- or 5-cyano-group in imidazoles have also been described. 1-(2-Hydroxyethyl)-5-nitroimidazole-2-carbonitrile, on treatment with a catalytic amount of sodium ethoxide in ethanol, cyclises to give 5,6-dihydro-8-imino-3-nitro-8*H*-imidazo[2,1-*c*]oxazine, which undergoes hydrolysis to the lactone; subsequent ammonolysis yields 1-hydroxyalkyl-5-nitroimidazole-2-carboxamide. The corresponding 1-(2-hydroxypropyl)-imidazole reacts similarly.[12] In contrast, the reaction of imidazole-4,5-dicarbonitrile with ethylene oxide in the presence of sodium hydroxide yields 4-cyano-1-vinylimidazole-5-carboxamide.[13] No mechanism for this reaction was reported; however, in view of the results of experiments concerning the elimination reactions of imidazo-oxazines presented here and the formation of an imidazo-oxazine in a similar reaction, it seems probable that a mechanism involving cleavage of a lactone intermediate is involved. This paper describes the reaction of dimethyl imidazole-4,5-dicarboxylate with styrene oxide, which is shown to yield a 1-styryl derivative *via* cleavage of a lactone intermediate.

The potassium salts of imidazoles have been used as intermediates in the preparation of 1-alkylimidazoles, but the preparation from molecular potassium and imidazole in boiling xylene is lengthy and requires some practical expertise. It was found, however, that these salts may be formed readily by reaction of the imidazole in dimethylformamide with potassium metal at room temperature. Hydrogen is evolved as the potassium dissolves producing a solution, or, in some cases, a suspension, of the potassium salt. Thus the potassium salt of dimethyl imidazole-4,5-dicarboxylate [14] (1) was formed easily at about 45°. This salt was only sparingly soluble; heating the suspension at 85—90° with styrene oxide gave 4-methoxycarbonyl-*trans*-1-styrylimidazole-5-carboxylic acid (3). The temperature was critical. At lower temperatures, the reaction was very slow and at higher temperatures atmospheric moisture tended to cause formation of potassium hydroxide, which hydrolysed the 4- and 5-ester groups before reaction with styrene oxide could occur.

The structure of the product was confirmed by spectroscopy (see Experimental section). By analogy with the reaction of 2-methyl 3-ethyl 4,5-dimethylpyrrole-2,3-dicarboxylate [3] and styrene oxide, in which only the 2-ester group was transformed into a carboxy-group, the acid group of this olefin-acid (3) was assumed to be at the 5-position. This assumption was supported by comparison of the mass spectra of the acid (3), its methyl ester (4) (synthesized by esterification with diazomethane), and methyl *trans*-1-styrylimidazole-4-carboxylate (6), produced by decarboxylation of the acid in refluxing dimethylformamide. The mass spectrum of the acid (3) showed a loss of 119 mass units, corresponding to a radical of styrene oxide, to give a base peak at *m/e* 153. The mass spectrum of the diester (4) showed a similar interaction involving intramolecular OCH_3 transfer in contrast to O atom transfer to give a base peak at *m/e* 134 ($C_9H_{10}O^{+\cdot}$). This type of intramolecular rearrangement was not shown in the mass spectrum of the decarboxylated product and was

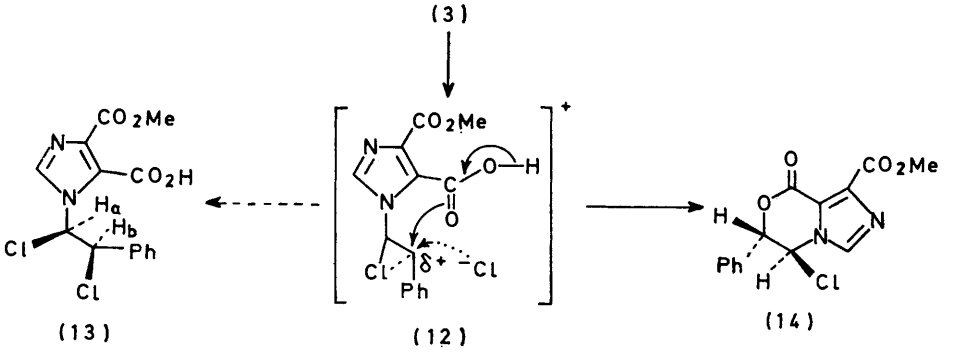


thus consistent with the presence of the carboxy-group at position 5. This orientation of the acid function was also indicated by ^{18}O studies and by cyclisation of the olefin-acid to a lactone (10). The potassium salt of dimethyl 2-methylimidazole-4,5-dicarboxylate (2) underwent a similar reaction with styrene oxide to yield the 2-methyl acid-ester (5) (although a higher temperature was required in this case owing to the more hindered nature of the imidazole anion), which underwent decarboxylation to give methyl 2-methyl-*trans*-1-styryl-imidazole-4-carboxylate (8).

The cyclisation of suitably substituted olefin-acids to give γ- and δ-lactones has been extensively studied and reviewed.[15] Berti [16] has described the production of diastereoisomeric 4-chloro-3,4-dihydro-3-phenylisocoumarins from the reaction of *trans*- and *cis*-stilbene-2-carboxylic acid with chlorine in chloroform at room

[12] D. W. Henry, U.S. Pat., 3,390,150/1968.
[13] Y. Yamada, I. Kumashiro, and T. Takeniski, *Bull. Chem. Soc. Japan*, 1968, **41**, 1237.
[14] R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 1945, 232.
[15] M. F. Ansell and M. H. Palmer, *Quart. Rev.*, 1964, **18**, 211.
[16] G. Berti, *Tetrahedron*, 1958, **4**, 393.

temperature. The action of chlorine on the olefin-acid (3) in chloroform at room temperature yielded approximately equal amounts of an acidic and a basic product. On the basis of i.r., n.m.r., and mass spectrometry the products were formulated as 1-(1,2-dichloro-2-phenylethyl)-4-methoxycarbonylimidazole-5-carboxylic acid (13) and methyl 5-chloro-5,6-dihydro-8-oxo-6-phenylimidazo[5,1-*c*][1,4]oxazin-1-carboxylate (14). The



mechanism for the formation of this lactone and the dichloro-acid involves the same intermediate chloronium ion (12), which is attacked by either chloride anion or the carbonyl oxygen atom in competing reactions to give the respective products. The dichloro-acid may be assigned the *erythro*-configuration formed by *trans*-addition of chlorine to the double bond.

The monoester (6) was hydrolysed with concentrated hydrochloric acid to give a precipitate of *trans*-1-styrylimidazole-4-carboxylic acid (7). Decarboxylation of this acid was observed at its m.p. (265°) and the process was repeated on a preparative scale by brief heat treatment in refluxing diethylene glycol (b.p. 245°) to yield *trans*-1-styrylimidazole (9). Prolonged heating of the acid gave only a polymeric oil.

Table 1 records the chemical shifts of the olefinic and imidazole protons of a series of *trans*-1-styrylimidazole-carboxylates and -carboxylic acids. The chemical shift

4-carboxylic acid at 1595 cm^{-1} may be assigned to a carboxylate anion stretch. This is consistent with a zwitterionic structure in which a positive charge is delocalized over the 1-, 2-, and 3-positions of the imidazole ring, so causing the deshielding effect. The n.m.r. signals of H_a and H_b (Table 1) are differentiated by *ca.* 0·6 p.p.m. except in the compounds in which there is a 5-acid or ester group. In these cases H_a is deshielded, whereas H_b is relatively unaffected. The same effect is seen in *trans*-1-styrylpyrroles,[17] and also in the saturated analogue (13). Table 1 also records u.v. data for the series of *trans*-1-styrylimidazoles. The absorption is presumably due to conjugation of the imidazole ring with the styryl group, since the imidazole ring does not absorb in this region, and is therefore a $\pi \rightarrow \pi^*$ absorption, comparable with the absorption of *trans*-stilbene. The reduction in the conjugation of the compounds on removal of the carboxy-functions is best reflected by the long wavelength minimum which is shifted, on removal of both 4- and 5-ester groups, by 35 nm.

The formation of the olefin-acid (3) may be envisaged as either a cleavage–hydrolysis of an intermediate alcohol diester or, in view of the known ability of epoxides to yield cyclic derivatives during reaction with suitably substituted anions,[8,17] an elimination reaction

TABLE 1

N.m.r. and u.v. data for *trans*-1-styrylimidazoles

	τ							
Compound	H_a	H_b	$\Delta(H_b - H_a)$	2-H	5-H	$\lambda_{max.}$/nm	long $\lambda_{min.}$/nm	$\varepsilon_{max.}$
(3)	1·87	3·16	1·29	1·95		281	345	20,700
(4)	2·50	3·36	0·86	2·30		282	350	19,900
(6)	2·62	3·15	0·63	2·06	2·2	293	325	27,000
(7)	2·13	2·75	0·62	1·65	1·8			
(9)	2·78	3·4	0·62	2·35	2·88	272	315	20,600

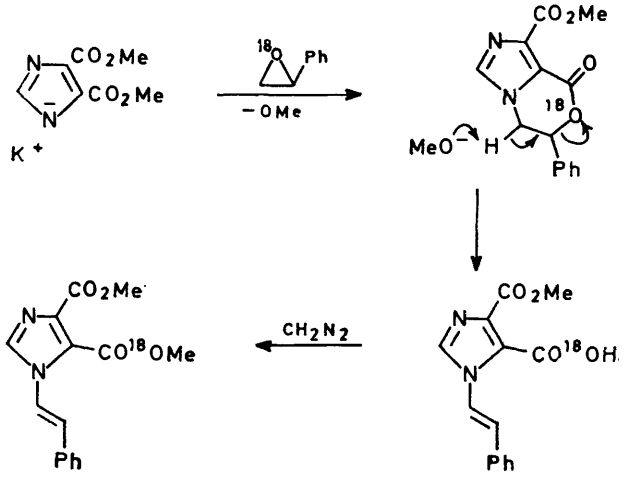
values of all the protons gradually move to higher field as the electron-withdrawing ester and carboxy-groups are removed. The protons of the imidazole-4-carboxylic acid (7), however, show lower chemical shifts than would have been predicted for a covalent structure. Also, whereas the 5-carboxylic acid (3) melts at 164° and is freely soluble in non-polar organic solvents, the 4-carboxylic acid (7) melts at 265° and is insoluble in non-polar organic solvents. The i.r. absorption of the

of a lactone. On the assumption that initial opening of the epoxide ring is faster than subsequent elimination or hydrolysis we considered that it should be possible to cause reaction between styrene oxide and dimethyl imidazole-4,5-dicarboxylate with only a catalytic amount of potassium. Further, this should also enable the

[17] A. Rosowsky, 'Heterocyclic Compounds with Three- and Four-membered Rings,' ed. A. Weissberger, Interscience, New York and London, 1964.

isolation and identification of the intermediate. This reaction was therefore repeated with 0·1 mol. equiv. of potassium and this resulted in the isolation of methyl 5,6-dihydro-8-oxo-6-phenyl-8*H*-imidazo[5,1-*c*][1,4]oxazine-1-carboxylate (10). Confirmation that this lactone was the required intermediate was sought by an attempted cleavage with an excess of sodium methoxide in dimethylformamide. The acidic product showed $\nu_{max.}$ 1725w (ester C=O) and 1610s,br cm^{-1} (acid C=O), but no absorption due to hydroxylic O–H. It was concluded that the lactone had undergone cleavage to yield the expected product (3) but that subsequent contamination with atmospheric moisture had partially hydrolysed the remaining ester group. This hypothesis was confirmed by esterifying the mixture of acids with diazomethane to give the diester (4). Godefroi *et al.*[18] have reported the synthesis of imidazo[5,1-*c*][1,4]oxazin-8-ones, and a similar type of elimination reaction to give 1-(1-phenylvinyl)imidazole *via* decarboxylation of the lactone.

In view of the ambiguous result of this elimination experiment further proof regarding the intermediacy of the lactone was obtained by studying the reaction of styrene [^{18}O]oxide with the diester (1) (Scheme). Mass spectrometric analysis[19] of the labelled acid showed an $^{18}O : {}^{16}O_4$ ratio of 0·0499 (Table 2) whereas the $^{18}O : {}^{16}O$



SCHEME

ratio of the styrene [^{18}O]oxide was 0·047. The poor agreement of the two determinations of isotopic content was thought to be due to the small size of the molecular ion peak (15%) of the acid, because of ready decarboxylation in the mass spectrometer, so making accurate measurements of peak intensities difficult. Errors due to ion–molecule interactions may also have occurred since relatively large source pressures were employed to make visible the molecular ion peak. The diester (4), however, has a more intense molecular ion (40%), and so the labelled acid was esterified with diazomethane. Determination of the isotopic content (Table 3) then gave an $^{18}O : {}^{16}O_4$ ratio of 0·0461, indicating complete retention of the label.

[18] E. F. Godefroi, C. A. M. Van der Eycken, and C. Van der Westeringh, *J. Org. Chem.*, 1964, **29**, 3707; E. F. Godefroi, C. A. M. Van der Eycken, and P. A. J. Janssen, *ibid.*, 1966, **31**, 806.

EXPERIMENTAL

I.r. spectra were determined for Nujol mulls, unless otherwise stated, with a Unicam SP 200 spectrophotometer. N.m.r. spectra were determined for solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal standard on a Varian A60-A spectrometer. Mass spectra were determined on an A.E.I. MS9 spectrometer, operating at 100 μA and 70 eV. U.v. spectra were determined for solutions in methanol on a Beckman Acta V spectrophotometer. Reaction temperatures quoted are those of an external oil-bath. Light petroleum refers to the fraction of b.p. 60—80°.

4-Methoxycarbonyl-2-methyl-trans-1-*styrylimidazole-5-carboxylic Acid* (5).—The potassium salt of dimethyl 2-methylimidazole-4,5-dicarboxylate [from the diester (1·0 g, 0·005 mol) and potassium (0·2 g, 0·005 mol)] was stirred with styrene oxide (0·66 g, 0·0055 mol) in dimethyl formamide (DMF) (5 cm^3) at 100° for 17 h. Water was added and the basic solution was washed with ether. The aqueous solution was extracted twice with chloroform after acidification to pH 3. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to leave the styryl acid (0·5 g, 35%), m.p. 146—147° (with decarboxylation), as cream plates (from chloroform–light petroleum); $\nu_{max.}$ 1630 (C=O), 1720 (C=O), and 2600 cm^{-1} (O–H); τ ($CDCl_3$) 2·45 (1H, d, *J* 14·5 Hz, N–CH=), 2·6 (5H, m, Ph), 3·45 (1H, d, *J* 14·5 Hz, PhCH=), 5·95 (3H, s, OCH_3), and 7·47 (3H, s, 2-CH_3).

Methyl 2-Methyl-trans-1-*styrylimidazole-4-carboxylate* (8).—The acid (5) (1·4 g) was heated under reflux in DMF (5 cm^3) for 2 min. The solution was poured into water (100 cm^3) and extracted twice with chloroform. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to leave the *olefin* (0·85 g, 71%), m.p. 142—143°, as needles (from chloroform–light petroleum) (Found: C, 69·6; H, 5·9; N, 11·65. $C_{14}H_{14}N_2O_2$ requires C, 69·4; H, 5·8; N, 11·55%); $\nu_{max.}$ 1720 (C=O) and 1669 cm^{-1} (C=C); τ ($CDCl_3$) 2·15 (1H, s, 5-H), 2·65 (5H, s, Ph), 2·8 (1H, d, *J* 14·5 Hz, N–CH=), and 3·33 (1H, d, *J* 14·5 Hz, PhCH=), 6·2 (3H, s, OCH_3), and 7·56 (3H, s, 2-CH_3); $\lambda_{max.}$ 282·5 nm (ε 25,500).

4-Methoxycarbonyl-trans-1-*styrylimidazole-5-carboxylic Acid* (3).—The potassium salt of dimethyl imidazole-4,5-dicarboxylate [from the diester (4·5 g, 0·025 mol) and potassium (1 g, 0·025 mol)] was stirred with styrene oxide (3·3 g, 0·0275 mol) in DMF (40 cm^3) at 85—90° for 17 h. Addition of water and acidification gave the *styrylimidazole acid* (2·2 g, 32%), m.p. 164—165° (with decarboxylation), as silvery plates (from methanol) (Found: C, 61·55; H, 4·5; N, 10·1. $C_{14}H_{12}N_2O_4$ requires C, 61·75; H, 4·4; N, 10·3%); $\nu_{max.}$ 1725 (ester C=O), 1630 (acid C=O), and 2600 cm^{-1} (O–H); τ ($CDCl_3$) 1·87 (1H, d, *J* 14·5 Hz, N–CH=), 1·95 (1H, s, 2-H), 2·4—2·75 (5H, m, Ph), 3·16 (1H, d, *J* 14·5 Hz, PhCH=), and 5·92 (3H, s, CH_3); $\lambda_{max.}$ 281 nm (ε 20,700); *m/e* 272 (17%), 229 (8), 228 (53), 227 (8), 223 (5), 198 (9), 197 (60), 196 (5), 195 (33), 170 (27), 169 (22), 168 (8), 155 (5), 154 (8), 153 (100), 145 (17), 142 (9), 141 (5), 140 (12), 130 (21), 129 (6), 128 (6), 121 (7), 120 (8), 117 (5),

[19] G. G. Swain, G. Tauchihaski, and L. J. Taylor, *Analyt. Chem.*, 1963, **35**, 1415.

116 (21), 115 (23), 114 (5), 104 (8), 103 (62), 102 (90), 95 (12), 91 (17), 89 (12), 78 (13), 77 (66), 76 (8), 75 (6), 65 (8), 63 (13), 53 (8), 52 (12), 51 (29), 56 (8), 44 (65), 39 (13), 32 (8), 29 (5), 28 (36), and 27 (5).

The remaining acidic mother liquors were evaporated under reduced pressure and the residue was dissolved in alkali (NaOH; 40%). Acidification (conc. HCl) precipitated a mixture of imidazole acids (2·4 g).

4-*Methoxycarbonyl*-trans-1-*styrylimidazole*-5-*carboxylic* [^{18}O]*Acid*.—Potassium 4,5-bismethoxycarbonylimidazolide [from the diester (0·225 g) and potassium (0·05 g)] was stirred with styrene [^{18}O]oxide [3] (0·17 g) in DMF (5 cm^3) at 85—90° for 17 h. Addition of water and acidification (conc. HCl) gave the styrylimidazole [^{18}O]acid (0·09 g, 30%). The labelled product was analysed by mass spectrometry. Six successive scans of the molecular ion peaks were run and the light sensitive chart paper was sprayed to prevent fogging. The lengths of the lines were measured with a travelling microscope (Table 2).

TABLE 2

Mass spectra of the styrylimidazole [^{18}O]acid

	M (*m/e* 272)	*M* + 1 (*m/e* 273)	*M* + 2 (*m/e* 274)	$^{18}O : {}^{16}O_4$ ratio
Scan 1	100	16·68	6·93	0·0490
2	100	17·70	6·94	0·0490
3	100	16·44	7·47	0·0543
4	100	17·12	7·39	0·0535
5	100	16·76	6·57	0·0447
6	100	16·88	6·93	0·0489
Unlabelled	100	16·24	2·04	

$^{18}O : {}^{16}O_4$ ratio = 0·0499 ± 0·0017

Dimethyl trans-1-*Styrylimidazole*-4,5-*dicarboxylate* (4).—The acid (3) (1 g, 0·0037 mol) was added to ethereal diazomethane (1 g, 0·024 mol) and the mixture was allowed to evaporate overnight at room temperature to yield the *diester* (0·725 g, 74%), m.p. 118—119°, as needles (from ether) (Found: C, 62·6; H, 4·95; N, 9·65. $C_{15}H_{14}N_2O_4$ requires C, 62·95; H, 4·9; N, 9·8%); $\nu_{max.}$ 1660 (C=C), 1710 (C=O), and 1720 cm^{-1} (C=O); τ ($CDCl_3$) 2·30 (1H, s, 2-H), 2·50 (1H, d, *J* 14 Hz, N–CH=), 3·36 (1H, d, *J* 14 Hz, PhCH=), 2·8 (5H, s, Ph), and 6·19 (6H, d, 2 × CH_3); $\lambda_{max.}$ 282 nm (ε 19,900); *m/e* 287 (8%), 286 (40), 255 (15), 253 (8), 223 (23), 198 (13), 196 (11), 195 (50), 170 (6), 169 (8), 168 (8), 187 (45), 153 (8), 140 (10), 137 (6), 135 (10), 134 (100), 128 (5), 121 (8), 115 (9), 110 (5), 105 (5), 103 (34), 102 (50), 91 (10), 89 (5), 82 (8), 78 (5), 77 (45), 76 (5), 70 (10), 68 (8), 63 (5), 59 (9), 52 (5), 51 (18), 50 (5), 44 (14), 42 (5), and 39 (8).

[^{18}O]*Dimethyl* trans-1-*Styrylimidazole*-4,5-*dicarboxylate*.—The [^{18}O]acid (3) (0·09 g) was added to ethereal diazomethane (0·1 g) to yield the [^{18}O]diester (0·075 g, 73%). Mass spectrometric analysis of the isotopic abundance was carried out as described earlier (Table 3).

trans-1-*Styrylimidazole* (9).—The ester (6) (2·0 g) was dissolved in conc. HCl (20 cm^3) and heated under reflux for 2 h to yield a precipitate of the acid (7) (1·79 g, 85%), m.p. 265° (with decarboxylation) (a satisfactory analysis was not obtained); $\nu_{max.}$ 1665 (C=C), 1595 (COO^-), and 2500 cm^{-1} (N^+–H); τ [$(CD_3)_2SO$] 1·62 (1H, s, 2-H), 1·76 (1H, s, 5-H), 2·08 (1H, d, *J* 14 Hz, N–CH=), 2·55 (5H, m, Ph), 2·74 (1H, d, *J* 14 Hz, PhC*H*=), and 3·4br (1H, s, removed on deuteriation).

The acid (7) (1·5 g) was heated in diethylene glycol (10 cm^3) to reflux temperature as rapidly as possible and the solution was then poured into water (100 cm^3) and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated to leave the styrylimidazole (9) (0·8 g, 79%), $\nu_{max.}$ 1660 cm^{-1} (C=C); τ ($CDCl_3$) 2·35 (1H, s, 2-H), 2·78 (1H, d, *J* 14·5 Hz, N–CH=), 2·72 (5H, s, Ph), 2·88 (2H, m, 4- and 5-H), and 3·4 (1H, d, *J* 14·5 Hz, PhCH=); $\lambda_{max.}$ 272 nm (ε 20,600).

TABLE 3

Mass spectra of the [^{18}O]diester

	M (*m/e* 286)	*M* + 1 (*m/e* 287)	*M* + 2 (*m/e* 288)	$^{18}O : {}^{16}O_4$ ratio
Scan 1	100	17·91	7·15	0·0493
2	100	18·74	6·77	0·0455
3	100	18·52	6·50	0·0428
4	100	17·64	6·75	0·0453
5	100	17·79	6·67	0·0445
6	100	17·91	7·71	0·0490
Unlabelled	100	17·35	2·22	

$^{18}O : {}^{16}O_4$ ratio = 0·0461 ± 0·0012

Methyl trans-1-*Styrylimidazole*-4-*carboxylate* (6).—The acid (3) (1·3 g), dissolved in DMF (20 cm^3), was refluxed for 30 min. The solution was poured into water (200 cm^3) to precipitate the *ester* (0·87 g, 81%), m.p. 157—158° (from methanol), as white plates (Found: C, 68·4; H, 5·4; N, 12·05. $C_{13}H_{12}N_2O_2$ requires C, 68·4; H, 5·3; N, 12·3%); $\nu_{max.}$ 1700 (C=O) and 1660 cm^{-1} (C=C); τ ($CDCl_3$) 2·06 (1H, d, *J* 1·3 Hz, 2-H), 2·2 (1H, d, *J* 1·3 Hz, 5-H), 2·6 (5H, s, Ph), 2·62 (1H, d, *J* 14·5 Hz, =CH–N), 3·15 (1H, d, *J* 14·5 Hz, =CHPh), and 6·1 (3H, s, CH_3); $\lambda_{max.}$ 283 nm (ε 27,000); *m/e* 229 (14%), 228 (100), 227 (10), 198 (12), 197 (95), 195 (21), 170 (38), 169 (28), 168 (8), 144 (8), 143 (23), 142 (11), 140 (5), 130 (21), 116 (13), 115 (25), 104 (6), 163 (51), 102 (14), 95 (15), 91 (11), 90 (8), 89 (12), 77 (50), 76 (11), 65 (6), 63 (12), 53 (10), 52 (12), 51 (27), 50 (8), 40 (5), 39 (15), 28 (8), and 27 (6); *m** 127 (228 ⟶ 170).

Methyl 5-*Chloro*-5,6-*dihydro*-8-*oxo*-6-*phenylimidazo*[5,1-c]-[1,4]*oxazine*-1-*carboxylate* (14).—Chlorine was passed through a solution of the acid (3) (1·0 g) in chloroform (20 cm^3). A colloidal precipitate appeared. The solution was evaporated to remove any dissolved chlorine and the residue was partitioned between chloroform and potassium hydrogen carbonate solution (20%). The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated to leave the chloro-lactone as an amorphous solid which proved difficult to recrystallize; $\nu_{max.}$ 1720 (C=O) and 1750 cm^{-1} (C=O); τ ($CDCl_3$) 1·75 (1H, s, 3-H), 2·52 (5H, s, Ph), 2·86 (1H, d, *J* 4 Hz, 5-H), 3·97 (1H, d, *J* 4 Hz, 6-H), and 5·96 (3H, s, CH_3).

Hydrogen chloride was passed through a solution of the chloro-lactone in ethyl acetate to precipitate the hydrochloride salt (0·35 g, 27%), m.p. 155—160°, obtained as white microprisms from ethyl acetate containing a drop of conc. HCl. The initial aqueous alkaline solution was washed with chloroform and boiled briefly to remove entrained chloroform. The solution was cooled and acidified (conc. HCl) to precipitate 1-(1,2-*dichloro*-2-*phenylethyl*)-4-*methoxycarbonylimidazole*-5-*carboxylic acid* (13) (0·4 g, 30%), m.p. 159—160° (with decarboxylation), as prisms (from benzene) (Found: C, 49·1; H, 3·65; N, 7·95. $C_{14}H_{12}Cl_2N_2O_4$ requires C, 49·0; H, 3·5; N, 8·15%); $\nu_{max.}$ 1640 (C=O), 1720 (C=O), and 2250 cm^{-1} (O–H); τ ($CDCl_3$) 2·12 (1H, s, 2-H), 2·15 (1H, d, *J* 7·5 Hz, N–CH), 2·85 (5H, s, Ph), 4·76 (1H, d, *J* 7·5 Hz, PhCH), and 6·02 (3H, s, CH_3).

Methyl 5,6-*Dihydro*-8-*oxo*-6-*phenyl*-8H-*imidazo*[5,1-c]-

[1,4]*oxazine*-1-*carboxylate* (10).—The potassium salt of dimethyl imidazole-4,5-dicarboxylate [from the diester (3·0 g, 0·0133 mol) and potassium (0·07 g, 0·0014 mol)] was stirred with styrene oxide (2·2 g, 0·015 mol) in DMF (20 cm^3) at 90° for 17 h. Water was added to precipitate the *lactone* (2·1 g, 42%), m.p. 199—200°, as needles (from dioxan) (Found: C, 61·45; H, 4·6; N, 10·1. $C_{14}H_{12}N_2O_4$ requires C, 61·75; H, 4·4; N, 10·3%); $\nu_{max.}$ 1720 cm^{-1} (C=O); τ [$(CD_3)_2SO$] 1·93 (1H, s, 3-H), 2·53 (5H, s, Ph), 4·07 (1H, q, *J* 3 and 11 Hz, 6-H), 5·4 (2H, m, $J_{5,5'}$ 13·75 Hz, 5-H_2), and 6·2 (3H, s, CH_3).

Reaction of the Lactone (10) *with Sodium Methoxide.*—The lactone (10) (0·544 g, 0·002 mol) was stirred with sodium methoxide (1·08 g, 0·02 mol) in DMF (10 cm^3) for 17 h in a stoppered flask. Water was added and the solution was acidified (conc. HCl) to precipitate a mixture of imidazole acids (0·435 g), m.p. 210—220°. The acids (0·42 g) were added to ethereal diazomethane (0·6 g) with stirring and the solution was allowed to evaporate. The residue was dissolved in ether (150 cm^3) and clarified. Evaporation gave the diester (4) (0·25 g, 46%), identical with that synthesized by esterification of the acid (3).

Attempted Dehydrogenation of the Lactone (10) *with* 2,3-*Dichloro*-5,6-*dicyano*-1,4-*benzoquinone* (*DDQ*).—The lactone (0·4 g) was heated under reflux in dioxan with DDQ (0·6 g, 1·5 equiv.) for 5 days. The black solution was evaporated and some reduced DDQ was filtered off. The black filtrate was passed down a column of neutral alumina with methanol. The resulting solution was evaporated to yield starting material (0·11 g).

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