Photo-oxygenation of *N*-Unsubstituted Pyrazin-2-ones and Alkoxypyrazines

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Dye-sensitized photo-oxygenation of *N*-unsubstituted pyrazin-2-ones (**1b—d**) afforded the endoperoxides (**2b—d**) in 61—72% yield. On being heated the endoperoxides (**2**) decomposed to give the unsymmetrical imides (**4**) accompanied by a loss of benzonitrile. 2-Alkoxypyrazines (**5**) also reacted with singlet oxygen, to yield the endoperoxides (**6**).

Photo-oxygenation of organic compounds has been studied extensively.[1—4] Singlet oxygen, for example, is known to react with conjugated dienoids (cyclic and a few other *s-cis* dienes, polycyclic aromatics, and some heterocycles) to give 1,4-endoperoxides as primary products, which are often unstable, being transformed into further oxidation products. However, the additions of singlet oxygen to nitrogen-containing heterocycles are largely limited to five-membered ring systems such as pyrroles, indoles, and imidazoles.[1,3] The formation of the endoperoxides of six-membered heterocycles containing nitrogen atoms such as pyrazines, pyrimidines, and pyrimidinium-4-olates has been reported by Markham and Sammes[5] and Gotthardt and Schenk.[6] Recently, we reported that dye-sensitized photo-oxygenation of *N*-substituted pyrazin-2-ones gave the stable pyrazin-2-one 3,6-endoperoxides.[7] We report herein that singlet oxygen also adds to *N*-unsubstituted pyrazin-2-ones (**1**) and alkoxypyrazines (**5**).

Results and Discussion

N-unsubstitued pyrazin-2-ones (**1a—d**) showed an i.r. absorption band between 1 635—1 650 cm^{-1} for the amide carbonyl group, while the *N*-methylpyrazin-2-one (**7**) showed this band at 1 640 cm^{-1}. The u.v. spectrum of compound (**1a**) in ethanol was similar to that of (**7**), but different from that of the 2-methoxypyrazine (**5a**) (see Table 1). These facts suggested that compounds (**1**) exist in the keto rather than the enol form. Irradiation of an oxygenated solution of 5,6-diphenylpyrazin-2-(1*H*)-one (**1a**) in dichloromethane, in the presence of Methylene Blue as a sensitizer, with visible light at room temperature for 1.5 h resulted in complex mixtures. Meanwhile, the stable pyrazin-2-one 3,6-endoperoxide (**2b**) was obtained in 72% yield when an oxygen-saturated solution of 3-ethyl-5,6-diphenylpyrazin-2(1*H*)-one (**1b**) in dichloromethane was irradiated in the presence of Methylene Blue under the same conditions. The structure of the product of (**2b**) was elucidated on the basis of its spectroscopic properties and elemental analysis. The usual analytical and mass spectral data (*m/z* 309, QM^+: $C_{18}H_{16}N_2O_3$, chemical ionization) of compound (**2b**) indicated the product to

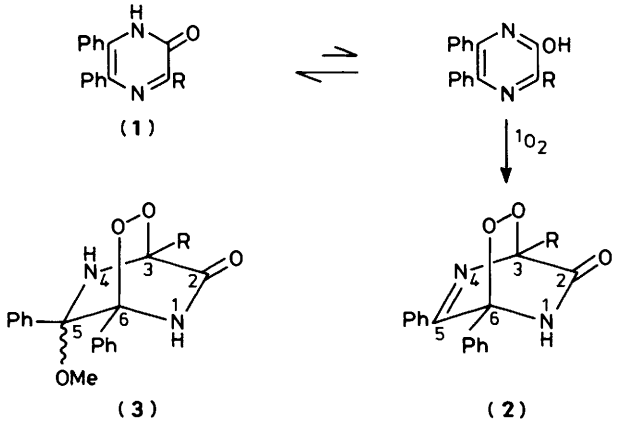


Table 1. Physical properties of *N*-unsubstituted pyrazin-2-ones (**1a—d**), alkoxypyrazines (**5a—b**), and the 2-methylpyrazin-2-one (**7**)

	M.p. (°C)	$\lambda_{max.}$(EtOH)/nm (ε)	$\nu_{max.}$(KBr)/cm^{-1}	δ_H
(**1a**)	230—240 (lit.,[8] 243—244; lit.,[9] 225—227)	272 (1.20 × 10^4), 330 (6.0 × 10^3), 350 (sh, 5.7 × 10^3)	1 650, 1 600, 1 585, 1 215, 890, 760, 745, 725, 695	[$(CD_3)_2SO$] 7.33 (5 H, s), 7.45 (5 H, s), 8.27 (1 H, s), 12.37 (1 H br s)
(**1b**)	205—206 (lit.,[8] 207—208)	280 (1.09 × 10^4), 342 (7.9 × 10^3)	1 640, 1 590, 1 235, 765, 740, 700, 690	[$(CD_3)_2SO$] 1.35 (3 H, t), 2.90 (2 H, q), 7.31 (5 H, s), 7.45 (5 H, s), 12.34 (1 H, br s)
(**1c**)	198—200 (lit.,[8] 205—206)	280 (1.47 × 10^4), 342 (1.10 × 10^4)	1 640, 1 605, 1 590, 1 235, 765, 755, 695, 690	[$(CD_3)_2SO$] 1.10 (3 H, t), 1.67—2.05 (2 H, m), 2.87 (2 H, t), 7.31 (5 H, s), 744 (5 H, s), 12.37 (1 H, br s)
(**1d**)[a]	281—282	230 (1.56 × 10^4), 278 (1.33 × 10^4), 378 (1.39 × 10^4)	1 635, 1 585, 765, 740, 695, 685	[$(CD_3)_2SO$] 7.30—7.63 (13 H, m), 844—857 (2 H, m), 12.69 (1 H, br s)
(**5a**)[b]	130—131.5	221 (1.19 × 10^4), 268 (1.08 × 10^4), 319 (9.2 × 10^3)	1 580, 1 560, 755, 700, 695	($CDCl_3$) 4.04 (3 H, s), 7.25—7.52 (10 H, m), 8.25 (1 H, s)
(**5b**)[c]	90—92	222 (1.96 × 10^4), 273 (1.10 × 10^4), 321 (9.9 × 10^3)	1 580, 1 550, 775, 760, 740, 695	($CDCl_3$) 1.43 (3 H, t), 4.50 (2 H, q), 7.10—7.55 (10 H, m), 8.25 (1 H, s)
(**7**)	165—167	266 (1.20 × 10^4), 347 (7.3 × 10^3)	1 640, 1 580, 1 240, 780, 760, 735, 700	($CDCl_3$) 3.31 (3 H, s), 7.10—7.45 (10 H, m), 8.30 (1 H, s)

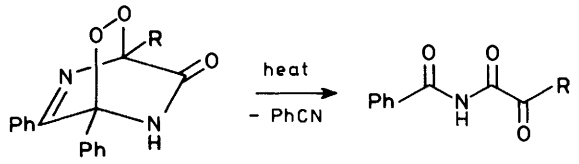
[a] Found: C, 81.6; H, 4.95; N, 8.35. $C_{22}H_{16}N_2O$ requires C, 81.45; H, 4.95; N, 8.35%. [b] Found: C, 78.05; H, 5.25; N, 10.9. $C_{17}H_{14}N_2O$ requires C, 77.85; H, 5.35; N, 10.7%. [c] Found: C, 78.2; H, 5.75; N, 10.2. $C_{18}H_{16}N_2O$ requires C, 78.25; H, 5.85; N, 10.15%.

Table 2. Yield of the endoperoxides (**2**) and (**3d**)

		Solvent	Sensitizer	Yield of the endoperoxide (%)[a] (2)	(3)
(**1a**)	R = H	CH_2Cl_2	MB[b]	Complex mixtures	
(**1b**)	R = Et	CH_2Cl_2	MB	72	
(**1c**)	R = Pr^n	CH_2Cl_2	MB	61	
(**1d**)	R = Ph	CH_2Cl_2	MB	68	
(**1d**)		CH_2Cl_2	RB[c]	64	
(**1d**)		CH_2Cl_2–MeOH[d]	MB		46

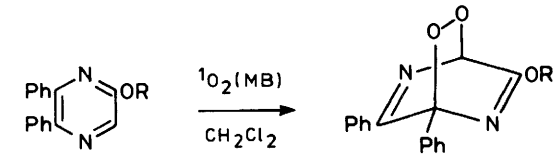
[a] Isolated yield. [b] Methylene Blue. [c] Rose Bengal. [d] Compound (**1d**) was less soluble in MeOH.

be the 1:1-adduct of (**1b**) and one molecule of oxygen. The i.r. spectrum of compound (**2b**) showed a carbonyl stretching band at 1 725 cm^{-1}; *cf.* 1 640 cm^{-1} for (**1b**). The ^1H n.m.r. spectrum of compound (**2b**) indicated the presence of an ethyl group [δ 1.29 (3 H, t) and 2.07—2.53 (2 H, m), which appeared as an ABX_3 pattern], a phenyl group [δ 7.03—7.40 (10 H, m)], and an amino group [δ 8.72 (1 H, br s)]. The ^{13}C n.m.r. spectrum of compound (**2b**) showed peaks at δ_C 6.9 (q), 23.8 (t), 87.1 (s), 93.3 (s), 171.2 (s), and 177.8 p.p.m. (s) due to methyl and methylene carbons and carbons 6 (or 3), 3 (or 6), and 5, and carbonyl carbon, respectively, in addition to aromatic carbon signals. Similarly, irradiation of an oxygenated solution of the *N*-unsubstituted pyrazin-2-ones (**1c** and **d**) in dichloromethane in the presence of Methylene Blue or Rose Bengal under the same conditions gave the endoperoxides (**2c** and **d**) in 61—68% yield. The endoperoxides (**2b**—**d**) thus obtained were stable at room temperature; however, on being heated to reflux in toluene they decomposed to yield the unsymmetrical imides (**4b**—**d**) as the

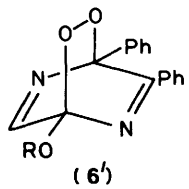


(**2**) (**4**) **b**; R = Et (54%) **c**; R = Pr^n (41%) **d**; R = Ph (38%)

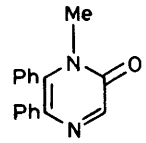
main product, accompanied by benzonitrile. The formation of the unsymmetrical imides (**4**) could be readily explained in terms of electrocyclic ring opening of the endoperoxides (**2**) with loss of benzonitrile. When a solution of 3,5,6-triphenylpyrazin-2-one (**1d**) in methanol–dichloromethane mixture was photooxygenated in the presence of Methylene Blue under the same conditions as described above, dihydroendoperoxide (**3d**), a 1:1-adduct of the endoperoxide (**2d**) and methanol, was obtained in 46% yield. 2-Alkoxypyrazines (**5a** and **b**), which were *O*-alkylated forms of the pyrazin-2-one, also reacted with singlet oxygen to yield the endoperoxides (**6a** and **b**) in high yield. However, the endoperoxides (**6**) could not be isolated in pure form since they decomposed on attempted purification *via* silica gel column chromatography or by distillation. Evidence for their formation was obtained by n.m.r. spectroscopy. The ^1H n.m.r. spectrum of compound (**6a**) showed a new signal at δ 6.18 (1 H, s), due to bridgehead proton, and a signal at δ 8.25, present for the pyrazine (**5a**), and which was assigned to the pyrazine ring proton, disappeared. Furthermore, the ^{13}C n.m.r. spectrum



(**5**) (**6**) **a**; R = Me (>80%) **b**; R = Et (>80%)



(**6'**)



(**7**)

of compound (**6a**) showed new signals at δ_C 82.3 (d) and 90.6 p.p.m. (s), assignable to bridgehead carbons. Another possible structure (**6'**) for the alkoxypyrazine endoperoxides could be excluded since in the ^{13}C n.m.r. spectrum one bridgehead carbon signal appeared to be a doublet.

Experimental

M.p.s are uncorrected and were measured with a Yanaco micro-melting apparatus. U.v. spectra were recorded on Shimadzu UV-365 or JASCO UVIDED-505 spectrophotometers. I.r. spectra were determined with JASCO IRA-1 or Hitachi 260-30 spectrophotometers. ^1H And ^{13}C n.m.r. spectra were run on a JEOL FX-100 spectrometer (100 MHz). Mass spectra were measured with a Hitachi M-80 spectrometer. Silica gel (Merck, Kieselgel 60 for flash chromatography) was used for column chromatography.

Starting Materials.—*N*-Unsubstituted pyrazin-2-ones (**1a**—**c**) were prepared according to methods previously described in the literature[8,9] and compound (**1d**) was prepared by modification of this method. Alkoxypyrazines (**5a** and **b**) were prepared by alkylation of the corresponding pyrazin-2-ols as described in ref. 7. Physical properties of the *N*-unsubstituted pyrazin-2-ones (**1**) and alkoxypyrazines (**5**) are shown in Table 1.

General Procedure for the Reaction of N-*Unsubstituted Pyrazin-2-ones* (**1a**—**d**) *and Alkoxypyrazines* (**5a** *and* **b**) *with Singlet Oxygen.*—A solution of an *N*-unsubstituted pyrazin-2-one (**1**) (200 mg) in dichloromethane (50 ml) or 1:1 dichloromethane–methanol (50 ml) in the presence of the sensitizer (~2 mg) was irradiated in a Pyrex tube with a halogen lamp for 1.5 h while oxygen was continuously passed through at room temperature, and then the solution was passed through a short silica gel column (*ca.* 3 cm) to remove the sensitizer. After evaporation of the solvent, the residual oil was chromatographed on a silica gel column with benzene–ethyl acetate (4:1—20:1) as eluant to yield the corresponding endoperoxides (**2**) and the methanol-addition product (**3d**). Similar treatment of alkoxypyrazines (**5**) gave the corresponding endoperoxides (**6**). The following compounds were thus prepared.

3-*Ethyl*-3,6-*dihydro*-5,6-*diphenyl*-3,6-*epidioxypyrazin*-2(1H)-*one* (**2b**), m.p. 130—131.5 °C (decomp.) (Found: C, 69.95; H, 5.25; N, 9.05. $C_{18}H_{16}N_2O_3$ requires C, 70.1; H, 5.25; N, 9.1%); $\nu_{max.}$(KBr) 3 170, 1 725, 1 640, and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 1.29 (3 H, t, CH_2CH_3), 2.07—2.53 (2 H, m, CH_2CH_3), 7.03—7.40 (10 H, m, Ph), and 8.72 (1 H, s, NH); $\delta_C(CDCl_3)$ 6.9 (q, CH_2CH_3), 23.8 (t, CH_2CH_3), 87.1 (s, *C*Ph or *C*Et), 93.3 (s, *C*Et or *C*Ph),

126.3 (d), 127.9 (d), 128.9 (d), 130.4 (d), 130.7 (d), and 133.2 (s) (aromatic carbons), 171.2 (s, C=O), and 177.8 p.p.m. (s, *C*=N); *m/z* (chemical ionization) 309 (QM^+).

3,6-*Dihydro*-5,6-*diphenyl*-3-*propyl*-3,6-*epidioxypyrazin*-2-(1H)-*one* (**2c**), m.p. 128—129.5 °C (decomp.) (Found: C, 70.7; H, 5.7; N, 8.65. $C_{19}H_{18}N_2O_3$ requires C, 70.8; H, 5.6; N, 8.7%); $\nu_{max.}$(KBr) 3 190, 1 725, and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 1.08 (3 H, t, $CH_2CH_2CH_3$), 1.68—2.00 (2 H, m, $CH_2CH_2CH_3$), 2.10—2.27 (2 H, m, $CH_2CH_2CH_3$), 7.10—7.45 (10 H, m, Ph), and 8.65 (1 H, br s, NH); $\delta_C(CDCl_3)$ 14.6 (q, $CH_2CH_2CH_3$), 15.9 (t, $CH_2CH_2CH_3$), 32.5 (t, $CH_2CH_2CH_3$), 87.1 (s, *C*Ph or *C*Pr), 93.2 (s, *C*Pr or *C*Ph), 126.3 (d), 128.6 (d), 130.4 (d), 130.7 (d), and 133.2 (s) (aromatic carbons), 171.1 (s, C=O), and 177.7 p.p.m. (s, C=N); *m/z* (chemical ionization) 323 (QM^+).

3,6-*Dihydro*-3,5,6-*triphenyl*-3,6-*epidioxypyrazin*-2(1H)-*one* (**2d**), m.p. 116—117 °C (decomp.) (Found: C, 74.0; H, 4.55; N, 7.7. $C_{22}H_{16}N_2O_3$ requires C, 74.15; H, 4.5; N, 7.7%); $\nu_{max.}$(KBr) 3 160, 1 715, and 1 640 cm^{-1}; $\delta_H(CDCl_3)$ 7.15—7.60 (13 H, m, ArH), 7.87—8.09 (2 H, m, ArH), and 8.41 (1 H, br s, NH); $\delta_C(CDCl_3)$ 87.6 (s, *C*Ph), 93.1 (s, *C*Ph), 126.2 (d), 127.9 (d), 128.0 (d), 128.7 (d), 128.9 (d), 129.3 (d), 129.8 (d), 130.2 (d), 130.4 (d), 130.7 (d) 130.9 (d), 133.2 (s), and 134.2 (s) (aromatic carbons), 170.5 (s, C=O), and 177.5 p.p.m. (s, C=N); *m/z* (chemical ionization) 357 (QM^+).

The *dihydroendoperoxide* (**3d**), m.p. 112—113 °C (Found: C, 71.3; H, 5.1; N, 7.15. $C_{23}H_{20}N_2O_4$ requires C, 71.1; H, 5.2; N, 7.2%); $\nu_{max.}$(KBr) 3 390, 3 220, 1 720, 1 450, 750, 710, and 700 cm^{-1}; $\delta_H(CDCl_3)$ 3.31 (3 H, s, OCH_3), 6.95—8.13 (16 H, m, Ph and NH), and 10.38 (1 H, br s, NH); $\delta_C(CDCl_3)$ 48.7 (q, OCH_3), 89.9 [s, C-3 or C-5 (or 6)], 91.3 [2 × s, C-5 and C-6, (or C-3), and 166.6 p.p.m. (s, C=O) in addition to aromatic carbon peaks.

The endoperoxide (**6a**), oil; $\nu_{max.}(CDCl_3)$ 3 360 and 1 640 cm^{-1}; $\delta_H(CDCl_3)$ 4.02 (3 H, s, OCH_3), 6.12 (1 H, s, CH), and 7.1—7.8 (10 H, m, Ph); $\delta_C(CDCl_3)$ 50.6 (q, OCH_3), 82.3 (d, CH), 90.6 (s, *C*Ph), 170.5 (s, C=N), and 182.9 p.p.m. (s, C=N), in addition to aromatic carbon peaks; *m/z* (chemical ionization) 295 (QM^+).

The endoperoxide (**6b**), oil; $\nu_{max.}(CDCl_3)$ 3 360 and 1 640 cm^{-1}; $\delta_H(CDCl_3)$ 1.42 (3 H, t, OCH_2CH_3), 4.47 (2 H, q, OCH_2CH_3), 6.10 (1 H, s, CH), and 7.1—7.8 (10 H, m, Ph); $\delta_C(CDCl_3)$ 13.8 (q, OCH_2CH_3), 63.7 (t, OCH_2CH_3), 82.4 (d, CH), 90.4 (s, *C*Ph), 174.4 (s, C=N), and 183.0 p.p.m. (s, C=N), in addition to aromatic carbon peaks; *m/z* (chemical ionization) 309 (QM^+).

Thermal Reaction of the Pyrazin-2-*one* 3,6-*Endoperoxides* (**2b—d**).—A solution of the a pyrazin-2-one 3,6-endoperoxide (**2**) (200 mg) in toluene (50 ml) was refluxed for 3 h under argon. After removal of the solvent, the residual oil was chromatographed with benzene–ethyl acetate (19:1) on a silica gel column to give the corresponding unsymmetrical imide (**4**), along with benzonitrile. The following compounds were thus prepared.

The *unsymmetrical imide* (**4b**), m.p. 62.5—64 °C (Found: C, 64.3; H, 5.4; N, 6.8. $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.8%); $\nu_{max.}$(KBr) 3 260, 1 715, 1 700, 1 675, and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 1.18 (3 H, t, CH_2CH_3), 2.96 (2 H, q, CH_2CH_3), 7.28—7.70 (5 H, m, Ph), and 10.08 (1 H, br s, NH); $\delta_C(CDCl_3)$ 6.9 (q, CH_2CH_3), 30.2 (t, CH_2CH_3), 127.9 (d), 128.9 (d), 131.9 (s), and 133.6 (d) (aromatic carbons), 160.6 (s, C=O), 164.9 (s, C=O), and 198.1 p.p.m. (s, C=O).

The *unsymmetrical imide* (**4c**), m.p. 98.5—100 °C (Found: C, 65.6; H, 5.95; N, 6.35. $C_{12}H_{13}NO_3$ requires C, 65.75; H, 5.95; N, 6.4%); $\nu_{max.}$(KBr) 3 260, 1 720, 1 700, 1 675, and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 0.98 (3 H, t, $CH_2CH_2CH_3$), 1.50—1.87 (2 H, m, $CH_2CH_2CH_3$), 2.85 (2 H, t, $CH_2CH_2CH_3$), 7.33—7.64 (3 H, m, ArH), 7.78—7.89 (2 H, m, ArH), and 11.11 (1 H, br s, NH); $\delta_C(CDCl_3)$ 13.5 (q, $CH_2CH_2CH_3$), 16.6 (t, $CH_2CH_2CH_3$), 40.6 (t, $CH_2CH_2CH_3$), 127.5 (d), 128.6 (d), 132.5 (s), and 132.5 (d) (aromatic carbons), 162.9 (s, C=O), 171.3 (s, C=O), and 196.2 p.p.m. (s, C=O).

The *unsymmetrical imide* (**4d**), m.p. 145—146 °C (Found: C, 71.1; H, 4.45; N, 5.65. $C_{15}H_{11}NO_3$ requires C, 71.15; H, 4.35; N, 5.55%); $\nu_{max.}$(KBr) 3 280, 1 720, 1 685, 1 670, and 1 595 cm^{-1}; $\delta_H(CDCl_3)$ 7.22—7.70 (6 H, m, ArH), 7.89—8.13 (4 H, m, ArH), and 10.27 (1 H, br s, NH); $\delta_C(CDCl_3)$ 128.2 (d), 128.6 (d), 128.9 (d), 129.9 (d), 130.7 (s), 132.2 (s), 133.9 (d), and 134.5 (d) (aromatic carbons), 165.5 (s, C=O), 167.5 (s, C=O), and 186.7 p.p.m. (s, C=O).

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