361. *The Deoxygenation of Heterocyclic* N-*Oxides. Part II.*[1] *Polarographic Reduction.*[1]

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Half-wave potentials for the polarographic reduction of a series of heterocyclic mono- and di-*N*-oxides have been measured in buffered aqueous solution of constant ionic strength. The relation between this potential and molecular structure, and the possible intermediates in multi-stage reductions, are discussed briefly.

Di-*N*-oxides are not, in general, more easily reduced than the corresponding mono-*N*-oxides and the half-wave reduction potential does not provide a guide to the reactivity of the $N^+–O^-$ bonds in oxygen-transfer reactions.

Ochiai[2] has shown that certain pyridine 1-oxides are reduced only at considerably more negative potentials than simple aliphatic and aromatic tertiary amine oxides; *e.g.*, dimethylaniline oxide is reduced at —0·7 v (all half-wave potentials quoted refer to the saturated calomel electrode) and pyridine 1-oxide at —1·3 v. This difference is a measure of the greater stability of the *N*-oxide bond when, as in pyridine 1-oxide, its electrons form part of a delocalised system giving rise, in the extreme, to contributions such as (I).[2] The reduction potentials of a series of related *N*-oxides might, similarly, be expected to provide a measure of the comparative reactivity of the *N*-oxide bonds. With this in view several heterocyclic mono- and di-*N*-oxides and the corresponding bases were reduced at the dropping-mercury electrode under standard conditions, and the half-wave potentials were measured. An aqueous buffer of pH 7·0 and ionic strength 0·50M at 25° was chosen since, though better polarograms are often obtained with acidic solutions, we were particularly interested in the forms of our substrates present under physiological conditions.

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[1] Part I, Emerson and Rees, *J.*, preceding paper.

[2] Ochiai, *Proc. Imp. Acad.* (*Tokyo*), 1943, **19**, 307, 574; *J. Org. Chem.*, 1953, **18**, 534.

Previous workers [2–7] have investigated the polarography of heterocyclic *N*-oxides under various conditions but have rarely compared the results with those for the parent base. This is important, since we have found from such comparisons that only in the simplest cases does initial reduction involve the $N^+–O^-$ bond alone, to yield the parent base.

EXPERIMENTAL

M. p. samples were introduced into the block preheated to *ca.* 20° below the m. p.

Materials.—Compounds for polarography were carefully purified and their dilute solutions, which in some cases decompose on storage, were freshly prepared. 4-Nitro- and 4-methoxypyridine and their 1-oxides were prepared as in Part I.[1] Isonicotinic acid 1-oxide, prepared by oxidation of the acid with peracetic acid and crystallised twice from ethanol, had m. p. 271·5—272° (Found: C, 51·95; H, 3·6. Calc. for $C_6H_5NO_3$: C, 51·8; H, 3·6%) (lit.,[8] m. p. 263—265°). Quinoxaline was prepared by Jones and McLaughlin's method [9] and its *N*-oxides by Landquist's method.[10] Quinoxaline 1-oxide could only be completely purified by percolation of a solution in chloroform through a column of charcoal over alumina; final crystallisation from light petroleum gave colourless crystals, m. p. 126·5° (lit.,[10] m. p. 122—123°). 3,4-Benzocinnoline, prepared according to directions of Badger *et al.*,[11] who report m. p. 156°, had m. p. 158·5—160° (Found: C, 79·9; H, 4·7. Calc. for $C_{12}H_8N_2$: C, 80·0; H, 4·5%); the 5-oxide, prepared according to directions of King and King,[12] had m. p. 141—142° (lit.,[12] m. p. 138°) (Found: C, 72·7; H, 3·9. Calc. for $C_{12}H_8N_2O$: C, 73·5; H, 4·1%); the 5,6-dioxide, prepared according to directions of Tauber,[14] who reported m. p. 240°, had m. p. 243° (Found: C, 67·7; H, 3·4. Calc. for $C_{12}H_8N_2O_2$: C, 67·9; H, 3·8%). Phenazine 5-oxide, prepared by Pachter and Kloetzel's method [14] for 2-chlorophenazine 5-oxide, had m. p. 229° (Found: C, 73·3; H, 3·8. Calc. for $C_{12}H_8N_2O$: C, 73·5; H, 4·1%) (Clemo and McIlwain [15] report m. p. 223°). Phenazine 5,10-dioxide, prepared by oxidation of phenazine or its monooxide with peracetic acid, had m. p. 189° (Found: C, 68·5; H, 3·7; N, 12·9. Calc. for $C_{12}H_8N_2O_2$: C, 67·9; H, 3·8; N, 13·2%) (Clemo and McIlwain [15] report m. p. 204°, and Pushkareva *et al.*[16] report two forms with m. p.s 190—191° and 202°).

Polarographic Method.—A Cambridge polarograph with photographic recorder was used; half-wave potentials, measured with respect to the saturated calomel electrode,[17] could be estimated to 0·01 v. The polarographic cell used and the general procedure were conventional. Reductions were measured at 25° ± 1° under nitrogen with *ca.* 10^{-4}M-solutions in an aqueous buffer of pH 7·0 and constant ionic strength (0·50M). The buffer (1 l.) was prepared [18] by dissolving disodium hydrogen phosphate dodecahydrate (58·9 g.), citric acid monohydrate (3·7 g.), and potassium chloride (5·44 g.) in doubly distilled water, and its pH was checked with a glass electrode. The internal resistance of the cell containing this buffer was *ca.* 500 ohms and therefore no correction for the *iR* drop across the cell was required. The apparatus and procedure were checked by reduction of a standard cadmium sulphate solution, good agreement with the accepted value being obtained.[19] Half-wave reduction potentials,

[3] Foffani and Fornasari, *Gazzetta*, 1953, **83**, 1051.

[4] Fornasari and Foffani, *Gazzetta*, 1953, **83**, 1059.

[5] Foffani and Fornasari, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1957, **23**, 62; *Chem. Abs.*, 1959, **53**, 1960.

[6] Sartori and Furlani, *Ann. Chim. (Italy)*, 1955, **45**, 251.

[7] Varyukhina and Pushkareva, *Zhur. obshchei Khim.*, 1956, **26**, 1740; *J. Gen. Chem. (U.S.S.R.)*, 1956, **26**, 1953.

[8] Katritzky, *J.*, 1956, 2404.

[9] Jones and McLaughlin, *Org. Synth.*, 1950, **30**, 86.

[10] Landquist, *J.*, 1953, 2816.

[11] Badger, Seidler, and Thomson, *J.*, 1951, 3207.

[12] King and King, *J.*, 1945, 824.

[13] Tauber, *Ber.*, 1891, **24**, 3081.

[14] Pachter and Kloetzel, *J. Amer. Chem. Soc.*, 1952, **74**, 971.

[15] Clemo and McIlwain, *J.*, 1938, 479.

[16] Pushkareva, Varyukhina, and Kokoshko, *Doklady Akad. Nauk S.S.S.R.*, 1956, **108**, 1098.

[17] Palmer, " Experimental Physical Chemistry," Cambridge University Press, 1949, p. 214.

[18] Elving, Markowitz, and Rosenthal, *Analyt. Chem.*, 1956, **28**, 1179.

[19] Kolthoff and Lingane, " Polarography," Interscience Publ. Inc., New York, 1952, 2nd edn., Vol. I, p. 196.

$E_{\frac{1}{2}}$, were estimated graphically.[20] The values recorded in the Table are the means of from three to seven determinations, agreeing to ±0·01 v. Diffusion currents were not measured.

Half-wave reduction potentials, $-E_{\frac{1}{2}}$ (v), measured against the saturated calomel electrode at 25°.

Pyridine			1·75
Pyridine 1-oxide		1·41	1·73
4-Methoxypyridine			1·80
4-Methoxypyridine 1-oxide		1·56	
4-Nitropyridine	0·28	1·34	
4-Nitropyridine 1-oxide	0·25	1·53	
Isonicotinic acid	1·19	1·56	1·74
Isonicotinic acid 1-oxide	1·21 *	1·39	1·76
Quinoxaline		0·66	1·52 †
Quinoxaline 1-oxide	0·52	0·68	1·52 †
Quinoxaline 1,4-dioxide (II)	0·52	0·68	1·53 †
Phenazine		0·36	
Phenazine 5-oxide	0·19	0·36	1·26 †
Phenazine 5,10-dioxide (III)	0·23	0·36	1·27 †
2,2′-Dinitrobiphenyl	0·42	1·29	
3,4-Benzocinnoline	0·58	1·39 *	
3,4-Benzocinnoline 5-oxide	0·69		
3,4-Benzocinnoline 5,6-dioxide (IV)	0·60	1·36 *	

* Obtained from a wave of very small step height.
† Doubtful values obtained from waves of poor form.

DISCUSSION

The half-wave reduction potential, $E_{\frac{1}{2}}$, for pyridine 1-oxide has been reported by Ochiai [2] to be —1·28 v at pH 3·5 and by Foffani and Fornasari [3] to be —1·4 v at pH 7. No details were given of a second wave; the latter workers attributed the single wave observed to a bivalent reduction of 1-hydroxypyridinium ions to pyridinium ions. At pH 7 we found $E_{\frac{1}{2}} = -1{\cdot}41$ v and a second wave ($E_{\frac{1}{2}} = -1{\cdot}73$ v) very similar to that for pyridine ($E_{\frac{1}{2}} = -1{\cdot}75$ v). 4-Methoxypyridine 1-oxide required a more negative potential than pyridine 1-oxide for its reduction, as would be expected since electron-release by the methoxyl group will hinder approach of electrons to the *para*-position. Isonicotinic acid was reduced more easily than its *N*-oxide, and the effect of the carboxyl group on reduction of the N^+-O^- bond could not, therefore, be determined. Fornasari and Foffani [4] reported $E_{\frac{1}{2}} = -1{\cdot}30$ v at pH 6·85 for this *N*-oxide, but did not record a second wave or a reduction of isonicotinic acid. The nitro-groups of 4-nitropyridine and its *N*-oxide are both reduced first, at low negative potentials. The second wave obtained with this *N*-oxide may correspond to reduction of the N^+-O^- bond, since this step is more difficult than with pyridine 1-oxide, as would be expected if the nitro-group had been reduced, as is usual polarographically, to the electron-releasing hydroxyamino-group. This case is complicated, however, by the possible formation of a series of dimeric reduction products such as have been described [21] for the chemical reduction of 4-nitropyridine 1-oxide.

The polarography of quinoxaline has been fully investigated by Strier and Cavagnol,[22] who postulated reduction to 1,4-dihydroquinoxaline in a two-electron step, at $E_{\frac{1}{2}} = -0{\cdot}676$ v for conditions similar to ours. We found, rather surprisingly, that the mono- and di-*N*-oxide (II) of quinoxaline were reduced at exactly the same half-wave potential (—0·52 v) and in both cases the subsequent waves coincided with those for quinoxaline itself ($E_{\frac{1}{2}} = -0{\cdot}68$ and $-1{\cdot}52$ v). Sartori and Furlani had suggested [6] that quinoxaline 1,4-dioxide (II) was reduced in a four-electron step to quinoxaline, which was later reduced in a two-electron step to dihydroquinoxaline. Although we have not determined the diffusion currents, the ratios of the step-heights we obtained for these three compounds, under identical conditions, fully support this sequence. The ratios are 1·9 : 4·0 for the

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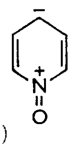
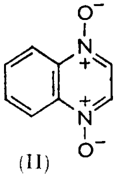
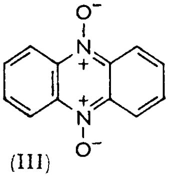
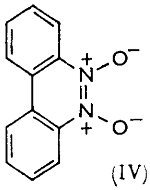
[20] Lewis, *Ind. Chemist*, 1953, **29**, 58.
[21] den Hertog, Henkens, and Van Roon, *Rec. Trav. chim.*, 1952, **71**, 1145.
[22] Strier and Cavagnol, *J. Amer. Chem. Soc.*, 1957, **79**, 4331.

first wave of the mono- and di-oxide, and 2·0 : 2·0 : 1·9 for the quinoxaline wave and the second wave of the mono- and di-oxide, respectively. The waves obtained with these compounds at —1·52 v were of poor form and were presumably catalytic hydrogen waves, the origin of which has been discussed by Strier and Cavagnol [22] who observed them, however, only at lower pH's.


(I)


(II)


(III)


(IV)

Because of the unexpected results with the quinoxaline oxides, phenazine and its mono- and di-*N*-oxide (III) were investigated. These were all more easily reduced than the quinoxalines but the results followed the same pattern, though here the mono-oxide was actually reduced slightly more easily than the di-oxide. The second wave for both oxides corresponded exactly with that for reduction of phenazine to 5,10-dihydrophenazine (cf. ref. 23), so again each *N*-oxide appears to be reduced directly to the base in one step. It is most unlikely that these mono-*N*-oxides would be as reactive as, or more reactive than, the corresponding dioxides in oxygen transfer reactions; indeed, the much greater reactivity of the dioxides towards phosphorus trichloride will be described in Part III. Therefore these polarographic results with the quinoxalines and phenazines show that half-wave reduction potentials of the *N*-oxides do not provide a reliable indication of this chemical reactivity of the $N^+–O^-$ bond.

The polarographic reductions of benzocinnoline and its mono- and di-*N*-oxide (IV) were more complex. These three compounds may be prepared by increasingly powerful reduction of 2,2′-dinitrobiphenyl, and the following sequence of reductions at the dropping-mercury electrode might have been expected:

$$\begin{matrix}\text{2,2′-Dinitro-} \\ \text{biphenyl}\end{matrix} \xrightarrow[4e]{4H^+} \begin{matrix}\text{Di-N-oxide} \\ \text{(IV)}\end{matrix} \xrightarrow[2e]{2H^+} \begin{matrix}\text{Mono-}N\text{-} \\ \text{oxide}\end{matrix} \xrightarrow[2e]{2H^+} \begin{matrix}\text{Benzo-} \\ \text{cinnoline}\end{matrix} \xrightarrow[2e]{2H^+} \text{Dihydrobenzocinnoline}$$

A claim by Ross *et al.*[24] to have demonstrated this sequence is referred to below. 2,2′-Dinitrobiphenyl was the most readily reduced polarographically of these compounds, but it was apparently not reduced *via* the benzocinnoline compounds since the waves corresponding to their reduction were not observed. Further, benzocinnoline was more easily reduced than either *N*-oxide; it was thus not possible to see if the oxides were reduced *via* benzocinnoline itself. Since the latter was probably reduced to 5,6-dihydrobenzocinnoline it is likely that the *N*-oxides were each reduced directly to the same compound, in one step. Finally, the dioxide was clearly not reduced *via* the mono-oxide since, in this case, the dioxide is the more easily reduced and no second wave corresponding to the mono-oxide was observed. In view of these results, and the ratio of the step heights observed, it is probable that 2,2′-dinitrobiphenyl was first reduced to the bishydroxyamino-compound (eight-electron step) which was then reduced directly to dihydrobenzocinnoline (two-electron step). The most interesting feature of the results with the benzocinnolines is that both *N*-oxides were more difficult to reduce than the base. This enhanced stability of the oxides, compared with those of quinoxaline and phenazine, was also encountered in deoxygenation reactions with phosphorus trichloride and will be discussed later.

The sequence described above, showing benzocinnoline and its *N*-oxides as " members of a series derived by progressive reduction from 2,2′-dinitrobiphenyl," was claimed by

[23] Kaye and Stonehill, *J.*, 1952, 3240.
[24] Ross, Kahan, and Leach, *J. Amer. Chem. Soc.*, 1952, **74**, 4122.

Ross *et al.*[24] to be confirmed by their polarographic results. These workers used unbuffered aqueous-ethanolic solutions of certain " apparent " pH values for their measurements; this is very unreliable for the study of organic compounds especially when, as here, $E_{\frac{1}{2}}$ will vary with pH.[25] At " pH 5·2," *i.e.*, in 0·1M-aqueous-ethanolic ammonium chloride, their results show these compounds to be reduced at increasingly negative potentials in the order: benzocinnoline, benzocinnoline 5,6-dioxide, 2,2′-dinitrobiphenyl, benzocinnoline 5-oxide. Further, only one wave was observed for each compound, and the individual diffusion currents agreed very well with the number of electrons required for complete reduction of each compound to dihydrobenzocinnoline in one step. Postulation of the above sequence of intermediates in the electrochemical reduction of 2,2′-dinitrobiphenyl would thus hardly be justified.

These results, as a whole, considered together with those of Varyukhina and Pushkareva,[7] show that in agreement with expectation, fusion of a benzene ring on to a heterocyclic compound, or introduction of a second nitrogen atom into the ring, generally increases the ease of polarographic reduction, *e.g.*, pyridine, quinoline, and quinoxaline 1-oxides have $E_{\frac{1}{2}} = -1·4$, $-1·1$,[7] and $-0·5$ v, respectively. However, *N*-oxidation of the second nitrogen atom has little effect on the half-wave reduction potential, electron-withdrawal by this nitrogen atom apparently being little changed by its co-ordination with oxygen.

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[25] Kolthoff and Lingane, " Polarography," Interscience Publ., Inc., New York, 1952, 2nd edn., Vol. II, p. 624.