ACID TREATMENT OF 2-METHYL-2-PHENYL-3-OXO-INDOLIN-1-OXYL

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Abstract—2-Methyl-3-oxo-indolin-1-oxyl 10 with trifluoroacetic acid gives the disproportionation products 11 and 12. With dry HCl or HBr it undergoes halogenation and deoxygenation and yields halogenated indoxyls 13a-c and 14a-c, and with HI it undergoes deoxygenation to indoxyl 11 or reduction to hydroxylamine 15, depending on the reaction solvent. A deoxygenation mechanism is proposed on the basis of experimental evidence.

Acid treatment of tetramethylpiperidine-1-oxyl 1 and tetramethylpyrrolidine-1-oxyl 2 has been described.^{1,2} The formation of the oxoammonium salt 4 and the hydroxylamine 5 has been interpreted as a disproportionation involving the protonated form 3 (Scheme 1).

This behaviour is specific for nitroxide radicals such as 1 and 2, because they have the unpaired electron localised on the N-O group. Nitroxide radicals such as alkylphenyl nitroxide 6, in which the N-O group is in a conjugated position of the π system of the benzene ring, undergo a spontaneous disproportionation in solution, yielding the quinoneimine-N-oxide 8 and the amine 9³ (Scheme 2), this reaction being catalyzed by protic acids.⁴

2-Methyl-2-phenyl-3-oxo-indoline-1-oxyl 10, despite having the N-O group in a conjegated position of the π system of the indoline ring, is stable in solution for a long time.⁵ The stability and the structure of nitroxide 10 enabled the study of several reactions, such as homolytic substitutions,⁶ bromination,⁷ acetyloxylation,⁸ methoxylation,⁸ and oxidation.⁴ In the present paper we described the acid treatment of nitroxide 10, which, apart from the disproportionation process shown in Scheme 2, behaves quite differently from the above-mentioned nitroxides 1, 2 and 6.

RESULTS

The reaction of nitroxide 10 with trifluoroacetic acid in benzene gave 2-methyl-2-phenyl-3-oxo-indoline (indoxyl) 11 and the quinoneimine-N-oxide 12 (Scheme 3).

Treatment of 10 with dry hydrogen chloride in benzene yielded the indoxyl 11 the quinoneimine-N-oxide 12 and the chlorinated indoxyls 13a-c (Scheme 3, Table 3). In a similar way the reaction of 10 with hydrogen bromide gave the brominated indoxyls 14a-c, although 11 and 12 were now present only as traces (Scheme 3, Table 3). The reaction of nitroxide 10 with hydrogen iodide gave indoxyl 11 or the hydroxylamine 15 depending on the reaction solvent (acetonitrile or methanol, respectively).

Indoxyls 13a-c were identified from the analytical and spectroscopic data (Table 2) on the basis of the arguments already described for indoxyls 14a-c.⁷ Nitroxides 18a-c and 18d-f⁷ were identified by their ESR spectra. For chlorinated nitroxides 18a-c the natural abundance and distribution of the ³⁵Cl and ³⁷Cl isotopes had to be considered. The interpretation was made on the basis that the coupling constants for the two isotopes were in the ratio of their nuclear magnetic moments. The spectra computed with the distribution and the coupling constants shown in Table 1 coincide with the experimental spectra. Quinoneimine N-oxide 12 was identified by comparison with an authentic sample.⁵C



⁶⁷⁷





Table 1. Hyperfine coupling constants $(G)^*$ of nitroxides $18n(c^{**})$.

	R	R ₁	a _N	a _{H-4} =a _{H-6}	a H-5	а. Н-7	^a 35 _{C1}	^a 37 _{C1}
1 8 a	Cl	Cl	8,90	0.85(2H)	-	-	0.31(201)	• 0.26(201)
1 8 0	Cl	н	9.30	0.84(2H)	-	3.05	0.42	0.35
1 8 0	٠н	Cl	9.10	0.86(2H)	3.15	-	0.42	0.35

• 1G = 10^{-4} T.

** from CHCl₃ solutions.

Table 2	Analytical and	spectroscopic	data for	compounds	130-0*
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	м.,	Found (%)***					/	
Compound	(°C)	Formula	с	н	N	V _{max} /cm ⁻	Ø _H (J in HZ)	
1 5 a	141	C ₁₅ H ₁₁ C1 ₂ NO	61.73 (61.66)	3.86 (3.79)	4.87 (4.79)	1620 ⁸ 1695 ^b 3340 ^c	1.76(3H,s,Me); 5.26(1H,broad, NH); 7.26-7.58(7H,m,arom.).	
18 b	153	C ₁₅ H ₁₂ C1 NO	69.83 (69.90)	4.78 (4.69)	5.26 (5.43)	1617 ⁸ 1670 ⁵ 3320 ⁶	1.74(3H,s,Me); 5.06(1H,broad, NH); 6.88(1H,d,H-7,J8.5);7.24-7.60 (7H,m, arom.).	
134	117	С ₁₅ Н ₁₂ С1 NO	69.85 (69.90)	4.89 (4,69)	5.60 (5.43)	1618 ^a 1695 ^b 3320 ^c	1.78(3H,s,Me); 5.24(1H,broad, NH); 6.8(1H,2 d,H-5,J,7.3,7.6) 7.24- 7.68(7H,m,arom.).	

Each compound gave the expected molecular ion peak in the mass spectrum.
From petroleum, b.p. 100-135°C.

*** Calc. values in parentheses.

a,Ph-N-C-; b, >C=0; c, :NH.

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Compound Products (% yield) Acid 10 F_CCO_H 11 (25); 12 (25). HC1^a ... 11 (5); 12 (45); 13a (10); 13b (25); 13c (8). HBra 11 (6); 12 (4); 14a (32); 14b (46); 14c (12). HBrb <u>11</u> (3); <u>12</u> (4); <u>14a</u> (35); <u>14b</u> (40); <u>14c</u> (10). нı^с 11 (95). нıр 15 (90).

Table 3. Reaction product percent yields

a, in $C_{6}H_{6}$; b, in MeOH; c, MeCN.

DISCUSSION

The formation of indoxyl 11 and the quinoneimine-Noxide 12, obtained in the reaction with trifluoroacetic acid, can be explained on the basis of the disproportionation described in Scheme 2 for alkyl-phenyl nitroxide radicals. As in the reaction with hydrogen chloride the total amount of compounds 13a-c corresponded to the amount of the quinoneimine-N-oxide 12, we think that the reaction proceeds through the mechanism described in Scheme 4. The formation of chlorinated nitroxydes 18a-c may be explained by the sequence shown in Scheme 5. In fact, it is assumable that the first reaction to occur is the nitroxide 10 reduction, which yields hydroxylamine 15 and chlorine.¹ Successively, chlorine can oxidize nitroxide 10 to the oxoammonium salt 16,10 which reacts with chlorine anion yielding chlorinated hydroxylamines 17a-c as already described in reaction of 10 with bromine.⁷ Hydroxylamines 17a-c are in equilibrium with the corresponding nitroxides 18ac in the presence of chlorine.

In the reaction of nitroxide 10 and dry hydrogen bromide, which yielded brominated indoxyls 14a-c together with traces of quinoneimine N-oxide 12, the first product formed was again hydroxylamine 15 (Scheme 3 and 5). The steps shown in Scheme 5 were demonstrated by treating hydroxylamine 15 with dry hydrogen bromide. No change was observed with time: however the brominated hydroxylamines 17d-f were formed in a few hours when two drops of bromine were added to the mixture. Because of the small amount of quinoneimine-N-oxide 12 formed in this case, one can exclude that the reaction proceeds through the mechanism indicated in Scheme 4. Brominated indoxyls 14a-c can be alternatively formed through the intermediate formation of the nitrenium ion 20, as shown in Scheme 6. Although it is not clear why the nitrenium ion does not form when starting from hydroxylamine 15, it is possible that the

stabilizing effect due to the presence of one (or two) Br atoms in the indoline ring is vital for the formation of this labile species.

With the aim of finding experimental evidence for the existence of the nitrenium ion 20, we carried out the reaction between nitroxide 10 and hydrogen bromide in methanol, as in this medium the nitrenium ion would be expected to give 5- or 7-methoxy substituted indoxyls 21.¹¹ Unfortunately the latter derivatives could not be isolated. However the failure to detect compounds 21 does not rule out the formation of cation 20, which, once formed, could undergo a fast reduction in the reaction medium, thus preventing the attack by the methanol molecules.

The reaction between 10 and hydrogen iodide poses more of a problem, as compared with those with hydrogen chloride and bromide (Experimental). Although we are as yet unable to formulate a well-grounded explanation for this different behaviour, we feel that it may be due to the presence of water in the mixture.

EXPERIMENTAL

IR spectra were recorded for Nujol mulls with a Perkin-Elmer 257 spectrophotometer. ¹H NMR spectra were recorded with a Varian XL-100 spectrometer for CDCl₃ solns with Me₄Si as internal standard. ESR spectra were recorded with a Varian E4 spectrometer, and Mass spectra with a Varian 112-S apparatus. Compound 10 was prepared as described.⁵

Reaction of nitroxide 10 and trifluoroacetic acid. Nitroxide 10 (1 mmole in 30 ml of benzene) and trifluoroacetic acid (2 ml) were mixed at room temp. After 24 hr the solution was treated with 10% Na₂CO₃ aq. The benzene layer was separated, dried on Na₂SO₄ and evaporated to dryness. The residue was chromatographed on SiO₂ column with benzene. The starting nitroxide was recovered in 50% yield, and the other 50% was indoxyl 11 and quinone-imine N-oxide 12 (Table 3).

Reaction of nitroxide 10 with hydrogen chloride and bromide. Soln of 10 (2 mmole in 60 ml of benzene) was saturated with dry



Scheme 4.

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a	R = R, = Cl	d	$R = R_1 = Br$
b	$R = Cl; R_i = H$	е	$R = Br, R_1 = H$
с	R = H; R _I = Cl	f	$R = H, R_1 = Br$

Scheme 5.



Scheme 6.

HCl or HBr bubbled through decalin to trap traces of Br₂. In few min the red soln turned yellow. After 15 min a portion of the soln (2 ml) was oxidised with PbO₂ and chromotographed on SiO₂ preparative TLC with benzene. The well-separated **18a**-t were extracted with CHCl₃ and their ESR spectra recorded. After 24 hr the whole soln was neutralized with 10% Na₂CO₃ aq. The benzene layer was separated, dried on Na₂SO₄ and chromato-graphed on SiO₂ column with benzene. The yields of isolated compounds are reported in Table 3.

The reaction of 10 with HBr in MeOH gave the same results as the reaction carried out in benzene.

Reaction of nitroxide 10 with 57% hydrogen iodide. Nitroxide

10 (1 mmole in 50 ml acetonitrile) and 57% HI (10 ml) were mixed at room temp. After 6 hr the soln was poured into water (100 ml), neutralized with solid Na_2CO_3 and extracted with benzene (50 ml). The benzene layer was separated, dried on Na_2SO_4 and evaporated to dryness. The residue was 11.

The same reaction carried out in MeOH and worked up as described gave 15.

Reaction of hydroxylamine 15 with hydrogen bromide and bromine. Hydroxilamine 15 (200 mg in 30 ml of benzene) was saturated with pure, dry HBr. During the first 30 min no change was observed. Then two drops of Br_2 were added to the soln. In 15 min brominated 174-4 were observed through their cor-

responding nitroxides 18d-f as described above. Working up the mixture after 24 hr, 11, 12 and 14a-c were isolated in the same yields obtained for the reaction of 10 and HBr

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