1,2-Nucleophilic addition on 2-phenyl-3*H*-indol-3-one and 2-phenyl-3-phenylimino-3*H*-indole and their corresponding 1-oxides. An attempt to synthesize water-soluble aminoxyls. Crystal structure of 3-ethoxycarbonyl-2,3,3a,4-tetrahydro-2,4-dioxo-3a-phenylisoxazolo[2,3-*a*]indole

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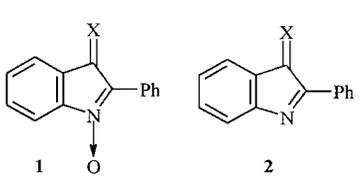
3-Indolinonic (**1a**) and 3-phenyliminoindolinonic (**1b**) 1-oxides react at carbon 2 with diethyl malonate and ethyl acetoacetate anions, yielding intermediate anions which undergo cyclization in the reaction medium to form an isoxazolidine ring. The cyclization occurs through the interaction of the oxygen of the primitive *N*-oxide function with a carbonyl group of the reagents. The same substrates react with dilithium phenylacetate anion, leading to the formation of stable and water-soluble carboxylated aminoxyls. The indolenin-3-one **2a** and its corresponding 3-phenylimino derivative **2b** also react with the above-mentioned nucleophiles to form carboxylated 3-indoxyls without cyclization; oxidation with *m*-chloroperbenzoic acid does not yield carboxylated aminoxyls in appreciable amount. The structure of the product of cycloaddition obtained from the reaction of compound **1a** with diethyl malonate was determined by X-ray analysis.

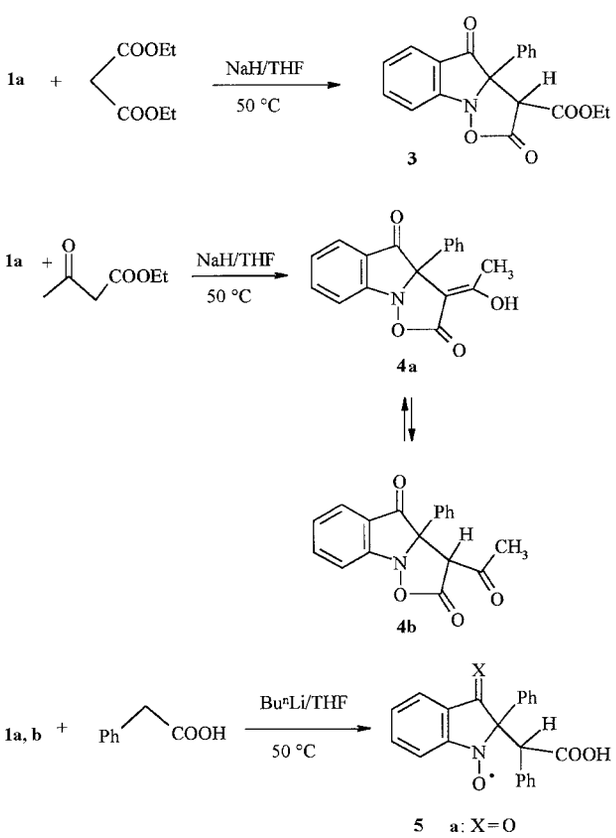
Aminoxyls have received widespread interest for their involvement in polymer,[1] rubber[2] and oil stabilization,[3] being intermediates in the cycle of hindered aliphatic and aromatic secondary amines used as photostabilizers and stabilizers.[4] Aliphatic aminoxyls have also been applied in biological systems, mainly as spin labels[5] and as antioxidants: the latter property is partly due to their superoxide dismutase (SOD)-mimic[6] activity. Furthermore, they are products formed during spin-trapping experiments.[7] More recently, lipid-soluble aromatic aminoxyls have been used as antioxidants in preventing oxidative stress in lipids,[8] proteins,[9] low-density protein[10] and DNA.[11] With the aim of improving the biological applications of aromatic aminoxyls, we tried to functionalize their structure with one or more carboxylic groups to make them more water soluble. Addition of carboxylate α-anions to compounds **1** and **2**, which are precursors of aromatic stable aminoxyls, was planned as the synthetic route.

Results and discussion

It is well known that nitrones[12] and aromatic *N*-oxides[13] undergo nucleophilic addition to yield hydroxylamines, which in some cases are oxidized to stable aminoxyls.



a: X = O
b: X = NPh



Scheme 1

Compounds **1a** and **1b** were allowed to react with diethyl malonate, ethyl acetoacetate and phenylacetic acid in the presence of a base. The products isolated are shown in Scheme 1 and their yields are reported in Table 1. The reaction with diethyl malonate and ethyl acetoacetate anions occurs only with compound **1a** (2-phenylisatogen). The structure of compound

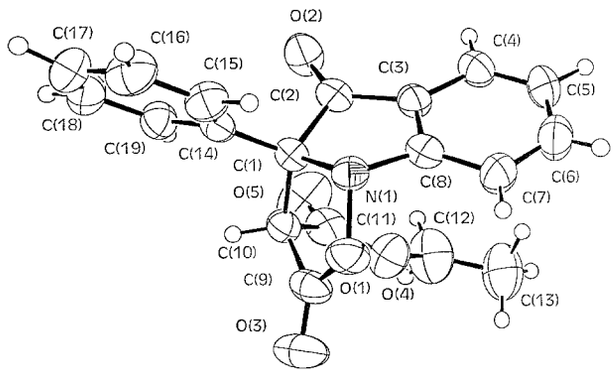


Fig. 1 ORTEP view of molecule 1 of compound **3**. The thermal ellipsoids are given at 50% probability.

Table 1 Yields of compounds **3**–**5** and **8**–**10**

Compound	Yield (%)
3	90
4	89
5a	72
5b	32
7	65
8a	85
8b	82
9	40
10a	48
10b	45

3, which derives from the reaction with diethyl malonate anion, was determined by X-ray analysis (Fig. 1) and its spectroscopic data. In particular, in its IR spectrum the absorptions at 1797 and 1735 cm^{-1} agree with the absorptions of the carbonyl group of the isoxazolidine moiety and the ethoxycarbonyl group, respectively; the ^1H NMR spectrum shows a singlet due to the CH moiety in between the two carbonyl groups at δ 4.3; the mass spectrum shows the corresponding molecular-ion peak (*m*/*z* 337) and typical fragmentation arising from loss of an ethyl group (*m*/*z* 308), an ethoxycarbonyl group (*m*/*z* 264) and both an ethoxycarbonyl group and CO_2 (*m*/*z* 220).

Compound **4**, obtained from the reaction of compound **1a** with ethyl acetoacetate anion, may exist in two tautomeric forms **4a/4b** as shown in Scheme 1, but its spectroscopic data are in favour of the enolic form **4a**. In fact, if compared to that of ester **3**, the ^1H NMR spectrum of compound **4** lacks the CH singlet that must be present in the ketonic form. The IR spectrum of compound **4** shows a very broad OH absorption over the aliphatic CH bonds stretchings, and three overlapped signals between 1763 and 1710 cm^{-1}. These could be due to the α,β unsaturated carbonyl group of the tautomeric form **4a**, which is certainly stabilized by a hydrogen bond of the OH group with the adjacent carbonyl group of the isoxazolidine, leading to a six-membered ring. Both NMR and IR signals due to the hydroxy group disappear after deuteration.

The reactions of compound **1a** with diethyl malonate and ethyl acetoacetate occur by addition of the anion to the carbon 2 of the penta-atomic ring of the indole molecule. The intermediate anion reacts further, leading to the formation of an isoxazolidine ring, as previously observed in the reaction of phenylisatogen with α-anions of substituted acetonitriles.[14] Every attempt to force imine **1b** to react with the same anions failed and, at present, we are unable to explain this different behaviour. The reactions of compounds **1a** and **1b** with dilithium phenylacetate α-anion led to the formation of aminoxyls **5a** and **5b**. Both compounds were identified by their spectroscopic data, in particular mass (even if in the case of imine **5b** the highest-mass-ion peak is M − COOH) and EPR

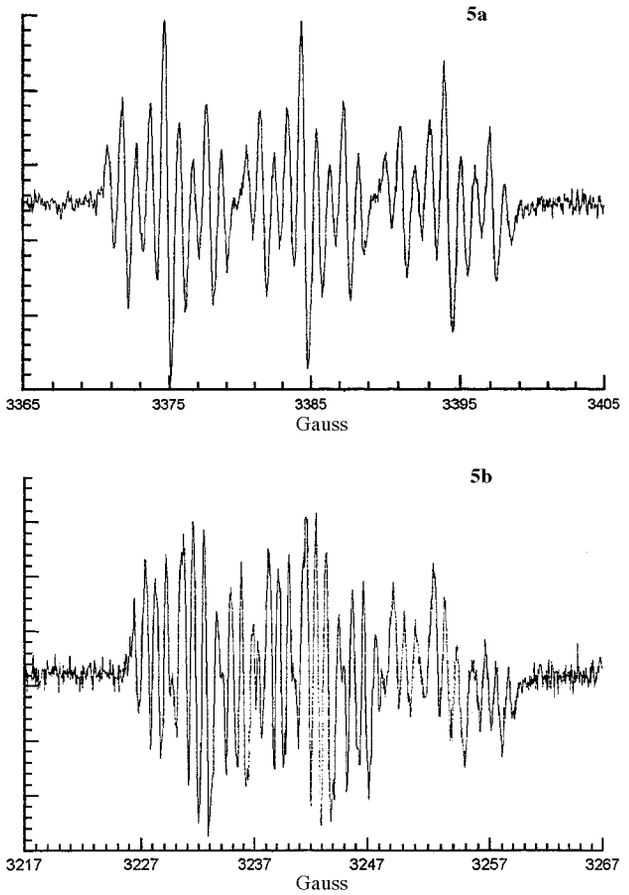
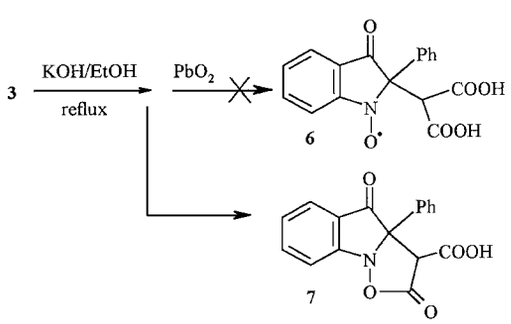


Fig. 2 Experimental EPR spectra of aminoxyls **5a** and **5b** in water.

spectra (Fig. 2), that show hyperfine coupling constants (hfccs, Table 2) in agreement with those of other indolinonic and aryliminoindolinonic aminoxyls.[15] The particularly high hfcc of the nitrogen ($a_N \cong 11$ Gauss) of these two aminoxyls is certainly due to the aqueous solvent: in fact, it is well known that in aminoxyls the a_N-value increases with the polarity of the solvent.[16]

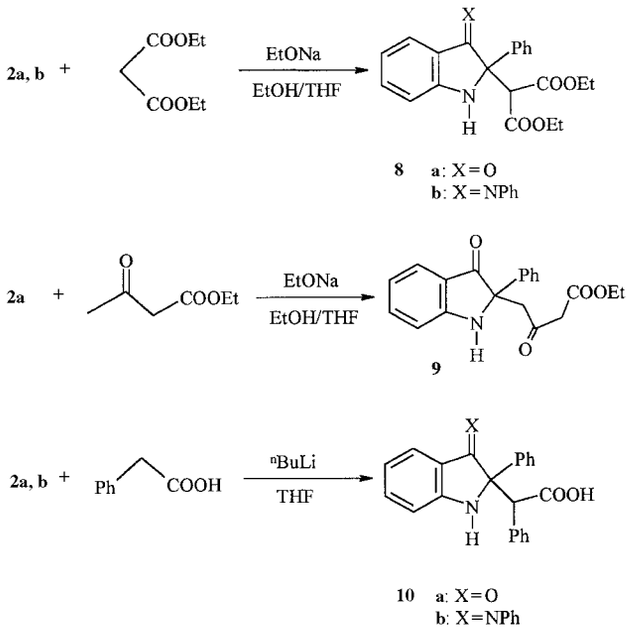
In order to obtain products containing carboxylic groups, such as aminoxyl **6**, compound **3** was hydrolysed: however, instead of compound **6**, the reaction afforded tricyclic compound **7** which was isolated and characterized.



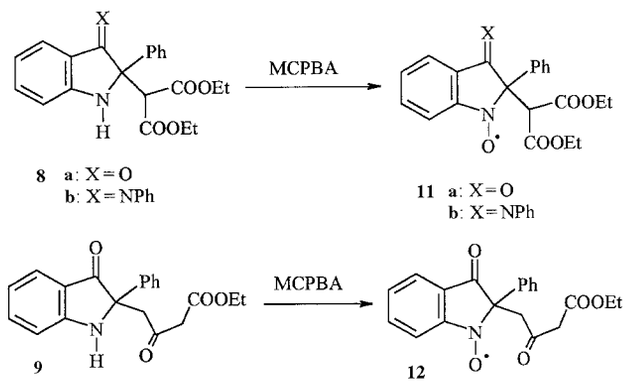
An alternative path to carboxylic-substituted aminoxyls is shown in Scheme 2. Compounds **2a** and **2b** react with the carbanions already described in Scheme 1 to form the indoxyls **8**–**10**, which are obtained in good yields (Table 1) and are suitable precursors for the synthesis of stable aminoxyls.[17] Compounds **2a** and **2b** react easily with diethyl malonate anion, to yield diesters **8a** and **8b**, which were characterized by comparing their spectroscopic data with those of indoxyls previously described.[18] It is noteworthy that the two ethyl groups of the malonate moiety bonded at C-2 are not magnetically equivalent

Table 2 Simulated coupling constants of aminoxyls **5a**, **5b, 11a, 11b** and **12**

Compound (solvent)	a_N	a_{HC-5}	a_{HC-7}	a_{HC-4}	a_{HC-6}	a_{NC-3}	a_{HC-2}
5a (water)	10.52(1N)	3.15(1H)	3.03(1H)	1.02(1H)	1.01(1H)		0.12(1H)
5b (water)	10.89(1N)	3.36(1H)	3.19(1H)	1.14(1H)	1.03(1H)	0.83(1N)	
11a ($CHCl_3$)	9.62(1N)	3.04(1H)	2.92(1H)	1.01(1H)	0.99(1H)		0.29(1H)
11b ($CHCl_3$)	9.70(1N)	3.15(1H)	2.34(1H)	1.16(1H)	1.02(1H)	0.90(1N)	0.31(1H)
12 ($CHCl_3$)	9.16(1N)	2.92(1H)	2.78(1H)	0.99(1H)	0.92(1H)		0.28(1H)
							0.42(1H)



Scheme 2



Scheme 3

and this may be due to the chirality of the adjacent C-2, which renders these two groups diastereotopic.

Ethyl acetoacetate anion reacts only with compound **2a**, and the product isolated is the unexpected compound **9**. Given the lack of a suitable explanation, this behaviour could be justified by the steric hindrance at the α-anion of ethyl acetoacetate. The structure of product **9** was demonstrated by a two-dimensional NMR experiment (HETCOR): it can be observed that the two doublets at δ 2.89 and δ 3.87, having a coupling constant of 18 Hz, are correlated to the same carbon at δ 49.6. Clearly, this carbon is the C-4 of the ethyl acetoacetate moiety, bonded to the chiral C-2 of the indole ring of substrate **2a**, that makes the two protons bonded to C-4 geminally coupled.

The reactions of imines **2a** and **2b** with the anion of phenyl acetate led to products **10a** and **10b**, which were isolated and characterized by their spectroscopic data (see Experimental section). These two compounds are quite unstable; in fact, under mild acidic conditions or during chromatography, they undergo retrogression to give back the starting material **2a** and **2b**, respectively.

Aminoxyls **11a**, **11b** and **12** can be easily obtained by oxidizing amines **8a**, **8b** and **9** respectively, with *m*-chloroperbenzoic acid (MCPBA) (Scheme 3). Unfortunately, these reactions give rise to mixtures of products from which aminoxyls **11a**, **11b** and **12** cannot be separated in appreciable yields. However, aminoxyls **11** and **12**, whose signals are reported in Fig. 3, were characterized by their EPR parameters (Table 2).

The antioxidant activity of indolinonic aminoxyls in biological systems is today very well documented.[19,20] Aminoxyl **5a** is sufficiently soluble in phosphate buffer at pH 7.4, whereas aminoxyl **5b** is soluble in aqueous sodium hydrogen carbonate; however, because the biological applications of antioxidants do not usually require concentrations higher than 100 μM, the solubility of compound **5a** is high enough for experiments in a hydrophilic medium.

Molecular geometry of 3-ethoxycarbonyl-2,3,3a,4-tetrahydro-2,4-dioxo-3a-phenylisoxazol[2,3-*a*]indole 3

The intramolecular bond distances and angles (Table 3) are coherent with the hybridization expected for the atoms involved and comparable with those of analogous compounds reported in the literature[21] and in particular from ref. 22, in which the same system of three condensed rings is described. In the isoxazolidine ring the O(1)–N(1) bond [1.463(3) and 1.459(4) Å in molecule 1 and 2 respectively (see later)] is longer, as expected, than O(1)–C(9) 1.370(4) and 1.364(5) Å, indicative of a partial π delocalization involving endo and hexocyclic oxygens.

In both independent molecules the five-membered rings are not planar; the Cremer and Pople parameters[23,24] reveal that the pyrrole rings adopt a *twist* conformation with a pseudo-two-fold axis through C(3), and that the isoxazole rings adopt an *envelope* conformation with a pseudo-symmetry plane through C(1). The angles between the mean planes of the indolic benzene and the isoxazolidine ring, with respect to the pyrrole ring, are 6.7(2) and 117.7(1) and 6.4(2) and 117.4(1)° in molecule 1 and 2 respectively. Packing is consistent with Van der Waals interactions. The structure was solved in the space group *Cc* with two molecules in the asymmetric unit. The two molecules are very similar and are correlated by a non-crystallographic two-fold axis in the *x* direction. Any attempt to solve the structure in another space group of the monoclinic or orthorhombic *F* system failed. On the other hand our attempts to describe this crystal structure with a non-*Cc* group space were also unsuccessful.

Experimental

Mps are uncorrected and were measured with an Electrothermal apparatus. IR spectra were recorded in the solid state on a Nicolet Fourier Transform Infrared 20–SX spectrophotometer equipped with a Spectra Tech. "Collector" for DRIFT measurements. ^{1}H NMR and ^{13}C NMR spectra were recorded at rt in $CDCl_3$ or C_6D_6 solution on a Varian Gemini 200 spectrometer (TMS was taken as reference peak). Mass spectra were performed on a Carlo Erba QMD 1000 mass

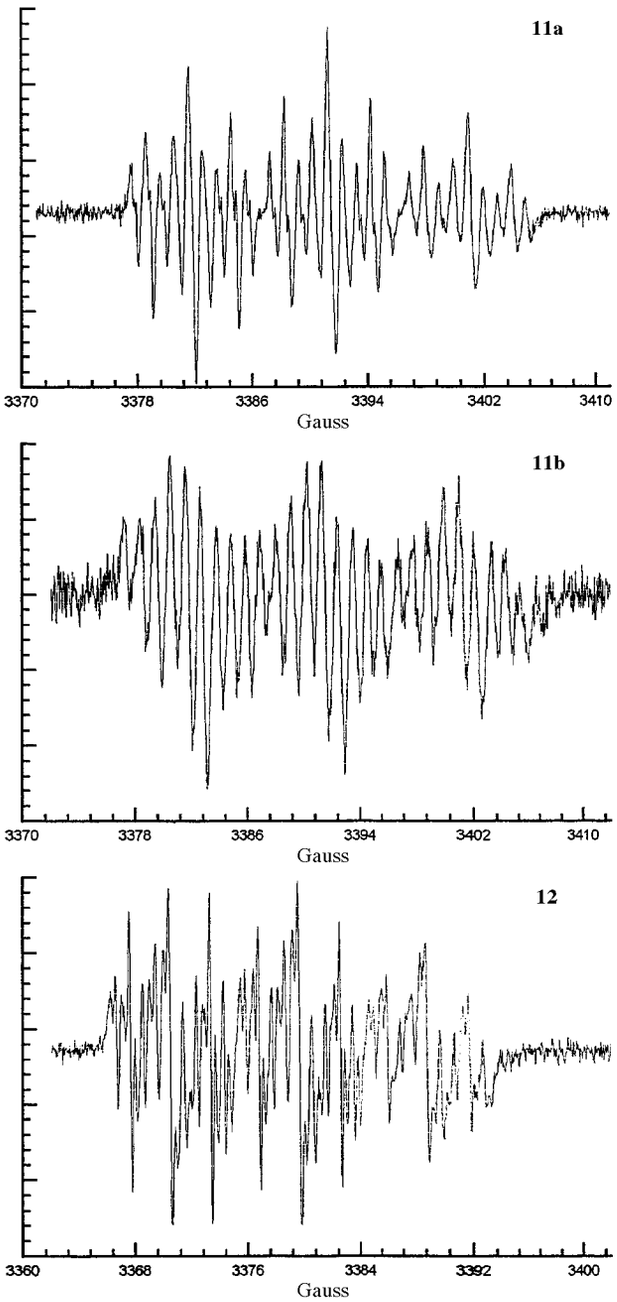


Fig. 3 EPR spectra of compounds **11a**, **11b** and **12** in $CHCl_3$.

spectrometer, equipped with a Fisons GC 8060 gas chromatograph. EPR spectra were recorded on a Varian E4 spectrometer interfaced with a computer (for acquisition, editing and simulation of experimental signals) and equipped with an XL microwave 3120 frequency counter and with a ruby in the cavity as reference.

Compounds **1a**,[25] **1b**,[26] **2a**[27] and **2b**[28] were prepared according to the literature. Diethyl malonate, ethyl acetoacetate, phenylacetic acid and MCPBA were purchased from Aldrich and used without further purification. All reactions were performed using different bases and solvents: the best results were obtained with the reported conditions.

Reaction of compound 1a with diethyl malonate

Na (0.24 g, 10 mmol) was dissolved in absolute EtOH (30 ml) under argon, then ethyl malonate (1.52 ml, 10 mmol) was added. The solution was heated to 45 °C, and a solution of compound **1** (1.00 g, 4.5 mmol in 80 ml of THF) was then added dropwise in 60 min. The mixture was stirred for 15 min, poured into water, NH_4Cl added and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried on Na_2SO_4 and concentrated to dryness. The crude residue was then chromatographed on a SiO_2 column using cyclohexane–ethyl acetate from 9 : 1 to 7 : 3 as eluant. The isolated compound **3** was crystallized from CH_3OH: (90% yield), mp 90 °C; IR(KBr)/cm^{-1} 1797, 1735, 1604 and 1448; ^1H NMR, $\delta(CDCl_3)$ 1.11 (t, 3H, J = 7.2 Hz), 4.12 (q, 2H, J = 7.2 Hz), 4.31 (s, 1H), 7.4 (m, 4H) and 7.75 (m, 5H); M^+ ($C_{19}H_{15}NO_5$), 337.33; MS (EI^+): *m*/*z* 337 (M^+, 2%), 308 (6), 292 (10), 264 (23), 248 (25) and 220 (100) (Calc. for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 68.15; H, 4.4; N, 4.05%).

Table 3 Selected bond distances (Å) and angles (deg) with esd's in parentheses for compound **3**[a]

	Molecule 1	Molecule 3
O(1)–N(1)	1.463(3)	1.459(4)
O(1)–C(9)	1.370(4)	1.364(5)
O(2)–C(2)	1.214(4)	1.220(4)
O(3)–C(9)	1.181(4)	1.189(4)
N(1)–C(1)	1.494(4)	1.486(4)
N(1)–C(8)	1.425(4)	1.426(4)
C(1)–C(2)	1.561(4)	1.557(4)
C(1)–C(10)	1.541(5)	1.544(4)
C(2)–C(3)	1.456(4)	1.459(4)
C(3)–C(8)	1.385(4)	1.392(4)
C(7)–C(8)	1.391(5)	1.387(5)
C(9)–C(10)	1.512(5)	1.513(5)
N(1)–O(1)–C(9)	109.6(2)	109.6(3)
O(1)–N(1)–C(8)	110.4(2)	110.3(2)
O(1)–N(1)–C(1)	107.5(2)	107.7(2)
N(1)–C(1)–C(10)	103.3(2)	103.4(2)
N(1)–C(1)–C(2)	101.7(2)	102.0(2)
C(1)–C(2)–C(3)	106.0(2)	106.4(2)
C(2)–C(3)–C(8)	109.0(2)	108.3(2)
N(1)–C(8)–C(3)	110.7(2)	110.9(2)
O(1)–C(9)–C(10)	110.1(3)	110.3(3)
C(1)–C(10)–C(9)	104.1(3)	103.6(2)

[a] The crystallographic numbering scheme shown in Fig. 1 is used.

Reaction of compound 1a with ethyl acetoacetate

The reaction was carried out as described above, using the same molar quantities. Compound **4** was isolated by chromatography on SiO_2 column by using cyclohexane–ethyl acetate from 9 : 1 to 7 : 3 as eluant, and was crystallized from EtOH (89% yield), mp 95 °C; IR(KBr)/cm^{-1} 3170–2850 (stretching O-H, br, which disappears with D_2O), 1763, 1718, 1471 and 1359; ^1H NMR, $\delta(CDCl_3)$ 1.90 (s, 3H), 6.71 (t, 1H, J = 7.4 Hz), 7.04 (m, 5H), 7.27 (m, 2H), 8.03 (d, 1H, J = 7.3 Hz) and 11.92 (br, disappears with D_2O); M^+ ($C_{18}H_{13}NO_4$), 307.31; MS (EI^+) *m*/*z* 307 (M^+, 4%), 263 (52), 248 (96), 220 (100) and 208 (18) (Calc. for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56. Found: C, 70.2; H, 4.3; N, 4.45%).

Reaction of compound 1a with phenylacetic acid

Bu^nLi (3.2 ml, 7.92 mmol) was added dropwise under argon to a solution of phenylacetic acid (0.6 g, 4.4 mmol in 25 ml of THF). After 10 min a solution of compound **1** (0.5 g, 2.2 mmol in 25 ml of THF) was added dropwise. The solution was stirred for 6 h, then freshly prepared PbO_2 (4 g, 16.7 mmol) was added. After 30 min the mixture was filtered and the filtrate was evaporated to dryness and chromatographed on a SiO_2 column, using $CHCl_3$–CH_3OH from 99 : 1 to 80 : 20 as eluant, gave compound **5a** (72% yield) mp 85 °C; IR(KBr)/cm^{-1} 1724, 1587, 1488 and 1390; M^+ ($C_{22}H_{16}NO_4$), 358.37; MS (EI^+) *m*/*z* 357 ($M^+ - H$, 3%), 223 (40), 207 (36), 179 (80) and 105 (79) (Calc. for $C_{22}H_{16}NO_4$: C, 73.73; H, 4.5; N, 3.91. Found: C, 73.9; H, 4.4; N, 3.8%). The EPR parameters are reported in Table 2.

Reaction of compound 1b with phenylacetic acid

Compound **5b** was obtained with the procedure described for the parent ketone **5a** starting from the same molar quantities (32% yield), mp 102 °C; IR(KBr)/cm^{-1}: 1727, 1656, 1592, 1488 and 1440; M$^+$, 433.49; MS(EI$^+$) *m*/*z* 388 (M$^+$ − COOH, 3%), 372 (4), 298 (3), 282 (58), 205 (20) and 179 (65) (Calc. for $C_{28}H_{21}N_2O_3$: C, 77.58; H, 4.88; N, 6.46. Found: C, 77.35; H, 4.6; N, 6.5%). The EPR parameters are reported in Table 2.

Basic hydrolysis of compound 3

Compound **3** (1 mmol) was dissolved in hot EtOH 95% (20 ml), then KOH (10 mmol) was added and the mixture was stirred under reflux for 7 h. Potassium salt of product **7** was filtered off and dissolved in water (100 ml). After acidification, the solution was extracted with $CHCl_3$ (3 × 30 ml). The organic layer was dried (Na_2SO_4), and concentrated under vacuum. Compound **7** was crystallized from EtOH (65% yield), mp 126 °C; ^{1}H NMR (200 MHz; DMSO; 25 °C) δ 7.42 (m, 3H), 7.51 (m, 3H), 7.67 (d, 1H, J = 7.8 Hz) and 7.76 (d, 2H, J = 7.8 Hz); IR(KBr)/cm^{-1} 3500–2800br (COO-H stretching), 1753, 1728, 1703, 1450 and 1387; M$^+$, 309.28; MS(EI$^+$) *m*/*z* 309 (M$^+$, 1%), 265 (7), 220 (76), 208 (24) and 105 (90) (Calc. for $C_{17}H_{11}NO_5$: C, 66.02; H, 3.58; N, 4.53. Found: C, 66.4; H, 3.5; N, 4.5%).

Reaction of compound 2a with ethyl malonate

Na (0.115 g, 4.8 mmol) was dissolved in absolute EtOH (30 ml) under argon, then ethyl malonate (7.6 ml, 5 mmol) was added. The solution was stirred at rt, then a solution of compound **2a** (1.00 g, 4.8 mmol in 50 ml of THF) was added dropwise. After 60 min the reaction mixture was poured into water, NH_4Cl added and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried on Na_2SO_4 and concentrated to dryness. The crude residue when washed with diethyl ether gave product **8a**, which was filtered off and crystallized from EtOH (85% yield), mp 128 °C; IR(KBr)/cm^{-1} 3305, 1747, 1729, 1619, 1469 and 1388; ^{1}H NMR, δ($CDCl_3$) 0.85 (t, 3H, J = 7.2 Hz), 1.02 (t, 3H, J = 7.2 Hz), 4.03 (q, 2H, J = 7.2 Hz), 4.04 (q, 2H, J = 7.2 Hz), 4.71 (s, 1H), 6.06 (s, 1H), 6.81 (t, 1H, J = 7.5 Hz), 6.97 (d, 1H, J = 8.3 Hz), 7.28 (m, 3H) and 7.51 (m, 4H); M$^+$, 367.40; MS(EI$^+$) *m*/*z* 367 (M$^+$, 1%), 207 (35) and 179 (100) (Calc. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.9; H, 5.6; N, 3.9%).

Reaction of compound 2a with ethyl acetoacetate

The same procedure described above, starting from the same molar quantities, was used to obtain compound **9**, which was isolated as an oil at rt (40% yield), IR(KBr)/cm^{-1} 3386, 1747, 1729, 1702, 1614, 1477 and 1375; ^{1}H NMR, δ($CDCl_3$) 1.24 (t, 3H, J = 7.2 Hz), 2.89 (d, 1H, J = 18 Hz), 3.38 (s, 2H), 3.87 (d, 1H, J = 18 Hz), 4.15 (q, 2H, J = 7.2 Hz), 6.02 (br), 6.81 (t, 1H, J = 7.5 Hz), 6.94 (d, 1H, J = 8.3 Hz), 7.28 (m, 4H) and 7.52 (m, 3H); M$^+$ ($C_{20}H_{19}NO_4$), 337.38; MS(EI$^+$) *m*/*z* 337 (M$^+$, 18%), 295 (78), 266 (54), 222 (46), 208 (100), 193 (60) and 180 (36).

Reaction of compound 2a with phenylacetic acid

Bu^{n}Li (3.3 ml, 8.2 mmol) was added dropwise to a solution of phenylacetic acid (0.65 g, 4.8 mmol in 15 ml of THF) under argon. This mixture was then added to a solution of compound **2a** (0.5 g, 2.4 mmol in 15 ml of THF). The resulting mixture was stirred for 1 h, poured into water, NH_4Cl added and extracted with three portions of diethyl ether (3 × 20 ml). The combined organic layers were dried on Na_2SO_4 and concentrated to give a crude residue, which was chromatographed on SiO_2 column, using $CHCl_3$–CH_3OH from 9 : 1 to 5 : 5 as an eluant. Compound **10a** was crystallized from $CHCl_3$ (48% yield), mp 215–217 °C (decomp.); IR(KBr)/cm^{-1} 3419, 3300–3050br, 1749, 1658, 1619, 1490 and 1385; ^{1}H NMR, δ($CDCl_3$) 4.78 (s, 1H), 5.12 (br, 1H), 6.80 (t, 1H, J = 7.6 Hz), 6.94 (d, 1H, J = 8.1 Hz), 7.04 (m, 2H), 7.20 (m, 5H) and 7.55 (d, 1H, J = 7.4 Hz); M$^+$, 343.38; MS(EI$^+$) *m*/*z* 343 (M$^+$, 5%), 299 (4), 267 (47), 208 (100), 180 (45) and 105 (21) (Calc. for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.65; H, 4.9; N, 4.1%).

Reaction of compound 2b with diethyl malonate

Following the conditions described for the reaction of ketone **2a** and starting from the same molar quantities, compound **8b** was isolated and crystallized from EtOH (82% yield), mp 17 °C; IR(KBr)/cm^{-1} 3438, 1745, 1608, 1446 and 1390; ^{1}H NMR, δ($CDCl_3$) 0.96 (t, 3H, J = 7.2 Hz), 1.03 (t, 3H, J = 7.2 Hz), 4.05 (m, 4H), 4.89 (s, 1H), 5.88 (s, 1H), 6.37 (s, 1H), 6.39 (s, 1H), 6.80 (d, 2H, J = 7.7 Hz), 6.87 (d, 1H, J = 7.5 Hz), 7.22 (m, 7H) and 7.63 (d, 2H, J = 7.7 Hz); M$^+$, 442.51; MS(EI$^+$) *m*/*z* 442 (M$^+$, 1%), 282 (90), 206 (4), 179 (100), 103 (4) and 77 (45) (Calc. for $C_{27}H_{26}N_2O_4$: C, 73.29; H, 5.92; N, 6.33. Found: C, 73.35; H, 5.8; N, 6.25%).

Reaction of compound 2b with phenylacetic acid

The reaction was carried out as described for ketone **2a** starting from the same molar quantities. Compound **10b** was not crystallized due to its instability (45% yield); IR(KBr)/cm^{-1} 3415, 1706, 1608, 1467 and 1381; ^{1}H NMR, δ($CDCl_3$) 3.94 (s, 1H), 5.66 (br), 6.13 (d, 1H, J = 7.4 Hz), 6.18 (t, 1H, J = 8.0 Hz), 6.58 (d, 2H, J = 7.6 Hz), 6.77 (d, 1H, J = 7.4 Hz), 7.07 (q, 2H, J = 7.3 Hz), 7.37 (m, 5H) and 7.93 (d, 2H, J = 8.0 Hz); M$^+$ ($C_{28}H_{22}N_2O_2$), 418.49; MS(EI$^+$) *m*/*z* 374 (M$^+$ − CO_2, 5%), 297 (3), 284 (70), 204 (50) and 180 (45).

Oxidation of amines 8 and 9 to aminoxyls 11 and 12. General procedure

Solid MCPBA (0.1 mmol) was added to a solution of the amine (0.01 mmol) in 1 ml of $CHCl_3$. The mixture was stirred for 2 min, then deaerated with argon for 2 min. EPR spectra were periodically recorded until the signal of the aminoxyls appeared. With time the signal of the appropriate aminoxyl disappeared and an unresolved signal appeared. In all cases TLC of the reaction mixture showed the formation of a mixture of products.

Crystal structure of isoxazolo[2,3-*a*]indole 3-ethoxycarbonyl-2,3,3a,4-tetrahydro-2,4-dioxo-3a-phenyl 3

Table 4 shows the experimental and crystallographic data for compound **3**. The intensities I_{hkl} were determined by analysing the reflection profiles by the Lehmann and Larsen procedure.[29] Corrections for Lorentz and polarization effects were performed; there were no corrections for polarization effects.

Atomic scattering factors were from the International Tables for X-ray Crystallography.[30] Bibliographic searches were carried out using the Cambridge Structural Database Files through the Servizio Italiano di Diffusione Dati Cristallografici, Parma, Italy.

Full crystallographic data, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/300.

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Table 4 Experimental data for the X-ray diffraction studies on crystalline compound **3**

Formula	$C_{19}H_{15}NO_5$
Crystal habit	Prism
Crystal colour	Orange
Fw $F(000)$	337.3, 1408
Crystal system	Monoclinic
Space group	*Cc*
Cell parameters at 295 K [a]	
a (Å)	9.772(2)
b (Å)	13.098(3)
c (Å)	26.490(4)
α (deg)	90
β (deg)	100.6
γ (deg)	90
V (Å^3)	3332.7(16)
Z	8
D_{calc} (g cm^{-3})	1.34
Crystal dimensions (mm)	0.19 × 0.17 × 0.47
Linear absorbtion coefficient (cm^{-1})	7.8
Diffractometer	Siemens AED
Scan type	−2
Scan width (deg)	[b]
Radiation	[c]
2θ-range collection (deg)	3–140
hkl-range	h, k, l
Unique total data	7026
Criterion of observation	$(I) > 2$
Unique observed data (NO)	2265
No. of refined parameters (NV)	284
Overdetermination ratio (NO/NV)	8.0
Absorption	[d]
Solution	[e]
H-atoms	[f]
R	0.029
R_w	0.031
GOF	0.75
Largest shift/esd	0.22
Largest peak (e Å^{-3})	0.21
Computer and programs	[g]

[a] Unit-cell parameters were obtained by least-squares analysis of the setting angles of 30 carefully centred reflections chosen from diverse regions of reciprocal space. [b] From $(\theta - 0.6)°$ to $[\theta + (0.6 + \Delta\theta)]°$; $\Delta\theta = [(\lambda a_2 - \lambda a_1)/\lambda]$ tan θ. [c] Ni-filtered Cu-Kα $\lambda = 1.541\,78$ Å. [d] No correction applied. [e] Direct methods. [f] Located in *F*-map and isotropically refined. [g] ENCORE e91, SHELXS86,[31] SHELX76,[32] PARST.[33] $R = \Sigma||\Delta F|/\Sigma|F_o||$, $R_w = [\Sigma w(\Delta F^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, GOF $= [\Sigma w|\Delta F|^2/(NO - NV)]^{1/2}$.

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