

## Thermal Oxygen Atom Transfer from Benz[*cd*]indazole 1,2-Dioxide to Benzenoid Derivatives

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Thermolysis of benz[*cd*]indazole 1,2-dioxide at 105–110 °C in the presence of various benzenoid derivatives gave benz[*cd*]indazole 1-oxide and oxidation products of the benzenoid substrates. Toluene was oxidised to benzyl alcohol (40% yield based on the dioxide), benzaldehyde (19%), benzoic acid (0.5%), *o*-cresol (11%), *m*-cresol (3%), and *p*-cresol (>4%); an experiment with [4-<sup>3</sup>H]toluene showed no appreciable migration and retention of tritium (NIH shift) during formation of *p*-cresol. [4-<sup>2</sup>H]Anisole was converted mainly into deuteriated phenol (14%) and 2-hydroxyanisole (13%) together with 4-hydroxyanisole (4%) containing no significant amounts of deuterium. Naphthalene gave  $\alpha$ - and  $\beta$ -naphthol in low yield. In contrast, 4-methylcinnoline 1,2-dioxide was stable in hot anisole. The results are compared with those reported for other, related oxidising systems.

PHOTOCHEMICALLY induced transfer of oxygen from heteroaromatic *N*-oxides to organic substrates is well known.<sup>1</sup> The hydroxylation of aromatic rings in this manner has received special attention and there is evidence<sup>2</sup> for the involvement of arene oxides which isomerise to phenols with the characteristic migration (the NIH shift) of hydrogen from the site of hydroxylation to neighbouring carbon. Alder *et al.*<sup>3</sup> observed that benz[*cd*]indazole 1,2-dioxide (1) decomposed upon melting to give the corresponding mono-oxide; the fate of the second oxygen atom was not determined. It seemed to us that a study of the decomposition of (1) in aromatic solvents would be mechanistically interesting

and might provide examples of thermal, rather than photochemical, oxygen atom transfer from an *N*-oxide to an aromatic ring.

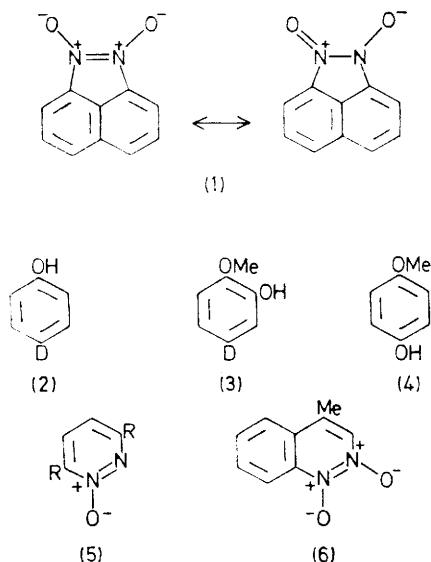
In preliminary experiments, the dioxide (1) was heated under reflux, in the dark under nitrogen, in toluene until decomposition was complete (*ca.* 5 h). The reaction mixture contained, besides benzindazole monoxide, various products derived from the toluene. G.l.c. analysis gave the following composition (% yields based on the dioxide): benzyl alcohol (37), benzaldehyde (12), *o*-cresol (11), and *m*- and *p*-cresol (together 5.3). No significant amounts (>1%) of bibenzyl were detected. Qualitatively similar results were obtained when the reaction was carried out without exclusion of light or air. The benzindazole mono-oxide did not oxidise

<sup>1</sup> (a) J. Streith, B. Danner, and C. Sigwalt, *Chem. Comm.*, 1967, 979; (b) H. Igeta, T. Tsuchiya, M. Yamada, and H. Arai, *Chem. and Pharm. Bull. (Japan)*, 1968, **16**, 767; (c) T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Letters*, 1969, 2747; 1970, 2213; (d) G. Serra-Errante and P. G. Sammes, *J.C.S. Chem. Comm.*, 1975, 573.

<sup>2</sup> D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Letters*, 1970, 457.

<sup>3</sup> R. W. Alder, G. A. Niazi, and M. C. Whiting, *J. Chem. Soc. (C)*, 1970, 1693.

toluene significantly even on prolonged (18 h) heating under reflux; also, benzyl alcohol was not oxidised appreciably by the mono-oxide under the thermolysis conditions. Isotopic labelling methods were then used



(a) to confirm the identity of the oxidation products, (b) to provide an alternative measure of the yields, and (c) to determine whether formation of *p*-cresol involved the NIH shift.

Benzindazole dioxide (1) was decomposed, as before, in the dark under nitrogen, in [ $4\text{-}^3\text{H}$ ; *methyl*- $^{14}\text{C}$ ]toluene

of tritium. *p*-Cresol, unfortunately, proved to be a minor product and the 3,5-dinitrobenzoate was not obtained radiochemically pure even after many recrystallisations; the tabulated yield and  $^3\text{H} : ^{14}\text{C}$  ratio represent upper limits. However it was apparent that little, if any, migration and retention of tritium had occurred during *p*-hydroxylation of toluene. A control experiment demonstrated that no serious loss of tritium, at positions *ortho* to the hydroxy-group, from *p*-cresol took place under the conditions of its formation and isolation. 4-Hydroxy[3,5- $^3\text{H}_2$ ]toluene was heated under reflux for 12 h in toluene containing benzyl alcohol, benzaldehyde, *o*-cresol, and benzindazole mono-oxide, and then was recovered and converted into the 3,5-dinitrobenzoate. This derivative retained 87% of the original tritium; a separate experiment showed that formation of the 3,5-dinitrobenzoate directly from tritiated *p*-cresol proceeded with 98% retention of tritium.

The oxidation of deuteriated anisole was studied next with the aid of combined g.l.c.-mass spectrometry. The dioxide (1) was heated at 105 °C in 1,1,2,2-tetrachloroethane containing a large excess of [4- $^2\text{H}$ ]methoxybenzene (88% deuterium). The phenolic products were extracted with alkali and examined by g.l.c.-mass spectrometry to provide, by comparison with standards, their yields and deuterium retentions (Table 2). The major products, phenol (2) and 2-hydroxyanisole (3) were, as expected, mono-deuteriated, whereas 4-hydroxyanisole (4) was virtually free from deuterium. 3-Hydroxyanisole was present, if at all, in only trace

TABLE 1

Product distribution from the oxidation of [ $4\text{-}^3\text{H}$ ; *methyl*- $^{14}\text{C}$ ]toluene ( $^3\text{H} : ^{14}\text{C}$  ratio, 17.5 : 1) with benz[*cd*]indazole 1,2-dioxide (1)

Product	Benzyl alcohol	Benzaldehyde	Benzoic acid	<i>o</i> -Cresol	<i>m</i> -Cresol	<i>p</i> -Cresol
Yield [% based on (1)]	40	19	0.5	11	3	>4
$^3\text{H} : ^{14}\text{C}$ ratio	16.2 : 1	16.5 : 1	16.2 : 1	16.3 : 1	16.2 : 1	>3.5 : 1
% Retention of $^3\text{H}$	93	94	93	93	93	>20

in three separate experiments. The reaction mixture from the first experiment was diluted with known amounts of non-radioactive benzyl alcohol and *p*-cresol. These components were separated from the mixture chromatographically and by extraction with alkali and converted into 3,5-dinitrobenzoates which were repeatedly crystallised and counted for  $^3\text{H}$  and  $^{14}\text{C}$ . Similarly, benzaldehyde and *o*-cresol were isolated, by dilution, from the second reaction mixture, and benzoic acid and *m*-cresol from the third. *o*- and *m*-Cresol were purified as their 3,5-dinitrobenzoates and benzaldehyde as its semicarbazone; benzoic acid was crystallised directly. The yields of products (Table 1) agreed well with those determined by g.l.c. analysis. Benzoic acid was present

amounts. Again it appeared that *p*-hydroxylation had caused loss, rather than migration and retention, of deuterium. Deuterium loss from 4-hydroxyanisole as a

TABLE 2

Product distribution from the oxidation of [4- $^2\text{H}$ ]anisole (88%  $^2\text{H}_1$ ) with benz[*cd*]indazole 1,2-dioxide (1)

Product	Phenol (2)	2-Hydroxyanisole (3)	4-Hydroxyanisole (4)
Yield [% based on (1)]	14	13	4
% $^2\text{H}_1$	90	83	4
% $^2\text{H}_1$ after $\text{Et}_3\text{N-H}_2\text{O}$ exchange	5.5	83	3

consequence of secondary reactions may be discounted since the isotope was retained in both phenol and 2-

of deuterium from hydrogen *ortho* and *para* to phenolic hydroxy-groups. G.l.c.-mass spectrometric analysis of the product mixture showed deuterium loss from (2) but not from (3), in accord with the expected labelling patterns.

The oxidation of naphthalene by (1) in 1,1,2,2-tetrachloroethane at 110 °C was briefly studied but the product mixture was complex and the yields of phenols consistently small. 2-Naphthol (2.0% based on the dioxide) and 1-naphthol (0.6%) were isolated by t.l.c. The yields are too low to have much mechanistic significance but the predominance of the 2-hydroxy-isomer is interesting (see below).

The product distributions obtained with benzindazole dioxide (1) as oxidant differ significantly from those reported for other, related oxidising systems. Photolytic oxidation<sup>1b</sup> of toluene with pyridazine *N*-oxides (5) gave cresols but, apparently, no benzyl alcohol was formed. Moreover, Jerina *et al.*<sup>2</sup> found that photochemical hydroxylation of [4-<sup>2</sup>H] toluene with pyridine *N*-oxide gave *p*-cresol with 59–60% retention of deuterium. Under similar conditions, anisole gave phenol, 2-hydroxyanisole, and 4-hydroxyanisole, as in our experiments, but 4-hydroxyanisole was the major product and 4-hydroxylation of [4-<sup>2</sup>H] anisole took place with substantial (45%) retention of deuterium. Naphthalene was converted, by irradiation in the presence of pyridine *N*-oxide, into 1,2-epoxy-1,2-dihydronaphthalene and naphthol in low yield. The latter was largely (*ca.* 95%) the 1-isomer and was probably formed *via* the epoxide. An earlier experiment<sup>1b</sup> with the pyridazine oxides (5) gave 1- and 2-hydroxynaphthalene in the ratio 1:0.8. The vapour-phase hydroxylation of benzenoid systems by triplet oxygen atoms, O(<sup>3</sup>P), generated by mercury-sensitised photolysis of nitrous oxide, has also been reported.<sup>5</sup> As in our oxidations, nuclear hydroxylation of toluene occurred predominantly *ortho* to the methyl group but *para* attack was the next most favoured process and there was little if any attack at the methyl carbon. Anisole underwent hydroxylation<sup>5c</sup> *ortho*, *meta*, and *para* with rate ratios 64:2:14; phenol was also formed but this may have arisen, at least in part, by direct photolysis of anisole. Oxidation of benzene derivatives by singlet oxygen, O(<sup>1</sup>D), does not appear to have been studied.<sup>6</sup> Fenton's reagent, a source of hydroxyl radicals, oxidises toluene<sup>7</sup> with formation of substantial amounts of benzyl alcohol and benzaldehyde as well as cresols. However benzoic acid is also produced in quantity and bibenzyl is a characteristic, major product of this radical process.

Thermal oxidations with benzindazole dioxide (1) do not therefore conform with any easily recognisable mechanistic type and indeed the thermal instability of the dioxide is unusual. Certainly, oxygen atom transfer

thermally from heteroaromatic di-*N*-oxides is not a general phenomenon at moderate temperatures. For example, we find that the cinnoline dioxide<sup>8</sup> (6) is stable in anisole at 155 °C for up to 48 h. A search for *N*-oxides less stable than (1) and with superior solubility properties appears worthwhile since thermal oxygen atom transfer is rare and may have preparative value.

## EXPERIMENTAL

*Benz[cd]indazole 1,2-Dioxide*.—This was prepared from 1,8-diaminonaphthalene by using 4-nitroperbenzoic<sup>3</sup> or, more conveniently, 3-chloroperbenzoic acid in chloroform. The latter oxidant (*ca.* 8.4 mol. equiv.) gave the dioxide in 45% yield.

*4-Methylcinnoline 1,2-Dioxide*.—Oxidation of 4-methylcinnoline with trifluoroperacetic rather than peracetic<sup>8</sup> acid gave better yields of the dioxide. 4-Methylcinnoline (2 g) was heated at 80 °C for 20 h in trifluoroacetic acid (10 ml) containing aqueous 27% hydrogen peroxide (10 ml). Work-up and chromatography in the usual way<sup>8</sup> gave the dioxide (706 mg, m.p. 165–173° (decomp.) (lit.,<sup>8</sup> 171–172°) (Found: C, 61.5; H, 4.75; N, 16.1. Calc. for C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>: C, 61.4; H, 4.6; N, 15.9%), accompanied by lesser amounts of the isomeric mono-oxides.

*Deuterium- and Tritium-labelled Derivatives*.—[4-<sup>3</sup>H]Toluene was prepared from 4-iodotoluene as before.<sup>9</sup> [4-<sup>2</sup>H]Anisole (88% <sup>2</sup>H<sub>1</sub>) was obtained similarly by addition of deuterium oxide to an ethereal solution of 4-methoxyphenylmagnesium iodide. Heating 4-hydroxyanisole (100 mg) in D<sub>2</sub>O (0.5 ml) containing triethylamine (81 mg) under nitrogen in a sealed tube at 120 °C for 24 h gave 4-hydroxy[3,5-<sup>2</sup>H<sub>2</sub>]anisole. The same conditions were used for the removal of deuterium from the deuterated hydroxylation products of anisole (see main text and below). 4-Hydroxy[3,5-<sup>3</sup>H<sub>2</sub>]toluene was prepared similarly by using tritiated water.

*Thermolysis of Benz[cd]indazole 1,2-Dioxide in Toluene*.—The dioxide in toluene (1.25 mg ml<sup>-1</sup>) was heated under reflux in the dark under nitrogen. Decomposition of the dioxide was complete (t.l.c. control) in 5 h, the corresponding mono-oxide being the major product. G.l.c. (10% tricresyl phosphate on Chromosorb W at 160 °C) revealed products derived from toluene (see main text for yields): *m*- and *p*-cresol were not separable by this system. When benz[cd]indazole 1-oxide was heated in toluene (1 mg ml<sup>-1</sup>) under reflux for 18 h the mixture contained (g.l.c.) no significant amounts of toluene oxidation products.

*Thermolysis of Benz[cd]indazole 1,2-Dioxide in [4-<sup>3</sup>H]-methyl-<sup>14</sup>C]Toluene*.—[4-<sup>3</sup>H]Toluene (*ca.* 4.2 mCi) and [methyl-<sup>14</sup>C]toluene (*ca.* 0.24 mCi) (Radiochemical Centre, Amersham) were mixed and diluted with non-radioactive toluene (final volume 24 ml). Benz[cd]indazole 1,2-dioxide (30 mg) in this doubly labelled toluene (24 ml) was heated under reflux for 5 h as before. Three thermolyses were carried out and the products were analysed for 6 constituents (2 for each thermolysis) by radio-dilution.

(1) Non-radioactive *p*-cresol (40 mg) and benzyl alcohol

<sup>5</sup> (a) G. R. H. Jones and R. J. Cventanović, *Canad. J. Chem.*, 1961, **39**, 2444; (b) G. Boocock and R. J. Cventanović, *ibid.*, p. 2436; (c) E. Grovenstein and A. J. Mosher, *J. Amer. Chem. Soc.*, 1970, **92**, 3810.

<sup>6</sup> See T. H. Varkony, S. Pass, and Y. Mazur, *J.C.S. Chem. Comm.*, 1975, 457; W. B. DeMore, *J. Phys. Chem.*, 1969, **73**, 391.

<sup>7</sup> J. H. Merz and W. A. Waters, *J. Chem. Soc.*, 1949, 2427; J. R. Lindsay Smith and R. O. C. Norman, *ibid.*, 1963, 2897; C. Walling and R. A. Johnston, *J. Amer. Chem. Soc.*, 1975, **97**, 363.

<sup>8</sup> M. H. Palmer and E. R. R. Russell, *J. Chem. Soc. (C)*, 1968, 2621.

<sup>9</sup> W. R. Bowman, W. R. Gretton, and G. W. Kirby, *J.C.S. Perkin I*, 1973, 218.

(50 mg) were added to the reaction mixture and the resulting mixture was chromatographed on neutral alumina (grade III; 30 g). Pentane (100 ml) eluted toluene, which was fractionally distilled for re-use. Ether (150 ml) eluted cresols and benzyl alcohol. The ethereal eluate was extracted with *N*-sodium hydroxide (5 × 8 ml) to remove the cresols, which were isolated by acidification of the aqueous extract and extraction into ether. The original ethereal solution was evaporated to give benzyl alcohol. Derivatives of *p*-cresol and benzyl alcohol were formed by heating in pyridine containing 3,5-dinitrobenzoyl chloride. The derivatives were recrystallised to constant specific activity and  $^3\text{H} : ^{14}\text{C}$  ratio.

(2) *o*-Cresol (40 mg) and benzaldehyde (63 mg) were next added to a thermolysis mixture. Toluene was eluted from alumina (as before) with pentane, benzaldehyde with pentane-ether (5 : 1; 50 ml), and *o*-cresol with ether. Benzaldehyde was purified as the semicarbazone and *o*-cresol as the 3,5-dinitrobenzoate.

(3) Finally, a thermolysis mixture was diluted with *m*-cresol (40 mg) and benzoic acid (56 mg). Toluene and *m*-cresol were eluted from alumina as before. The alumina was washed well with ether then stirred with water (30 ml) containing sodium hydroxide (pH *ca.* 9). Acidification of the aqueous extract and extraction with chloroform gave benzoic acid, which was sublimed and crystallised from water. *m*-Cresol was purified as the 3,5-dinitrobenzoate.

*Control Experiments with 4-Hydroxy[3,5- $^3\text{H}_2$ ]toluene.*—4-Hydroxy[3,5- $^3\text{H}_2$ ]toluene (19 mg) was heated under reflux for 12 h in toluene containing *o*-cresol (0.08 mg ml<sup>-1</sup>), benzyl alcohol (0.25 mg ml<sup>-1</sup>), benzaldehyde (0.09 mg ml<sup>-1</sup>), and benz[*cd*]indazole 1-oxide (1 mg ml<sup>-1</sup>). The *p*-cresol was

isolated (see above) and purified as the 3,5-dinitrobenzoate which showed a tritium activity corresponding to 87% retention of the label. 4-Hydroxy[3,5- $^3\text{H}_2$ ]toluene was converted into the 3,5-dinitrobenzoate, under the standard conditions, with retention of 98% of the tritium.

*Thermolysis of Benz[*cd*]indazole 1,2-Dioxide in the Presence of [4- $^3\text{H}$ ]Anisole.*—[4- $^3\text{H}$ ]Anisole (88%  $^3\text{H}$ ) (2 g), benz[*cd*]indazole 1,2-oxide (100 mg), and 1,1,2,2-tetrachloroethane (1 ml) were heated at 105 °C for 12 h. The cooled mixture was diluted with ether and extracted with 0.5*N*-sodium hydroxide. The extract was acidified and the liberated phenols (86 mg) were extracted into ether. The mixture of phenols was examined (see main text) by g.l.c.—mass spectrometry (3 m column of 7% F-60 on 1% EGSP-Z, temperature programmed from 70 to 130 °C at 4 °C min<sup>-1</sup>; LKB 9000 mass spectrometer).

*Thermolysis of Benz[*cd*]indazole 1,2-Dioxide in the Presence of Naphthalene.*—Naphthalene (4 g), benz[*cd*]indazole 1,2-dioxide (400 mg), and 1,1,2,2-tetrachloroethane (5 ml) were heated at 110 °C for 17 h. The cooled mixture was diluted with ether (100 ml) and extracted with *N*-sodium hydroxide (4 × 25 ml). The alkaline extract was acidified and the liberated naphthols were extracted into ether. Preparative t.l.c. (silica plates developed with pentane-ether, 4 : 1) gave 2-hydroxynaphthalene (6.1 mg) and 1-hydroxynaphthalene (2 mg), identified by m.p. and mixed m.p.

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