Synthesis of 1,2-Oxazaheterocycles Containing an Isoindolone Moiety from *N*-Hydroxyphthalimide

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Dedicated to the memory of Professor Raymond N. Castle

Syntheses of the isoindolobenzoxazinone **1a** and thienoxazinoisoindolones **1b,c** was developed from *N*-hydroxyphthalimide **3** and halogenomethylaryl derivatives. The resulting aryloxy phthalimides **4a-c** were reduced to hydroxylactams **5a-c** which cyclized in acidic conditions. A Wittig reaction on **5a** using carbethoxymethylidenetriphenylphosphorane gave the corresponding acid **6** which treated in Friedel and Crafts conditions led to the isoxazolinone **8** by cleavage of the benzyl C-O bond.

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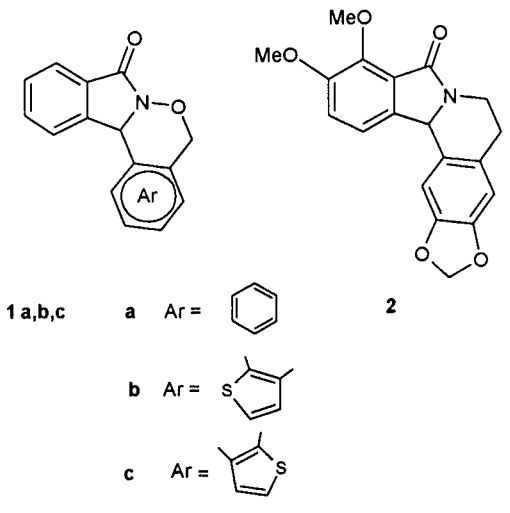
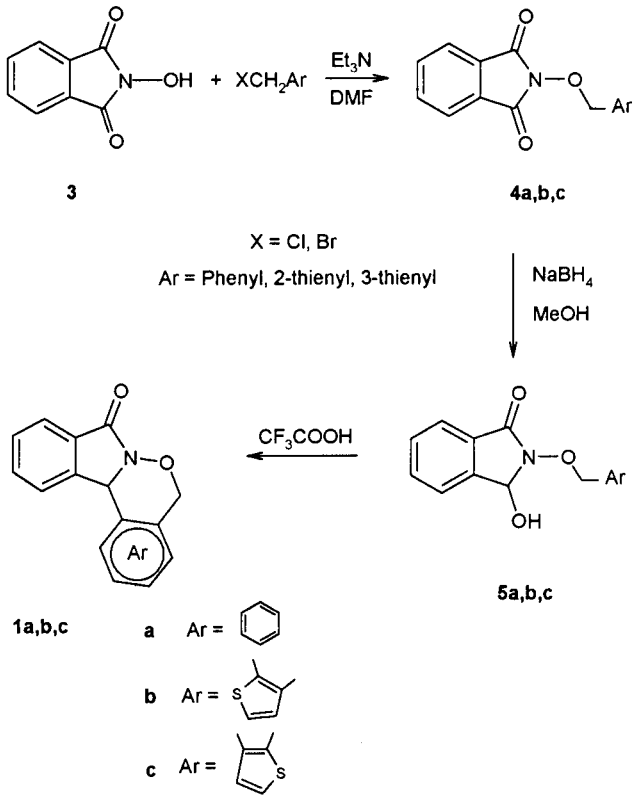
As a development of our long standing interest in the synthesis of polyheterocycles containing the isoindole system we have previously shown that *N*-acyliminium ions generated from 3-hydroxyisoindole derivatives could lead easily to isoindolobenzazepines, thienothiazinoisoindoles or isoindolobenzodiazepines through aromatic π-cyclization reactions [1a-c]. More recently, we focused our attention on the synthesis of N-O fused heterocyclic systems. We have previously shown that *N*-hydroxyphthalimide could be easily alkylated and led to fused-dioxaza-ring systems *via* a reduction of the phthalimide in 3-hydroxylactam [2]. To our knowledge, little is known on substituted [1,3]benzoxazine and only few examples of [1,3]oxazines fused to a saturated or insaturated isoindole are reported including our recent paper [3a-c]. We now wish to report a facile synthesis of isoindolobenzoxazinone **1a** or thienoxazinoisoindoles **1b,c** which were analogous to the alkaloïd Nuevamine **2** [4]. Starting material was the commercially available *N*-hydroxyphthalimide **3** which led to tetracyclic systems in three steps.

Scheme 1

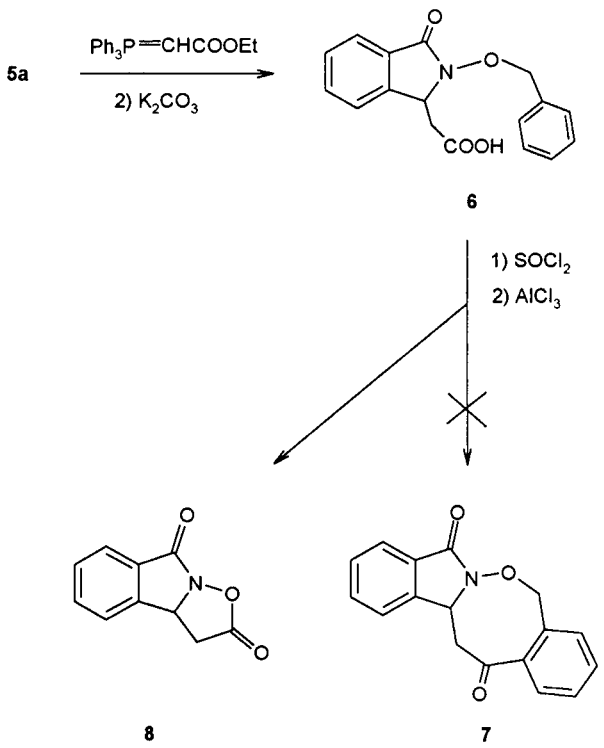


Scheme 2



As indicated in the Scheme 2, starting N-hydroxyphthalimide **3** was O-alkylated by appropriate halogenomethylaryl derivative in the presence of triethylamine in dry N,N dimethylformamide at 70° for 4 hours (64 to 92% yields). The 2-arylmethoxyphthalimides **4a-c** were then reduced with sodium borohydride in dry methanol at

Scheme 3

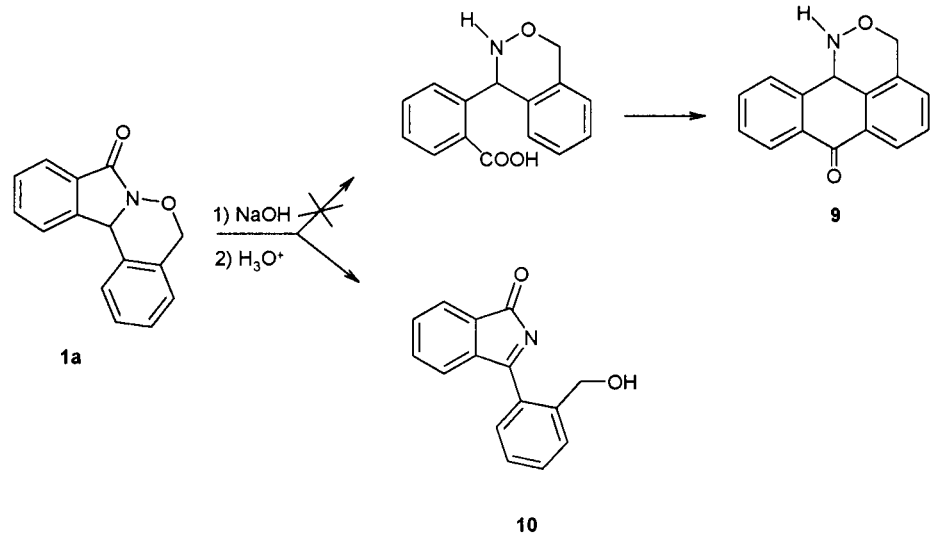


polycyclic systems was supported by ir, ^1H and ^{13}C spectroscopy and microanalysis. For example ^1H nmr spectrum of **1b** shows typical two AB systems corresponding to the thiophene protons (J = 5.1 Hz) and CH_2 protons of the oxazine ring (J = 14 Hz). In addition, the signal of the 11b proton appears as a singlet (5.85 ppm).

On the other hand, the hydroxylactam **5a** could be a precursor of the isoindolobenzoxazocine **7**, according to a route previously used for the synthesis of isoindolothienoazepine [6]. Thus, a Wittig reaction using ethoxycarbonylmethylidenetriphenylphosphorane on **5a** followed by basic hydrolysis of the non isolated ester gave the isoindolone acetic acid **6**. In contrast with our previous reports [1b, 7a,b] showing that 2-arylisoindole-3-acetic acids could give cyclic ketones by treatment with polyphosphoric acid, thionyl chloride in dichloromethane or successive action of *N*-ethylpiperidine, ethylchloroformate and boron trifluoride etherate, the acid **6** did not lead to the expected compound. Whatever the conditions used, each failed to cyclize **6** to the isoindolobenzoxazocine. Actually, Friedel and Crafts conditions using aluminium trichloride led to the isoxazolinone **8** resulting from a cleavage of the benzyl C-O bond in the presence of the Lewis acid.

Furthermore, in view of the reported synthesis of the anthra[5,6-*c*,*d*][1,2]oxazine **9** we tested the hydrolysis of the amide function of **1a** which might give an acid precursor of the new tetracyclic system [8]. However,

Scheme 4



0-5° for 1 hour without addition of acid as previously reported [5,6]. The hydroxylactams **5a-c** were obtained in good yields (79-86%) and then were cyclized with trifluoroacetic acid at room temperature to lead to the isoindolobenzoxazinone **1a** and the thienoxazinoisoindolones **1b,c** (84 to 93% yields). The structure of these new

treatment of the benzoxazine **1a** under basic conditions led to the 3-(2 hydroxymethylphenyl)-isoindolone **10**. This apparently resulting from the cleavage of the N-O bond of the oxazine ring rather than the aryl-substituted benzoxazine which should be obtained from lactam hydrolysis.

In conclusion, the present work described a general methodology for the synthesis of [1,2]oxaza-systems annelated to an isoindole ring and will facilitate the access of analogs containing N-O atoms in 1,2 position in the synthesis of new biologically active molecules.

EXPERIMENTAL

Melting points were determinated using a Kofler block and are uncorrected. Infrared spectra were recorded on PU 9800 FTIR infrared spectrometer (potassium bromide). The nmr spectra were recorded on a Bruker AC- 200 spectrometer (200 MHz) in deuteriochloroform except compounds **1a**, **1c**, **5c** and **6** in DMSO-d_6. The elemental analyses were carried out using a Carlo Erba Model 1108 elemental analyzer. Mass spectral measurement of **8** was recorded on a AEI MS 902 S spectrometer. *N*-hydroxyphthalimide **3** [9], 2-chloromethyl-thiophene [10], 3-bromomethylthiophene [11] used as starting materials were prepared according to reported procedures. Benzyl chloride was a commercial product.

General Procedure for the Synthesis of 2-Arylmethoxyphthalimides (**4a-c**).

A stirred solution of 16.3 g (0.1 mole) of *N*-hydroxyphthalimide, 0.1 mole of the appropriate halogenomethylaryl derivative and 22.2 ml (0.11 mole) of triethylamine in 100 ml of dry dimethylformamide was slowly heated to 70° in 1 hour, and maintained at 70° for 2-3 hours. Then, half the amount of solvent was evaporated under reduced pressure. After cooling, the mixture was poured into 100 ml of cold water. The precipitate was separated by filtration, the filter cake washed with water and dried to give white crude products. The pure materials were obtained by crystallization from ethanol.

2-(Benzyloxy)phthalimide (**4a**).

This compound was obtained in a yield of 92%, mp 142-143°; ir: ν 1730 (C=O) cm^{-1}; ^1H nmr: δ 5.16 (s, 2H, CH_2O), 7.30-7.40 (m, 3H, H_{arom}), 7.45-7.55 (m, 2H, H_{arom}), 7.65-7.80 (m, 4H, H_{arom}).

Anal. Calcd. for $C_{15}H_{11}NO_3$ (253.25): C, 71.14; H, 4.38; N, 5.53. Found: C, 71.05; H, 4.47; N, 5.31.

2-(Thien-2′-ylmethoxy)phthalimide (**4b**).

This compound was obtained in a yield of 70%, mp 135-136°; ir: ν 1738 (C=O) cm^{-1}; ^1H nmr: δ 5.33 (s, 2H, CH_2O), 6.95 (dd, 1H, $H_{4'}$, J = 3.5, 4.8 Hz), 7.16 (d, 1H, $H_{3'}$, J = 3.5 Hz), 7.38 (d, 1H, $H_{5'}$, J = 4.8 Hz), 7.63-7.72 (m, 4H, H_{arom}).

Anal. Calcd. for $C_{13}H_9NO_3S$ (259.28): C, 60.22; H, 3.50; N, 5.40. Found: C, 60.05; H, 3.47; N, 5.21.

2-(Thien-3′-ylmethoxy)phthalimide (**4c**).

This compound was obtained in a yield of 64%, mp 140-142°; ir: ν 1728 (C=O) cm^{-1}; ^1H nmr: δ 5.21 (s, 2H, CH_2O), 7.23-7.32 (m, 2H, H_{arom}), 7.38-7.42 (m, 1H, H_{arom}), 7.65-7.82 (m, 4H, H_{arom}).

Anal. Calcd. for $C_{13}H_9NO_3S$ (259.28): C, 60.22; H, 3.50; N, 5.40. Found: C, 60.11; H, 3.36; N, 5.19.

General Procedure for the Synthesis of 2,3-Dihydro-3-hydroxy-2-(arylmethoxy)-1*H*-isoindol-1-ones (**5a-c**).

To 0.05 mole of arylmethoxyphthalimide (**4a-c**) suspended in 100 ml of methanol was added portionwise 1.89 g (0.05 mole) of sodium borohydride at 0-5° over a period of 1 hour. The mixture was then stirred at this temperature for 3 hours. The methanol was removed *in vaccuo* and 80 ml of water was added to the residue. The suspension was acidified with 10% hydrochloric acid, the white precipitate which formed was filtered and washed with water. Recrystallization from ethanol afforded the hydroxylactams **5a-c** as white crystals.

2,3-Dihydro-3-hydroxy-2-(benzyloxy)-*1H*-isoindol-1-one (**5a**).

This compound was obtained in a yield of 79%, mp 176-178°; ir: ν 3295 (OH), 1701 (C=O) cm^{-1}; ^1H nmr: δ 5.15 (d, 1H, CH_2O, J = 11 Hz), 5.25 (d, 1H, CH_2O, J = 11 Hz), 5.70 (d, 1H, H_3, J = 8.6 Hz), 7.32-7.42 (m, 3H, H_{arom}), 7.45-7.60 (m, 4H, H_{arom}), 7.68-7.82 (m, 2H, H_{arom}).

Anal. Calcd. for $C_{15}H_{13}NO_3$ (255.27): C, 70.58; H, 5.13; N, 5.49. Found: C, 70.72; H, 5.08; N, 5.60.

2,3-Dihydro-3-hydroxy-2-(thien-2′-ylmethoxy)-1*H*-isoindol-1-one (**5b**).

This compound was obtained in a yield of 86%, mp 112-114°; ir: ν 3297 (OH), 1698 (C=O) cm^{-1}; ^1H nmr: δ 5.27 (d, 1H, CH_2O, J = 12.1 Hz), 5.35 (d, 1H, CH_2O, J = 12.1 Hz), 5.69 (s, 1H, H_3), 6.93 (dd, 1H, $H_{4'}$, J = 3.5, 5.1 Hz), 7.14 (dd, 1H, $H_{3'}$, J = 1.1, 3.5 Hz), 7.33 (dd, 1H, $H_{5'}$, J = 1.1, 5.1 Hz), 7.38-7.60 (m, 3H, H_{arom}), 7.66-7.74 (m, 1H, H_{arom}).

Anal. Calcd. for $C_{13}H_{11}NO_3S$ (261.29): C, 59.76; H, 4.24; N, 5.36. Found: C, 59.82; H, 4.17; N, 5.32.

2,3-Dihydro-3-hydroxy-2-(thien-3′-ylmethoxy)-*1H*-isoindol-1-one (**5c**).

This compound was obtained in a yield of 81%, mp 179-180°; ir: ν 3281 (OH), 1697 (C=O) cm^{-1}; ^1H nmr: δ 5.35 (s, 2H, CH_2O), 6.15 (d, 1H, H_3, J = 7 Hz), 7.35 (d, 1H, OH, J = 7 Hz), 7.42-7.70 (m, 7H, H_{arom}).

Anal. Calcd. for $C_{13}H_{11}NO_3S$ (261.29): C, 59.76; H, 4.24; N, 5.36. Found: C, 59.72; H, 4.31; N, 5.17.

General Procedure for the Cyclization of Hydroxylactams.

A solution of 0.02 mole of hydroxylactam **5a-c** in 15 ml of trifluoroacetic acid was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure. Dichloromethane (20 ml) was added to the residue, the organic layer was neutralized by a solution of sodium hydrogencarbonate, washed twice with water and dried over anhydrous magnesium sulfate. The dichloromethane was evaporated under reduced pressure and the residue was crystallized from methanol (**1a**) or toluene (**1b,c**).

5,12b-Dihydroisoindolo[2,1-*c*][2,3]benzoxazin-8-one (**1a**).

This compound was obtained in a yield of 93%, mp 138-140°; ir: ν 1717(C=O) cm^{-1}; ^1H nmr: δ 5.07 (s, 2H, CH_2O), 6.13 (s, 1H, H_{12b}), 7.15-8.15 (m, 8H, H_{arom}); ^{13}C nmr: δ 57.2 (C_{12b}), 70.9 (CH_2), 123.4 (CH), 124.5 (CH), 125.5 (CH), 126.5 (CH), 127.1 (CH), 127.7 (CH), 128.8 (C_q), 129.3 (CH), 131.3 (C_q), 131.9 (C_q), 133.5 (CH), 143.2 (C_q), 165.5 (C=O).

Anal. Calcd. for $C_{15}H_{11}NO_2$ (237.25): C, 75.94; H, 4.67; N, 5.90. Found: C, 76.06; H, 4.59; N, 5.71.

4,11b-Dihydrothieno[2′,3′:4,5][1,2]oxazino[3,2-*a*]isoindol-7-one (**1b**).

This compound was obtained in a yield of 86%, mp 196-198°; ir: ν 1721(C=O) cm^{-1}; ^1H nmr: δ 5.03 (d, 1H, CH_2O, J = 14 Hz),

5.37 (d, 1H, CH_2O, J = 14 Hz), 5.83 (s, 1H, H_{11b}), 7.17 (d, 1H, H_3, J = 5.1 Hz), 7.26 (d, 1H, H_2, J = 5.1 Hz), 7.42-7.54 (m, 1H, H_{arom}), 7.58-7.70 (m, 2H, H_{arom}), 7.86 (d, 1H, H_{arom}, J = 7.5 Hz); ^{13}C nmr: δ 57.9 (CH_2), 68.8 (C_{11b}), 123.5 (CH), 124.3 (CH), 124.7 (CH), 125.6 (CH), 128.5 (C_q), 129.0 (CH), 130.1 (C_q), 131.5 (C_q), 133.3 (CH), 143.0 (C_q), 165.7 (C=O).

Anal. Calcd. for $C_{13}H_9NO_2S$ (243.28): C, 64.18; H, 3.73; N, 5.76. Found: C, 64.25; H, 3.70; N, 5.54.

4,11b-Dihydrothieno[3',2':4,5][1,2]oxazino[3,2-*a*]-isoindol-7-one (**1c**).

This compound was obtained in a yield of 84%, mp 149-151°; ir: ν 1705 (C=O) cm^{-1}; ^1H nmr: δ 5.05 (s, 2H, CH_2O), 6.22 (s, 1H, H_{11b}), 6.89 (d, 1H, H_3, J = 5.1 Hz), 7.53 (d, 1H, H_2, J = 5.1 Hz), 7.55-7.86 (m, 4H, H_{arom}); ^{13}C nmr: δ 57.2 (CH_2), 70.0 (C_{11b}), 123.7 (CH), 124.0 (CH), 124.8 (CH), 125.9 (CH), 128.5 (C_q), 129.3 (CH), 131.3 (C_q), 131.9 (C_q), 133.5 (CH), 143.2 (C_q), 165.5 (C=O).

Anal. Calcd. for $C_{13}H_9NO_2S$ (243.28): C, 64.18; H, 3.73; N, 5.76. Found: C, 64.33; H, 3.59; N, 5.82.

2,3-Dihydro-1-oxo-2-(benzyloxy)-1*H*-isoindol-3-acetic Acid (**6**).

A solution of 8.36 g (0.024 mole) of ethoxycarbonylmethylidenetriphenylphosphorane and 5.11 g (0.02 mole) of hydroxylactam **5a** in 60 ml of toluene was refluxed with stirring for 1 hour. The solvent was evaporated under reduced pressure to give a residue. A mixture of water (15 ml), methanol (60 ml) and 5.52 g (0.04 mole) of potassium carbonate was added to the residue and the solution was refluxed for 2 hours. The mixture was concentrated, diluted with water and washed with dichloromethane. The aqueous phase was acidified with 10% hydrochloric acid to *p*H = 3. The white precipitate was collected by filtration, washed with water and dried. The crude product was crystallized from ethanol to afford 4.95 g (83%) of the acid **6** as white crystals, mp 166-168 °; ir: ν 1728, 1669 (C=O) cm^{-1}; ^1H nmr: δ 2.59 (dd, 1H, CH_2, J = 7.2, 16.5 Hz), 2.93 (dd, 1H, CH_2, J = 5.8, 16.5 Hz), 4.82 (t, 1H, H_3), 5.13 (s, 2H, CH_2O), 7.11-7.86 (m, 9H, H_{arom}).

Anal. Calcd. for $C_{17}H_{15}NO_4$ (297.31): C, 68.68; H, 5.09; N, 4.71. Found: C, 68.62; H, 4.98; N, 4.58.

1*H*-1,2-Isoxazolino[3,2-*a*]isoindol-2,5-dione (**8**).

A solution of 15 ml of dichloromethane containing 1.04 g (0.0035 mole) of acid **6** and 0.3 ml (0.0041 mole) of thionyl chloride was refluxed for 2 hours. The solvent and the excess thionyl chloride were evaporated under reduced pressure. The oily residue was dissolved in 20 ml of dichloromethane and the solution was added by drops into a stirred suspension of 1.5 g of aluminium chloride (0.011 mole) in 50 ml of dichloromethane during 20 minutes. The mixture was stirred at room temperature for 1 hour and poured into 80 ml of cold water. After separation, the aqueous layer was extracted twice with 15 ml of dichloromethane and collected organic layers were washed with water and dried over magnesium sulfate. The solvent was removed and the residue was crystallized from ethanol to give compound **7** in a yield of 63%, mp 179-181°; ir: ν 1829, 1723 (C=O) cm^{-1}; ^1H nmr: δ 2.52 (dd, 1H, CH_2, J = 10.2, 17.2 Hz), 3.25 (dd, 1H, CH_2, J = 8.1, 17.2 Hz), 5.38 (dd, 1H, H_{9b}, J = 8.1, 10.2 Hz), 7.50-7.73 (m, 3H, H_{arom}), 7.95 (d, 1H, H_{arom}, J = 7.5 Hz); ^{13}C nmr: δ 34.1 (CH_2), 61.1 (C_{9b}), 124.7 (CH), 124.9 (CH), 127.7 (CH), 129.9 (C_q), 134.7 (CH), 145.1 (C_q), 172.4 (C=O), 176.1 (C=O); ms: m/z 189 (M+)

Anal. Calcd. for $C_{10}H_7NO_3$ (189.17): C, 63.49; H, 3.73; N, 7.40. Found: C, 63.52; H, 3.74; N, 7.32.

1-Oxo-3-(2-hydroxymethylphenyl)-1*H*-isoindole (**10**).

To a solution of 5% sodium hydroxide (4 ml) was added 0.475 g (0.002 mole) of **1a**. The mixture was stirred and heated at 80° for 2 hours. The solution was filtered and acidified with 10% hydrochloric acid to *p*H = 4. The white precipitate was filtered, washed with water and dried. Recrystallization from ethanol afforded 0.350 g (74%) of **10** as colorless crystals, mp 201-203°; ir: ν 3214 (OH), 1705 (C=O) cm^{-1}; ^1H nmr: δ 5.30 (s, 2H, CH_2), 6.95-7.55 (m, 7H, H_{arom}), 7.80 (m, 1H, H_{arom}); ^{13}C nmr: δ 71.5 (CH_2), 98.5 (CH_2O), 121.6 (CH), 122.0 (CH), 122.6 (CH), 123.0 (CH), 128.1 (CH), 129.1 (CH), 129.8 (CH), 130.9 (C_q), 132.7 (CH), 138.0 (C_q), 140.1 (C_q), 147.8 (C_q), 167.8 (C=O).

Anal. Calcd. for $C_{15}H_{11}NO_2$ (237.25): C, 75.94; H, 4.67; N, 5.90. Found: C, 76.00; H, 4.70; N, 6.12.

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