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Ring-Opening Reactions of *N*-Aryl-1,2,3,4-tetrahydroisoquinolines: Synthesis of Novel Isoquino[2,1-*a*][3,1]benzoxazine Derivatives

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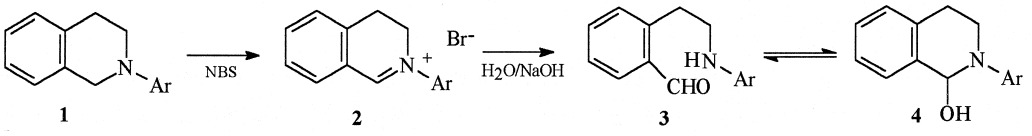
Abstract—The aldehydes **7e** and **7h** were prepared by treatment of the 1,2,3,4-tetrahydroisoquinolines **5e** and **5h,**, respectively, with *N*-bromosuccinimide (NBS). Basic hydrolysis of compounds **7e** and **7h** gave the 4b*H*,6*H*-isoquino[2,1-*a*][3,1]benzoxazine derivatives **9** (R=H, OMe). Heterocycle **10** was obtained from the reaction of compound **5c** with NBS and isolated as the ethyl derivative **11**.

Introduction

We have recently been interested in the *N*-bromosuccinimide (NBS) mediated oxidation of *N*-aryl-1,2,3,4-tetrahydroisoquinoline derivatives **1** in which the aryl group was electron-deficient (nitroaryl, nitropyridyl, fluorinated aryl, fluorinated pyridyl).[1–4] After hydrolysis of the intermediate iminium salts **2** the aldehydes **3** rather than their tautomeric hemi-aminals **4** were normally isolated (Scheme 1). The preference for the formation of the aldehyde structures **3** was rationalised in terms of electronic, steric and hydrogen bonding effects.

The iminium salt **6a** (Scheme 2) has been prepared[5–7] on several occasions from the reaction of 2-(2-bromoethyl)-benzaldehyde and 2-nitroaniline. Hydrolysis of this iminium salt **6a** was reported to give only the hemi-aminal **8a**.[7] In view of this result we anticipated that hydrolysis of iminium salt **6b** would also give the hemi-aminal **8b** because the inductive effect of the methyl group would render the amine nitrogen atom in aldehyde **7b** more nucleophilic than in compound **7a**. However, oxidation of compound **5b** with NBS gave, after hydroylsis of the intermediate **6b**, only the aldehyde **7b**.[1] The preference for formation of this aldehyde **7b** was attributed to unfavourable steric interactions between the methyl group and the hydroxy group in the aminal structure **8b**. When electron-deficient groups are located at the *ortho* position of the *N*-4-nitroaryl ring, for example, in compounds **5** (R=H, X=NO_2[1] and R=H, X=F[4]), the corresponding aldehyde structures **7** are produced. In these cases, the amine nitrogen atoms in structures **7** are not sufficiently nucleophilic to allow cyclisation to the hemi-aminals to occur. Additionally, in the former compound intramolecular hydrogen bonding between the *ortho* nitro group and the amine NH group favours the aldehyde structure.

It is reasonable to assume that an equilibrium exists between the tautomers **7** and **8** even though only one of the tautomers may be evident by ^{1}H NMR spectroscopy. In this paper we report our studies on trapping some hemi-aminal tautomers **8** from the NBS mediated oxidation reactions of some *N*-4-nitroaryl-tetrahydroisoquinolines **5** which would normally be expected to yield aldehyde structures **7**. These studies have also enabled the synthesis of some novel 4b*H*,6*H*-isoquino[2,1-*a*][3,1]benzoxazine derivatives (Scheme 2).



Scheme 1.

Keywords: tetrahydroisoquinolines; isoquino[2,1-*a*][3,1]benzoxazines; ring-opening.

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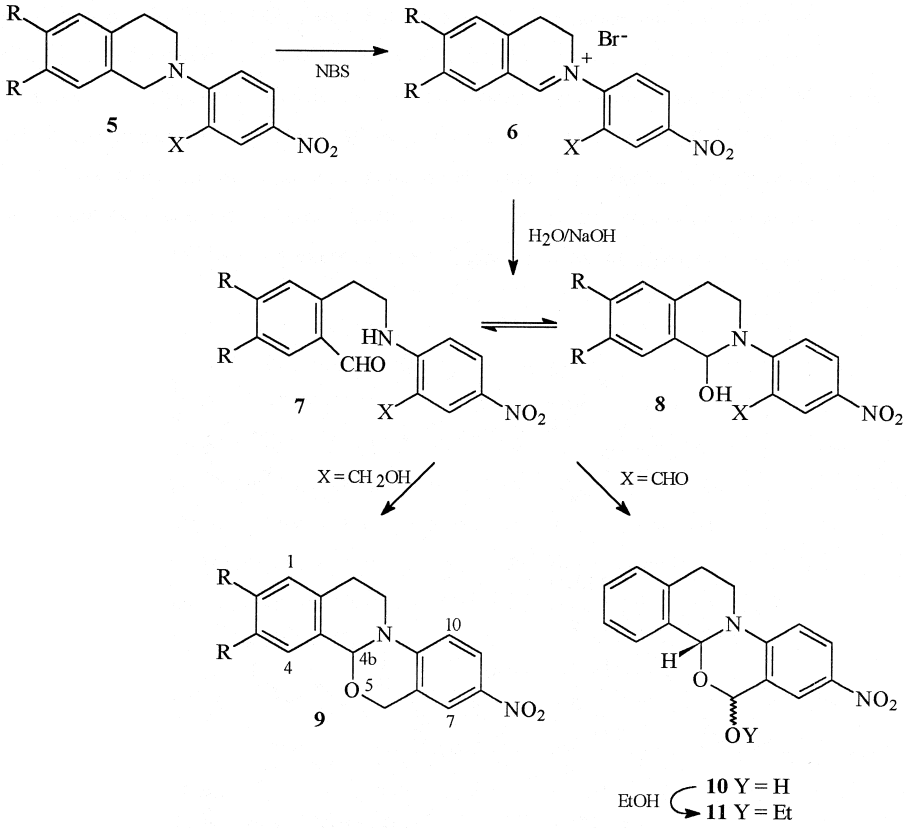

Scheme 2. (**a**) R=H, X=H; (**b**) R=H, X=CH_3; (**c**) R=H, X=CHO; (**d**) R=H, X=CH_2OH; (**e**) R=H, X=CH_2OAc; (**f**) R=OMe, X=CHO; (**g**) R=OMe, X=CH_2OH; (**h**) R=OMe, X=CH_2OAc.

Oxidation Reactions

Compound **5c** (95% yield) was prepared from 1,2,3,4-tetrahydroisoquinoline and 2-chloro-5-nitrobenzaldehyde. Reduction of compound **5c** with $NaBH_4$ yielded the hydroxymethyl derivative **5d** which was readily acylated with acetic anhydride in the presence of triethylamine giving compound **5e** (73%). Similarly, compound **5f** (52%) was prepared from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride and 2-chloro-5-nitrobenzaldehyde. Reduction of compound **5f** with $NaBH_4$ gave compound **5g** which was acylated as described above affording compound **5h** (81%).

We anticipated that the reaction between compound **5e** and NBS would yield the aldehyde **7e** by comparison with the results described above for oxidation of methyl-substituted compound **5b**. When compound **5e** was treated with NBS the aldehyde **7e** (77%) was obtained in accordance with expectations. Deacylation of this compound by boiling with ethanolic potassium hydroxide solution afforded the novel 4b*H*,6*H*-isoquino[2,1-*a*][3,1]benzoxazine derivative **9** (R=H) directly in excellent yield. The formation of heterocycle **9** (R=H) occurs *via* the aldehyde **7d** and hemi-aminal **8d** intermediates, neither of which could be isolated. The hydroxy group of the hemi-aminal intermediate **7d** is rapidly displaced by the *ortho* hydroxymethyl group giving the product **9** (R=H). The ^{1}H NMR spectrum of compound **9** (R=H) was consistent with its proposed structure, in particular a singlet (δ 5.65) was attributed to the O–CH–N proton, the diastereotopic methylene group was observed as an AB system and the $-CH_2CH_2-$ group was seen as an ABCD system.

In an analogous series of reactions, compound **5h** and NBS gave the aldehyde **7h** in excellent yield as expected. Treatment of this aldehyde **7h** with ethanolic potassium hydroxide solution gave the 4b*H*,6*H*-isoquino[2,1-*a*]-[3,1]benzoxazine derivative **9** (R=OMe) in 71% yield *via* the intermediates **7g** and **8g**. The ^{1}H NMR spectrum of compound **9** (R=OMe) was similar to that of compound **9** (R=H) exhibiting a singlet (δ 5.65) for the O–CH–N proton, an AB system for the methylene group and an ABCD system for the $-CH_2CH_2-$ group.

We have also investigated the oxidation of compound **5c** using NBS. As noted above, the oxidation of systems **5** in which the X group is electron deficient gave aldehyde structures and it was therefore of interest to establish whether the dialdehyde **7c** could be prepared. Treatment of heterocycle **5c** with NBS did not give the dialdehyde **7c** but instead the 4b*H*,6*H*-isoquino[2,1-*a*][3,1]benzoxazine derivative **11** was obtained in good yield (71%) essentially as one diastereoisomer after crystallisation from ethanol. The relative stereochemistry of the asymmetric centres has not been established. Evidently, the hydroxy group of the hemi-aminal tautomer **8c** reacts as a nucleophile at the *ortho* aldehyde group giving the intermediate **10** which is subsequently converted to the ethoxy derivative **11** when treated with ethanol in the crystallisation process. The ^{1}H NMR

spectrum of compound **11** showed two singlets (δ 5.82 and 5.68) which were attributed to the O–CH–O and O–CH–N protons as well as the familiar ABCD system for the $-CH_2CH_2-$ moiety.

These studies have successfully produced the novel 4b*H*,6*H*-isoquino[2,1-*a*][3,1]benzoxazine derivatives **9** (R=H, OMe) and **11** by intramolecular trapping of hemi-aminal intermediates. The hemi-aminal hydroxy group can behave either as a leaving group giving heterocycles **9** (R=H, OMe) or as a nucleophile giving compound **11**.

Experimental

^{1}H NMR spectra were recorded at either 90 or 270 MHz in $CDCl_3$ solution. Infra red spectra were determined as KBr discs.

2-(1,2,3,4-Tetrahydroisoquinol-2-yl)-5-nitrobenzaldehyde 5c. To a stirred mixture of 1,2,3,4-tetrahydroisoquinoline (1.3 g, 9.8 mmol) and K_2CO_3 (2.0 g, 14.5 mmol) in dimethylsulfoxide (DMSO) (10 mL) at room temperature was added 2-chloro-5-nitrobenzaldehyde (1.7 g, 9.2 mmol) in portions over 1 min. The mixture became dark in colour and was then heated at 70–75°C (oil-bath temperature) for 2 h. The reaction mixture was allowed to cool to room temperature, poured into water, and extracted with dichloromethane (DCM). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated giving compound **5c** (2.62 g, 95%) as a yellow oil which solidified upon standing. Compound **5c** was recrystallised from DCM/ethanol giving yellow crystals, mp 115–117°C. [Found: C, 68.0; H, 4.85; N, 10.15. $C_{16}H_{14}N_2O_3$ requires C, 68.1; H, 5.0; N, 9.9%], ν_{max}1686, 1598 and 1318 cm^{-1}, δ 10.10 (1H, s, –C*H*O), 8.63 (1H, d, *J*=3 Hz, Ar*H*), 8.30 (1H, dd, *J*=9 and 3 Hz, Ar*H*), 7.30–7.00 (5H, m, Ar*H*), 4.55 (2H, s, >CH_2), 3.72 (2H, t, *J*=6 Hz, –CH_2CH$_2$–) and 3.15 (2H, t, *J*=6 Hz, –CH$_2$CH_2–).

2-(1,2,3,4-Tetrahydroisoquinol-2-yl)-5-nitrobenzyl acetate 5e. To a suspension of compound **5c** (0.56 g, 2.0 mmol) in methanol (10 mL) at room temperature was added $NaBH_4$ (0.10 g, 2.6 mmol). The mixture was heated at reflux for 1 h, allowed to cool to room temperature, evaporated and water was added to the residue. The mixture was extracted with DCM, the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated giving *2-(1,2,3,4-tetrahydroisoquino-2-yl)-5-nitrobenzyl alcohol* **5d** (0.54 g) as a yellow oil, δ 8.31 (1H, d, *J*=3 Hz, Ar*H*), 8.12 (1H, dd, *J*=9 and 3 Hz, Ar*H*), 7.30–7.00 (5H, m, Ar*H*), 5.30 (1H, s, –O*H*), 4.81 (2H, s, >CH_2), 4.28 (2H, s, >CH_2), 3.40 (2H, t, *J*=6 Hz, –CH_2CH$_2$–) and 3.05 (2H, t, *J*=6 Hz, –CH$_2$CH_2–). Compound **5d** was dissolved in DCM (5 mL) and triethylamine (0.2 mL) and then acetic anhydride (0.2 mL) was added. The reaction mixture was allowed to stand (1.5 h) and then a further portion (0.05 mL) of acetic anhydride was added. After standing (1.5 h), the mixture was washed with dilute hydrochloric acid, water and dried ($MgSO_4$). The solvent was evaporated giving compound **5e** (0.47 g, 73%) as a yellow oil which was triturated with ethanol affording a bright yellow solid. Recrystallisation from ethanol gave yellow needles, mp 95–96°C. [Found: C, 66.05; H, 5.3; N, 8.35. $C_{18}H_{18}N_2O_4$ requires C, 66.2; H, 5.6; N, 8.6%], ν_{max} 1736, 1519, 1341, 1243 and 1224 cm^{-1}, δ 8.30 (1H, d, *J*=3 Hz, Ar*H*), 8.15 (1H, dd, *J*=9 and 3 Hz, Ar*H*), 7.30–7.00 (5H, m, Ar*H*), 5.22 (2H, s, >CH_2), 4.29 (2H, s, >CH_2), 3.38 (2H, t, *J*=6 Hz, –CH_2CH$_2$–), 3.05 (2H, t, *J*=6 Hz, –CH$_2$CH_2–) and 2.18 (3H, s, –CH_3).

2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)-5-nitrobenzaldehyde 5f. In a similar manner to that described above for compound **5c**, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.45 g, 10.7 mmol), 2-chloro-5-nitrobenzaldehyde (2.1 g, 11.3 mmol) and K_2CO_3 (3.5 g, 25.4 mmol) in DMSO (15 mL) gave compound **5f** (1.9 g, 52%) as a yellow solid after trituration with ethanol. Recrystallisation from methanol/DCM gave fluffy yellow needles, mp 178°C. [Found: C, 63.4; H, 5.2; N, 8.15. $C_{18}H_{18}N_2O_5$ requires C, 63.1; H, 5.3; N, 8.2%], ν_{max} 1675, 1601, 1520, 1324 and 1262 cm^{-1}, δ 10.09 (1H, s, –C*H*O), 8.69 (1H, d, *J*=3 Hz, Ar*H*), 8.28 (1H, dd, *J*=9 and 3 Hz, Ar*H*), 7.13 (1H, d, *J*=9 Hz, Ar*H*), 6.68 (1H, s, Ar*H*), 6.60 (1H, s, Ar*H*), 4.46 (2H, s, >CH_2), 3.88 (3H, s, –OCH_3), 3.87 (3H, s, –OCH_3), 3.69 (2H, t, *J*=6 Hz, –CH_2CH$_2$–) and 3.02 (2H, t, *J*=6 Hz, –CH$_2$CH_2–).

2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)-5-nitrobenzyl acetate 5h. In a similar manner to that described above for the preparation of compound **5e**, compound **5f** (0.70 g, 2.1 mmol) and $NaBH_4$ (0.1 g, 2.6 mmol) gave *2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)-5-nitrobenzyl alcohol* **5g** (0.68 g) as a yellow foam, δ 8.30 (1H, d, *J*=3 Hz, Ar*H*), 8.10 (1H, dd, *J*=9 and 3 Hz, Ar*H*), 7.20 (1H, d, *J*=9 Hz, Ar*H*), 6.65 (1H, s, Ar*H*), 6.60 (1H, s, Ar*H*), 5.30 (2H, s, >CH_2), 4.80 (1H, s, –O*H*), 4.20 (2H, s, >CH_2), 3.85 (6H, s, 2× –OCH_3), 3.40 (2H, t, *J*=6 Hz, –CH_2CH$_2$–) and 3.00 (2H, t, *J*=6 Hz, –CH$_2$CH_2–). Compound **5g** (0.62 g), acetic anhydride (0.30 mL) and triethylamine (0.20 mL) in DCM (5 mL) then gave compound **5h** (0.64 g, 81%) as a yellow solid, mp 162–163°C (from ethanol). [Found: C, 62.25; H, 5.45; N, 7.2. $C_{20}H_{22}N_2O_6$ requires C, 62.2; H, 5.75; N, 7.25%], ν_{max} 1736, 1617, 1522, and 1240 cm^{-1}, δ 8.30 (1H, d, *J*=3 Hz, Ar*H*), 8.15 (1H, dd, *J*=9 and 3 Hz, Ar*H*), 7.15 (1H, d, *J*=9 Hz, Ar*H*), 6.66 (1H, s, Ar*H*), 6.59 (1H, s, Ar*H*), 5.24 (2H, s, >CH_2), 4.23 (2H, s, >CH_2), 3.88 (6H, s, 2× –OCH_3), 3.36 (2H, t, *J*=6 Hz, –CH_2CH$_2$–), 2.92 (2H, t, *J*=6 Hz, –CH$_2$CH_2–) and 2.18 (3H, s, –CH_3).

2-[2-(2-Formylphenyl)ethylamino)]-5-nitrobenzyl acetate 7e. To a solution of compound **5e** (1.60 g, 4.9 mmol) in DCM (20 mL) at room temperature was added NBS (0.9 g, 5.1 mmol) portionwise over 2 min with swirling. The mixture was heated at reflux (10 min), allowed to cool to room temperature, washed with dilute sodium hydroxide solution and then water and dried ($MgSO_4$). The solvent was evaporated giving a yellow oil (1.66 g) which was triturated with ethanol giving compound **7e** (1.30 g, 77%) as a bright yellow solid, mp 103°C (from ethanol). [Found: C, 62.8; H, 5.4; N, 8.15. $C_{18}H_{18}N_2O_5$ requires C, 63.1; H, 5.3; N, 8.2%], ν_{max} 3425, 1743, 1695, 1592 and 1299 cm^{-1}, δ 10.11 (1H, s, –C*H*O), 8.20–7.20 (6H, m, Ar*H*), 6.68 (1H, d, *J*=10 Hz, Ar*H*), 5.64 (1H, broad

s, >N*H*), 5.00 (2H, s, >CH_2), 3.50 (4H, m, –CH_2CH_2–) and 2.09 (3H, s, –CH_3).

2-[2-(4,5-Dimethoxy-2-formylphenyl)ethylamino)]-5-nitrobenzyl acetate 7h. In a similar manner to that described above for compound **7e**, compound **5h** (0.19 g, 0.049 mmol) and NBS (0.09 g, 0.051 mmol) gave compound **7h** (0.20 g, 100%) as feathery yellow needles, mp 191°C (from ethanol). [Found: C, 59.9; H, 5.35; N, 6.9. $C_{20}H_{22}N_2O_7$ requires, C, 59.7, H, 5.5, N, 7.0%], ν_{max} 3317, 1736, 1676, 1590, 1516, 1331, 1304, 1272, 1237 and 1107 cm^{-1}, δ 10.05 (1H, s, –C*H*O), 8.15 (2H, m, Ar*H*), 7.31 (1H, s, Ar*H*), 6.78 (1H, s, Ar*H*), 7.65 (1H, d, *J*=9 Hz, Ar*H*), 5.70 (1H, broad t, *J*=5 Hz, >N*H*), 5.00 (2H, s, >CH_2), 3.95 (6H, s, 2×–OCH_3), 3.56 (2H, m, –CH_2CH_2–), 3.38 (2H, t, *J*=6 Hz, –CH$_2$CH_2–) and 2.03 (3H, s, –OCOCH_3).

8-Nitro-12*H*,13*H*-dihydro-4b*H*,6*H*-isoquino[2,1-*a*][3,1]-benzoxazine 9 (R=H). A mixture of compound **7e** (0.15 g, 0.44 mmol), potassium hydroxide (0.05 g, 0.89 mmol) and ethanol (3 mL) was heated at reflux for 0.5 h. The mixture was then allowed to cool to room temperature and the solvent was evaporated. Dilute hydrochloric acid and DCM was added to the residue and the organic layer was separated, washed with water, dried ($MgSO_4$) and evaporated giving compound **9** (R=H) (0.15 g, 100%) as small yellow needles, mp 179–180°C (from ethanol). [Found: C, 67.9; H, 4.7; N, 9.85. $C_{16}H_{14}N_2O_3$ requires C, 68.1, H, 5.0, N, 9.9%], ν_{max} 1608, 1511, 1488, 1311, 1265, 1202 and 1092 cm^{-1}, δ 8.13 (1H, dd, *J*=9 and 3 Hz, Ar*H*), 7.89 (1H, d, *J*=2 Hz, Ar*H*), 7.56 (1H, m, Ar*H*), 7.35–7.20 (3H, m, Ar*H*), 6.86 (1H, d, *J*=9 Hz, Ar*H*), (5.75 1H, s, >C*H*–), 5.10 (AB system, δ_A 5.18 δ_B 5.02, J_{AB}=14 Hz, >CH_2), 3.82–3.56 [2H, m (AB part of ABCD system), –CH_2CH_2–] and 3.18–2.90 [2H, m (CD part of ABCD system), –CH$_2$CH_2–].

2,3-Dimethoxy-8-nitro-12*H*,13*H*-dihydro-4b*H*,6*H*-isoquino[2,1-*a*][3,1]benzoxazine 9 (R=OMe). In a similar manner to that described above for compound **9** (R=H), compound **7h** (0.10 g, 0.25 mmol), potassium hydroxide (0.10 g, 1.79 mmol) and ethanol (10 mL) gave compound **9** (R=OMe) (0.06 g, 71%) as yellow/orange needles, mp 195–197°C. [Found: C, 63.0; H, 5.05; N, 8.15. $C_{18}H_{18}N_2O_5$ requires C, 63.1; H, 5.3; N, 8.2%], ν_{max} 1607, 1585, 1506, 1393, 1307, 1268, 1226, 1202, 1120 and 1091 cm^{-1}, δ 8.14 (1H, dd, *J*=9 and 3 Hz, Ar*H*), 7.88 (1H, d, *J*=2 Hz, Ar*H*), 7.02 (1H, s, Ar*H*), 6.90 (1H, d, *J*=9 Hz, Ar*H*), 6.68 (1H, s, Ar*H*), 5.65 (1H, s, >C*H*–), 5.08 (AB system, δ_A 5.19 δ_B 4.98, J_{AB}=14 Hz, >CH_2), 3.90 (3H, s, –OCH_3), 3.88 (3H, s, –OCH_3), 3.84–3.50 [2H, m (AB part of ABCD system), –CH_2CH_2–] and 3.20–2.00 [2H, m (CD part of ABCD system), –CH$_2$CH_2–].

6-Ethoxy-8-nitro-12*H*,13*H*-dihydro-4b*H*,6*H*-isoquino-[2,1-*a*][3,1]benzoxazine 11. To a solution of compound **5c** (1.4 g, 4.97 mmol) in DCM at room temperature was added NBS (1.0 g, 5.62 mmol) portionwise over a few minutes with swirling. The mixture became warm and an orange colour developed. The mixture was heated at reflux for 1.25 h, allowed to cool to room temperature, washed with dilute sodium hydroxide solution and then water, and dried ($MgSO_4$). The solvent was evaporated giving a yellow foam (1.5 g) to which ethanol was added. After standing over the weekend, compound **11** (1.15 g, 71%), a yellow solid, was collected. A small sample was recrystallised from ethanol giving yellow needles, mp 182°C. [Found: C, 66.3; H, 5.5; N, 8.6. $C_{18}H_{18}N_2O_4$ requires: C, 66.2; H, 5.7; N, 8.6%], ν_{max} 1586, 1609, 1496, 1405, 1319 and 1096 cm^{-1}, δ 8.17 (2H, m, Ar*H*), 7.50 (1H, m, Ar*H*), 7.36 (2H, m, Ar*H*), 7.24 (1H, m, Ar*H*), 6.97 (1H, d, *J*=9 Hz, Ar*H*), 5.82 (1H, s, >C*H*–), 5.68 (1H, s, >C*H*–), 4.20 (1H, m, –CH_2CH$_3$), 3.85 (1H, m, –OCH_2CH$_3$), 3.82–3.60 [2H, m (AB part of ABCD system), –CH_2CH_2–], 3.08 [2H, m, (CD part of ABCD system), –CH$_2$CH_2–] and 1.42 (3H, t, *J*=7 Hz, –CH_3).

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