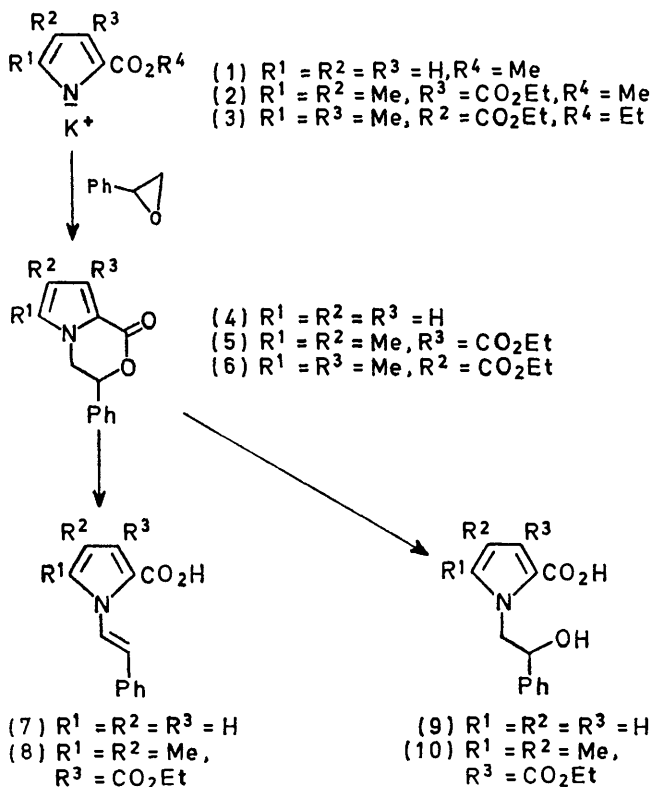


Mechanism of the Reaction between Pyrrole Esters and Styrene Oxide

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The reaction between potassium 2-alkoxycarbonylpyrrolides and styrene oxide, to yield 1-styrylpyrrole-2-carboxylic acids, is shown to proceed *via* a lactone intermediate.

PREVIOUS work^{1,2} has shown that under dry conditions potassium 2-methoxycarbonylpyrrolide (1) reacts readily with styrene oxide to yield *trans*-1-styrylpyrrole-2-carboxylic acid (7), whereas under moist conditions 1-(2-hydroxyphenethyl)pyrrole-2-carboxylic acid (9) is



obtained. Other epoxides similarly yielded the corresponding 1-vinylpyrrole-2-carboxylic acids *via* a mild, stereospecific elimination reaction, and cyclisation products were not isolated although the reactions of

¹ G. Cooper, W. J. Irwin, and D. L. Wheeler, *Tetrahedron Letters*, 1971, 4321.

² W. J. Irwin and D. L. Wheeler, *Tetrahedron*, 1972, 28, 1113.

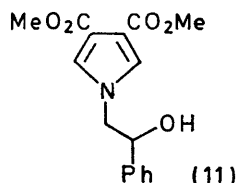
epoxides with suitable carbanions, such as that derived from diethyl malonate, to yield γ -lactones are well known.³ In order to account for certain observations, such as the hydrolysis of the ester group, the mild conditions required for the elimination,⁴ and the isolation of a lactone from the reaction with cyclohexene oxide (*cis*-axial, equatorial disposition of H and O atoms) it was proposed that the reaction proceeded *via* a lactone intermediate [*e.g.* (4)] which underwent elimination (dry conditions) to yield an olefin, or hydrolysis (moist conditions) to yield an alcohol. We now present evidence, including the isolation and elimination of lactones, which confirms our earlier hypothesis.

The involvement of the 2-ester function in the elimination sequence was confirmed by treating the potassium 3-ethoxycarbonyl-2-methoxycarbonyl-4,5-dimethylpyrrolide (2), in which the 2- and 3-ester groups may readily be distinguished, with styrene oxide in dimethylformamide. When this reaction was carried out in a dry atmosphere, equal amounts of *trans*-3-ethoxycarbonyl-4,5-dimethyl-1-styrylpyrrole-2-carboxylic acid (8) and 3-ethoxycarbonyl-1-(2-hydroxyphenethyl)-4,5-dimethylpyrrole-2-carboxylic acid (10) were obtained. In both compounds the orientation of the remaining ester group was confirmed by ¹H n.m.r. measurements. Under similar conditions potassium 3,4-bismethoxycarbonylpyrrolide yielded dimethyl 1-(2-hydroxyphenethyl)pyrrole-3,4-dicarboxylate (11). No hydrolysis or elimination products were isolated. The 2,3-diester (2) and styrene oxide under normal atmospheric conditions yielded the hydroxypyrrole acid (10), a trace of the styryl acid (8), and an appreciable amount (30%) of the lactone, ethyl 3,4-dihydro-6,7-dimethyl-1-oxo-3-phenylpyrrolo[2,1-*c*][1,4]oxazine-8-carboxylate (5). Conceivably, the presence of atmospheric moisture

³ V. N. Yandovskii, V. S. Karavan, and T. I. Temnikova, *Russ. Chem. Rev.*, 1970, 39, 265; A. Rosowsky, 'Heterocyclic Compounds with 3- and 4-Membered Rings,' ed. A. Weissberger, Interscience, 1964, p. 418.

⁴ M. F. Shostakovskii, G. G. Skvortsova, and E. S. Domina, *Russ. Chem. Rev.*, 1969, 38, 407.

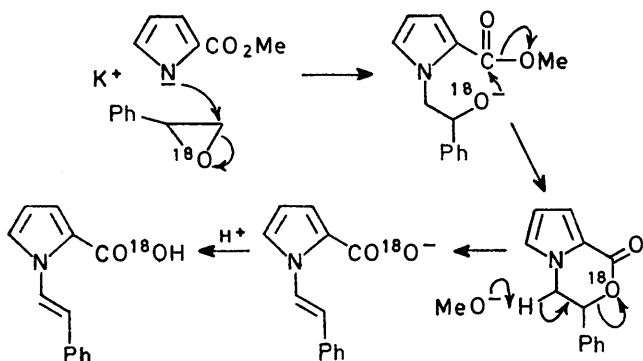
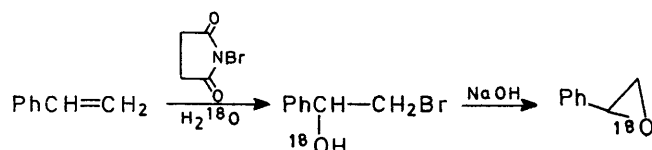
transforms the nucleophile from methoxide to hydroxide, which reduces the rate of elimination. The further modification of using one tenth of an equivalent of potassium, which again might be expected to reduce the rate of elimination, results in a further increase in



the yield of the lactone (47%). Treatment of the lactone (5) with 10 mol. equiv. of potassium ethoxide at room temperature resulted in the anticipated elimination reaction to yield the *trans*-1-styryl acid (8).

Under suitable conditions a lactone (6) could be isolated from the reaction of potassium 2,4-bismethoxycarbonyl-3,5-dimethylpyrrolide (Knorr's pyrrole) (3) and styrene oxide.

We have thus shown that the reaction of pyrrole-2-carboxylates with styrene oxide may yield a lactone, and that this lactone can undergo elimination. Final evidence to confirm that these events do occur was



obtained by use of potassium 2-methoxycarbonylpyrrolide (1). On reaction with styrene oxide no lactone was isolated. However, 3,4-dihydro-3-phenylpyrrolo[2,1-*c*][1,4]oxazin-1-one (4), prepared from the alcohol acid (9) and polyphosphoric acid, yielded the *trans*-1-styrylpyrrole acid (7) on treatment with base. This indicates its possible intermediacy and this was confirmed by the use of styrene [¹⁸O]oxide. The epoxide was prepared from styrene, *N*-bromosuccin-

imide, and H₂¹⁸O (5%) (Scheme 1), and mass spectrometric analysis⁵ indicated an ¹⁸O : ¹⁶O ratio of 0.0470 ± 0.00040. Scheme 2 shows the distribution of the ¹⁸O label expected from the reaction of potassium 2-methoxycarbonylpyrrolide and styrene [¹⁸O]oxide. Mass spectrometric analysis indicated that the ¹⁸O : ¹⁶O₂ ratio in the *trans*-1-styrylpyrrole-2-carboxylic acid was 0.0480 ± 0.00030, *i.e.* complete retention of the label had occurred.

TABLE 1

Normalised mass spectral data for styrene [¹⁸ O]oxide					
	<i>M</i> - 1 (<i>m/e</i> 119)	<i>M</i> (<i>m/e</i> 120)	<i>M</i> + 1 (<i>m/e</i> 121)	<i>M</i> + 2 (<i>m/e</i> 122)	¹⁸ O : ¹⁶ O ratio
Scan 1	39.87	100	10.40	5.37	0.0482
2	37.88	100	10.96	5.09	0.0455
3	35.30	100	10.79	5.22	0.0468
4	33.32	100	10.72	5.16	0.0461
5	32.23	100	10.76	5.22	0.0467
6	31.27	100	10.79	5.23	0.0469
Unlabelled		100	8.81	0.54	

$$^{18}\text{O} : ^{16}\text{O} = 0.0470 \pm 0.00040.$$

TABLE 2

Normalised mass spectral data for [¹⁸ O]-1-styrylpyrrole-2-carboxylic acid					
	<i>M</i> - 1 (<i>m/e</i> 212)	<i>M</i> (<i>m/e</i> 213)	<i>M</i> + 1 (<i>m/e</i> 214)	<i>M</i> + 2 (<i>m/e</i> 215)	¹⁸ O : ¹⁶ O ₂ ratio
Scan 1	29.64	100	16.32	6.25	0.0485
2	29.92	100	16.37	6.16	0.0476
3	29.70	100	16.16	6.33	0.0493
4	29.83	100	16.36	6.21	0.0481
5	29.81	100	16.30	6.23	0.0482
6	29.44	100	16.49	6.14	0.0474
Unlabelled		100	14.68	1.40	

$$^{18}\text{O} : ^{16}\text{O}_2 = 0.0480 \pm 0.00030.$$

EXPERIMENTAL

¹H N.m.r. spectra were determined for solutions in deuteriochloroform with a Varian A60A spectrometer (tetramethylsilane as internal reference). I.r. spectra were obtained with a Unicam SP 200 spectrophotometer. Mass spectra were measured with an A.E.I. MS9 spectrometer (ionising voltage 70 eV, trap current 100 μA, accelerating voltage 8 kV). Samples were introduced through the heated inlet system at 150°. Mass spectral determination of ¹⁸O label used previously published methods.⁵

Styrene [¹⁸O]Oxide.⁶—Redistilled styrene (2.6 g, 0.025 mol), *N*-bromosuccinimide (recrystallised from water; 4.7 g, 0.025 mol), and water (5% ¹⁸O-enriched; 10 cm³) was stirred vigorously until all the *N*-bromosuccinimide had disappeared (1 h). The bromohydrin layer was separated with ether and the aqueous layer extracted with ether. The water (containing succinimide) was then recycled twice with more styrene and *N*-bromosuccinimide. The combined ether extracts were dried and evaporated. The resultant oil was stirred with sodium hydroxide (4.5 g) in water (22 cm³) at 60° for 30 min. The mixture was cooled and extracted twice with ether. The extracts were washed with water, dried, and evaporated to yield the epoxide, which was redistilled at 42–44° (1 mmHg) to yield an oil (6 g, 65%), ¹⁸O : ¹⁶O = 0.0470 ± 0.00040.

[¹⁸O]-*trans*-1-Styrylpyrrole-2-carboxylic Acid.—Potassium 2-methoxycarbonylpyrrolide [from potassium (0.16 g)

⁵ C. G. Swain, G. Tsuchihashi, and L. J. Taylor, *Analyt. Chem.*, 1963, **35**, 1415; J. H. Beynon, 'Mass Spectrometry and its Applications to Organic Chemistry,' Elsevier, Amsterdam, 1960, p. 294.

⁶ C. O. Guss and R. Rosenthal, *J. Amer. Chem. Soc.*, 1955, **77**, 2549.

and methyl pyrrole-2-carboxylate (0.5 g)] in dimethylformamide was stirred with styrene [^{18}O]oxide (0.48 g) in a dry box under nitrogen for 18 h. The mixture was washed with ether and acidified by addition to hydrochloric acid (20 cm³; 0.5N) to precipitate the product. Chromatographic separation on Chromar 1000 preparative silica sheets with acetic acid (5%) in benzene yielded the *trans*-1-styrylpyrrole acid (0.17 g, 21%) as cream platelets, m.p. 178–179° (from chloroform–petroleum), $^{18}\text{O} : ^{16}\text{O}_2 = 0.0480 \pm 0.00040$.

Reaction of 3,4-Dihydro-3-phenylpyrrolo[2,1-c][1,4]oxazin-1-one with Sodium Methoxide.—(i) With 1 mol. equiv. of methoxide. The lactone (0.11 g, 0.5 mmol) was stirred with sodium methoxide (0.03 g, 0.5 mmol) in dimethylformamide (2 cm³) in a stoppered flask overnight. Water was added (to 10 cm³) and unchanged lactone (0.03 g) was filtered off. The filtrate was acidified (dil. HCl) and extracted with chloroform; the extract was washed with water, dried (MgSO₄), and evaporated to yield an oil which, when examined by n.m.r. spectroscopy and by t.l.c. on alumina with benzene–acetic acid (95 : 5), proved to be a mixture of compounds (7) (40%) and (9) (60%).

(ii) The reaction was repeated with 10 mol. equiv. of methoxide (0.27 g, 5 mmol). No lactone was isolated. On acidification (dil. HCl) and scratching a solid (0.06 g) precipitated, which after filtering and drying was shown by n.m.r. and t.l.c., as before, to be the olefin acid (7).

Dimethyl 1-(2-Hydroxyphenethyl)pyrrole-3,4-dicarboxylate (11).—Dimethyl pyrrole-3,4-dicarboxylate (0.46 g, 2.5 mmol) was stirred in dimethylformamide (10 cm³), and potassium (0.1 g, 2.5 mmol) and styrene oxide (0.5 g, 4.0 mmol) were added. The mixture was heated overnight at 85° in an oil-bath. Water was added (to 50 cm³) and the solution was extracted with chloroform; the extract was washed with water (slightly acidified with dil. HCl), dried (MgSO₄), and evaporated to yield an oil which on trituration with the minimum amount of ether gave the *pyrrole* (0.2 g, 20%), prisms, m.p. 99–100° (ether) (Found: C, 63.1; H, 5.7; N, 4.5. C₁₆H₁₇NO₅ requires C, 63.4; H, 5.6; N, 4.6%), ν_{max} (Nujol) 3520 (OH) and 1740 cm⁻¹ (C=O), τ (CDCl₃) 2.75 (5H, m, Ph), 2.82 (2H, s, 2-H and 5-H), 5.15 (1H, t, J 6 Hz, CH₂·CH), 6.05 (2H, d, J 6 Hz, CH₂·CH), and 6.33 (6H, s, 2 × OMe).

Ethyl 3,4-Dihydro-6,7-dimethyl-1-oxo-3-phenylpyrrolo[2,1-c][1,4]oxazine-8-carboxylate (5).—2-Methyl 3-ethyl 4,5-dimethylpyrrole-2,3-dicarboxylate (0.56 g, 2.5 mmol) was dissolved in dimethylformamide (5 cm³). Potassium (0.1 g, 2.5 mmol) and styrene oxide (0.5 g, 4 mmol) were added and the mixture was heated at 70–80° overnight. Water was added (to 50 cm³) and the mixture was shaken with a little ether (10 cm³). The product was precipitated and was filtered off and dried to yield the *lactone* (0.3 g, 30%), m.p. 168–169° (chloroform–petroleum) as needles (Found: C, 69.3; H, 6.3; N, 4.4. C₁₈H₁₉NO₄ requires C, 69.0; H, 6.1; N, 4.5%), ν_{max} (Nujol) 1705 (C=O) and 1720 cm⁻¹ (C=O), τ (CDCl₃) 2.6 (5H, s, Ph), 4.5 (1H, q, J 4 and 10 Hz, 3-H), 5.5–6.2 (4H, m, 4-H₂ and CH₃·CH₂), 7.9 (6H, d, 6-Me and 7-Me), and 8.7 (3H, t, CH₃·CH₂).

The ethereal portion of the filtrate was separated and the remaining aqueous solution was boiled briefly to remove entrained ether. The solution was cooled, acidified (conc. HCl), and extracted with chloroform. The extract was washed thoroughly with water (slightly acidified with dil. HCl), dried (MgSO₄), and evaporated to yield an oil which crystallised; this product was filtered from a little

ether (0.24 g) and showed two spots on t.l.c. [alumina with benzene–acetic acid (95 : 5)], one more fluorescent and faster running. The n.m.r. spectrum showed the presence of a mixture of 3-ethoxycarbonyl-4,5-dimethyl-1-styrylpyrrole-2-carboxylic acid and 3-ethoxycarbonyl-1-(2-hydroxyphenethyl)-4,5-dimethylpyrrole-2-carboxylic acid. The very small olefinic signal at τ 3.5–4.0 indicated that the hydroxy-compound was the main component.

(ii) The reaction was repeated on the same scale with one tenth of the amount of potassium (*i.e.* 0.01 g, 0.25 mmol). The products were the lactone (0.4 g, 47%) and the same mixture of acids (0.07 g).

(iii) The reaction was repeated on the same scale with precautions to exclude moisture (in a dry box under nitrogen). No lactone was formed and the same mixture of acids was isolated and was found by n.m.r. to contain equal amounts of the olefin (8) [τ 3.65 (d, J 15 Hz, =CH)] and the hydroxy-acid (10) [τ 4.95 (q, CH·OH)].

Ethyl 3,4-Dihydro-6,8-dimethyl-1-oxo-3-phenylpyrrolo[2,1-c][1,4]oxazine-2-carboxylate (6).—Diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate (Knorr's pyrrole) (0.6 g, 2.5 mmol) was dissolved in dimethylformamide (5 cm³) and potassium (0.1 g, 2.5 mmol) was added. When this had dissolved, styrene oxide (0.5 g, 4.0 mmol) was added, and the mixture was heated at 90° for 6 h. Water was added (to 50 cm³) and the solution was extracted with chloroform. The extract was washed thoroughly with water (slightly acidified with dil. HCl), dried (MgSO₄), and evaporated to yield an oil which crystallised on trituration with the minimum volume of ether to yield the lactone (0.07 g, 8%). This product had the same m.p. and spectroscopic properties as the lactone produced from the reaction of 4-ethoxycarbonyl-1-(2-hydroxyphenethyl)-3,5-dimethylpyrrole-2-carboxylic acid with polyphosphoric acid.²

Reaction of the Lactone (5) with Sodium Methoxide.—The lactone (0.16 g, 0.5 mmol) was stirred with sodium methoxide (0.03 g, 0.5 mmol) in dimethylformamide (2 cm³) overnight in a stoppered flask. Water was added (to 10 cm³) and unchanged lactone (0.1 g) filtered off. The filtrate was acidified (dil. HCl) and extracted with chloroform; the extract was washed with water, dried (MgSO₄), and evaporated. The resulting oil was examined by n.m.r. spectroscopy and by t.l.c. on alumina with benzene–acetic acid (95 : 5) which showed two spots identical to those from a mixture of compounds (8) (25%) and (10) (75%).

3-Ethoxycarbonyl-4,5-dimethyl-1-styrylpyrrole-2-carboxylic Acid (8).—The above reaction with the lactone (5) was repeated on the same scale with 10 times the amount of sodium ethoxide (0.34 g, 5 mmol), to avoid ester exchange. No lactone was precipitated on addition of water. Acidification (dil. HCl) precipitated the product, which was filtered off and dried to yield the *olefin* (0.09 g, 50%), m.p. 148–149° (methanol) as needles (Found: C, 68.25; H, 6.15; N, 4.35. C₁₈H₁₉NO₄ requires C, 69.0; H, 6.05; N, 4.45%), M^+ 313.131399 (calc. 313.131243), ν_{max} (KBr) 1610 (C=O), 1705 (C=O), and 2550 cm⁻¹ (OH), τ (CDCl₃) 2.4 (1H, d, J 14.5 Hz, =CH·N), 2.6 (5H, m, Ph), 3.6 (1H, d, J 14.5 Hz, =CH·Ph), 5.53 (2H, q, J 7 Hz, CH₃·CH₂), 7.73 (6H, s, 2-Me and 3-Me), and 8.55 (3H, t, J 7 Hz, CH₃·CH₂).

3-Ethoxycarbonyl-1-(2-hydroxyphenethyl)-4,5-dimethylpyrrole-2-carboxylic Acid (10).—The lactone (5) (0.156 g, 0.5 mmole) was stirred overnight with sodium hydroxide (0.2 g, 5 mmol) in water (1 cm³) and dimethylformamide (4 cm³) in a stoppered flask. Water was added (to 20

cm³) and the solution was acidified (dil. HCl) and scratched. The product was filtered off and dried (0.15 g, 90%); m.p. 167—168° (methanol), microprisms (Found: C, 65.2; H, 6.5; N, 4.3. C₁₈H₂₁NO₅ requires C, 65.25; H, 6.35; N, 4.25%), ν_{\max} (Nujol) 1605 (C=O), 1680 (C=O),

2500 (OH), and 3400 cm⁻¹ (OH), τ (CDCl₃) 2.6 (5H, m, Ph), 4.95 (1H, q, *J* 5 and 8 Hz, CH₂·CH), 5.3—5.8 (4H, m, CH₂·CH and CH₃·CH₂), 7.8 (6H, d, 2-Me and 3-Me), and 8.57 (3H, t, *J* 7 Hz, CH₃·CH₂).

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