

Reactions of 1,2-Dihydro-2-methyl-2-phenyl-3*H*-indole-3-one with Various Halogenating Reagents

Patricia Carloni, Elisabetta Damiani, Lucedio Greci* and Pierluigi Stipa

Dipartimento di Scienze dei Materiali e della Terra, Università di Ancona, Via Brecce Bianche, I-60131 Ancona, Italy

Dedicated to Professor Lennart Ebersson on the occasion of his 65th birthday

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1,2-Dihydro-2-methyl-2-phenyl-3*H*-indole-3-one (indoxyl) undergoes halogenation with *N*-chloro- and *N*-bromosuccinimide and *N*-chlorobenzotriazole forming 5- and/or 7-halogenated indoxyls. Initial one-electron transfer could be ruled out, and the reaction seems to occur either by an electrophilic aromatic substitution process or by the intermediate formation of *N*-haloindoxyl, which rearranges via a nitrenium ion to the reaction products. In experiments with I₂/AgClO₄, FeCl₃, Ar₃NSbCl₆/Bu₄NCl, where the radical cation is really formed, 5,5'-dimers and halogenated dimers were always obtained together with halogenated monomers. In the reaction with CuCl₂ only the 5-substituted monomer was obtained.

Previously, anodic oxidation of a long series of indoxyls of the type 1,2-dihydro-2-alkyl-2-phenyl-3*H*-indole-3-ones substituted at the nitrogen and at C-5 and C-7 have been studied.¹ The generated radical cations underwent fast dimerization giving rise to the corresponding 5,5'-dimer radical cations when the starting molecule was devoid of substituents at C-5; in one case nitrogen–nitrogen dimerization was also observed. The monomer radical cation was obtained only when the indoxyl was substituted at C-5 and C-7 or at C-5 and at the nitrogen with an alkyl group. Chemical oxidation carried out with FeCl₃ gave the indoxyl 5,5'-dimer and the 7-chloro-5,5'-dimer.

In general radical cations can dimerize by radical cation–radical cation or by radical cation-free base coupling, or they can react with nucleophiles present in the solution.² Radical cations may also react with oxygen leading to oxygenated products.³ In order to gain more information on their reactivity, we studied the reactions of 1,2-dihydro-2-methyl-2-phenyl-3*H*-indole-3-one (**1**) with a series of halogenating reagents which could give rise to radical cation formation as well as to direct electrophilic substitutions.

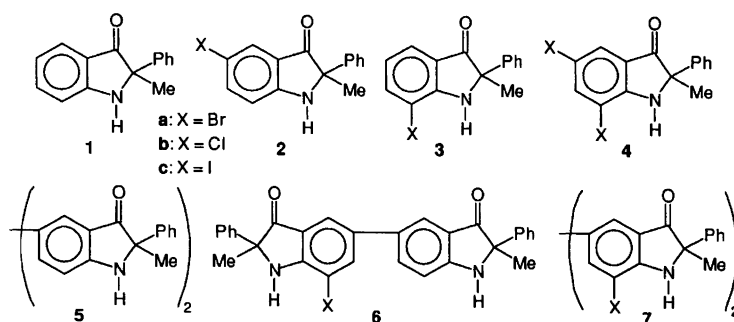
Results

The reactions of indoxyl **1** with different reagents [*N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS),

*To whom correspondence should be addressed.

N-chlorobenzotriazole (NCBT), tris(4-bromophenyl)-aminium hexachloroantimonate (BPA)/tetrabutylammonium chloride, Br₂, I₂/AgClO₄ (Gomberg reagent), FeCl₃ and CuCl₂] were performed in dry acetonitrile (MeCN) at room temperature with 2 equiv. of the reagents. All the isolated products are shown in Scheme 1. Yields are reported in Table 1.

The reactions of indoxyl **1** with NBS, NCS, NCBT led to the formation of 5- (**2a,b**) and 7-monohalogenated (**3a,b**) and 5,7-dihalogenated indoxyls (**4a,b**) identified by comparison with authentic samples.⁴ The reaction of indoxyl (**1**) with BPA in the presence of tetrabutylammonium chloride led to the formation of monobromoindoxyl (**2a**) and of 7-bromo- (**6a**) and 7,7'-dibromo-5,5'-dimers (**7a**). These compounds were identified through their ¹H NMR, IR and characteristic mass spectra. When molecular bromine was the halogenating agent, the only isolated product was 5,7-dibromoindoxyl (**4a**) while using CuCl₂ the reaction gave rise exclusively to 5-chloroindoxyl (**2b**). On oxidizing indoxyl (**1**) with the Gomberg reagent (I₂/AgClO₄), monomers (**2c**, **3c** and **4c**) and dimers (**5**, **6c** and **7c**) were obtained. 5-Iodo- (**2c**), 7-iodo- (**3c**) and 5,7-diiodo-indoxyls (**4c**) were identified by comparing their spectroscopic data with those of the parent compounds (**2a,b**, **3a,b** and **4a,b**), whereas structures of 5,5'-dimer (**5**), 7-iodo- (**6c**), and 7,7'-diiodo-5,5'-dimers (**7c**) were assigned on the basis of the spectroscopic data (¹H NMR, IR and mass spectra). The reaction with FeCl₃ gave rise to the 5,5'-



Scheme 1.

Table 1. Products and yields obtained by the reaction of indoxyl **1** with halogenating agents.

Reagents \ Products	1	X	2	X	3	X	4	5	X	6	X	7
NBS	—	Br	40	Br	7	Br	53	—	—	—	—	—
NCS	28	Cl	33	Cl	15	Cl	24	—	—	—	—	—
NCBT	—	Cl	47	Cl	13	Cl	40	—	—	—	—	—
BPA + Cl ⁻	21	Br	42	—	—	—	—	—	Br	10	Br	27
Br ₂	—	—	—	—	—	Br	100	—	—	—	—	—
I ₂ + AgClO ₄	5	I	47	I	3	I	27	6	I	8	I	4
FeCl ₃	86	—	—	—	—	—	—	5	Cl	9	—	—
CuCl ₂	—	Cl	100	—	—	—	—	—	—	—	—	—

dimer (**5**) and to the 7-chloro-5,5'-dimer (**6b**) identified through its spectra.

Discussion

All the reactions studied could be interpreted assuming the initial formation of the indoxyl radical cation **1**^{•+}. However, the results obtained with NBS, NCS and NCBT seem to point out that initial one electron transfer does not occur: in fact, whenever the monomer radical cation arises, dimers are invariably formed,¹ but in these reactions the dimers were never isolated. In fact, the redox potential of **1**^{•+} and of the reactants NBS,^{5,6} NCS⁷ and NCBT⁸ are such that a one-electron transfer could be excluded.⁹ In addition, the results obtained using these three oxidants were very similar although NBS and NCS when acting as one-electron oxidants give rise to different species [eqns. (1)⁵ and (2)⁷].

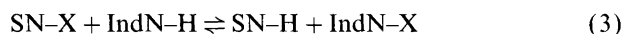


Therefore a different distribution of the reaction products was expected in the two cases.

Mechanisms similar to that described by Goldfinger,¹⁰ considered to be one of the most probable in halogenation reactions,¹¹ and that of Bloomfield,¹² which both involve radical intermediates, can be excluded, since initial electron transfer between the reactants is required to trigger these mechanisms.

A possible reaction mechanism is direct electrophilic attack at positions 5 and 7. However, previous results¹³ obtained by reacting indoxyl derivatives with sodium hypochlorite, suggest that initial halogenation at the

indoxyl nitrogen atom [eqn. (3)] could be an alternative mechanism operating in these systems.

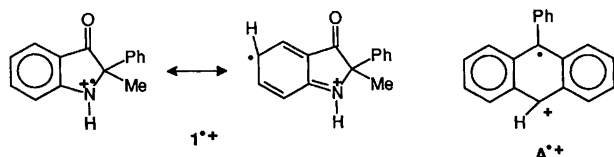


The *N*-haloindoxyl intermediate could then transpose via nitrenium ion formation giving rise to 5- and 7-substituted halides, in agreement with the chemistry of aromatic *N*-haloderivatives.¹⁴

Because the reactions with the chlorinating agents could also take place via attack of the halogen anion on the radical cation, a reaction using BPA as oxidant in the presence of tetrabutylammonium chloride as a Cl⁻ donor was carried out. In this case brominated dimers and monomer were obtained, instead of chloro-substituted indoxyls. The formation of the dimers is in agreement with radical cation formation, and bromination may arise from an electrophilic attack of molecular bromine originating from decomposition of the aminium salt as demonstrated by Ebersson.¹⁵ In fact when molecular bromine was reacted with **1**, dimers were never isolated, since bromine attacks the benzene ring of the indoxyl in an electrophilic aromatic substitution process. The fact that chlorosubstituted indoxyls were not obtained indirectly confirms that in the case of NBS, NCS and NCBT initial electron transfer is not involved.

It is well known that the Gomberg reagent is a good oxidant for radical cation generation from nitrogen compounds¹⁶ and this has already been demonstrated with indoxyl (**1**).¹ By oxidation of **1** with the Gomberg reagent directly in the EPR cavity, the immediate formation of the radical cation dimer was observed as revealed by a typical green colour. When the reaction was carried out in large scale, the mono- and diiodo-monomers together

with small quantities of the dimers were formed. Various observations have been reported on the reactivity of radical cations: some authors state that these species are poorly reactive toward nucleophiles,¹⁷ while others have observed that they react fast.¹⁸ It is our opinion that radicals such as $1^{+\cdot}$, having a localized charge on the nitrogen, react slowly with nucleophiles, while radicals such as phenylanthracene ($A^{+\cdot}$), where the positive charge is localized on a carbon atom, can be highly reactive towards nucleophiles.^{18,19}



Therefore, the formation of the monomer iodo derivatives **2c**, **3c** and **4c** may arise by coupling of the radical cation monomer and the iodine radical, even if $I^{\cdot-}$ possesses a high nucleophilicity.²⁰ The dimerization

observed for the indoxyl radical cation $1^{+\cdot}$ occurs through coupling of two radicals as had been previously described.¹

Dimerization was observed with $FeCl_3$, while with $CuCl_2$ a selective chlorination of the monomer was obtained. These results suggest that $FeCl_3$ ($E_{1/2} = 1.1$ V in MeCN vs. SCE)²¹ oxidizes indoxyl (**1**) with the formation of $1^{+\cdot}$. Subsequent dimerization is followed by slow chlorination through attack of a Cl^- on the dimer radical cation $5^{+\cdot}$ which lives longer than the monomer. In the reaction with $CuCl_2$ the selective formation of **2b** implies that the radical cation $1^{+\cdot}$ is not formed, although the redox potential of $CuCl_2$ ($E^\circ = 1.2$ V in MeCN)²² is close to that of $FeCl_3$, and substrates having a similar oxidation potential react via radical cation.²³ At this stage we are unable to suggest any mechanistic proposals for this reaction.

Experimental

Melting points are uncorrected. IR were recorded on a Perkin-Elmer model 298 spectrophotometer. 1H NMR

Table 2. M.p. and spectroscopic data of compounds **2c**, **3c**, **4c**, **5**, **6a-c**, **7a** and **7c**.

	1H NMR: δ (ppm)	IR: ν/cm^{-1}	MS (EI $^+$): m/z (%)	M.p./ $^\circ C$
2c	1.74 (3 H, s, Me); 5.04 (1 H, broad, NH); 6.76 (1 H, d, H7, $J=8.6$ Hz); 7.22–7.40 (3 H, m, arom.); 7.42–7.51 (2 H, m, arom.); 7.71 (1 H, dd, H6, $J=8.6$ and 1.9 Hz); 7.90 (1 H, d, H4, $J=1.9$ Hz)	3360 (NH), 1680, 1620	349 (M^+ , 81); 320 (85); 193 (100)	195–197
3c	1.79 (3 H, s, Me); 5.14 (1 H, broad, NH); 6.66 (1 H, d, H5, $J=7.7$ Hz); 7.23–7.42 (3 H, m, arom.); 7.43–7.54 (2 H, m, arom.); 7.57 (1 H, d, H4, $J=7.5$ Hz); 7.88 (1 H, dd, H6, $J=7.7$ and 1.1 Hz)	3340 (NH), 1695, 1610	349 (M^+ , 47); 320 (48); 194 (100)	—
4c	1.78 (3 H, s, Me); 5.20 (1 H, broad, NH); 7.28–7.49 (5 H, m, arom.); 7.85 (1 H, dd, H4, $J=1.5$ and 0.7 Hz); 8.11 (1 H, d, H6, $J=1.7$ Hz)	3340 (NH), 1695, 1590	475 (M^+ , 40); 446 (31); 193 (100)	155–159
5	1.79 (6 H, s, Me); 5.07 (2 H, broad, NH); 7.01 (2 H, dd, H7, $J=8.4$ and 0.8 Hz); 7.24–7.41 (6 H, m, arom.); 7.49–7.57 (4 H, m, arom.); 7.69–7.78 (4 H, m, arom.)	3310 (NH), 1675, 1615	444 (M^+ , 55); 193 (6); 57 (100)	134–138
6a	1.77 (3 H, s, Me); 1.81 (3 H, s, Me'); 5.10 (1 H, broad, NH); 5.30 (1 H, broad, NH'); 7.01 (1 H, d, H7, $J=8.3$ Hz); 7.22–7.42 (6 H, m, arom.); 7.46–7.56 (4 H, m, arom.); 7.63–7.76 (4 H, m, arom.)	3315 (NH), 1680, 1615	524 (M^+ , 30) and 522 (M^+ , 30); 478 (100)	103–107
6b	1.78 (3 H, s, Me); 1.81 (3 H, s, Me'); 5.10 (1 H, broad, NH); 5.28 (1 H, broad, NH'); 7.01 (1 H, d, H7, $J=8.4$ Hz); 7.24–7.42 (6 H, m, arom.); 7.48–7.57 (4 H, m, arom.); 7.65–7.78 (4 H, m, arom.)	3310 (NH), 1675, 1615	480 (M^+ , 46) and 478 (M^+ , 100); 451 (28) and 449 (57); 104 (85)	123–125
6c	1.78 (3 H, s, Me); 1.82 (3 H, s, Me'); 5.15 (1 H, broad, NH); 5.22 (1 H, broad, NH'); 7.03 (1 H, d, H7, $J=8.4$ Hz); 7.22–7.42 (6 H, m, arom.); 7.46–7.58 (4 H, m, arom.); 7.64–7.75 (3 H, m, arom.); 8.12 (1 H, d, H6, $J=1.8$ Hz)	3320–40 (NH), 1685, 1615	570 (M^+ , 100); 541 (40); 104 (77)	114–116
7a	1.81 (6 H, s, Me); 5.28 (2 H, broad, NH); 7.28–7.42 (6 H, m, arom.); 7.46–7.56 (4 H, m, arom.); 7.62–7.74 (4 H, m, arom.)	3335 (NH), 1700, 1620	604 (M^+ , 7) and 602 (M^+ , 13) and 600 (M^+ , 7); 512 (66); 104 (100)	123–125
7c	1.82 (6 H, s, Me); 5.30 (2 H, broad, NH); 7.28–7.43 (6 H, m, arom.); 7.46–7.54 (4 H, m, arom.); 7.70 (2 H, d, H4, $J=1.8$ Hz); 8.07 (2 H, d, H6, $J=1.8$ Hz)	3320 (NH), 1690, 1605	696 (M^+ , 77); 104 (100)	120–122

spectra were recorded at room temperature in CDCl_3 solution on a Varian Gemini 200 spectrometer (δ in ppm referred to Me_4Si). Mass spectra were recorded on a Carlo Erba QMD 1000 spectrometer. NBS, NCS, Bu_4NCl , Br_2 , I_2 , AgClO_4 , FeCl_3 , CuCl_2 , and solvents were all Aldrich commercial reagent grade products. Indoxyl (1),²⁴ NCBT²⁵ and BPA²⁶ were prepared according to the literature.

Reaction of indoxyl (1) with NBS, NCS, NCBT, Br_2 , FeCl_3 , CuCl_2 . General procedure. A MeCN (10 ml) solution of the reagent (0.5 mmol) was added dropwise to a solution of indoxyl (1) (0.056 g, 0.25 mmol) in 5 ml of the same solvent. The mixture was left to react for 5 h, evaporated to dryness, taken up with CH_2Cl_2 , washed with distilled water, dried over Na_2SO_4 , filtered and concentrated to a small volume. The residue was then chromatographed on silica-gel preparative plates eluting with benzene/cyclohexane 7:3 and/or cyclohexane/ethyl acetate 7:3. Products and yields are reported in Table 1.

Reaction of indoxyl (1) with tris(4-bromophenyl)aminium hexachloroantimonate (BPA) in the presence of tetrabutylammonium chloride. A MeCN (10 ml) solution of BPA (0.41 g, 0.5 mmol) was added dropwise to a MeCN (5 ml) solution of indoxyl (1) (0.056 g, 0.25 mmol) and tetrabutylammonium chloride (0.28 g, 1 mmol). The mixture was left to react for 5 h, evaporated to dryness, taken up with CH_2Cl_2 , washed with distilled water, dried over Na_2SO_4 , filtered and concentrated to a small volume. The residue was then chromatographed on silica-gel preparative plates eluting with benzene/cyclohexane 7:3 and cyclohexane/ethyl acetate 7:3. Products and yields are reported in Table 1.

Reaction of indoxyl (1) with $\text{I}_2/\text{AgClO}_4$. A 0.1 M MeCN solution of AgClO_4 (10 ml, 1 mmol) was added dropwise to a MeCN (10 ml) solution containing indoxyl (1) (0.056 g, 0.25 mmol) and I_2 (0.127 g, 0.5 mmol). The mixture was left to react for 5 h, evaporated to dryness, taken up with CH_2Cl_2 , washed with distilled water, dried over Na_2SO_4 , filtered and concentrated to a small volume. The residue was then chromatographed on silica-gel preparative plates eluting with benzene/cyclohexane 7:3 and cyclohexane/ethyl acetate 7:3. Products and yields are reported in Table 1.

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