Pyrazine Chemistry. Part 14.† On the Preparation and Oxygenation of Pyrazines and Some Reactions of the Product Peroxides

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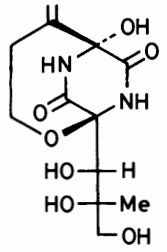
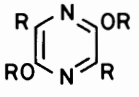
Some new methods for preparing substituted pyrazines are reported. 2,6-Dimethoxy substituted pyrazines undergo facile addition of singlet oxygen to form endoperoxides, some of which are remarkably stable. The behaviour of these compounds has been explored. In particular, deoxygenation is effected with triphenylphosphine to induce skeletal rearrangements, the pyrazines undergoing ring contraction to substituted imidazoles. The rearrangement occurs *via* intermediate oxadiazepines which can be intercepted by intramolecular trapping with a pendant hydroxy group, leading to a novel method for entry into the 3,6,1-oxadiazecine system. Reductive cleavage of the peroxide bond leads to unstable dihydroxydihydropyrazines.

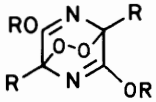
The reaction of singlet oxygen with heteroaromatic systems has attracted recent attention,[1] for example, the imidazole system of histidine residues in peptides has been shown to react rapidly with this reagent.[2] As an approach to the oxygenated system present in the antibiotic bicyclomycin (**1**) we considered the

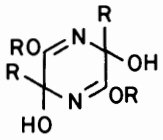


(**1**)

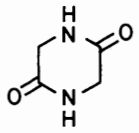
reaction of pyrazine derivatives with singlet oxygen and subsequent selective reduction of the endoperoxides, *e.g.* (**2**) to (**3**) to (**4**). This paper gives a fuller account of our preliminary note.[3]







In previous papers in this series we have described the ready dehydrogenation of dihydropyrazines, prepared by oxygen alkylation of the readily available piperazine-2,5-diones,[4] to produce the corresponding pyrazines. Such pyrazines may also be prepared by initially condensing a piperazinedione with an aldehyde to give the alkylidene or arylidene derivative, such as the conversion of glycine anhydride (**5**) into the derivatives (**6**) and (**7**), followed by the base-catalysed migration of the exocyclic double bond into the heterocyclic ring. However, this procedure is variable and although it works well for the arylidene derivatives, producing pyrazinediols,[5] ‡ isomerisation



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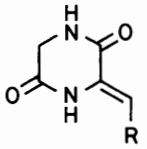
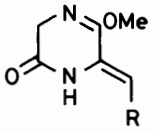
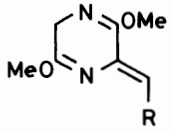


(**6**) R = Me_2CH
(**7**) R = Ph

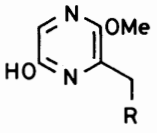
of the alkylidene derivatives (**6**) gave mixtures of the isomers and starting materials. For this reason the isomerisation of the *O*-alkylated derivatives was briefly explored. For the isobutyraldehyde adduct (**6**), alkylation with trimethyloxonium tetrafluoroborate affords both the mono- and bis-imino ethers, (**8**) and (**9**) respectively. Whilst base catalysed the isomerisation of the former to the pyrazinol (**12**), the bis-alkylated compound (**9**) could be converted by either base or mild acid treatment into the dimethoxypyrazine (**13**); even chromatography through silica was sufficient to catalyse this latter isomerisation. A similar behaviour was observed for the benzylidene derivative (**7**), yielding the mono-imino ether (**10**), the bis-imino ether (**11**) and the corresponding pyrazinol (**14**) and dimethoxypyrazine (**15**). The pyrazinols could be further methylated, for example with methyl iodide and silver oxide to give the corresponding dimethoxypyrazines.



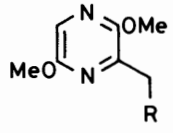
(**8**) R = Me_2CH
(**10**) R = Ph



(**9**) R = Me_2CH
(**11**) R = Ph



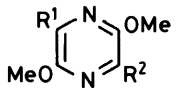
(**12**) R = Me_2CH
(**14**) R = Ph



(**13**) R = Me_2CH
(**15**) R = Ph

† Part 13, A. K. Göktürk, A. E. A. Porter, and P. G. Sammes, *J. Chem. Soc., Perkin Trans 1*, 1982, 953.
‡ The pyrazinol can exist as a mixture with the corresponding pyrazinone; for convenience we refer to this mixture as the 'pyrazinol'.

These isomerisation studies on the model methoxypiperazines were of value since they opened up a more direct route to substituted pyrazines of the type (**16**) required for our synthetic approach to bicyclomycin. For this, direct alkylation of the parent dimethoxydihydropyrazine (**17**) was envisaged, using a



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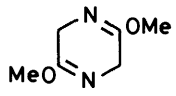
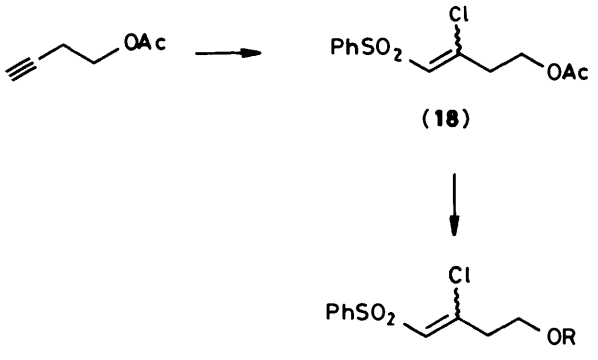


(**17**)

reagent that introduced an unsaturated link into the side chain followed by its subsequent migration into the heterocyclic ring in the manner described above. After many preliminary studies, the side-chain synthon eventually chosen was the unsaturated sulphone (**20**). This was prepared by the route outlined in Scheme 1. Direct addition of benzenesulphonyl chloride to



(**18**)

(**19**) R = H

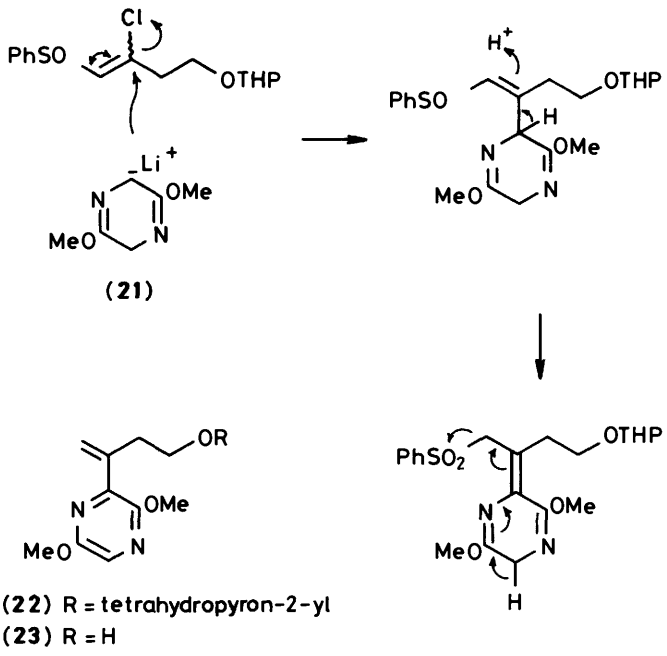
(**20**) R = tetrahydropyran-2-yl

Scheme 1.

either but-3-ynol or the tetrahydropyranyl derivative failed, but use of the acetate ester gave a reasonable yield of adduct (**18**) (*ca.* 50%) that could be hydrolysed to the corresponding alcohol (**19**) and the hydroxy group then protected as required.

The chloro sulphone (**20**) was added to the lithium salt of the dimethoxydihydropyrazine (**21**) in tetrahydrofuran (THF) at −70 °C, conditions shown not to destroy the reactive chloro sulphone, before adding t-butyl alcohol as a proton source and the reaction mixture allowed to warm to 0 °C before work-up. This procedure was essential to give optimum yields of the major product, shown to be the required, substituted pyrazine (**22**). As predicted, this is formed by an initial Michael-type addition of the carbanion to the β-position of the unsaturated sulphone, followed by elimination of chloride ion to form the α,β-unsaturated sulphone, the double bond of which then undergoes migration to the βγ-position, to give an alkylidene derivative (*vide supra*) that isomerizes to the hetero-aromatic pyrazine product by further migration of the double bond into the ring with concomitant loss of the sulphone entity to generate the exocyclic olefin bond (Scheme 2); overall yields of 40—50% were achieved. The pyrazine product was readily identified by its characteristic ^{1}H n.m.r. spectra, and comparison with the model pyrazines described above; the ring proton occurs at about δ 7.6.

Having obtained the key pyrazine (**22**) by a simple route, its behaviour towards singlet oxygen was examined. This proved to be a very efficient process and readily afforded the corresponding peroxide (**24**); the model pyrazines (**9**) and (**15**) also gave endoperoxides, (**25**) and (**26**), with singlet oxygen. The



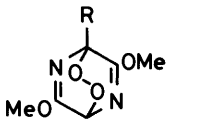
(**21**)

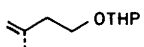
(**22**) R = tetrahydropyron-2-yl

(**23**) R = H

Scheme 2.

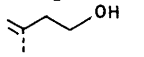
peroxides were relatively stable entities, remaining intact after several months when stored at 0—5 °C but decomposing when heated or upon melting. The model peroxides (**25**) and (**26**) both decomposed mainly by loss of oxygen, regenerating the pyrazines in high yield; we did not test to see if the liberated oxygen was in an excited or ground state.



(**24**) R = 

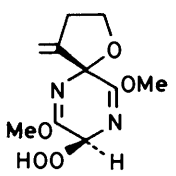
(**25**) R = Me_2CHCH

(**26**) R = $PhCH_2$

(**27**) R = 

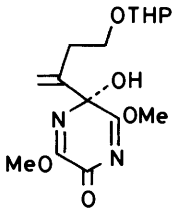
One further pyrazine was oxygenated, the alcohol (**23**), formed by removal of the tetrahydropyranyl protecting group. In this case the initial endoperoxide (**27**) was unstable, isomerizing within a few hours to give the stable, crystalline hydroperoxide (**28**); this compound showed a notable coupling of 4 Hz between the hydroperoxy proton and the adjacent ring proton. The relative configuration was assigned assuming that displacement of the bridged peroxide occurs by rearside attack of the pendant alcohol group.

Previous work on reduction of endoperoxides in the piperazinedione series, had shown that sodium borohydride could be



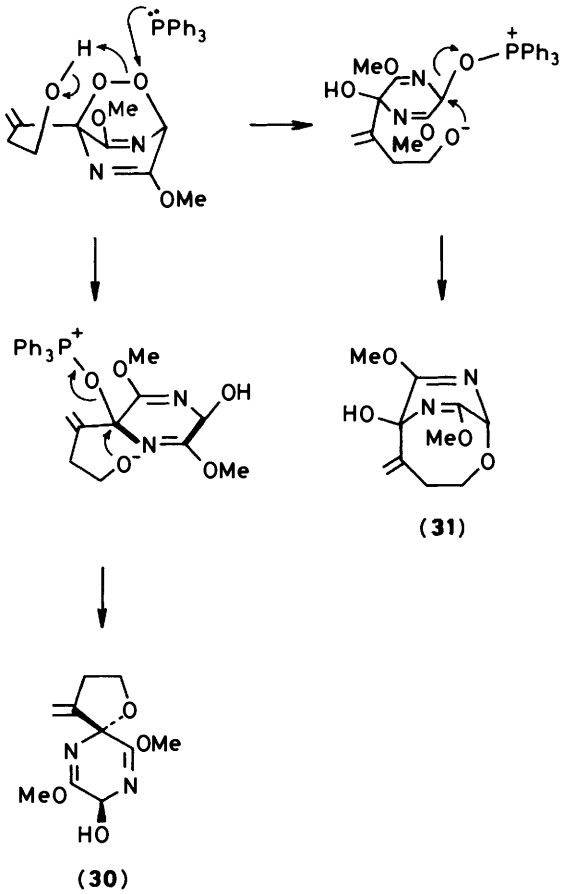
(**28**)

used as reductant.[6] Reduction of the endoperoxides (**25**) and (**26**) could be effected by sodium borohydride in methanol but the product diols were very unstable and could not be isolated under these reaction conditions. For the peroxide (**24**) a major product was isolated but proved to be the result of base-catalysed cleavage of the endoperoxide group to produce the hydroxy-keto isomer (**29**). Use of a poisoned palladium catalyst, as used in the reduction of alicyclic peroxides,[7] gave similar results, the reduced diols [*cf.* (**4**)] initially formed being too unstable to isolate.



(**29**)

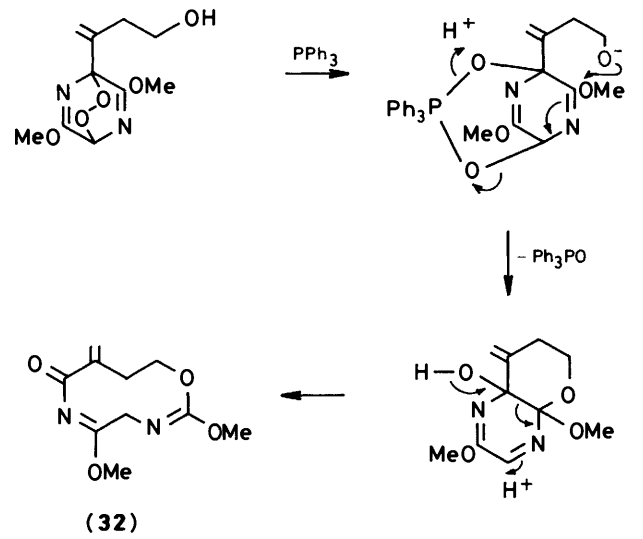
Since trivalent phosphorus reagents are reported to reduce peroxides to diols,[8] our attention turned to the possible use of trivalent phosphorus reagents to effect the desired reduction whilst simultaneously forming the cyclic ether function, as outlined in Scheme 3. Two possible fates were expected for the alcohol (**27**), either attack by the pendant alcohol group at the proximal ring position, to generate the unstable five-membered ring ether (**30**), an authentic sample of which was readily prepared by the reduction of the hydroperoxide (**28**) with triphenylphosphine,[9] or attack at the distal ring position to yield the required eight-membered ring (**31**). In the event a completely different reaction took place.



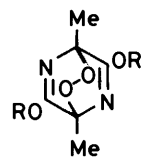
Scheme 3.

Treatment of the endoperoxide (**27**) with triphenylphosphine in chloroform gave a yellow reaction mixture with subsequent triphenylphosphine oxide formation being accompanied by production of one major product, identified as a 2:1 mixture of interconverting isomers. Highfield (400 MHz) ^{1}H n.m.r. spectroscopy separated out most of the proton signals and indicated the presence of two methoxy groups, the olefinic methylene group and three saturated methylene groups. Spin saturated transfer experiments showed that the major and minor isomers were interconverting; the two isomers could not be separated by t.l.c. ^{13}C N.m.r. spectroscopy showed the isomers contained four quaternary carbon atoms, one of which was a carbonyl carbon, and the four methylene carbons and two methoxy carbons indicated by the proton spectrum. This mixture was assigned as the 10-membered oxadiazecane (**32**). Because of the six ring sp^2 hybridised atoms, transannular repulsions are minimised and both molecular models and computer modelling using a molecular mechanics program indicate that the structure possesses a fairly flexible structure that can adopt several conformations, including those with the two methoxy groups either *syn* or *anti* with respect to the 10-membered ring.

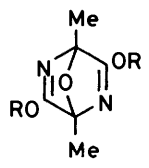
Formation of this new ring system is envisaged to occur by initial insertion of the phosphorus reagent into the peroxide bond, followed by an S_N2' type of attack of the side chain alcohol group on the imino-ether carbon (Scheme 4) to release the triphenylphosphine oxide group and then ring opening by collapse of the intermediate alcohol. This unusual sequence of events prompted an examination of the behaviour of the other endoperoxides, (**24**), (**25**), and (**26**) with triphenylphosphine, since, for these, the intramolecular alcohol group cannot interfere. Some earlier work [10] had indicated that deoxygenation of simple pyrazine endoperoxides, such as (**33**; R = Et), gave



Scheme 4.



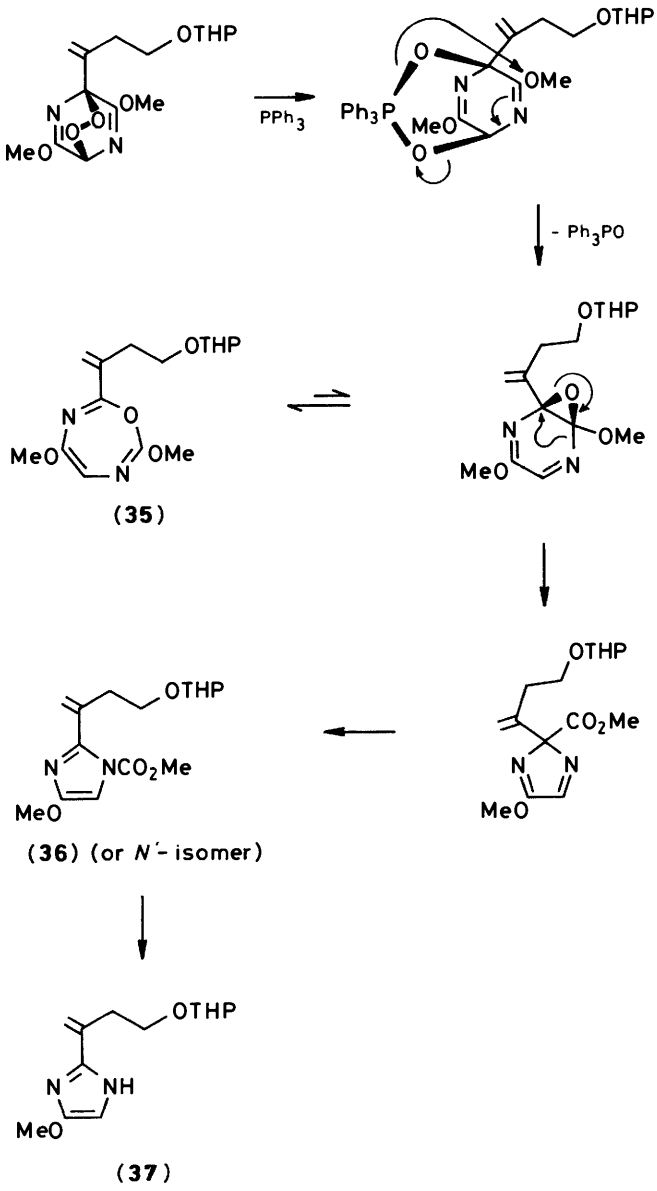
(**33**)



(**36**)

oxygen extrusion and the product was tentatively assigned as the bridged epoxide (**34**; R = Et). The following results require a correction of this earlier assignment.

In all cases triphenylphosphine oxide was slowly liberated to form an unstable, yellow intermediate that gradually disappeared with formation of a new product; the time taken for the intermediate to disappear varied both with the solvent used and with the presence or absence of traces of acid or base. For example, with the endoperoxide (**24**), the intermediate was isolated and showed three vinylic protons in its ^{1}H n.m.r. spectrum; two of these, δ 5.6 and 6.3 were due to the *exo*-methylene group, the third, at 5.9 was a singlet, other proton signals indicated an intact side chain. Again the ^{13}C n.m.r. spectrum showed four quaternary carbon atoms but none of these indicated the presence of a carbonyl group. These features indicate the 1,3,6-oxadiazepine structure (**35**) and this assignment was supported by the u.v. spectrum, which possessed a long wavelength band at $\lambda_{max.}$ 354 nm (ε 3 000), extending to 450 nm. This spectrum is similar to that shown by 2,7-dimethyloxepine, $\lambda_{max.}$ 297 nm (ε 1 800) extending to 430 nm.[11]



Scheme 5.

Upon leaving (**35**) in the absence of solvent the compound soon polymerised to a glassy, insoluble material. In a solution of aqueous THF the oxadiazepine underwent rearrangement to give an isomer characterised by the appearance of a carbonyl function, $\nu_{max.}$ 1 750 cm^{-1}. That this was due to a methoxycarbonyl group was shown by treatment with benzylamine, which readily afforded methyl *N*-benzylcarbamate. The ease of this reaction, a few hours at room temperature, together with the u.v. spectrum of the rearranged compound, suggested an *N*-methoxycarbonylimidazole structure, so the compound was assigned structure (**36**), or its *N'*-methoxycarbonylated isomer; we were not able to distinguish between these two isomeric possibilities. The parent imidazole (**37**) proved to be unstable to air.

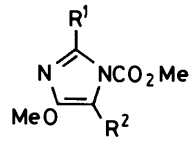
A possible mechanism for this rearrangement is given in Scheme 5. The 1,5-migration of the acyl group is known to be preferred to that of an alkyl group.[12] This ring contraction, of a pyrazine, *via* an oxadiazepine to an imidazole is unprecedented. However the rearrangement resembles certain photochemical rearrangements,[13] such as that observed by Burrell *et al.* during the irradiation of a quinoxaline *N*-oxide to produce a benzimidazole. That the endoperoxide rearranges under thermal conditions is attributed to the presence of the weak peroxide bond and the strong affinity of the reductant triphenylphosphine for oxygen. The model endoperoxides (**25**) and (**26**) behaved in a similar fashion to produce, *via* oxadiazepines, the corresponding imidazoles (**38**) and (**39**). The Table lists some of the ^{1}H n.m.r. assignments in these series of reactions. An examination of the reaction of the dimethyl-substituted pyrazine (**2**; R = Me) showed that the derived peroxide (**33**; R = Me) also gave an imidazole (**40**) and none of the bridged epoxide (**34**; R = Me). All the free imidazoles, produced by decarboxymethylation, *e.g.* (**37**), Scheme 5, tended to be rather unstable compounds, rapidly turning brown in air.

In an attempt to divert the reductive rearrangement of the endoperoxides to the imidazoles, the triphenylphosphine reaction was carried out on the model endoperoxides (**25**) and (**26**) in aqueous THF. Under these conditions the yield of imidazoles was reduced and new products formed. These products were very polar and unstable. Mass spectral analysis indicated that they corresponded to the endoperoxide plus two hydrogens. On this basis they were tentatively assigned as the

Table. ^{1}H N.m.r. chemical shifts[a]

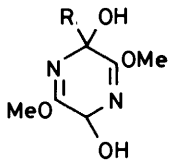
Compound	MeO	Ring proton (methyl)
Pyrazines		
(**13**)[b]	3.90	7.57
(**14**)[c]	3.89, 3.92	7.62
(**22**)[d]	3.77, 3.93	7.65
(**2**), R = Me[e]	3.90	(2.34)
Peroxides		
(**25**)[b]	3.87	5.79
(**26**)[c]	3.78, 3.84	5.66
(**24**)[d]	3.84, 3.90	5.72
(**33**)[e]	3.80	(1.69)
Imidazoles		
(**38**)[b]	3.75, 3.95	6.57
(**39**)[c]	3.77, 3.87	6.58
(**36**)[d]	3.81, 3.96	6.65
(**40**)[e]	3.87, 3.95	(2.23, 2.57)

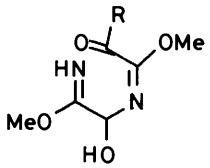
[a] All in $CDCl_3$. [b] Isobutyl series. [c] Benzyl series. [d] 'Bicyclomycin' series. [e] Dimethyl series.



(**38**) $R^1 = Me_2CHCH_2$, $R^2 = H$
(**39**) $R^1 = PhCH_2$, $R^2 = H$
(**40**) $R^1 = R^2 = Me$
} or *N'*-isomer

hydroxy compounds (**41**) and (**42**), arising by the interception of the phosphonium intermediates by water. As suggested by the results of the attempted reductions, *vide supra*, these polar materials behaved as tautomeric mixtures. Whilst the methoxy and side chain protons of the starting peroxides were still present, the i.r. spectra showed a carbonyl absorption at 1 729 cm^{-1}, an imine at 1 640 cm^{-1} and strong NH and OH absorptions around 3 275 cm^{-1}; these features indicate some equilibrium with the ring-opened forms such as (**43**) and (**44**).





(**41**) R = Me_2CHCH_2
(**42**) R = $PhCH_2$

(**43**) R = Me_2CHCH_2
(**44**) R = $PhCH_2$

Because of the observed instability of the dihydropyrazine diols no further work was carried out using these as intermediates for the synthesis of bicyclomycin and an alternative strategy was utilised.[14]

Experimental

M.p.s were determined on a Kofler block and are uncorrected. I.r. were recorded on a Perkin-Elmer 1420 Ratio Recording spectrophotometer either on solutions in chloroform, Nujol mulls or, for liquids, as films. ^1H N.m.r. spectra were recorded on a Varian 360A (60 MHz), Perkin-Elmer R32 (90 MHz), Jeol FX90Q (90 MHz) or Bruker AM400 (400 MHz) spectrometer and are quoted in p.p.m. relative to tetramethylsilane as internal reference, for solutions in deuteriochloroform; ^{13}C spectra were recorded on the Jeol and Bruker instruments using off resonance decoupling. Mass spectra were obtained using a Kratos MS25 instrument and accurate mass determinations were obtained using an AEI-Kratos MS 9/50 instrument. Microanalytical determinations were performed by the University of Leeds Microanalytical Laboratory. U.v. spectra were recorded on ethanolic solutions. All chiral compounds were obtained as racemates. T.l.c. was carried out on aluminium or glass plates precoated with Merck Kieselgel $60GF_{254}$. Column chromatography was carried out on either MN-Kieselgel 60 (Camlab) or Kieselgel 60G (Merck); columns were generally packed and run under pressure. Solvents were dried and distilled before use using standard methods.[15] Light petroleum refers to the fraction of boiling range 40—60 °C and ether refers to diethyl ether. Solutions of organic compounds from extractions were dried over anhydrous sodium sulphate before being filtered and evaporated under reduced pressure on a rotary evaporator. Dry nitrogen was generally employed as the atmosphere for most reactions. Ethanol was removed from chloroform by passing it through an activated alumina column immediately before use. Solutions of lithium amides were prepared according to the following general procedure. *N*-Butyl-lithium (1.5M solution in hexane; 1.05 equiv.) was added dropwise to a stirred solution of the amine (1 equiv.) in THF at −78 °C under nitrogen and stirred for a further 1 h after addition was complete. For more hindered amines, such as dicyclohexylamine, the lithium amide was prepared at −10 °C. Singlet oxygenations were performed using a flask fitted with a fritted glass oxygen inlet and a $CaCl_2$ drying tube. The apparatus was externally cooled by running water at 10—15 °C whilst irradiating with a 275 W spotlight. T.l.c. plates used to monitor these reactions were visualised using a starch/KI spray, composed of 1 g soluble starch and 0.5 g KI per 100 ml of water.

(*Z*)-3-*Isobutyrylidenepiperazine*-2,5-*dione* (**6**).—This compound was prepared using a modified method of Gallina and Liberatori[16] piperazine-2,5-dione (**5**) (5 g) was heated in refluxing acetic anhydride (50 ml), under a drying tube for 6 h. The excess of acetic anhydride was then distilled off and the solid residue crystallised and recrystallised from ethanol to give 1,4-diacetylpiperazine-2,5-dione (7.1 g, 82%), m.p. 100—101 °C (lit.,[17] m.p. 102 °C), δ 2.68 (6 H, s, 2 × Me) and 4.60 (4 H, s, 2 × CH_2). The diacetyl compound (1.98 g, 10 mmol) and isobutyraldehyde (3.6 ml, 4 equiv.) were dissolved in dry dimethylformamide (DMF) (20 ml) under nitrogen and to the solution at 0 °C was added potassium t-butoxide (0.5M solution in DMF; 20 ml, 1 equiv.); the mixture was then stirred at room temperature for 6 h. The suspension was acidified with glacial acetic acid, poured into water, and extracted with ethyl acetate (2 × 35 ml). The organic extracts were combined, washed with water, evaporated, and the residue crystallised from ethyl acetate–light petroleum to give (*Z*)-1-acetyl-3-isobutyrylidenepiperazine-2,5-dione (1.20 g, 55%), m.p. 145—148 °C (lit.,[16] 146—147 °C). This material (1.05 g, 5 mmol) was dissolved in DMF (6 ml) and stirred with hydrazine hydrate (0.3 ml, excess) at room temperature for 2 h. The resulting suspension was collected, washed with water, and dried to give the title compound (**6**)[16] (730 mg, 87%), m.p. > 280 °C (decomp.).

(*Z*)-3-*Benzylidenepiperazine*-2,5-*dione* (**7**).—This compound was prepared in a similar manner to compound (**6**): the diacetylpiperazinedione (3.96 g) was condensed with benzaldehyde (8.5 ml), using potassium t-butoxide as base and DMF as solvent, to give, after crystallisation from ethanol, (*Z*)-1-acetyl-3-benzylidenepiperazine-2,5-dione (2.9 g, 64%), m.p. 198—200 °C (lit.,[16] 201 °C). The latter compound (122 mg, 0.5 mmol) in DMF (4 ml) and hydrazine hydrate (55 mg, excess) were stirred at room temperature for 2 h after which the precipitate was collected, washed with water and dried to give the benzylidene (**7**) (89 mg, 89%), m.p. 260 °C (lit.,[16] m.p. 274—276 °C).

Methylation of Compound (**6**).—The isobutylidene derivative (10.1 g, 60 mmol) and trimethyloxonium tetrafluoroborate (35 g, 0.24 mol) were suspended in dry dichloromethane (150 ml) and dry nitromethane (80 ml) and the mixture stirred vigorously at room temperature under nitrogen for 3 days. The initial suspension dissolved in the first 3 h, and this was followed by the slow formation of a precipitate. The yellow mixture was poured into saturated aqueous sodium hydrogen carbonate (300 ml), and stirred for 10 min; the organic layer was then separated. The aqueous layer was extracted with chloroform (2 × 200 ml) and the combined organic fractions were dried and evaporated. The crude product was chromatographed through silica gel, eluting with ethyl acetate–light petroleum (1:4), to give, as the least polar component, (*Z*)-3,6-*dihydro*-3-*isobutylidene*-2,5-*dimethoxypyrazine* (**9**) (0.75 g, 6.4%) as a pale yellow liquid; $\nu_{max.}$(film) 2 940, 1 665, 1 655, 1 625, 1 435, and 1 245 cm^{-1}; δ 1.03 (6 H, d, *J* 7 Hz, Me_2CH), 3.20 (1 H, m), 3.72 (3 H, s, MeO), 3.80 (3 H, s, MeO), 4.22 (2 H, d, *J* 1.8 Hz, CH_2), and 5.76 (1 H, m, vinyl H).

This material was contaminated with some of the isomeric pyrazine (**13**) (see below) and was characterised by conversion into this compound. The more polar fraction afforded, after crystallisation from ethanol–light petroleum, (*Z*)-3,6-*dihydro*-6-*isobutylidene*-5-*methoxypyrazin*-2(1H)-*one* (**8**) (5 g, 45%), m.p. 145—148 °C; $\nu_{max.}$ 3 400, 2 980, 1 685, and 1 650 cm^{-1}; δ 1.40 (6 H, d, *J* 7 Hz, Me_2CH), 2.50 (1 H, m, CH), 3.76 (3 H, s, MeO), 4.32 (2 H, s, CH_2), 5.42 (1 H, d, *J* 11 Hz, vinyl H), 8.02 (1 H, br s, NH) (Found: C, 59.6; H, 7.8; N, 15.1. $C_9H_{14}N_2O_2$ requires C, 59.3; H, 7.7; N, 15.4%).

Methylation of Compound (**7**).—The benzylidene derivative (9 g, 45 mmol) and trimethyloxonium tetrafluoroborate (26 g, 0.18 mol) were suspended in dry dichloromethane (220 ml) and nitromethane (30 ml). The mixture was stirred at room temperature under nitrogen for 1 week. The resulting suspension was poured into saturated aqueous sodium hydrogen carbonate and the mixture stirred for 10 min; the organic layer was then separated. The aqueous layer was extracted with chloroform (2 × 200 ml) and the organic layers were combined and evaporated. The crude residue was chromatographed through silica gel, using ethyl acetate–light petroleum (1:4) as eluant, to afford, initially, (*Z*)-3-*benzylidene*-3,6-*dihydro*-2,5-*dimethoxypyrazine* (**11**) (0.45 g, 4.5%) as a pale yellow liquid, $\nu_{max.}$(film) 1 655, 1 645, 1 615, 1 435, 1 275, 1 250, 1 070, and 1 010 cm^{-1}; δ 3.80 (3 H, s, MeO), 3.90 (3 H, s, MeO), 4.35 (2 H, s, CH_2), 6.74 (1 H, s, vinyl H), and 7.20—8.15 (5 H, m, Ph). This material was rapidly converted into the pyrazine (**15**) (see below) and was characterised as this compound. The more polar fraction afforded, after crystallisation from ethanol–light petroleum, (*Z*)-6-*benzylidene*-3,6-*dihydro*-5-*methoxypyrazin*-2(1H)-*one* (**10**) (5.51 g, 57%), as pale yellow needles, m.p. 120—121 °C; $\nu_{max.}$ 3 380, 1 690, 1 680, and 1 640 cm^{-1}; δ 3.82 (3 H, s, MeO), 4.40 (2 H, s, CH_2), 6.52 (1 H, s, vinyl H), 7.35 (5 H, m, Ph), and 7.87 (1 H, br s, NH) (Found: C, 66.6; H, 5.6; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.6; H, 5.6; N, 13.0%).

Base-catalysed Isomerisation of the Mono Imino Ethers (**8**) *and* (**10**).—The pyrazinone (0.5 mmol) was suspended in aqueous sodium hydroxide (1M; 2 ml) and heated on a steam-bath. The solid rapidly dissolved to give a yellow solution. This was cooled in ice before being quenched with hydrochloric acid (2M; 2 ml), added in portions. The precipitate was filtered off and crystallised from aqueous ethanol to give the corresponding pyrazine.

5-*Hydroxy*-3-*isobutyl*-2-*methoxypyrazine* (**12**) (81%), was obtained as yellow needles, showed m.p. 96—99 °C; $\nu_{max.}$ 3 200—2 200, 1 550, 1 450, 1 295, and 1 020 cm^{-1}; $\lambda_{max.}$ 224, 278, 321, and 360 nm (log ε 3.95, 3.45, 3.90, and 2.90); δ 0.94 (6 H, d, *J* 7 Hz, Me_2CH), 2.14 (1 H, m, Me_2CH), 2.63 (2 H, d, *J* 7 Hz, CH_2CH), 3.90 (3 H, s, MeO), and 7.67 (1 H, s, ring H) (Found: C, 59.5; H, 7.7; N, 15.3. $C_9H_{14}N_2O_2$ requires C, 59.3; H, 7.7; N, 15.4%).

3-*Benzyl*-5-*hydroxy*-2-*methoxypyrazine* (**14**) (83%), was obtained as yellow needles, m.p. 142—143 °C; $\nu_{max.}$ 3 200—2 200, 1 545, 1 480, 1 420, 1 160, 1 125, 720, and 695 cm^{-1}; $\lambda_{max.}$ 223, 280, 322, and 360sh nm (log ε 4.03, 3.32, and 3.98); δ 3.94 (3 H, s, MeO), 4.04 (2 H, s, CH_2), 7.27 (5 H, m, Ph), and 7.71 (1 H, ring H) (Found: C, 66.6; H, 5.6; N, 2.6. $C_{12}H_{12}N_2O_2$ requires C, 66.6; H, 5.6; N, 13.0%).

Methylation of the Hydroxypyrazines (**13**) *and* (**14**).—The hydroxypyrazine (0.5 mmol) was dissolved in chloroform (5 ml) and freshly prepared silver oxide (232 mg, 1 mmol) and methyl iodide (0.2 ml, excess) were added. The mixture was stirred at room temperature for 2.5 h and then filtered through Celite, the solids being washed with a little chloroform; the filtrate was then evaporated. The pale yellow product was chromatographed through silica gel, using ethyl acetate—light petroleum (1:5) as eluant, to give the dimethoxy derivative.

3-*Isobutyl*-2,5-*dimethoxypyrazine* (**13**) (83 mg, 85%) was a pale yellow liquid, strongly fluorescent, b.p. 78—79 °C/1 mmHg; n_D 1.4943; $\nu_{max.}$(film) 2 950, 1 470, 1 390, 1 295, 1 270, 1 160, and 1 040 cm^{-1}; $\lambda_{max.}$ 229, 279, and 319 nm (log ε 4.01, 3.22, and 3.95); δ 1.94 (6 H, d, *J* 7 Hz, Me_2CH), 2.19 (1 H, m, Me_2CH), 2.64 (2 H, d, *J* 7 Hz, CH_2), 3.90 (6 H, s, 2 × MeO), and 7.57 (1 H, s, ring H) (Found: C, 60.9; 8.2; N, 14.0. $C_{10}H_{16}N_2O_2$ requires C, 61.2; H, 8.2; N, 14.3%).

3-*Benzyl*-2,5-*dimethoxypyrazine* (**14**) (83 mg, 72%) was a very pale yellow liquid, strongly fluorescent, b.p. 117—118 °C/1 mmHg; n_D 1.5655; $\nu_{max.}$(film) 2 940, 1 470, 1 390, 1 280, 1 155, 1 040, and 1 010 cm^{-1}; $\lambda_{max.}$ 228, 280, and 321 nm (log ε 3.84, 3.16, and 3.88); δ 3.89 (3 H, s, MeO), 3.92 (3 H, s, MeO), 4.26 (2 H, s, CH_2), 7.27 (5 H, m, Ph), and 7.62 (1 H, s, ring H) (Found: C, 67.5; H, 6.1; N, 12.4. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%).

Isomerisation of the Dimethoxydihydropyrazines (**9**) *and* (**11**).—This could be monitored by u.v. spectroscopy. Addition of either a drop of 4M hydrochloric acid or 2M sodium hydroxide to a solution of the dihydropyrazines in ethanol rapidly (within 30 min) catalysed the disappearance of the starting material and appearance of the characteristic absorption bands of the pyrazine. Examination of the solutions by t.l.c., after treatment with the acid or base, showed the appearance of the pyrazines characterised by their fluorescence and similar behaviour to authentic samples. Stirring a solution of the dihydropyrazines in dichloromethane with silica gel also caused rearrangement to the pyrazines.

4-*Acetoxy*-2-*chloro*-1-*phenylsulphonylbut*-1-*ene* (**18**). 4-Acetoxybut-1-yne (1.0 g, 8.9 mmol), benzenesulphonyl chloride (1.40 g, 8.0 mmol), acetonitrile (2 ml), and copper(I) chloride (0.0475 g, 0.48 mmol) were heated together under dry nitrogen at 100 °C for 18 h. The mixture was cooled, ether (200 ml) added and the precipitated copper salts filtered off. The ethereal solution was washed with water (100 ml), saturated aqueous dipotassium tartrate (50 ml) and then more water (100 ml), dried, and evaporated to afford a crystalline residue. This was crystallised from ethyl acetate–light petroleum to give the *title compound* (1.2 g, 47%), m.p. 72 °C; $\nu_{max.}$ 1 735, 1 620, 1 600, 1 460, 1 380, 1 370, 1 340, 1 320, 1 310, 1 287, 1 270, 1 215, 1 150, 760, and 690 cm^{-1}; δ 2.03 (3 H, s, Me), 3.35 (2 H, t, *J* 7 Hz, CH_2), 4.35 (2 H, t, *J* 7 Hz, CH_2), 6.63 (1 H, s, vinyl H), and 7.3—8.0 (5 H, m, Ph) (Found: C, 49.9; H, 4.6; Cl, 12.3; S, 11.0. $C_{12}H_{13}ClO_4S$ requires C, 49.9; H, 4.5; Cl, 12.3; S, 11.1%).

2-*Chloro*-1-*phenylsulphonyl*-4-(*tetrahydropyran*-2-*yloxy*)*but*-1-*ene* (**20**).—The acetate (**18**) (9.3 g, 32 mmol) was heated in methanol (500 ml) in the presence of Amberlyst 15 (H^+) ion exchange resin (20 g) for 8 h. The mixture was then cooled, filtered, and evaporated. The residual crude alcohol (**19**) was not isolated but was dissolved in dichloromethane (50 ml) and to the solution was added toluene-*p*-sulphonic acid (100 mg) and dihydropyran (3.5 g, 42 mmol). The solution was stirred at room temperature overnight, washed with saturated aqueous sodium hydrogen carbonate (100 ml) and the organic layer was dried and evaporated. The viscous residue was chromatographed through silica gel, using ethyl acetate–light petroleum (1:4) as eluant, to afford the title compound as a colourless oil (7.0 g, 66%), $\nu_{max.}$ 2 940, 1 640, 1 450, 1 315, and 1 150 cm^{-1}; δ 1.2—2.0 (6 H, m, 3 × CH_2), 3.2—4.2 (6 H, m, 3 × CH_2), 4.63 (1 H, m, OCHO), 6.62 (1 H, s, vinyl H), and 7.4—8.1 (Ph). (Found: C, 52.7; H, 5.6: Cl, 10.2; S, 9.2. $C_{15}H_{19}ClO_4S$ requires C, 52.8; H, 5.6; Cl, 10.4; S, 9.4%).

2,5-*Dimethoxy*-3-[4-(*tetrahydropyran*-2-*yloxy*)*but*-1-*en*-2-*yl*]*pyrazine* (**22**).—A solution of lithium dicyclohexylamide (5.3

mmol) in THF (10 ml) was added to a stirred solution of 2,5-dimethoxy-3,6-dihydropyrazine (**21**) (0.30 g, 2.1 mmol) in dry THF (35 ml) at −78 °C under nitrogen. The mixture was stirred for 2 h before dropwise addition, over 40 min, of a solution of the chloro sulphone (**19**) (0.83 g, 2.5 mmol) in dry tetrahydrofuran (20 ml) the temperature being maintained at −78 °C. After a further 1 h t-butyl alcohol (6 ml) was added and the solution was allowed to warm slowly to −10 °C. During this quenching reaction the colour of the solution changed from dark orange to pale orange and then darkened. The mixture was maintained at −10—0 °C for a further 4 h before it was quenched with aqueous ammonium chloride and, diluted with dichloromethane (50 ml). The organic layer was then separated, dried, and evaporated to leave a brown oil which was charomatographed through silica gel, using ethyl acetate–light petroleum (1:4) as eluant, to give, as the major fraction, the *title pyrazine* (0.26 g, 42%) as a colourless oil, $\nu_{max.}$(film) 2 950, 1 575, 1 470, 1 445, 1 395, 1 320, 1 280, 1 200, 1 170, 1 140, 1 120, 1 110, 1 075, 985, and 970 cm^{-1}; $\lambda_{max.}$ 244 and 336 nm (log ε 3.78 and 3.92); δ 1.3—2.0 (6 H, m, 3 × CH_2), 2.97 (2 H, m, =CCH_2), 3.3—4.0 (4 H, m, 2 × CH_2), 3.93 (3 H, s, MeO), 3.77 (3 H, s, MeO), 4.60 (1 H, m, OC*H*O), 5.65 (1 H, m, vinyl H), 6.20 (1 H, m, vinyl H), and 7.65 (1 H, s, ring H) (Found: C, 61.4; H, 7.45; N, 9.5. $C_{15}H_{22}N_2O_4$ requires C, 61.2; H, 7.5; N, 9.5%).

3-(4-*Hydroxybut*-1-*en*-2-*yl*)-2,5-*dimethoxypyrazine* (**23**).—The pyrazine (**22**) (1.5 g, 5.1 mmol) was stirred in methanol (35 ml) containing toluene-*p*-sulphonic acid (5 mg) at room temperature for 16 h. A few drops of 2M aqueous sodium hydrogen carbonate were added and the solvent was removed under reduced pressure to leave a residue which was chromatographed through silica gel, using ethyl acetate–light petroleum (1:3) as eluant, to give the *alcohol* (0.95 g, 87%) as a colourless liquid, $\nu_{max.}$(film) 3 450, 2 950, 2 880, 1 615, 1 575, 1 475, 1 390, 1 320, 1 285, 1 200, 1 165, 1 100, 1 035, and 1 010 cm^{-1}; δ 2.45 (1 H, br s, OH), 2.80 (2 H, t, *J* 7 Hz, CH_2), 3.6—4.0 (2 H, m, CH_2), 3.34 (3 H, s, MeO), 3.39 (3 H, s, MeO), 5.58 and 6.12 (2 H, m, C=CH_2), and 7.60 (1 H, s, ArH) (Found: C, 57.5; H, 6.7; N, 13.4. $C_{10}H_{14}N_2O_3$ requires C, 57.5; H, 6.7; N, 13.3%).

Formation of Peroxides.—A solution of the pyrazine (1 mmol) and Methylene Blue (10 mg) in dichloromethane (60 ml) was cooled to 5 °C whilst oxygen was passed through it and it was simultaneously irradiated with a 275 W tungsten lamp. When t.l.c. monitoring of the solution showed that all the starting material had been consumed (30—60 min) it was evaporated and the residue filtered through silica gel, using ethyl acetate–light petroleum mixtures as solvent to give the endoperoxide.

3,6-*Epidioxy*-3,6-*dihydro*-2,5-*dimethoxy*-3-(4-*tetrahydropyran*-2-*yloxybut*-1-*en*-2-*yl*)*pyrazine* (**24**) obtained from the pyrazine (**22**) (84%) was obtained as a colourless oil, $\nu_{max.}$(film) 2 940, 2 860, 1 630, 1 435, 1 330, 1 270, 1 198, 1 140, 1 030, and 900 cm^{-1}; δ 1.3—2.0 (6 H, m), 2.6 (2 H, allylic H), 3.3—4.1 (4 H, m), 3.84 (3 H, s, MeO), 3.90 (3 H, s, MeO), 4.62 (1 H, br s, OC*H*O), 5.5 (1 H, s, br s, vinylic H), 5.72 (1 H, s, ring H), and 5.88 (1 H, br s, vinylic H) (Found: C, 55.0; H, 6.8; N, 8.4. $C_{15}H_{22}N_2O_6$ requires C, 55.2; H, 6.8; N, 8.6%).

3,6-*Epidioxy*-3,6-*dihydro*-3-*isobutyl*-2,5-*dimethoxypyrazine* (**25**), obtained from the pyrazine (**13**) (88%) as a pale yellow oil; $\nu_{max.}$(film) 1 660, 1 445, 1 345, 1 205, 1 030, 1 000, 970, and 905 cm^{-1}; δ 1.06 (6 H, dd, *J* 7 Hz, Me_2CH), 1.8—2.4 (3 H, m), 3.87 (6 H, s, 2 × MeO), and 5.79 (1 H, s, ring H) (Found: C, 53.0; H, 7.0; N, 12.3. $C_{10}H_{16}N_2O_4$ requires C, 52.6; H, 7.1; N, 12.3%).

3-*Benzyl*-3,6-*epidioxy*-3,6-*dihydro*-2,5-*dimethoxypyrazine* (**26**), obtained from the pyrazine (**15**) (95%) as a pale yellow solid, m.p. 70—71 °C (decomp.); $\nu_{max.}$ 1 630, 1 490, 1 435, 1 375, 1 340, 1 250, 1 195, 1 180, 1 070, 1 030, 1 000, and 970 cm^{-1}; δ 3.42 (2 H, d, *J* 2.5 Hz, CH_2), 3.78 (3 H, s, MeO), 3.84 (3 H, s, MeO), 5.66 (1 H, s, ring H), and 7.3 (5 H, s, Ph) (Found: 59.4; H, 5.3; N, 10.8. $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.4; N, 10.7%).

3,6-*Epidioxy*-3,6-*dihydro*-3-(4-*hydroxybut*-1-*en*-2-*yl*)-2,5-*dimethoxypyrazine* (**27**), obtained from the alcohol (**23**) (87%) as a colourless, viscous oil; $\nu_{max.}$(film) 3 480, 1 655, 1 640, 1 340, 1 035, and 760 cm^{-1}; δ 2.62 (2 H, t, *J* 7 Hz, allylic CH_2), 3.7—4.0 (2 H, m, CH_2), 3.90 (3 H, s, MeO), 3.93 (3 H, s, MeO), 5.47 (1 H, s, ring H), and 5.78 (2 H, s, CH_2=C). When this endoperoxide was left at room temperature for a week, or heated in benzene at 50 °C for several hours the compound isomerised to the *spirohydroperoxide* (**28**) in quantitative yield. A sample was purified by chromatography through silica gel, using ethyl acetate–light petroleum (1:2) as eluant, to give the hydroperoxide as a colourless crystalline solid, m.p. 127—130 °C; $\nu_{max.}$(Nujol) 3 330, 1 660, 1 640, 1 465, and 1 060 cm^{-1}, δ 2.1—3.0 (2 H, m, allylic H), 3.00 (1 H, d, *J* 4 Hz, OOH), 3.13 (3 H, s, MeO), 3.6—4.0 (2 H, m, CH_2O), 3.92 (3 H, s, MeO), 5.10 (1 H, d, *J* 4 Hz, C*H*OOH), and 5.40 and 6.00 (2 H, br s, CH_2=C) (Found: C, 49.5; H, 5.7; N, 11.5. $C_{10}H_{14}N_2O_5$ requires C, 49.6; H, 5.8; N, 11.6%).

3,6-*Epidioxy*-3,6-*dihydro*-2,5-*dimethoxy*-3,6-*dimethylpyrazine* (**33**). The known pyrazine (**2**), R = Me[18] gave the *peroxide* (95%), as a colourless solid, m.p. 116—120 °C (decomp.); $\nu_{max.}$ 1 640, 1 445, 1 390, 1 335, 1 280, 1 145, 1 100, and 955 cm^{-1}; δ 1.69 (6 H, s, 2 × Me), and 3.80 (6 H, s, 2 × MeO) (Found: C, 48.1; H, 6.1; N, 13.8. $C_8H_{12}N_2O_4$ requires C, 48.0; H, 6.0; N, 13.8%).

3,6-*Dihydro*-3-*hydroxy*-2,5-*dimethoxy*-6-*oxo*-3-(4-*tetrahydropyranyloxybut*-1-*en*-2-*yl*)*pyrazine* (**29**).—A solution of the endoperoxide (**24**) (0.50 g, 1.53 mmol), and sodium borohydride (50 mg) in THF–water (1:1) (80 ml) was stirred at room temperature for 6 h. Monitoring of the reaction mixture by t.l.c. indicated the appearance of 1 major new compound and 4 others. The mixture was neutralised with dilute hydrochloric acid, the organic solvent removed under reduced pressure, and the residue extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried and evaporated to leave an oil (0.28 g) which was chromatographed using ethyl acetate–light petroleum (4:1) as eluant, to afford the *title compound* (0.18 g, 36%) as a colourless oil, $\nu_{max.}$(film) 3 400, 1 740, 1 715, 1 670, 1 280, 1 260, 1 200, 1 180, 1 135, 1 075, and 1 030 cm^{-1}; δ 1.2—2.0 (6 H, m, aliphatic H), 2.1—2.6 (2 H, m, allylic H), 3.0—4.0 (5 H, m, OH, 2 × OCH_2), 3.25 (3 H, OMe), 3.75 (3 H, s, MeO), 4.47 (1 H, br s, OCHO), and 4.95 and 5.03 (2 H, br s, CH_2=C) (Found: C, 55.3; H, 6.9; N, 8.4. $C_{15}H_{22}N_2O_6$ requires C, 55.2; H, 6.8; N, 8.6%).

Reduction of the Hydroperoxide (**28**).—Triphenylphosphine (54 mg, 0.21 mmol) was added to a solution of the hydroperoxide (**28**) (50 mg, 0.21 mmol) in $CDCl_3$ (1 ml) in an n.m.r. tube. After a period of 30 min the mixture was examined by n.m.r. spectroscopy, which showed quantitative conversion of the phosphine to the phosphine oxide and of the hydroperoxide to the spiro alcohol (**30**); the latter showed signals at δ 2.2—2.9 (2 H, m, allylic H), 2.6—2.9 (1 H, br s, OH), 3.27 (3 H, s, MeO), 3.8—4.0 (2 H, m, OCH_2), 3.95 (3 H, s, MeO), 5.34 (1 H, s, ring H), and 5.40 and 5.95 (2 H, br s, CH_2=C). The product was unstable and, on isolation from solution, it gradually decomposed at room temperature to give a mixture of products.

Reduction of the Hydroxy Endoperoxide (**27**) *with Triphenylphosphine.*—Triphenylphosphine (0.25 g, 0.95 mmol) was added to a solution of the endoperoxide (0.23 g, 0.95 mmol) in dichloromethane (30 ml) at room temperature. The mixture immediately became yellow. After 5 min the organic solvent was removed to give an unstable yellow oil, which decomposed during silica gel chromatography to give a more polar colour-

less compound. Thus silica gel chromatography, using ethyl acetate–light petroleum (3:2) as eluant, gave as the major product, 2,5-*dimethoxy*-8-*methylene*-1-*oxa*-3,6-*diazacyclodeca*-2,5-*dien*-7-*one* (**32**) (0.140 g, 74%), as a pale yellow oil, $\nu_{max.}$ 2 960, 2 880, 1 710, 1 665, 1 440, 1 360, 1 110, 1 040, 990, and 770 cm^{-1}; δ 2.7—3.2 (2 H, m, allylic H), 3.72 (3 H, s, MeO), 3.97 (3 H, s, MeO), 4.05—4.55 (4 H, m, 2 × CH_2), and 4.90 and 5.23 (2 H, m, CH_2=C); δ_C 31.9 t, 49.7 t, 52.3 q, 56.1 q, 67.6 t, 108.4 t, 113.9 s, 149.5 s, 152.9 s, and 168.9 s; *m/z* 226 (M^+, 49%), 211 (73), 196 (100), 181 (23), 151 (61), 141 (42), 124 (49), 110 (24), 81 (39), 70 (40), and 59 (49) (Found: C, 52.9; H, 6.5; N, 12.4. $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.2; N, 12.4%).

Reduction of the Endoperoxide (**24**) *with Triphenylphosphine.*—(*a*) *In anhydrous THF.* Triphenylphosphine (0.22 g, 0.84 mmol) was added to a solution of the endoperoxide (0.27 g, 0.83 mmol) in THF (20 ml) under nitrogen at room temperature. An exothermic reaction ensued, the colour of the solution turning yellow. The solvent was evaporated under reduced pressure to leave a residue which was immediately separated by chromatography through silica gel, using ethyl acetate–light petroleum (7:3) as eluant, to give as the major product 4,7-*dimethoxy*-2-(4-*tetrahydropyran*-2-*yloxybut*-1-*en*-2-*yl*)-1,3,6-*oxadiazepine* (**35**) (0.20 g, 76%) as a yellow-orange liquid, $\nu_{max.}$(film) 2 950, 1 655, 1 275, 1 240, 1 200, 1 160, 1 080, 1 065, and 1 035 cm^{-1}; δ 1.4—1.9 (6 H, m, 3 × CH_2), 2.78 (2 H, m, allylic H), 3.3—4.0 (4 H, m, CH_2O), 3.68 (3 H, s, MeO), 3.85 (3 H, s, MeO), 4.60 (1 H, m, OCHO), 5.70 and 6.30 (2 H, m, CH_2=C), and 5.90 (1 H, s, CH=N); δ_C 19.5 t, 25.5 t, 30.7 t, 33.1 t, 55.6 q, 57.6 q, 62.1 t, 65.7 t, 98.6 d, 107.0 d, 126.4 t, 137.2 s, 141.9 s, 144.3 s, and 151.3 s. With time the oil set to a glassy solid, assumed to be a polymer; this was the material analysed (Found: C, 58.0; H, 7.1; N, 9.0. $C_{15}H_{22}N_2O_5$ requires C, 58.0; H, 7.1; N, 9.0%).

(*b*) *In aqueous THF.* The reduction was repeated but after initial reaction of the peroxide (0.20 g, 0.61 mmol) with triphenylphosphine (0.16 g, 0.61 mmol) in dry THF (15 ml) at room temperature for 10 min, water (2 ml) was added and the mixture heated at 80 °C under nitrogen for 6 h. The solvent was removed by freeze drying and the residue chromatographed through silica gel, using ethyl acetate–light petroleum (1:1) as eluant, to produce the *imidazole* (**36**), or its *N'*-isomer (90 mg, 48%), as a colourless solid, m.p. 26 °C; $\nu_{max.}$ 2 930, 1 750, 1 730 (sh), 1 600, 1 370, 1 300, 1 250, 1 085, 1 030, and 730 cm^{-1}; $\lambda_{max.}$ 224 and 275 nm (ε 32 000 and 37 000); δ 1.3—1.8 (6 H, m, 3 × CH_2), 2.80 (2 H, m, allylic H), 3.3—3.7 (2 H, m, CH_2), 3.7—4.0 (2 H, m, CH_2), 3.81 (3 H, s, MeO), 3.96 (3 H, s, MeO), 4.55 (1 H, m, OCHO), 5.4—5.5 (2 H, m, vinylic H), and 6.65 (1 H, s, ring H); δ_C 19.3 t, 25.4 t, 30.6 t, 35.8 t, 54.2 q, 56.7 q, 68.1 t, 66.2 t, 94.9 d, 98.5 d, 120.2 t, 137.9 s, 146.3 s, 149.2 s, and 155.9 s (Found: C, 57.6; H, 7.1; N, 9.0. $C_{15}H_{22}N_2O_5$ requires C, 58.0; H, 7.1; N, 9.0%).

Reaction of the Imidazole (**36**) *with Benzylamine.*—The imidazole (5 mg) was treated with benzylamine (20 mg) in dichloromethane (0.2 ml) at room temperature for 1 h. The solvent was removed and the residue separated by preparative t.l.c., using ethyl acetate–light petroleum (3:7) as eluant, to give methyl *N*-benzylurethane (3 mg), the t.l.c. properties of which were identical with those of an authentic sample, *m/z* 165 (M^+ 45%), 150 (91), 133 (15), 106 (84), 91 (82), 79 (77), 65 (29), 51 (41), and 28 (100). The more polar material was the *imidazole* (**37**) (3 mg), isolated as an oil which rapidly turned brown on exposure to air. A freshly isolated sample showed *m/z* 252 (M^+ 14%), 168 (82), 151 (40), 139 (32), 124 (19), 107 (17), 85 (100), and 80 (22).

Reaction of the Peroxides (**25**), (**26**), *and* (**33**) *with Triphenylphosphine.*—The following general method was used. The peroxide (2 mmol) and triphenylphosphine (1 equiv.) in water–THF (1:4; 10 ml) were stirred at room temperature under nitrogen for 7 days. The solvent was removed and the residue chromatographed through silica gel, using ethyl acetate—light petroleum as eluant, to give the products. The peroxide (**33**; R = Me) afforded, as colourless oil, 4-*methoxy*-1-*methoxycarbonyl*-2,5-*dimethylimidazole* (**40**) or its *N'*-isomer (144 mg, 39%), $\nu_{max.}$ 2 960, 1 755, 1 640, 1 440, 1 350, 1 320, and 1 105 cm^{-1}; $\lambda_{max.}$ 215 and 266 nm; δ 2.23 (3 H, s, Me), 2.57 (3 H, s, Me), 3.87 (3 H, s, MeO), and 3.95 (3 H, s, MeO); *m/z* 184 (M^+ 61%), 125 (16) and 56 (100) (Found: M^+ 184.0850; $C_8H_{12}N_2O_3$ requires 184.0848).

The peroxide (**25**) gave two fractions, the less polar material being identified as 1,2-*isobutyl*-4-*methoxy*-1-*methoxycarbonylimidazole* (**38**), or its *N'*-isomer, (224 mg, 52%), isolated as an oil, $\nu_{max.}$ 1 760, 1 605, 1 440, 1 395, 1 310, 1 260, 1 110, 1 100, and 770 cm^{-1}; $\lambda_{max.}$ 213 and 262 nm; δ 0.96 (6 H, d, *J* 6.8 Hz, Me_2CH), 2.13 (1 H, m, CH), 2.85 (2 H, d, *J* 6.8 Hz, CH_2), 3.75 (3 H, s, MeO), 3.95 (3 H, s, MeO), and 6.57 (1 H, s, ring H) (Found: C, 56.3; H, 8.2; N, 13.1. $C_{10}H_{16}N_2O_3$ requires C, 56.6; H, 7.6; N, 13.2%). The polar fraction was tentatively assigned as 3,6-*dihydro*-3,6-*dihydroxy*-3-*isobutyl*-2,5-*dimethoxypyrazine* (**41**) (118 mg, 20%) as a mixture with its ring-opened tautomers, *e.g.* (**43**), $\nu_{max.}$ 3 280 (br), 1 720, 1 630, 1 480, 1 365, 1 335, 1 220, 1 160, 1 065, 1 030, and 785 cm^{-1}; $\lambda_{max.}$ 212 nm; δ 0.98 (6 H, d, *J* 6.5 Hz, Me_2CH), 1.63 (1 H, s), 2.20 (2 H, m), 3.58 and 3.69 (6 H, s, 2 × MeO), and 6.75 (2 H, br s, exchanged with D_2O) (Found: M^+, 230.126 35; $C_{10}H_{18}N_2O_4$ requires 230.126 65).

The peroxide (**26**) also gave two fractions after reduction, the less polar fraction, isolated as a viscous oil, was identified as 2-*benzyl*-4-*methoxy*-1-*methoxycarbonylimidazole* (**39**), or its N^+-isomer (55 mg, 11%), $\nu_{max.}$ 1 745, 1 590, 1 255, 1 105, 760, 735, and 700 cm^{-1}; δ 3.77 (3 H, s, MeO), 3.87 (3 H, s, MeO), 4.33 (2 H, s, CH_2), 6.58 (1 H, s, ring H), and 7.25 (5 H, s, Ph); *m/z* 246 (M^+, 100%), 187 (57), 172 (14), and 91 (42) (Found: M^+, 246.100 43. $C_{13}H_{14}N_2O_3$ requires M^+, 246.100 44).

The polar fraction was tentatively identified as a tautomeric mixture of 3-*benzyl*-3,6-*dihydro*-2,5-*dimethoxypyrazine*-3,6-*diol* (**42**) and the corresponding ring-opened isomers, *e.g.* (**44**) (138 mg, 27%), $\nu_{max.}$ 3 340, 3 260, 3 180, 1 750—1 600 (br), 1 070, 770, 725, and 695 cm^{-1}; δ 3.48 (2 H, s), 3.66 (6 H, s) 3.77 (1 H, s), 5.73 (1 H, d, *J* 7 Hz), 6.7 (1 H, br s), and 7.27 (5 H, br s, Ph); *m/z* 264 (M^+, 10%), 246 (2) and 173 (100) (Found: M^+, 264.110 75. $C_{13}H_{14}N_2O_4$ requires M^+, 264.111 00).

Acknowledgements

We thank the S.E.R.C. for full support of this work and, with G. D. Searle and Co., for a C.A.S.E. award (to A. J. P.).

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Received 24*th May* 1988; *Paper* 8/02073F