Reaction of indolinonic aminoxyls with nitric oxide

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2-Methyl-2-phenyl-3-oxoindolin-1-yloxyl and 2-methyl-2-phenyl-3-aryliminoindolin-1-yloxyl radicals react with nitric oxide in the absence and presence of oxygen to form both substituted and unsubstituted *N*-nitro and *N*-nitroso stable compounds as the main products, while mono and dinitro compounds are formed in minor yields. In the presence of oxygen, the formation of the corresponding quinone imine *N*-oxide is observed. Mechanisms for the formation of the reaction products are proposed and discussed, leading to new insights into the chemistry of nitric oxide with aminoxyls. Crystal structures of 2-methyl-2-phenyl-*N*-nitrosoindolin-3-one and 2-methyl-2-phenyl-*N*-nitroindolin-3-one have been determined.

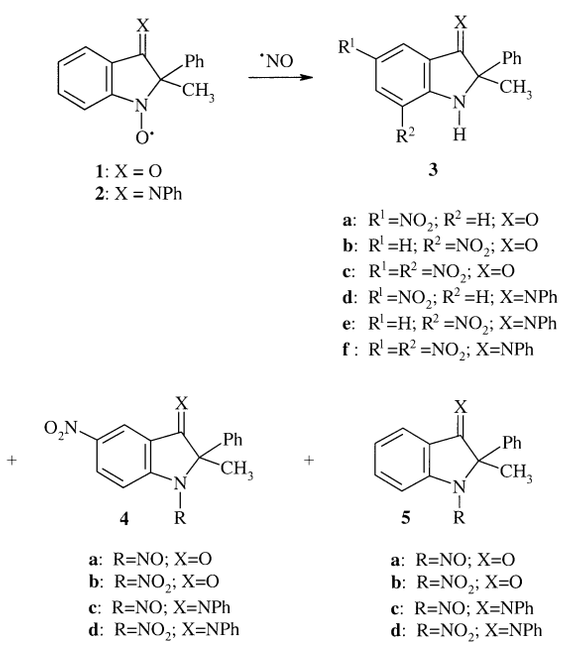
Introduction

The radical scavenging activity of indolinonic aminoxyls has now been well established; in fact, they are extremely versatile in reacting with oxygen-centered radicals (peroxyls,[1] alkoxyls,[2] hydroxyl,[3] superoxide [3,4]), with sulfur-centered radicals (thiyls),[5] and with carbon-centered radicals [6] yielding products substituted on the benzene ring in the first two cases and alkylated hydroxylamines in the third. The above mentioned reactive oxygen radicals are all involved in a cascade of events that ultimately lead to conditions of 'oxidative stress' in biological systems.[7] Recently, however, nitric oxide has been added to the list of paramagnetic species implicated in physiological and patho-physiological events [8,9] and this has led to an explosion in research centering on this diatomic free radical. It was therefore of interest to study the chemical behaviour of indolinonic aminoxyls with this hydrophobic, paramagnetic gas produced in biological systems.[10] In fact, although the reaction of aromatic quinolinic aminoxyls with nitric oxide generated by different means has already been studied by others,[11] the reactions of indolinonic aminoxyls have not been previously investigated. Here, we report on the data of the reaction of 2-methyl-2-phenyl-3-oxoindolin-1-yloxyl (**1**) and 2-methyl-2-phenyl-3-aryliminoindolin-1-yloxyl (**2**) with nitric oxide in the absence and in the presence of oxygen. The results described and the mechanisms proposed give new insights into the chemistry of this class of aminoxyls towards another biologically relevant free radical species. In addition, the secondary reactions of nitric oxide, either with superoxide to give peroxynitrite or with oxygen yielding the nitrosoperoxyl radical and nitrogen dioxide, are worthy of attention. In fact, because of these secondary reactions, different reaction products arise when nitric oxide and aminoxyls react in the presence of oxygen.

Results

The reactions of 2-methyl-2-phenyl-3-oxoindolin-1-yloxyl (**1**) and 2-methyl-2-phenyl-3-aryliminoindolin-1-yloxyl (**2**) with nitric oxide in the absence and in the presence of oxygen were performed in benzene at room temperature either under argon or air. The results show that there is interaction of nitric oxide or nitrogen dioxide with the aminoxyl function and/or its conjugated benzene ring. All compounds were separated by chromatography after concentration of the reaction mixture under reduced pressure, and their yields, reported in Table 1, are the average of two individual runs.

The reaction between 2-methyl-3-oxo-2-phenylindolin-1-yloxyl (**1**) and nitric oxide in the absence of oxygen led to the products **3**–**5** shown in Scheme 1. The main products were the



Scheme 1

unsubstituted *N*-nitroso (**5a**) and *N*-nitro (**5b**) compounds, together with their corresponding 5-nitroso substituted derivatives (**4a** and **4b**). Other minor products were the mono and dinitro substituted amines **3a–c**. The same reaction performed in the presence of oxygen yielded the same products as those reported in Scheme 1, with the exception of compound **3b**. In addition, however, the quinone imine *N*-oxide **6a** was isolated and this was the main reaction product (Fig. 1).

Likewise, the reaction between 2-methyl-3-arylimino-2-phenylindolin-1-yloxyl (**2**) and nitric oxide in the absence of

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Table 1 Percentage yields of products of the reaction between indolinonic aminoxyls **1** or **2** and nitric oxide in the presence or absence of oxygen

Reagents	Products (% yields)
1 + $^{\bullet}$NO	**3a** (4); **3b** (6); **3c** (3); **4a** (16); **4b** (15); **5a** (15); **5b** (15)
1 + $^{\bullet}$NO + O_2	**3a** (16); **3c** (3); **4a** (17); **4b** (16); **5a** (7); **5b** (4); **6a** (26)
2 + $^{\bullet}$NO	**3d** (6); **3e** (7); **3f** (4); **4c** (15); **4d** (14); **5c** (23); **5d** (17)
2 + $^{\bullet}$NO + O_2	**3e** (6); **3f** (7); **4c** (13); **4d** (11); **5c** (8); **5d** (6); **6b** (29); **7** (7)

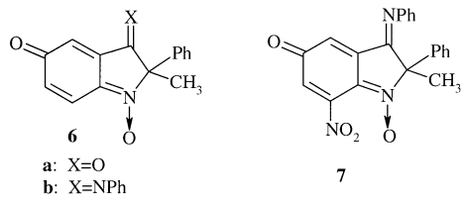


Fig. 1

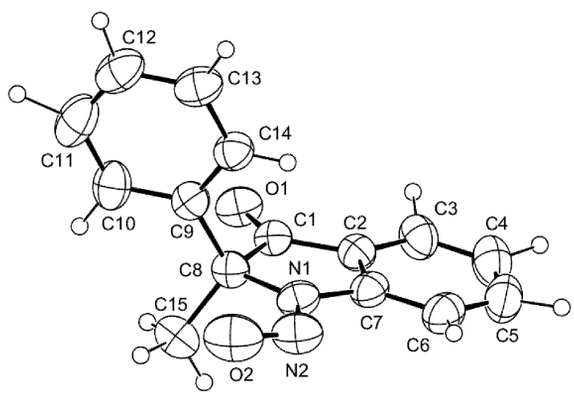


Fig. 2 An ORTEP perspective view (30% probability ellipsoids) of compound **5a**.

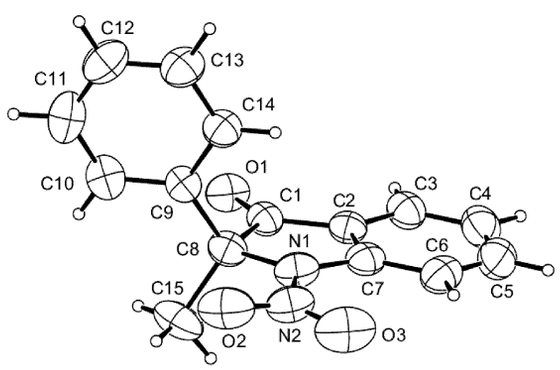


Fig. 3 An ORTEP perspective view (30% probability ellipsoids) of compound **5b**.

oxygen led to the products **3**–**5** shown in Scheme 1 with a similar product distribution to that for aminoxyl **1**. When the reaction was performed in the presence of oxygen, similar products to those in its absence were isolated, except for compound **3d**, and with the addition of the nitro-substituted quinone imine *N*-oxide **7**. The main reaction product was, in this case too, the quinone imine *N*-oxide **6b** (Fig. 1).

All the products **2**–**7** isolated were identified by their spectroscopic data (^{1}H NMR, high resolution mass spectroscopy, FT-IR) and by comparison with data for similar compounds in the case of quinone imine *N*-oxides **6**.[1,2] In addition, the structures of compounds **5a** and **5b** were determined by X-ray analysis (Fig. 2 and 3).

The ^{1}H NMR spectra of compounds **5a** and **5c** show, in both cases, two methyl singlets corresponding to the two conformers *Z* and *E* produced by the *N*-nitroso group. This is not observed when a nitro group is bonded to the indole nitrogen as in compounds **5b** and **5d**. A similar pattern was observed between compounds **4a** and **4c**, and **4b** and **4d** where a nitroso and nitro group are attached to the indole nitrogen, respectively. This is in agreement with the findings of Korth *et al.*[11] in their study of quinolinic aminoxyls with nitric oxide, and is the typical ^{1}H NMR behaviour of *N*-nitroso compounds.[12]

With regard to the substituted amines **3**, the position in which the nitro group is attached to the benzene ring of the indolinic moiety was determined by comparing the differences in the patterns of the H-4, H-5, H-6 and H-7 in their ^{1}H NMR spectra, due to the loss of the signals from H-5 and/or H-7 to which the nitro group is attached. In particular, compounds substituted at C-5 show a doublet ($J \cong 2.3$ Hz) due to H-4, a pseudo-quartet ($J \cong 9.2$ and 2.3 Hz) due to H-6 and a doublet ($J = 9.2$ Hz) due to H-7; whereas compounds substituted at C-7 show two pseudo-quartets for H-4 and H-6 and a pseudo-triplet for H-5. This is particularly evident in derivatives of aminoxyl **1**. Interestingly, the N–H proton in the 7-substituted amines **3b** and **3e** and in the 5,7-disubstituted amines **3c** and **3f** is deshielded due to hydrogen bonding between the N–H group and the nitro group causing a downfield chemical shift.[13]

Additional support for the structural assignments was obtained from the FT-IR spectra. The compounds bearing a nitro group on the benzene ring typically absorb in the 1370–1300 cm^{-1} range, and/or those bearing this same group on the nitrogen of the indole nucleus absorb between 1300–1250 cm^{-1}. The nitroso derivatives instead show characteristic absorption peaks between 1500–1430 cm^{-1}. High resolution mass spectra of all new compounds showed the expected molecular ion peak and in most cases the fragmentation due to the substituent was characteristic.

In the solid state, compounds **5a** (Fig. 2) and **5b** (Fig. 3) show very close geometry. Bond distances and angles are in agreement with the hybridization expected for the atoms involved. In both compounds, the oxoindole system is planar (maximum deviation from planarity: 0.050(4) Å for C(5) and 0.024(4) Å for C(8) in **5a** and **5b**, respectively); the dihedral angles that it forms with the mean plane through N(1), N(2), O(2) in **5a** and N(1), N(2), O(2), O(3) in **5b** are 1.2(2) and 6.8(2)° respectively. The phenyl rings are almost perpendicular to the oxoindole ring in both compounds, the dihedral angle that they form being 79.5(1) and 80.3(2)° for **5a** and **5b** respectively. The orientation of the phenyl ring is determined by an attractive intramolecular C(14)–H(14) ··· N(1) interaction (see Table 2) causing a C(14)–C(9)–C(8)–N(1) torsion angle of 29.2(3) and 32.2(6)° in compounds **5a** and **5b**, respectively. Molecular packing in both compounds is mainly determined by C–H ··· O intermolecular attractive interactions (see Table 2) of the same type. In compound **5b**, two intramolecular C–H ··· O interactions cooperate to keep the nitro group approximately coplanar with the pyrrole ring as shown by torsion angles of C(8)–N(1)–N(2)–O(2) = − 8.6(9) and C(7)–N(1)–N(2)–O(3) = −2.5(10)° .

Discussion

The main purpose of this work was to study the interaction between aromatic indolinonic aminoxyls with nitric oxide in order to increase our knowledge of the chemical behaviour of these aminoxyls towards different radical species implicated in the oxidation of biomolecules. The chemistry of indolinonic aminoxyls, deduced from the type of products obtained, is not much different from that previously observed for aromatic

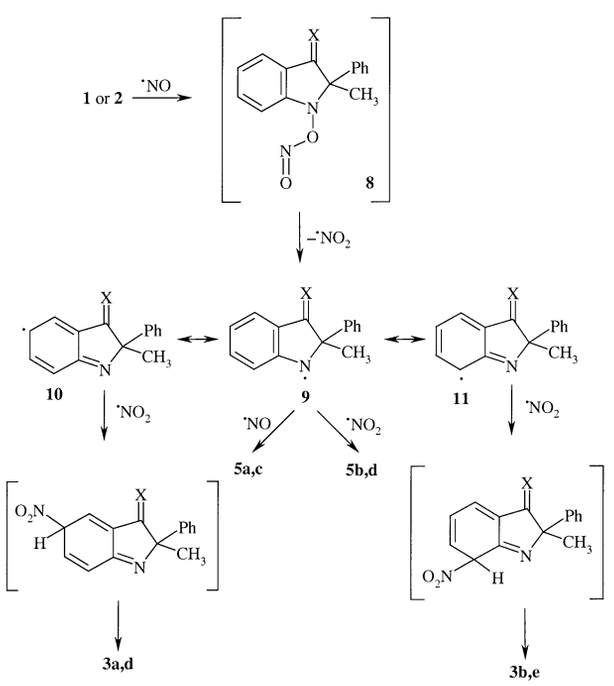
Table 2 Relevant hydrogen bonds in compounds **5a** and **5b**

	D–H/Å	H ··· A/Å	D ··· A/Å	D–H ··· A/°	Action
Compound **5a**					
C(14)–H(14) ··· N(1)	0.95	2.50	2.847(3)	102	Phenyl orientation
C(6)–H(6) ··· O(1) [a]	0.98	2.37	3.285(5)	154	Packing
C(11)–H(11) ··· O(2) [b]	1.12	2.32	3.307(5)	147	Packing
Compound **5b**					
C(14)–H(14) ··· N(1)	0.93	2.54	2.857(6)	100	Phenyl orientation
C(6)–H(6) ··· O(3)	0.93	2.32	2.808(11)	112	Nitro-group orientation
C(15)–H(153) ··· O(2)	0.96	2.40	2.920(8)	113	Nitro-group orientation
C(15)–H(151) ··· O(2) [c]	0.96	2.50	3.313(8)	142	Packing
C(6)–H(6) ··· O(1) [d]	0.93	2.56	3.414(8)	154	Packing
C(11)–H(11) ··· O(2) [e]	0.93	2.52	3.309(11)	143	Packing

[a] $-0.5 - x, 0.5 + y, 0.5 - z$. [b] $0.5 - x, -0.5 + y, 0.5 - z$. [c] $-0.5 + x, 1.5 - y, -0.5 + z$. [d] $0.5 - x, 0.5 + y, -0.5 - z$. [e] $1.5 - x, -0.5 + y, -0.5 - z$.

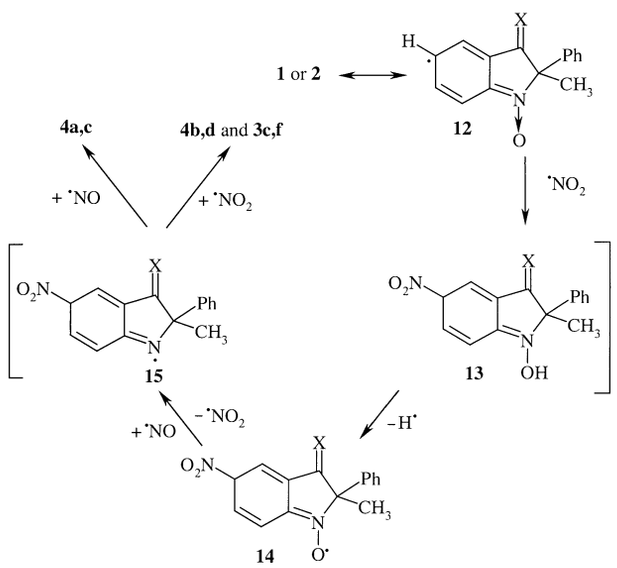
quinolinic aminoxyls[11] even if new compounds have been obtained in the present work, such as the *N*-nitro substituted derivatives **4b** and **4d** and the unsubstituted derivatives **5b** and **5d**. However, on the basis of the reaction products and of the chemical behaviour of aminoxyls studied extensively by this research group,[1–6,14] a few, new significant considerations may be put forth.

Previously, when investigating the reaction of aminoxyls with thiyl radicals,[5,14] we observed that the first step was the formation of the –O–S– bond between the oxygen of the >N–O moiety and the thiyl radical. This combination, which is also in agreement with other literature data,[15] strongly weakens the >N–O– bond; consequently, the adduct with the >N–O–S– group undergoes homolytic cleavage at the >N–O– bond. We believe that in this case too, the first step of the reaction leads to formation of an adduct >N–O–NO (**8**) (Scheme 2) in which the



Scheme 2

same bond is weakened. Cleavage of this bond produces $^{\bullet}NO_2$ and the aminyl radical (**9**). This is the key step which leads to the formation of the isolated products reported in Scheme 1, while Schemes 2 and 3 show the steps involved. Even in alkoxyamines (>N–O–R), which have recently attracted considerable interest in controlled radical polymerization,[16] the oxygen–nitrogen bond, in many cases, is weaker than the oxygen–carbon bond, favouring homolytic cleavage of the former. This leads to aminyl and alkoxyl radicals. The reasons



Scheme 3

for this behaviour are the fact that there is the formation of an aminyl radical which is stabilized by resonance and the fact that the >N–O– bond is weaker because of the α-effect.[17]

Aminyl radical **9** may couple with either nitric oxide or nitrogen dioxide at the indole nitrogen to give the unsubstituted nitroso or nitro derivatives **5** respectively, while the monosubstituted nitroamines **3** derive from coupling of nitrogen dioxide with the mesomeric forms of the aminyl radical (**10**, **11**), as shown in Scheme 2. The 5-nitro substituted *N*-nitro or -nitroso derivatives **4** are likely to arise from coupling of nitric oxide with the mesomeric form of the starting aminoxyls (**12**) to give the 5-substituted nitroaminoxyl (**14**) (Scheme 3). This then undergoes a similar reaction to that described in Scheme 2, leading to an aminyl radical (**15**) which readily reacts with either nitric oxide or nitrogen dioxide to give the above mentioned compounds. A similar mechanism may be invoked for the formation of the di-substituted nitroamines **3**. Attempts were made to isolate the intermediate nitroaminoxyl such as **14** but they failed because of the impossibility of controlling the amount of nitric oxide added in our reaction system from the nitric oxide gas cylinder. Nevertheless, our knowledge of the chemistry of indolinonic aminoxyls[1–6] leads us to believe that this is the most likely path for formation of products **4a–d** and **3c,f**. However, it is important to underline that the two mechanisms depicted in Schemes 2 and 3 are in competition with each other and neither of the two can rule out the other.

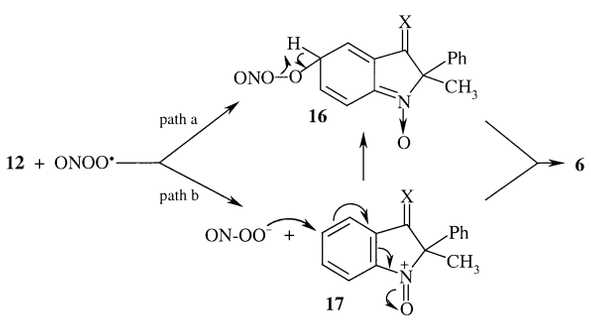
The reactions performed in the presence of oxygen led to almost the same products as those reported in Scheme 1, but in addition, quinone imine *N*-oxides **6** were obtained as the main

products. These compounds were never observed when the reactions were performed in the absence of oxygen. This result leads to new insights into the reactions of nitric oxide with aminoxyls. In fact, as stated in the introduction, nitric oxide reacts with oxygen to give the nitrosoperoxyl radical, which is in all aspects a peroxyl radical [eqns. (1) and (2)].

$$^{\bullet}NO + O_2 \longrightarrow ONOO^{\bullet} \quad (1)$$

$$ONOO^{\bullet} + {}^{\bullet}NO \longrightarrow ONOONO \longrightarrow 2{}^{\bullet}NO_2 \quad (2)$$

Therefore, the chemical behaviour of this species may be regarded as being similar to that of alkylperoxyls. Previously, we demonstrated that aromatic aminoxyls react with peroxyl radicals leading to the formation of the quinone imine *N*-oxide in very high yield.[1] This same mechanism may be invoked to explain the attainment of compounds **6** arising from the interaction between the nitrosoperoxyl radical and aminoxyls **1** and **2** as well as the formation of compound **7**.[1] An interesting point worth commenting on, is that in the presence of oxygen, the yields of compounds **5** are rather reduced with respect to those obtained in the reactions performed under argon. This could possibly be due to the fact that when oxygen is present, it readily reacts with nitric oxide to form the nitrosoperoxyl radical which attacks the conjugated benzene ring of the indole nucleus, forming the intermediate **16**. This then rearranges to compound **6** (Scheme 4, path a).



Scheme 4

An alternative mechanism for the formation of compounds **6** could be *via* the oxoammonium ion **17** (Scheme 4, path b) but on the basis of the reduction potential of $ONOO^{\bullet}$ reported in the literature ($E^{\circ}_{ONOO^{\bullet}/ONOO^{-}} = 0.4$ V),[18] it is unlikely that this species can oxidize the aminoxyl to the oxoammonium ion. However, we believe that the E° value of the couple $ONOO^{\bullet}/ONOO^{-}$ may be of the same order of magnitude as those of alkylperoxyls[19] or even higher and thus the possibility that the quinone imine *N*-oxides could be formed in this way is feasible.

In conclusion, the results obtained upon reaction of aminoxyls **1** and **2** with nitric oxide in the presence or absence of oxygen are not much different from those obtained with aromatic quinolinic aminoxyls.[11] However, besides the new reaction products identified in the present work and the mechanisms hypothesized, we have shown that the chemistry of nitric oxide may be different according to whether it is in an aerobic or anaerobic milieu. Although this is expected considering the rapid oxidation of nitric oxide to nitrogen dioxide, here we show that this conversion involves the formation of the nitrosoperoxyl radical which is believed to be the species responsible for the production of the quinone imine *N*-oxides. Other studies performed recently by our group on the interaction of nitric oxide with naphthols in the presence or absence of oxygen, showed that there is no reaction when oxygen is absent, whereas in its presence, high yields of nitronaphthols are obtained.[20] In addition, the results obtained are interesting from the antioxidant perspective of these indolinonic aminoxyls. Several studies have now highlighted the excellent antioxidant efficacy of these compounds in diverse biological systems subjected to different forms and levels of oxidation.[21] The results reported here, now suggest that indolinonic aminoxyls could also offer protection in biological systems exposed to oxidative stress mediated by nitric oxide, with the understanding, however, that *in vitro* results may differ substantially from *in vivo* transformations.

Experimental

FT-IR spectra were recorded in KBr on a Perkin Elmer Spectrum MGX1 spectrophotometer equipped with a Spectra Tech. "Collector" for DRIFT measurements. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$ solution on a Varian Gemini 200 MHz spectrometer (δ in ppm are relative to Me_4Si). High resolution mass spectra were recorded on a VG7070-E 5000 spectrometer with PFK as the resolution and calibration standard. Aminoxyls **1** and **2** were prepared according to the literature methods;[22] nitric oxide, 98.5%, was purchased from Aldrich (Milan, Italy) while all solvents were either Carlo Erba (Milan, Italy) or Aldrich RP-ACS grade products.

Reaction of aminoxyls 1 and 2 with nitric oxide. General procedure

To a solution of aminoxyl **1** (0.85 mmol) or **2** (0.64 mmol) in 50 ml dry benzene, a vacuum was first applied followed by degassing with argon; this procedure was repeated three times in order to exclude air as much as possible. To this solution under vacuum, nitric oxide was added to regenerate atmospheric pressure, at room temperature and under magnetic stirring. The reaction occurs at the gas/liquid interface and the quantity of nitric oxide added, calculated on the basis of the ideal gas law, was about four times in excess. The mixture was left to react for 3 hours during which the reaction solution turned from the typical red colour to dark yellow. The mixture was then degassed well with argon and evaporated to dryness. The residue was chromatographed on a silica column using petroleum ether as eluant to which ethyl ether was progressively added until an 8 : 2 ratio was obtained. The products were isolated in the following order for aminoxyl **1**: **5b**, **5a**, **3b**, **4a**, **4b**, **3a**, **3c** and in the following order for aminoxyl **2**: **5d**, **5c**, **3e**, **4c**, **4d**, **3d**, **3f**. The isolated products were further purified two or three times on silica-gel preparative plates, eluting with either benzene or petroleum ether–diethyl ether 9 : 1.

2-Methyl-2-phenyl-5-nitroindolin-3-one (3a). ^{1}H NMR δ 1.81 (3 H, s, -CH_3), 5.79 (1 H, br, NH), 6.95 (1 H, d, $J = 9.2$ Hz, 7-H), 7.4 (5 H, m, arom), 8.40 (1 H, dd, $J_1 = 9.2$, $J_2 = 2.3$ Hz, 6-H), 8.51 (1 H, d, $J = 2.3$ Hz, 4-H); IR (DRIFT) ν_{max} 3324 (NH), 1701 (C=O), 1620, 1490, 1329 (NO_2) cm^{-1}; MS *m/z* (rel. int.) 268 (M^+, 54), 239 (100), 193 (100); HRMS calcd. for $C_{15}H_{12}N_2O_8$ 268.0848, found 268.0844.

2-Methyl-2-phenyl-7-nitroindolin-3-one (3b). ^{1}H NMR δ 1.84 (3 H, s, -CH_3), 6.89 (1 H, pseudo-t, $J_1 = 7.3$, $J_2 = 8.3$ Hz, 5-H), 7.4 (5 H, m, arom), 7.64 (1 H, br, NH), 7.91 (1 H, dd, $J_1 = 7.3$, $J_2 = 0.9$ Hz, 6-H), 8.37 (1 H, dd, $J_1 = 8.3$, $J_2 = 1.3$ Hz, 4-H); IR (DRIFT) ν_{max} 3444 (NH), 1722 (C=O), 1635, 1476, 1317 (NO_2) cm^{-1}; MS *m/z* (rel. int.) 268 (M^+, 100), 239 (64), 210 (53), 193 (74); HRMS calcd. for $C_{15}H_{12}N_2O_8$ 268.0848, found 268.0845.

2-Methyl-2-phenyl-5,7-dinitroindolin-3-one (3c). ^{1}H NMR δ 1.91 (3 H, s, -CH_3), 7.41 (5 H, m, arom), 8.16 (1 H, br, NH), 8.72 (1 H, d, $J = 2.3$ Hz, 5-H), 9.29 (1 H, d, $J = 2.3$ Hz, 4-H); IR (DRIFT) ν_{max} 3359 (NH), 1717 (C=O), 1459, 1335 (br, $2NO_2$) cm^{-1}; MS *m/z* (rel. int.) 313 (M^+, 100), 284 (69), 255 (65), 192 (91); HRMS calcd. for $C_{15}H_{11}N_3O_5$ 313.0699, found 313.0694.

2-Methyl-2-phenyl-3-phenylimino-5-nitroindoline (3d). ^{1}H NMR δ 2.02 (3 H, s, -CH_3), 5.92 (1 H, br, NH), 6.83 (4 H, m, arom), 7.32–7.62 (8 H, m, arom), 8.17 (1 H, dd, J_1 = 9.1, J_2 = 2.2 Hz, 7-H); IR (DRIFT) ν_{max} 3357 (NH), 1653, 1615, 1317 (NO_2) cm^{-1}; MS *m*/*z* (rel. int.) 343 (M^+, 100), 328 (23), 266 (93), 220 (31); HRMS calcd. for $C_{21}H_{17}N_3O_2$ 343.1321, found 343.1316.

2-Methyl-2-phenyl-3-phenylimino-7-nitroindoline (3e). ^{1}H NMR δ 2.01 (3 H, s, -CH_3), 6.42 (1 H, dd, J_1 = 8.0, J_2 = 7.9 Hz, 5-H), 6.64 (1 H, d, J = 7.4 Hz, arom), 6.77 (2 H, m, arom), 7.14 (1 H, m, arom), 7.35 (5 H, m, arom), 7.58 (2 H, m, arom), 7.71 (1 H, s, br, NH), 8.07 (1 H, dd, J_1 = 8.4, J_2 = 1.2 Hz, 4-H); IR (DRIFT) ν_{max} 3444 (NH), 1644, 1622, 1474, 1317 (NO_2) cm^{-1}; MS *m*/*z* (rel. int.) 343 (M^+, 36), 326 (100), 295 (76); HRMS calcd. for $C_{21}H_{17}N_3O_2$ 343.1321, found 343.1317.

2-Methyl-2-phenyl-3-phenylimino-5,7-dinitroindoline (3f). ^{1}H NMR δ 2.07 (3 H, s, -CH_3), 6.77 (2 H, m, arom), 7.3–7.59 (9 H, m, arom), 8.20 (1 H, s, br, NH), 9.03 (1 H, d, J = 2.2 Hz, 4-H); IR (DRIFT) ν_{max} 3398 (NH), 1663, 1621, 1522, 1333 (NO_2) cm^{-1}; MS *m*/*z* (rel. int.) 388 (M^+, 53), 372 (100), 341 (100), 294 (89); HRMS calcd. for $C_{21}H_{16}N_4O_4$ 388.1171, found 388.1165.

2-Methyl-2-phenyl-5-nitro-*N*-nitrosoindolin-3-one (4a). The ^{1}H NMR spectrum was recorded on a mixture of both *Z* and *E* isomers (6 : 1 ratio). Only the major isomer could be fully described. Major isomer: ^{1}H NMR δ 1.99 (3 H, s, -CH_3), 7.09 (2 H, m, arom), 7.35 (3 H, m, arom), 8.39 (1 H, dd, J_1 = 8.3, J_2 = 1.3 Hz, 6-H), 8.70–8.78 (2 H, m, 4-H, 7-H). Minor isomer: ^{1}H NMR (incomplete description) δ 2.32 (3 H, s, -CH_3); IR (DRIFT) ν_{max} 1741 (C=O), 1613, 1533, 1468 (NO), 1344 (NO_2) cm^{-1}; MS *m*/*z* (rel. int.) 297 (M^+, 1), 267 (100), 221 (50), 193 (29); HRMS calcd. for $C_{15}H_{11}N_3O_4$ 297.0749, found 297.0741.

2-Methyl-2-phenyl-5-nitro-*N*-nitroindolin-3-one (4b). ^{1}H NMR δ 2.20 (1 H, s, -CH_3), 7.21 (2 H, m, arom), 7.37 (3 H, m, arom), 8.67 (3 H, m, arom); IR (DRIFT) ν_{max} 1742 (C=O), 1613, 1530, 1345 (C-NO_2), 1272 (N-NO_2) cm^{-1}; MS *m*/*z* (rel. int.) 313 (M^+, 6), 267 (100), 239 (31), 221 (45), 193 (38); HRMS calcd. for $C_{15}H_{11}N_3O_5$ 313.0699, found 313.0692.

2-Methyl-2-phenyl-3-phenylimino-5-nitro-*N*-nitrosoindoline (4c). The ^{1}H NMR spectrum was recorded on a mixture of both *Z* and *E* isomers (4 : 1 ratio). Only the major isomer could be fully described. Major isomer: ^{1}H NMR δ 2.19 (3 H, s, -CH_3), 6.72 (1 H, m, arom), 7.2–7.5 (10 H, m, arom), 8.24 (1 H, d, J = 9.0 Hz, 7-H), 8.46 (1 H, dd, J_1 = 9.1, J_2 = 2.2 Hz, 6-H). Minor isomer: ^{1}H NMR (incomplete description) δ 2.47 (3 H, s, -CH_3); IR (DRIFT) ν_{max} 1678, 1594, 1528, 1462 (NO), 1342 (NO_2) cm^{-1}; MS *m*/*z* (rel. int.) 372 (M^+, 2), 342 (100), 326 (20), 266 (89); HRMS calcd. for $C_{21}H_{16}N_4O_3$ 372.1222, found 372.1215.

2-Methyl-2-phenyl-3-phenylimino-5-nitro-*N*-nitroindoline (4d). ^{1}H NMR δ 2.40 (3 H, s, -CH_3), 6.69 (3 H, m, arom), 7.2–7.47 (7 H, m, arom), 8.38–8.58 (3 H, m, arom); IR (DRIFT) ν_{max} 1684, 1611, 1553, 1525, 1342 (C-NO_2), 1262 (N-NO_2) cm^{-1}; MS *m*/*z* (rel. int.) 388 (M^+, 14), 371 (39), 348 (46), 266 (45); HRMS calcd. for $C_{21}H_{16}N_4O_4$ 388.1171, found 388.1165.

2-Methyl-2-phenyl-*N*-nitrosoindolin-3-one (5a). The ^{1}H NMR spectrum was recorded on a mixture of both *Z* and *E* isomers (3 : 1 ratio). ^{1}H NMR δ 1.97 (3 H, s, -CH_3, *Z*-form), 2.26 (3 H, s, -CH_3, *E*-form), 7.1–7.92 (16 H, m, 4-H, 5-H, 6-H, 5 arom H), 8.25 (1 H, dd, J_1 = 8.5, J_2 = 1.0 Hz, 7-H, *Z*-form), 8.81 (1 H, dd, J_1 = 8.5, J_2 = 0.9 Hz, 7-H, *E*-form); IR (DRIFT) ν_{max} 1728 (C=O), 1636, 1605, 1459, 1437 (NO) cm^{-1}; MS *m*/*z* (rel. int.) 252 (M^+, 2), 222 (100), 194 (99); HRMS calcd. for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0894.

2-Methyl-2-phenyl-*N*-nitroindolin-3-one (5b). ^{1}H NMR δ 2.16 (3 H, s, -CH_3), 7.24 (2 H, m, arom), 7.39 (4 H, m, arom), 7.87 (2 H, m, arom), 8.49 (1 H, d, J = 8.1 Hz, 7-H); IR (DRIFT) ν_{max} 1729 (C=O), 1597, 1538, 1451, 1284 (NO_2) cm^{-1}; MS *m*/*z* (rel. int.) 268 (M^+, 6), 222 (100), 194 (23), 152 (27); HRMS calcd. for $C_{15}H_{12}N_2O_3$ 268.0848, found 268.0845.

2-Methyl-2-phenyl-3-phenylimino-*N*-nitrosoindoline (5c). The ^{1}H NMR spectrum was recorded on a mixture of both *Z* and *E* isomers (3 : 1 ratio). ^{1}H NMR δ 2.18 (3 H, s, -CH_3, *Z*-form), 2.42 (3 H, s, -CH_3, *E*-form), 6.59–6.82 (6 H, m, arom), 6.89–7.61 (20 H, m, arom), 8.13 (1 H, dd, J_1 = 8.2, J_2 = 0.9 Hz, 7-H, *Z*-form), 8.78 (1 H, dd, J_1 = 8.3, J_2 = 0.9 Hz, 7-H, *E*-form); IR (DRIFT) ν_{max} 1668, 1590, 1441 (NO) cm^{-1}; MS *m*/*z* (rel. int.) 327 (M^+, 2), 297 (100), 221 (65); HRMS calcd. for $C_{21}H_{17}N_3O$ 327.1372, found 327.1364.

2-Methyl-2-phenyl-3-phenylimino-*N*-nitroindoline (5d). ^{1}H NMR δ 2.37 (3 H, s, -CH_3), 6.67 (3 H, m, arom), 6.97 (1 H, m, arom), 7.14 (1 H, m, arom), 7.35 (7 H, m, arom), 7.57 (1 H, m, arom), 8.41 (1 H, dd, J_1 = 8.4, J_2 = 0.9 Hz, 7-H); IR (DRIFT) ν_{max} 1668, 1593, 1536, 1450, 1280 (NO_2) cm^{-1}; MS *m*/*z* (rel. int.) 343 (M^+, 23), 326 (45), 297 (96), 221 (100), 206 (76); HRMS calcd. for $C_{21}H_{17}N_3O_2$ 343.1321, found 343.1315.

Reaction of aminoxyls 1 and 2 with nitric oxide in the presence of oxygen. General procedure

To a solution of aminoxyl **1** (0.85 mmol) or **2** (0.64 mmol) in 50 ml dry benzene, nitric oxide was bubbled through for 15 min at room temperature and under magnetic stirring. The reaction occurs in the benzene solution, but in this case the amount of nitric oxide added in excess was unquantifiable. The mixture was left to react for 3 hours during which the reaction solution turned from the typical red colour to dark yellow. The mixture was then degassed well with argon and evaporated to dryness. The residue was chromatographed on a silica column using petroleum ether as eluant to which diethyl ether was progressively added until an 8 : 2 ratio was obtained. The products were isolated in the following order for aminoxyl **1**: **5b**, **5a**, **4a**, **4b**, **3a**, **3c**, **6a** and in the following order for aminoxyl **2**: **5d**, **5c**, **3e**, **4c**, **4d**, **3f**, **7**, **6b**. The isolated products were further purified two or three times on silica-gel preparative plates, eluting with either benzene or petroleum ether–diethyl ether 9 : 1. The quinone imine *N*-oxides **6a** and **6b** were identified by comparison with authentic products.[1]

2-Methyl-2-phenyl-3-phenylimino-5-oxo-7-nitro-3,5-dihydro-2*H*-indole 1-oxide (7). ^{1}H NMR δ 2.19 (3 H, s, -CH_3), 5.90 (1 H, s, 7-H), 6.81 (3 H, m, arom), 7.3–7.5 (7 H, m, arom), 8.15 (1 H, s, 4-H); IR (DRIFT) ν_{max} 1633 (C=O), 1523, 1336 (NO_2); MS *m*/*z* (rel. int.) 373 (M^+, 5), 359 (12), 342 (52), 266 (17); HRMS calcd. for $C_{21}H_{15}N_3O_4$ 373.1062, found 373.1057.

Experimental data for the X-ray diffraction studies on crystalline compounds 5a and 5b[23]

Data for compound **5a** were collected on an Enraf-Nonius CAD4 four-circle diffractometer with graphite-monochromatized Cu-Kα radiation using the $\omega/2\theta$ scan mode. Unit cell parameters were determined by automatic centering of 24 strong reflections ($18 < \theta < 35°$) and refined by the least-squares method. Data for compound **5b** were collected on a Siemens AED three-circle diffractometer with graphite-monochromatized Cu-Kα radiation using the $\theta/2\theta$ scan mode. Unit cell parameters were determined by automatic centering of 25 strong reflections ($16 < \theta < 29.5°$) and refined by the least-squares method. The details of the X-ray data collection, structure solution, and refinement are given in Table 3. After every 150 (for **5a**) or 100 (for **5b**) reflections, three reflections were collected in order to monitor orientation and crystal decay. For

Table 3 Experimental data for the X-ray crystal structure determination of compounds **5a** and **5b**

	5a	**5b**
Molecular formula	$C_{15}H_{12}N_2O_2$	$C_{15}H_{12}N_2O_3$
Molecular mass	252.3	268.3
Temperature/K	293(3)	293(3)
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$ (#14)	$P2_1/n$ (#14)
Cell parameters	[a]	[a]
a/Å	10.076(2)	9.871(2)
b/Å	13.318(3)	13.901(3)
c/Å	10.721(2)	10.714(2)
α/°	90	90
β/°	117.39(2)	115.3(2)
γ/°	90	90
V/Å^3	1277.4(5)	1329.1(5)
Z	4	4
F(000)	528	560
d(calcd.)/Mg m^{-3}	1.312	1.341
Size of crystal/mm	0.43 × 0.48 × 0.68	0.24 × 0.34 × 0.42
Measured reflections	2665	2765
Independent reflections	2418	2514
Observed reflections	1639	970
Criterion for observation	$I>2\sigma(I)$	$I>\sigma(I)$
μ(Cu-Kα)/mm^{-1} [b]	0.69	0.75
R	0.071	0.087
$wR2$	0.216	0.231
$\Delta\rho_{max}$ [c]/e Å^{-3}	0.47	0.31
$\Delta\rho_{min}$ [d]/e Å^{-3}	−0.25	−0.23
Refined parameters	161	182
Max. shift/s.u.	<0.001	<0.001

[a] Determined by centering of 24 ($18 < \theta < 35°$) and 25 ($16 < \theta < 29.5°$) reflections for **5a** and **5b**, respectively. [b] Radiation Cu-Kα ($\lambda = 1.54178$ Å). [c] Maximum peaks in final difference synthesis. [d] Minimum peaks in final difference synthesis.

both compounds, no significant intensity decay was observed. Lorentz polarization but not absorption correction was applied. The crystal quality was tested by ψ scans showing that crystal absorption effects could be neglected. Both structures were solved by direct methods using the SHELXS[24] computer program and refined with the SHELX93[25] computer program using the observed reflections. Refinement was done by full matrix least-squares first isotropically and then anisotropically for all non-H atoms. The function minimized was $\Sigma w(\Delta F^2)^2$. Anomalous scattering corrections were included in all structure factor calculations.[26b] Scattering factors for neutral atoms were taken from ref. 26*a* for non-hydrogen atoms and from ref. 27 for H. The hydrogen atoms in **5a** were located from a difference Fourier map and introduced in the refinement as fixed atom contributors ($U_{iso} = 0.10$ Å^2). The hydrogen atoms in **5b** were put in geometrically calculated positions and refined with an overall isotropic thermal parameter using a riding model. For both compounds the weighting scheme $w = 1/[\sigma^2(F_o^2) + (aP)^2]$ [with $P = (|F_o|^2 + 2|F_c|^2)/3$] was applied in the last stage of refinement, with a resulting in the value of 0.1067 and 0.1957 for **5a** and **5b**, respectively. In compound **5b** the ratio reflections–parameters = 970/182 = 5.3 is particularly unfavorable, possibly due to the rather high thermal parameters (average $U_{eq} = 0.123$ Å^{-2}). Despite this, the results of the refinement appear to be quite acceptable in terms of geometric description of the structure.

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