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Synthesis of indazole-*N*-oxides via the 1,7-electrocyclization of azomethine ylides

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Abstract—The first examples of the 1,7-electrocyclization of azomethine ylides onto a nitro group, to give benz-1,2,6-oxadiazepine intermediates are reported. Subsequent ring contraction results in the formation of indazole-*N*-oxides.

1. Introduction

As part of our continuing work on the synthesis of the pyrrolo[3,2-*c*]quinoline ring system of the martinelline alkaloids (bradykinin receptor antagonist)[1] we have investigated the formation and reactions of the non-stabilised azomethine ylide **2a**. This azomethine ylide **2a** was formed by the reaction of *o*-nitrobenzaldehyde **1a** with sarcosine in refluxing benzene[2] and, despite the presence of a large excess of active dipolarophiles, for example, ethyl acrylate or methyl vinyl ketone, we did not observe any trace of the expected cycloadduct **3** in the ^{1}H NMR spectrum of the crude reaction mixture.

Two products, an indazole-*N*-oxide **5a** and an oxazolidine **7a** were, however, isolated after chromatographic separation (in 40 and 43% yields respectively) and their structures confirmed by spectroscopic analysis, Scheme 1. The isoxazoline product **7a** was independently synthesized by a method recently described by us,[3] and was found to be identical with the product **7a** obtained from the reaction of nitrobenzaldehyde **1a** and sarcosine. The indazole-*N*-oxide **5a** was deoxygenated in the presence of Pd-on-C, resulting in the formation of the known 2-methyl-2*H*-indazole **8**, Scheme 2.[4]

Keywords: Cycloadditions; Electrocyclic reactions; Indazoles; Isoquinolines; Nitro compounds.
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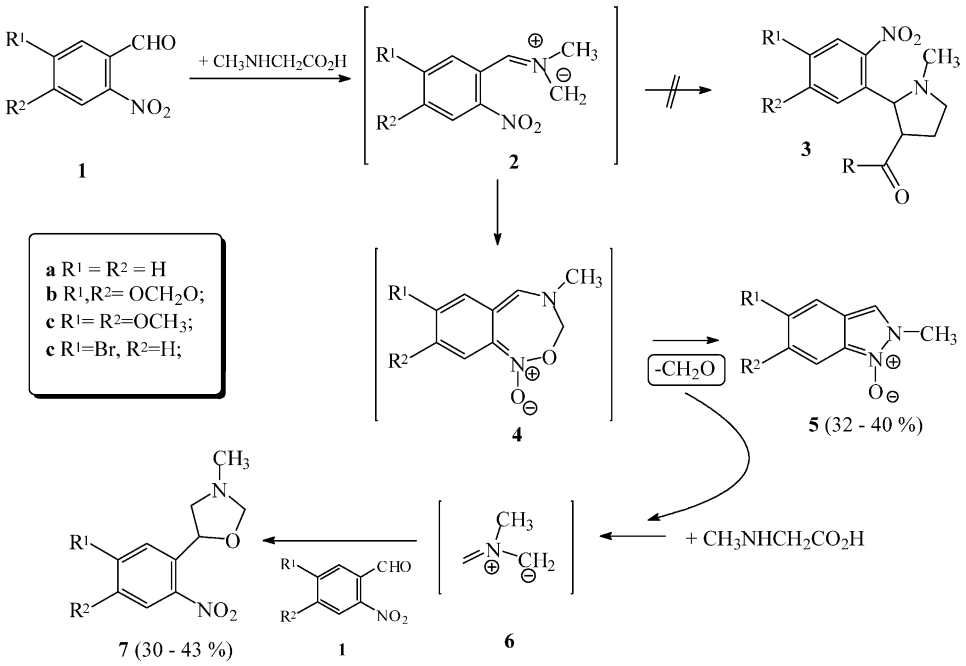
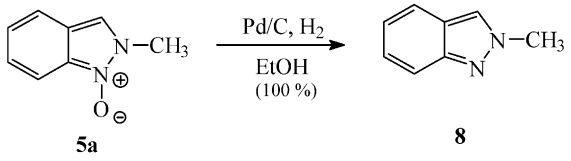
2. Results and discussion

The indazole-*N*-oxide **5a** and the isoxazolidine **7a** probably arise from the fragmentation of the unstable benz-1,2,6-oxadiazepine intermediate **4**, Scheme 1, formed by the decarboxylative condensation[5] of *o*-nitro-benzaldehyde **1** and sarcosine, followed by a 1,7-electrocyclization[6] of the non-stabilised azomethine ylide **2**. As such, this represents the first 1,7-electrocyclization of an azomethine ylide onto a pendant nitro group. The seven-membered ring of **4** subsequently then undergoes a ring contraction, resulting in the elimination of formaldehyde and the production of 2-methyl-2*H*-indazol-*N*-oxide **5a**. The formaldehyde by-product is then able to react with the excess sarcosine present in the reaction mixture, resulting in the formation of azomethine ylide **6**, which can then react with the other starting material, *o*-nitrobenzaldehyde **1**, to yield the 3-methyl-5-aryl-oxazolidine **7a** as the second product.[3] Similar processes have been reported for the 1,7-electrocyclization of an azomethine imine and a nitrile ylide onto a nitro group, leading to the formation of the corresponding benzotriazole-*N*-oxide[7] and 1-acyloxyindazoles,[8] respectively.

We have investigated the scope of this reaction via the generation of further azomethine ylides and found that substitution on the aromatic ring does not have a significant effect, although the yields were somewhat lower than in the unsubsubstituted case, Table 1. The reaction of *o*-nitro-benzaldehyde **1a** and *N*-benzylglycine **9** proceeded in a



Scheme 1.



Scheme 2.

Table 1

Entry	R^1	R^2	Reaction time (h)	Products	
1	H	H	2	5a 40%	7a 43%
2	CH_3O	CH_3O	6	5b 32%	7b 30%
3	OCH_2O		8	5c 34%	7c 38%
4	Br	H	3	5d 37%	7d 33%

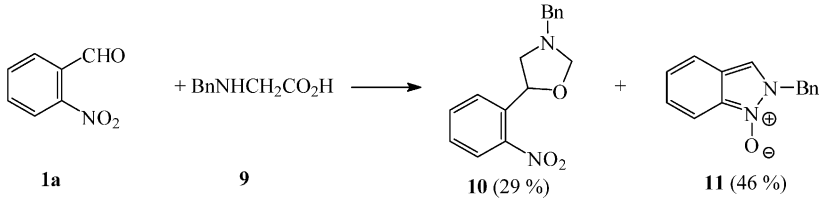
similar manner to give the analogue isoxazoline **10** and 2-benzyl-indazole-*N*-oxide **11**, Scheme 3.

We next chose to form the azomethine ylide **14** from 6,7-dimethoxy-3,4-dihydro-*N*-(2-nitrobenzyl)isoquinolinium chloride **13** (prepared from 3,4-dimethoxy-6,7-dihydro-isoquinoline **12** and 2-nitro-benzylchloride)[9] by dehydrohalogenation with triethylamine, Scheme 4.[10] In the presence of *N*-phenylmaleimide a 2:1 mixture of the cycloadduct **17** (as a single isomer, shown by NOE experiments to have *syn-endo* stereochemistry) and an indazole-*N*-oxide, **16** were obtained, while in the absence of the dipolarophile the *N*-oxide **16** was formed in quantitative yield. In contrast to the examples described above, the aldehyde in this case (which remains attached to the indazole component), arising from the fragmentation of **15**, is not sufficiently reactive to act as a C=O dipolarophile in a 1,3-dipolar cycloaddition process in competition with the 1,7-electrocyclization.

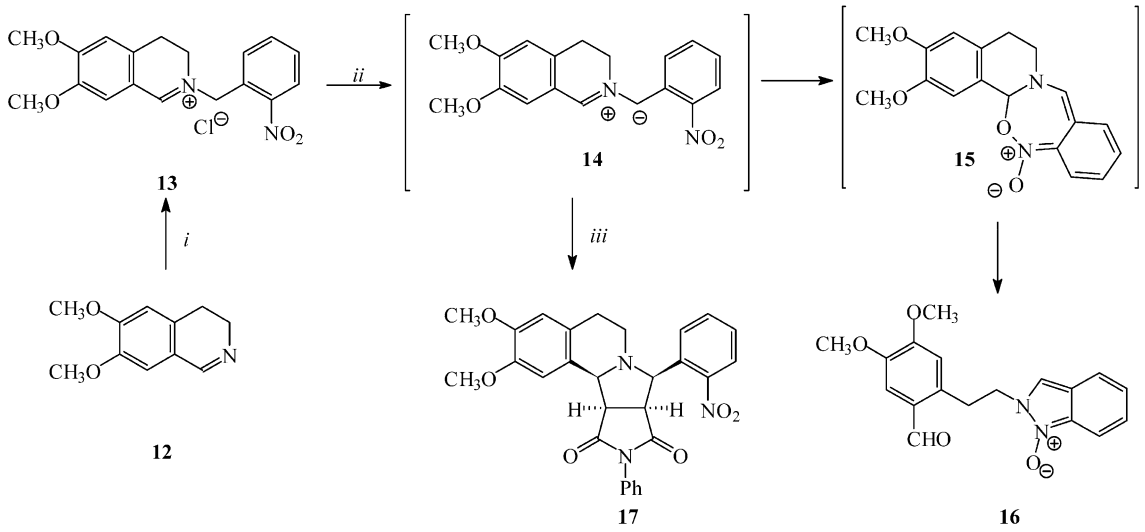
With regard to the proposed mechanism we performed the next series of experiments with 3,4-dihydro-1-(2-nitrophenyl)-*N*-substituted-isoquinolinium bromides **20** (prepared from the corresponding halide and 3,4-dihydroisoquinoline **18**). In all cases the isoquinoline fused indazole-*N*-oxide **22** was formed, Scheme 5, Table 2. In one case (**20a** R=CO_2CH_3) the competitive formation of the 1,3-dipolar cycloadduct **23** as a single isomer (the relative stereochemistry of the which was again proven by NOE experiments) was observed (ratio of **22a**:**23** approx. 3:1) due to the high reactivity of the electron-deficient C=O double bond of the aldehyde by-product.

3. Experimental

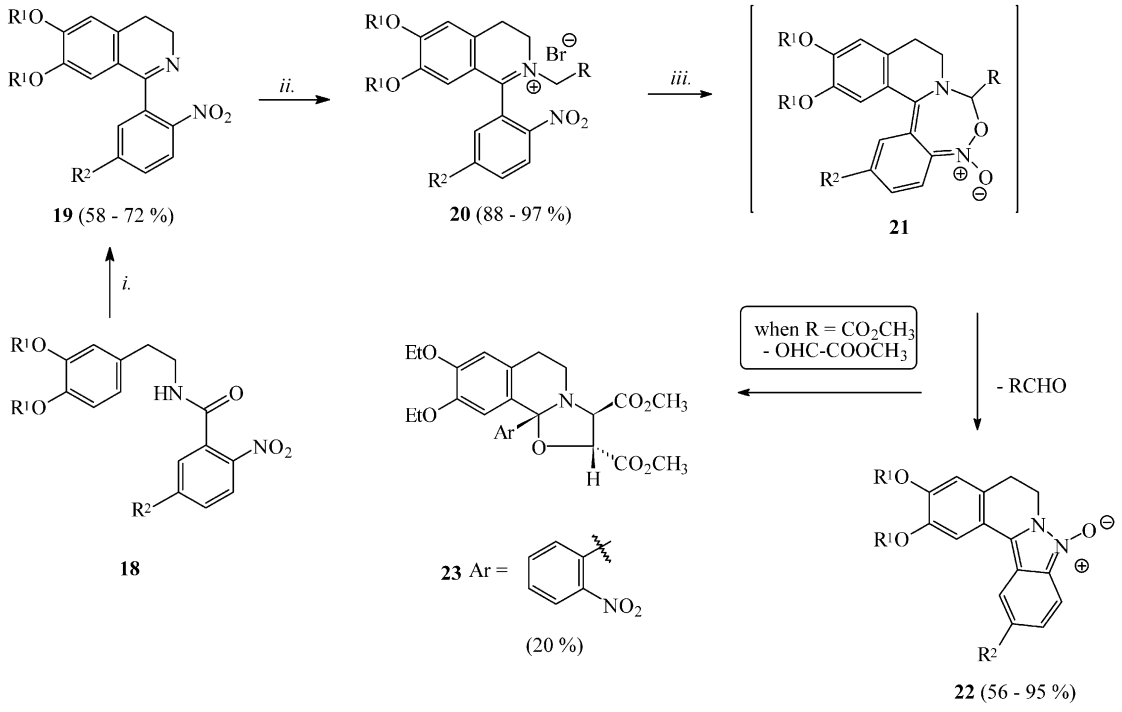
Melting points were determined on a Gallenkamp apparatus



Scheme 3.



Scheme 4. Reagents and conditions: (i) 2-$O_2NC_6H_4CH_2Cl$, dry Et_2O, 95%; (ii) Et_3N, MeOH, rt, 85%; (iii) *N*-phenylmaleimide, Et_3N, MeOH, rt, 58%.



Scheme 5. Reagents and conditions: (i) $POCl_3$, P_2O_5, xylene, reflux; (ii) RCH_2Br; (iii) Et_3N, MeOH.

and are uncorrected. Column chromatography was performed using Merck Kieselgel 60 70–230 mesh, TLC on aluminium sheets coated with Kieselgel 60 F_{254}. Plates were stained with anisaldehyde solution (100 mL glacial acetic acid, 2 mL cc. sulphuric acid and 1 mL anisaldehyde) and heated at ca. 150 °C. IR spectra were measured on a NICOLET FT-IR instrument. NMR spectra were obtained on a Bruker 250 instrument. Chemical shifts are given

Table 2

Entry	R^1	R^2	R	Yield of 20	Yield of 22
1	Et	H	$–CO_2Me$	20a 97%	22a: 56%
2	Et	H	$–CH_2Ph$	20b 95%	22a: 66%
3	Et	H	$–CH{=}CH_2$	20c 92%	22a: 88%
4	Me	H	$–CH{=}CH_2$	20d 88%	22b: 95%
5	Me	Cl	$–CH{=}CH_2$	20e 94%	22c: 95%
6	Et	Cl	$–CH{=}CH_2$	20f 96%	22d: 92%

relative to δ_{TMS}. All solvents were purified according to standard procedures and the amides **18** were prepared by the method of Cortes et al.[11]

3.1. Reaction of 2-nitrobenzaldehydes with sarcosine. General procedure

The appropriate 2-nitrobenzaldehyde (1 mmol) was dissolved in benzene or toluene (50 mL) and sarcosine (0.18 g, 2 mmol) was added. The reaction mixture was refluxed for 2–8 h and the water formed was removed with the aid of a Dean–Stark trap. After cooling, the precipitated solid was filtered off and all the solvent was removed in vacuo. The resulting products were separated by column chromatography on silica, eluting with hexane–ethyl acetate (50:50 to 0:100). The corresponding yields are given in Table 1.

3.1.1. 3-Methyl-5-(2′-nitrophenyl)oxazolidine (7a). As a pale yellow oil; δ_H (250 MHz, $CDCl_3$) 8.03 (1H, d, J=8.2 Hz, Ar–3′H), 7.87 (1H, d, J=8.2 Hz, Ar–6′H), 7.65 (1H, t, J=8.2 Hz, Ar–5′H), 7.41 (1H, t, J=8.2 Hz, Ar–4′H), 5.53 (1H, t, J=6.7 Hz, H-5), 4.64 (1H, d, J=5.1 Hz, H-2), 4.47 (1H, d, J=5.1 Hz, H-2), 3.62 (1H, dd, J=11.6, 6.7 Hz, H-4), 2.80 (1H, dd, J=11.6, 6.7 Hz, H-4), 2.49 (3H, s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 147.8 (quat., C-1′), 139.3 (quat.), 133.8 (CH), 127.6 (CH), 127.0 (CH), 124.5 (CH), 89.3 (CH_2, C-2), 73.3 (CH, C-5), 61.1 (CH_2, C-4), 41.5 (N–CH_3); ν_{max}/cm^{-1} (liquid film) 2851, 2867, 2799, 1524, 1452, 1346, 1058; (HRMS Found: m/z 208.0822. $C_{10}H_{12}N_2O_3$ requires 208.0835).

3.1.2. 2-Methyl-2*H*-indazole-*N*-oxide (5a). As a pale yellow powder, mp 90 °C [Found: C, 64.9; H, 5.6; N, 19.0. $C_8H_8N_2O$ requires C 64.8; H 5.45; N 18.9%]; δ_H (250 MHz, DMSO-d_6) 7.95 (1H, s, H-3), 7.60 (1H, d, J=8.1 Hz, H-7), 7.50 (1H, d, J=8.1 Hz, H-4), 7.20 (1H, t, J=8.1 Hz, H-5), 7.06 (1H, t, J=8.1 Hz, H-6), 3.95 (3H, s, CH_3); δ_C (62.5 MHz, DMSO-d_6) 127.6 (quat.), 125.6 (CH), 123.0 (CH), 120.9 (CH), 115.1 (quat.), 112.2 (CH), 110.5 (CH), 33.0 (CH_3); ν_{max}/cm^{-1} (liquid film) 3224, 3098, 1670, 1622, 1510, 1458, 1374, 1240, 1178, 1112, 757.

3.1.3. 3-Methyl-5-(3′,4′-dimethoxy-6′-nitrophenyl)oxazolidine (7b). As a pale yellow oil; δ_H (250 MHz, $CDCl_3$) 7.57 (1H, s, Ar–5′H), 7.24 (1H, s, Ar–2′H), 5.49 (1H, t, J=5.0 Hz, H-5), 4.54 (1H, d, J=5.0 Hz, H-2), 4.35 (1H, d, J=5.0 Hz, H-2), 3.90 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.52 (1H, dd, J=11.4, 5.0 Hz, H-4), 2.73 (1H, dd, J=11.4, 5.0 Hz, H-4), 2.39 (3H, s, NCH_3); δ_C (62.5 MHz, $CDCl_3$) 153.6 (quat.), 147.3 (quat.), 138.6 (quat.), 134.8 (quat.), 107.8 (CH), 107.7 (CH), 89.1 (CH_2), 73.7 (CH), 61.8 (CH_2), 56.1 (OCH_3), 56.0 (OCH_3), 41.5 (CH_3); ν_{max}/cm^{-1} (liquid film) 2949, 2896, 2857, 1580, 1518, 1471, 1440, 1336, 1275, 1220, 1067, 1030, 1015, 986; (HRMS Found: m/z 268.1021. $C_{12}H_{16}N_2O_5$ requires 268.1029).

3.1.4. 2-Methyl-5,6-dimethoxy-2*H*-indazole-*N*-oxide (5b). As a pale yellow powder, mp 122–3 °C [Found: C, 57.9; H, 5.8; N, 13.6. $C_{10}H_{12}N_2O_3$ requires C 57.7; H 5.8; N 13.5%]; δ_H (250 MHz, DMSO-d_6) 8.24 (1H, s, H-3), 7.41 (1H, s, H-7), 7.08 (1H, s, H-4), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.47 (3H, s, NCH_3); δ_C (62.5 MHz, DMSO-d_6) 154.3 (quat.), 148.7 (quat.), 146.9 (CH), 144.2 (quat.), 114.5 (quat.), 107.7 (CH), 104.8 (CH), 55.9 (CH_3), 55.7 (CH_3), 33.5 (CH_3); ν_{max}/cm^{-1} (KBr) 3428, 2940, 2832, 1665, 1612, 1500, 1457, 1436, 1398, 1362, 1341, 1270, 1217, 1167, 1131, 1051, 1013.

3.1.5. 3-Methyl-5-(3′,4′-methylenedioxy-6′-nitrophenyl)-oxazolidine (7c). As a pale yellow oil; δ_H (250 MHz, $CDCl_3$) 7.42 (1H, s, H-5′), 7.16 (1H, s, H-2′), 6.00 (2H, s, OCH_2O) 5.39 (1H, t, J=6.3 Hz, H-5), 4.50 (1H, d, J=4.9 Hz, H-2), 4.30 (1H, d, J=4.9 Hz, H-2), 3.46 (1H, dd, J=11.5, 6.3 Hz, H-4), 2.73 (1H, dd, J=11.5, 6.3 Hz, H-4), 2.36 (3H, s, NCH_3); δ_C (62.5 MHz, $CDCl_3$) 152.5 (quat.), 146.6 (quat.), 140.3 (quat.), 137.4 (quat.), 105.8 (CH), 105.0 (CH), 102.8 (CH_2), 89.1 (CH_2), 73.9 (CH), 62.1 (CH_2), 41.5 (CH_3); ν_{max}/cm^{-1} (liquid film) 2951, 2894, 1581, 1515, 1472, 1441, 1332, 1221, 1067, 1031, 1015; (Found: 252.0740. $C_{11}H_{12}N_2O_5$ requires 252.0746).

3.1.6. 2-Methyl-5,6-methylenedioxy)-2*H*-indazole-*N*-oxide (5c). As a pale yellow powder; mp 118–9 °C; [Found: C, 56.2; H, 4.3; N, 14.4. $C_9H_8N_2O_3$ requires C 56.25; H 4.2; N 14.6%]; δ_H (250 MHz, DMSO-d_6) 8.23 (1H, s, H-3), 7.40 (1H, s, H-7), 7.07 (1H, s, H-4), 6.18 (2H, s, OCH_2O), 3.46 (3H, s, NCH_3); δ_C (62.5 MHz, DMSO-d_6) 154.6 (quat.), 148.4 (quat.), 147.1 (CH), 144.1 (quat.), 114.5 (quat.), 107.6 (CH), 105.0 (CH), 102.7 (CH_2), 33.4 (CH_3); ν_{max}/cm^{-1} (KBr) 3422, 2942, 2838, 1664, 1611, 1504, 1453, 1402, 1364, 1343, 1212, 1167, 1132, 1011.

3.1.7. 3-Methyl-5-(3′-bromo-6′-nitrophenyl)oxazolidine (7d). As a pale yellow oil; δ_H (250 MHz, $CDCl_3$) 8.00 (1H, d, J=2.0 Hz, H-2′), 7.92 (1H, d, J=8.7 Hz, H-5′), 7.52 (1H, dd, J=8.7, 2.0 Hz, H-4′), 5.50 (1H, t, J=6.7 Hz, H-5), 4.62 (1H, d, J=5.2 Hz, H-2), 4.43 (1H, d, J=5.2 Hz, H-2), 3.58 (1H, dd, J=11.6, 6.7 Hz, H-4), 2.78 (1H, dd, J=11.6, 6.7 Hz, H-4), 2.46 (3H, s, NCH_3); δ_C (62.5 MHz, $CDCl_3$) 141.5 (quat.), 138.1 (quat.), 131.1 (CH), 130.5 (CH), 129.5 (quat.), 126.4 (CH), 89.5 (CH_2), 73.3 (CH), 62.0 (CH_2), 41.6 (CH_3); ν_{max}/cm^{-1} (liquid film) 3432, 2951, 1662, 1611, 1501, 1458, 1431, 1367, 1279, 1168, 1132, 1051, 1009; (Found: 252.9991. $C_{10}H_{11}N_2O_3Br$ requires 285.9953).

3.1.8. 2-Methyl-5-bromo-2*H*-indazole-*N*-oxide (5d). As a pale yellow powder, mp 130–1 °C; [Found: C, 42.6; H, 3.2; N, 12.3. $C_8H_7N_2OBr$ requires C 42.3; H 3.1; N 12.3%]; δ_H (250 MHz, DMSO-d_6) 8.15 (1H, s, H-3), 7.85 (1H, s, H-4), 7.62 (1H, d, J=8.5 Hz, H-7), 7.44 (1H, d, J=8.5 Hz, H-6), 3.48 (3H, s, NCH_3); δ_C (62.5 MHz, DMSO-d_6) 137.6 (quat.), 132.0 (quat.) 124.6 (CH), 122.9 (CH), 120.1 (quat.), 119.2 (CH), 114.5 (CH), 33.5 (CH_3); ν_{max}/cm^{-1} (KBr) 3228, 3100, 1673, 1629, 1511, 1375, 1311, 1242, 1177, 1100.

3.1.9. 2-Methyl-2*H*-indazole (8).[4] The indazole-*N*-oxide **5a** (0.15 g, 1 mmol) was dissolved in ethanol (25 mL) and palladium on charcoal (10%, 10 mg) was added. The reaction mixture was stirred under an hydrogen atmosphere (1 atm), at room temperature, for 12 h. The catalyst was then filtered of with the aid of Celite© and the solvent was removed in vacuo to give the product as a colourless oil, (0.13 g, 100%); δ_H (250 MHz, $CDCl_3$) 7.81 (1H, s, H-3), 7.69 (1H, d, J=8.7 Hz, H-7), 7.61 (1H, d, J=8.7 Hz, H-4), 7.26 (1H, t, J=8.7 Hz, H-6), 7.05 (1H, t, J=8.7 Hz, H-5),

4.14 (3H, s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 127.3 (quat.), 125.8 (CH), 123.5 (CH), 121.6 (quat.), 121.5 (CH), 119.9 (CH), 116.9 (CH), 40.2 (CH_3); ν_{max}/cm^{-1} (nujol) 3416, 2932, 1730, 1628, 1517, 1386, 1300, 1159, 1009; *m/z* 42 (100%), 51 (52), 63 (57), 77 (18), 104 (6), 133 (M, 43).

3.1.10. 3-Benzyl-5-(2-nitrophenyl)oxazolidine (10) and 2-benzyl-2*H*-indazole-*N*-oxide (11). To a solution of 2-nitrobenzaldehyde (0.50 g, 3.3 mmol) in dry THF (50 mL) was added *N*-benzylglycine (0.80 g, 4.97 mmol) and molecular sieves (4 Å, 2 g). The reaction mixture was heated at reflux for 5 h, under nitrogen. After cooling, the solid was filtered off and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica, eluting with hexane–ethyl acetate (from 80:20 to 0:100) to give two products; **10**: as a yellow solid (0.27 g, 29%), mp 133 °C; δ_H ($CDCl_3$, 270 MHz): 8.03 (1H, dd, J=7.9, 1.3 Hz, H-3′), 7.90 (1H, d, J=7.9 Hz, H-6′), 7.63 (1H, t, J=7.9 Hz, H-5′), 7.21–7.41 (6H, m, H-4′ and Ar–H), 5.55 (1H, t, J=6.6 Hz, H-5), 4.66 (1H, d, J=5.9 Hz, H-2′), 4.59 (1H, d, J=5.9 Hz, H-2), 3.72–3.80 (3H, m, Bn–CH_2 and H-5), 2.82 (1H, dd, J=11.9, 6.6 Hz, H-5); δ_C ($CDCl_3$, 67.5 MHz): 146.8 (quat.), 139.5 (quat.), 138.4 (quat.), 134.0 (CH), 128.7 (2×CH), 128.4 (2×CH), 127.8 (CH), 127.3 (CH), 127.1 (CH), 124.7 (CH), 87.4 (CH_2), 73.3 (CH), 60.2 (CH_2), 58.3 (CH_2); ν_{max}/cm^{-1} (KBr) 2921, 2855, 2801, 1527, 1455, 1368, 1347, 1166, 1052; (Found: 284.1132. $C_{16}H_{16}N_2O_3$ requires 284.1160); **11**: as a white solid (0.33 g, 46%), mp 155–6 °C; δ_H ($CDCl_3$, 270 MHz) 5.60 (2H, s, CH_2), 7.06 (1H, t, J=7.5 Hz, Ar–H), 7.21–7.45 (8H, m, Ar–H), 7.71 (1H, d, J=8.0 Hz, Ar–H); δ_C ($CDCl_3$, 67.5 MHz) 49.5 (CH_2), 108.6 (CH), 112.9 (CH), 116.0 (quat.), 120.2 (CH), 123.7 (CH), 126.3 (CH), 128.7 (3×CH) 129.0 (2×CH and 1 quat.), 133.7 (quat.); ν_{max}/cm^{-1} (KBr) 3229, 3111, 1666, 1611, 1517, 1459, 1373, 1246, 1167, 1115; (Found: 224.0922. $C_{14}H_{12}N_2O$ requires 224.0950).

3.1.11. 4,5-Dimethoxy-2-[2′-(2″*H*-2″-indazolyl-1″-*N*-oxide)ethyl]benzaldehyde (16). 6,7-Dimethoxy-3,4-dihydro-2-(2′-nitrobenzyl)isoquinolinium chloride (0.36 g, 1.0 mmol) was dissolved in methanol (5 mL) and triethylamine (0.14 mL, 0.10 g, 1.0 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, then the solvent was removed in vacuo. The residue was dissolved in dichloromethane (30 mL) and washed with water (3× 20 mL). The organic layer was dried over magnesium sulphate and evaporated to give the product as a pale brown solid (0.28 g, 85%), mp 114–6 °C; [Found: C, 66.2; H, 5.6; N, 8.5. $C_{18}H_{18}N_2O_4$ requires C 66.3; H 5.6; N 8.6%]; δ_H (250 MHz, $CDCl_3$) 10.06 (1H, s, CHO), 7.70 (1H, d, J=8.8 Hz, H-7″), 7.44 (1H, d, J=8.8 Hz, H-4″), 7.28 (1H, s, H-3″), 7.25 (1H, t, J=8.8 Hz, H-5″), 7.21 (1H, s, H-3), 7.07 (1H, t, J=8.8 Hz, H-6″), 6.51 (1H, s, H-6), 4.69 (2H, t, J=6.9 Hz, CH_2), 3.92 (3H, s, *O*CH_3), 3.65 (3H, s, *O*CH_3), 3.64 (2H, t, J=6.9 Hz, CH_2); δ_C (62.5 MHz, $CDCl_3$) 191.3 (CHO), 153.3 (quat.), 150.2 (quat.), 148.0 (quat.), 133.7 (quat.), 129.4 (quat.), 126.8 (quat.), 126.5 (CH), 123.7 (CH), 120.3 (CH), 115.7 (CH), 114.3 (CH), 112.6 (CH), 109.7 (CH), 56.1 (CH_3), 56.0 (CH_3), 47.6 (CH_2), 31.7 (CH_2); ν_{max}/cm^{-1} (KBr) 2902, 1710, 1562, 1490, 1444, 1251, 1105, 1037.

3.1.12. 2,3-Dimethoxy-8-(2-nitrophenyl)-10-phenyl-8,8a,11a,11b-tetrahydro-6*H*-pyrrolo[3′,4′:3,4]pyrrolo-[2,1-*a*]isoquinoline-9,11(5*H*,10*H*)-dione (17). Isoquinolinium, 3,4-dihydro-6,7-dimethoxy-2-[(2-nitrophenyl)-methyl]-, chloride (**13**) (0.50 g, 1.4 mmol) and *N*-phenylmaleimide (0.23 g, 1.4 mmol) were dissolved in methanol (15 mL) and triethylamine (0.20 mL, 0.14 g, 1.4 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo, and the residue was dissolved in dichloromethane (30 mL) and it washed with water (3×20 mL). The organic layer was dried over magnesium sulphate and evaporated to give a pale brown solid which was further purified by column chromatography on silica, eluting with ethyl acetate–hexane (1:1). The product was obtained as a white powder (0.41 g, 58%), mp 236–8 °C; [Found: C, 67.5; H, 5.0; N, 8.5. $C_{28}H_{25}N_3O_6$ requires C 67.3; H 5.0; N 8.4%]; δ_H (250 MHz, $CDCl_3$) 8.07 (1H, d, J=7.7 Hz, H-3′), 7.94 (1H, d, J=7.7 Hz, Ar–H), 7.66 (1H, t, J=7.7 Hz, Ar–H), 7.46 (1H, t, J=7.7 Hz, Ar–H), 7.43–7.30 (3H, m, Ar–H), 7.15 (2H, m, Ar–H), 6.81 (1H, s, H-1), 6.55 (1H, s, H-4), 5.13 (1H, s, H-11b), 4.95 (1H, d, J=8.6 Hz, H-8), 4.01 (1H, t, J=8.6 Hz, H-8a), 3.93 (3H, s, CH_3), 3.88 (3H, s, CH_3), 3.73 (1H, d, J=8.6 Hz, H-11a), 3.17 (1H, dt, J=13.3, 4.5 Hz, CH_2), 3.00–2.70 (2H, m, CH_2), 2.30 (1H, dd, J=16.7, 3.9 Hz, CH_2); δ_C (62.5 MHz, $CDCl_3$) 177.6 (quat.), 174.7 (quat.), 149.7 (quat.), 148.3 (quat.), 148.2 (quat.), 133.6 (CH), 133.3 (quat.), 131.8 (quat.), 129.1 (2×CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 126.2 (2×CH), 126.1 (quat.), 125.8 (quat.), 125.2 (CH), 111.9 (C-4), 108.7 (C-1), 64.0 (C-11b), 59.1 (CH), 56.1 (CH_3), 55.9 (CH_3), 51.0 (CH), 49.0 (CH), 41.9 (CH_2), 20.5 (CH_2); ν_{max}/cm^{-1} (KBr) 3099, 2992, 2931, 2834, 1714, 1515, 1450, 1376, 1357, 1253, 1182, 1099, 1020.

3.2. Synthesis of isoquinolines (19). General procedure

Phosphorus pentoxide (14.2 g, 0.1 mol) was suspended at 0 °C in dry xylene (300 mL) and freshly distilled phosphorus oxychloride (18.5 mL, 30.7 g, 0.2 M) was added dropwise to the well-stirred mixture. To this mixture was added the corresponding amide **18** and the reaction mixture was stirred at reflux for 3 h followed by cooling to room temperature. The xylene was decanted and the semi-solid residue was stirred overnight with an excess of 10% aqueous sodium hydroxide solution. The solid precipitate which formed was filtered off and recrystallized from ethanol.

3.2.1. 6,7-Dimethoxy-1-(2′-nitrophenyl)-3,4-dihydro-isoquinoline (19a). As a pale yellow solid (58%), mp 112–3 °C (lit.[11] 110–2 °C); δ_H (250 MHz, $CDCl_3$) 8.00 (1H, d, J=7.5 Hz, H-3′), 7.67 (1H, t, J=8.3 Hz, H-5′), 7.54 (1H, t, J=8.3 Hz, H-4′), 7.52 (1H, d, J=8.3 Hz, H-6′), 6.73 (1H, s, H-8), 6.29 (1H, s, H-5), 3.86 (3H, s, OCH_3), 3.79 (2H, t, J=7.6 Hz, CH_2), 3.58 (3H, s, OCH_3), 2.77 (2H, t, J=7.6 Hz, CH_2); δ_C (62.5 MHz, $CDCl_3$) 164.2 (quat.), 151.2 (quat.), 148.4 (quat.), 147.3 (quat.), 134.7 (quat.), 133.3 (CH), 131.3 (quat.), 130.9 (CH), 129.5 (CH), 124.2 (CH), 121.3 (quat.), 110.3 (CH), 109.1 (CH), 55.9 (CH_3), 55.8 (CH_3), 47.6 (CH_2), 25.3 (CH_2); ν_{max}/cm^{-1} (KBr) 2966, 2836, 1606, 1568, 1526, 1353, 1324, 1284, 1270, 1215, 1123, 1024.

3.2.2. 6,7-Diethoxy-1-(2′-nitrophenyl)-3,4-dihydroisoquinoline (19b). As a pale yellow solid (65%), [Found: C, 67.2; H, 5.9; N, 8.4. $C_{19}H_{20}N_2O_4$ requires C 67.05; H 5.9; N 8.2%]; mp 118–20 °C; δ_H (250 MHz, $CDCl_3$) 8.07 (1H, d, 1H, $J=7.8$ Hz, H-3′), 7.68 (1H, t, $J=7.8$ Hz, H-5′), 7.68 (1H, t, $J=7.8$ Hz, H-4′), 7.58 (1H, d, $J=7.8$ Hz, H-6′), 6.76 (1H, s, H-8), 6.34 (1H, s, H-5), 4.14 (2H, q, $J=6.9$ Hz, OCH_2), 3.83 (2H, m, $2\times CH_2$), 2.80 (2H, t, $J=7.6$ Hz, CH_2), 1.47 (3H, t, $J=6.9$ Hz, CH_3), 1.30 (3H, t, $J=6.9$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 164.5 (quat.), 151.5 (quat.), 147.5 (quat.), 145.9 (quat.), 136.0 (quat.), 133.1 (CH), 131.2 (quat.), 129.9 (CH), 129.6 (CH), 124.0 (CH), 121.5 (quat.), 110.6 (CH), 109.8 (CH), 65.5 (CH_2), 65.2 (CH_2), 47.6 (CH_2), 25.3 (CH_2), 14.5 ($2\times CH_3$); ν_{max}/cm^{-1} (KBr) 2968, 2830, 1611, 1564, 1525, 1320, 1283, 1271, 1215, 1175, 1122, 1054, 1021.

3.2.3. 6,7-Dimethoxy-1-(5′-chloro-2′-nitrophenyl)-3,4-dihydroisoquinoline (19c). As a yellow solid (72%), mp 128–9 °C; [Found: C, 60.0; H, 4.5; N, 8.0. $C_{17}H_{15}N_2O_4Cl$ requires C 59.9; H 4.4; N 8.1%]; δ_H (250 MHz, $CDCl_3$) 8.04 (1H, d, $J=8.3$ Hz, H-3′), 7.58 (1H, s, H-6′), 7.56 (1H, d, $J=8.3$ Hz, H-4′), 6.78 (1H, s, H-8), 6.31 (1H, s, H-5), 3.93 (3H, s, OCH_3), 3.85 (2H, t, $J=7.5$ Hz, CH_2), 3.66 (3H, s, OCH_3), 2.83 (2H, t, $J=7.5$ Hz, CH_2); δ_C (62.5 MHz, $CDCl_3$) 163.3 (quat.), 151.4 (quat.), 147.5 (quat.), 146.7 (quat.), 140.0 (quat.), 136.5 (quat.), 131.4 (quat.), 131.1 (CH), 129.6 (CH), 125.7 (CH), 120.9 (quat.), 110.5 (CH), 108.8 (CH), 56.1 (CH_3), 55.9 (CH_3), 47.7 (CH_2), 25.3 (CH_2); ν_{max}/cm^{-1} (KBr) 2986, 2947, 2904, 1606, 1564, 1523, 1397, 1357, 1312, 1213, 1132, 1111, 1087, 1039.

3.2.4. 6,7-Diethoxy-1-(5′-chloro-2′-nitrophenyl)-3,4-hydroisoquinoline (19d). As a yellow solid (70%), mp 126–8 °C; [Found: C, 60.8; H, 5.1; N, 7.5. $C_{19}H_{19}N_2O_4Cl$ requires C 60.9; H 5.1; N 7.5%]; δ_H (250 MHz, $CDCl_3$ + DMSO-d_6) 8.06 (1H, d, $J=8.1$ Hz, H-3′), 7.59 (1H, d, $J=8.1$ Hz, H-4′), 7.57 (1H, s, H-6′), 6.78 (1H, s, H-8), 6.32 (1H, s, H-5), 4.14 (2H, q, $J=7.0$ Hz, OCH_2), 3.86 (4H, m, $2\times CH_2$), 2.82 (2H, t, $J=7.5$ Hz, CH_2), 1.47 (3H, t, $J=7.0$ Hz, CH_3), 1.32 (3H, t, $J=7.0$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$ + d_6-DMSO) 163.4 (quat.), 151.6 (quat.), 146.7 (quat.), 146.4 (quat.), 139.8 (quat.), 136.0 (quat.), 131.6 (quat.), 130.9 (CH), 129.6 (CH), 125.6 (CH), 120.6 (quat.), 111.7 (CH), 111.6 (CH), 65.0 (CH_2), 64.2 (CH_2), 47.4 (CH_2), 25.1 (CH_2), 14.4 ($2\times CH_3$); ν_{max}/cm^{-1} (KBr) 2966, 2949, 2898, 2832, 1603, 1561, 1526, 1395, 1358, 1318, 1271, 1211, 1182, 1129, 1108, 1039.

3.3. Synthesis of quaternery salts. General procedures

Method A. The 3,4-dihydroisoquinoline (2.5 mmol) was dissolved in dry diethyl ether (25 mL) and 2-nitrobenzylchloride (0.44 g, 2.5 mmol) or methly bromoacetate (0.28 mL, 0.46 g, 3.0 mmol) were added. The mixture was left without stirring for 3 days at room temperature, under an argon atmosphere. The yellow precipitate was filtered off, washed with dry diethyl ether and dried in vacuo.

Method B. The 3,4-dihydroisoquinoline (2.5 mmol) was dissolved in allyl bromide (4 mL). The resulting solution was heated for 24 h under reflux, under an argon atmosphere. The excess allyl bromide was removed in vacuo and the residue was triturated with dry diethyl ether. The yellow precipitate was filtered off, washed with diethyl ether and dried in vacuo.

3.3.1. Isoquinolinium, 3,4-dihydro-6,7-dimethoxy-2-[(2-nitrophenyl)methyl]-, chloride (13). The title compound was prepared via method A to give a yellow powder (95%), mp 190–2 °C; [Found: C, 59.4; H, 5.1; N, 7.5. $C_{18}H_{19}N_2O_4Cl$ requires C 59.6; H 5.3; N 7.7%]; δ_H (250 MHz, DMSO-d_6) 9.25 (1H, s, H-1′), 8.25 (1H, d, $J=8.1$ Hz, H-3′), 7.87 (2H, m, H-4′ and H-5′), 7.76 (1H, d, $J=8.1$ Hz, H-6′), 7.56 (1H, s, H-8), 7.21 (1H, s, H-5), 5.55 (2H, s, NCH_2Ar), 3.99 (2H, t, $J=6.6$ Hz, CH_2), 3.97 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.20 (2H, t, $J=6.6$ Hz, CH_2); δ_C (62.5 MHz, DMSO-d_6) 165.8 (quat.), 157.7 (quat.), 148.5 (quat.), 148.1 (quat.), 134.9 (CH), 133.1 (CH), 132.4 (CH), 130.9 (CH), 127.0 (CH), 125.8 (quat.), 117.2 (quat.), 115.9 (CH), 111.5 (CH), 59.2 ($ArCH_2N$), 56.7 (CH_3), 56.0 (CH_3), 48.3 (CH_2), 25.0 (CH_2); ν_{max}/cm^{-1} (KBr) 3376, 3002, 2975, 1641, 1602, 1562, 1527, 1344, 1303, 1274, 1139, 1006.

3.3.2. 6,7-Diethoxy-3,4-dihydro-2-(methoxycarbonylmethyl)-1-(2′-nitrophenyl)isoquinolinium bromide (20a). The title compound was prepared via method A to give a yellow powder, mp 100–2 °C; [Found: C, 53.4; H, 5.2; N, 5.7. $C_{22}H_{25}N_2O_6Br$ requires C 53.6; H 5.1; N 5.7%]; δ_H (250 MHz, DMSO-d_6) 8.55 (1H, d, $J=8.0$ Hz, H-3′), 8.14 (1H, t, $J=8.0$ Hz, H-5′), 8.06 (1H, t, $J=8.0$ Hz, H-4′), 7.76 (1H, d, $J=8.0$ Hz, H-6′), 7.33 (1H, s, H-8), 6.18 (1H, s, H-5), 4.18 (2H, s, CH_2COO), 4.28 (4H, m, $2\times CH_2CH_3$), 3.76 (3H, s, $COOCH_3$), 3.37 (4H, m, H-6 and H-7), 1.36 (3H, t, $J=6.7$ Hz, CH_2CH_3), 1.11 (3H, t, $J=6.7$ Hz, CH_2CH_3); δ_C (62.5 MHz, DMSO-d_6) 173.0 (quat.), 166.1 (quat.), 157.0 (quat.), 147.1 (quat.), 145.7 (quat.), 135.9 (CH), 135.2 (quat.), 133.9 (CH), 129.3 (CH), 126.6 (CH), 124.2 (quat.), 118.1 (CH), 115.0 (CH), 112.3 (quat.), 65.3 (CH_2), 64.3 (CH_2), 58.1 (CH_2), 53.2 (CH_3), 51.5 (CH_2), 25.0 (CH_2), 14.4 (CH_3), 14.2 (CH_3); ν_{max}/cm^{-1} (KBr) 2988, 2955, 2913, 1720, 1625, 1523, 1375, 1234, 1222, 1137, 1039.

3.3.3. Isoquinolinium, 6,7-diethoxy-3,4-dihydro-1-(2-nitrophenyl)-2-(phenylmethyl)-, bromide (20b). 6,7-Diethoxy-1-(2′-nitrophenyl)-3,4-dihydroisoquinoline (1.0 g, 2.9 mmol) was dissolved in dry toluene (10 mL) and benzyl bromide (0.36 mL, 0.50 g, 3 mmol) was added. The resulted solution was heated for 48 h at reflux under an argon atmosphere. The solvent was removed in vacuo and the residue was triturated with dry diethyl ether. The yellow precipitate was filtered off, washed with diethyl ether and dried in vacuo to give a yellow powder (1.45 g, 95%), mp 190–2 °C; [Found: C, 59.9; H, 5.1; N, 5.5. $C_{26}H_{27}N_2O_4Br$ requires C 60.0; H 5.3; N 5.5%]; δ_H (250 MHz, $CDCl_3$) 8.92 (1H, d, $J=7.5$ Hz, H-3′), 8.47 (1H, d, $J=7.5$ Hz, H-6′), 8.18 (1H, t, $J=7.5$ Hz, H-4′), 8.08 (1H, t, $J=7.5$ Hz, H-5′), 7.35 (5H, s, ArH), 7.02 (1H, s, H-8), 6.09 (1H, s, H-5), 5.50 (1H, d, $J=14.9$ Hz, NCH_2Ph), 5.07 (1H, d, $J=14.9$ Hz, NCH_2Ph), 4.90–4.60 (1H, m, CH_2CH_2), 4.40–4.00 (4H, m, $2\times CH_2CH_3$), 3.88–3.52 (2H, m, CH_2CH_2), 3.50–3.15 (1H, m, CH_2CH_2), 1.48 (3H, t, $J=6.5$ Hz, CH_3), 1.27 (3H, t, $J=6.6$ Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 171.2 (quat.), 157.4 (quat.), 147.9 (quat.), 146.1 (quat.), 136.2 (CH), 134.3

(quat.), 133.8 (CH), 132.2 (CH), 131.7 (quat.), 129.5 (2× CH), 129.4 (CH), 128.9 (2×CH), 125.6 (CH), 125.4 (quat.), 118.6 (quat.), 114.9 (CH), 112.1 (CH), 65.5 (CH_2CH_3), 65.1 (CH_2CH_3), 61.8 (CH_2), 49.8 (CH_2), 26.0 (CH_2), 14.4 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} (KBr) 2979, 1602, 1552, 1525, 1386, 1342, 1272, 1213, 1186, 1029, 754.

3.3.4. 2-Allyl-6,7-diethoxy-3,4-dihydro-1-(2′-nitrophenyl)isoquinolinium bromide (20c). The title compound was prepared via method B to give a yellow powder, mp 245–7 °C; [Found: C, 57.0; H, 5.5; N, 6.0. $C_{22}H_{25}N_2O_4Br$ requires C 57.3; H 5.5; N 6.1%]; δ_H (250 MHz, $CDCl_3$) 8.43 (1H, d, J=7.5 Hz, H-3′), 8.38 (1H, d, J=7.5 Hz, H-6′), 8.24 (1H, t, J=7.5 Hz, H-4′), 7.93 (1H, t, J=7.5 Hz, H-5′), 6.98 (1H, s, H-8), 6.09 (1H, s, H-5), 5.83–5.63 (1H, m, allyl-H), 5.48–5.23 (2H, m, allyl-H), 4.85–4.60 (2H, m, allyl-H), 4.39–4.18 (4H, m, 2×CH_2CH$_3$), 3.82–3.53 (2H, m, CH_2), 3.29 (2H, m, CH_2), 1.47 (3H, t, J=6.9 Hz, CH_3), 1.26 (3H, t, J=6.9 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 170.9 (quat.), 157.3 (quat.), 147.7 (quat.), 145.6 (quat.), 137.0 (quat.), 134.5 (quat.), 133.1 (CH), 131.8 (CH), 131.7 (quat.), 128.3 (CH), 125.2 (CH), 123.5 (CH_2), 118.9 (CH), 115.3 (CH), 112.1 (CH), 65.5 (CH_2), 65.2 (CH_2), 61.1 (CH_2), 50.1 (CH_2), 25.9 (CH_2), 14.4 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} (KBr) 2984, 2888, 1712, 1635, 1553, 1381, 1277, 1202, 1124, 1103, 1039.

3.3.5. 2-Allyl-6,7-dimethoxy-3,4-dihydro-1-(2′-nitrophenyl)isoquinolinium bromide (20d). The title compound was prepared via method B to give a yellow powder, mp 237–8 °C; [Found: C, 55.2; H, 4.7; N, 6.5 $C_{20}H_{21}N_2O_4Br$ requires C 55.4; H 4.9; N 6.5%]; δ_H (250 MHz, $CDCl_3$) 8.89 (1H, d, J=7.5 Hz, H-3′), 8.46 (1H, d, J=7.5 Hz, H-6′), 8.14 (1H, t, J=7.5 Hz, H-4′), 8.00 (1H, t, J=7.5 Hz, H-5′), 7.03 (1H, s, H-8), 6.07 (1H, s, H-5), 5.91–5.80 (1H, m, allyl-H), 5.39–5.36 (2H, m, allyl-H), 4.89–4.69 (2H, m, allyl-H), 4.38 (1H, m, CH_2), 4.17 (1H, m, CH_2), 4.05 (3H, s, OCH_3), 3.66 (1H, m, CH_2), 3.58 (3H, s, OCH_3), 3.41 (1H, m, CH_2); δ_C (62.5 MHz, $CDCl_3$) 170.7 (quat.), 157.0 (quat.), 148.3 (quat.), 145.5 (quat.), 135.9 (quat.), 134.0 (quat.), 133.1 (CH), 131.5 (CH), 131.4 (quat.), 128.0 (CH), 125.2 (CH), 123.3 (CH_2), 118.8 (quat.), 112.5 (CH), 111.0 (CH), 60.9 (CH_2), 56.7 (CH_3), 55.8 (CH_3), 49.4 (CH_2), 25.6 (CH_2); ν_{max}/cm^{-1} (KBr) 3013, 2943, 1604, 1557, 1526, 1467, 1387, 1344, 1294, 1274, 1222, 1186, 1124, 1082.

3.3.6. 2-Allyl-6,7-dimethoxy-3,4-dihydro-1-(2′-nitro-5′-chlorophenyl)isoquinolinium bromide (20e). The title compound was prepared via method B to give a yellow powder, mp 252–3 °C; [Found: C, 51.2; H, 4.5; N, 6.1 $C_{20}H_{20}N_2O_4BrCl$ requires C 51.4; H 4.3; N 6.0%]; δ_H (250 MHz, $CDCl_3$) 9.01 (1H, s, H-6′), 8.48 (1H, d, J=8.8 Hz, H-3′), 7.98 (1H, d, J=8.8 Hz, H-4′), 7.07 (1H, s, H-8), 6.11 (1H, s, H-5), 5.90–5.77 (1H, m, allyl-H), 5.44–5.32 (2H, m, allyl-H), 4.88–4.32 (2H, m, allyl-H), 4.40 (1H, m, CH_2), 4.18 (1H, m, CH_2), 4.10 (3H, s, OCH_3), 3.71 (3H, s, OCH_3) 3.45 (2H, m, CH_2); δ_C (62.5 MHz, $CDCl_3$) 169.1 (quat.), 157.2 (quat.), 148.3 (quat.), 143.8 (quat.), 142.7 (quat.), 134.3 (quat.), 133.4 (CH), 131.0 (CH), 127.8 (CH), 126.8 (CH), 126.5 (CH), 123.4 (CH_2), 118.4 (quat.), 112.4 (CH), 111.2 (CH), 61.0 (CH_2), 56.7 (CH_3), 56.0 (CH_3), 49.6 (CH_2), 25.5 (CH_2); ν_{max}/cm^{-1} (KBr) 3088, 2974, 2933, 2866, 1598, 1565, 1551, 1525, 1393, 1373, 1339, 1299, 1272, 1217, 1187, 1108, 1029.

3.3.7. 2-Allyl-6,7-diethoxy-3,4-dihydro-1-(2′-nitro-5′-chlorophenyl)isoquinolinium bromide (20f). The title compound was prepared via method B to give a yellow powder (95%), mp 255 °C; [Found: C, 53.2; H, 4.9; N, 5.7 $C_{22}H_{24}N_2O_4BrCl$ requires C 53.3; H 4.9; N 5.65%]; δ_H (500 MHz, DMSO-d_6) 8.54 (1H, d, J=9.0 Hz, H-3′), 8.31 (1H, d, J=1.0 Hz, H-6′), 8.14 (1H, dd, J=9.0, 1.0 Hz, H-4′), 7.31 (1H, s, H-8), 6.32 (1H, s, H-5), 5.89–5.84 (1H, m, allyl-H), 5.36–5.32 (2H, m, allyl-H), 4.39 (2H, m, allyl-H), 4.29–4.22 (4H, m, 2×CH_2CH$_3$), 3.73 (2H, m, CH_2), 3.41 (1H, m, CH_2), 3.26 (1H, m, CH_2), 1.35 (3H, t, J=7.0 Hz, CH_3), 1.14 (3H, t, J=7.0 Hz, CH_3); δ_C (75.5 MHz, DMSO-d_6) 169.5 (quat.), 156.5 (quat.), 147.0 (quat.), 144.3 (quat.), 140.8.0 (quat.), 134.4 (quat.), 133.5 (CH), 129.6 (quat.), 129.2 (quat.), 128.3 (CH), 126.2 (CH), 121.7 (CH_2), 118.1 (quat.), 115.1 (CH), 112.3 (CH), 65.0 (CH_2), 64.4 (CH_2), 59.8 (CH_2), 49.7 (CH_2), 24.8 (CH_2), 14.3 (CH_3), 14.1 (CH_3); ν_{max}/cm^{-1} (KBr) 2982, 2877, 1713, 1633, 1566, 1377, 1284, 1226, 1200, 1124, 1101, 1037.

3.3.8. 1,7-Electrocyclizations. General procedures. The 3,4-dihydro-1-(2′-nitrophenyl)isoquinolinium halide (2.9 mmol) was dissolved in dry methanol (10 mL) and triethylamine (0.42 mL, 0.30 g, 3.0 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (50 mL) and washed with water (3×20 mL) and brine (20 mL). The organic layer was dried over magnesium sulphate and evaporated in vacuo. The residue was further purified by column chromatography on silica gel, eluting with acetone to give the product.

3.3.9. 2,3-Diethoxy-5,6-dihydroindazolo[3,2-*a*]isoquinoline-8-oxide (22a). The title compound was obtained as an orange solid, mp 90 °C; [Found: C, 70.6; H, 6.1; N, 8.5. $C_{19}H_{20}N_2O_3$ requires C 70.35; H 6.2; N 8.6%]; δ_H (250 MHz, $CDCl_3$) 7.87 (1H, d, J=8.6 Hz, H-9), 7.71 (1H, d, J=8.6 Hz, H-12), 7.38 (1H, s, H-1), 7.31 (1H, t, J=8.6 Hz, H-11), 7.16 (1H, t, J=8.6 Hz, H-10), 6.81 (1H, s, H-4), 4.57 (2H, t, J=7.0 Hz, H-6), 4.15 (2H, q, J=7.3 Hz, OCH_2), 4.12 (2H, q, J=7.3 Hz, OCH_2), 3.15 (2H, t, J=7.0 Hz, H-5), 1.50 (3H, t, J=7.3 Hz, CH_3), 1.47 (3H, t, J=7.3 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 149.5 (quat.), 148.1 (quat.), 131.3 (quat.), 127.0 (CH), 124.2 (quat.), 124.0 (CH), 120.1 (CH), 119.5 (quat.), 118.9 (quat.), 113.4 (CH), 112.9 (CH), 112.0 (quat.), 109.7 (CH), 65.1 (CH_2), 64.7 (CH_2), 39.9 (CH_2), 27.6 (CH_2), 14.8 (CH_3), 14.7 (CH_3); ν_{max}/cm^{-1} (KBr) 2983, 2938, 1604, 1558, 1525, 1388, 1344, 1274, 1031.

3.3.10. 2,3-Dimethoxy-5,6-dihydroindazolo[3,2-*a*]isoquinoline-8-oxide (22b). The title compound was obtained as an orange solid, mp 122–3 °C; [Found: C, 69.0; H, 5.6; N, 9.5 $C_{17}H_{16}N_2O_3$ requires C 68.9; H 5.4; N 9.45%]; δ_H (250 MHz, $CDCl_3$) 7.91 (1H, d, J=8.6 Hz, H-9), 7.70 (1H, d, J=8.6 Hz, H-12), 7.39 (1H, s, H-1), 7.31 (1H, t, J=8.6 Hz, H-11), 7.20 (1H, t, J=8.6 Hz, H-10), 6.87 (1H, s, H-4), 4.58 (2H, t, J=7.0 Hz, H-6), 4.01 (3H, s, CH_3), 3.94 (3H, s, CH_3), 3.21 (2H, t, J=7.0 Hz, H-5); δ_C (62.5 MHz, $CDCl_3$) 149.3 (quat.), 147.8 (quat.), 131.7 (quat.), 129.4

(CH), 125.9 (quat.), 123.5 (CH), 120.4 (CH), 120.1 (quat.), 118.1 (quat.), 112.4 (CH), 112.1 (quat.), 111.3 (CH), 106.6 (CH), 55.7 (CH_3), 55.5 (CH_3), 39.1 (CH_2), 27.0 (CH_2); ν_{max}/cm^{-1} (KBr) 3023, 2993, 2931, 2830, 1606, 1531, 1505, 1464, 1431, 1368, 1350, 1286, 1250, 1222, 1211, 1168, 1146, 1124, 1080, 1024.

3.3.11. 2,3-Dimethoxy-11-chloro-5,6-dihydroindazolo[3,2-*a*]isoquinoline-8-oxide (22c). The title compound was obtained as an orange solid, mp 133 °C; [Found: C, 61.7; H, 4.6; N, 8.5 $C_{17}H_{15}N_2O_3Cl$ requires C 61.7; H 4.6; N 8.5%]; δ_H (250 MHz, $CDCl_3$+DMSO-d_6) 7.86 (1H, s, H-12), 7.67 (1H, d, J=9.2 Hz, H-9), 7.28 (1H, s, H-1), 7.22 (1H, d, J=9.2 Hz, H-10), 6.87 (1H, s, H-4), 4.56 (2H, t, J=6.8 Hz, H-6), 4.02 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.21 (2H, t, J=6.8 Hz, H-5); δ_C (62.5 MHz, $CDCl_3$+DMSO-d_6) 148.9 (quat.), 148.3 (quat.), 129.2 (quat.), 127.8 (quat.), 127.2 (CH), 123.8 (quat.), 118.5 (CH), 118.2 (quat.), 117.4 (quat.), 114.2 (CH), 111.6 (quat.), 111.4 (CH), 106.7 (CH), 55.0 (CH_3), 55.7 (CH_3), 39.3 (CH_2), 27.2 (CH_2); ν_{max}/cm^{-1} (KBr) 3380, 3005, 1610, 1538, 1506, 1489, 1470, 1359, 1281, 1221, 1205, 1161, 1076, 1054, 1012, 989.

3.3.12. 2,3-Diethoxy-11-chloro-5,6-dihydroindazolo[3,2-*a*]isoquinoline-8-oxide (22d). The title compound was obtained as an orange solid, mp 129–30 °C; [Found: C, 63.6; H, 5.4; N, 7.6. $C_{19}H_{19}N_2O_3Cl$ requires C 63.6; H 5.3; N 7.8%]; δ_H (250 MHz, $CDCl_3$) 7.82 (1H, s, H-12), 7.68 (1H, d, J=9.2 Hz, H-9), 7.28 (1H, s, H-1), 7.21 (1H, d, J=9.2 Hz, H-10), 6.82 (1H, s, 1H, H-4), 4.56 (2H, t, J=7.0 Hz, H-6), 4.19 (2H, q, J=7.0 Hz, OCH_2), 4.16 (2H, q, J=7.0 Hz, OCH_2), 3.17 (2H, t, J=7.0 Hz, H-5), 1.53 (3H, t, J=7.0 Hz, CH_3), 1.49 (3H, t, J=7.0 Hz, CH_3); δ_C (62.5 MHz, $CDCl_3$) 148.8 (quat.), 147.8 (quat.), 129.0 (quat.), 127.7 (quat.), 127.1 (CH), 123.9 (quat.), 118.5 (CH), 118.1 (quat.), 117.8 (quat.), 114.0 (CH), 113.1 (CH), 111.5 (quat.), 109.3 (CH),64.9 (CH_2), 64.2 (CH_2), 39.3 (CH_2), 27.1 (CH_2), 14.4 (CH_3), 14.3 (CH_3); ν_{max}/cm^{-1} (KBr) 2975, 2914, 2867, 1613, 1603, 1534, 1505, 1472, 1445, 1396, 1360, 1344, 1284, 1250, 1217, 1198, 1170, 1080, 1056.

3.3.13. Dimethyl 8,9-diethoxy-10b-(2-nitrophenyl)-2,3,6,10b-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline-2,3-dicarboxylate (23). 6,7,-Diethoxy-3,4-dihydro-2-(methoxycarbonylmethyl)-1-(2′-nitrophenyl)isoquinolinium bromide (**20a**) (0.49 g, 1.0 mmol) was dissolved in methanol (5 mL) and triethylamine (0.14 mL, 0.10 g, 1.0 mmol) was added. The reaction mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (30 mL) and washed with water (3×20 mL). The organic layer was dried over magnesium sulphate and evaporated to give a mixture of 10,11-diethoxy-7,8-dihydroindazolo[3,2-a]isoquinoline-5-oxide **22a** and the title compound, which was separated by column chromatography, eluting with hexane–ethyl acetate (2:1) to give a white powder (0.10 g, 20%), mp 168–170 °C; [Found: C, 60.1; H, 5.7; N, 5.6. $C_{25}H_{28}N_2O_9$ requires C 59.99; H 5.64; N 5.60%]; δ_H (250 MHz, $CDCl_3$) 8.01 (1H, d, J=7.8 Hz, H-3′), 7.57 (1H, dt, J=7.8, 1.8 Hz, ArH), 7.49–7.38 (2H, m, ArH), 6.71 (1H, s, H-10), 6.67 (1H, s, H-7), 4.87 (1H, d, J=4.6 Hz, H-2), 4.08 (2H, q, J=7.0 Hz, OCH_2), 4.00–3.77 (3H, m, H-3 and OCH_2), 3.75 (OCH_3), 3.53 (OCH_3), 3.27–3.05 (3H, m, CH_2), 2.75–2.62 (1H, m, CH_2), 1.43 (3H, t, J=7.0 Hz, CH_3), 1.31 (3H, t, J=7.0 Hz CH_3); δ_C (62.5 MHz, $CDCl_3$) 170.8 (quat.), 169.9 (quat.), 149.5 (quat.), 148.7 (quat.), 146.8 (quat.), 135.5 (quat.), 131.2 (CH), 129.7 (CH), 129.4 (CH), 127.7 (quat.), 126.0 (quat.), 124.4 (CH), 113.4 (CH), 112.0 (CH), 99.6 (quat.), 74.0 (CH), 71.5 (CH), 64.6 (CH_2), 64.2 (CH_2), 52.6 (CH_3), 52.4 (CH_3), 50.1 (CH_2), 28.3 (CH_2), 14.7 (CH_3×2); ν_{max}/cm^{-1} (KBr) 1735 (C═O), 1535 (NO_2), 1367 (NO_2), 1263 (C–O).

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