Intramolecular Aromatic Hydroxylation *via* Irradiation of Pyridine *N*-Oxide Derivatives

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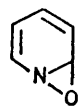
The photochemical behaviour of 2-benzyl-, 2-phenethyl-, and 2-phenoxy-pyridine *N*-oxides is reported. In the presence of boron trifluoride rearrangement reactions, involving migration of oxygen around the pyridine ring, are inhibited, resulting in an increase of hydroxylation of the attached phenyl system. The mechanism of the aromatic hydroxylation reaction is shown to involve transient formation of benzene oxides.

CONSIDERABLE interest has recently been shown in chemical systems which mimic the behaviour of the mono-oxygenase group of enzymes. Model processes that have been studied include the photolysis of nitrous oxide,[1] reactions involving molecular oxygen and metal ions (*e.g.* the Udenfriend system [2]), metal-catalysed decomposition of peroxides,[3] oxidations by peroxy-acids,[4] oxidations by chromyl species,[5] photolysis of diazoalkanes in oxygen,[6] and photolysis of heteroaromatic *N*-oxides.[7] Of these, the last named reactions have proven to be most similar in their chemical behaviour to the biological systems.[8] Thus, irradiation of pyridine, pyridazine, and pyrazine *N*-oxides in aromatic solvents produces phenols;[8] these reactions also exhibit the *para* to *meta* shift of label (the N.I.H. shift) when [4-^{2}H]anisole is hydroxylated. The photolysis of pyridine 1-oxide in various substituted aromatic solvents gives deuterium retention figures similar to those obtained by the hydroxylation of the same compounds by microsomal concentrates.[8] Although of mechanistic interest, the possible synthetic utility of hydroxylation reactions involving heteroaromatic *N*-oxides is severely limited, both by the tendency of such systems to undergo alternative photochemical reactions, and by the non-selective nature of the hydroxylation process. The results of current attempts to overcome these problems, and to explore the possibility of regioselective control of aromatic hydroxylations by utilising substituted pyridine *N*-oxides, are described in this paper.

RESULTS AND DISCUSSION

It has been reported that the photolysis of pyridine 1-oxide, in benzene solution at room temperature, affords phenol;[7] in one case [7b] a yield of 15% was recorded. Attempts to repeat these reactions, in a preparative manner, consistently gave phenol but only in yields of $<1\%$. The major products arose, formally, from the rearrangement product (1) leading to ring expansion, ring contraction, and further oxygen migration around the pyridine nucleus.[9] Considerable amounts of tarry products were also formed and, despite



(1)

efforts to the contrary (changing temperature, light sources, concentration, and addition of inert solvents), these tended to obliterate light input into the reactors; in the preparative runs some starting *N*-oxide always remained ($<20\%$) in the product. Addition of triplet sensitisers (*e.g.* benzophenone) to the reactants did not alter the major reaction profile.

Since the array of products arises mainly from the rearrangement intermediate (1), methods of suppressing this photochemical pathway, by complexation, were sought. It is known that pyridine *N*-oxide forms a stable 1 : 1 complex with boron trifluoride [10] and therefore a brief photochemical examination of this material was conducted. Whilst this work was in progress, Hata *et al.* independently reported [11] that in the presence of a large excess of boron trifluoride the photochemical behaviour of heteroaromatic *N*-oxides is always less complicated, and high yields of the deoxygenated bases can be obtained. In these studies, however, the fate of the oxygen atom was not determined and no mechanistic interpretation of the results was given. We believe the function of the Lewis acid is to bind the nucleophilic oxygen, and thus inhibit the undesired rearrangement to oxaziridine and its congeners.

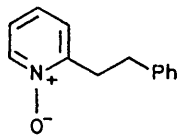
Irradiation of the 1 : 1 pyridine 1-oxide–boron trifluoride adduct in benzene–dichloromethane (the limited solubility of the complex precluding the use of pure benzene as solvent) afforded phenol in 7% (isolated) yield, characterised as its 2,4,6-tribromo-derivative. The reaction mixture was very clean, in comparison

[1] T. H. Varkony, S. Pass, and Y. Mazur. *J.C.S. Chem. Comm.*, 1975, 457.
[2] S. Udenfriend, C. J. Clark, J. Axelrod, and B. B. Brodie, *J. Biol. Chem.*, 1954, **208**, 731; B. B. Brodie, J. Axelrod, P. A. Shore, and S. Udenfriend, *ibid.*, p. 741.
[3] C. A. Hamilton and J. P. Friedman, *J. Amer. Chem. Soc.*, 1963, **85**, 1008.
[4] D. M. Jerina, J. W. Daly, and B. Witkop, *Biochemistry*, 1971, **10**, 366; A. Rotman and Y. Mazur, *J. Amer. Chem. Soc.*, 1972, **94**, 6228.
[5] K. B. Sharpless and T. C. Flood, *J. Amer. Chem. Soc.*, 1971, **93**, 2316.
[6] G. A. Hamilton and J. R. Giacin, *J. Amer. Chem. Soc.*, 1966, **88**, 1585.
[7] (*a*) J. Streith, B. Donner, and C. Sigwalt, *Chem. Comm.*, 1967, 979; (*b*) T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Letters*, 1969, 2747.
[8] D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Letters*, 1970, 457.
[9] G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, 1970, **70**, 241.
[10] N. Kuleosky and L. Svenn, *J. Inorg. Nuclear Chem.*, 1965, **27**, 2111.
[11] N. Hata, I. Ono, and M. Kawasaki, *Chem. Letters*, 1975, 25.

with the products produced from the uncomplexed oxide, the quantities of rearrangement products and tar being greatly reduced. Other products included pyridine, which was not estimated quantitatively, as well as some unchanged pyridine 1-oxide. Prolonged irradiation times led to a decrease in phenol yield, probably by subsequent photoreactions involving this product. A similar irradiation, using toluene in place of benzene, afforded benzyl alcohol (10%), *o*-cresol (1.7%), *m*-cresol (0.2%), and *p*-cresol (1.5%). The pyridine 1-oxide–boron trifluoride complex dissolved in anisole to give a deep blue solution. After irradiation *o*-methoxyphenol (7%) and phenol (0.5%) were isolated as the only phenols that could be easily characterised.

The increase in hydroxylation yields and simplification of reaction mixtures by prior formation of the boron trifluoride complex of pyridine 1-oxide was encouraging, although the results for the hydroxylation of toluene indicated a lack of stereoselectivity for the reaction. For this reason it was decided to investigate the behaviour of some compounds where the aromatic substate was held in close proximity to the source of oxygen, *i.e.* to use substituted pyridine 1-oxides. The compounds (2), (6), and (13) were accordingly prepared by standard methods.

Irradiation of 2-phenethylpyridine 1-oxide (2) in dichloromethane afforded the phenol (3) in only 0.6%



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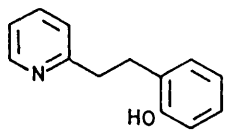

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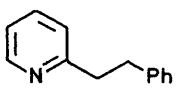

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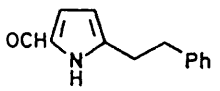
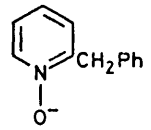


(5)

yield, the product being characterised by comparison with an authentic sample. The major products from this reaction were 2-phenethylpyridine (4) (18%) and the pyrrole (5) (17%). In a similar manner, photolysis of 2-benzylpyridine 1-oxide (6) in dichloromethane solution gave a 4% yield of the corresponding phenol (7), together with the deoxygenated compound 2-benzylpyridine (8) (15%) and the pyrrole (9) (10%); other products were also obtained which were not fully characterised.

A dramatic improvement in these reactions was observed when the corresponding boron trifluoride complexes were utilised. For the boron trifluoride complex of (6), irradiation produced the *o*-substituted phenol (7) in 44% yield identical with an authentic specimen (produced as shown in Scheme 1). In addition, two minor products were identified as 2-benzylpyridine (8) (8%) and phenyl-2-pyridylmethanol (10) (4%). The latter compound was also prepared by the reaction between phenylmagnesium bromide and 2-formylpyridine. Apart from these components the reaction



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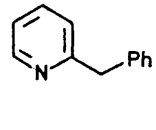

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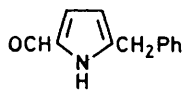

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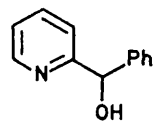

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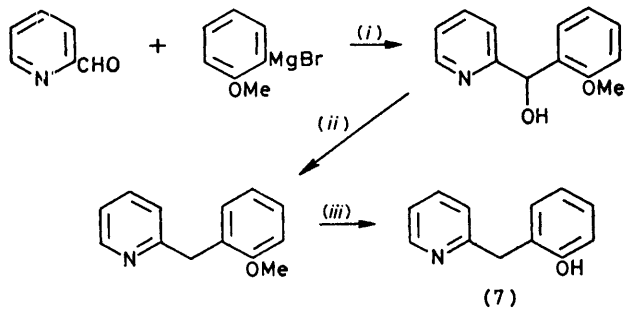
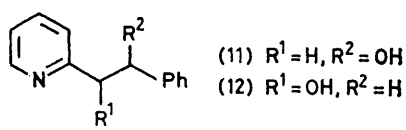
mixture, which was very clean, only afforded starting oxide. Prolonged irradiation times tended to give net decreases in yields of phenolic material. Irradiation of

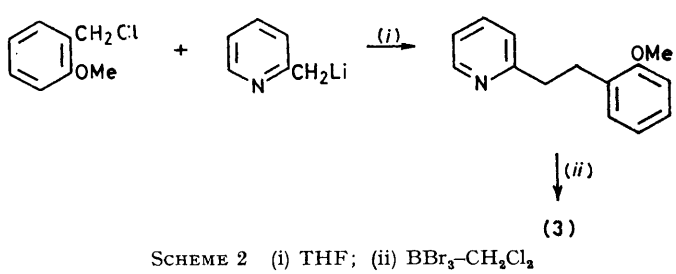


SCHEME 1 (i) THF; (ii) MeLi–ether, TsCl, $LiAlH_4$–ether; (iii) BBr_3–CH_2Cl_2

the boron trifluoride complex of the phenethyl derivative (2) afforded the *o*-substituted phenol (3), phenethylpyridine (4), and the benzylic alcohol (11) in 16, 19, and



15% yields, respectively. Compound (3) was characterised by direct comparison with authentic material prepared as in Scheme 2; the alcohol (11), was identical

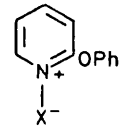


SCHEME 2 (i) THF; (ii) BBr_3–CH_2Cl_2

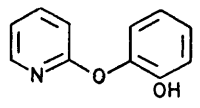
with the product of reaction of 2-pyridylmethyl-lithium and benzaldehyde. To date the isomeric alcohol (12) has not been isolated. If formed the yield must be low, indicating a selectivity for substitution into the

position adjacent to the phenyl, rather than the pyridyl, ring.

It was also found that protonation of the *N*-oxide (6) by mixed acids, such as dilute sulphuric acid, is as effective as formation of the boron trifluoride adduct in inhibiting the rearrangement reactions and favouring the hydroxylations. Thus, photolysis of (6) in aqueous sulphuric acid again afforded the *o*-substituted (7), 2-benzylpyridine (8), and the alcohol (10) in 16, 4, and



(13) X = ^{16}O
(18) X = ^{18}O



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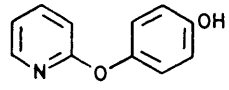

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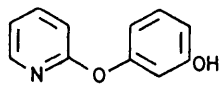
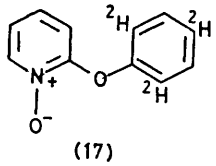


(16)

4% yields, respectively. A considerable quantity of the *N*-oxide (6) was also recovered under these conditions.

Irradiation of the boron trifluoride complex of 2-phenoxypyridine 1-oxide (13) in dichloromethane produced a mixture of 2-phenoxypyridine (20%), the *o*-substituted phenol (14) (44%), and the *p*-substituted phenol (15) (7%) (yields based on starting material consumed) with only traces of the *m*-substituted phenol (16) being detected. The nature of the phenolic products was again confirmed by comparison with authentic compounds made by treating the sodium salt of the appropriate hydroxyanisole derivative with 2-chloropyridine, followed by cleavage of the resulting methyl ether with boron tribromide. The ratio of *ortho*- to *para*-hydroxy derivatives obtained did not vary appreciably when the concentration of the reaction mixture was reduced by a factor of ten, thus suggesting the operation of an intramolecular transfer of oxygen.

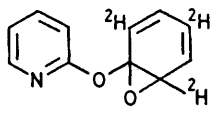
In order to gain an insight into the mechanism of the hydroxylation process some work using isotopically labelled substrates was carried out. Using 2-([2,4,6-$^2H_3$]-phenoxy)pyridine 1-oxide (17) (>95% $^2H_3$ content) the



(17)

o-, *m*-, and *p*-substituted phenols isolated from the reaction mixture by preparative high-pressure liquid chromatography (h.p.l.c.) showed, respectively, 40, 50, and 55% retention of the triple labelling [$^2H_3$]. The hydroxylation reaction thus proceeds with an appreciable N.I.H. shift in all three substituting positions. A preliminary isotopic exchange experiment using a mixture of the [$^2H_3$]oxide (17) and [^{18}O]oxide (18) indicated no cross-over of labels, thus confirming the essentially intramolecular nature of the hydroxylations.

It is proposed, on the basis of these results, that the reaction proceeds by an oxenoid mechanism (*i.e.* transfer of atomic oxygen) leading to either of, or both, the arene oxides (19) and (20), which in turn can rearrange to the cyclohexadienones (21) and (22). Aromatisation of the intermediate (21) can only occur with loss of deuterium, while (22) can lose either a proton or a deuteron and hence give rise to the N.I.H. shift. This possibly explains the deuterium retention in the *ortho*-substitution as compared to the other two positions. From the results of our initial isotope exchange experiment it appears that formation of the *para*-substituted isomer (16) arises from species such as (23) *via* an ' oxygen walk ' process. If this is confirmed one would expect to be able to inhibit this migration, for example by conducting the reaction at different pH values, and



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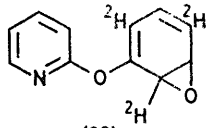

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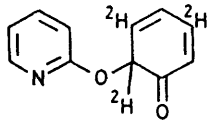

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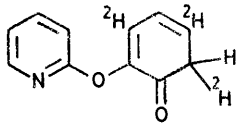

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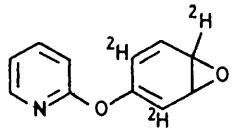

(23)

hence to increase the regioselectivity of the hydroxylation by increasing the amount of *ortho*-hydroxylation.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded in CCl_4 solution using a Perkin-Elmer 157G spectrophotometer. U.v. spectra were recorded on a Pye-Unicam SP 800 instrument using methanolic solutions. N.m.r. spectra were measured in [^2H]chloroform solution, unless otherwise stated, using Varian T60 or JEOL MH100 instruments. Low-resolution mass spectra were recorded on an A.E.I. MS9 spectrometer; high-resolution measurements were performed by the Physicochemical Measurements Unit, Harwell. T.l.c. and p.l.c. were carried out on plates made from Kieselgel GF254 (Merck) using methanol–chloroform (2—8% v/v methanol) unless otherwise indicated. Analyses of reactions were generally monitored by h.p.l.c. using authentic specimens for reference. Certain preparations, including those of

^{18}O-labelled peracids, are deposited as Supplementary Publication No. SUP 22276.*

Pyridine 1-Oxide–Boron Trifluoride Adduct.—Boron trifluoride–diethyl ether complex (1.45 ml) was added to a solution of pyridine 1-oxide (1.07 g) in dry chloroform (20 ml). The mixture was left for 40 min, then evaporated *in vacuo* to afford the adduct (1.84 g, 100%) as a solid, m.p. 97 °C (lit.,[10] 97—98 °C).

Irradiation of the Pyridine 1-Oxide–BF_3 Adduct in Benzene.—The adduct (1.05 g) in benzene (150 ml) and dichloromethane (200 ml) was irradiated in a quartz vessel for 4 h using a low-pressure mercury (254 nm) u.v. source. The resulting solution was concentrated, using a spinning-band column at 20 mmHg, to *ca.* 50 ml and then stirred with alumina (3 g). The solid was filtered off and washed with dichloromethane (6 × 10 ml) and the solution and washings were again concentrated to low bulk. Sodium hydroxide (2.5N; 30 ml) was added and the aqueous layer separated and acidified with dilute hydrochloric acid. The resulting suspension was cooled to 0 °C and bromine added until a permanent colour was observed. The solution was warmed to 45 °C, cooled, treated with N-sodium hydroxide until the precipitated material had dissolved, and washed with dichloromethane (2 × 10 ml). The aqueous layer was acidified and extracted with dichloromethane (5 × 10 ml), and the combined organic layers were dried and evaporated. The residue was separated by preparative t.l.c. to give 2,4,6-tribromophenol (145 mg, 7%) as a solid, m.p. 93 °C (lit., m.p. 95—96 °C), identical (i.r. and n.m.r.) with an authentic specimen. A control experiment showed that the recovery of phenol by this separation procedure was almost quantitative.

Irradiation of the Pyridine 1-Oxide–BF_3 Adduct in Toluene.—This reaction was carried out as above except that toluene was used in place of benzene. The resulting mixture was analysed by h.p.l.c. on Corosil II (Waters' Associates) using 2% ethyl acetate in cyclohexane as eluant. The calculated yields were benzyl alcohol 10.5%, *o*-cresol 1.7%, and *m*- and *p*-cresol 1.7%.

Irradiation of the Pyridine 1-Oxide–BF_3 Adduct in Anisole.—A solution of pyridine 1-oxide–BF_3 adduct (1.06 g) in anisole (100 ml) was irradiated in a quartz vessel (254 nm) for 3 h. The mixture was extracted with N-sodium hydroxide (4 × 20 ml) and the combined aqueous extracts were acidified with dilute hydrochloric acid and extracted with ether (6 × 20 ml). The extracts were dried, and evaporated. The crude product was separated by preparative t.l.c. to give *o*-methoxyphenol (55 mg, 7%), identical (t.l.c., i.r., and n.m.r.) with an authentic sample, and phenol (2 mg, 0.5%) as the only identifiable products.

Boron Trifluoride Complexes.—The boron trifluoride complexes of 2-phenethylpyridine 1-oxide (m.p. 113°) and 2-benzylpyridine 1-oxide (m.p. 140 °C) were prepared by the method described for the preparation of the pyridine 1-oxide complex.

Irradiation of 2-Phenethylpyridine 1-Oxide in Dichloromethane.—2-Phenethylpyridine 1-oxide (184 mg) in dichloromethane (40 ml) was irradiated at 320 nm (125 W lamp) for 2 h. Concentration of the resulting solution gave a brown oil which was separated by preparative t.l.c. into three main components: (*i*) 2-phenethylpyridine (4) (31 mg, 18%); (*ii*) 2-phenethylpyridine 1-oxide (2) (14 mg, 8%) (these compounds were identical with authentic materials); and (*iii*) a compound identified as 5-phenethylpyrrole-2-carbaldehyde (5) (30 mg, 17%), m.p. 80 °C; $\nu_{max.}$ 3 280 (NH) and 1 660 cm^{-1} (C=O); δ 3.02 (4 H, s, CH_2CH_2), 6.12 (1 H, m, pyrrole H), 6.95 (1 H, m, pyrrole H), 7.10—7.43 (5 H, m, ArH), 9.40 (1 H, s, CHO), and 12.00br (1 H, exchanges with D_2O, NH); *m/e* 199 (M^+, 74%), 170 ($[M - CHO]^+$, 25), 108 (100), and 91 (21). 2-[2-(*o*-Hydroxyphenyl)ethyl]pyridine (3) was present in only trace amounts (<1%). Irradiation at 254 nm produced similar results.

Irradiation of 2-Benzylpyridine 1-Oxide (6) in Dichloromethane.—2-Benzylpyridine 1-oxide (257 mg) in dichloromethane (50 ml) was irradiated at 254 nm for 2.5 h. After concentration and separation by preparative t.l.c. (eluting twice with 4 : 1 light petroleum–ethyl acetate, and twice with the normal system), three main compounds were isolated: (*i*) 2-benzylpyridine (8) (11 mg, 5%); (*ii*) 2-(*o*-hydroxybenzyl)pyridine (7) (10 mg, 4%), m.p. 96 °C (both compounds were identical with authentic materials); and (*iii*) a compound identified as 5-benzylpyrrole-2-carbaldehyde (9) (23 mg, 10%), $\nu_{max.}$ 3 280 (NH) and 1 640 (CO) cm^{-1}; δ 4.03 (2 H, s, $ArCH_2Ar'$), 6.20 (1 H, m, pyrrole H), 6.98 (1 H, m, pyrrole H), 7.26 (5 H, m, ArH), 9.43 (1 H, s, CHO), and 12.50br (1 H, exchanges with D_2O, NH).

Irradiation of the 2-Phenethylpyridine 1-Oxide–BF_3 Adduct.—The complex (687 mg) in dichloromethane (100 ml) was irradiated at 254 nm for 4 h. The mixture was evaporated to an oil which was dissolved in chloroform (40 ml); the solution was stirred with alumina (1.5 g) filtered, and evaporated. The residue was taken up in methanol (50 ml) and stirred overnight with charcoal; the solution was filtered and evaporated to give a solid (488 mg). Preparative t.l.c. as above afforded four products: (*i*) unchanged 2-phenethylpyridine 1-oxide (447 mg, 64% recovery); (*ii*) 2-(2-hydroxy-2-phenylethyl)pyridine (11) (25.6 mg, 15%) (identical with authentic material); (*iii*) 2-[2-(*o*-hydroxyphenyl)ethyl]pyridine (3) (26 mg, 16%) (identical with authentic material); and (*iv*) 2-phenethylpyridine (28 mg, 19%).

Irradiation of the 2-Benzylpyridine 1-Oxide–BF_3 Complex.—The complex (0.98 g) in dichloromethane (400 ml) was irradiated at 254 nm for 5 h and worked up as above. Three fractions were obtained: (*i*) 2-benzylpyridine (70 mg, 8%); (*ii*) 2-(*o*-hydroxybenzyl)pyridine (7) (0.43 g, 44%), m.p. 96 °C (identical with an authentic specimen); and (*iii*) 2-(α-hydroxybenzyl)pyridine (10) (40 mg, 4%), m.p. 82 °C (identical with an authentic specimen).

Irradiation of the BF_3 Complex of 2-Phenoxypyridine 1-Oxide.—The complex (279 mg) in dichloromethane (45 ml) was irradiated at 320 nm for 7 h. Evaporation gave an oil which was partitioned between aqueous sodium hydrogen carbonate (30 ml) and chloroform (50 ml). The aqueous layer was separated and extracted with chloroform (3 × 30 ml) and the extracts were combined with the original chloroform layer and evaporated to give a yellow oil (220 mg). The mixture was separated by preparative t.l.c. (eluting twice with 3 : 1 light petroleum–ethyl acetate and once with the normal eluant) into four components: (*i*) 2-phenoxypyridine (31 mg, 20%); (*ii*) 2-(*o*-hydroxyphenoxy)pyridine (14) (69.0 mg, 41%) (13); (*iii*) 2-(*p*-hydroxyphenoxy)pyridine (15) (15 mg, 7%); and (*iv*) 2-phenoxypyridine 1-oxide (13) (38 mg, 18%). All the materials were identical, by chromatography and spectroscopy, with authentic samples.

* See Notice to Authors No. 7 in *J.C.S. Perkin I*, 1977, Index issue.

2-([2,4,6-$^2H_3$]*Phenoxy*)*pyridine* 1-*Oxide* (17).—Sodium hydride (1.2 g, 60% dispersion in mineral oil), suspended in DMF (25 ml), was cooled to 0 °C, and [2,4,6-$^2H_3$]phenol [12] (2.9 g) in DMF (20 ml) was added dropwise. When hydrogen evolution had ceased 2-chloropyridine 1-oxide (3.1 g) in DMF (10 ml) was added and the solution was stirred at 70 °C for 2 h. Most of the DMF was distilled off at 40 mmHg and the residue partitioned between chloroform (50 ml) and aqueous sodium hydroxide (25 ml). The organic phase was separated and the aqueous phase extracted with chloroform (6 × 20 ml). The combined extracts were evaporated and the residual solid purified by column chromatography on alumina (250 g) using dichloromethane–methanol as eluant. The deuteriated phenoxypyridine oxide was obtained as crystals, m.p. 88 °C. The physical properties of this material were identical with those of the unlabelled compound except that the eight-proton n.m.r. multiplet at δ 6.72—7.52 was reduced in intensity by an amount equivalent to three protons and the mass spectrum showed *m/e* 190 (M^+, 0.6%), 189 (2), 174 (60), 173 (52), 172 (100), and 171 (28).

Irradiation of the 2-([2,4,6-$^2H_3$]*Phenoxy*)*pyridine* 1-*Oxide*–BF_3 *Complex*.—The BF_3 complex of the above deuteriated compound (600 mg) in dichloromethane (300 ml) was irradiated at 320 nm for 10 h in a Reading reactor. The solution was evaporated and the residue taken up in 4% methanol–chloroform; the solution was stirred over alumina (1 g) for 40 min, filtered, and evaporated. Part of the oil obtained was separated by preparative t.l.c. into two fractions. One of these (40 mg) contained the *o*-hydroxylated product, the other (18.8 mg) a mixture of the *m*- and *p*-isomers.

The crude fractions were further purified by h.p.l.c. on Porasil T (Waters' Associates) (3% propan-2-ol in cyclohexane as eluant) to give pure *o*-substituted phenol, and two other fractions consisting of a mixture of 90—95% of each of the *m*- or *p*-isomers contaminated with *ca.* 5—10% of the other isomer.

The deuterium content of the three isomers was estimated by mass spectrometry of the molecular-ion region according to Biemann's [13] method. The quantity of triply-labelled phenols produced was calculated as 40% *o*, 50% *m*, and 55% *p*.

Preparation of 2-*Phenoxypyridine* 1-[^{18}O]*Oxide* (18).—2-Phenoxypyridine (598 mg) was added to 1 equivalent of labelled *m*-chloroperbenzoic acid (prepared from 21.3 atom-% $^{18}O_2$) [14] in dichloromethane (50 ml) at room temperature and the solution was stirred for 30 h before a final reflux for 2 h. Water (25 ml) was added, the mixture treated with N-NaOH until alkaline, and the organic phase separated. After further extraction of the aqueous layer with dichloromethane (3 × 20 ml) the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. After preparative t.l.c. crystals of the labelled oxide (18) (350 mg), m.p. 88 °C, were obtained. Mass-spectral analysis was not quantitative but indicated an observed level of 10.8%.

On irradiation of a 1 : 1 mixture of this labelled oxide with the [$^2H_3$]-isomer under the conditions described above, mass spectral examination of the products gave no indication of any [$^2H_3$,^{18}O]-products, *i.e.* there was no exchange of oxygen. The method of analysis, together with the relatively low observed level of [^{18}O] labelling, meant that this result was only a qualitative measure.

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