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Application of Organolithium and Related Reagents in Synthesis. Part 23: Synthetic Strategies Based on *ortho*-Aromatic Metallation. Synthesis of 4b-Arylisoindolo[2,1-*a*]quinoline derivatives

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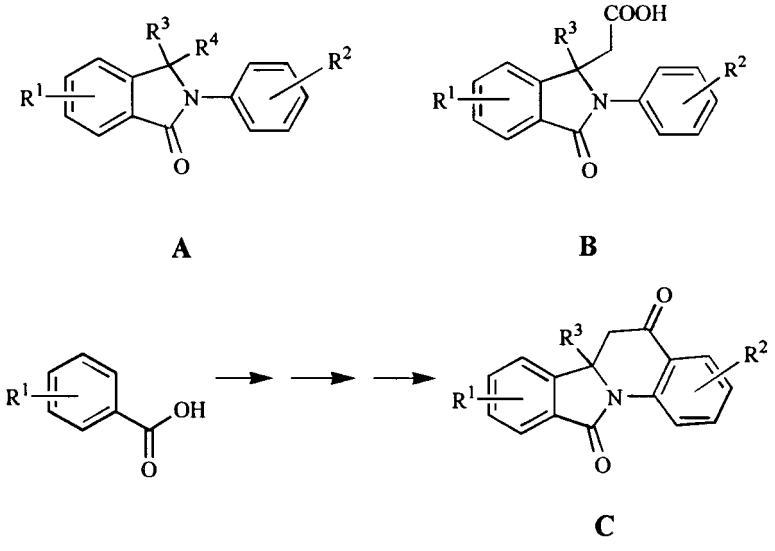
Abstract—The synthesis of the 2-aryl-3-hydroxyisoindol-1-ones **3** and their successive conversion via the reaction with 1-methoxy-1-trimethylsilyloxyethene in the presence of titanium(IV) chloride into 3-carboxymethylphthalimides **7** and subsequent cyclization via sequential treatment with oxalyl chloride and aluminium chloride as a way of regiospecific transformation of the benzenecarbocylic acids into the corresponding isoindolo[2,1-*a*]quinoline-5,11-diones **5** is described.

In the past few years we have witnessed a tremendous activity directed towards the synthesis of the dihydroisoindolin-1-ones **A**.[1] The dihydroisoindolin-1-ones **A** are central building blocks in a very large number of biologically active products, for example, non-nucleoside HIV-reverse transcriptase inhibitors,[2] and vasodilators.[3] Moreover, they possess potential utility as versatile key intermediates in the synthesis of alkaloid classes such as pyrolizidionones.[4] In particular, our attention has been focussed on the preparation of isoindolo[2,1-*a*]quinoline derivatives **C** (Scheme 1).

Available methods for preparation of the isoindolo[2,1-*a*]quinoline **C** skeleton generally require multistep reactions[5] and are often unsatisfactory both in yield and generality. The most attractive route so far reported for construction of the skeleton of isoindolo[2,1-*a*]quinolines **C** is the transformation of readily available



Scheme 1.

Keywords: lithiation; anilides; isoindole; *N*-acyliminium cation.

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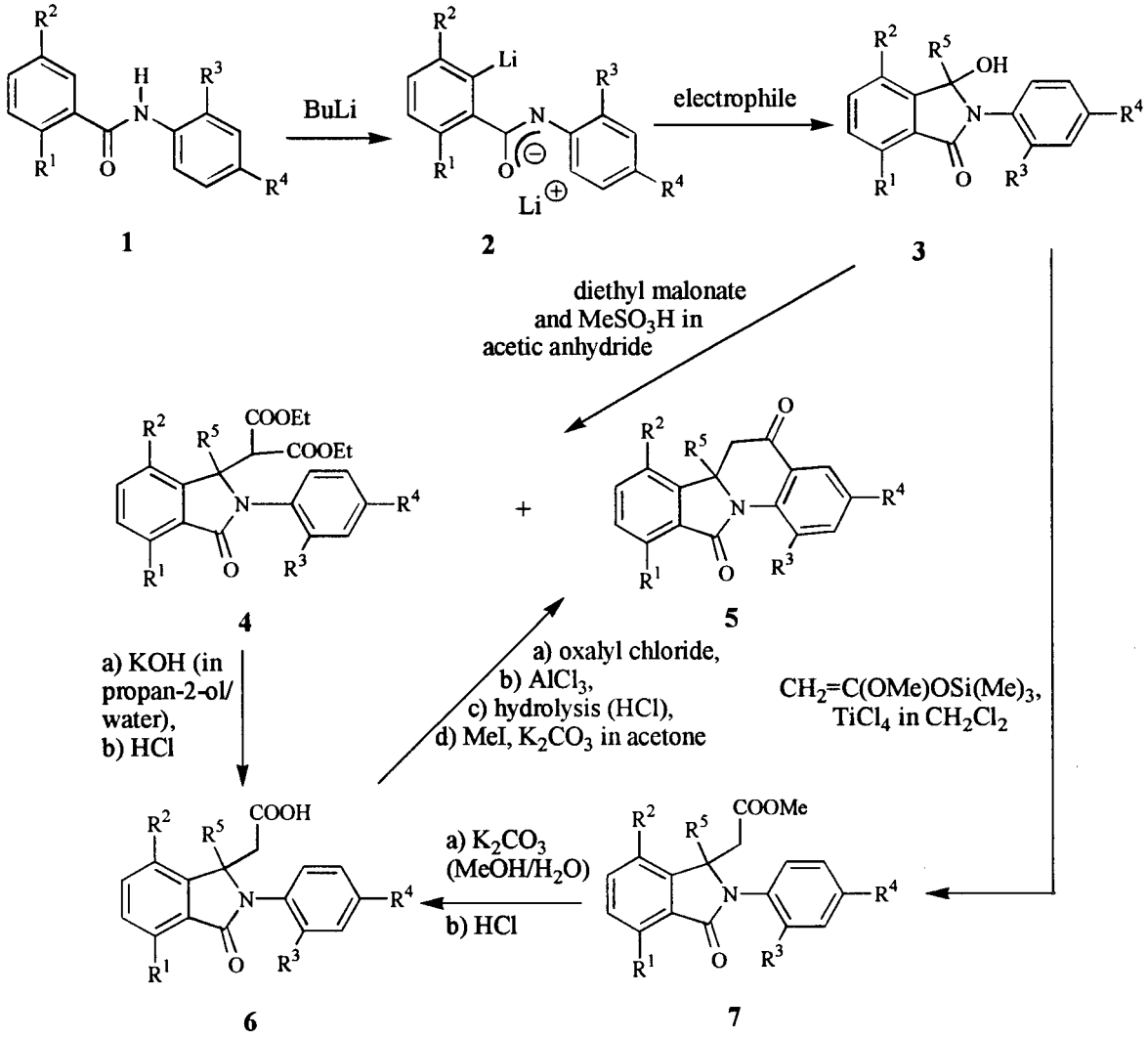
Table 1. A—an intractable mixture

Compounds	R^1	R^2	R^3	R^4	R^5	Electrophile	Yield (%)		
							3	**4+5**	**7**
a	H	H	H	OMe	Ph	PhCOOMe	82	59+21	85
b	H	H	OMe	H	4-(Cl)C_6H_4	4-(Cl)C_6H_4COOMe	55	–	66
c	H	OMe	H	H	H	DMF	72	A	60
d	H	OMe	H	H	4-(Cl)C_6H_4;	4-(Cl)C_6H_4COOMe	78	–	60
e	OMe	H	H	H	H	DMF	70	A	80
f	OMe	H	H	H	Ph	PhCOMe	71	52+28	85
g	OMe	H	H	H	4-(Cl)C_6H_4	4-(Cl)C_6H_4COOMe	52	49+26	60
h	OMe	H	H	OMe	Ph	PhCOOMe	74	56+26	80
i	OMe	H	H	H	4-(NO_2)C_6H_4	4-(NO_2)C_6H_4COOMe	53	0	–
j	OMe	H	H	H	4-Py	4-PyCON(Me_2)	80	0	–



Scheme 2.

3-hydroxyisoindol-1-ones **A**[6e,h] into 3-oxoisoindole-1-acetic acids **B** and then their Friedel-Crafts cyclization. Therefore, a general strategy for preparation of desired systems **C** boils down to obtaining an effective synthesis of phthalimides **B**.

The most frequently utilised route to systems **B** involves condensation of Wittig reagents[6] with 3-hydroxyisoindolinon-1-ones **A** (R^4=OH) as masked *ortho* carbonylamides. However, it has been found that this reaction is limited to the cases of compounds **A** in which R^3=H.[7] Alternative routes for preparation of phthalimides **B** require a conversion of 3-hydroxyisoindolinon-1-ones **A** (R^4=OH) into the corresponding *N*-acyliminium cation upon treatment with protic or Lewis acids and then a reaction with appropriate nucleophiles.[7,8] Nevertheless, it is still mostly related only

to specific instances. Till now there have been no reports concerning the synthesis and reaction of dihydroisoindol-1-one **A** in which R^1 and R^2 are not H. Therefore, the question remains to what extent formation of dihydroisoindol-1-ones and their conversion into *N*-acyliminium cations, as well as their reaction with nucleophiles as a route to formation of 3-carboxymethylphthalimides **B** are determined by the nature and position of the substituents.

Our aim was to extend the scope of this procedure to the synthesis of new polyheterocyclic systems such as isoindolo[2,1-*a*]quinoline-6,12-diones **C** with specific patterns of substituents, and we report here the results obtained starting with a series 3-hydroxyisoindloin-1-ones **3**. This provides access to an efficient and regiospecific synthetic sequence as a general strategy for the transformation of benzoic carboxylic acids into isoindolo[2,1-*a*]quinoline **B** in a four-step protocol starting from benzanilides **1**.

We have reported[6h,7,9] that the secondary carboxyamide group provides an excellent possibility for regiospecific preparation of 2-aryl-3-hydroxyisoindolin-1-ones, which are key starting materials here. Therefore 2-aryl-3-hydroxyisoindolin-1-ones **3** were obtained in a good yield by lithiation of benzanilides **1** using butyllithium (BuLi) in tetrahydrofuran (THF)[9] followed by a reaction of the generated bis-(*N*- and *C-ortho*) lithiated anilides **2** with methyl benzoates. In the next step the conversion of 2-aryl-3-hydroxyisoindolin-1-ones **3** into *N*-acyliminium cations and their subsequent alkylation by treatment with a nucleophilic reagent as a route to required 3-carboxymethylphthalimides **6** was applied. Thus, 2-aryl-3-hydroxyisoindolin-1-ones **3a**, **f**–**h** ($R^5 \neq H$) upon treatment in acetic anhydride in the presence of methanesulfonic acid reacted with diethyl malonate to give the desired isoindol-1-one-3-malonates **4** (49%–59%), which were unexpectedly accompanied by the corresponding dihydroisoindolo[2,1-*a*]quinolin-5,11-diones **5** (21–28%) (Table 1, Scheme 2).

Attempts to alter the ratio of products in favour of **5** via prolongation of the reaction time resulted only in disappearance of the isoindolo-1-one-3-malonates **4** without any improvement in the yield of the desired isoindolo[2,1-*a*]quinoline-5,11-diones. In the case of 3-aryl-3-hydroxyisoindolin-1-ones **3i**, **j**, in which substituent R^5 is 4-nitrophenyl or 4-pyridyl, the process failed. This is probably due to decreased stability of the *N*-acyliminium cations caused by strong electron-withdrawing effects of the substituents.

In the case of 2-aryl-3-hydroxyisoindolin-1-ones **3c**,**e** (R^5=H), a reaction with diethyl malonate in acetic anhydride in the presence of methanesulphonic acid gave only an intractable mixture. This obliged us to consider an alternative route. It is known that the alkylation at the carbon atom of *N*-hydroxymethylamides by their reaction with nucleophiles such as silyl enol ethers in the presence of Lewis acid generally proceeds in good yield.[8a,b,c,10–12] Thus, the reaction of 2-aryl-3-hydroxyisoindolin-1-ones **3** with 1-methoxy-1-trimethylsiloxyethene in the presence of titanium(IV) chloride in methylene chloride was attempted and, indeed, 3-carboxymethylphthalimides **7** were obtained in good yield. The observed independence of the reactivity with regard to the nature of substituent (R^5=H or Aryl) at position 3 of 2-aryl-3-hydroxyisoindolin-1-ones **3** suggests that the formation of 3-carboxymethylphthalimides **7** via a reaction of 1-methoxy-1-trimethylsiloxyethene with 2-aryl-3-hydroxyisoindolin-1-ones in the presence of titanium(IV) chloride is general.

In the final steps in the construction of isoindolo[2,1-*a*]quinolines **5** isoindolo-1-onyl-3-malonates **4** upon hydrolytic-decarboxylation and methyl 3-carboxymethylphthalimides **7** after base hydrolysis were quantitatively converted into corresponding 3-carboxymethylphthalimides **6**. Acids **6** after treatment with oxalyl chloride gave the acyl chlorides, which in the presence of aluminium chloride cyclized into desired isoindolo[2,1-*a*]quinolines **5**. In the case of methoxy derivatives of acids **6** the cyclization reaction was accompanied by partially demethylated products, but treatment of the reaction mixture with methyl iodide in the presence of potassium carbonate gave fully methylated isoindolo[2,1-*a*]quinoline-5,11-diones **5**.

This methodology for introduction of formyl or benzoyl groups at the *ortho* position of benzanilides and then the reaction of the resulting 2-aryl-3-hydroxyisoindolin-1-ones with 1-methoxy-1-trimethylsiloxyethene shows a considerable versatility for the regiospecific synthesis of 2-aryl-3-carboxymethylphthalimides. This coupled with an effective cyclization of 2-aryl-3-carboxymethylphthalimides to the corresponding isoindolo[2,1-*a*]quinoline-5,11-diones allows access to this type of aza-polyheterocyclic system.

Experimental

Melting points were determined using a Boetius hot-stage apparatus and they are uncorrected. IR spectra were recorded on a Zeiss–Jena Specord 71-IR. The ^{1}H NMR spectra were determined on a Varian-Gemini-200 (200 MHz) spectrometer using TMS as an internal standard. The ascending thin layer chromatography was performed on precoated silica gel 60 F 254 (Merck) and the spots were visualised using UV lamp or iodine vapour. Macherey Nagel & Co. (silica gel (100–200 mesh ATSM) was used for column chromatography. All reagents, commercially available materials, were used without purification unless otherwise stated. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl before use. Anilides **1** were prepared from benzoil chlorides and aromatic amines according to a known procedure.[15]

Preparation of 3-hydroxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-ones 3

To the anilide **1** (0.025 mol) stirred in THF (150 cm^3) at −78°C under argon was added BuLi (34.4 cm^3 1.6 mol/dm^3 solution in hexane, 0.055 mol). The solution was held at −78°C for 0.5 h then allowed to warm to 0°C and kept at 0°C for 6 min. The mixture was cooled to −78°C and the electrophile was added [in the cases **3c**, **3e**—DMF (2.56 g, 0.035 mol), **3a**, **3f**, **3h**—methyl benzoate (4.08 g, 0.03 mol), **3b**, **3d**, **3g**—methyl 4-chlorobenzoate (5.12 g, 0.03 mol), **3i**—methyl 4-nitrobenzoate (4.53 g, 0.025 mol), **3j**—*N*,*N*-dimethylisonicotinic amide (3.75 g, 0.025 mol) in THF (20 cm^3)]. The reaction mixture after 0.5 h at −78°C was

warmed to room temperature, and kept for 1 h. Then in the case of compounds **3a**–**h** water (25 cm^3) was added. The mixture was adjusted to pH≈2 with hydrochloric acid (2.0 mol/dm^3 solution in water) and the organic layer was separated. The water layer was extracted with $CHCl_3$/THF mixture 1:1 (3×30 cm^3). The combined organic solutions were dried with magnesium sulphate and evaporated to give the crude products **3a**–**h**. In the case of compounds **3i** and **3j** methanol (20 cm^3) was added and the solvents were removed under reduced pressure. To the residue water (100 cm^3) was added and the mixture was neutralised by addition of hydrochloric acid (2.0 mol/dm^3 solution in water). The insoluble crude products were filtered off and washed with water. The compounds **3** were purified by crystallisation.

3-Hydroxy-2-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-one 3a. Yield 82%, mp 199–202°C (crystallised from acetic acid) (lit.[13] mp 201–203°C).

3-Hydroxy-3-(4-chlorophenyl)-2-(2-methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 3b. Yield 55%, mp 134–137°C (crystallised from hexane/ethyl acetate 3:1); (Found: C, 69.1; H, 4.7; Cl, 9.4; N, 3.6: Calcd (for $C_{21}H_{16}ClNO_3$: C, 68.95; H, 4.41; Cl, 9.69; N, 3.83%); ν_{max}(KBr)/cm^{-1} 1700 (CO); δ_H($CDCl_3$) 7.90–7.84 (1H, m, 7-H), 7.63–7.53 (9H, 4-H, 5-H, 6-H, (4Cl)Ar, 6(2OMe)Ar and OH), 7.04–6.94 (1H, m, 5(2OMe)Ar), 6.90–6.80 (1H, m, 4(2OMe)Ar), 6.77–6.98 (1H, m, 3(2OMe)Ar), 3.79 (3H, s, OMe).

3-Hydroxy-4-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one 3c. Yield 72%, mp 168–170°C (crystallised from methanol) (lit.[9b] mp 167–169°C).

3-Hydroxy-3-(4-chlorphenyl)-4-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one 3d. Yield 78%, mp 244–245°C (crystallised from methanol); (Found: C, 69.0; H, 4.4; Cl, 9.8; N, 3.8: Calcd for $C_{21}H_{16}ClNO_3$: C, 68.95; H, 4.41; Cl, 9.69; N, 3.83%); ν_{max}(KBr)/cm^{-1} 1680 (CO); δ_H(DMSO-d_6) 7.64–7.08 (13H, m, 5-H, 6-H, 7-H, Ar, Ph and OH), 3.65 (3H, s, OMe).

3-Hydroxy-7-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one 3e. Yield 70%, mp 148–150°C (crystallised from methanol), (lit.[6d] mp 147–148°C).

3-Hydroxy-7-methoxy-2,3-diphenyl-2,3-dihydro-1*H*-isoindol-1-one 3f. Yield 71%, mp 221–223°C (crystallised from toluene); (Found: C, 76.0; H, 5.2; N, 4.3: Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23%); ν_{max}(KBr)/cm^{-1} 1690 (CO); δ_H(DMSO-d_6) 7.63–7.02 (13H, m, 4-H, 5-H, Ph, and OH), 6.78 (1H, d, J=7.5 Hz, 6-H), 3.92 (3H, s, OMe).

3-Hydroxy-3-(4-chlorophenyl)-7-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one 3g. Yield 52%, mp 259–262°C (crystallised from methanol); (Found: C, 69.1; H, 4.3; Cl, 9.6; N, 3.9: Calcd for $C_{21}H_{16}ClNO_3$: C, 68.95; H, 4.41; Cl, 9.69; N, 3.83%); ν_{max}(KBr)/cm^{-1} 1690 (CO); δ_H(DMSO-d_6) 7.66 (1H, s, OH), 7.57 (1H, dd J=8.2 and 7.5 Hz, 5-H), 7.49–7.05 (10H, m, 4-H, Ar and Ph), 6.80 (1H, d J=7.5 Hz, 6-H), 3.92 (3H, s, OMe).

3-Hydroxy-7-methoxy-3-(4-methoxyphenyl)-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one 3h. Yield 74%, mp 196–199°C (crystallised from water/acetone 1:1); (Found: C, 73.1; H, 5.2; N, 3.9: Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88%); ν_{max}(KBr)/cm^{-1} 1680 (CO); δ_H(DMSO-d_6) 7.58–7.45 (1H, m, 5-H), 7.42 (1H, s, OH), 7.40–7.05 (8H, m, 4-H, 2,6Ar-H and Ph), 6.88–6.75 (3H, m, 6-H and 3,5Ar), 3.90 (3H, s, OMe), 3,66 (3H, s, OMe).

3-Hydroxy-7-methoxy-3-(4-nitrophenyl)-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one 3i. Yield 53%, mp 285°C (decomp., crystallised from acetic acid); (Found: C, 66.7; H, 4.2; N, 7.5: Calcd for $C_{21}H_{16}N_2O_5$: C, 67.02; H, 4.28; N, 7.44%); ν_{max}(KBr)/cm^{-1} 1690 (CO); δ_H(DMSO-d_6) 8.18–8.06 (2H, m, 3,5Ar), 7.89 (1H, s, OH), 7,70–7.52 (3H, m, 5-H and 2,6Ar), 7.50–7.40 (2H, m, 2,6Ph), 7,34–7,04 (4H, m, 4-H and 3,4,5Ph), 6.81 (1H, d J=7.6 Hz, 5-H), 3.94 (3H, s, OMe).

3-Hydroxy-7-methoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1*H*-isoindol-1-one 3j. Yield 80%, mp 282–285°C (decompose, crystallised from methanol) (lit.[9c] mp 282–284°C decomp.).

Reaction of 3-hydroxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-ones 3a,f–h with diethyl malonate

To a mixture of acetic anhydride (5 cm^3) methanesulfonic acid (0.49 g, 0.005 mol) and diethyl malonate (2.40 g, 0.015 mol) 2-aryl-3-hydroxyisoindolone **3a**, **f**–**h** (0.005 mol) was added and the solution was heated at 110°C for 6 h. After cooling to room temperature the reaction mixture was poured into water (50 cm^3) and made alkaline (Na_2CO_3 saturated water solution). The mixture was extracted with $CHCl_3$ (3×15 cm^3). The extract was dried ($MgSO_4$) and the solvents were evaporated under reduced pressure. The brown residue was purified by chromatography to give the products **4a**,**f**–**h** and **5a**,**f**–**h**. Compounds **4a**,**f**–**h** and **5a**,**f**–**h** were purified by crystallisation.

Diethyl 2-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-malonate 4a. Yield 59%, R_f=0.42 (chloroform/ethyl acetate 5:1), mp 144–147°C (crystallised from ethyl acetate); (Found: C, 70.9; H, 5.7; N, 2.9: Calcd for $C_{28}H_{27}NO_6$: C, 71.02; H, 5.75; N, 2.96%); ν_{max}(KBr)/cm^{-1} 1750, 1730 and 1700 (CO); δ_H($CDCl_3$) 8.27–8.20 (1H, m, 7-H), 8.00–7.92 (1H, m, 4-H), 7.73–7.52 (2H, m, 5-H and 6-H), 7.35–7.11 (3H, m, 3,4,5Ph), 6.88–6.55 (6H, m, Ar and 2,6Ph), 4.69 (1H, s, CH), 4.10 (2H, q J=7.1 Hz, CH_2), 3.97–3.65 (5H, m, CH_2 and OMe), 1.15 (3H, t J=7.1 Hz, Me), 0.91 (3H, t J=7.1 Hz, Me).

Diethyl 7-methoxy-2,3-diphenyl-2,3-dihydro-1*H*-isoindol-1-on-3-malonate 4f. Yield 52%, R_f=0.22 (chloroform/ethyl acetate 5:1), mp 167–170°C (crystallised from hexane/ethyl acetate 1:1); (Found: C, 71.1; H, 5.8; N, 3.0: Calcd for $C_{28}H_{27}NO_6$: C, 71.02; H, 5.75; N, 2.96%); ν_{max}(KBr)/cm^{-1} 1750, 1730 and 1700 (CO); δ_H($CDCl_3$) 7.82–7.72 (1H, m, 4-H), 7.64–7.52 (1H, m, 5-H), 7.37–6.70 (11H, m, 6-H and Ph), 4.70 (1H, s, CH), 4.18–3.79 (7H, m, CH_2 and OMe), 1.14 (3H, t J=7.1 Hz, Me), 0.98 (3H, t J=7.1 Hz, Me).

Diethyl 3-(4-chlorphenyl)-7-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-malonate 4g. Yield 49%, R_f=0.22 (chloroform/ethyl acetate 5:1), mp 70°C (decomp., crystallised from hexane); (Found: C, 66.2; H, 5.1; Cl, 6.8; N, 2.9: Calcd for $C_{28}H_{26}ClNO_6$: C, 66.21; H, 5.16 Cl, 6.98; N, 2.76%); ν_{max}(KBr)/cm^{-1} 1750, 1730 and 1710 (CO); δ_H($CDCl_3$) 7.78–7.68 (1H, m, 4-H), 7.66–7.53 (1H, m, 5-H), 7.40–6.64 (10H, m, 6-H, Ar and Ph), 4.67 (1H, s, CH), 4.20–3.80 (7H, m, CH_2 and OMe), 1.15 (3H, t *J*=7.1 Hz, Me), 0.98 (3H, t *J*=7.1 Hz, Me).

Diethyl 7-methoxy-2-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-malonate 4h. Yield 56%, R_f=0.23 (chloroform/ethyl acetate 3:1), mp 148–151°C (crystallised from ethyl acetate); (Found: C, 69.1; H, 5.7; N, 2.9: Calcd for $C_{29}H_{29}NO_7$: C, 69.17; H, 5.80; N, 2.78%); ν_{max}(KBr)/cm^{-1} 1730 and 1700 (CO); δ_H($CDCl_3$) 7.81–7.67 (1H, m, 4-H), 7.65–7.52 (1H, m, 5-H), 7.35–7.08 (3H, m, 3,4,5Ph), 7.07–6.99 (1H, m, 6-H), 6.83–6.61 (6H, m, Ar and 2,6Ph), 4.68 (1H, s, CH), 4.18–3.74 (10H, m CH_2 and OMe), 1.14 (3H, t *J*=7.1 Hz, Me), 0.97 (3H, t *J*=7.1 Hz, Me).

3-Methoxy-6a-phenyl-6,6a-dihydroisoindolo[2,1-*a*]quinoline-5,11-dione 5a. Yield 21%, R_f=0.61 (chloroform/ethyl acetate 5:1), mp 205–206°C (crystallised from ethyl acetate); (Found: C, 77.8; H, 4.9; N, 4.0: Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94%); ν_{max}(KBr)/cm^{-1} 1710 and 1690 (CO); δ_H($CDCl_3$) 8.39 (1H, d, *J*=8.8Hz, 1-H), 8.06–7.77 (1H, m, 10-H), 7.62–7.45 (2H, m, 8-H and 9-H), 7.37 (1H, d *J*=3.2 Hz, 4-H), 7.33–7.11 (7H, m, 2-H, 7-H and Ph), 3.99 (1H, d *J*=16.4 Hz, 6-H), 3.78 (1H, s, OMe), 3.00 (1H, d *J*=16.4 Hz, 6-H).

10-Methoxy-6a-phenyl-6,6a-dihydroisoindolo[2,1-*a*]quinoline-5,11-dione 5f. Yield 28%, R_f=0.49 (chloroform/ethyl acetate 5:1), mp 275–277°C (crystallised from ethyl acetate); (Found: C, 70.8; H, 4.6; N, 4.0: Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94%); ν_{max}(KBr)/cm^{-1} 1710 and 1690 (CO); δ_H($CDCl_3$) 8.52–8.43 (1H, m, 1-H), 7.93–7.84 (1H, m, 4-H), 7.68–7.56 (1H, m, 2-H), 7.49 (1H, dd *J*=8.2 and 7.6 Hz, 8-H), 7.35–7.70 (6H, m, 3-H and Ph), 6.93 (1H, d *J*=8.2 Hz, 7-H), 6.84 (1H, d *J*=7.6 Hz, 9-H), 4.04(3H, s, OMe), 3.94 (1H, d *J*=16.4 Hz, 6-H), 3.02 (1H, d *J*=16.4 Hz, 6-H).

6a-(4-Chlorophenyl)-10-methoxy-6,6a-dihydroisoindolo-[2,1-*a*]quinoline-5,11-dione 5g. Yield 26%, R_f=0.48 (chloroform/ethyl acetate 5:1), mp 288–290°C (crystallised from ethyl acetate); (Found: C, 70.6; H, 4.1; Cl, 8.9; N, 3.6: Calcd for $C_{23}H_{16}ClNO_3$: C, 70.86; H, 4.14; Cl, 9.09; N, 3.59%); ν_{max}(KBr)/cm^{-1} 1710 and 1690 (CO); δ_H($CDCl_3$) 8.52–8.41 (1H, m, 1-H), 7.96–7.86 (1H, m, 4-H), 7.70–7.58 (1H, m, 2-H), 7.50 (1H, dd *J*=8.3 and 7.5 Hz, 8-H), 7.30–7.06 (5H, m, 3-H and Ar), 6.95 (1H, d *J*=8.3 Hz, 7-H), 6.82 (1H, d *J*=7.5 Hz, 9-H), 4.04 (3H, s, OMe), 3.88 (1H, d *J*=16.4 Hz, 6-H), 3.03 (1H, d *J*=16.4 Hz, 6-H).

3,10-Dimethoxy-6a-phenyl-6,6a-dihydroisoindolo[2,1-a]quinoline-5,11-dione 5h. Yield 26%, R_f=0.51 (chloroform/ethyl acetate 3:1), mp 264–268°C (crystallised from ethyl acetate); (Found: C, 74.7; H, 5.0; N, 3.7: Calcd for $C_{24}H_{19}NO_4$: C,74.79; H, 4.97; N, 3.63%); ν_{max}(KBr)/cm^{-1} 1710 and 1690 (CO); δ_H($CDCl_3$) 8.43–8.34 (1H, m, 1-H), 7.47 (1H, dd *J*=8.3 and 7.6 Hz, 8-H), 7.40–7.12 (7H, m, 2-H, 4-H and Ph), 6.92 (1H, d *J*=8.3 Hz, 7-H), 6.83 (1H, d *J*=7.6 Hz, 9-H), 4.03 (3H, s, OMe), 3.93 (1H, d *J*=16.4 Hz, 6-H), 3.77 (3H, s, OMe), 3.00 (1H, d *J*=16.4 Hz, 6-H).

Transformation of diethyl isoindol-1-on-3-malonate 4a,f–h into acetic acid derivatives 6a,f–h

The mixture of diethyl isoindol-1-on-3-malonate **4a**,**f**–**h** (0.001 mol) propan-2-ol (10 cm^3) water (7 cm^3) and potassium hydroxide (0.11 g, 0.003 mol) was refluxed for 30 h. After cooling to room temperature the solution was adjusted (HCl 1.0 mol/dm^3 solution in water) to pH≈2 and the resulting precipitate was washed with water (3×5 cm^3). Compounds **6a**,**f**–**h** were purified by crystallisation.

2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetic acid 6a. Yield 98%, mp 192°C (decomp., crystallised from methanol/water 1:1), (Found: C, 74.3 H, 5.1; N, 3.8: Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75%); ν_{max}(KBr)/cm^{-1} 1710 and 1660 (CO); δ_H(DMSO-d_6) 12.14 (1H, br s, OH), 7.83–7.75 (1H, m, 7-H), 7.65–7.44 (2H, m, 5-H and 6-H), 7.43–7.10 (6H, m, 4-H and Ph), 6.85 (4H, s, Ar), 3.84–3.66 (4H, overlapping 1H, d *J*=16.0 Hz, CH_2 and 3H, s, OMe), 3.18 (1H, d *J*=16.0 Hz, CH_2).

7-Methoxy-2,3-diphenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetic acid 6f. Yield 97%, mp 239°C (decomp., crystallised from methanol/water 1:2); (Found: C, 74.0; H, 4.9; N,3.8: Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H,5.13; N, 3.75%); ν_{max}(KBr)/cm^{-1} 1730 and 1660 (CO); δ_H(DMSO-d_6) 12.12 (1H, br s, OH), 7.55–7.43 (1H, m, 5-H), 7.40–6.85 (12H, m, 4-H, 6-H and Ph), 3.90 (3H, s, OMe), 3.81 (1H, d *J*=16.2 Hz, CH_2), 3.15 (1H, d *J*=16.2 Hz, CH_2).

3-(4-Chlorphenyl)-7-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetic acid 6g. Yield 94%, mp 248°C (decomp., crystallised from methanol/water 2:1); (Found: C, 67.7; H, 4.5; Cl, 8.6; N, 3.5: Calcd for $C_{23}H_{18}ClNO_4$: C,67.73; H, 4.45; Cl, 8.69; N, 3.43%); ν_{max}(KBr)/cm^{-1} 1720 and 1650 (CO); δ_H(DMSO-d_6) 12.16 (1H, br s, OH), 7.58–7.46 (1H, m, 5-H), 7.45–7.14 (7H, m, Ar and 3,4,5Ph), 7.09–6.85 (4H, m, 4-H, 6-H and 2,6Ph) 3.90 (3H, s, OMe), 3.80 (1H, d *J*=16.2 Hz, CH_2), 3.16 (1H, d *J*=16.2 Hz, CH_2).

7-Methoxy-2-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetic acid 6h. Yield 77%, mp 210°C (decomp., crystallised from methanol/water 2:1); (Found: C, 71.2; H, 5.1; N, 3.6: Calcd for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; N, 3.47%); ν_{max}(KBr)/cm^{-1} 1720 and 1650 (CO); δ_H(DMSO-d_6) 12.12 (1H, br s, OH), 7.55–7.43 (1H, m, 5-H), 7.40–6.85 (5H, m, Ph), 7.03 (1H, d *J*=8.2 Hz, 4-H), 6.92–6.79 (5H, m, 6-H and Ar) 3.90 (3H, s, OMe), 3.76–3.62 (4H, overlapping 1H, d *J*=16.0 Hz, CH_2 and 3H, s, OMe), 3.11 (1H, d *J*=16.0 Hz, CH_2).

Reaction of 3-hydroxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-ones 3 with 1-methoxy-1-trimethylsiloxyethene

A solution of hydroxyisoindolone **3** (0.0014 mol) and 1-methoxy-1-trimethylsiloxyethene (0.0042 mol) in dry

dichloromethane (30 cm^3) was added to a stirred solution of titanium(IV) chloride (0.81 g, 0042 mol) in dry dichloromethane (5 cm^3) under argon at 0°C. The resulting solution was allowed to warm slowly to room temperature and was left for 24 h. Then 5% aqueous $NaHSO_4$ solution (6 cm^3) was added. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The obtained crude product **7** was purified by crystallisation. [1-Methoxy-1-trimethylsiloxyethene was prepared according to a known procedure[14] from methyl acetate anion and chlorotrimethylsilane and was used as a mixture with methyl (trimethylsilyl)acetate. The isomeric composition of the used mixture of *C*- and *O*-silylated products was measured by integrating the OCH_3 proton signals in $CDCl_3$.]

Methyl 2-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetate 7a. Yield 85%, mp 164–165°C (crystallised from ethyl acetate/hexane 1:2); (Found: C, 74.5; H, 5.5; N, 3.6: Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62%); ν_{max}(KBr)/cm^{-1} 1750 and 1690 (CO); δ_H($CDCl_3$) 8.04–7.93 (1H, m, 7-H), 7.61–7.45 (2H, m, 5-H, 6-H), 7.37–7.03 (6H, m, 4-H, Ph), 6.90–6.71 (4H, m, Ar), 3.76 (3H, s, OMe), 3.50 (1H, d *J*=15.1, CH_2), 3.39 (3H, s, OMe), 3.30 (1H, d *J*=15.1, CH_2).

Methyl 3-(4-chlorophenyl)-2-(2-methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-on-3-acetate 7b. Yield 66%, mp 158–161°C (crystallised from ethyl acetate/hexane 1:1); (Found: C, 68.5; H, 4.7; Cl,8.6; N, 3.4: Calcd for $C_{24}H_{20}ClNO_4$: C, 68.33; H, 4.78; Cl, 8.40; N, 3.32%); ν_{max}(KBr)/cm^{-1} 1740 and 1700 (CO); δ_H($CDCl_3$) 8.04–7.96 (1H, m, 7-H), 7.70–7.43 (3H, m, 4-H, 5-H and 6-H), 7.40–6.74 (8H, m, (4Cl)Ar and (2OMe)Ar), 3.50 (3H, s OMe), 3.46 (3H, s, OMe), 3.36 (2H, d *J*=4.7 Hz, CH_2).

Methyl 4-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetate 7c. Yield 60%, mp 108–110°C (crystallised from ethyl acetate/hexane 1:3); (Found: C, 69.4; H, 5.4; N, 4.5: Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50%); ν_{max}(KBr)/cm^{-1} 1740 and 1690 (CO); δ_H($CDCl_3$) 7.63–7.36 (6H, m, 6-H, 7-H and 2,3,5,6Ph), 7.32–7.20 (1H, m, 4Ph), 7.08 (1H, dd *J*=7.3 and 1.7 Hz, m, 5-H), 5.61 (1H, t *J*=5.2 Hz, CH), 3.92 (3H, s, OMe) 3.45 (3H, s, OMe), 2.90–2.80 (2H, two overlapping d *J*=5.2 Hz, CH_2).

Methyl 3-(4-chlorophenyl)-4-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetate 7d. Yield 60%, mp 164–167°C (crystallised from ethyl acetate/hexane 1:1); (Found: C, 68.5; H, 4.6; Cl, 8.7; N, 3.4: Calcd for $C_{24}H_{20}ClNO_4$: C, 68.33; H, 4.78; Cl, 8.40; N, 3.32%); ν_{max}(KBr)/cm^{-1} 1750 and 1710 (CO); δ_H($CDCl_3$) 7.65–7.45 (2H, m, 6-H and 7-H), 7.35–6.89 (10H, m, 5-H, Ar and Ph), 3.85 (1H, d *J*=14.6 Hz, CH_2), 3.71 (3H, s, OMe), 3.38 (3H, s, OMe), 3.23 (1H, d *J*=14.6 Hz, CH_2).

Methyl 7-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetate 7e. Yield 80%, mp 129–132°C (crystallised from benzene/hexane 1:2); (Found: C, 69.7 H, 5.5 N, 4.51 Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50%); ν_{max}(KBr)/cm^{-1} 1750 and 1690 (CO); δ_H($CDCl_3$) 7.64–6.86 (8H, m, 4-H, 5-H, 6-H and Ph), 4.51 (1H, dd *J*=8.5 and 4.1 Hz, CH), 3.98 (3H, s, OMe), 3.63 (3H, s, OMe), 2.89 (1H, dd *J*=16.1 and 4.1 Hz, CH_2), 2.47 (1H, dd *J*=16.1 and 8,5 Hz, CH_2).

Methyl 7-methoxy-2,3-diphenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetate 7f. Yield 85%, mp 221–223°C (crystallised from ethyl acetate/hexane 2:1); (Found: C, 74.8; H, 5.5; N 3.6; Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62%); ν_{max}(KBr)/cm^{-1} 1750 and 1690 (CO); δ_H($CDCl_3$) 7.52–7.41 (1H, m, 5-H), 7.36–6.97 (10H, m, Ph-H), 6.93 (1H, d *J*=8.3, 4-H), 6.77 (1H, d *J*=7.5, 6-H), 4.02 (3H, s, OMe), 3.53 (1H, d *J*=14.8, CH_2), 3.42 (3H, s, OMe), 3.31 (1H, d *J*=14.8, CH_2).

Methyl 3-(4-chlorophenyl)-7-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetate 7g. Yield 60%, mp 225–227°C (crystallised from ethyl acetate/hexane 1:1); (Found: C, 68.4; H, 4.8; Cl, 8.1; N, 3.4: Calcd for $C_{24}H_{20}ClNO_4$: C, 68.33; H, 4.78; Cl, 8.40; N, 3.32%); ν_{max}(KBr)/cm^{-1} 1750 and 1700 (CO); δ_H($CDCl_3$) 7.54–7.42 (1H, m, 6-H), 7.33–6.90 (10H, m, 4-H, Ar and Ph,), 6.76 (1H, d *J*=7.7, 5-H), 4.02 (3H, s, OMe), 3.53–3.39 (4H, m, OMe, CH_2), 3.26 (1H, d *J*=15.1, CH_2).

Methyl 7-methoxy-2-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetate 7h. Yield 80%, mp 194–198°C (crystallised from ethyl acetate/hexane 1:1); (Found: C, 72.1; H, 5.5; N,3.4: Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36%); ν_{max}(KBr)/cm^{-1} 1730 and 1690 (CO); δ_H($CDCl_3$) 7.53–7.41 (1H, m, 5-H), 7.36–7.08 (5H, m, Ph), 6.97–6.69 (6H, m, 4-H, 6-H and Ar,), 4.01 (3H, s, OMe), 3.75 (3H, s, OMe), 3.52–3.40 (4H, m, OMe, CH_2), 3.27 (1H, d *J*=14.8, CH_2).

Hydrolysis of methyl esters 7 into acetic acid derivatives 6

A mixture of K_2CO_3 (0.50 g, 0.0036 mol) methyl acetate derivatives **7** (0.001 mol) water (2 cm^3) and methanol (10 cm^3) was refluxed for 5 h. Then methanol was removed under reduced pressure, water (20 cm^3) was added to the residue and solution lot was adjusted to pH≈2 to precipitated crude acids **6**. The compounds **6** were purified by crystallisation.

2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetic acid 6a. Yield 98%, mp 192°C (decomp., crystallised from methanol/water 1:1), identical to that made by other route.

4-Methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetic acid 6c. Yield 97%, mp 185°C (decomp., crystallised from ethyl acetate/methanol 6:1); (Found: C, 69.0; H, 5.1; N, 4.6: Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71%); ν_{max}(KBr)/cm^{-1} 1740 and 1650 (CO); δ_H(DMSO-d_6) 12.30–11.90 (1H, br s, OH), 7.80–7.08 (8H, m, 5-H, 6-H, 7-H and Ph), 5.63–5.55 (1H, m, CH), 3.80 (3H, s, OMe), 2.80 (1H, dd *J*=15.9 and 3.9 Hz, CH_2), 2.59 (1H, dd *J*=15.9 and 4,9 Hz, CH_2).

7-Methoxy-2,3-diphenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetic acid 6f. Yield 97%, mp 239°C (decomp., crystallised from methanol/water 1:2), identical to that made by other route.

3-(4-Chlorphenyl)-7-methoxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetic acid 6g. Yield 94%, mp 248°C (decomp., crystallised from methanol/water 2:1), identical to that made by other route.

7-Methoxy-2-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-on-3-acetic acid 6h. Yield 90%, mp 210°C (decomp., crystallised from methanol/water 2:1), identical to that made by other route.

Cyclization of acetic acid derivatives 6 into isoindolo[2,1-*a*]quinoline-5,11-dione system 5

To isoindolinone acetic acid **6** (0.001 mol) were added oxalyl chloride (0.76 g, 0.006 mol) and 1,2-dichloroethane (5 cm^3). The mixture was stirred and gently refluxed for 0.3 h. The excess of oxalyl chloride was removed under reduced pressure. Then 1,2-dichloroethane (5 cm^3) and aluminium chloride (0.40 g, 0.003 mol) were added and the mixture was gently refluxed for 2 h. The mixture was cooled to room temperature and water (5 cm^3) was added. The obtained mixture was adjusted (HCl) to pH≈2. The organic layer was separated and the solvents were removed under reduced pressure. Then acetone (20 cm^3) potassium carbonate (0.28 g, 0.002 mol) and methyl iodide (0.29 g, 0.002 mol) were added to the residue and the mixture was refluxed for 10 h. The solvent was removed under reduced pressure and to resulting residue was added chloroform (10 cm^3). Then the precipitate was separated and washed with chloroform (3×5 cm^3). The filtrate was concentrated and products **5** were separated by column chromatography and purified by crystallisation.

3-Methoxy-6a-phenyl-6,6a-dihydroisoindolo[2,1-*a*]quinoline-5,11-dione 5a. Yield 53%, R_f=0.61 (chloroform/ethyl acetate 5:1), mp 205–206°C (crystallised from ethyl acetate).

7-Methoxy-6,6a-dihydroisoindolo[2,1-*a*]quinoline-5,11-dione 5c. Yield 42%, R_f=0.55 (chloroform/ethyl acetate 4:1), mp 220°C (decomp., crystallised from ethyl acetate/heptane 1:1); (Found: C, 72.9 H, 4.7, N; 4.9; Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02%); ν_{max}(KBr)/cm^{-1} 1710 and 1680 (CO); δ_H($CDCl_3$) 8.58–8.46 (1H, m, 1-H), 8.10–8.02 (1H, m, 4-H), 7.73–7.42 (3H, m, 2-H, 9-H and 10-H), 7.30–7.06 (2H, m, 3-H and 8-H), 5.26 (1H, dd J=14.1 and 3.4 Hz, CH), 3.95 (3H, s, OMe), 3.63 (1H, dd J=16.4 and 3.4 Hz, CH_2), 2.57 (1H, dd J=16.4 and 14.1 Hz, CH_2).

10-Methoxy-6a-phenyl-6,6a-dihydroisoindolo[2,1-*a*]quinoline-5,11-dione 5f. Yield 94%, R_f=0.49 (chloroform/ethyl acetate 5:1), mp 275–277°C (crystallised from ethyl acetate), identical to that made by other route.

6a-(4-Chlorophenyl)-10-methoxy-6,6a-dihydroisoindolo-[2,1-*a*]quinoline-5,11-dione 5g. Yield 88%, R_f=0.48 (chloroform/ethyl acetate 5:1), mp 288–290°C (crystallised from ethyl acetate), identical to that made by other route.

3,10-Dimethoxy-6a-phenyl-6,6a-dihydroisoindolo[2,1-*a*]-quinoline-5,11-dione 5h. Yield 57%, R_f=0.51 (chloroform/ethyl acetate 3:1), mp 264–268°C (crystallised from ethyl acetate), identical to that made by other route.

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