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The Synthesis of (±)–Aminoglutethimide *via* Vicarious Nucleophilic Aromatic Substitution of Hydrogen

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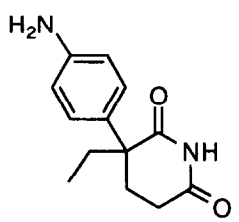
Abstract: The synthesis of aminoglutethimide *via* a one-pot coupling of nitrobenzene, ethyl 2-chlorobutyrate and 3-bromopropionitrile has been achieved *via* a process involving sequential vicarious nucleophilic aromatic substitution and alkylation.

The substituted glutarimide, aminoglutethimide **1** is an effective anticancer drug for the treatment of breast and prostate cancer.[1] Aminoglutethimide is a clinically important non-steroidal, type II aromatase inhibitor which suppresses steroid synthesis in the adrenals, and ultimately results in lower amounts of estrogens available to the cancer cells.[2,3] Aminoglutethimide, a first generation aromatase inhibitor, is still the most widely used aromatase inhibitor in treating advanced breast carcinoma. Aminoglutethimide seemed initially very toxic but with new schedules involving a daily 500 mg dose, there is a low toxicity profile, especially after the first few weeks of treatment.[4] Further interest has been stimulated by the finding that the enantiomers of **1** exhibit pronounced different pharmacological effects.[5] The (*R*)-isomer is responsible for the beneficial effects of aminoglutethimide therapy whilst both cause undesired side effects. This has led to the development of several enantioselective syntheses of (+)-(*R*)-aminoglutethimide.[6,7,8]



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As part of an investigation[9] into the aromatic vicarious nucleophilic substitution (VNS) of hydrogen[10] we have developed a synthesis of **1** and report the details in full herein. We recently reported the one-pot coupling reaction of three components **2**, **3** and **6** for the construction of nitroarenes **7** bearing an adjacent quaternary chiral centre, as illustrated in scheme 1.[11,12] This process first involves a VNS reaction between the nitroarene and the stabilised carbanion **3** that bears a leaving group X at the nucleophilic centre, to give the intermediate anion **5** *via* loss of HX from the σ-adduct **4**. This anion can be quenched *in situ* with a variety of electrophiles **6** to give the *para*-functionalised nitroarene **7**.

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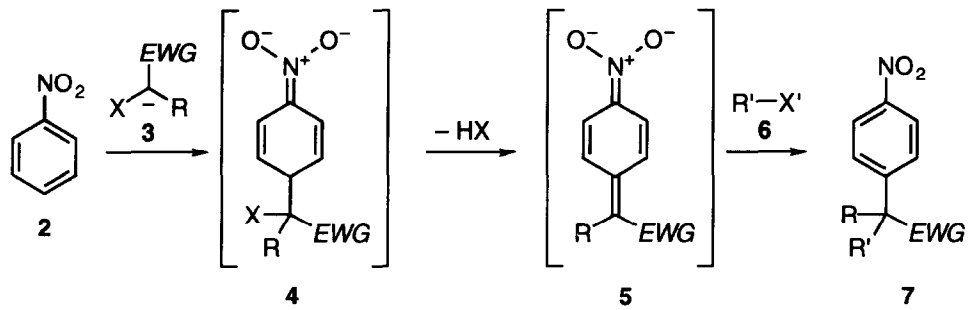
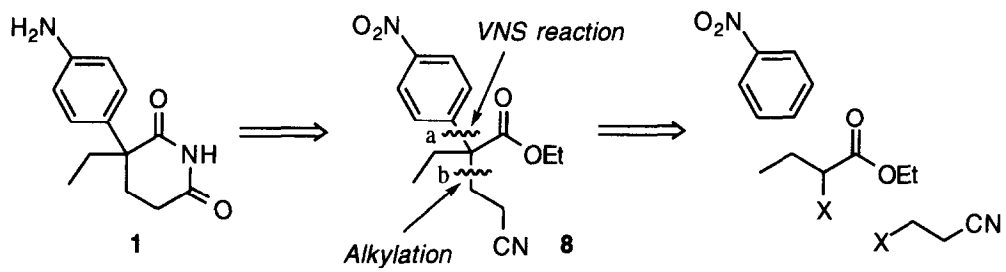


Scheme 1

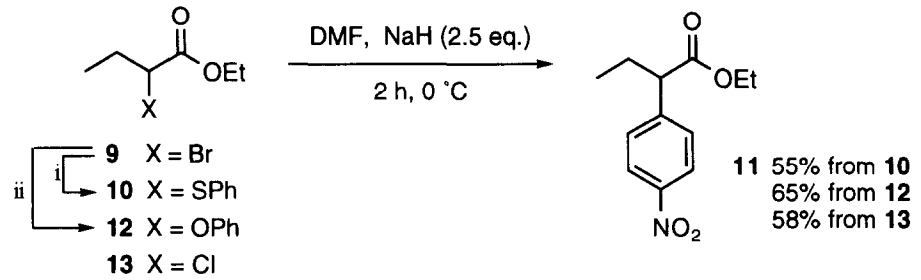
The one-pot VNS/alkylation reaction clearly offered an attractive route to aminoglutethimide and we envisaged that the cyanoester **8** would serve as a convenient precursor (scheme 2). The acid catalysed hydrolysis of the nitrile group of similar esters of 4-cyanobutyric acid[6] is known to give the corresponding glutarimide derivative, which in our case after reduction of the nitro group by catalytic hydrogenation will give **1**. In our strategy the carbon-carbon bond positioned *para* to the nitro group can be constructed by the vicarious nucleophilic substitution of the *para* hydrogen atom of nitrobenzene (disconnection a). The second carbon-carbon bond can be made by the alkylation of the VNS intermediate anion *via* disconnection b, using a propionitrile derivative that bears a leaving group at the 3-position. Although acrylonitrile would serve as the required electrophile, we have already found it to be a poor alkylating reagent in the VNS/alkylation reaction.[11] The initial nucleophile for the VNS reaction would therefore be a 2-substituted butyrate ester, some of which are commercially available and inexpensive. Overall, the synthesis is attractive for many reasons; it will be short and lead to the possible construction of a variety of analogues by the use of different nitroarenes, esters and propionitriles. Additionally, an asymmetric modification would be possible using the asymmetric VNS/alkylation reaction.[12]



Scheme 2

The α-thiophenylbutyrate **10** was readily prepared by the reaction of thiophenol with commercially available ethyl 2-bromobutyrate **9**. We first attempted the VNS reaction of **10** with nitrobenzene followed by a proton quench and isolated ethyl 2-(4'-nitrophenyl)butyrate **11** in 65% yield. The reaction was performed in anhydrous *N,N*-dimethylformamide (DMF) with 2.5 equivalents of sodium hydride; these reaction conditions and reagents give us consistently good yields in other VNS reactions.[11,12] The ^{1}H nmr spectrum of the crude reaction product indicated that only the *para* substituted product was formed. This is in agreement with the studies of Makosza and co-workers[10] who have found that tertiary carbanions give the *para* substitution for steric reasons. Although this reaction was satisfactory, the use of a thiophenyl leaving group is clearly disadvantageous as thiophenol is produced in the work-up. We therefore investigated the use of several other potential VNS nucleophiles for the synthesis of **11**. Simply replacing the thiophenyl group of **10** with a phenoxy group was successful. The reaction of ethyl 2-phenoxybutyrate **12**, derived from the reaction of ethyl

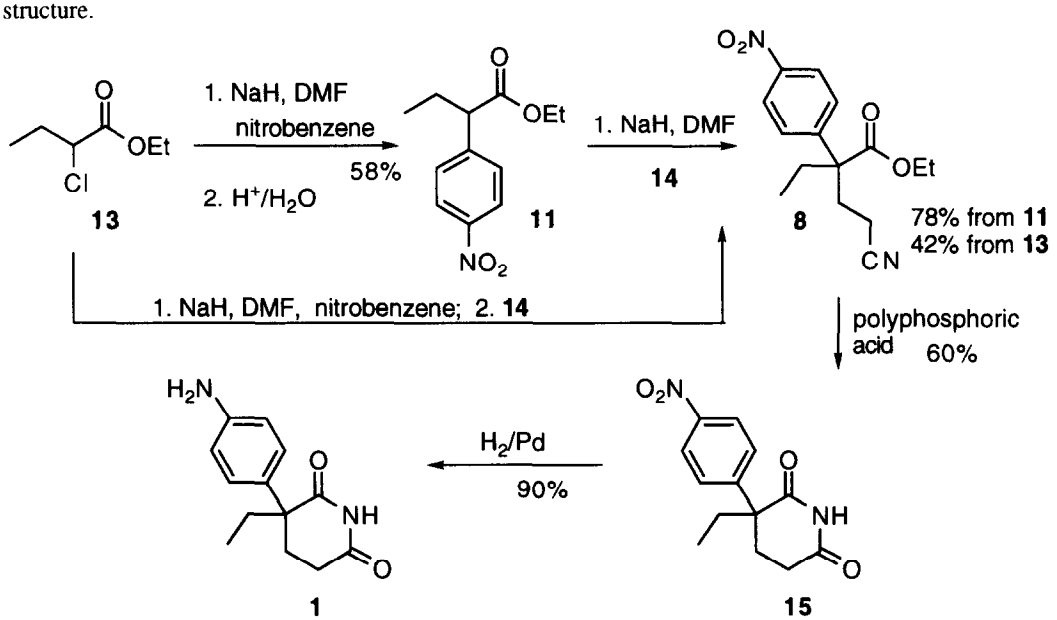
2-bromobutyrate **9** and phenol in butan-2-one (53%, after distillation),[13] with nitrobenzene again gave ethyl 2-(4'-nitrophenyl)butyrate **11**, now in 65% yield. This reaction is much preferred over the reaction of the thiophenyl derivative, as it lacks the obnoxious odour of thiophenol. We also prepared ethyl 2-chlorobutyrate **13** from commercially available 2-chlorobutyric acid (97%)[14] knowing that it would be less likely to undergo self condensation than ethyl 2-bromobutyrate **9**, a known competing process in the VNS reaction. Again, the VNS reaction proceeded satisfactorily to give the VNS adduct **11** in 58% yield.



Reagents and Conditions : i. PhSH, DBU, 18 h, r.t., 88%; ii. PhOH, K_2CO_3, 4.5 h, 80 °C, 53%.

Scheme 3

The alkylation of ethyl 2-(4'-nitrophenyl)butyrate **11**, *via* its sodium enolate generated from sodium hydride in DMF, with 3-bromopropionitrile **14** gave the desired cyanoester **8** in 78% yield. We chose these reaction conditions as a prelude to the one-pot VNS/alkylation reaction; the enolate is generated under the conditions used in the VNS reaction. Indeed, the anion generated from **11** gave the same bright purple-coloured solution which generated in the initial VNS reaction. Upon addition of the 3-bromopropionitrile **14** the colour instantly disappears. The cyanoester **8** was obtained as an oil that slowly crystallised over a period of several days, gave ^1H and ^{13}C nmr, infra red, mass spectral and microanalytical data consistent with the assigned structure.



Scheme 4

The one-pot VNS/alkylation reaction was performed by first reacting ethyl 2-chlorobutyrate **13** with nitrobenzene in DMF in the presence of sodium hydride (2.5 eq.) at 0 °C for 12 h. The bromopropionitrile **14** was then added to the purple solution and the mixture stirred for a further 5 h. The cyanoester **8** was isolated after chromatography in 42% yield, not much lower than the combined 45% yield from the sequential VNS (58%) and alkylation (78%) reaction of the chloroester **13**; a result similar to our previous findings.[10] The cyanoester was then reacted with polyphosphoric acid to give the cyclic imide **15** (60%), a material that has been used in many syntheses of aminoglutethimide. Finally, the nitro group of the imide was reduced by catalytic hydrogenation using palladium (10%) on carbon as the catalyst, to give aminoglutethimide **1** in 90% yield.

In summary, we have developed a novel way to construct aminoglutethimide in three steps and 23% overall yield from nitrobenzene using readily available inexpensive materials, in a way that will allow the rapid construction of many analogues. This clearly demonstrates the potential of the one-pot VNS/alkylation reaction.

Experimental

200 MHz ^{1}H nmr spectra were recorded using a Brucker AC 200 nmr spectrometer whilst all 300 MHz ^{1}H and 75 MHz ^{13}C nmr spectra were recorded using a Brucker AC 300. The ^{13}C NMR spectra were recorded using Distortionless Enhancement by Polarisation Transfer, (DEPT), and both ^{1}H and ^{13}C spectra were recorded using $CHCl_3$ as an internal standard. Chemical ionisation, (CI), and electron impact, (EI), mass spectra were recorded using a Kratos MS25 mass spectrometer; fast atom bombardment, (FAB), mass spectra were recorded using a Kratos MS50 mass spectrometer, using a *meta*-nitrobenzyl-alcohol matrix. Accurate mass determinations were performed using a Kratos Concept IS mass spectrometer. Elemental analysis were performed using a Carlo-Ebra 1106 elemental analyser. Infra red spectra were recorded using a Phillips Analytical PU9625 pulsed-FT spectrometer. All melting points were determined using a Büchi 510 melting point apparatus and were not corrected. Kugelrühr distillation, where appropriate, was performed using a Büchi GKR-51 apparatus. Column chromatography was conducted using silica gel, 60 230-400 mesh, (Merck & Co.), and silica TLC was conducted on pre-coated aluminium sheets, (60 F_{254}), with a 0.2 mm thickness, (Aldrich Chemical Co.). Ether refers to diethyl ether which was distilled prior to use. Hexane used for column chromatography was also distilled prior to use. Anhydrous ether, anhydrous dichloromethane, anhydrous methanol and anhydrous *N,N*-dimethylformamide, (DMF), were obtained from the Aldrich Chemical Co. and used as supplied. Anhydrous toluene was distilled from sodium metal and stored, under nitrogen, in the presence of type 4Å molecular sieves. Anhydrous dimethyl sulfoxide was distilled, under reduced pressure, and stored, under nitrogen, in the presence of type 4Å molecular sieves. THF was distilled from sodium metal in the presence of benzophenone immediately prior to use.

***Ethyl 2-thiophenoxybutyrate*—10.**—To a nitrogen flushed, well stirred solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)(8.37 g, 8.22 cm^3, 55 mmol) in anhydrous toluene (40 cm^3) at room temperature was added, successively, thiophenol (6.06 g, 5.62 cm^3, 55 mmol) and a solution of ethyl 2-bromobutyrate (9.73 g, 7.40 cm^3, 50 mmol) in anhydrous toluene (20 cm^3). The resulting suspension was stirred at room temperature overnight before the DBU·HBr salt was filtered off. The residue was washed with toluene (5 cm^3), the filtrate washed well with distilled water (5 × 20 cm^3), dilute hydrochloric acid (1 M, 3 × 20 cm^3), saturated aqueous sodium bicarbonate solution (3 × 50 cm^3), dried, (magnesium sulfate), and evaporated *in vacuo* to give the thiophenoxy ester **10** (10 g, 88%) as a pale yellow oil which was used without further purification. $\nu_{max.}$ (liq. film on NaCl plates), 2970 (s), 1740 (s), 1600 (s), 1580 (s), 1500 (s), 1200 (s), 1000 (s); δ_H (300 MHz; $CDCl_3$) 1.03 (3H, t, *J* 7.4 Hz, OCH_2CH_3), 1.18 (3H, t, *J* 7.1 Hz, CH_3), 1.73-1.99 (2H, m, CH_2), 3.58 (1H, dd, *J* 8.3 Hz, 6.4 Hz, EtCHSPh), 4.05-4.17 (2H, m, OCH_2CH_3), 7.19-7.34 (3H, m, Ph), 7.41-7.51 (2H, m, Ph); δ_C (75 MHz; $CDCl_3$) 11.9 (CH_3), 14.1 (CH_3), 25.1 (CH_2), 52.5 (CH), 60.1 (CH_2), 127.5 (CH), 127.8 (CH), 128.9 (CH), 129.1 (CH), 132.8 (CH), 133.6 (C), 172.3 (C=O); Found (CI): M^+, 224.0869, $C_{12}H_{16}SO_2$ requires M^+, 224.0871; *m/z* (FAB), 224 (M^+, 100%), 218 (20), 151 (90), 123 (20), 109 (30), 91 (10).

***Ethyl 2-(4'-nitrophenyl)butyrate*—11.**[15]—To a stirred slurry of sodium hydride (80% dispersion in oil, 0.75 g, 25 mmol), in anhydrous DMF (20 cm^3), at 0 °C and under an atmosphere of nitrogen was added, dropwise, a solution of phenoxybutyrate **12** (2.08 g, 10 mmol), and nitrobenzene (1.23 g, 1.02 cm^3, 10 mmol), in anhydrous DMF (20 cm^3). The resulting deep purple reaction mixture was stirred at 0 °C for a further 2.5 h before addition of ice/HCl (1 M, 20 cm^3). The resulting brown mixture was extracted with chloroform (3 × 30 cm^3). The combined extracts were washed with saturated aqueous sodium bicarbonate solution (6 × 50 cm^3), distilled water (3 × 50 cm^3), dried (magnesium sulfate), and the solvent removed under reduced pressure to give the nitrobenzyl ester **33** (1.54 g, 65%), as a brown oil after chromatography (silica, chloroform), R_f 0.7 (silica, chloroform); Found: C, 60.4; H, 6.5; N, 5.9; $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.4; N, 5.9%; $\nu_{max.}$ (liq. film on NaCl plates), 2960 (w), 1710 (s), 1600 (m), 1585 (w), 1510 (s), 1340 (s), 1230 (m), 1220 (m), 1005 (w), 850 (m), 740 (w), 700 (w); δ_H (300 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7.3 Hz, CH_3CH_2), 1.20 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.70-1.90 (1H, m, $CH_3CH_aH_b$), 2.05-2.20 (1H, m, $CH_3CH_aH_b$), 3.55 (1H, t, *J* 7.7 Hz, CH_cEt), 4.05-4.20 (2H, m, OCH_2CH_3), 7.50 (2H, d, *J* 8.7 Hz, H-2' and H-6'), 8.16 (2H, d, *J* 8.7 Hz, H-3' and H-5'); δ_C (75 MHz; $CDCl_3$) 12.1 (CH_3), 14.2 (CH_3), 26.9 (CH_2), 53.4 (CH), 61.2 (CH_2), 123.8 (CH, Ar), 129.1 (CH, Ar), 146.7 (C), 147.3 (C), 172.8 (C=O); Found (CI): $M+H^+$, 238.1073, $C_{12}H_{16}NO_4$ requires $M+H^+$, 238.1079; *m/z* (FAB), 475 ($2M+H^+$, 26%), 238 ($M+H^+$, 100), 221 (36).

***4-(Ethoxycarbonyl)-4-(4'-nitrophenyl)hexanonitrile*—8.**—To a stirred slurry of sodium hydride (80% dispersion in oil, 0.20 g, 6.0 mmol), in anhydrous DMF (5 cm^3), at 0 °C and under an atmosphere of nitrogen was added slowly nitrobenzyl ester **11** (1.0 g, 4.0 mmol). The resulting deep purple solution was stirred at 0 °C for a further 60 min before addition of 3-bromopropionitrile **14** (2.08 g, 16 mmol). The resulting brown solution was stirred for a further 0.5 h at 0 °C before addition of distilled water (10 cm^3). The mixture was extracted with chloroform (3 × 20 cm^3), the combined extracts were washed with water (6 × 50 cm^3), dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure to afford the nitrile **8** (0.90 g, 78%), as a brown oil after chromatography (silica, chloroform), R_f 0.2 (silica, chloroform), which on standing crystallised as a brown solid, m.p. 71-72 °C; Found: C, 61.9; H, 5.9; N, 9.8; $C_{13}H_{14}N_2O_4$ requires C, 62.1; H, 6.2; N, 9.5%; $\nu_{max.}$ (liq. film on NaCl plates), 2960 (m), 2250 (m), 1720 (s), 1600 (w), 1515 (s), 1410 (m), 1345 (s), 1270 (s), 1220 (s), 890 (w), 850 (m), 750 (w); δ_H (300 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7.2 Hz, CH_3CH_2), 1.20 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.96-2.50 (6H, m, CH_3CH_2 and CH_2CH_2CN), 4.10-4.25 (2H, m, OCH_2CH_3), 7.40 (2H, d, *J* 8.4 Hz, H-2' and H-6'), 8.20 (2H, *J* 8.4 Hz, H-3'and H-5'); δ_C (75 MHz; $CDCl_3$) 8.7 (CH_3), 12.7 (CH_2), 14.0 (CH_3), 21.9 (CH_2), 24.4 (CH_2), 54.3 (C), 61.7 (CH_2), 119.1 (CN), 123.8 (CH, Ar), 127.7 (CH, Ar), 147.0 (C), 148.1 (C), 173.2 (C=O); Found (CI): $(M+H)^+$, 291.1350, $C_{15}H_{19}N_2O_4$ requires $(M+H)^+$, 291.1345; *m/z* (FAB), 291 [$(M+H)^+$, 70%], 217 (60), 136 (84), 95 (100).

***4-(Ethoxycarbonyl)-4-(4'-nitrophenyl)hexanonitrile* 8 *via* the 'one-pot' reaction.**—To a stirred slurry of sodium hydride (80% dispersion in oil, 0.30 g, 10 mmol), in anhydrous DMF (15 cm^3), at 0 °C and under an atmosphere of nitrogen was added, dropwise, a solution of the chloroester **13** (0.60 g, 4 mmol), and nitrobenzene (0.49 g, 0.41 cm^3, 4.0 mmol), in anhydrous DMF (10 cm^3). The resulting deep purple reaction mixture was stirred at 0 °C for a further 12 h before addition of 3-bromopropionitrile **14** (0.52 g, 0.33 cm^3, 4.0 mmol). The resulting brown solution was stirred at 0°C for 5 h before addition of distilled water (10 cm^3). The mixture was extracted with chloroform (3 × 20 cm^3). The combined extracts were washed with water (5 × 50 cm^3), dried (magnesium sulfate), filtered, and the solvent removed under reduced pressure to give the cyanoester **8** (0.49 g, 42%), as a brown oil after chromatography (silica, chloroform), R_f 0.2 (silica, chloroform), which was identical to that prepared from **11**.

***3-Ethyl-3-(4'-nitrophenyl)piperidine-2,6-dione*—15.**[16]—To a nitrogen flushed flask containing polyphosphoric acid (4.0 g), was added the cyanoester **8** (0.5 g, 1.7 mmol), whilst stirring, and the mixture was then heated at 180 °C for 0.5 h. The resulting brown oil was allowed to cool to room temperature before the addition of ice (50 g), and the mixture was then extracted with chloroform (3 × 20 cm^3). The combined extracts were washed with saturated aqueous sodium bicarbonate solution (5 × 50 cm^3), and water (3 × 50 cm^3), dried (magnesium sulfate), filtered, and the solvent removed under reduced pressure to give the piperidinedione **31** (0.27 g, 60%), as a brown solid after recrystallisation from methanol, m.p. 139-140°C (lit.[16] 141-142°C), R_f 0.4, (silica, chloroform); Found: C, 59.4; H, 5.4; N, 10.9; $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.4; N, 10.7%; $\nu_{max.}$ (Nujol mull), 2960 (s), 2900 (s), 2840 (s), 1660 (w), 1455 (m), 1365 (m), 1355 (w), 1330 (m), 1195 (w);

δ_H (300 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7.4 Hz, CH_3CH_2), 1.90-2.00 (1H, dq, $J_{Ha\text{-}Hb}$ 14.8 Hz, $J_{Ha\text{-}Me}$ 7.4 Hz, $CH_aH_bCH_3$), 2.05-2.15 (1H, dq, $J_{Hb\text{-}Ha}$ 14.8 Hz, $J_{Hb\text{-}Me}$ 7.4 Hz, $CH_aH_bCH_3$), 2.25-2.48 (3H, m, $CH_2CH_cH_dCO$), 2.60-2.75 (1H, m, $CH_2CH_cH_dCO$), 7.52 (2H, d, *J* 7.0 Hz, H-3' and H-5'), 8.23 (2H, d, *J* 7.0 Hz, H-2' and H-6'), 8.37 (1H, br. S, NH); δ_C (75 MHz; $CDCl_3$) 8.9 (CH_3), 26.9 (CH_2), 29.0 (CH_2), 32.8 (CH_2), 51.3 (C), 124.1 (CH, Ar), 127.4 (CH, Ar), 146.3 (C), 147.3 (C), 171.6 (CO), 174.1 (CO); Found (CI): $M+H^+$, 263.1030, $C_{13}H_{14}N_2O_4$ requires $M+H^+$, 263.1032; *m/z* (FAB), 263 ($M+H^+$, 100%).

***3-Ethyl-3-(4'-aminophenyl)piperidine-2,6-dione*—1**.[16]—To a stirred slurry of 10% palladium on carbon (20 mg), in anhydrous methanol (10 cm^3), under an atmosphere of hydrogen was added, dropwise, a solution of the piperidinedione **31** (160 mg, 0.60 mmol), also in anhydrous methanol (5 cm^3). The mixture was stirred at room temperature for 5 h, until TLC showed the absence of starting material. The reaction mixture was filtered through Celite® and the solvent removed under reduced pressure to yield aminoglutethimide **1** (140 mg, 90%), as a brown solid after recrystallisation from hot methanol, m.p. 151-152 °C (lit.[16] 149-150 °C), R_f 0.8 (silica, ethyl acetate); $\nu_{max.}$ (Nujol mull on NaCl plates), 3400 (m), 3320 (m), 3190 (m), 2930 (s), 2900 (s), 2830 (s), 2700 (w), 1690 (s), 1665 (m), 1500 (w), 1450 (s), 1365 (s), 1355 (s), 1335 (s), 1255 (m), 1195 (s), 1175 (s), 755 (m), 740 (m), 715 (m); δ_H (300 MHz; d_6-DMSO) 0.85 (3H, t, *J* 7.2 Hz, CH_3CH_2), 1.60-1.85 (2H, m, CH_2CH_3), 1.90-2.30 (3H, m, $CH_2CH_cH_dCO$), 2.30-2.50 (1H, m, $CH_2CH_cH_dCO$), 3.40 (2H, br. s, NH_2), 6.60 (2H, d, *J* 8.2 Hz, H-3' and H-5'), 6.95 (2H, d, *J* 8.2 Hz, H-2' and H-6'), 10.80 (1H, br. s, NH); δ_C (75 MHz; d_6-DMSO) 9.1 (CH_3), 26.1 (CH_2), 29.3 (CH_2), 32.5 (CH_2), 49.4 (C), 114.4 (CH, Ar), 126.5 (C), 126.8 (CH, Ar), 147.3 (C), 173.1 (C=O), 176.4 (C=O); Found (CI): M^+, 232.1214, $C_{13}H_{16}O_2N_2$ requires M^+, 232.1212; *m/z* (FAB), 233 ($M+H^+$, 100%), 232 (M^+, 90).

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