Preparation of 3-Ethyloxindole-4,7-quinone†

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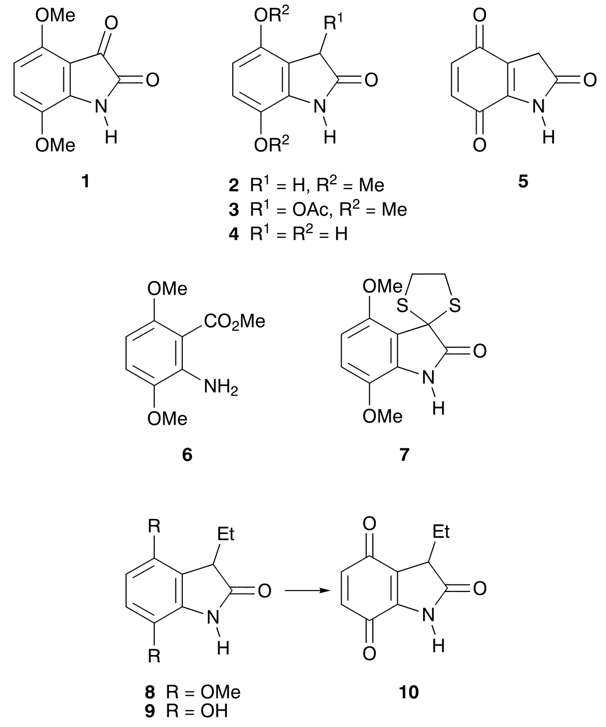
The preparation of 3-ethyloxindole-4,7-quinone **10** from 4,7-dimethoxyisatin **1** in four steps is described.

Quinone derivatives of simple heterocyclic systems are of considerable chemical and biological interest.[1] However, few simple oxindole quinones are known though some quinonoid, multi-ring systems containing the oxindole moiety are reported.[2] Our unsuccessful attempts to obtain isatin-4,7-quinone resulted in the formation of 3,3-diphenyloxindole-4,7-quinone.[3] We now describe attempts to obtain less substituted oxindole quinones.

An approach to oxindole-4,7-quinone **5** appeared to be by oxidation with ceric ammonium nitrate (CAN) of 4,7-dimethoxyoxindole **2** which was expected to be formed by reduction of the available 4,7-dimethoxyisatin **1**. Selective reduction of the ketonic carbonyl group of isatins has been achieved using a zinc–copper couple in acetic acid[4] or by the action of sodium ethoxide on the isatin hydrazone.[5] Neither procedure gave the oxindole **2** from **1**, though the former method gave 3-acetoxy-4,7-dimethoxyoxindole **3**. Treatment of the isatin **1** with sodium borohydride[6] in methanol and in the presence of air for an extended period of time gave 3,6-dimethoxyanthranilic acid (**6**) (79%). A similar reaction with isatin gave methyl anthranilate (61%) but when the reaction was performed under a nitrogen atmosphere only a trace quantity of the anthranilate was formed. The detailed mechanism for the formation of the anthranilates is not known but the evidence indicates that both reduction (by borohydride) and oxidation (by air) are essential. Solvolysis of an intermediate seems to be a likely process for the formation of the ester. As expected, the action of sodium methoxide in methanol did not give the anthranilate. More satisfactory for the formation of **2** was the application of another method used to convert isatin to oxindole.[7] Thus, reduction of the isatin **1** through formation of the dithioketal **7** and its decomposition in refluxing benzene in the presence of Raney nickel yielded 4,7-dimethoxyoxindole **2**. However, attempts to cause the formation of the parent oxindole quinone **5** from **2** by the action of CAN, periodate or nitric acid gave complex mixtures. Therefore **2** was demethylated with aluminium chloride in benzene to give the dihydroxyoxindole **4** but attempts to oxidise **4** to **5** with silver oxide, nitric acid, Fremy's salt or CAN again produced complex mixtures.

It seemed likely that failure to obtain **5** was due to the presence of the unsubstituted methylene group because 3,3-disubstituted oxindole-quinones are known.[3] The reduction of isatins through their dithioketals provided a means by which this idea might be tested because prolonged refluxing of isatin dithioketals in ethanol in the presence of Raney nickel is known to yield 3-ethyloxindoles.[8] Thus, refluxing an ethanolic solution of **7** in the presence of Raney nickel for 24 h gave a high yield of 3-ethyl-4,7-dimethoxyoxindole **8** and this was smoothly converted to the corresponding dihydroxy compound **9**. The phenol **9** was then oxidised by silver carbonate on celite to 3-ethyloxindole-4,7-quinone **10**, though in low yield (Scheme 1). The isolation of **10** does give support to the idea that the difficulties experienced in producing **5** do stem from the reactivity of the unsubstituted 3-position.



Scheme 1

Experimental

Experimental procedures to obtain melting points, spectroscopic data, elemental analyses and chromatographic separations were as described.[9] The accurate mass determination were performed by the EPSRC Mass Spectrometry Service Centre, University of Wales, Swansea. Raney nickel was obtained from Aldrich Chemical Company and petroleum spirit refers to light petroleum (bp 40–60 °C). Elemental analyses and ^{1}H NMR and mass spectral data are given in Table 1.

3-*Acetoxy*-4,7-*dimethoxyoxindole* **3**.—A mixture of 4,7-dimethoxyisatin[10] (**1**) (0.5 g, 2.4 mmol), a zinc–copper couple[11] (1.5 g) and glacial acetic acid (30 ml) was refluxed for 21 h. The mixture was filtered, the filtrate diluted and neutralised by the addition of sodium carbonate. Extraction with ether and the usual work-up gave an orange solid which was crystallised from a mixture of chloroform and petroleum spirit and then from ethanol to give **3** (0.37 g, 61%), mp 193–195 °C; $\nu_{\max}$/cm^{-1} 3190 (NH), 1730 (CO), 1640 (CO).

Methyl 2-*Amino*-3,6-*dimethoxybenzoate* **6**.—A mixture of 4,7-dimethoxyisatin **1** (0.5 g, 2.4 mmol), sodium borohydride (0.3 g) and methanol (40 ml) was stirred for 12 h and then a further quantity of borohydride (0.6 g) was added and the stirring continued for a further 24 h. The mixture was neutralised by the addition of hydrochloric acid and extracted with chloroform. The extract yielded an oil which was purified by flash column chromatography (petroleum spirit–ethyl acetate, 13:9) and distillation (bp 136 °C/0.7 mm Hg) to give **6** (0.35 g, 70%), bp 385 °C $\nu_{\max}$/cm^{-1} 3510, 3400 (NH$_2$), 1720 (CO).

4,7-*Dimethoxyisatin* 3,3-*Ethylenedithioketal* **7**.—A mixture of ethane-1,2-dithiol (2.2 ml), **1** (1 g, 4.8 mmol) and boron trifluoride etherate (1.2 ml) was stirred under nitrogen for 20 min. Methanol (5 ml) was added, the solid filtered off and crystallised from acetic

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Table 1 Elemental analyses–accurate mass and ^{1}H NMR and mass spectral data of **2**–**4**, **6**–**10**

Compound	Formula	Found (Calcd) (%)			δ_H/ppm	*m*/*z*
		C	H	N		
2	$C_{10}H_{11}NO_3$	61.88 (62.17)	5.68 (5.69)	7.20 (7.25)	^{a}3.55 (2 H, s, 3-H), 3.82 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 6.52 (1 H, d, *J* 9 Hz, 5-H), 6.81 (1 H, d, *J* 9 Hz, 6-H), 7.55 (1 H, s, NH^b)	193 (M^+, 100), 178 (M^+–CO, 50)
3	$C_{12}H_{13}NO_5$	57.21 (57.37)	5.43 (5.22)	5.41 (5.57)	^{a}2.15 (3 H, s, $COCH_3$), 3.74 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 6.11 (1 H, s, 3-H), 6.43 (1 H, d, *J* 9 Hz, 6-H), 6.78 (1 H, d, *J* 9 Hz, 5-H), 7.32 (1 H, s, NH^b)	251 (M^+, 37), 209 (M^+–COMe, 100)
4	$C_8H_7NO_3$	52.19 (52.46)	4.96 (4.95)	7.46 (7.64)	^{c}3.25 (2 H, s, 3-H), 6.17 (1 H, d, *J* 8 Hz, 5-H), 6.47 (1 H, d, *J* 8 Hz, 6-H), 8.49 (1 H, s, OH^b), 8.69 (1 H, s, OH^c), 9.86 (1 H, s, NH^b)	165 (M^+, 100), 137 (M^+–CO, 50)
6	$C_{10}H_{13}NO_4$	57.15 (56.87)	6.24 (6.20)	6.40 (6.63)	^{a}3.78 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 3.90 (3 H, s, CH_3), 5.42 (2 H, s, $NH_2{}^b$), 6.14 (1 H, d, *J* 9 Hz, 4-H), 6.74 (1 H, d, *J* 9 Hz, 5-H)	211 (M^+, 100)
7	$C_{12}H_{13}NO_3S_2$	50.84 (50.86)	4.62 (4.62)	4.92 (4.94)	^{a}3.76 (4 H, m, 2xCH_2), 3.81 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 6.61 (1 H, d, *J* 9 Hz, 5-H), 6.79 (1 H, d, *J* 9 Hz, 6-H), 7.35 (1 H, s, NH^b)	283 (M^+, 100), 223 (85)
8	$C_{12}H_{15}NO_3$	65.08 (65.14)	7.05 (6.83)	6.27 (6.33)	^{a}0.77 (3 H, t, *J* 7 Hz, CH_3), 2.08 (2 H, dd, *J* 7 and 5 Hz, CH_2), 3.56 (1 H, t, *J* 5 Hz, 3-H), 3.77 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 6.42 (1 H, d, *J* 9 Hz, 6-H), 7.32 (1 H, s, NH^b)	221 (M^+, 100), 206 (M^+–Me, 52), 178 (58)
9	$C_{10}H_{11}NO_3$	62.17 (62.17)	5.89 (5.74)	7.07 (7.25)	^{c}0.63 (3 H, t, *J* 7 Hz, CH_3), 1.95 (2 H, dd, *J* 7 and 5 Hz, CH_2), 3.25 (1 H, t, *J* 5 Hz, 3-H), 6.17 (1 H, d, *J* 11 Hz, 5-H), 6.45 (1 H, d, *J* 11 Hz, 6-H), 8.46 (1 H, s, OH^b) 8.67 (1 H, s, OH^b), 9.79 (1 H, s, NH^b)	193 (M^+, 100), 164 (M^+–Et, 53)
10	$C_{10}H_9NO_3$	191.0583 (M^+, 191.0582)^d			^{a}0.64 (3 H, t, *J* 7 Hz, CH_3), 2.43 (2 H, dd, *J* 7 and 4 Hz, CH_2), 3.38 (1 H, t, *J* 4 Hz 3-H), 6.61 (1 H, s, 5-H), 7.15 (1 H, s, 6-H), 9.91 (1 H, s, NH^b)	191 (M^+, 56), 189 (100)

^{a}In $CDCl_3$. ^{b}Exchanges with D_2O. ^{c}[$^2H_6$]DMSO. ^{d}Accurate mass determination by E.I. mass spectrometry.

acid to give **7** (1.09 g, 80%), mp 225–226 °C; ν_{max}/cm^{-1} 3180 (NH), 1715 (CO).

4,7-*Dimethoxyoxindole* **2**.—A mixture of **7** (0.6 g, 2.1 mmol), ethanol (50 ml) and Raney nickel was stirred and refluxed for 2.5 h. The solution was decanted and the solid washed seven times with warm ethanol. Evaporation of the solution gave a residue which was crystallised from ethanol as **2** (0.3 g, 73%), mp 201–202 °C; ν_{max}/cm^{-1} 3200 (NH), 1690 (CO).

4,7-*Dihydroxyoxindole* **4**.—A mixture of **2** (0.83 g, 4.3 mmol), sublimed aluminium chloride (12.63 g) and benzene (60 ml) was boiled under reflux for 2 h. The reaction mixture was poured into crushed ice, extracted with ether, and the extract evaporated. Flash chromatography (chloroform–methanol 13:1) gave a product which was crystallised from water to give **4** (0.55 g, 79%), mp > 300 °C (decomp. 210 °C); ν_{max}/cm^{-1} 3970 (OH), 1680 (CO).

3-*Ethyl*-4,7-*dimethoxyoxindole* **8**.—A mixture of **7** (0.8 g, 2.8 mmol), ethanol (100 ml) and Raney nickel (5 g) was stirred and refluxed for 24 h. The solid was filtered off, the filtrate evaporated and the residue crystallised from ethyl acetate to give **8** (0.5 g, 80%), mp 134–135 °C; ν_{max}/cm^{-1} 3180 (NH), 1700 (CO).

3-*Ethyl*-4,7-*dihydroxyoxindole* **9**.—Dry benzene (30 ml) was added to **8** (0.28 g, 1.26 mmol) and sublimed aluminium chloride (3.73 g) and the mixture refluxed for 2 h. The mixture was poured into crushed ice, extracted with ether and the solvent evaporated. The residue was purified by flash chromatography (chloroform–methanol, 19:1) and crystallised from ethyl acetate to give **9** (0.24 g, 79%), mp 213–215 °C ν_{max}/cm^{-1} 3340 (OH), 3200 (NH), 1730 (CO).

3-*Ethyloxindole*-4,7-*dione* **10**.—A mixture of **9** (0.16 g, 0.8 mmol), dry THF (50 ml) and freshly prepared silver carbonate on celite[12] (1.9 g) was refluxed for 2 h. The solid was separated, the solution evaporated and the residue purified by flash column chromatography (ethyl acetate–petroleum spirit) to give red crystals of **10** (40 mg, 27%), mp > 300 °C (decomp. 140 °C); ν_{max}/cm^{-1} 3260 (NH), 1720 (CO), 1670 (CO).

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References

1 R. W. Middleton and J. Parrick, in *The Chemistry of Quinonoid Compounds*, ed. S. Patai and Z. Rappoport, Wiley, Chichester, 1988, vol. 2, part 2, p. 1019.
2 M. Tišler, *Adv. Heterocycl. Chem.*, 1989, **45**, 37.
3 A. S. Ijaz, J. Parrick and A. Yahya, *J. Chem. Res.*, 1990, (*S*) 116; (*M*) 0833.
4 T. A. Foglia and D. Swern, *J. Org. Chem.*, 1968, **33**, 4440.
5 A. H. Jackson, *Chem. Ind.* (*London*), 1965, 1652.
6 Products arising by reductive dimerization have been reported from the action of sodium borohydride on isatins; R. L. Autrey and F. C. Tahk, *Tetrahedron*, 1967, **23**, 901.
7 C. Djerassi, M. Gorman and J. A. Henry, *J. Am. Chem. Soc.*, 1955, **77**, 4647.
8 C. Djerassi and D. H. Williams, *J. Chem. Soc.*, 1963, 4046.
9 A. R. Ahmad, L. K. Mehta and J. Parrick, *J. Chem. Soc. Perkin Trans 1*, 1996, 2443.
10 P. Nickel and R. Zimmermann, *Arch. Pharm.*, 1977, **310**, 537.
11 E. Le Goff, *J. Am. Chem. Soc.*, 1964, **29**, 2048.
12 V. Balogh, M. Fetizon and M. Golfier, *J. Org. Chem.*, 1971, **36**, 1339.