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Electroörganic Preparations

XXVIII. Preparation of Some Heteroaromatic *N*-Oxides by Ring Closure

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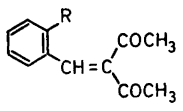
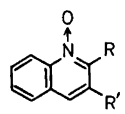
Heteroaromatic *N*-oxides are prepared by controlled potential reduction of suitable *ortho*-substituted nitrocompounds to the hydroxylamines which then condense to the cyclic compounds. *N*-oxides of some quinolines, benzothiazoles, and benzimidazoles are prepared by this method; in some cases, *e.g.* benzoxazine, a substituted compound rather than the *N*-oxide is the product.

Heteroaromatic *N*-oxides may be prepared by ring closure of suitable compounds;[1] controlled potential electrolysis is well-suited for the partial reductions required in such reactions. Below is reported on the reductive cyclization of some *ortho*-substituted nitro compounds.

The following compounds are included in the investigation: 2-Nitrobenzylidene acetylacetone (Ib), benzylidene acetylacetone (Ia), 3-acetyl-2-methylquinoline-*N*-oxide (IIa), 3-acetyl-2-methylquinoline (IIIa), *N*-oxide of 1-(2′-methyl-3-quinolyl)-ethanol (IIb), ethyl 2-cyano-2′-nitrocinnamate (IVb), 2-amino-3-carboxyquinoline-*N*-oxide (IIc), 2-nitrophenylthiocyanate (Va), 2-nitrophenylisothiocyanate (Vb), 2-nitroformanilide (Vc), and 2-nitrophenoxyacetic acid (Vd).



I a R=H
b R=NO_2



II a R=CH_3, R′=$COCH_3$
b R=CH_3, R′=$CHOHCH_3$
c R=NH_2 R′=COOH

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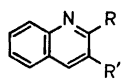
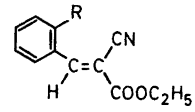
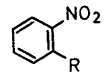


III a $R=CH_3$, $R'=COCH_3$
b $R=NH_2$, $R'=COOH$



IV a $R=H$
b $R=NO_2$



V a $R=SCN$ c $R=NHCHO$
b $R=NCS$ d $R=OCH_2COOH$

RESULTS AND DISCUSSION

In Fig. 1 the polarographic behaviour of 2′-nitrobenzylidene acetylacetone (Ib) between pH 0 and 11 is depicted; at pH >11 the attack by base interferes with the polarographic measurement. In Figs. 2, 3, 4, and 5 are plotted the

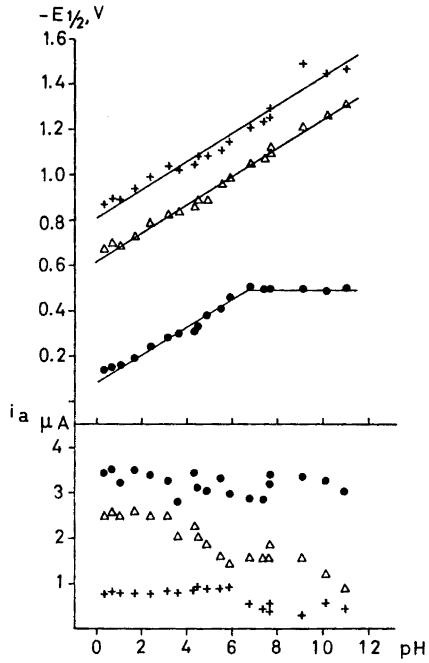


Fig. 1. Limiting currents (in μA) and half-wave potentials (*vs.* SCE) of 2′-nitrobenzylidene acetylacetone (Ib) in 40 % aqueous ethanol at different pH. ●, △, and + Data of 1., 2., and 3. wave, respectively. Concentration: 3.5×10^{-4} M.

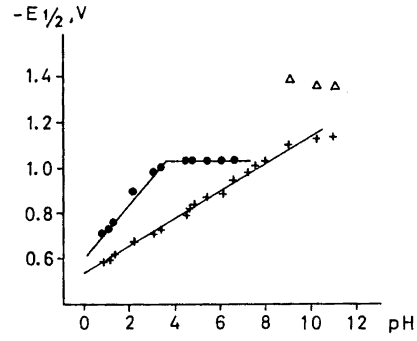


Fig. 2. Half-wave potentials (*vs.* SCE) of benzylidene acetylacetone (Ia) in 40 % aqueous ethanol at different pH.

half-wave potentials of benzylidene acetylacetone (Ia), 3-acetyl-2-methylquinoline-1-oxide (IIa), 3-acetyl-2-methylquinoline (IIIa), and the *N*-oxide of 1-(2-methylquinolyl-3)-ethanol (IIb), respectively.

The first wave of Ib (Fig. 1) is caused by a four-electron reduction of the nitro group to a hydroxylamino group; the slope of the $E_{\frac{1}{2}}$-pH curve is 0.059 V/pH from pH 0 to 7 and 0 at pH >7. Controlled potential reduction of Ib in N hydrochloric acid containing 40 % ethanol yielded (Table 1) with consumption of 4 F/mole a product which was formulated as IIa from the

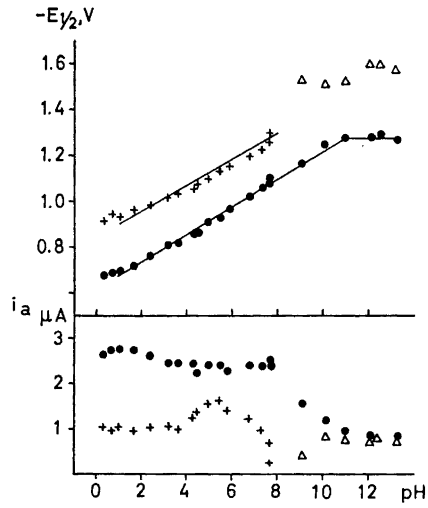
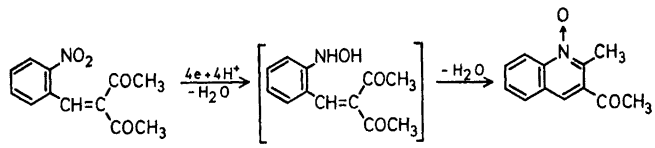


Fig. 3. Limiting currents (in μA) and half-wave potentials (*vs.* SCE) of 3-acetyl-2-methylquinoline-1-oxide (IIa) in 40 % aqueous ethanol at different pH. ● Data of 1. wave; + and △ data of 2. wave in acid and alkaline medium, respectively. Concentration 4×10^{-4} M.

empirical formula, $C_{12}H_{11}NO_2$, the NMR-spectrum ($CDCl_3$, two singlets ($\sum H=3$) at $\delta=2.72$ and 2.83, two multiplets, one ($\sum H=4$) at $\delta=7.4-8.0$, and another ($\sum H=1$) at $\delta=8.65-8.85$), the IR-spectrum ($\nu_{CO}=1680$), and the polarographic data (Fig. 3). Reduction with sodium borohydride produced an alcohol (IIb) which still possessed an *N*-oxide group, according to the polarographic evidence. The reaction can be formulated as



Ib VI IIa

where the hydroxylamino group attacks the carbonyl group with formation of a cyclic nitrone. In Table 1 the yields of IIa in the reduction are given.

The second wave of Ib has the height of a three-electron wave from pH 0 to about 4, but diminishes to the height of a two-electron wave between pH 4 and 6; between pH 6 and 10 the height is constant. The slope of the $E_{\frac{1}{2}}$-pH

Table 1. Yields of 3-acetyl-2-methylquinoline-*N*-oxide (IIa) in reduction of 2-nitrobenzylidene acetylacetone (Ib) in N hydrochloric acid containing 40 % ethanol.

$-E$ (V *vs.* SCE)	n	Yield %	
		Polarographically determined	Isolated
0.25	4.28	80	73
0.30	3.95	80	73
0.35	4.25	—	72
0.35	4.01	86	69

curve is 0.059 in the whole region. The second wave of Ib could be due to the further reduction of VI or of the ring closed product IIa, if the ring closure were sufficiently fast at the dropping mercury electrode. This is discussed further below.

The third wave has the height of a one-electron wave up to pH 6; above that the height is somewhat lower. The reason for that is not clear; the wave-height is not easy to measure as accurately as the first two waves, and irregularities of the limiting current are found in alkaline solution.

Benzylidene acetylacetone (Ia) is reduced (Fig. 2) in two one-electron waves at most pH; at pH < 0 and in a small interval around pH 8 a single two-electron wave is found. The slope of the first wave is 0.059 V/pH from pH 0 to 10; that of the second wave is 0.118 V/pH from pH 0 to 3.5 and 0 from pH 3.5 to 8. At pH >10 the compound is attacked by base. The half-wave potentials of the first wave of Ia are about 0.1 V less negative than those of the second wave of Ib.

3-Acetyl-2-methylquinoline-1-oxide (IIa) gives two polarographic waves (Fig. 3). Below pH about 9 the half-wave potentials of the 1. and 2. wave of IIa are nearly identical with those of the 2. and 3. wave of Ib, respectively. Below pH 8 the first wave has the height of a three-electron wave and the second one that of a one-electron wave. Above pH 10 both waves have the height of a one-electron wave.

The three-electron wave in acid solution is probably due to a two-electron reduction of the *N*-oxide and a one-electron reduction of the carbonyl group; the second wave would then be a further reduction of the radical formed in the first reaction. A selective removal of the *N*-oxide group is difficult in this case; one reason is that the resulting quinoline is a stronger base than the *N*-oxide and the protonated quinoline ring lowers the reduction potential of the carbonyl group more than does the quinoline-*N*-oxide. In alkaline solution the reduction may also take place in the nucleus. Controlled potential reduction of IIa in acid solution produces some IIIa, but a considerable amount of other compounds is formed as well.

The half-wave potentials of the first wave of IIb are depicted in Fig. 4; the wave disappears about pH 9 as the preprotonation step becomes too slow. The slope of the $E_{\frac{1}{2}}$/pH-curve is about 0.06 V/pH. Besides the wave shown in Fig. 4 a further wave, possibly of catalytic nature, is found at some pH-values.

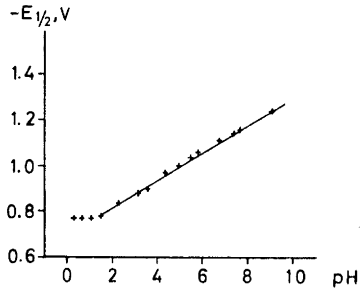


Fig. 4. Half-wave potentials of the *N*-oxide of 1-(2-methylquinolyl-3)ethanol in 40 % ethanol at different pH.

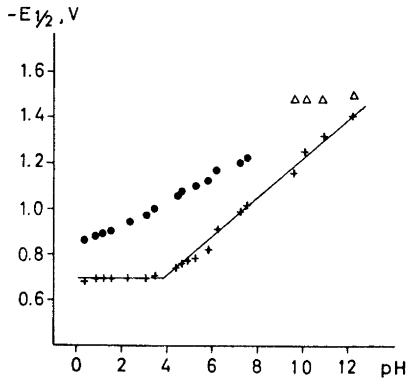


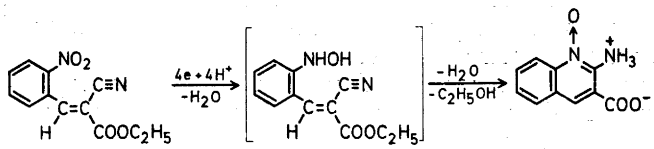
Fig. 5. Half-wave potentials of 3-acetyl-2-methylquinoline (IIIa) in 40 % aqueous ethanol at different pH. ● and + Data of 1. and 2. wave, respectively.

In alkaline solution one or two smaller waves are found. A comparison of the half-wave potentials of IIb with those of IIa shows that the first wave of the latter is about 0.1 V less negative than the first wave of IIb.

In Fig. 5 is a plot of the half-wave potentials of IIIa. A comparison of Figs. 3 and 5 reveals that IIIa is about 0.1 V easier reducible at pH 4 than IIa, whereas this is not the case at pH 0. The difference in pK of the two compounds is responsible for that.

The polarographic behaviour of the intermediate (VI) cannot be tested by classical polarography, but may be inferred from the polarographic data of the second wave of nitrobenzene (VII) and Ia. If it is assumed that VI would behave both as VII and Ia it is not easy to explain the second and third waves of Ib, because the slopes of the $E_{\frac{1}{2}}$-pH curves of VII and of the second wave of Ia do not match those of the second and third waves of Ib. A comparison of Figs. 1 and 3, however, shows that the further polarographic reduction of Ib can be explained as a reduction of IIa. Presumably a cyclic voltammetric investigation in which the presence or absence of VI could be shown from the anodic oxidation of the hydroxylamino group would be able to answer the question conclusively.

Ethyl α-cyano-*o*-nitrocinnamate (IVb) gives three or four polarographic waves, depending on pH (Fig. 6). The first wave is a four-electron reduction of the nitro group to the hydroxylamino group; controlled potential reduction



IVb VIII IIc

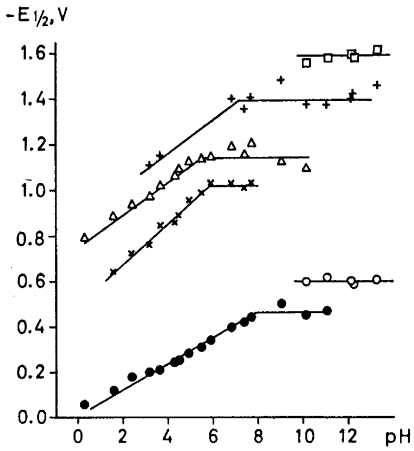


Fig. 6. Half-wave potentials (*vs.* SCE) of ethyl α-cyano-*o*-nitrocinnamate (IVb) in 40 % aqueous ethanol at different pH.

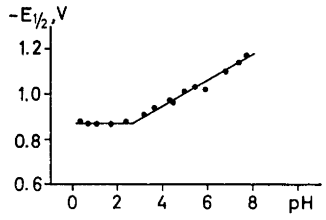


Fig. 7. Half-wave potentials (*vs.* SCE) of 2-amino-3-carboxyquinoline-1-oxide (IIc) in 40 % aqueous ethanol at different pH.

of IVb in hydrochloric acid at the plateau of the first wave produced a compound, $C_{10}H_8N_2O_3$, which was shown to be 2-amino-3-carboxyquinoline-1-oxide (IIc); the IR-spectrum suggested that the compound was present as the zwitterion.

The half-wave potentials of IIc are shown in Fig. 7; the wave is a two-electron reduction from pH 0 to 8. A comparison of Figs. 6 and 7 shows that the further polarographic waves of IVb are not due to the reduction of IIc, but rather of VIII. The ring closure reaction is thus too slow to influence the polarographic curve of IVb. Compound VIII was not isolated and its further reduction was not investigated.

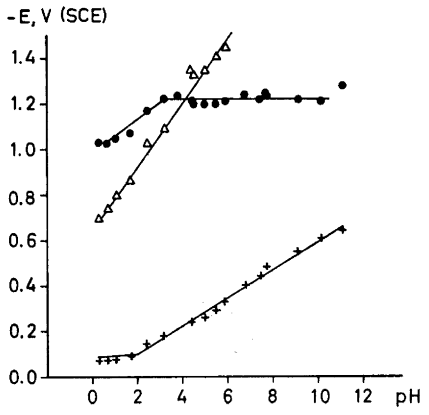
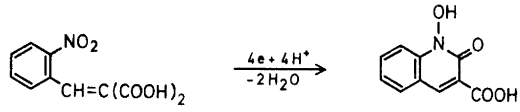
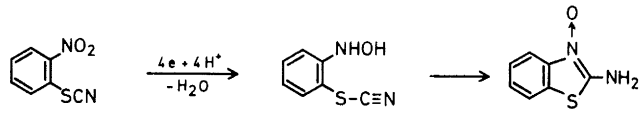


Fig. 8. Half-wave potentials (*vs.* SCE) of 2-nitrophenylthiocyanate (Va) in 40 % aqueous ethanol at different pH.

A similar ring closure is observed in the reduction of *o*-nitrobenzylidene malonic acid which produces *N*-hydroxy-3-carboxy-carbostyrile in a four-electron reduction.[2]



The half-wave potentials of 2-nitrophenylthiocyanate (Va) are plotted in Fig. 8. The first wave is a well-defined four-electron wave, whereas the second and third waves are from pH 0 to 6 rather poorly defined two-electron waves with half-wave potentials near the reduction wave of the hydrogen ions. Between pH 6 and 10 two welldefined waves ($n=4$ and 2) occur, but the second wave disappears at pH >10.

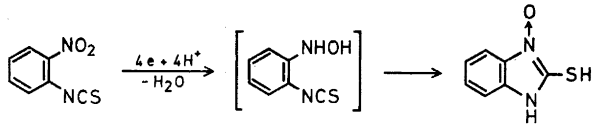


Va IX X

Electrolysis of Va at pH 1 at the potential of the first wave produced 2-aminobenzothiazole-3-oxide; the hydroxylamino group of the intermediate IX attacks the cyano group with ring closure to X.

Phenylthiocyanate gives a pH-independent wave at pH >3, whereas X only gives an ill-defined wave at negative potentials in acid solution, and from this and the polarographic behaviour of nitrobenzene it seems most likely that the ring closure of IX to X is too slow to influence the polarographic curve. The second wave of Va would thus in acid solution probably be the further reduction of the hydroxylamino group, whereas the second wave at pH >5 rather is the reductive loss of cyanide ion from the thiocyanate group.

2-Nitrophenylisothiocyanate (Vb) shows only one well-defined wave from pH 0 to 6 with a wave-height corresponding to between 4 and 6 F/mole. Electrolysis of Vb in 0.5 N hydrochloric acid (40 % ethanol) consumed 4.8 F/mole and a compound, $C_7H_6N_2OS$, shown to be 2-mercaptobenzimidazole-*N*-oxide (XI), was isolated in 58 % yield (polarographically determined yield in catholyte 86 %).



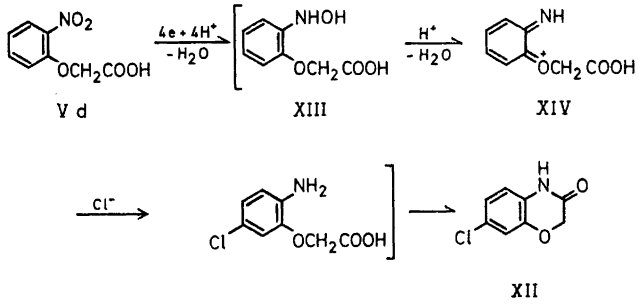
Vb XI

The molecular ion in the mass spectrum was $m/e=166$, whereas the base peak was at $m/e=150$ (Table 2). The further fragmentation pattern resembled to a very high degree that of 2-mercaptobenzimidazole (XIa), also showing the same doubly charged and metastable ions. This fragmentation is best explained by a primary loss of oxygen from the *N*-oxide XI to the parent compound.

In a preparation of XI by chemical oxidation of 2-mercaptobenzimidazole it might be difficult to avoid oxidation of the sulfur, and the reductive cyclization described here seems to be the best way of preparing such compounds.

Sometimes other reactions may interfere with the formation of a cyclized hydroxylamino derivative. When 2-nitrophenoxyacetic acid was reduced in 2 N hydrochloric acid (50 % ethanol) 5-chloro-2H-1,4-benzoxazin-3(4H)-one (XII) rather than the cyclic hydroxamic acid or the parent benzoxazinone was the main product (70 %).

The isolated compound was formulated as XII on the following grounds. The analysis corresponded to $C_8H_6ClNO_2$ and this was substantiated by the mass spectrum. The fragmentation pattern of XII resembled that of the parent benzoxazinone. The m.p. 197° suggests strongly that XII is identical with the x-chlorobenzoxazinone (m.p. 195°) previously isolated from the reduction of 2-nitrophenoxyacetic acid on reduction with tin and hydrochloric acid.[3] As the NMR-spectrum suggests an 1,2,4-trisubstitution and the 6-chlorobenzoxazinone has m.p. 215°,[4] XII has been formulated as 5-chlorobenzoxazinone. An analogous reaction is the reduction of 2-nitroanisole with tin and hydrochloric acid in which 5-chloro-2-aminoanisole is formed.[5] The reduction of Vd may be formulated as:



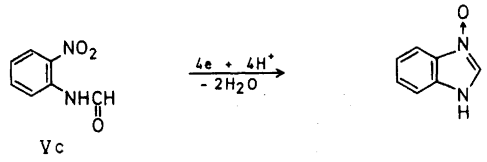
Vd XIII XIV XII

When the reduction is performed in an acetate buffer, highly coloured products result, probably formed by condensation reactions of the intermediate XIV.

The failure to prepare the *N*-oxides of Vd by electrolytic reductive cyclization is thus probably due to the relatively low rate of the cyclization compared to the competing reactions. It is well known that the nitro group in *o*- or *p*-nitroanilines or -phenols are reduced in a single six-electron reaction which is made possible by an acid catalyzed dehydration to a similar quinoid intermediate. It is thus to be expected that it will be difficult to catch a hydroxylamino group in a ring closure reaction when it has an amino or hydroxyl

group in the *o*-position. An attempt to make dihydrobenzotriazine by reduction of an *o*-nitrophenylhydrazone failed for the same reason.[6]

Acylation of the amino group in *o*-nitroaniline, as in *o*-nitroformanilide (Vc), makes the dehydration step less favoured and the ring closure reaction competes better with the competing reactions. Accordingly, electrolysis of Vc at −0.8 V in an acetate buffer yielded some benzimidazole-*N*-oxide according to



Vc

Reductive cyclizations of *o*-substituted nitro compounds to *N*-oxides have been attained by chemical and catalytic reduction.[1] The electrolytic method offers another means of accomplishing the reduction, and the convenient way to avoid overreduction by control of the potential together with the predictions of suitable reaction conditions made possible from polarographic investigations make controlled potential electrolysis attractive in many such reactions.

EXPERIMENTAL

The polarograph was a recording polarograph PO4 (Radiometer, Copenhagen); for the electrolysis was used a transistorized potentiostat (Tage Juhl electronics, Copenhagen). The NMR-spectra were recorded on a Varian Associates A 60 Spectrometer and the mass spectra were obtained from a Hitachi-Perkin Elmer RMU-6D.

Materials: *o*-Nitrobenzylidene acetylacetone,[7] ethyl α-cyano-*o*-nitrocinnamate,[8] *o*-nitrophenylthiocyanate,[9] *o*-nitrophenylisothiocyanate,[10] *o*-nitrophenoxyacetic acid [11] were prepared according to the references given.

N-Oxide of 1-(2′-nitrophenyl)ethanol (IIb) was prepared by reduction of 3-acetyl-2-methylquinoline-1-oxide (IIa) with sodium borohydride in aqueous methanol, evaporation of the methanol, and extraction with chloroform, m.p. 162−165°. (Found: C 70.44; H 5.99; N 6.89. Calc. for $C_{12}H_{13}NO_2$: C 70.92; H 6.45; N 6.89). NMR-spectrum ($CDCl_3$): $\delta=1.40$ (doublet, $J=6.5$ Hz) $\sum H=3$; $\delta=2.47$ (singlet) $\sum H=3$; $\delta=4.93$ (quartet, $J=6.5$ Hz) $\sum H=1$; $\delta=5.3$ (broad) $\sum H=1$; $\delta=7.2-7.8$ (multiplet) $\sum H=4$.

Reduction of o-*nitrobenzylidene acetylacetone (Ib).* Ib (3 g) was reduced at −0.35 V (SCE) in 150 ml of prereduced N hydrochloric acid containing 40 % ethanol. The reduction consumed about 4 F/mole (Table 1); the yield of 3-acetyl-2-methylquinoline-*N*-oxide was determined polarographically in the reduced solution (80−86 %). Most of the solvent was evaporated *in vacuo*, pH adjusted to 2−3 with sodium hydroxide, and the precipitate filtered after cooling, 1.98 g (77 %), m.p. 142−145°. Recrystallization from water yielded 1.77 g (69 %) m.p. 147−148°. (Found: C 71.19; H 5.65; N 6.69. Calc. for $C_{13}H_{11}NO_2$: C 71.63; H 5.51; N 6.26). NMR-spectrum (CF_3COOH): $\delta=3.00$ (singlet) $\sum H=3$; $\delta=3.31$ (singlet) $\sum H=3$; $\delta=8.0-8.8$ (multiplet) $\sum H=4$; $\delta=9.35$ (singlet) $\sum H=1$.

Reduction of α-*cyano*-o-*nitrocinnamic acid (IVb).* IVb (1 g) was reduced in N hydrochloric acid containing 70 % ethanol at −0.2 V SCE). The reduction consumed 4.2 F/mole; the yield of 2-amino-3-carboxyquinoline-*N*-oxide (90 %) was determined polarographically in an aliquot of the catholyte. The catholyte was evaporated *in vacuo*, the residue dissolved in sodium hydroxide, filtered, and on addition of glacial acetic acid a precipitate was obtained, m.p. 302° (decomp.) (305−307°),[8] yield 77 %. (Found: C 58.16; H 4.12; N 13.50. Calc. for $C_{10}H_8N_2O_3$: C 58.82; H 3.95; N 13.72).

Reduction of o-*nitrophenylthiocyanate (Va).* Va (1 g) was reduced in 0.4 N hydrochloric acid containing 65 % ethanol at −0.4 V (SCE), $n=4.7$; most of the solvent was removed *in vacuo*, the remainder made alkaline with 33 % NaOH-solution, filtered, and pH of the filtrate adjusted to 6 with hydrochloric acid. The precipitate, 0.70 g (75 % yield), was dissolved in abs. ethanol and dry hydrogen chloride added. The precipitate, the hydrochloride of 2-aminobenzothiazole-3-oxide, had m.p. 230° (decomp.) (231−232°)[12] (Found: C 40.93; H 3.50; N 13.68. Calc. for $C_7H_7ClN_2OS$: C 41.3; H 3.44; N 13.75).

Reduction of 2-nitrophenylisothiocyanate (Vb). A suspension of Vb (1 g) in 150 ml 0.5 N hydrochloric acid containing 40−75 % ethanol was reduced at −0.6 V (SCE), $n=4.7$ to 4.9. The alcohol was removed *in vacuo* from the resulting yellow solution, the remainder made alkaline with sodium hydroxide; some impurities were removed by extraction with chloroform and glacial acetic acid was gradually added to the warm alkaline solution. At first, a small amount of coloured material precipitated and was filtered off, and from the nearly colourless solution a white compound, 2-mercaptobenzimidazole-*N*-oxide (XI), was precipitated on further addition of glacial acetic acid (to pH 5),465 to 535 mg (50−58 %). (Found: C 50.73; H 4.00; N 16.79; S 18.68. Calc. for $C_7H_6N_2OS$: C 50.61; H 3.64; N 16.86; S 19.26). Polarographically determined yield in the catholyte 69−86 %. The compound XI decomposed at 162° (1°/5 sec). After thermal decomposition at 180° for 5 min, 2-mercaptobenzimidazole could be detected in the reaction mixture by TLC. Mass spectrum: Table 2.

Table 2. Mass spectrometric data for 2-mercaptobenzimidazole-*N*-oxide (XI) and 2-mercaptobenzimidazole (XIa).

m/e	Relative abundance %		*m/e*	Relative abundance %		*m/e*	Relative abundance %	
	XI	XIa		XI	XIa		XI	XIa
38	7	5	75	17	19	106	14	7
39	12	10	75.2	[a]	[a]	118	20	12
44	14	12	75.5	1.5	2	122	21	10
50	6	4	78	9	6	123	9	6
51	9	6	79	8	2.5	133	6	—
52	10	8	82.5	0.3	—	134	9	—
60.5	0.8	0.6	83.5	0.4	—	149	20	10
61.5	1.0	1.0	90	13	5	150	100	100
63	17	11	91	12	7	151	12	10
64	12	8.5	92	9	8	152	6	5
65	18	16	96	7	5.5	165	3	—
			100.8	[a]	[a]			
74.5	0.8	0.6	105	10	4.5	166	23	—
						167	2.6	—
						168	1.3	—

[a] metastable ion.

Reduction of 2-nitroformanilide (Vc). Vc (1 g) was reduced in an acetate buffer containing 40 % ethanol at −0.8 V; a slow stream of nitrogen was bubbled through the solution during the reduction; $n=4.3$. The brownish catholyte was evaporated *in vacuo*, the residue washed with water and the remainder dissolved in a small volume of ethanol. On cooling (carbon dioxide/acetone bath) a precipitate, benzimidazole-*N*-oxide, was formed, which was recrystallized from alcohol, 175 mg, m.p. 211−214° (decomp. 215°) (215°, decomp.).[13] (Found: C 61.83; H 4.66; N 20.58. Calc. for $C_7H_6N_2O$: C 62.68; H 4.51; N 20.88).

Reduction of 2-nitrophenoxyacetic acid (Vd). Vd (0.5 g) was reduced in 2 N hydrochloric acid containing 50 % ethanol at −0.6 V (SCE), $n=4.8$. The reduction completed, the solvent of the catholyte was evaporated *in vacuo* and the residue purified by sublimation *in vacuo*; obtained were 325 mg (70 %) compound XII, m.p. 195−197°. (Found: C 52.25; H 3.49; N 7.57. Calc. for $C_8H_6ClNO_2$: C 52.45; H 3.27; N 7.65). In the mass spectrum the molecular ion (183) was also the base peak, M+2=33 %. Compound XII was shown to be 5-chloro-2H-1,4-benzoxazin-3(4H)-one.

REFERENCES

1. Ochiai, E. *Aromatic Amino Oxides*, Elsevier, Amsterdam, London, New York 1967, p. 57 ff.
2. Lund, H. and Hakl, J. *To be published.*
3. Duparc, L. *Ber.* **20** (1887) 1942.
4. *Brit. Pat.* 729 441 (1955); *Chem. Abstr.* **50** (1956) 8730.
5. Reverdin, F. and Eckhard, F. *Ber.* **32** (1899) 2622.
6. Kwee, S. and Lund, H. *Acta Chem. Scand.* **23** (1969) 2711.
7. Courts, A. and Petrow, V. *J. Chem. Soc.* **1952** 1.
8. Bauer, K. H. *Ber.* **B 71** (1938) 2226.
9. Wagner-Jauregg, T. and Helmert, E. *Ber.* **75** (1942) 935.
10. Arndt, F. and Rosenau, B. *Ber.* **50** (1917) 1248.
11. Jacobs, W. A. and Heidelberger, M. *J. Am. Chem. Soc.* **39** (1917) 2188.
12. Liss, T. A. *Chem. Ind. (London)* **1964** 368.
13. Takahashi, S. and Kano, H. *Chem. Pharm. Bull. (Tokyo)* **11** (1963) 1375.

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