Syntheses of Isobenzofuran-4,7-quinone and Isoindole-4,7-quinone

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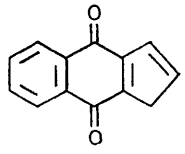
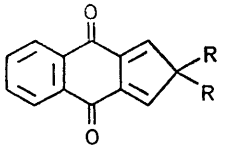
The syntheses of the title compounds *via* the 1,4-epoxy- (9) and 1,4-imino- (21) 5,8-naphthoquinones are described.

We have sought routes to the quinone (1),[1] one of which involved the intermediacy of the species (2). However, both (2) and its spiro-derivative (3) proved too unstable to be isolated under the reaction conditions employed.

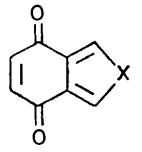
It would be expected that both the heterocyclic analogues (4) and (5) would possess considerable stability relative to (2) or (3) through resonance. Substituted derivatives of both (4) and (5) are known,[2] and the syntheses of the parent systems are reported here. Compounds (4) and (5) are formally stable derivatives of the highly unstable isobenzofuran (6) and isoindole (7), respectively.



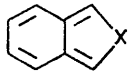
(1)



(2) R = H
(3) RR = $[CH_2]_2$



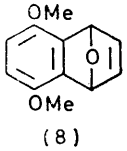
(4) X = O
(5) X = NH



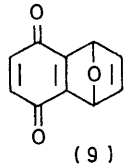
(6) X = O
(7) X = NH

Oxidation of the 3,6-dimethoxybenzyne–furan adduct (8)[3] with silver(II) oxide[4] gave the oxygen-bridged quinone (9). Treatment of this with 3,6-di-(2-pyridyl)-*s*-tetrazine[1,5] in chloroform gave furan (4).[6] Irradiation of the quinone (9) in benzene solution with sunlight afforded juglone (10).

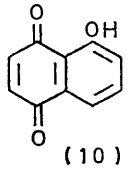
The previously reported routes to 3,6-dimethoxybenzyne involved the synthesis of the precursor 1-amino-4,7-dimethoxybenzotriazole[3] or 2-amino-3,6-dimethoxybenzoic acid,[7] or the reaction of 2,5-dimethoxybromobenzene with sodamide and sodium t-butoxide at low temperature.[8] We obtained the adduct (8) in 77% yield from



(8)

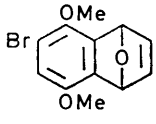


(9)



(10)

2,5-dimethoxybromobenzene by treatment with sodamide in the presence of furan under reflux in tetrahydrofuran. Similar treatment of 1,4-dibromo-2,5-dimethoxybenzene gave the mono-adduct (11), which in turn afforded the diadduct (12), presumably as a mixture of *syn*- and *anti*-isomers. This was supported by the appearance of two spots with very close R_F values on t.l.c. of the analytically pure product. Attempts to carry out



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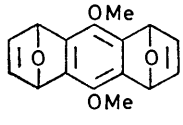

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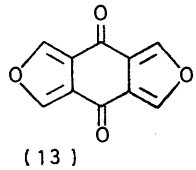


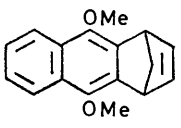
(13)

oxidative demethylation of the diadduct (12) with silver(II) oxide to form the corresponding quinone, from which the furan (13) might be derived, failed. This is probably attributable to steric hindrance: the less crowded, but structurally not unrelated, dimethyl ether (14) readily afforded the corresponding quinone (15) with this reagent.[9]

Generation of 3,6-dimethoxybenzyne *via* either the aminotriazole or the anthranilic acid route in the presence of *N*-ethoxycarbonylpyrrole afforded the nitrogen-bridged adduct (16). This gave rise to the amine (17) on

[1] R. G. F. Giles and I. R. Green, *J.C.S. Perkin I*, 1974, 228.
[2] *E.g.* E. Ghera, Y. Gaoni, and D. H. Perry, *J.C.S. Chem. Comm.*, 1974, 1034.
[3] C. W. Rees and D. E. West, *J. Chem. Soc.* (*C*), 1970, 583.
[4] C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, 1972, **94**, 227.
[5] W. S. Wilson and R. N. Warrener, *J.C.S. Chem. Comm.*, 1972, 211.
[6] The u.v., i.r., and n.m.r. data only for this compound have been reported: S. E. Fumagalli and C. H. Eugster, *Helv. Chim. Acta*, 1971, **54**, 959.
[7] H. Heaney, J. H. Hollinshead, G. W. Kirby, S. V. Ley, R. P. Sharma, and K. W. Bentley, *J.C.S. Perkin I*, 1973, 1840.
[8] P. G. Sammes and T. W. Wallace, *J.C.S. Chem. Comm.*, 1973, 524.
[9] R. G. F. Giles and P. R. K. Mitchell, unpublished results.

basic hydrolysis, or the *N*-methyl analogue (18) on treatment with lithium aluminium hydride in ether. The



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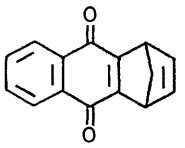
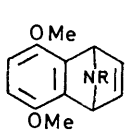
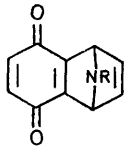
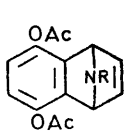


(15)

adduct (16) underwent oxidation by silver(II) oxide to the quinone (19), but on attempted removal of the ethylene bridge with the tetrazine, no reaction took place. Treatment of either of the bases (17) and (18) with silver(II) oxide did not yield the corresponding quinone, but led to extensive decomposition. The secondary







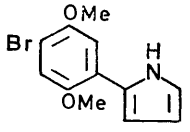
(16) R = CO_2Et (19) R = CO_2Et (22) R = CO_2Et
(17) R = H (21) R = Ac (23) R = Ac
(18) R = Me
(20) R = Ac

amine (17) gave the *N*-acetyl derivative (20) with pyridine and acetic anhydride. Oxidation of this compound with silver(II) gave the quinone (21), which was immediately treated with the tetrazine. Chromatographic purification of the product, during which deacetylation took place, afforded the yellow, crystalline pyrrole (5).

Both the quinones (19) and (21) were unstable, and were therefore not fully characterised as such. The structure of each was established by reductive acetylation to the diacetate (22) or (23), respectively, with zinc in pyridine and acetic anhydride.

The ^1H n.m.r. spectra of the *N*-acetyl derivatives (20), (21), and (23) showed that they lacked the symmetry of all the other *N*-bridged species reported here in that the bridgehead protons of the former showed different chemical shifts, owing to restricted rotation about the amide N–C bond.

Having been successful in the formation of the diadduct (12) in the oxygen series, we attempted to obtain a nitrogen analogue. Reaction of 1,4-dibromo-2,5-dimethoxybenzene with sodamide in tetrahydrofuran in the presence of *N*-ethoxycarbonylpyrrole afforded crystalline material whose spectral properties indicated it to be compound (24). The same product was obtained by



(24)

reaction of the dibromo-compound with sodamide and pyrrole. That the pyrrole group was *para* to bromine was suggested by the ^1H n.m.r. spectrum, which showed signals for two benzenoid protons as separate singlets, a low-field NH absorption, and three signals consistent with 2-substitution on the pyrrole nucleus.

EXPERIMENTAL

Unless otherwise stated i.r. spectra were measured for Nujol mulls and n.m.r. spectra for solutions in [^2H]chloroform with tetramethylsilane as internal reference. Chromatography was carried out with Merck Kieselgel (30—70 mesh) in wet columns, unless dry columns are indicated, in which cases Merck Kieselgel 60 (70—230 mesh) was used. Sodamide refers to B.D.H. material and light petroleum to the fraction of b.p. 60—80°. N.m.r. spectra were recorded at 100 MHz with a Varian XL-100 spectrometer.

1,4-*Dihydro*-5,8-*dimethoxy*-1,4-*epoxynaphthalene* (8).—Sodamide (14.6 g) was rapidly ground under dry tetrahydrofuran (120 ml) and transferred to a round-bottom flask. Dry furan (100 ml) in tetrahydrofuran was added at room temperature. The mixture was warmed to 50 °C and 2,5-dimethoxybromobenzene (21 g) was added dropwise in tetrahydrofuran (40 ml). The solution was stirred at this temperature for 56 h under nitrogen, then cooled, filtered, and partitioned between water and ethyl acetate. The organic layer was dried and evaporated and the residue chromatographed over silica gel with 10% ethyl acetate–light petroleum, to afford the adduct (15 g, 77%), which gave prisms, m.p. 86—87° (lit.,[3] 86—87°), from light petroleum.

1,4-*Dihydro*-1,4-*epoxy*-5,8-*naphthoquinone* (9).—The dimethyl ether (8) (0.79 g), silver(II) oxide (1.63 g), and dioxan (dried over sodium hydride; 20 ml) were mixed, and oxidation was initiated by addition of 6N-nitric acid (3.2 ml). As soon as all the silver oxide had been consumed, the reaction was stopped by addition of chloroform (30 ml) and water (8 ml). The chloroform layer was washed with water, dried, and evaporated and the residue was sublimed at 75° and 0.5 mmHg to give the *quinone* (0.19 g, 33%) as yellow needles, m.p. 117—118° (Found: C, 68.7; H, 3.5. $C_{10}H_6O_3$ requires 68.9; H, 3.5%), $\lambda_{max.}$ 255 and 396 nm (log ε 4.24 and 2.82), $\nu_{max.}$ ($CHCl_3$) 1 665 and 1 581 cm^{-1}, τ 2.88 (2H, s, CH=CH), 3.45 (2H, s, quinone H), and 4.22 (2H, s, bridgehead H).

Isobenzofuran-4,7-*quinone* (4).—The quinone (9) (0.100 g) and 3,6-di-(2-pyridyl)-*s*-tetrazine (0.138 g) were dissolved in chloroform (25 ml). Nitrogen bubbled off and the solution was stirred until the red colour disappeared. The solution was evaporated and the residue sublimed at 70° and 0.8 mmHg to give the *furan* (0.60 g, 70%) as fine needles, m.p. 140—142° (Found: C, 64.6; H, 3.0%; M^+, 148.1580. $C_8H_4O_3$ requires C, 64.8; H, 2.7%; *M*, 148.1604), $\lambda_{max.}$ 240 and 340 nm (log ε 4.10 and 3.43), $\nu_{max.}$ 1 642 and 1 585 cm^{-1}, τ 1.91 (2H, s, 1- and 3-H) and 3.16 (2H, s, 5- and 6-H).

Irradiation of the Quinone (9); *Formation of Juglone* (10).—The quinone (25 mg) in dry benzene (3 ml) was kept in a Pyrex container in sunlight for 15 h, during which time the initially pale yellow solution became dark orange. Evaporation and sublimation afforded juglone (20 mg), identical with an authentic sample (m.p., i.r., n.m.r.). A similar solution of (9) kept in the dark remained unchanged during this period.

6-*Bromo*-1,4-*dihydro*-5,8-*dimethoxy*-1,4-*epoxynaphthalene* (11).—Sodamide (5 g) which had been rapidly ground under dry tetrahydrofuran (60 ml) was treated with furan (30 ml)

in tetrahydrofuran (30 ml). 1,4-Dibromo-2,5-dimethoxybenzene (2.07 g) was added dropwise in tetrahydrofuran (30 ml) and the solution was stirred at 65 °C under nitrogen for 24 h. The solution was filtered and partitioned between water and ethyl acetate. The organic layer was dried and evaporated. The residue was recrystallised from methylene chloride–light petroleum to give the *bromo-adduct* (1.24 g, 63%). A sample was sublimed at 75° and 0.6 mmHg to yield white needles, m.p. 105° (Found: C, 51.0; H, 3.8. $C_{12}H_{11}BrO_3$ requires C, 50.9; H, 3.9%), $\nu_{max.}$ 1 610 cm^{-1}, τ 3.05br (2H, s, CH=CH), 3.32 (1H, s, 7-H), 4.19br (1H, s, bridgehead H), 4.27br (1H, s, bridgehead H), 6.21 (3H, s, OCH_3), and 6.26 (3H, s, OCH_3).

1,4,5,8-*Tetrahydro*-9,10-*dimethoxy*-1,4:5,8-*diepoxyanthracene* (12).—Sodamide (11 g) was rapidly ground as before under dimethoxyethane (dried over sodium hydride; 60 ml), and dry furan (50 ml) in dimethoxyethane (50 ml) was added. The bromo-adduct (11) (3.5 g) in dimethoxyethane (40 ml) was added dropwise and the solution stirred under nitrogen under reflux for 60 h. The volume of the solution was kept constant by addition of furan. The solution was filtered and evaporated to half its volume, then partitioned between ethyl acetate and water. The organic layer was dried and evaporated to yield the *diadduct* (1.88 g, 57%), as needles, m.p. 203—223° (from ethanol) (mixture of *syn*- and *anti*-isomers shown by t.l.c. with methylene chloride as solvent) (Found: C, 70.8; H, 5.5. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%), τ 2.96br (4H, s, CH=CH), 4.16br (4H, s, bridgehead H), and 6.16 (6H, s, 2 × OCH_3).

Ethyl 1,4-*Dihydro*-5,8-*dimethoxy*-1,4-*iminonaphthalene*-9-*carboxylate* (16).—(a) *From* 1-*amino*-4,7-*dimethoxybenzotriazole*. To the triazole (0.946 g) and *N*-ethoxycarbonylpyrrole (0.800 g) in dry methylene chloride (25 ml) was added in small portions a suspension of lead tetra-acetate (3.0 g) in methylene chloride (50 ml). The solution was stirred until the evolution of nitrogen ceased, then filtered; the precipitate was washed with methylene chloride and the organic solution evaporated. The residue was chromatographed over silica gel (10% chloroform–benzene). The clear oil (1.16 g, 86%) was sufficiently pure for further reaction. Preparative t.l.c. (5% ethyl acetate–benzene) gave the *adduct* as needles, m.p. 53—53.5° (Found: C, 65.2; H, 6.1; N, 5.1. $C_{15}H_{17}NO_4$ requires C, 65.45, H, 6.25; N, 5.1%), $\lambda_{max.}$ 235 and 299 nm (log ε 3.67 and 3.46), $\nu_{max.}$ 1 709 and 1 619 cm^{-1}, τ 2.99br (2H, s, CH=CH), 3.46 (2H, s, ArH), 4.22br (2H, s, bridgehead H), 5.92 (2H, q, CH_2), 6.20 (6H, s, OCH_3), and 8.80 (3H, t, OCH_3).

(b) *From* 2-*amino*-3,6-*dimethoxybenzoic acid*. To a solution of *N*-ethoxycarbonylpyrrole (0.85 g) in acetonitrile (40 ml), the acid (1.0 g) in methylene chloride (25 ml) and pentyl nitrite (1.2 g) in acetonitrile (20 ml) were added dropwise during 30 min. The solution was heated under reflux for 2 h, and then evaporated. The residue was chromatographed as in (a) to yield identical material (1 g, 72%).

1,4-*Dihydro*-5,8-*dimethoxy*-1,4-*iminonaphthalene* (17).—The foregoing carbamate (2.9 g) in sodium hydroxide (10%, 40 ml) was heated under reflux for 3 h. The solution was cooled and extracted with methylene chloride. The organic layer was dried and evaporated. The residue was sublimed at 70° and 0.5 mmHg to yield white *needles* (1.83 g, 85%), m.p. 80—81° (Found: C, 71.1; H. 6.7; N, 6.6. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.4; N, 6.9%), $\lambda_{max.}$ 240 and 302 nm (log ε 3.46 and 3.55), $\nu_{max.}$ 3 262 cm^{-1}, τ 2.98br (2H, s, CH=CH), 3.54 (2H, s, ArH), 4.87br (2H, s, bridgehead H), 6.21 6H, s, OCH_3), and 7.01 (1H, s, D_2O exchangeable, NH).

1,4-*Dihydro*-5,8-*dimethoxy*-9-*methyl*-1,4-*iminonaphthalene* (18).—The carbamate (16) (1.20 g) in ether (10 ml) was added dropwise to a suspension of lithium aluminium hydride (0.3 g) in ether (5 ml). The mixture was heated under reflux for 1 h. A saturated ammonium chloride solution was added, and the ethereal solution was filtered, dried, and evaporated. The residue was sublimed at 65° and 0.5 mmHg to give white *needles*, m.p. 84—86° (0.70 g, 69%) (Found: C, 72.0; H, 7.1; N, 6.6. $C_{13}H_{15}NO_2$ requires C, 71.95; H, 6.9; N, 6.45%), $\lambda_{max.}$ 240 and 301 nm (log ε 3.35 and 3.45), τ 3.00br (2H, s, CH=CH), 3.43 (2H, s, ArH), 5.23br (2H, s, bridgehead H), 6.21 (6H, s, OCH_3), and 7.84br (3H, s, NCH_3).

9-*Ethoxycarbonyl*-1,4-*dihydro*-1,4-*imino*-5,8-*naphthoquinone* (19).—The carbamate (16) (85 mg) and silver(II) oxide (500 mg) in dry dioxan (10 ml) were treated with 6N-nitric acid (1.2 ml) for 5 min. Chloroform (16 ml) and water (4 ml) were added and the organic layer was separated, washed with water, dried, and evaporated. The resulting oil was chromatographed over silica gel with chloroform as eluant; $\nu_{max.}$ 1 718 and 1 655 cm^{-1}, τ 2.88br (2H, s, CH=CH), 3.40 (2H, s, quinone H), 4.29br (2H, s, bridgehead H), 5.89 (2H, q, CH_2), and 8.77 (3H, t, CH_3).

Ethyl 5,8-*Diacetoxy*-1,4-*dihydro*-1,4-*iminonaphthalene*-9-*carboxylate* (22).—The foregoing quinone (0.50 g) was mixed with zinc dust (0.43 g) in acetic anhydride (5 ml) and pyridine (1.7 ml). The mixture was heated on a steam-bath and further additions of similar quantities of zinc were made after 10 and 15 min. The mixture was heated under reflux for 15 min, poured onto ice and extracted with ethyl acetate (5 × 15 ml). The extract was washed with saturated brine, dried, and evaporated. The residue was chromatographed (dry column) with 10% ethyl acetate–benzene as eluant. The white crystalline *product* was recrystallised from methylene chloride–light petroleum; m.p. 107.5—108.5° (0.20 g, 30%) (Found: C, 61.6; H, 4.8, N, 4.5. $C_{17}H_{17}NO_6$ requires C, 61.6; H, 5.15; N, 4.25%), $\nu_{max.}$ 1 755 and 1 710 cm^{-1}, τ 2.92br (2H, s, CH=CH), 3.29 (2H, s, ArH), 4.46br (2H, s, bridgehead H), 5.92 (2H, q, CH_2CH_3), 7.67 (6H, s, Ac), and 8.80 (3H, t, CH_2CH_3).

9-*Acetyl*-1,4-*dihydro*-5,8-*dimethoxy*-1,4-*iminonaphthalene* (20).—The amine (17) (0.80 g) in pyridine (3 ml) and acetic anhydride (8 ml) was heated on a steam-bath for 30 min. The solution was thrown into a large excess of water and extracted with chloroform. The organic layer was dried and evaporated. The residue (0.95 g, 98%) was recrystallised from ethyl acetate–light petroleum to give white *needles*, m.p. 115.5—116.5° (Found: C, 68.4; H, 6.25; N, 5.9. $C_{14}H_{15}NO_3$ requires C, 68.6; H, 6.1; N, 5.7%), $\lambda_{max.}$ 259 and 306 nm (log ε 3.33 and 3.54), $\nu_{max.}$ 1 717, 1 631, and 1 602 cm^{-1}, τ 2.98 (2H, m, CH=CH), 3.47 (2H, s, ArH), 3.91 and 4.26 (1H each, m, bridgehead H), 6.22 (6H, s, OCH_3), and 8.06 (3H, s, Ac).

9-*Acetyl*-1,4-*dihydro*-1,4-*imino*-5,8-*naphthoquinone* (21).—The foregoing diether (70 mg) and silver(II) oxide (145 mg) in dry dioxan (3 ml) were treated with 6N-nitric acid (0.25 ml). When the silver oxide was consumed, chloroform (16 ml) and water (4 ml) were added. The chloroform layer was washed with water, dried, and evaporated. The residue (57 mg) was purified by preparative t.l.c. (5% ethanol–chloroform) to give a yellow oil (50 mg, 82%), τ 2.80 (2H, m, CH=CH), 3.37 (2H, s, quinone H), 4.00 and 4.25 (1H each, m, bridgehead H), and 8.03 (3H, s, Ac).

5,8-*Diacetoxy*-9-*acetyl*-1,4-*dihydro*-1,4-*iminonaphthalene* (23).—The foregoing quinone (21) was reductively acetylated

as described for the quinone (19). The reaction residue was sublimed at 75° and 0.2 mmHg to give white *crystals*, m.p. 155—156° (Found: C, 63.4; H, 5.1; N, 4.7. $C_{16}H_{15}NO_5$, requires C, 63.8; H, 5.0; N, 4.6%), $\nu_{max.}$ ($CHCl_3$) 1 760 and 1 645 cm^{-1}, τ 2.90 (2H, m, CH=CH), 3.30 (2H, s, ArH), 4.16br and 4.52br (1H each, s, bridgehead H), 7.64 and 7.66 (3H each, s, OAc), and 8.03 (3H, s, NAc).

Isoindole-4,7-quinone (5).—A solution of the quinone (21) (41 mg) and 3,6-di-(2-pyridyl)-*s*-tetrazine (45 mg) in [^{2}H]-chloroform (0.5 ml) was monitored by ^{1}H n.m.r. spectroscopy. Nitrogen evolution took place. Signals due to starting materials had disappeared after 1.5 h. The solution was evaporated and the product purified by preparative t.l.c. (eluant benzene). The yellow band was collected and sublimed at 110° and 0.5 mmHg to yield the *product* (20 mg, 71%), m.p. 180—181° (decomp.) (Found: C, 65.4; H, 3.4; N, 9.3%; M^+, 147.032 12. $C_8H_5NO_2$ requires C, 65.3; H, 3.4; N, 9.5%; *M*, 147.032 02), $\nu_{max.}$ 3 250, 1 647, and 1 582 cm^{-1}, τ [$(CD_3)_2CO$] 2.50 (2H, s, 1- and 3-H) 3.34 (2H, s, 5- and 6-H), and 7.18br (1H, s, NH, D_2O exchangeable).

2-*Bromo*-1,4-*dimethoxy*-5-(*pyrrol*-2-*yl*)*benzene* (24).—(*a*) *From* N-*ethoxycarbonylpyrrole*. 1,4-Dibromo-2,5-dimethoxybenzene (1.6 g) in dry tetrahydrofuran was added dropwise to a stirred mixture of finely ground sodamide (5 g) and *N*-ethoxycarbonylpyrrole (3 g) in more tetrahydrofuran at 65 °C under nitrogen. After 20 h the solution was filtered and partitioned between ethyl acetate and water. The organic layer was dried and evaporated. The brown residue was chromatographed (dry column; 15% ethyl acetate–light petroleum) to give white *rosettes*, m.p. 119° (from methylene chloride–light petroleum) (1 g, 65%) (Found: C, 50.8; H, 4.15; N, 5.0. $C_{12}H_{12}BrNO_2$ requires C, 51.0; H, 4.25; N, 5.0%), $\nu_{max.}$ 3 440 cm^{-1}, τ 0.23br (1H, D_2O exchangeable, NH), 2.84 and 2.88 (1H each, s, 3- and 6-H), 3.13, (1H, m, pyrrole 5-H), 3.40 (1H, m, pyrrole 3-H), 3.70 (1H, m, pyrrole 4-H), and 6.12 (6H, s, OCH_3).

(b) *From pyrrole*. Pyrrole was substituted for *N*-ethoxycarbonylpyrrole in procedure (a). Product (24), identical (m.p., mixed m.p., and n.m.r.) with that from (a), was obtained.

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