# Pyrazine Chemistry. Part 9.[1] Oxygenation of Pyrazines and Pyrimidines

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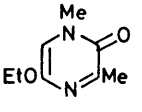
Singlet oxygen adds to certain substituted pyrazines and pyrimidines to form the *endo*-peroxides in high yield. The peroxides derived from the pyrazines are often stable compounds. 2,5-Diethoxy-3,6-dimethyl-3,6-epidioxy-3,6-dihydropyrazine can be reduced to the corresponding diol with sodium borohydride, whilst the parent pyrazine is regenerated by treatment with acid. The properties of the oxidation products have been briefly explored.

THE addition of singlet oxygen across dienes or diene functions incorporated into aromatic or five-membered-heteroaromatic systems, such as furan, is well established. The primary product from such oxidations is generally the corresponding *endo*-peroxide,[2] although these are often unstable, transforming into further oxidation products.[3] In earlier work in this series we found that certain pyrazine derivatives, in particular the pyrazinone (1) readily reacted with oxygen, even in the



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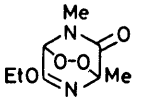
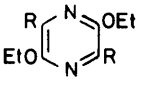


(2)

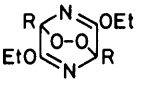
absence of light, to form a cyclic peroxide (2).[4] Since pyrazines, especially alkoxy-substituted pyrazines, are important flavouring constituents [5] we wished to examine the generality of these earlier observations.

## RESULTS AND DISCUSSION

Irradiation of a solution of 3,6-dibenzyl-2,5-diethoxypyrazine (3) in dichloromethane containing Methylene Blue as a sensitiser, whilst gently passing through it a stream of oxygen, afforded the *endo*-peroxide (4) in quantitative yield. The peroxide was readily characterised by both its $^1$H n.m.r. spectrum and its positive peroxide test.[6] When control experiments were run in the absence of light, traces of the same peroxide (4) were



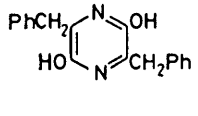
(3) R = $PhCH_2$
(9) R = Me



(4) R = $PhCH_2$
(10) R = Me

repeatedly formed, although the yield was always low (<5%). Addition of radical quenching agents, such as 4-t-butyl-2,6-dimethylphenol or quinol did not affect the peroxide formation, nor did the presence of radical chain initiators such as di-t-butyl peroxide. The influence of cation radical catalysts [7] on the oxidation step was not explored.

Addition of singlet oxygen to the dihydroxy-equivalent of compound (3), *i.e.* compound (5), also proceeded smoothly to afford the epidioxypiperazine (6) in high yield. In this case the polar, reactive nature of the product caused problems when trying to separate it from the Methylene Blue sensitiser. This problem could be overcome by using polymer-based forms of either eosin or Rose Bengal as sensitisers.[8] The peroxide (6) could be reduced, by mild treatment with sodium borohydride, to the diol (7). Proof of structure of the latter was obtained by its acid-catalysed dehydration, to produce the known dibenzylidene derivative (8).[9]



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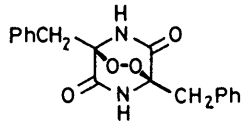

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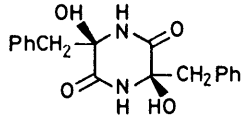

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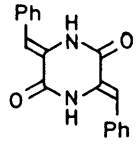
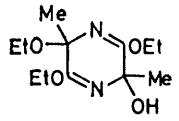


(8)

The dimethyl analogue (9) of the dibenzyldiethoxypyrazine (3) behaved similarly with singlet oxygen, to give the *endo*-peroxide (10). In contrast to the dibenzyl compound, the dimethylpyrazine (9) did not afford any peroxide in the control experiments, *i.e.* either in the absence of light or the absence of a sensitiser. The product peroxide was surprisingly stable and could be stored at room temperature, in the dark, without appreciable decomposition for several weeks. Reduction with potassium iodide was slow. Because of solubility problems this was carried out in ethanol, to give, as the major product, one of the crystalline triethoxy alcohols (11). This must arise *via* the expected diol (12) by acid-catalysed substitution of one of the alcohol groups. Such a ready exchange at this junction has been observed previously. Indeed, reduction of the



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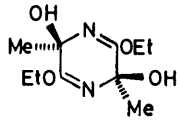
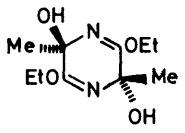


(12)

peroxide (10) by sodium borohydride in aqueous THF gave not only the expected *cis*-diol (12) but, after work-up, a mixture of this with the *trans*-substituted isomer (13).

Since the peroxides (4), (6), and (10) are analogues of their naturally-occurring disulphide counterparts, such as (14),[10] it was of interest to see if they behaved similarly



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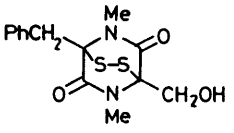

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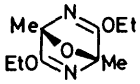
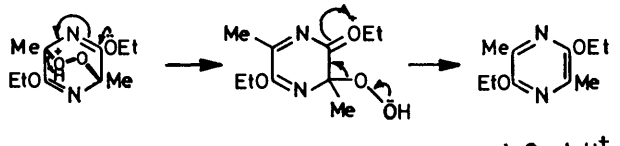


(15)

on treatment with triphenylphosphine. The latter reagent is reported to produce the corresponding bridged monosulphide from disulphides by extrusion of one sulphur atom.[11] With the *endo*-peroxide (10), reaction with triphenylphosphine in dry benzene did occur, but the product proved to be extremely unstable and its formation irregular. $^1$H N.m.r. spectroscopy on a purified sample indicated a symmetrical structure, with the methyl groups appearing slightly downfield ($\tau$ 7.94) compared to their position in the peroxide (10) ($\tau$ 8.37). Since triphenylphosphine oxide could be detected as the other, major reaction product, the epoxy-structure (15) has been tentatively assigned to this unstable material.

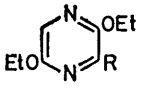
An interesting reaction was observed in attempting to hydrolyse the imino-ether functions of either of the peroxides (4) or (10) under aqueous acidic conditions. With dilute acid no reaction was observed but, when stronger acid conditions were employed, the principal



SCHEME

reaction observed was not hydrolysis but, instead, regeneration of the parent pyrazine. The Scheme indicated might explain this result. By the law of microscopic reversibility this suggests that acid-catalysed oxygenations should be possible with these substrates. This possibility needs to be explored.

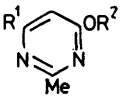
Compared to the results obtained with the 3,6-disubstituted pyrazines, oxidations of monosubstituted or unsubstituted diethoxypyrazines were disappointing. Oxygenation of either 2,5-diethoxypyrazine (16) or 2,5-diethoxy-3-(3-hydroxypropyl)pyrazine (17), for example,



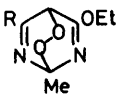
(16) R = H
(17) R = $CH_2CH_2CH_2OH$

rapidly consumed the starting materials but mixtures of unstable products were obtained. The presence of ring protons in the starting materials is presumably responsible for the instability of the intermediate peroxide.

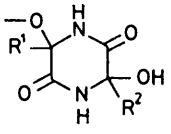
In previous work the analogous behaviour of certain pyrimidine derivatives to that of the pyrazines has been noted,[4] although the pyrimidines tended to be less reactive towards cycloadditions. A brief study of the behaviour of some pyrimidines towards singlet oxygen addition has now been made. In contrast to the pyrazine (5) the dihydroxypyrimidine (18) did not appear to react with singlet oxygen under our reaction conditions. After *O*-ethylation, however, the product (19) was found to be sensitive to oxygenation and afforded a crystalline



(18) $R^1$ = OH, $R^2$ = H
(19) $R^1$ = EtO, $R^2$ = Et
(21) $R^1$ = Me, $R^2$ = Et



(20) R = OEt
(22) R = Me



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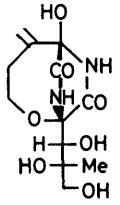

(24)

adduct assigned as the *endo*-peroxide (20). Similarly the pyrimidine (21) also afforded the *endo*-peroxide (22) but both these adducts were relatively unstable materials.

Because of the known tendency of the pyridazines to undergo cycloadditions [12] it would not be surprising if these systems also undergo photo-oxidation to peroxides. The ready oxygenation of the disubstituted pyrazine system of the type (5) is of interest as a method for generating the part structure (23), which occurs in the interesting antibiotic bicyclomycin (24).[13] Some experiments directed towards this end are described in the following paper.[14]

## EXPERIMENTAL

M.p.s were recorded with a Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer spectrometer. $^1$H N.m.r. spectra were obtained with either a Varian T60 or JEOL MH100 instrument with deuteriochloroform as solvent, unless otherwise stated, and tetramethylsilane as internal reference. Mass spectra were obtained with an A.E.I. MS9 instrument. T.l.c. was carried out with Merck silica gel $GF_{254}$, and p.l.c. using 1-mm thick plates of silica gel G. All solvents were freshly distilled before use.

*Singlet Oxygen Oxygenations.*—All singlet oxygen additions were performed in dichloromethane (10 ml) with a dye sensitiser. This sensitiser was most frequently Methylene Blue (1—2 mg), but polymer-bound eosin and Rose Bengal were also used (5—10 mg). Oxygen was bubbled slowly through the solutions cooled to 15—20 °C with water and irradiating the solution with light from a 350 W tungsten lamp. Polymer-bound sensitisers were removed by filtration; Methylene Blue was removed chromatographically.

The reactions were monitored by t.l.c. and the peroxides were purified by p.l.c.

3,6-*Dibenzyl*-2,5-*diethoxy*-3,6-*epidioxy*-3,6-*dihydropyrazine* (4).—A solution of 3,6-dibenzyl-2,5-diethoxypyrazine (3) [15] (60 mg) and Methylene Blue (1 mg) was photo-oxidised for 19 h, when no starting material remained. The reaction mixture was evaporated to small volume under reduced pressure and purified by p.l.c. ($CHCl_3$) to give the *peroxide* (4), in virtually quantitative yield, as a colourless oil, positive starch–iodide test, $\nu_{max.}$ (film) 3 140—2 820, 1 745, 1 630, 1 500, 1 375, 1 325, 1 225, 1 080, 1 040, 1 020, 865, 800, 750, and 695 $cm^{-1}$; $\tau$ 8.66 (6 H, t, *J* 6 Hz), 6.64 (4 H, s), 5.76 (4 H, q, *J* 6 Hz), and 2.66 (10 H, br s, aromatic H) (Found: C, 69.3; H, 6.2; N, 7.2. $C_{22}H_{24}N_2O_4$ requires C, 69.5; H, 6.3; N, 7.4%).

Repeated reaction in the absence of Methylene Blue for 19 h gave the peroxide (4) in small yield (<5%) as did a solution with oxygen passing slowly through it in the dark for 19 h. Photo-oxidation of the pyrazine in the presence of radical quenching agents and radical chain initiators did not appear to alter the course of the reaction.

2,5-*Diethoxy*-3,6-*dimethyl*-3,6-*epidioxy*-3,6-*dihydropyrazine* (10).—The pyrazine (9) [16] was irradiated in the presence of Methylene Blue to give, after isolation by p.l.c., an almost quantitative yield of the crystalline peroxide, positive starch–iodide test, m.p. 81 °C (decomp.); $\nu_{max.}$ (Nujol), 1 625, 1 320, 1 275, 1 140, 1 012, 905, 730, and 647 $cm^{-1}$; $\tau$ 8.67 (6 H, t, *J* 7 Hz), 8.37 (6 H, s), and 5.77 (4 H, q, *J* 7 Hz); *m/e* 228 (3%), 196 (100), 181 (43), 168 (31), 140 (45), 112 (20), 111 (21), 86 (30), 70 (25), and 71 (33) (Found: C, 52.5; H, 7.1; N, 12.3. $C_{10}H_{16}N_2O_4$ requires C, 52.6; H, 7.0; N, 12.3%). Control experiments, carried out as for the dibenzylpyrazine, did not produce any of the peroxide.

2,6-*Dibenzyl*-3,6-*epidioxypiperazine*-2,5-*dione* (6).—The dibenzyldihydroxypyrazine (5) (100 mg) was suspended in dimethyl sulphoxide–dichloromethane (1 : 10) (15 ml) in the presence of polymer-bound eosin (10 mg). The suspension was photo-oxygenated for 45 h. The mixture was filtered and the filtrate evaporated to dryness in *vacuo* to give the 3,6-peroxide as a pale yellow solid (100 mg), positive starch–iodide test, slow decomposition above 100 °C; $\nu_{max.}$ (Nujol) 3 600—2 650, 1 640, 1 964, 1 370, 1 290, 1 135, 1 020, 1 000, 760, and 700 $cm^{-1}$; $\lambda_{max.}$ (EtOH) 220 and 313 nm ($\varepsilon$ 7 700 and 3 100 respectively); $\tau$[$CDCl_3$ and $(CD_3)_2SO$] 7.1 (4 H, s) and 2.7 (10 H, m); *m/e* 324 (0.6%), 306 (2.6), 290 (4.2), 105 (44), 94 (39), 91 (36), 84 (100), 79 (76), 77 (32), 66 (100), and 46 (69).

3,6-*Dibenzyl*-3,6-*dihydroxypiperazine*-2,5-*dione* (7).—The dibenzylperoxide (6) (30 mg) was stirred with an excess of sodium borohydride in ethanol (10 ml) at room temperature for 1 h. The solution was neutralised with 2N HCl, filtered, and concentrated under reduced pressure to small volume when the *dihydroxy-compound* precipitated out as an off-white solid (20 mg), m.p. >150 °C (decomp.); $\nu_{max.}$ (Nujol) 3 700—3 000, 1 650, 1 400, and 1 185 $cm^{-1}$; $\lambda_{max.}$ (EtOH) 287 nm ($\varepsilon$ 2 500); $\tau(D_2O)$ 8.97 (4 H, s) and 2.7 (10 H, m); *m/e* 292 ($[M - 20\ H]^+$, 29%), 290 ($[M - 2H_2O]^+$, 34), 276 (18), 201 (34), 153 (18), 118 (34), 117 (28), 103 (13), and 91 (100).

The structure of the diol (7) was confirmed by heating a sample in refluxing methanol, containing one crystal of toluene-*p*-sulphonic acid (*ca.* 1 mg), over molecular sieves for 12 h. P.l.c. on the reaction products gave 3,6-dibenzylidenepiperazine-2,5-dione (8), m.p. and mixed m.p. 298 °C (decomp), having identical mass-spectral and i.r. properties to an authentic specimen.

*Reductions of* 2,5-*Diethoxy*-3,6-*dimethyl*-3,6-*epidioxy*-3,6-*dihydropyrazine* (10).—(*a*) *With potassium iodide.* The peroxide (90 mg) was dissolved in a saturated ethanolic potassium iodide solution and stirred at room temperature for 30 min. The reaction solution was then treated dropwise, with stirring, with a solution of 2N sodium thiosulphate until the iodine colour was liberated. The mixture was adjusted to pH 7, filtered, and concentrated *in vacuo*. The residue was extracted with chloroform and concentrated *in vacuo*. The residue was extracted with chloroform, washed with $H_2O$, dried, and concentrated. After p.l.c. ($CHCl_3$), a crystalline solid was obtained as the major product. This proved to be one isomer of 2,3,5-triethoxy-6-hydroxy-3,6-dimethyl-3,6-dihydropyrazine (45 mg), m.p. 76—77 °C; $\nu_{max.}$ ($CHCl_3$) 3 000—2 900, 1 625, 1 440, 1 365, 1 320, 1 270, 1 210, 1 145, 1 100, 895, and 860 $cm^{-1}$; $\tau$ 8.8—8.04 (15 H, m), 8.0 (1 H, br s, exchangeable in $D_2O$), and 6.6 (6 H, q, *J* 6 Hz). The n.m.r. spectrum and the behaviour of the material on t.l.c. suggested this material was a single isomer.

(*b*) *With* $NaBH_4$ *in aqueous THF.* The peroxide (100 mg) was stirred in aqueous, peroxide-free THF (1 : 1 v/v) for 5 h at room temperature in the presence of an excess of sodium borohydride (25 mg). The solution was neutralised with 2N aqueous HCl, filtered, and concentrated to afford the reduction product as a yellow oil. Extraction into dry THF, filtration, and re-evaporation gave a purer product as a pale yellow oil (75 mg), which proved to be a 1 : 1 mixture of the *cis*- and *trans*-diols (12) and (13); $\tau$ 8.70 (6 H, t, *J* 4 Hz), 8.44 (3 H, s), 8.38 (3 H, s), 7.84 (2 H, br s, exchangeable with $D_2O$), and 5.92—5.68 (4 H, m, as two superimposed q); $\nu_{max.}$ (film) 3 390, 3 320, 2 980, 1 740, 1 670, 1 440, 1 360, 1 340, 1 270, 1 200, 1 140, 1 100, 1 020, 960, 900, 850, 780, 750, and 710 $cm^{-1}$; *m/e* 230 ($M^+$, 1%), 215 (41), 174 (47), 142 (100), 128 (21), 114 (26), 112 (32), 87 (21), and 61 (38).

(*c*) *With triphenylphosphine.* The peroxide (35 mg, 0.15 mmol) was stirred in dry benzene (10 ml) containing triphenylphosphine (80 mg, 0.3 mmol). After stirring the solution at room temperature for 16 h it was evaporated to small volume under reduced pressure, and the products isolated by p.l.c. ($CHCl_3$). The major product from the pyrazine (15 mg), tentatively assigned as the oxide (15), initially showed $\tau$ 8.3 (6 H, t, *J* 7 Hz), 7.94 (6 H, s), and 5.93 (4 H, q, *J* 7 Hz). On leaving for periods of a day or more it decomposed to give a mixture of products. Repeated runs, with and without varying the peroxide : phosphine ratio, gave variable yields of the oxide.

*Attempted Oxidations of Other* 2,5-*Diethoxypyrazines.*—2,5-Diethoxypyrazine (16), prepared by the literature route, was oxidised under the standard conditions, using Rose Bengal polymer. The starting material disappeared within a few hours but, on work-up, only a complex mixture of products could be detected by t.l.c.; several of the products gave a positive starch–iodide test.

The hydroxypropylpyrazine (17) [14] was oxidised under similar conditions. Monitoring by t.l.c. showed that the starting material was consumed within a few hours. After filtration a sample was evaporated to dryness under reduced pressure to give an oily product which showed a positive peroxide test. T.l.c. analysis indicated this material was decomposing (streaking on plate), hence the bulk of the solution was washed with a saturated aqueous solution of

potassium iodide until evolution of the yellow colouration ceased and the starch–iodide test was negative. After drying and concentrating, p.l.c. afforded mixtures of compounds and the reaction was therefore abandoned.

*Preparation and Oxidation of* 4,6-*Diethoxy*-2-*methylpyrimidine* (19).—The dihydroxypyrimidine (18) (100 mg) was suspended in dry dichloromethane (10 ml) and a solution of triethyloxonium tetrafluoroborate (1.0 g) in dry dichloromethane (1.0 ml) added. The resultant slurry was heated at reflux with efficient stirring until the solids dissolved (4 h). The solution was cooled, and then washed with saturated aqueous sodium hydrogencarbonate solution, dried, and concentrated. Purification by p.l.c. [$CHCl_3$–MeOH (99 : 1)] afforded the alkylated product (20 mg) as an extremely volatile oil; $\nu_{max.}$ (film) 2 980, 2 920, 2 900, 2 860, 1 600—1 530, 1 380, 1 350, 1 340, 1 300, 1 240, 1 170, 1 070, 1 020, and 990 $cm^{-1}$, $\tau$($CCl_4$) 9.0 (6 H, t, *J* 6 Hz) 7.92 (3 H, s), 6.06 (4 H, q, *J* 6 Hz), and 4.70 (1 H, s); *m/e* 182 ($M^+$, 6%), 177 (35), 154 (11), 139 (23), 121 (29), 119 (100), 117 (97), 84 (45), 72 (29), 68 (23), and 49 (45).

Freshly prepared diethoxypyrimidine (19) (0.11 g) was photo-oxidised for 8 h in dichloromethane (20 ml), using polymer-bound eosin as sensitiser. The resulting solution was filtered, washed with water, dried, and purified by p.l.c. ($CHCl_3$) to afford, in high yield, 4,6-diethoxy-2,5-epidioxy-2-methyl-2,5-dihydropyrimidine (20) as a low-melting solid, m.p. 10—15 °C. The material gave a positive starch–iodide test; $\nu_{max.}$ (film) 2 940, 1 585, 1 420, 1 385, 1 347, 1 250, 1 155, and 837 $cm^{-1}$; $\tau$ 8.67 (6 H, t, *J* 6 Hz), 7.50 (3 H, s), 5.67 (4 H, q, 6 Hz), and 4.2 (1 H, s); it slowly and continuously decomposed in storage at 0 °C and room temperature.

*Preparation and Oxidation of* 4-*Ethoxy*-2,6-*dimethylpyrimidine* (21).—2,6-Dimethyl-4-hydroxypyrimidine was alkylated with triethyloxonium tetrafluoroborate in the manner described previously. The product was purified by p.l.c. [$CHCl_3$–MeOH (99 : 1)] to afford the title compound (12%) as an oil. Again losses were observed owing to the high volatility of the materials. The oil had $\nu_{max.}$ (film) 2 980, 2 920, 2 860, 1 730, 1 590, 1 440, 1 380, 1 365, 1 340, 1 170, 1 070, 1 030, 960, and 840 $cm^{-1}$; $\tau$ 9.0 (3 H, t, *J* 6 Hz), 8.04 (3 H, s), 7.92 (3 H, s), 6.04 (2 H, q, *J* 6 Hz), and 4.20 (1 H, s); *m/e* 152 ($M^+$, 9%), 137 (20), 124 (17), 121 (30), 118 (86), 117 (100), 86 (29), 84 (51), 82 (17), 67 (17), and 49 (37).

A freshly prepared portion of the pyrimidine (21) was photo-oxidised under standard conditions, using Methylene Blue as sensitiser. After work-up the product was purified by p.l.c. [$CHCl_3$–MeOH (99 : 1)] to give 4-ethoxy-2,6-dimethyl-2,5-epidioxy-2,5-dihydropyrimidine (22) as an unstable oil, positive starch–iodide test; $\nu_{max.}$ (film) 2 950, 1 605, 1 355, 1 187, 1 090, and 750 $cm^{-1}$; $\tau$ 8.60 (3 H, t, *J* 6 Hz), 7.60 (3 H, s), 7.40 (3 H, s), 5.57 (2 H, q, *J* 6 Hz), and 3.45 (1 H, s).

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