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PHOTOINDUCED REACTIONS—LX

ARENE PEROXIDE INTERMEDIATES IN THE PHOTOSENSITIZED OXYGENATION OF METHOXYBENZENES[1,2]

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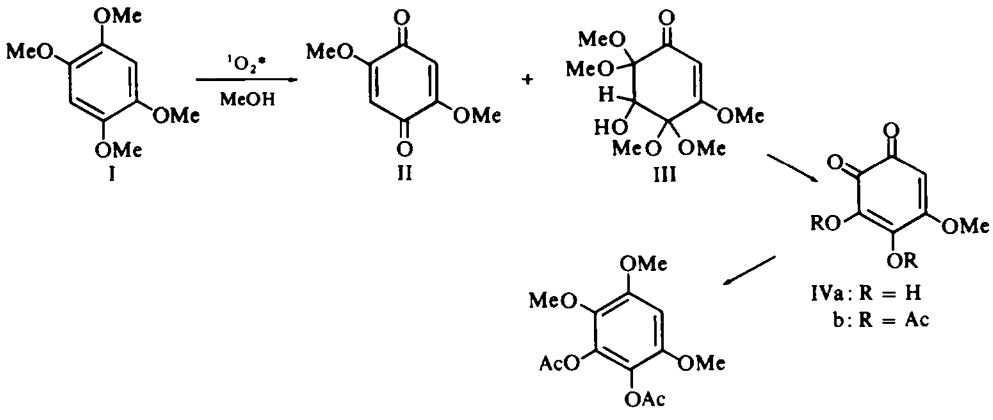
Abstract— Photosensitized oxygenation products of a series of methoxybenzenes in methanol were isolated and their structures elucidated. 1,2,4,5-Tetramethoxybenzene (I) gave 2,5-dimethoxy-*p*-benzoquinone (II) and an enone (III). 1,2,3,5-Tetramethoxybenzene (IXa) and pentamethoxybenzene (XXII) yielded diketones Xa and XXIII, respectively. Hexamethoxybenzene (XIV) gave a triketone hydrate (XVII). Mechanisms involving initial attack of singlet oxygen onto the benzene ring forming an arene 1,4-peroxide intermediate are proposed.

DURING our investigation of the photosensitized oxygenation of certain phenolic compounds, we found that singlet oxygen, which is generated in the system, can cyclo-add to electron-rich monocyclic aromatic compounds.[3,4] The cycloaddition of molecular oxygen to aromatic nuclei has recently drawn much attention, in relation to the biological oxidation of aromatic compounds catalyzed by oxygenases.[5,6] In a systematic investigation of the photosensitized oxygenation of methoxybenzenes, we demonstrated that singlet oxygen ($^1\Delta g$ state) is indeed the reactive species in the reaction, and that methoxybenzenes with lower π-ionization potentials are more reactive to singlet oxygen.[1,7] The present paper deals with the isolation and the structure elucidation of products obtained from the reaction of several methoxybenzenes with singlet oxygen and discusses the mechanism of the reaction which involves an arene peroxide intermediate.

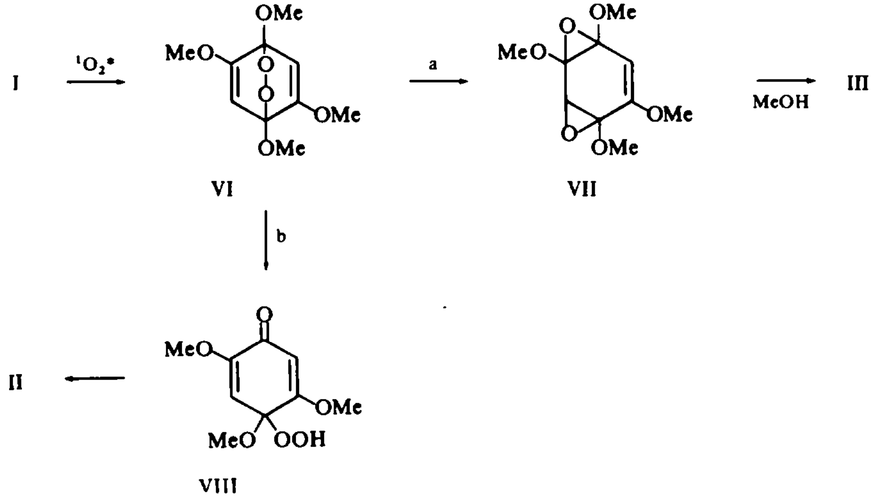
When 1,2,4,5-tetramethoxybenzene (I) was photooxygenated in MeOH containing rose bengal as sensitizer, 1·0 mole of oxygen was rapidly consumed and 2,5-dimethoxy-*p*-benzoquinone (II) and an enone (III) were obtained in 5 and 20% yield, respectively. The structure of III was derived from its spectral and chemical properties. The UV (254 nm), IR (3450, 1670, 1620 cm^{-1}) and NMR spectrum (τ 4·63 (s, 6H); 4·75 (d, $J = 5$ Hz, OH), 5·91 (d, $J = 5$ Hz, $\overset{|}{\text{C}}\text{H—OH}$), 6·24 (s, 3H), 6·70 (s, 6H), 6·76 (s, 3H), 6·92 (s, 3H) in DMSO-d_6) are in accordance with structure III. On acid hydrolysis III gave an *o*-benzoquinone (IVa). Reduction with hydrosulphite of its di-acetate (IVb) followed by methylation with CH_2N_2 gave V (Scheme 1).[8]

The formation of II and III can be rationalized by a mechanism involving an arene-peroxide (VI) as key intermediate, which is, in all probability, formed by 1,4-cycloaddition of singlet oxygen to the aromatic ring of I.[3,4] The arene-peroxide VI may either thermally[9] or photochemically[10,11] rearrange to a bis-epoxide VII



Scheme 1

(Scheme 2, path a) which would be solvolyzed by MeOH to give III. Alternatively, VI may be solvolyzed to VIII which would decompose to give a *p*-benzoquinone II (path b).[11]

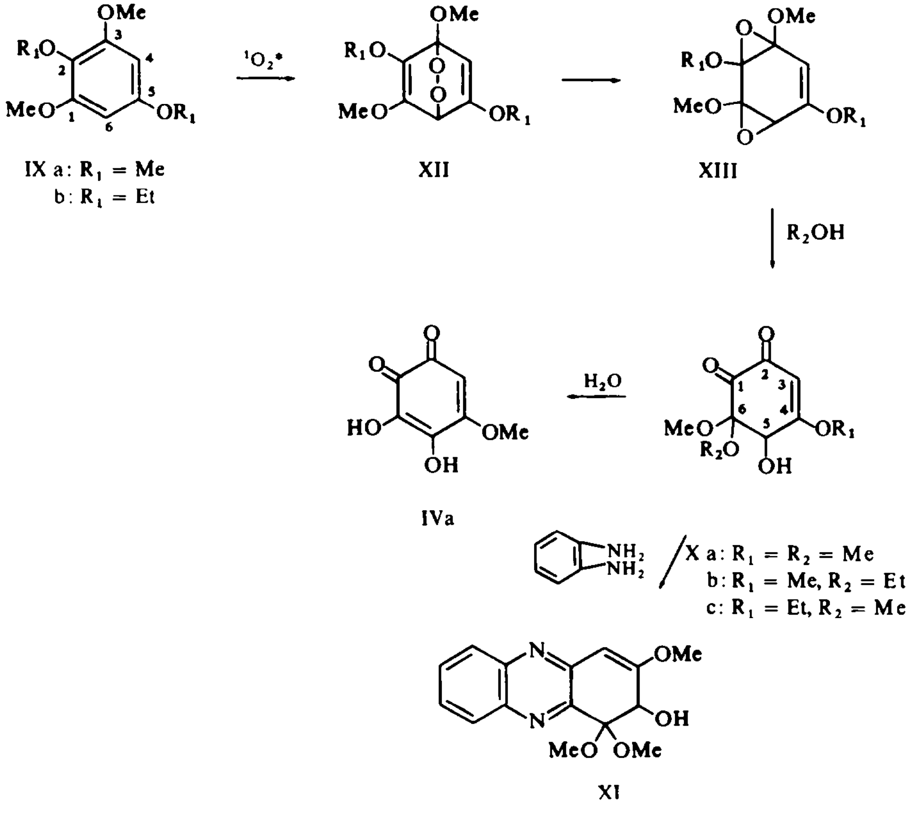


Scheme 2

Photosensitized oxygenation of 1,2,3,5-tetramethoxybenzene (IXa) in MeOH containing rose bengal gave 3,4-dihydroxy-5-methoxy-*o*-benzoquinone (IVa) (5%) and a diketone Xa (53%). The structure of diketone Xa was assigned on the basis of its spectral and chemical properties. The diketone Xa shows IR bands at 1750 (broad) cm^{-1} and 1610 cm^{-1} and UV absorption at 272 nm characteristic of an ene-1,2-dione system. The NMR spectrum exhibits signals at τ 3·86 (d, J = 1·5 Hz, 1H), 5·41 (d, J = 1·5 Hz, 1H), 6·11 (s, 3H), 6·25 (s, OH), 6·40 (s, 3H) and 6·70 (s, 3H). Treatment of Xa with *o*-phenylenediamine in AcOH gave a 1:1 adduct, the spectral properties of which are in accordance with structure XI. Diketone Xa was found to convert to *o*-quinone IVa on silica gel column chromatogram in the isolation process.

Photooxygenation of IXa in EtOH under similar conditions gave a diketone Xb (15%), while 2,5-diethoxy-1,3-dimethoxybenzene (IXb) in MeOH gave a diketone Xc (35%). Both products exhibit spectral properties analogous to those of Xa. The results clearly indicate that alkoxy group (R_1O) at position 2 of IX was expelled in the course of the formation of X and that alkoxy group (R_2O) at position 6 of diketone X was introduced from the solvent (R_2OH).

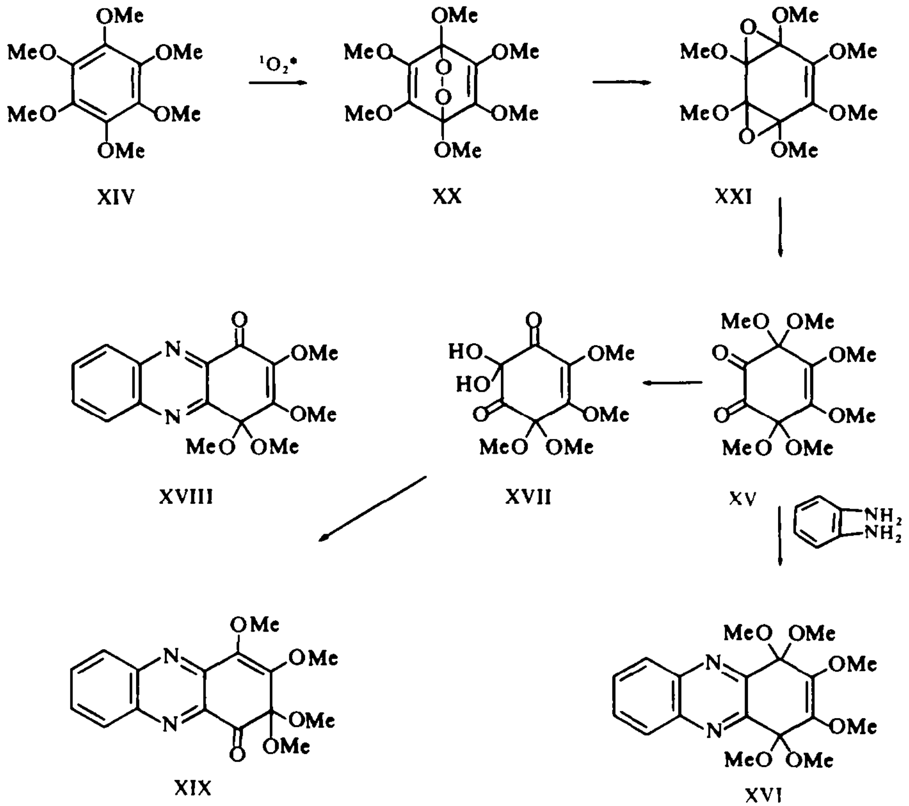
An arene peroxide XII analogous to VI would be also the intermediate for the formation of X (Scheme 3). In a similar manner to VI, peroxide XII rearranges to a bis-epoxide XIII which is transformed into X with the participation of the solvent (R_2OH). Any other arene peroxide cannot account for the formation of X (Scheme 3).



Scheme 3

Rose bengal-sensitized photooxygenation of hexamethoxybenzene (XIV) in MeOH gave a diketone XV, which could not be isolated but characterized as an *o*-phenylenediamine adduct XVI (48%). The UV (λ_{max}^{EtOH} 331 nm) and IR (1655 cm^{-1}) spectra exhibit characteristic absorption bands of a quinoxaline derivative. The NMR spectrum shows two equivalent methoxyls (τ 6·63) besides four aromatic protons (τ 1·55 ∼ 2·30). An attempt to isolate XV by silica gel column chromatography gave rise to the formation of a triketone hydrate XVII (54%). The IR spectrum of XVII shows bands at 3400 (OH), 1710, 1685 and 1605 cm^{-1}. The NMR spectrum exhibits two equivalent hydroxyls (τ 5·85 $\sim$ 5·95), two OMe's (τ 5·90 and 5·96) and two equivalent OMe's (τ 6·50). Treatment of XVII with *o*-phenylenediamine gave an adduct, the spectral data of which would not allow us to distinguish between structures XVIII and XIX.

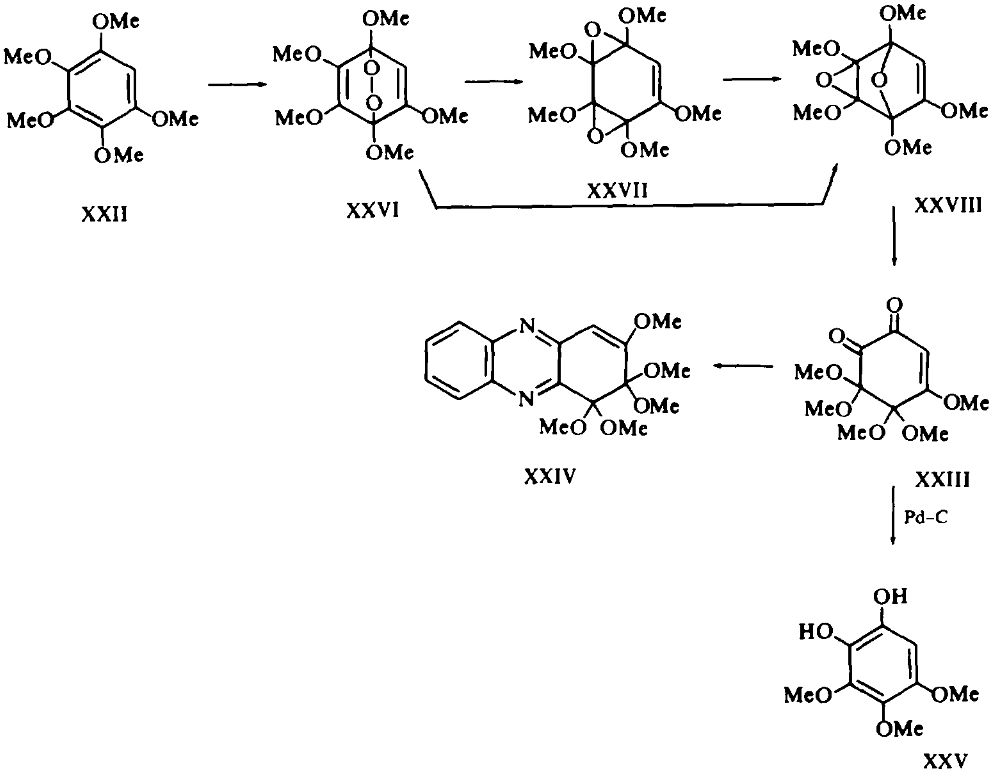
The formation of XV can be similarly rationalized by a mechanism involving an arene peroxide XX, which may rearrange to a bis-epoxide XXI. In the case of XXI, diketone XV may be formed by 1,2-migration of two OMe groups. The finding that photooxygenation of XIV either in MeOH or in methanol-d_4 gave the same product XVII supports this mechanism involving migration of OMe groups (Scheme 4).



SCHEME 4

When pentamethoxybenzene (XXII) was photooxygenated in MeOH under similar conditions, diketone XXIII was obtained in 57% yield. The UV (286 nm) and IR (1770, 1680 and 1610 cm^{-1}) spectra indicate the existence of an ene-1,2-dione system. The NMR spectrum shows signals of an olefinic proton (singlet, τ 4·10) and five OMe's (τ 6·04 (3H), 6·42 (6H), 6·44 (6H)). Treatment of XXIII with *o*-phenylenediamine gave an adduct, the structure of which was assigned as XXIV. Hydrogenation (Pd/C) of XXIII in EtOH gave 3,4,5-trimethoxycatechol XXV.[8] The above results are in accordance with the structure XXIII for the diketone.

By analogy with the transformation of I or XIV, an arene peroxide XXVI can account for the formation of XXIII from XXII (Scheme 5). In this case, bis-epoxide XXVII cannot be the immediate precursor for XXIII. We, therefore, propose another type of bis-epoxide intermediate XXVIII, which may be formed by rearrangement of XXVII or directly from XXVI. The bis-epoxide XXVIII may be transformed into the diketone XXIII with the participation of MeOH analogous to the transformation of VII to III (Scheme 2) or by migration of OMe groups similar to the case of XXI (Scheme 4).



Scheme 5

As described above, rose bengal-sensitized photooxygenation of methoxybenzenes in MeOH gave various products. On the other hand, methylene blue-sensitized photooxygenation of methoxybenzenes gave the same products (Experimental). Since the participation of singlet oxygen in the reaction has been elucidated,[1] the initial step of the reaction is attack of singlet oxygen ($^1\Delta g$) to the benzene ring giving an arene-peroxide, which rearranges to an unstable bis-epoxide intermediate. The bis-epoxide decomposes to give various products by participation of solvent MeOH.

EXPERIMENTAL

Photosensitized oxygenation of 1,2,4,5-*tetramethoxybenzene* (I)

In methanol. A soln of I[12] (3·0 g, 15 mmoles) in dry MeOH (300 ml) containing rose bengal (20 mg) was irradiated by a tungsten-bromine lamp with oxygen circulating through the reaction vessel. After oxygen

(370 ml, 16 mmoles) had been consumed (2 hr), the mixture was evaporated and the residue chromatographed on silica gel (50 g). Elution with $CHCl_3$ (*ca.* 300 ml) yielded a yellow solid (0·13 g, 5%), identified as 2,5-dimethoxy-*p*-benzoquinone (II) (IR). Further elution with $CHCl_3$ (*ca.* 800 ml) gave III as a semisolid. Crystals from acetone (0·8 g, 20%): m.p. 125 ~ 126°: λ_{max}^{EtOH} 254 nm (log ε 3·94): ν_{max}^{nujol} 3450, 1670, 1620 cm^{-1}, (*m/e*), 230 (M-32), 201, 186, 171, 156. (Found: C, 50·50: H, 6·97. $C_{11}H_{18}O_7$ requires: C, 50·37: H, 6·92%). No other product was isolated in pure form.

Acid hydrolysis of III. To a soln of III (120 mg) in MeOH was added 6N HCl (2 ml), and the solution was kept at 100° for 1 hr. After evaporation of the coloured soln, the residue was purified by prep. TLC on silica gel (acetone–AcOH 1 :1). From the band of R_f 0·8, a dark violet precipitate (12 mg, 15%) was obtained, which recrystallized from EtOAc to give 3,4-dihydroxy-5-methoxy-*o*-benzoquinone (IVa): m.p. 213 ~ 214°: λ_{max}^{EtOH} 450 nm (log ε 2.86), 330 nm (log ε 3.27), 290 nm (log ε 4.11); ν_{max}^{nujol} 3400, 1700, 1670, 1630, 1600 cm^{-1}; τ_{TMS} (in acetone-d_6) 1·72 (s, 1H, OH), 1·88 (s, 1H, OH), 4·20 (s, 1H), 6·13 (s, 3H). (Found: C, 49·42: H, 4·23. $C_7H_6O_5$ requires: C, 49·41: H, 4·12%). Diacetate IVb (35 mg), prepared from IVa and Ac_2O, was reduced with hydrosulphite (50 mg) in MeOH aq. (10 ml). The mixture was diluted with 1N HCl (50 ml) and extracted with ether. To the extracts dissolved in MeOH, ethereal CH_2N_2 was added. After standing cold over night the mixture was purified by prep. TLC (silica gel, $CHCl_3$–benzene (1 :1)). From the band of R_f 0·4, a solid (5 mg) was obtained, shown to be V by IR.

Photosensitized oxygenation of 1,2,3,5-*tetramethoxybenzene* (IXa)

In methanol. A soln of IXa[8] (3·0 g, 15 mmoles) in dry MeOH (250 ml) containing rose bengal (20 mg) was irradiated for 3 hr as above. After oxygen (293 ml, 13 mmoles) had been consumed, the mixture was evaporated. The residue was chromatographed on silica gel (50 g). Elution with $CHCl_3$ (*ca.* 200 ml) gave the unreacted IXa (0·21 g). Elution with $CHCl_3$-acetone (10:1) yielded Xa as a semisolid. Crystals from benzene (1·65 g, 53%): m.p. 104°: λ_{max}^{EtOH} 272 nm (log ε 3·92): ν_{max}^{nujol} 3400, 1750 (broad), 1610 cm^{-1}: τ_{TMS} (in $CDCl_3$) 3·68 (d, J = 1·5 Hz, 1H), 5·41 (d, J = 1·5 Hz, 1H), 6·11 (s, 3H), 6·25 (s, OH), 6·40 (s, 3H), 6·70 (s, 3H): (*m/e*) 216 (M^+), 199, 184 (base peak), 169, 141, 113. (Found: C, 49·90: H, 5·49. $C_9H_{12}O_6$ requires: C, 50·00: H, 5·60%).

Further elution with acetone (200 ml) gave 3,4-dihydroxy-5-methoxy-*o*-benzoquinone (IVa) (0·12 g, 5%). The diketone Xa was found to be sensitive to silica gel chromatography to form partly IVa.

o-*Phenylenediamine adduct of* Xa. A soln of Xa (200 mg, 0·93 mmoles) and *o*-phenylenediamine (100 mg, 0·93 mmoles) in AcOH (10 ml) was kept at 100° for 3 hr. The resulting blue-coloured solution was poured into H_2O (200 ml) and the mixture ether extracted (200 ml). After solvent evaporation, the residue was chromatographed on silica gel (10 g). Elution with $CHCl_3$ (400 ml) gave adduct XI as a semisolid (38 mg, 15%): λ_{max}^{EtOH} 366 nm (log ε 3·88), 354 nm (log ε 3·87), 269 nm (log ε 4·25), 250 nm (log 4·01): ν_{max}^{nujol} 1640, 1560 cm^{-1}: τ_{TMS} (in $CDCl_3$) 1·8 ~ 2·4 (m, 4H), 4·02 (d, J = 1·5 Hz, 1H), 5·58 (d, J = 1·5 Hz, 1H), 5·90 (s, OH), 6·15 (s, 3H), 6·37 (s, 3H), 6·92 (s, 3H).

In ethanol. A soln of IXa (2·2 g, 11 mmoles) in abs. EtOH (300 ml) containing rose bengal (50 mg) was photooxygenated under the same conditions for 4 hr. After solvent evaporation, the residue was chromatographed on silica gel (40 g). Elution with $CHCl_3$-acetone (98 :2) yielded a semisolid, crystals from benzene of Xb (0·38 g, 15%): m.p. 148–150°: ν_{max}^{nujol} 1750, 1675, 1610 cm^{-1}: τ_{TMS} (in $CDCl_3$) 3·89 (d, J = 1·5 Hz, 1H), 5·43 (d, J = 1·5 Hz, 1H), 6·12 (s, 3H), 6·40 (s, OH), 6·35 (q, J = 7 Hz, 2H), 6·70 (s, 3H), 8·68 (t, J = 7 Hz, 3H): (*m/e*), 230 (M^+), 213, 198, 184 (base peak).

Photosensitized oxygenation of 2,5-*diethoxy*-1,3-*dimethoxybenzene* (IXb)

A methanolic solution of IXb (2·0 g, 8·9 mmoles), prepared by treatment of 2,6-dimethoxyhydroquinone with EtI and alkali, was photooxygenated using rose bengal (20 mg) as sensitizer. After oxygen (185 ml, 8 mmoles) had been consumed, the mixture was evaporated. The residue was chromatographed on silica gel (50 g). Elution with $CHCl_3$ (*ca.* 800 ml) yielded Xc (0·72 g, 35%): m.p. 72–74°: ν_{max}^{nujol} 1750, 1670, 1605 cm^{-1}: τ_{TMS} (in $CDCl_3$) 3·88 (d, J = 1·5 Hz, 1H), 6·25 (s, OH), 6·24 (s, 3H), 6·68 (s, 3H), 5·90 (q, J = 7 Hz, 2H), 8·48 (t, J = 7 Hz, 3H): (*m/e*) 230 (M^+), 213 (base peak), 198. (Found: C, 51·58: H, 6·09. $C_{10}H_{14}O_6$ requires C, 52·17: H, 6·13%).

Photosensnitized oxygenation of hexamethoxybenzene (XIV)

In methanol. A soln of XIV[13] (1·50 g, 5·8 mmoles) in MeOH (350 ml) containing rose bengal (55 mg) was photooxygenated. After 150 ml (6 mmoles) of oxygen had been consumed, the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel (38 g). Elution with $CHCl_3$ (*ca.* 800 ml) yielded a semisolid (0·81 g, 54%), crystals from ether of XVII: m.p. 113 ∼ 115°: λ_{max}^{EtOH} 264 nm (log ε. 4·05): ν_{max}^{nujol} 3400, 1710, 1687, 1605 cm^{-1}: τ_{1MS} (in $CDCl_3$) 5·85 ∼ 5·95 (broad s, 2H, OH), 5·90 (s, 3H), 5·96 (s, 3H), 6·50 (s, 6H). (Found: C, 45·99: H, 5·13. $C_{10}H_{14}O_8$ requires C, 45·80, H: 5·34%).

o-*Phenylenediamine adduct of* XVII. A soln of XVII (182 mg, 0·7 mmoles) and *o*-phenylenediamine (150 mg, 1·4 mmoles) in EtOH (10 ml) was kept at 100° for 2 hr. After solvent removal, the residue was chromatographed on silica gel (20 g). Elution with $CHCl_3$ yielded the adduct (XVIII or XIX) as yellow crystals (175 mg, 80%): m.p. 119°: λ_{max}^{EtOH} 345 nm (log ε 4·05), 266 nm (log ε 4·27), 237 nm (log ε 4·33): ν_{max}^{nujol} 1680 cm^{-1}: τ_{TMS} (in $CDCl_3$) 1·65 ∼ 2·35 (m, 4H), 5·60 (s, 3H), 6·02 (s, 3H), 6·50 (s, 6H). (Found: C, 60·57: H, 5·35: N, 8·73. $C_{16}H_{16}N_2O_5$ requires C, 60·75: H, 5·10: N, 8·86%).

Characterization of XV *as an* o-*phenylenediamine adduct*. A soln of XIV (500 mg, 1·9 mmoles) in MeOH (150 ml) containing rose bengal (15 mg) was photooxygenated as described. After removal of solvent, the residue and *o*-phenylenediamine (206 mg) were dissolved in EtOH (150 ml). The solution was refluxed for 3 hr. After removal of EtOH, the residue was chromatographed on silica gel (30 g). Elution with $CHCl_3$ gave adduct XVI as a semisolid (340 mg, 38%), crystals from acetone: m.p. 139 ∼ 140°: λ_{max}^{EtOH} 331 nm (log ε 3·99), 239 nm (log ε 4·56): ν_{max}^{nujol} 1655 cm^{-1}: τ_{TMS} (in $CDCl_3$) 1·55 ∼ 2·30 (m, 4H), 5·93 (s, 6H), 6·63 (s, 12H): (*m/e*) 362 (M^+). (Found: C, 59·57: H, 6·19: N, 7·69. $C_{18}H_{22}O_6N_2$ requires C, 59·66: H, 6·12: N, 7·73%).

In methanol-d_4. A soln of XIV (300 mg, 1·2 mmoles) in CD_3OD (10 ml) containing rose bengal (20 mg) was photooxygenated. After removal of solvent, the residue was chromatographed as described. Recrystallization of the eluents from ether gave colourless crystals (20 mg, 8·2%): m.p. 110°, which was identified as XVII (IR and NMR).

Photosensitized oxygenation of pentamethoxybenzene XXII

In methanol. A soln of XXII (3·0 g, 13 mmoles) in dry MeOH (400 ml) containing rose bengal (30 mg) was photooxygenated. After solvent evaporation the residue was chromatographed on silica gel (50 g). Elution with $CHCl_3$ (*ca*. 300 ml) gave unreacted XXII (0·3 g). Further elution with $CHCl_3$ (*ca*. 500 ∼ 700 ml) yielded a crystalline solid (1·75 g, 57%). Recrystallization from cold acetone gave XXIII as yellow prisms: m.p. 120 ∼ 122°: λ_{max}^{EtOH} 286 nm (log ε 3·86), 244 nm (log ε 3·80): $\nu_{max}^{CHCl_3}$ 1770 (broad), 1680, 1610 cm^{-1}: τ_{TMS} (in $CDCl_3$) 4·10 (1H), 6·04 (3H), 6·42 (6H), 6·44 (6H), (all appears as singlet): (*m/e*) 260 (M^+), 245, 217, 201, 143 (base peak). (Found: C, 50·93: H, 6·36. $C_{11}H_{16}O_7$ requires C, 50·77: H, 6·20%).

o-*Phenylenediamine adduct of* XXIII. A soln of XXIII (80 mg) and *o*-phenylenediamine (35 mg) in EtOH (5 ml) was kept at 60 ∼ 80° for 1 hr. Blue-coloured soln was poured into 20 ml of H_2O, which was ether extracted. After solvent removal, the residue recrystallized from acetone to give adduct XXIV: m.p. 145 ∼ 146°: λ_{max}^{EtOH} 368 nm (log ε 4·13), 354 nm (log ε 4·17), 280 nm (log ε 4·41), 250 nm (log ε 4·16), 222 nm (log ε 4·16), 222 nm (log ε 4·48): ν_{max}^{nujol} 1650, 1560 cm^{-1}: τ_{TMS} (in $CDCl_3$) 1·8 ∼ 2·50 (m, 4H), 3·95 (s, 1H), 6·05 (s, 3H), 6·41 (s, 6H), 6·42 (s, 6H). (Found: C, 60·59: H, 5·96: N, 8·20. $C_{17}H_{20}N_2O_5$ requires: C, 61·43: H, 6·07: N, 8·43%).

Hydrogenation of XXIII. To a soln of XXIII (130 mg, 0·5 mmoles) in EtOH (10 ml) was added 30 mg of Pd–C (10%). The soln was shaken under a hydrogen atmosphere at room temp. After 3 hr, 35 ml of hydrogen was absorbed. After catalyst removal the solvent was evaporated *in vacuo* under N_2. To the residual oil 3 ml of Ac_2O was added. The solution was refluxed for 2 hr. After removal of solvent, the residue was recrystallized from EtOH to give XXV: m.p. 74 ∼ 75° (lit.,[8] m.p. 77°), which was identical with an authentic sample prepared by the known method.[8]

Methylene blue-sensitized photooxygenation

A soln of I (300 mg, 1·5 mmoles) in dry MeOH (100 ml) containing methylene blue (20 mg) was photooxygenated as described above. TLC analysis of the mixture showed it to consist of unchanged I, the *p*-benzoquinone II, and the enone III. The chromatogram was virtually the same as products from rose bengal-sensitized photooxygenation.

Similarly, methylene blue-sensitized photooxygenation of IXa in MeOH gave Xa in comparable yield.

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