Thermal Intramolecular Hydroxylation Reactions involving 5-Nitropyridine *N*-Oxide Derivatives

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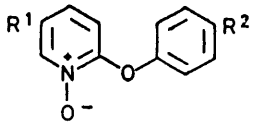
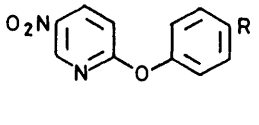
The *N*-oxides of 5-nitro-2-(aryloxy)pyridine, *e.g.* (2), undergo rearrangement on heating in an inert solvent to produce, as the major product, the corresponding 5-nitro-2-(2'-hydroxyaryloxy)pyridine, *e.g.* (4). Competition experiments indicate an intramolecular transfer of oxygen. The product (4) can be cleaved by hydrazine to produce the corresponding pyrocatechol and the scope of the net transformation, phenol to catechol, is briefly explored. Certain metals, in particular vanadium, affect the ratio of phenols produced.

THE enzymic introduction of hydroxy-groups into aliphatic or aromatic compounds is an important biological transformation [1] and, in recent years, many attempts to mimic this process have been described.[2] In particular, aromatic systems are often hydroxylated by use of reactions which exhibit the N.I.H. shift, a process indicative of the formation of intermediates akin to arene oxides.[3] Recently, details of some related hydroxylations, involving heteroaromatic *N*-oxides in photocatalysed hydroxylation reactions, have been published.[4,5] In contrast, thermally-induced hydroxylations involving heteroaromatic *N*-oxides are rare.[6] In this paper we report an example of a system in which oxygen transfer from a pyridine *N*-oxide onto an aromatic ring occurs under thermal conditions.

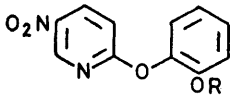
In previous work [7] we reported the photochemical transfer of oxygen from systems of the type (1). In the hope of preparing a system in which the cleavage of the product phenol, of the type (2), would be facilitated, the 5-nitro-substituted derivative (2) was prepared. The nitro-group in this position facilitates nucleophilic aromatic substitutions.[8]



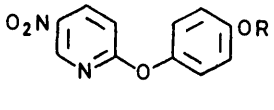
(1) $R^1 = R^2 = H$
(2) $R^1 = NO_2$, $R^2 = H$
(3) $R^1 = NO_2$, $R^2 = Me$
(4) $R^1 = NO_2$, $R^2 = Cl$



(3) R = H
(14) R = Me
(15) R = Cl



(4) R = H
(6) R = Me



(5) R = H
(7) R = Me

5-Nitro-2-phenoxypyridine (3) was prepared by the action of sodium phenoxide, generated *in situ* with sodium hydride and phenol, on 2-chloro-5-nitropyridine in dimethylformamide at 60 °C for 2 h in quantitative yield. Oxidation of the pyridine (3) to its 1-oxide (2) was accomplished with pertrifluoroacetic acid in dichloromethane. The *N*-oxide was an unstable solid which decomposed on heating in the solid state, especially above 140 °C, to yield a complex mixture of products. Attempted photolysis of the *N*-oxide, under a variety of conditions, also gave mixtures and was not investigated in depth.

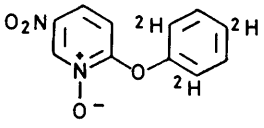
When the thermolysis of the *N*-oxide (2) was performed in inert solvents more selective changes occurred. On heating (2) under reflux in pentachloroethane solution (6 h, 162 °C, 0.1% w/v, under N_2) no *N*-oxide remained and two major products were formed. The reaction mixture was analysed by h.p.l.c. (see Experimental section), the products being compared against the standard, authentic phenols (4) and (5). The reference phenols were prepared by reaction of the appropriate methoxyphenoxide with 2-chloro-5-nitropyridine, as described above, to give the ethers (6) and (7). Removal of the methyl protecting groups, with boron tribromide in dichloromethane,[9] afforded the required phenols.

It was found that the thermolysis of (2) in pentachloroethane gave 36% of the *o*-phenol (4) and 5% of the *p*-hydroxy-compound (5). A similar run, without the blanket nitrogen but just the refluxing solvent vapour, gave 31% and 6% of the phenols (4) and (5) in a 0.1% w/v solution and a ratio of 26% to 4% when the concentration was increased to 1% w/v. Thus an increased concentration lowered the yield of the product phenols. The remaining products from these thermolyses consisted mainly of a polar, tarry substance, which was not investigated further, and small quantities (*ca.* 5%) of the deoxygenated pyridine (3). Although the reference *m*-isomer was not synthesised, no major peaks occurred in the h.p.l.c. traces where this compound would be expected. If present it must be in yields of less than 1%.

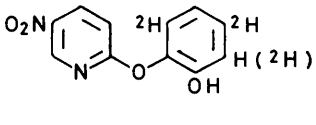
The thermolysis was also attempted at lower temperatures. In dibromoethane at 130 °C the decomposition required over 24 h to approach completion and lower yields of the product phenols were obtained. In dioxan at 100 °C only about 7% of the phenol (4) formed after 36 h. Thus, although decomposition of the *N*-oxide (2) occurs at temperatures as low as 100 °C, this rate is inconveniently slow and side reactions compete with product formation.

The thermal conversion of heteroaromatic *N*-oxides into isomeric phenols has few precedents. One *N*-oxide which has been reported to undergo thermal transfer of oxygen to aromatic solvents is benz[*cd*]indazole-1,2-dioxide.[6] In this case, however, no examples of intramolecular oxygen transfer to bound aromatic groups were reported. Some previous attempts to achieve such oxygen transfer proved unsuccessful.[10]

The formation of the phenols (4) and (5) from the *N*-oxide (2) is of mechanistic interest. The reaction appeared to be intramolecular, since dilution tended to enhance yields and the addition of anisole to the reaction mixture did not affect yields of products. In order to gain evidence for the intermediacy of arene oxides in the oxygen transfer step, the deuteriated derivative (8) was prepared. ^{1}H N.m.r. analysis indicated 96% of the deuterium in the 2′, 4′, and 6′

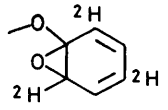


(8)

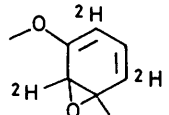


(9)

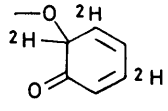
positions. Thermolysis of this, in the manner described above, gave a similar ratio of products from which a sample of the purified, deuteriated phenol (9) was isolated. Analysis of this by both ^{1}H n.m.r. spectroscopy and mass spectroscopy indicated a 35% excess (retention) of deuterium in the product, a figure similar to that observed in the photolysis of 2-([2′,4′,6′-$^2H_3$]-phenoxy)pyridine *N*-oxide.[7] The observed excess of deuterium in the product (9) suggests a shift of the label, as is observed in the enzymic hydroxylation of aromatic substrates, and implies, but does not necessarily prove, the intermediacy of arene oxides. The degree of retention of label was lower than that observed in biological systems. This difference could imply the



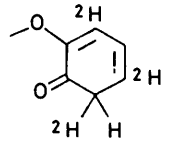
(10)



(11)



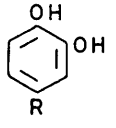
(12)



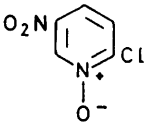
(13)

existence of more than one hydroxylation process leading to (9). Alternatively, if arene oxides are involved, one might expect formation of both the oxides (10) and (11). Of these the former should rearrange to the cyclohexadienone (12), which can only lose deuterium during aromatisation, whilst the latter, (11), rearranging through the isomeric intermediate (13), would give the expected isotopic ratio. In this way the observed level of deuterium retention might depend on the ratio of the two arene oxide intermediates formed during rearrangement.

Cleavage of the pyridyl ether bond was achieved by heating either the pyridine (3) or the phenol (4) with hydrazine hydrate in refluxing methanol for a few minutes, to give 2-hydrazino-5-nitropyridine and phenol and catechol, respectively, in high yield (>80%). The latter reaction completes the conversion of phenol, *via* the ethers (3) and (2) and thermolysis, into catechol in overall 20% yield. In order to check the generality of this four-step procedure it has been applied to two other cases, starting with *p*-cresol and *p*-chlorophenol. Preparation of the corresponding 5-nitropyridyl ethers (14) and (15) and their *N*-oxides (16) and (17) was achieved as for phenol. Thermolysis, of dilute solutions in pentachloroethane, followed directly by liberation of the catechols with hydrazine hydrate, gave 4-methylpyrocatechol (18) (29% overall yield from *p*-cresol) and 4-chloropyrocatechol (19) (9% overall yield from *p*-chlorophenol).



(18) R = Me
(19) R = Cl



(20)

$MoO_5 \cdot 2DMF$

(21)

The above method suffers from the need to prepare the *N*-oxides after formation of the pyridyl ether. Attempts to prepare the phenoxy-derivatives directly from 2-chloro-5-nitropyridine 1-oxide [11] (20) and the phenol gave lower yields of ethers, in the order of 50% for the parent compound (1).

As an alternative to the need to oxidise the pyridine

TABLE

Effect of metal additives on the thermolysis of *N*-oxide (2) [a]

Additive [b]	Yield (4) + (5) (%)	Ratio (4) : (5)	Comments
None	41	7 : 1	
CuO	37	6 : 1	No effect
Cu_2O	30	7 : 1	Slight decrease in yield
$Cu(acac)_2 \cdot H_2O$	25	7 : 1	*ca.* 10% Phenol also produced
V_2O_5	32	1.5 : 1	Ratio affected; rate increase noted [c]
$VO(acac)_2$	25	1.5 : 1	Ratio affected; rate increase noted; [c] phenol produced (8%)
MoO_3	35	11 : 1	Selectivity increased
$Mo(CO)_6$	29	9 : 1	Yield lowered
$W(CO)_6$	36	8 : 1	No effect
Bi_2O_3	40	7 : 1	No effect

[a] 1% w/v solution heated in refluxing pentachloroethane for 5 h under N_2 atmosphere. [b] *ca.* 5 Mol % of metal ion used based on concentration of the *N*-oxide. [c] A reaction time of 1 h was sufficient in these cases.

ether (3) with peracids, followed by thermolysis, use of other oxidants at higher temperatures was briefly investigated. Of these studies only heating the ether (3) in refluxing pentachloroethane in the presence of the molybdenum pentaoxide complex (21) showed any promise, albeit with a low yield. The phenol (4) could be obtained in up to 9% yield by this method.

The effect of some metal ions on the course of the thermolysis reaction was also briefly explored. The results are tabulated and, of these results, the effect of vanadium is noteworthy. This both increased the rate of rearrangement and altered the ratio of phenols produced, tending to increase the proportion of the *p*-isomer.

EXPERIMENTAL

M.p.s were recorded on a Kofler block. All reactions were monitored by t.l.c. (Merck, SiO_2, GF_{254}), generally using acetone–toluene, ethyl acetate–toluene, or ethyl acetate–dichloromethane as eluants. Thermolyses were generally carried out under O_2-free nitrogen. All solvents were purified and dried before use. Known compounds were generally compared by direct comparison with authentic samples. H.p.l.c. analyses were carried out on a 3-ft × $\frac{1}{8}$-in column filled with Corasil II, using isopropyl alcohol–cyclohexane (1.5% v/v) as solvent; flow rates of 1—1.5 ml min^{-1} were employed.

Spectral information was obtained as described previously.[7]

2-Aryloxy-5-nitropyridine 1-Oxides.—The phenol (0.01 mol) was treated with sodium hydride (1.1 mol. equiv.) in anhydrous *NN*-dimethylformamide (DMF) (50 ml) with stirring at 0—20 °C. After evolution of hydrogen ceased, 2-chloro-5-nitropyridine (1.75, 1.0 mol. equiv.) was added and the mixture heated, with stirring, to 60 °C for 2 h. The product was poured into ice–water and extracted with dichloromethane. After drying (Na_2SO_4) and filtering, the solvent was removed *in vacuo* to afford the corresponding 2-aryloxy-5-nitropyridine in almost quantitative yields. Thus 5-nitro-2-phenoxypyridine (2) had m.p. 92—94° (lit.,[12] 93—94°); 5-nitro-2-(4-methylphenoxy)pyridine (16) had m.p. 80° (lit.,[13] 80°); and 5-nitro-2-(4-chlorophenoxy)-pyridine (17) had m.p. 94—95° (lit.,[14] 93—95°).

Oxidation of the 2-aryloxy-5-nitropyridines was accomplished by stirring the ether (0.01 mol) in dichloromethane (100 ml) at room temperature in the presence of freshly prepared pertrifluoroacetic acid (1 mol. equiv.). Oxidations took between 6—16 h to go to completion (t.l.c. assay). The organic solution was washed with aqueous sodium hydrogen carbonate solution until neutral, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford the corresponding *N*-oxides as yellow, thermally unstable products. On storage at room temperature the products generally deteriorated to gummy solids within a few months. Attempted recrystallisation of the *N*-oxides also caused decomposition. Because of their unstable character the compounds were not analysed for their elemental composition. The *N*-oxides were generally prepared as required, or else stored at −5 °C for short periods before use. When necessary, the *N*-oxides could be separated from the starting pyridine by preparative t.l.c. (elution with ethyl acetate–dichloromethane mixtures).

The alternative route to the 2-aryloxy-5-nitropyridine ethers involved reaction of 2-chloro-5-nitropyridine *N*-oxide[11] (20) with the appropriate phenol in dichloromethane, using triethylamine (1 mol. equiv.) as base. After stirring these mixtures for 2 h at room temperature deep red solutions formed; these were washed with water (3 ×), dried, and evaporated to dryness *in vacuo*. From the mixture of products the desired ethers could be isolated by preparative t.l.c. The highest yield of (2) obtained in this manner was 51%. The former method gave overall yields of the *N*-oxides in the range 70—75%.

Thermolysis of 5-Nitro-2-phenoxypyridine 1-Oxide (2).—A solution of the *N*-oxide (0.1% w/v) in pentachloroethane was heated at reflux (162 °C) for 6 h under nitrogen. T.l.c. indicated complete disappearance of the starting material with relatively clean formation of less polar products; only a small amount of highly polar material formed, in contrast to the results obtained from attempted photolysis. H.p.l.c. analysis of the reaction mixture indicated formation of the phenols (4) (36%) and (5) (5%). Isolation, by preparative t.l.c., confirmed these yields. In the absence of nitrogen the product ratio (4) : (5) was 31 : 6 and, from a 1% w/v solution the ratio was 6 : 1. H.p.l.c. analysis also indicated the formation of small quantities (4—6% various runs) of deoxygenated material, (3), which was absent in the starting material. Formation of 5-nitro-2-(3-hydroxyphenoxy)pyridine was not investigated in this study. H.p.l.c. analysis also indicated formation of varying, small quantities of more polar materials amongst the reaction products, although these were not characterised.

A similar product ratio was observed in different solvents; in general lower boiling solvents required increased reaction times, *e.g.* 24 h in 1,2-dibromomethane (130 °C). The presence of 25% v/v anisole in a reaction in pentachloroethane made no substantial difference to the result. In dioxan (101 °C), 7% of the phenol (4) formed after 36 h and only traces of compounds (5) (< 1%) could be detected.

5-Nitro-2-(2-hydroxyphenoxyl)pyridine (4).—Guaiacol (0.01 mol) was treated with sodium hydride in DMF and 2-chloro-5-nitropyridine, as described above, to afford 5-nitro-2-(2-*methoxyphenoxy*)*pyridine* (6) (85%), m.p. 124—125°, $\nu_{max.}$ (Nujol) 1 600, 1 570, 1 500, 1 350, 1 270, 1 250, 1 180, 1 100, and 760 cm^{-1}, τ 6.23 (3 H, s), 2.8 (5 H, m), 1.51 (1 H, m), and 0.97 (1 H, d, *J* 3 Hz) (Found: C, 58.5; H, 4.1; N, 11.4. $C_{12}H_{10}N_2O_4$ requires C, 58.5; H, 4.0; N, 11.4%).

Demethylation of the methyl ether[9] was carried out in dichloromethane. Boron tribromide (2 mol. equiv.) was added at room temperature and the solution was kept, protected from moisture, overnight before addition of water, neutralisation with sodium hydrogen carbonate, and separation of the layers. After further washing with water the organic layer was dried and evaporated to dryness to afford the *title phenol* (85%), m.p. 105° (from EtOAc), $\nu_{max.}$ (Nujol) 3 360, 1 590, 1 570, 1 340, 1 260, 1 170, 1 110, 1 090, and 750 cm^{-1}, τ 4.4 (1 H, br s), 2.8 (5 H, m), 1.44 (H, dd, *J* 9, 3 Hz), and 0.95 (1 H, d, *J* 3 Hz) (Found: C, 56.7; H, 3.4; N, 11.6. $C_{11}H_8N_2O_4$ requires C, 56.9; H, 3.5; N, 12.1%).

5-Nitro-2-(4-hydroxyphenoxy)pyridine (5).—This was prepared in a similar manner to the 2-hydroxyphenoxy ether but using quinol monomethyl ether as starting material. *5-Nitro-2-(4-methoxyphenoxy)pyridine* (7) had m.p. 117—118°, $\nu_{max.}$ 1 590, 1 580, 1 500, 1 350, 1 230, 1 180, 1 110, 1 000, 830, and 760 cm^{-1}, τ 6.12 (3 H, s), 2.9 (5 H, m), 1.47 (1 H, dd, *J* 9, 3 Hz), and 0.88 (1 H, d, *J* 3 Hz) (Found: C,

58.5; H, 4.1; N, 11.3. $C_{12}H_{10}N_2O_4$ requires C, 58.5; H, 4.1; N, 11.4%). 5-*Nitro*-2-(4-*hydroxyphenoxypyridine*) (5) had m.p. 173—175°, $\nu_{max.}$ (Nujol) 3 400, 1 590, 1 570, 1500, 1 300, 1 250, 1 185, 1 115, 1 000, 890, and 840 cm^{-1}, τ 2.95 (5 H, m), 1.50 (1 H, dd, *J* 3, 9 Hz), 0.95 (1 H, d, *J* 3 Hz) (Found: C, 56.6; H, 3.5; N, 11.8. $C_{11}H_8N_2O_4$ requires C, 56.9; H, 3.5; N, 12.1%).

Reaction of 5-*Nitro*-2-*pyridyl Ethers with Hydrazine.*—A solution of the pyridyl ether in methanol (5% w/v) was heated to reflux in the presence of hydrazine hydrate (1 mol. equiv.). After 45 min the mixture was cooled and the green-yellow precipitate of 2-hydrazino-5-nitropyridine was removed by filtration. Removal of the solvent and either base then acid extraction of the phenol, or preparative t.l.c., afforded the desired phenol. In this manner the 2-hydroxyphenoxy-ether (4) gave pyrocatechol (82%). When the freshly prepared *N*-oxide (2) was heated and the reaction mixture, after removal of solvent, directly treated with methanolic hydrazine, pyrocatechol was isolated in 20% overall yield from phenol.

Thermolysis of the N-*Oxides* (16) *and* (17).—The freshly prepared *N*-oxides were separately thermolysed in refluxing pentachloroethane for 6 h. After removal of solvents *in vacuo* the residues were taken up in methanol and treated with hydrazine. The catechols were isolated by preparative t.l.c. In this manner the *N*-oxide (16) afforded 3,4-dihydroxytoluene (18) (32% overall yield from *p*-cresol), m.p. and mixed m.p. 65°. The *N*-oxide (17) gave 4-chlorocatechol (19), m.p. 88° (lit.,[15] 88°).

Preparation and Reaction of the [$^2H_3$]-*ether* (8).—The ether was prepared from 2-chloro-5-nitropyridine and 2,4,6-[$^2H_3$]phenol [16] in the manner described above. ^1H N.m.r. and mass spectral analysis indicated at least 94% of the deuterium in the *o*- and *p*-positions of the phenol moiety. Oxidation to the *N*-oxide was carried out with pertrifluoroacetic acid in dichloromethane and the product was checked for retention of deuterium by n.m.r. spectroscopy. Thermolysis of the *N*-oxide in pentachloroethane was followed by isolation of the *ortho*-phenol fraction by preparative h.p.l.c. The retention of deuterium in the product was analysed by mass spectroscopy and indicated a 35% excess of one deuterium atom (*i.e.* 2.35 atoms) in the product (9). In the ^1H n.m.r. spectrum of (9) the protons of the pyridine ring at positions 4 and 6 appeared downfield of those at position 3 and in the phenol moiety; from the relative areas of these peaks a 30—45% deuterium retention in the product (9) was observed.

Use of Metal Additives.—The thermolysis of (2) was carried out under the normal conditions, under nitrogen, except that portions of the appropriate catalyst (see Table) were added. The products were analysed by quantitative h.p.l.c.

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