360. *The Deoxygenation of Heterocyclic* N*-Oxides. Part I. A Novel Oxygen- and Peroxide-catalysed Reduction of Pyridine* 1*-Oxide with Triethyl Phosphite.*

By T. R. Emerson and C. W. Rees.

Pyridine 1-oxide is shown to be reduced to pyridine at room temperature by triethyl phosphite in diethylene glycol diethyl ether if both oxygen and a peroxide, formed adventitiously from the solvent, are present. 4-Methoxypyridine 1-oxide reacts similarly. These reductions do not go to completion even with triethyl phosphite in a hundred-fold excess. The results are discussed and a free-radical chain mechanism is proposed to explain them.

The usefulness and versatility of heterocyclic *N*-oxides in organic synthesis have been amply demonstrated in recent years. An important step in many synthetic procedures is removal of the oxide-oxygen atom, leaving other substituents unaffected, and this has been achieved with a variety of reagents such as phosphorus trichloride and tribromide,[1]

[1] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.

triphenylphosphine,[2] triphenyl,[3] diethyl, and triethyl phosphite,[2] sulphur dioxide,[4] and benzenesulphenyl chloride.[5] However, very little, if anything, is known of the mechanism of these deoxygenations or of the comparative reactivity of different *N*-oxides. Deoxygenation is also of potential chemotherapeutic importance since the pronounced biological activity of many simple heterocyclic *N*-oxides may be closely related to their ability to act as specific oxygen-transfer agents. Examples of this activity are the powerful protection against radiation sickness in mice afforded by quinoxaline di-*N*-oxide,[6] the antibacterial activity, greater in range than that of penicillin, of aspergillic acid,[7] the high activity of 2-methylquinoxaline di-*N*-oxide against amœbiasis in rats,[8] and the effective carcinostatic activity, for the Ehrlich ascites tumour, of phenazine di-*N*-oxide when administered to mice intraperitoneally.[9]

The work to be reported here and later was directed at finding a system in which deoxygenation rates for mono- and di-*N*-oxides of various heterocyclic bases could be compared quantitatively, the mechanism investigated, and any correlation between these rates and biological activity uncovered. As the analytical method employed involved ultraviolet spectrophotometry a deoxygenating agent and a solvent transparent in this region were preferred. Triethyl phosphite was chosen for the former and since there was an indication that high temperatures would be necessary [2] the high-boiling diethylene glycol diethyl ether, in which the polar *N*-oxides are soluble, was chosen for the latter. However, pyridine 1-oxide was found to react with triethyl phosphite in this solvent at room temperature, and this unexpectedly rapid reaction was then investigated in some detail.

Experimental

The Unicam spectrophotometer SP. 500 and Perkin–Elmer Vapor Fraktometer were used.

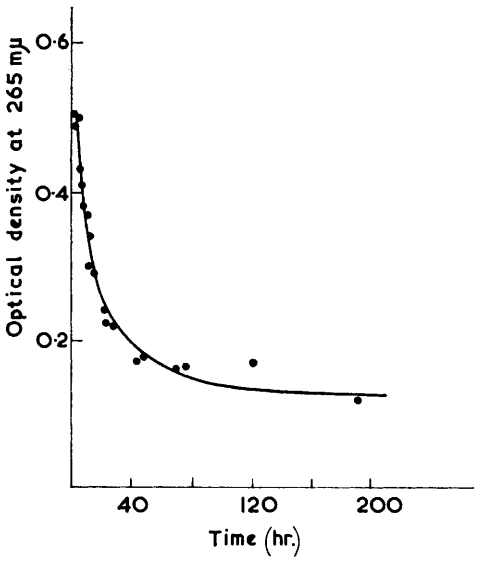
Materials.—Pyridine 1-oxide, 4-nitropyridine 1-oxide, and 4-nitropyridine were prepared by Ochiai's method.[1] The last was only satisfactorily purified by percolation of a benzene solution through alumina followed by crystallisation from light petroleum (b. p. 60—80°), to give colourless crystals, m. p. 46·5—48° (Found: C, 48·0; H, 3·25. Calc. for $C_5H_4N_2O_2$: C, 48·4; H, 3·25%). Ochiai [1] gives m. p. 50°. 4-Nitropyridine, which decomposes slowly, was stored at low temperature and repurified when necessary by boiling it with light petroleum and recrystallisation of the soluble portion. 4-Methoxypyridine 1-oxide was prepared from 4-nitropyridine 1-oxide and sodium methoxide in methanol: [10] it crystallised from ethyl acetate as the monohydrate, m. p. 80—82° (Found: C, 50·55; H, 6·1. Calc. for $C_6H_7NO_2,H_2O$: C, 50·3; H, 6·3%) (picrate, m. p. 142—144°). Ochiai [1] gives m. p.s 81·5—82·5° and 143—145°, respectively. This oxide was reduced to 4-methoxypyridine, b. p. 75—77°/18 mm., $n_D^{25\cdot2}$ 1·5148, by den Hertog and Combé's method [10] for 4-ethoxypyridine.

Triethyl phosphite (from Albright & Wilson Ltd.) was treated with sodium and set aside overnight. After removal of the sodium the phosphite was distilled and the fraction of b. p. 46—47°/13 mm. was collected. Diethylene glycol diethyl ether (from L. Light & Co. Ltd.) was fractionally distilled through a heated column (40 × 2 cm.) packed with Fenske helices, and the fraction of b. p. 189—190° was collected. This solvent gave no indication of impurity when subjected to gas–liquid chromatography, but was subsequently found to react with sodium, to give a brown gelatinous solid. It was then treated twice with sodium wire and refractionated. Some later batches of solvent were purified by being stored in turn over anhydrous magnesium sulphate, calcium hydride (8 hr.), and fresh calcium hydride (several days), followed by fractionation, as before; finally, the solvent was redistilled under reduced pressure from lithium aluminium hydride in nitrogen.

[2] Ramirez and Aguiar, Abs. Papers, 134th Meeting Amer. Chem. Soc., Sept., 1956, N42.
[3] Hamana, *J. Pharm. Soc. Japan*, 1955, **75**, 139.
[4] Haginiwa and Skiomi, *J. Phar. Soc. Japan*, 1956, **76**, 858.
[5] Furukawa, *Pharm. Bull.* (*Japan*), 1955, **3**, 230.
[6] Haley, Flesher, Veomett, and Vincent, *Proc. Soc. Exp. Biol. Med.*, 1957, **96**, 579.
[7] Newbold and Spring, *J.*, 1947, 373.
[8] Landquist, *J.*, 1953, 2816.
[9] Furst, Klausner, and Cutting, *Nature*, 1959, **184**, 908.
[10] Cf. den Hertog and Combé, *Rec. Trav. chim.*, 1951, **70**, 581.

Kinetic Procedure.—The deoxygenations were followed spectrophotometrically by using the $\lambda_{max.}$ of the *N*-oxides, in 2% v/v diethylene glycol diethyl ether in ethanol, as the analytical wavelength. These were as follows: pyridine 1-oxide, 265 mμ, log ε 4·09 (3·10); 4-methoxypyridine 1-oxide, 269 mμ, log ε 4·22; 4-nitropyridine 1-oxide, 232 and 330 mμ, log ε 3·91 (3·85) and 4·14 respectively; the figures in parentheses are log ε's of the parent bases at the analytical wavelength. The measured extinction was corrected when necessary, by a graphical method, for that due to the product formed. Beer's law was shown to hold over the concentrations concerned.

Separate solutions of the reactants in diethylene glycol diethyl ether were mixed, to give the required concentrations of *N*-oxide (10^{-3}M) and triethyl phosphite (10^{-1}M), in an " automatic " pipette capable of rapidly and repeatedly delivering a fixed volume (2·02 ml.) into separate tubes which were placed in a thermostat bath at the required temperature. At appropriate



Deoxygenation of pyridine 1-oxide with triethyl phosphite in diethylene glycol diethyl ether at 30°.

times the contents were diluted suitably with absolute ethanol and the extinctions measured; this dilution arrested the reaction. In most experiments " blank " solutions (with the triethyl phosphite omitted) were treated identically, and these gave the initial extinctions corresponding to zero time. In certain reactions performed under nitrogen or oxygen the reaction mixture was placed in a thermostat bath in a single vessel equipped for passage of the required gas. Aliquot parts were withdrawn at suitable times and diluted with absolute ethanol, as before. Since it was found that the reactions did not go to completion the full ultraviolet spectrum of the reaction mixture was sometimes measured and compared with that of a mixture of the base and its *N*-oxide in the proportions indicated by the extinction at the analytical wavelength.

Kinetic Results.—Preliminary work showed that pyridine *N*-oxide obeyed Beer's law and was stable at room temperature in diethylene glycol diethyl ether, but was deoxygenated by triethyl phosphite under these conditions. At 85°, however, its solution (10^{-3}M) in this solvent decomposed erratically with or without triethyl phosphite. Pyridine did not react with triethyl phosphite, though it did react with diethyl phosphite, which was not therefore used as a deoxygenating agent.

Reactions in fractionally distilled solvent. For the reactions of pyridine 1-oxide (10^{-3}M) and triethyl phosphite (10^{-1}M) in this solvent at 30°, a plot of extinction at 265 mμ against time is shown in the Figure; this is typical of many similar experiments. The reactions did not go to completion and the spectra of the final solutions agreed well with those of mixtures of pyridine and its *N*-oxide in the required proportions. This formation of a " plateau " after about 70% reaction was characteristic of all the triethyl phosphite reactions in this solvent. The addition of pyridine (10^{-3}M) did not affect the rate or characteristics of the reaction, nor did pyridine react with the *N*-oxide in the absence of triethyl phosphite.

After 48 hr., when the reaction "plateau" had been reached, further additions of the *N*-oxide to the reaction mixture were made, but no more deoxygenation occurred, the fresh *N*-oxide being unchanged. Triethyl phosphite (2×10^{-1}M), after storage at 30° for 48 hr., gave the normal rate of reaction with pyridine 1-oxide, but after 48 hours' reaction further additions of *N*-oxide remained unchanged, as before. Vapour-phase chromatography showed an increase of from 1% to only 1·5% in the concentration of triethyl phosphate in triethyl phosphite after air was drawn through the phosphite for 90 min.

4-Methoxypyridine 1-oxide was deoxygenated with triethyl phosphite very similarly to pyridine 1-oxide. 4-Nitropyridine 1-oxide was deoxygenated more slowly (8% in 24 hr.) and when pyridine 1-oxide was added after 48 hr. to this reaction the pyridine 1-oxide was deoxygenated normally.

When reactions were conducted in an atmosphere of nitrogen no deoxygenation took place; if the solution was exposed to the air or, better, if air or oxygen was passed through it, deoxygenation began. Small amounts of water (*ca.* 1%) added to the reaction mixture under nitrogen did not initiate reaction.

Reactions in sodium-treated solvent. When the solvent used in the experiments just described was purified with sodium and freshly distilled, very little or no reaction occurred between the *N*-oxides and triethyl phosphite. Addition of water to the reaction mixture had no effect. Deoxygenation did proceed, however, when a small amount of the earlier batch of solvent was added to the reaction mixture.

Treatment of the different batches of solvent with potassium iodide and acetic acid revealed that the old stock, and standard solutions of reactants in it, were heavily peroxidised, whilst

Deoxygenation of pyridine 1-oxide (10^{-3}M) with triethyl phosphite (10^{-1}M) in diethylene glycol diethyl ether at 30°.

	Treatment of the solvent	Time (hr.)	Reaction (%)
1.	Old stock, fractionally distilled	24	60
		48	67
2.	New stock, fractionally distilled	24	40
3.	Treated with sodium and freshly distilled	23	5
4a.	As for 3, but with little water added	23	0
b.	As for 3, but with some old stock solvent (1) added	24	10
c.	As for 3, but after passing oxygen through for 3 days at room temp.	24	15
d.	As for 3, but after passing oxygen and irradiation (U.V.) for 18 hr. at room temp.	24	16
5.	As for 3, but after passing oxygen and irradiation (U.V.) for 72 hr. and then dilution with peroxide-free solvent to give the following approximate concentrations of active oxygen:		
	$3·5 \times 10^{-2}$ g.-atom: run 1	24	43
		48	60
	run 2	24	53
		48	68
	$7·0 \times 10^{-2}$ g.-atom	48	42
		66	56
	$7·5 \times 10^{-2}$ g.-atom	24	33
		48	34
6a.	As for 1, but under nitrogen	31	0
	then opened to air for 64 hr.	95	65
b.	As for 5 ($3·5 \times 10^{-2}$ g.-atom of active oxygen, but under nitrogen)	24	4
	then opened to air for 18 hr.	42	40 *
	Parallel run not under nitrogen	24	50

* In one, anomalous, experiment similar to this, the reaction did not proceed on opening to the air.

that which had been freshly treated with sodium and distilled, was not. The latter could be re-peroxidised slowly by passing oxygen through it, and rapidly if the solvent was simultaneously irradiated with ultraviolet light. The peroxide concentration, expressed in g.-atoms of active oxygen, was determined by titration of the liberated iodine with sodium thiosulphate. A summary of representative results for various treatments of the solvent or reaction mixture is presented in the Table.

Pyridine 1-oxide (10^{-3}M) in fairly heavily peroxidised solvent ($4·6 \times 10^{-2}$ g.-atom of active oxygen) was unchanged after 86 hr. at 30°, and also after 64 hr. at 30° in the presence of triethyl phosphate (10^{-1}M).

Reactions at higher temperatures and with other reagents. At 85° and 100° deoxygenations were much more erratic, " blank " decompositions were important being sometimes faster than the reaction with phosphite, and the reaction mixtures developed considerable absorption in the ultraviolet region additional to that due to pyridine and its *N*-oxide. These reactions at temperatures above 30° were not investigated further.

Preliminary experiments with pyridine 1-oxide (10^{-3}M) and diethyl sulphide, tetrahydrothiophen, or dimethyl sulphoxide (all 10^{-1}M) as deoxygenating agent, in diethylene glycol diethyl ether from 30° to 80°, showed that in all cases the reactions were much slower than with triethyl phosphite and were as slow as, or slower than, the " blank " *N*-oxide decompositions, and moreover these decompositions were very erratic.

Discussion

The unexpected reaction between pyridine 1-oxide and triethyl phosphite in diethylene glycol diethyl ether at room temperature exhibits certain unusual features. Its rate was not very reproducible and depended markedly on the history of the solvent. It was usually *ca.* 70% complete in 48 hr., after which the rate dropped rapidly; at this stage the ultraviolet spectrum of the mixture was identical with that of a synthetic mixture of pyridine and its *N*-oxide in the appropriate proportions. Addition of pyridine had no effect upon the rate or the final extent of the reaction which was not, therefore, inhibited by this product, nor was a position of equilibrium attained.

In spite of the hundred-fold excess of triethyl phosphite, further quantities of the *N*-oxide, added after 48 hr. when the initial reaction had virtually ceased, were not deoxygenated. This was not due to spontaneous decomposition of the phosphite since this reacted normally after storage at 30° for 48 hr. in the solvent. 4-Methoxypyridine 1-oxide behaved like pyridine 1-oxide, but the 4-nitro-compound was deoxygenated much more slowly, and if, after 48 hr., pyridine 1-oxide was added to this reaction mixture it was deoxygenated at the normal rate. Thus it appears that there was present a small amount of a reactive compound, essential for reaction under these mild conditions, which was consumed as the reaction proceeded. Further, this substance appeared to be removed when the solvent was freshly treated with sodium and distilled, since then deoxygenation was either very slow or did not occur at all. This lack of reactivity was not due to the dryness of the solvent since small additions of water were without effect, but addition of a small amount of previous batches of solvent not purified with sodium caused the reaction to proceed once more. The important difference between these batches of solvent lay in their peroxide content; diethylene glycol diethyl ether is reported to form peroxides readily.[11] Deoxygenation was rapid in heavily peroxidised solvent, slower when the peroxide concentration was reduced by distillation and fresh use of the solvent, and very slow when the peroxide was almost all destroyed. The reaction proceeded normally again when the most highly purified solvent was re-peroxidised by exposure to oxygen and ultraviolet light. However, attempts to initiate deoxygenation in peroxide-free solvent by addition of di-t-butyl peroxide were unsuccessful, presumably because this peroxide is too stable at 30°.

Reactions performed under nitrogen, with later admission of oxygen or air, showed that oxygen was also necessary for deoxygenation at room temperature, even in the most heavily peroxidised solvent. It was shown, by titration, that the standard procedure for removing dissolved oxygen by displacement with nitrogen did not decompose the peroxides in the solvent. Little is known of the nature of the peroxides, conveniently formulated as ROOR, involved in these reactions. They are unlikely to be hydroperoxides, since these react almost instantaneously with triethyl phosphite even at low temperatures,[12,13] and would thus be destroyed at the beginning of our reactions where phosphite is in large

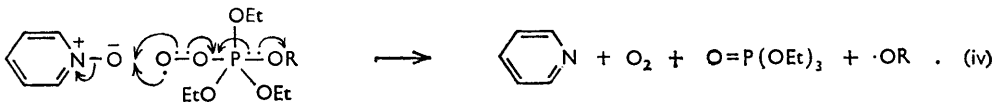
[11] Ramsey and Aldridge, *J. Amer. Chem. Soc.*, 1955, **77**, 2561.
[12] Walling and Rabinowitz, *J. Amer. Chem. Soc.*, 1959, **81**, 1243.
[13] Denney, Goodyear, and Goldstein, *J. Amer. Chem. Soc.*, 1960, **82**, 1393.

excess. Indeed, when our solvent was very heavily peroxidised by prolonged exposure to ultraviolet light and oxygen, hydroperoxides were presumably formed since addition of triethyl phosphite then resulted in a rapid exothermic reaction. The peroxides normally present reacted rapidly with cold potassium iodide solution and must presumably be reactive enough to provide some free radicals at room temperature, as the need for both oxygen and peroxide for deoxygenation strongly suggests a free-radical mechanism, in spite of the polar nature of the *N*-oxides. To account for all the known facts the free-radical mechanism (i—iv) is proposed.

$$ROOR \longrightarrow 2RO\cdot \quad \text{(i)}$$

$$RO\cdot + (EtO)_3P \longrightarrow (EtO)_3\dot{P}(OR) \quad \text{(ii)}$$

$$(EtO)_3\dot{P}(OR) + O_2 \longrightarrow (EtO)_3(RO)POO\cdot \quad \text{(iii)}$$

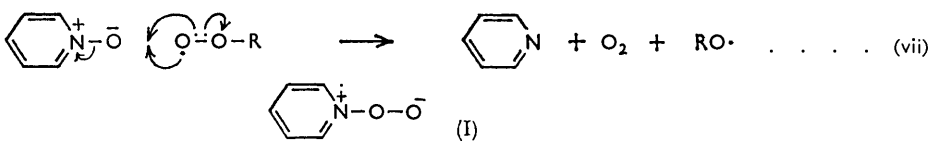


(iv)

Formation of the phosphoranyl radical in stage (ii) has been discussed by Walling and Rabinowitz [12] for the reaction of triethyl phosphite with alkoxy-radicals; triethyl phosphite has also been shown to be very reactive towards other free radicals.[12,14] This phosphoranyl radical may decompose into triethyl phosphate and a new radical, R·, capable of reacting with oxygen,[12] and an alternative mechanism (v—vii) for deoxygenation is then possible.

$$(EtO)_3\dot{P}(OR) \longrightarrow (EtO)_3P{=}O + R\cdot \quad \text{(v)}$$

$$R\cdot + O_2 \longrightarrow ROO\cdot \quad \text{(vi)}$$



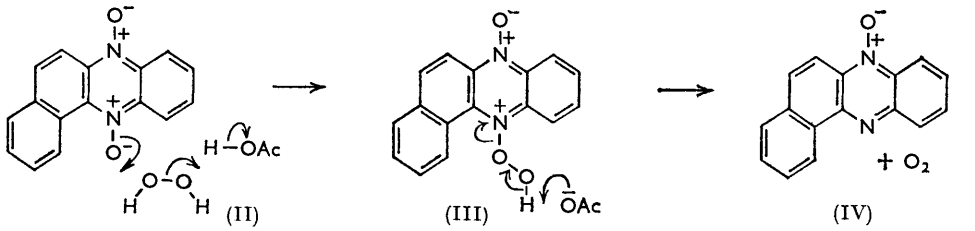
(vii)

Stage (iv) [or (vii)] could proceed by the homolysis shown or could involve the intermediate (I) resulting from nucleophilic attack of the peroxy-radical by the *N*-oxide. In both of the above reaction schemes oxygen is regenerated, in agreement with the finding that little is required to sustain the reaction, and so apparently is the radical RO·. However, more than a trace of peroxide was required for appreciable reaction rate and, moreover, the deoxygenation rate invariably fell off rapidly after *ca.* 70% reaction. Both these facts indicate a loss of the chain-carrying radical RO· and this loss must in some way involve the *N*-oxide, since in its absence the reducing power of the medium is undiminished on storage at 30°. A possible explanation is that in its regeneration, in steps (iv) or (vii), the radical RO· undergoes decomposition or rearrangement to a new radical which cannot take part in chain propagation. Such a transformation of the radical RO· is reasonable since the peroxide which generates it is formed from the aliphatic polyether solvent and probably has an essentially hemiacetal or acetal structure; [15] various modes of decomposition or rearrangement of the radical can then be envisaged.

The complexity of the reaction between pyridine 1-oxide and triethyl phosphite in diethylene glycol diethyl ether plainly makes this an unsuitable system for the quantitative comparison of the reactivity of *N*-oxides generally. However, their oxidising action, under such mild conditions, in the presence of both oxygen and peroxides, may well be involved in the protection afforded by quinoxaline di-*N*-oxide against radiation damage *in vivo*.[6]

[14] Kuhn, Doali, and Wellman, *J. Amer. Chem. Soc.*, 1960, **82**, 4792 and references cited therein.
[15] Cheves Walling, " Free Radicals in Solution," Chapman and Hall Ltd., London, 1957, p. 412.

In the form of the conjugate acid (III), an intermediate of type (I) is probably involved in the deoxygenation of benzo[*a*]phenazine 7,12-dioxide (II) to the 7-mono-oxide (IV) by hydrogen peroxide and acetic acid.[16] This reduction does not occur when the hydrogen



peroxide is omitted. Regeneration of the di-*N*-oxide, which would normally occur under these conditions, is here inhibited by steric hindrance.

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KING'S COLLEGE (UNIVERSITY OF LONDON),
STRAND, LONDON, W.C.2. [*Received, September 26th*, 1961.]

[16] Pachter and Kloetzel, *J. Amer. Chem. Soc.*, 1951, **73**, 4958.