Acta Chemica Scandinavica, 1999: 53: 48 56
Printed in UK all rights reserved

ACTA
CHEMICA SCANDINAVICA
ISSN 0904 213X

Addition of Secondary Amines to Maleamic Esters and Maleimides

Jan Bergman* and Thomas Brimert

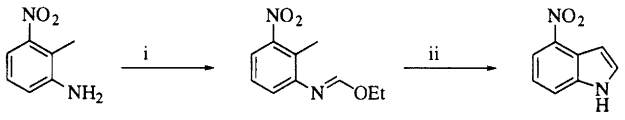
Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden and Department of Organic Chemistry, CNT, NOVUM Research Park, S-141 57 Huddinge, Sweden

Bergman, J. and Brimert, T., 1999. Addition of Secondary Amines to Maleamic Esters and Maleimides. Acta Chem. Scand. 53: 48–56. © Acta Chemica Scandinavica 1999.

Contrary to some literature claims, secondary amines such as piperidine or their acetates do not promote the cyclization of maleanilic esters with activated *ortho*-alkyl groups to form 2-quinolones, but instead they add to the maleic double bond, to produce 3-aminosuccinimides or 3-aminosuccinamic esters, depending on the conditions used. This and similar reactions were studied and also an alternative synthesis of 7-nitro-3-(2-oxo-2-piperidin-1-ylethyl)-3,4-dihydroquinolin-2(1*H*)-one was achieved utilizing the Schmidt reaction as the key step.

We have recently developed a method[1] to construct 4- and 6-nitroindoles via the anions of imidate derivatives of 3- or 5-nitro-2-alkylanilines as indicated in Scheme 1. The presence of a nitro group in an activating position was found to be necessary for the reaction to take place at room temperature. Base-induced cyclizations of non-activated imidates such as **1** and **2** to **3**, and **4** (Fig. 1), respectively, do[2] occur around 180–200 °C, i.e. only 100 °C lower than a normal Madelung cyclization,[3,4] a reaction which presumably involves the formation of a dianion[5] from the substrate (an *N*-acyl-2-alkylaniline) and the base (alkoxide or amide).

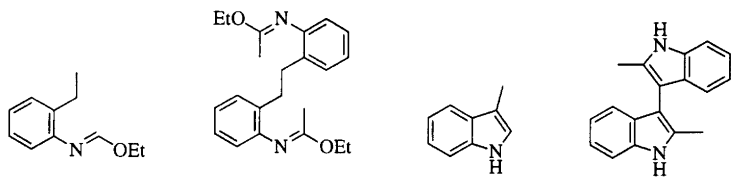
In connection with these studies we became interested in a reported, seemingly related, cyclization[6] of the maleanilic ester **5b** to the quinolone **7** in the presence of piperidinium acetate at 100 °C. Furthermore if **5b** could be converted into an imidate, the mode of cyclization might be changed providing a route towards 2-vinylindoles, such as **8**. Repetition of the reported sequence gave the precursor **5b** in a good yield; however, the purported cyclization to a quinolone did not occur, as evidenced by the presence of an intact methyl group in the product. However, incorporation of a molecule of piperidine had clearly occurred.



Scheme 1. Synthesis of indoles from imidates. i, $HC(OEt)_3$, reflux; ii, KOEt, $(CO_2Et)_2$, DMF, RT.

Results

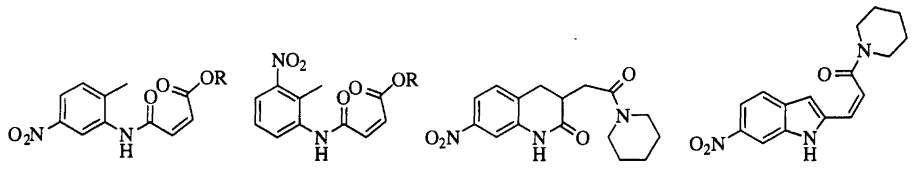
Treatment of **5b** with piperidinium acetate at 90–100 °C, readily gave a product which featured a signal at 2.2 ppm (this peak is a doublet for reasons discussed below) in the ^{1}HNMR spectrum, that integrated to 3 H and thus originates from a methyl group as was also confirmed by a DEPT experiment. Furthermore, signals from the piperidine ring appeared at 2.9, 1.6 and 1.5 ppm. These data, together with the fact that the IR and ^{1}HNMR spectra lacked NH signals, strongly suggest that the



1 **2** **3** **4**

Fig. 1. Imidates **1** and **2** cyclise to the corresponding indoles **3** and **4** when treated with base at 180–200 °C.

* To whom correspondence should be addressed.



5a: R=H
5b: R=Me

6a: R=H
6b: R=Me

7

8

Fig. 2. Quinolone **7** was claimed in the literature to be the product of the reaction between ester **5b** and piperidinium acetate.

product is *N*-(2-methyl-5-nitrophenyl)-3-(piperidin-1-yl)pyrrolidine-2,5-dione (**9a**).

Less basic amines react in the same manner, e.g. indoline and **5b** gave **11**. The same is also true for more basic amines such as pyrrolidine, which under the same conditions reacts with **5b** to form the succinimide **9c**.

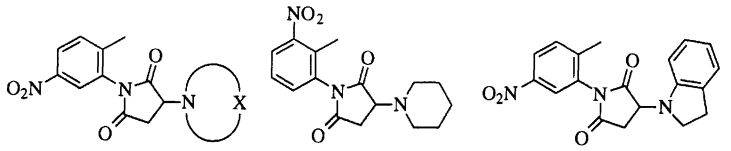
Changing the position of the nitro group from the 5- to the 3- position did not affect the general outcome of the reaction. Thus the methyl ester **6b** gave *N*-(2-methyl-3-nitrophenyl)-3-(piperidin-1-yl)pyrrolidine-2,5-dione (**10**) when treated with piperidinium acetate at 90–100 °C.

When performed at room temperature, the reaction yielded the amide **13a** and the *E*-methyl ester **12** in a 1:2 ratio, but then a solvent (we chose DMF) was needed since the reactants are solids. Once again, other amines react in the same fashion. Thus morpholine and pyrrolidine gave **13b** and **13c**, respectively.

The work-up and chromatographic purification of the crude reaction mixtures from these reactions, containing **12**, **13** and occasionally some of the imide **9**, proved to be rather tedious. It was then found that if the free amine was employed with methanol instead of DMF as the solvent, the work-up was simplified considerably and in most cases high yields of **13** spontaneously crystallised from the reaction mixture and could easily be obtained in a pure state by simple filtration. No traces of the *E*-ester **12** were found, and only in the case of pyrrolidine as the base were **17a** and **9c** formed as well. If ethanol was used as the solvent, transesterification occurred and the ethyl esters **13d–f** were also formed in good yields.

An experiment with piperidinium acetate was also performed at 0 °C resulting, after 30 min, in a 20% conversion of the *Z*-ester **5b** into the *E*-ester **12** with the other 80% unaffected. The esters were distinguished by their NMR coupling constants, 13.3 Hz for the *Z*-isomer and 15.5 Hz for the *E*-isomer.

The structures of **9a–c** were proved by independent syntheses from the maleimide **14** (see Scheme 2). *N*-Phenyl maleimide likewise added piperidine yielding

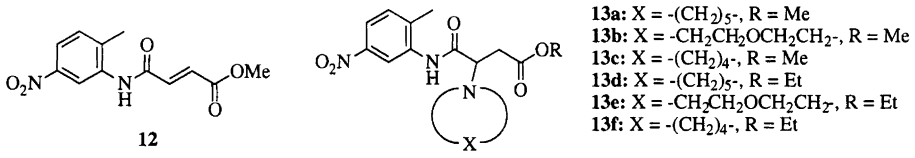


9a: X = -$(CH_2)_5$-
9b: X = -$CH_2CH_2OCH_2CH_2$-
9c: X = -$(CH_2)_4$-

10

11

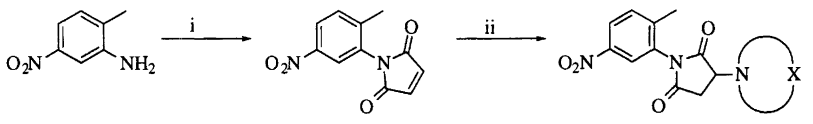
Fig. 3. Succinimides formed when maleamic esters were heated with secondary ammonium acetates.



12

13a: X = -$(CH_2)_5$-, R = Me
13b: X = -$CH_2CH_2OCH_2CH_2$-, R = Me
13c: X = -$(CH_2)_4$-, R = Me
13d: X = -$(CH_2)_5$-, R = Et
13e: X = -$CH_2CH_2OCH_2CH_2$-, R = Et
13f: X = -$(CH_2)_4$-, R = Et

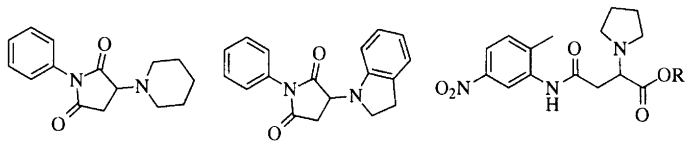
Fig. 4. Products from the reaction of maleamic ester **5b** with secondary amines at room temperature.



14

9a: X = -$(CH_2)_5$-
9b: X = -$CH_2CH_2OCH_2CH_2$-
9c: X = -$(CH_2)_4$-

Scheme 2. Independent synthesis of **9a–c**: i, Maleic anhydride, heat; ii, piperidinium, morpholinium or pyrrolidinium acetate and DMF.



15 **16** **17a**: R = Me **17b**: R = Et

Fig. 5. Products from the reactions between maleimides and secondary amines.

the *N*-phenylsuccinimide **15**. Similar additions are known in the literature, e.g. Hill *et al.*[7] have added indoline to *N*-phenylmaleimide using acetic acid as the solvent and isolated 3-(indolin-1-yl)-*N*-phenylpyrrolidine-2,5-dione (**16**). Repetition of this reaction gave a product with similar ^{1}H NMR data to Hill's adduct, but with a dissimilar melting point and IR spectrum, than those reported. As evidenced by mass spectrometry, which featured a retro addition to indoline and *N*-phenylmaleimide, however, the structure is without doubt 3-(indolin-1-yl)-*N*-phenylpyrrolidine-2,5-dione. Furthermore the ^{13}C NMR spectrum exhibited three CH_2 signals (δ 48.1, 31.1 and 27.6) and one CH signal (δ 54.9) as well as two carbonyl signals (δ 174.9 and 173.9) that coincided (vibrating at 1711 cm^{-1}) in the infrared spectrum.

If, in the reaction between maleimide **14** and an appropriate amine (see Scheme 2) the solvent is changed to methanol or ethanol, **13a–f** are formed as the main products. The reactions of pyrrolidine were the only cases where formation of the other regioisomers (**17a** and **17b**) could be observed.

The quinolone **7** was eventually prepared by an alternative route as outlined in Scheme 3. Thus (6-nitro-1-oxoindan-2-yl)acetic acid[8] was treated[9] with oxalyl chloride to give the acid chloride, which was directly converted into the piperidide **18** in a good yield. This piperidide was then subjected to a Schmidt reaction[10] which afforded the desired product **7**.

No traces of the other possible product 7-nitro-3-(1-oxo-2-piperidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one could be detected, which is consistent with the observation[10] that alkyl aryl ketones prefer to undergo an aryl migration in the Schmidt reaction. This behavior is even more pronounced with substrates bearing a nitro group *meta* or *para* to the ketone carbonyl, as Tomita *et al.* have shown.[11]

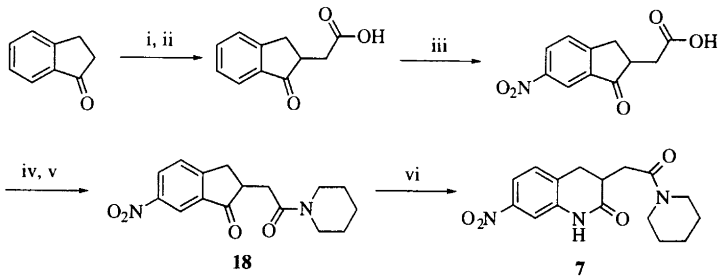
The quinolone **7** was readily characterized, using IR and NMR spectroscopy, and the data were, as expected, quite different from those of the compound previously claimed to have the structure **7**. Furthermore it was demonstrated that **7** was not even formed in trace amounts when **5b** was treated with piperidinium acetate, at 100 °C.

Discussion

Contrary to assertions in a recent paper,[12] addition of amines to *N*-substituted maleimides are known and used[7,13–26] in organic syntheses of various 3-aminosuccinimides. Thus Sharpless and Flavin[18] for instance readily obtained an adduct from maleimide and piperidine. However, to our knowledge there is no report involving addition of amines to maleanilic esters with concurrent cyclisation to 3-aminosuccinimides.

From the results we conclude that the reaction proceeds through an attack of the amine on the maleanilic ester, either on the *E*-isomer or on the *Z*-isomer. Then, if the temperature is elevated, the resulting succinamic ester can cyclize to form an imide. If, on the other hand, a lower temperature is used, the amine will not add, although at 0 °C it still promotes the isomerisation of the double bond. It should be noted that an attempted isomerisation with thiourea (24 h, RT in DMF) afforded only starting materials and no traces of the *E*-isomer.

Interestingly the ^{1}H NMR spectra of the 3-amino-*N*-(2-methylphenyl)pyrrolidine-2,5-diones like **9a–c**, **10** and **11** are more complex than expected. The methyl group of these compounds appears as a doublet and in the ^{13}C NMR spectrum most peaks (except for some in the aromatic area, perhaps because of coinciding signals) are doublets. This phenomenon does not appear in the spectra of the *N*-phenyl-3-(piperidin-1-yl)pyrrolidine-2,5-dione (**15**) owing to the lack of an *ortho*-methyl



18 **7**

Scheme 3. Synthesis of **7** utilizing the Schmidt reaction: i, HCOCOOH, dioxane, cat. H_2SO_4; ii, Zn, HOAc, H_2O; iii, HNO_3; iv, $(COCl)_2$; v, piperidine; vi, NaN_3, H_2SO_4, benzene.

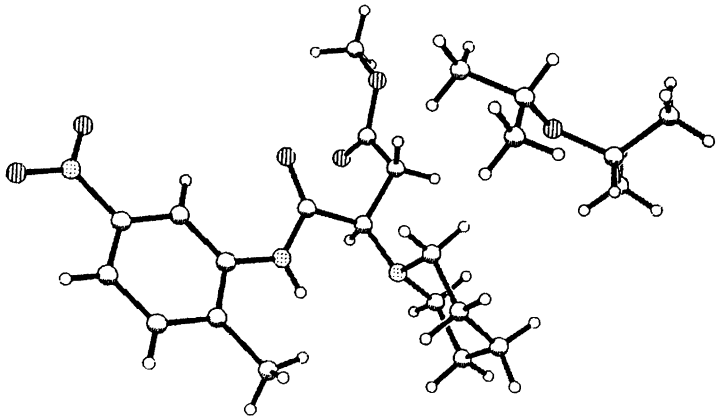


Fig. 6. X-Ray structure of **13a** ($C_{17}H_{23}N_3O_5 \cdot \frac{1}{2}C_6H_{14}O$).

group, indicating hindered rotation[27] of the imide nitrogen to phenyl ring bond in **9a–c**, **10**, and **11**.

The rotational barrier of **9a** ($\Delta G_c^{\ddagger}$) was estimated as 82 kJ mol^{-1} from its coalescence at approximately 120 °C, as observed in the ^{1}H NMR spectrum.

Kishikawa[17] *et al.* added benzylamine to *N*-(2-alkylphenyl)maleimides and measured the rotational barrier of the resulting 3-benzylamino-*N*-(2-alkylphenyl)pyrrolidine-2,5-diones. With methyl as the *ortho*-alkyl group, they observed a rotational barrier of 86.7 kJ mol^{-1}. If the methyl group is exchanged for a *tert*-butyl group the barrier increases to 118.9 kJ mol^{-1} and accordingly they could isolate the latter compound as a single rotamer. Ohno and coworkers prepared some 3-(2-alkylphenyl)-5-deazaflavin derivatives and observed very similar rotational barriers.[28,29] Thus with an *ortho*-methyl, the barrier is 108 kJ mol^{-1}.

N-(2-*tert*-butylphenyl)-3-methylmaleimide was prepared in an optically pure form and used by Taguchi and coworkers to carry out diastereospecific Diels–Alder reactions.[30]

Compare this also with, e.g., the rotational hindrance of 9-(*ortho*-methylaryl)fluorenes.[31] In this context one could also mention that Joseph-Nathan and co-workers prepared[26] the *N*-(4-methoxyphenyl)-3-(aziridin-1-yl) pyrrolidine-2,5-dione and found that the hydrogen atoms in the aziridine ring were not equivalent, which they ascribed to hindered rotation around the bond between the aziridine nitrogen and the succinimide ring.[32]

The structures **13a–f** were assigned on the following grounds. In all the studied additions of amines to the ester/amide **5b** only one of the two possible uncyclised products could be isolated. They all gave very similar ^{1}H NMR spectra, wherein especially three signals, ≈4.0 (1 H, dd, $J \approx 5$ Hz, $J' \approx 8$ Hz), ≈2.9 (1 H, dd, $J \approx 8$ Hz, $J' \approx 16$ Hz) and ≈2.7 (1 H, dd, $J \approx 5$ Hz, $J' \approx 16$ Hz) ppm, that belong to the –CHN– and the diastereotopic –CH_2– protons, are of interest to our discussion here. Furthermore all these products showed similar melting points and also had very similar retention times on TLC.

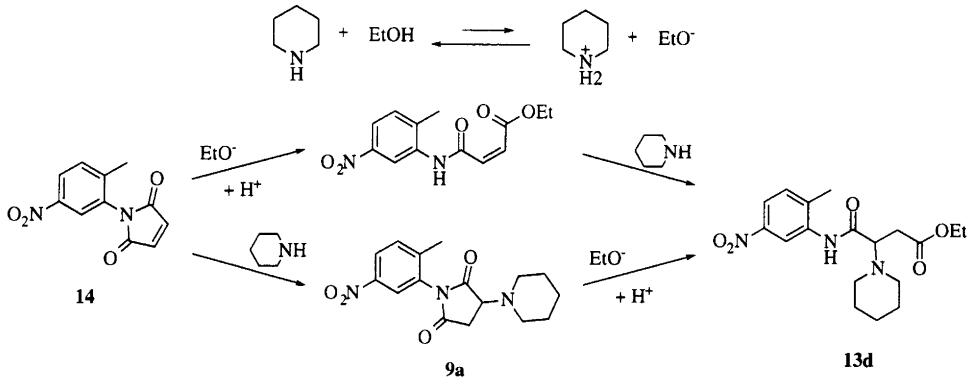
The only exception to this was in the case pyrrolidine as the amine. Reaction between pyrrolidine and **5b** gave two products that in their ^{1}H and ^{13}C NMR spectra featured the same set of signals, albeit with somewhat different chemical shifts, but with very dissimilar physical properties. Thus they could very easily be separated by silica gel column chromatography. One of the products from this reaction was again very similar to the other adducts in the series of additions, whereas the other product was more polar and lower-melting, and in the ^{1}H NMR spectra the –CHN– hydrogen appeared as a triplet and the diastereotopic –CH_2– protons as a doublet.

The two compounds were obviously the two regioisomers **13c** and **17a** (or **13f** and **17b** if ethanol was used as the solvent). The problem was then to assign which compound corresponded to which structure. Compound **13a** crystallised nicely from diisopropyl ether and the structure was confirmed by X-ray crystallography.[33] It crystallised with 0.5 mol of diisopropyl ether which slowly left the crystal, thereby somewhat effecting the precision of the determination of the structure parameters. The structures of compounds **13b–f** were then assigned from their similarity to **13a** in chemical and physical behavior.

As already mentioned, the compounds **13a–f** are also formed in the reactions of the maleimide **14** with the corresponding amine if ethanol or methanol are used as solvents. Since neither the amine nor the alcohol by themselves are capable of performing this ring-opening, the conclusion that can be drawn is that the amine abstracts a proton from the alcohol and the alkoxide formed opens the imide ring (of either the maleimide **14** or the succinimide **9** or both) to form an ester (see Scheme 4).

This is consistent with the observation that a less basic amine, like indoline [p$K_a \approx 5$]* (compared with piperidine [p$K_a = 11.1$],* morpholine [p$K_a = 8.3$]* and pyrrolidine [p$K_a = 11.3$]*), does not produce the ring-opened product, but instead the succinimide **11**, probably because the

* pK_a of the protonated amine.



Scheme 4. Mechanism of the reaction of **14** with piperidine in ethanol.

equilibrium for formation of alkoxide anions is unfavorable.

The same explanation accounts for the fact that methanol [$pK_a = 15.2$] and ethanol [$pK_a = 15.9$] with piperidine, morpholine or pyrrolidine give the ring-opened products **13a–f**, whereas *tert*-butyl alcohol [$pK_a \approx 17$] does not, but the succinimides **9a–c** are formed.

If the reaction proceeds via the maleanilic ester, then the observed regioselectivity could be explained by the more electrophilic character of the carbon β to the ester than the carbon atom β to the amide. If, on the other hand, the reaction proceeds via the succinimide, then the product is formed by an attack at the least sterically hindered carbonyl. This kind of steric interaction has been shown to be able to induce regiospecific ring-opening of *N*-protected aspartic and glutamic acid anhydrides in their reactions with aniline.[34]

Experimental

Melting points were measured on a Reichert VME Kofler bench. IR spectra were recorded with a Perkin Elmer 1600 FTIR, NMR spectra with a Bruker AM400 or DPX300 spectrometer and mass spectra with a Finnigan MATSSQ710 instrument with direct inlet at 70 eV.

N-*(2-Methyl-5-nitrophenyl)maleamic acid* (**5a**).[35] A solution of maleic anhydride (2.0 g, 20 mmol) in ether (20 ml) was added to a solution of 2-methyl-5-nitroaniline (3.0 g, 20 mmol) in ether (10 ml). This mixture was left overnight and then filtered and washed with cold ether, giving 3.04 g (62%) of the pure product. M.p. 147–148 °C. IR (KBr): 3256, 1718, 1628, 1552, 1350 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.90 (1 H, s), 10.03 (1 H, s), 8.49 (1 H, s), 7.95 (1 H, d), 7.93 (1 H, d), 7.50 (1 H, s), 6.62 (1 H, d, $J = 12.0$ Hz), 6.33 (1 H, d, $J = 12.0$ Hz), 2.36 (3 H, s). ^{13}C NMR (DMSO-d_6): δ 166.7 (s), 164.1 (s), 145.6 (s), 139.25 (s), 136.7 (s), 132.5 (d), 131.4 (d), 129.6 (d), 119.6 (d), 118.5 (d), 18.1 (q). A second crop (1.55 g), was isolated from the filtrate; total yield >90%.

N-*(2-Methyl-3-nitrophenyl)maleamic acid* (**6a**). A solution of maleic anhydride (2.0 g, 20 mmol) in ether (20 ml) was added to a solution of 2-methyl-3-nitroaniline (3.0 g, 20 mmol) in ether (70 ml). This mixture was left to stand for 60 h and then filtered and washed with cold ether, giving 4.53 g (91%) of long white needles. M.p. 154 °C. IR (KBr): 3253, 1714, 1632, 1578, 1531, 1360, 850, 734 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.9 (1 H, s) 10.13 (1 H, s), 7.73 (1 H, d), 7.68 (1 H, d), 7.43 (1 H, t), 6.60 (1 H, d, $J = 12.1$ Hz), 6.28 (1 H, d, $J = 12.1$ Hz), 2.28 (3 H, s). ^{13}C NMR (DMSO-d_6): δ 166.5 (s), 164.0 (s), 150.8 (s), 137.4 (s), 132.9 (d), 129.9 (d), 129.1 (d), 126.7 (s), 126.5 (d), 121.0 (d), 13.6 (q).

N-*(2-Methyl-5-nitrophenyl)maleamic acid methyl ester* (**5b**).[6] *N*-(2-Methyl-5-nitrophenyl)maleamic acid (**5a**, 2.50 g, 10 mmol), methanol (25 ml) and sulfuric acid ($d = 1.84$, 0.04 ml, 0.8 mmol) were heated to boiling and then left at RT for 48 h. Long white needles were then collected, yielding 1.96 g (74%). M.p. 119–120 °C. IR (KBr): 1716, 1519, 1553, 1345 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.65 (1 H, s), 8.88 (1 H, s), 7.85 (1 H, d), 7.28 (1 H, d), 6.44 (1 H, d, $J = 13.28$ Hz), 6.24 (1 H, d, $J = 13.27$ Hz), 3.81 (3 H, s), 2.40 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 166.9 (s), 162.0 (s), 146.4 (s), 139.2 (d), 136.6 (s), 136.5 (s), 130.7 (d), 125.7 (d), 119.5 (d), 117.4 (d), 52.8 (q), 18.5 (q).

N-*(2-Methyl-3-nitrophenyl)maleamic acid methyl ester* (**6b**). *N*-(2-Methyl-3-nitrophenyl)maleamic acid (**6a**, 4.50 g, 18 mmol), methanol (150 ml) and sulfuric acid ($d = 1.84$, 3 drops from a Pasteur pipette) were heated to boiling and then left to stand for 60 h. The solution was then concentrated and the product crystallized from the remaining solution as long pale yellow needles, which were collected by filtration and washed with cool methanol. This gave 3.07 g (65% yield) of pure **6b**. M.p. 120–121 °C. IR (KBr): 2940, 1725, 1649, 1530, 1366, 1282 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.03 (1 H, s), 8.43 (1 H, d), 7.95 (1 H, d), 7.66 (1 H, t), 6.82 (1 H, d, $J = 13.31$ Hz), 6.62 (1 H, d, $J = 13.33$ Hz), 4.18 (3 H, s), 2.78 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 167.4 (s), 162.6 (s), 151.6 (s), 140.1 (d), 137.8 (s), 128.3 (d), 127.0 (d), 126.0 (d), 126.0 (s), 121.3 (d), 53.3 (q), 14.2 (q).

'Ring closure' experiment.[6] A mixture of methyl *N*-(2-methyl-5-nitrophenyl)maleamic acid methyl ester (**5b**, 0.26 g, 1 mmol) and piperidinium acetate (1 mmol), prepared by mixing piperidine (0.090 g) and acetic acid (0.060 g), was heated to 90–100 °C for 30 min. Crushed ice was added and then extraction with toluene (2 × 100 ml; benzene was used in the literature procedure), drying with $MgSO_4$ and evaporation of the toluene, gave 0.30 g of an amorphous solid, which was a mixture of approximately 80% **9a**, 18% **13a** and 2% **14** as revealed by ^1H NMR spectroscopy. Recrystallization from acetone–water gave pure **9a**.

RT and 0 °C variation. Piperidinium acetate made from piperidine (0.090 g, 1 mmol) and acetic acid (0.060 g, 1 mmol) was dissolved in DMF (2 ml) and cooled to RT or 0 °C. To this solution was added *N*-(2-methyl-5-nitrophenyl)maleamic acid methyl ester (**5b**, 0.26 g, 1 mmol) and after 30 min the reaction mixture was poured onto ice, filtered and washed with water. In the RT case, ^1H NMR spectroscopy showed that the products formed were **13a** and **12** in a 1:2 ratio with some **9a** present as well. Recrystallization from acetone–water gave pure **13a**. The 0 °C experiment gave only the *trans* ester (**12**, 20%) and unreacted starting material **5b**.

The crude product mixture from the RT reaction (containing **12**, **13a** and **9a**), was separated by successive column chromatography on silica gel. Elution with 1% MeCN in EtOAc gave two fractions (R_f = 0.61 and R_f = 0.31). The slower running fraction was identified as **9a** while the first fraction was rechromatographed, this time with Et_2O as the eluent, which gave the trans ester **12** (R_f = 0.53) and the amide **13a** (R_f = 0.40).

N-*(2-Methyl-5-nitrophenyl)pyrrole-2,5-dione* (**14**). 2-Methyl-5-nitroaniline (5.50 g, 36 mmol) and maleic anhydride (3.50 g, 36 mmol) were melted and heated to 150 °C for 3 h. The reaction mixture was allowed to cool and then suspended in EtOAc (30 ml) followed by filtration. The filtrate was diluted with more EtOAc (150 ml), washed with water and brine and then dried with $MgSO_4$. Evaporation of the solvent gave, with the first crop included, 6.50 g (78%) of **14**. M.p. 166–167 °C. IR (KBr): 3112, 3082, 1714, 1524, 1349, 1158, 825 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.20 (1 H, d), 8.03 (1 H, s), 7.50 (1 H, d), 6.93 (2 H, s), 2.26 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 166.7 (s), 146.6 (s), 144.7 (s), 134.6 (d), 131.7 (d), 130.7 (s), 124.3 (d), 124.02 (d), 16.4 (q).

N-*(2-Methyl-5-nitrophenyl)-3-(piperidin-1-yl)pyrrolidine-2,5-dione* (**9a**). Piperidine (0.10 ml, 10 mmol), *N*-(2-methyl-5-nitrophenyl)pyrrole-2,5-dione (**14**, 0.23 g, 1 mmol) and *tert*-butyl alcohol (5 ml) were allowed to react for 24 h at RT. The mixture was filtered and the white crystals washed with diisopropyl ether to give 0.25 g (79%) of **9a**. M.p. 156 °C. IR (KBr): 2944, 1703, 1523, 1361, 1346, 1184, 1170 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.17 (1 H, d), 7.94 (1 H, d), 7.49 (0.5 H, s), 7.46 (0.5 H, s), 4.03 (1 H, m), 3.08 (1 H, m), 2.88 (4 + 1 H, m), 2.57 (2 H, m), 2.24 (1.5 H, s), 2.20 (1.5 H, s), 1.62 (4 H, m), 1.48 (2 H, t). ^{13}C NMR ($CDCl_3$): δ 174,9 (s), 174.7 (s), 173.7 (s), 173.6 (s), 146.6 (s), 143.8 (s), 131.6 (d), 131.6 (d), 124.1 (d), 123.6 (d), 123.7 (d), 63.6 (d), 63.3 (d), 50.3 (t), 50.2 (t), 32.0 (t), 31.9 (t), 25.9 (t), 23.8 (t), 18.5 (q), 18.7 (q).

N-*(2-Methyl-5-nitrophenyl)-3-(morpholin-1-yl)pyrrolidine-2,5-dione* (**9b**). Morpholine (0.9 ml, 10 mmol) was allowed to react with imide **14** (0.23 g, 1 mmol) with ethanol (5 ml) as the solvent for 24 h. The solvent was then evaporated off and the viscous oil thus obtained was chromatographed on silica gel yielding 77 mg (21%) of **13e** and 88 mg (28%) **9b**. M.p. 136 °C. IR (KBr): 2856, 1716, 1525, 1349, 1175, 1114, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.18 (1 H, d), 7.95 (1 H, d), 7.50 (0.5 H, s), 7.47 (0.5 H, s), 3.99 (1 H, dd, J = 5.26 Hz, J' = 9.07 Hz), 3.73 (4 H, m) 3.10 (1 H, dd, J = 9.11 Hz, J' = 18.68 Hz), 2.94–2.84 (2 + 1 H, m), 2.66–2.59 (2 H, m), 2.24 (1.5 H, s), 2.20 (1.5 H, s). ^{13}C NMR ($CDCl_3$): δ 174.8 (s), 174.6 (s), 173.7 (s), 173.5 (s), 147.1 (s), 147.0 (s), 144.2 (s), 144.7 (s), 132.4 (d), 132.4 (d), 132.2 (s), 131.9 (s), 124.8 (d), 124.7 (d), 124.3 (d), 124.1 (d), 67.2 (t), 67.2 (t), 63.5 (d), 63.3 (d), 50.1 (t), 50.0 (t), 32.3 (t), 18.9 (q), 18.8 (q).

N-*(2-Methyl-5-nitrophenyl)-3-(pyrrolidine-1-yl)pyrrolidine-2,5-dione* (**9c**). *N*-(2-Methyl-5-nitrophenyl)maleamic acid methyl ester (**5b**, 0.26 g, 1 mmol) and pyrrolidine (0.071 g, 1 mmol) were stirred for 24 h in ethanol (40 ml) and then poured into water. The resulting solid was collected and recrystallized from petroleum ether, which gave 0.23 g (75%) of **9c**. M.p. 126–128 °C. IR (KBr): 1713, 1522, 1348, 1174, 782, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.19 (1 H, d), 7.99 (1 H, s), 7.48 (1 H, d), 3.99 (1 H, dd, J = 5.21 Hz, J' = 8.50 Hz), 3.11 (1 H, dt, J = 8.26 Hz, J' = 18.27 Hz), 3.02–2.89 (2 + 1 H, m), 2.79–2.70 (2 H, m), 2.27 (1.5 H, s), 2.23 (1.5 H, s), 1.87–1.83 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 175.3 (s), 175.2 (s), 173.8 (s), 173.7 (8s), 147.1 (s), 144.4 (s), 144.1 (s), 132.3 (d), 132.1 (s), 124.6 (d), 124.3 (d), 124.2 (d), 61.1 (d), 60.8 (d), 51.3 (t), 51.3 (t), 34.5 (t), 34.2 (t), 23.9 (t), 23.9 (t), 18.8 (q), 18.6 (q).

N-*(2-Methyl-3-nitrophenyl)-3-(piperidin-1-yl)pyrrolidine-2,5-dione* (**10**). The 'ring closure' procedure (se above) was used. Yield 40%. M.p. 117–119 °C. IR (KBr): 2934, 1707, 1532, 1376, 1355, 1162 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.95 (1 H, m), 7.43 (1 H, m), 7.29 (1 H, m), 4.01 (1 H, m), 3.05 (1 H, m), 2.94–2.83 (4 H, m), 2.58 (2 H, m), 2.28 (1.5 H, s), 2.25 (1.5 H, s), 1.64 (4 H, m), 1.48 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 175.1 (s), 174.8 (s), 173.7 (s), 151.1 (s), 133.1 (s), 132.9 (d), 132.7 (d), 131.4 (s), 127.2 (d), 127.1 (d), 125.43 (d), 125.4 (s), 63.8 (t), 63.4 (t), 50.5 (d), 50.3 (d), 32.4 (d), 32.0 (d), 26.0 (q), 26.0 (q), 23.9 (d), 14.7 (t), 14.4 (t).

N-*(2-Methyl-5-nitrophenyl)-3-(indolin-1-yl)pyrrolidine-2,5-dione* (**11**). Imide **14** (0.23 g, 1 mmol) and indoline (0.36 g, 3 mmol) were mixed in methanol (5 ml) and left

overnight. In the morning 0.29 g (82%) of pure **11** was isolated by filtration and washing with diisopropyl ether. M.p. 151–152 °C. IR (KBr): 2845, 1716, 1529, 1354, 1174, 747 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.21 (1 H, d), 8.03 (1 H, d), 7.51 (1 H, d), 7.16–7.07 (2 H, m), 6.78 (1 H, t), 6.52 (1 H, t), 5.01–4.93 (1 H, m), 3.59–3.42 (2 H, m), 3.30–3.19 (1 H, m), 3.11–2.96 (3 H, m), 2.31 (1.5 H, s), 2.28 (1.5 H, s). ^{13}C NMR ($CDCl_3$): δ 174.3 (s), 174.2 (s), 173.2 (s), 173.1 (s), 149.7 (s), 149.6 (s), 147.2 (s), 144.2 (s), 144.0 (s), 132.4 (d), 132.2 (d), 130.5 (s), 130.4 (s), 127.9 (d), 127.8 (d), 125.6 (d), 125.5 (d), 124.8 (d), 124.2 (d), 124.2 (d), 120.0 (d), 119.9 (d), 107.7 (d), 107.6 (d), 56.5 (d), 56.3 (d), 49.9 (t), 49.8 (t), 31.9 (t), 31.7 (t), 28.8 (t), 18.9 (q), 18.7 (q).

N-*(2-Methyl-5-nitrophenyl)fumaramic acid methyl ester* (**12**). M.p. 158–159 °C. IR (KBr): 3219, 1732, 1719, 1668, 1654, 1531, 1348, 1286 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.09 (1 H, s), 8.66 (1 H, s), 7.94 (1 H, d), 7.51 (1 H, d), 7.44 (1 H, d, J=15.5 Hz), 6.76 (1 H, d, J=15.5 Hz), 3.76 (3 H, s), 2.37 (3 H, s). ^{13}C NMR (DMSO-d_6): δ 165.3 (s), 162.0 (s), 145.6 (s), 136.4 (s), 137.3 (d), 136.6 (s), 131.4 (d), 129.7 (d), 119.7 (d), 117.2 (d), 52.1 (q), 16.1 (q).

N-*(2-Methyl-5-nitrophenyl)-3-(piperidin-1-yl)succinamic acid methyl ester* (**13a**). Ester **5b** (0.26 g, 1 mmol), piperidine (0.26 g, 3 mmol) and methanol were mixed and then left overnight. In the morning 0.26 g (74%) of pure **13a** was collected by filtration and washing with diisopropyl ether. M.p. 127–128 °C. IR (KBr): 2944, 1748, 1702, 1538, 1341 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.71 (1 H, s), 9.11 (1 H, d), 7.84 (1 H, d), 7.30 (1 H, d), 4.00–3.96 (1 H, dd, J=5.02 Hz, J'=8.26 Hz), 3.76 (3 H, s), 2.91–2.83 (1 H, dd, J=8.30 Hz, J'=15.77 Hz), 2.62–2.54 (4+1 H, m), 2.38 (3 H, s), 1.65 (4 H, m), 1.50 (2 H, d). ^{13}C NMR ($CDCl_3$): δ 173.2 (s),170.7 (s), 147.5 (s), 1137.2 (s), 133.7 (s), 131.0 (d), 119.0 (d), 115.3 (d), 66.9 (d), 52.5 (q), 51.3 (t), 28.8 (t), 27.2 (t), 24.2 (t), 18.5 (q).

N-*(2-Methyl-5-nitrophenyl)-3-(morpholin-1-yl)succinamic acid methyl ester* (**13b**). *Method A.* Ester **5b** (1.32 g, 10 mmol) and morpholinium acetate (10 mmol) were mixed in DMF (5 ml) and heated to approximately 60 °C for 30 min, then poured onto ice and filtered and washed with water. The crude product (0.64 g) contained **13b** and the fumaric ester **12** in a 7:3 ratio. These were separated by column chromatography on silica gel with EtOAc as the eluent.

Method B. Imide **14** (0.23 g, 1.0 mmol) and morpholine (96 mg, 1.1 mmol) were mixed in methanol (5 ml) and left overnight. In the morning pure **13b** was collected by filtration and washed with diisopropyl ether. From the filtrate another 53 mg crystallised. Total yield 0.19 g (54%). M.p. 135 °C. IR (KBr): 3321, 1732, 1690, 1538, 1348 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.51 (1 H, s), 9.04 (1 H, s), 7.85 (1 H, d), 7.30 (1 H, d), 4.02–3.97 (1 H, dd, J=5.11 Hz, J'=8.03 Hz), 3.81–3.76 (4+3 H, m), 2.96–2.88 (1 H, dd, J=8.06 Hz, J'=15.98 Hz), 2.69–2.58 (4+1 H, m), 2.38 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 172.8 (s), 169.8 (s), 147.4 (s), 136.9 (s), 133.9 (s), 131.1 (d), 119.3 (d), 115.6 (d), 67.8 (t), 66.3 (d), 52.6 (q), 50.3 (t), 29.1 (t), 18.5 (q).

N-*(2-Methyl-5-nitrophenyl)-3-(pyrrolidine-1-yl)succinamic acid methyl ester* (**13c**). *Method A.* Ester **5b** (1.32 g, 5 mmol) and pyrrolidinium acetate (from 0.36 g pyrrolidine and 0.30 g acetic acid) were stirred at RT for 15 min, then poured onto ice and filtered, giving 1.20 g of a mixture of the succinamide **13c** and the *E*-ester **12** in the ratio 48:52 (as calculated from ^1H NMR integrals).

Method B. Imide **14** (0.23 g, 1.0 mmol) and pyrrolidine (78 mg, 1.1 mmol) were mixed in methanol (5 ml) and then left overnight. The next day the solvent was evaporated off and the remaining viscous oil was chromatographed on a silica gel column with EtOAc as the eluent. Two compounds were isolated as oils. The less polar one was identified as **13c**. Yield 0.13 g (39%). IR (KBr): 2941, 2846, 1730, 1694, 1525, 1344, 1155 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.60 (1 H, s), 8.99 (1 H, s), 7.80 (1 H, d), 7.27 (1 H, d), 4.08–4.03 (1 H, dd, J=5.39 Hz, J'=7.39 Hz), 3.71 (3 H, s), 2.92–2.84 (1 H, dd, J=7.42 Hz, J'=15.91 Hz), 2.7 (4 H, m), 2.69–2.62 (1 H, dd, J=5.39 Hz, J'=15.94 Hz), 2.30 (3 H, s), 1.85–1.80 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 172.8 (s), 170.9 (s), 147.3 (s), 137.1 (s), 134.4 (s), 131.1 (d), 119.1 (d), 115.6 (d), 62.1 (d), 52.5 (q), 50.0 (t), 30.9 (t), 24.1 (t), 18.0 (q). The slower component actually contained two compounds, which were further separated by chromatography, namely **9c** and the regioisomeric amide **17a** in a 3:2 ratio.

N-*(2-Methyl-5-nitrophenyl)-2-(pyrrolidine-1-yl)succinamic acid methyl ester* (**17a**). M.p. 112–122 °C. IR (KBr): 1729, 1692, 1512, 1344, 798, 744 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.6 (1 H, s), 9.00 (1 H, s), 7.81 (1 H, d), 7.25 (1 H, d), 3.75 (1 H, t, J=6.35 Hz), 3.72 (3 H, s), 2.95–2.85 (4+2 H, m), 2.32 (3 H, s), 1.90–1.83 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 171.3 (s), 169.1 (s), 147.2 (s), 138.0 (s), 134.8 (s), 131.0 (d), 118.9 (d), 116.8 (d), 61.6 (d), 52.3 (q), 50.2 (t), 37.7 (t), 24.3 (t), 18.6 (q).

N-*(2-Methyl-5-nitrophenyl)-3-(piperidin-1-yl)succinamic acid ethyl ester* (**13d**). *Method A.* Methyl 2-methyl-5-nitromaleanilate (**5b**, 0.26 g, 1 mmol) and piperidine (0.26 g, 3 mmol) were mixed in ethanol (5 ml) and then left to stand at RT overnight. In the morning 0.24 g (67% yield) of pure **13d** was collected by filtration and washing with diisopropyl ether. M.p. 135 °C.

Method B. Imide **14** (0.23 g, 1.0 mmol) and piperidine (0.85 g, 10 mmol) were mixed in ethanol and left at RT overnight. The next day 0.19 g (52%) of **13d** was collected by filtration. M.p. 130 °C. IR (KBr): 3274, 2930, 2852, 1734, 1702, 1539, 1342, 1248, 1162, 737 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.72 (1 H, s), 9.11 (1 H, s), 7.84 (1 H, d), 7.29 (1 H, d), 4.25–4.18 (2 H, q, J=7.11), 4.00–3.96 (1 H, dd, J=5.20 Hz, J'=7.98 Hz), 2.93–2.61 (1 H, dd, J=8.06 Hz, J'=15.82 Hz), 2.58–2.54 (4+1 H, m), 2.38 (3 H, s), 1.68–1.61 (4 H, m), 1.50 (2 H, m), 1.33–1.28

(3 H, t, J=7.14 Hz). ^{13}C NMR ($CDCl_3$): δ 172.7 (s), 170.7 (s), 147.5 (s), 137.3 (s), 133.7 (s), 131.0 (d), 118.9 (d), 115.4 (d), 66.9 (d), 61.3 (t), 51.4 (t), 29.1 (t), 27.2 (t), 24.2 (t), 18.5 (q), 14.6 (q).

N-*(2-Methyl-5-nitrophenyl)-3-(morpholin-1-yl)succinamic acid ethyl ester* (**13e**). *Method A.* Ester **5b** (0.26 g, 1 mmol) and morpholine (0.26 g, 3 mmol) was mixed in ethanol (5 ml) and then left to stand at RT overnight. Filtration and washing with diisopropyl ether yielded 0.19 g (51%). M.p. 130–132 °C.

Method B. Imide **14** (0.23 g, 1 mmol) and morpholine (0.87 ml, 10 mmol) was mixed with ethanol (5 ml) and left overnight. Then the solvent was evaporated off and the resulting oil chromatographed on a silica gel column with ether as the eluent. The fastest component was identified as **13d**. Yield 77 mg (21%). M.p. 136 °C. IR (KBr): 3322, 2974, 2853, 1734, 1690, 1535, 1348, 1116, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.50 (1 H, s), 8.98 (1 H, s), 7.80 (H, d), 7.27 (1 H, d), 3.99–3.95 (1 H, dd, J= 5.13 Hz, J'=8.02 Hz), 3.78–3.73 (4+3 H, m), 3.70–3.63 (2 H, q, J=7.03 Hz), 2.93–2.85 (1 H, dd, J=8.07 Hz, J'=15.99 Hz), 2.65–2.58 (4+1 H, m), 2.35 (3 H, s), 1.19 (3 H, t, J=7.03 Hz). ^{13}C NMR ($CDCl_3$): δ 172.8 (s), 169.8 (s), 147.3 (s), 136.9 (s), 134.0 (s), 131.1 (d), 119.2 (d), 115.5 (d), 67.8 (t), 66.3 (d), 58.7 (t), 52.6 (q), 50.3 (t), 29.1 (t), 18.5 (q).

N-*(2-Methyl-5-nitrophenyl)-3-(pyrrolidine-1-yl)succinamic acid ethyl ester* (**13f**). Ester **5b** (0.26 g, 1 mmol) and pyrrolidine (0.21 g, 3 mmol) were mixed in ethanol (5 ml) and then left to stand at RT overnight. The next day, the reaction mixture was extracted with ether–water. The residue left after evaporation was chromatographed on a silica gel column with ether as the eluent. This gave two poducts with a distinct difference in R_f-values. The less polar component was identified as **13f**. Yield 0.12 g (33 %), oil. ^{1}H NMR ($CDCl_3$): δ 9.60 (1 H, s), 8.99 (1 H, s), 7.79 (1 H, d), 7.25 (1 H, d), 4.19–4.12 (2 H, q, J=7.14 Hz), 4.05–4.00 1 H, dd, J=5.63 Hz, J'= 7.09 Hz), 2.90–2.82 (1 H, dd, J=7.18 Hz, J'=15.98 Hz), 2.73–2.69 (4 H, m), 2.67–2.58 (1 H, dd, J=5.55 Hz, J'= 15.97 Hz) 2.29 (3 H, s), 1.84–1.79 (4 H, m), 1.24 (3 H, t, J=7.14 Hz). ^{13}C NMR ($CDCl_3$): δ 172.3 (s), 170.9 (s), 147.3 (s), 137.1 (s), 134.4 (s), 131.1 (d), 119.0 (d), 115.6 (d), 62.1 (d), 61.3 (t), 50.1 (t), 31.4 (t), 24.1 (t), 18.0 (q), 14.5 (q). The slower running component was identified as the regioisomeric compound **17b**.

N-*(2-Methyl-5-nitrophenyl)-2-(pyrrolidine-1-yl)succinamic acid ethyl ester* (**17b**). Isolated yield 76 mg (22%), oil. ^{1}H NMR ($CDCl_3$): δ 10.70 (1 H, s), 9.01 (1 H, s), 7.80 (1 H, d), 7.25 (1 H, d), 4.21–4.14 (2 H, q, J= 7.13 Hz), 3.71 (1 H, t, J=6.33 Hz), 2.94–2.86 (4+1 H, m), 2.32 (3 H, s), 1.90–1.85 (4 H, m), 1.25 (3 H, t, J=7.13 Hz). ^{13}C NMR ($CDCl_3$): δ 170.8 (s), 169.2 (s), 147.2 (s), 138.0 (s), 134.8 (s), 131.0 (d), 119.0 (d), 116.7 (d), 61.7 (d), 61.5 (t), 50.2 (t), 37.7 (t), 24.4 (t), 18.5 (q), 14.6 (q)

N-*Phenyl-3-(piperidin-1-yl)pyrrolidine-2,5-dione* (**15**). *N*-Phenylmaleimide (1.73 g, 10 mmol) and piperidinium acetate (1.45 g, 10 mmol) were stirred in DMF (20 ml) for 3 h, whereupon water (40 ml) was added and after 1 h 1.52 g (59%) pure **15** was collected. M.p. 161–163 °C. IR (KBr): 2936, 1705, 1168, 752, 702 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.50–7.40 (3 H, m), 7.25–7.22 (2 H, m), 4.03–3.96 (1 H, dd, J=4.9 Hz, J'=9.0 Hz), 3.0–2.9 (1 H, dd, J=9 Hz, J'=18.2 Hz), 2.78–2.72 (1+2 H, m), 2.50–2.43 (2 H, m), 1.50 (4 H, m), 1.39 (2 H, m). ^{13}C NMR (DMSO-d_6): δ 175.8 (s), 175.1 (s), 132.6 (s), 129.2 (d), 128.7 (d), 127.5 (d), 63.3 (d), 49.9 (t), 31.9 (t), 26.2 (t), 24.2 (t).

N-*Phenyl-3-(indolin-1-yl)pyrrolidine-2,5-dione* (**16**). Hill's procedure was used. M.p. 143 °C (lit. 118–120 °C).[7] IR (KBr): 1711, 1184, 742 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.52–7.41 (3 H, m), 7.34–7.31 (2 H, m), 7.14–7.06 (2 H, m), 6.76 (1 H, t, J=7.25 Hz), 6.48 (1 H, d, J=7.82 Hz), 4.87–4.82 (1 H, dd, J=5.72 Hz, J'= 9.14 Hz), 3.55–3.45 (2 H, m), 3.22–3.12 (1 H, dd, J= 9.17 Hz, J'=18.48 Hz), 3.09–3.03 (1 H, m), 2.98–2.90 (1 H, dd, J=5.72 Hz, J'=18.48 Hz). ^{13}C NMR (DMSO-d_6): δ 174.9 (s), 173.9 (s), 150.3 (s), 132.1 (s), 129.4 (s), 128.8 (d), 128.3 (d), 127.0 (d), 126.9 (d), 124.5 (d), 117.9 (d), 106.9 (d), 54.9 (d), 48.1 (t), 31.1 (t), 27.6 (t). *m/z* 292.2 (96), 175.1 (16), 172.2 (21), 145.1 (100), 130.2 (26), 118.2 (96), 77.2 (11).

6-Nitro-2-(2-oxo-2-piperidin-1-ylethyl)indan-1-one (**18**). To a stirred suspension of (6-nitro-1-oxoindan-2-yl)acetic acid[8] (0.42 g, 1.4 mmol) in chloroform (25 ml) was added dropwise, oxalyl chloride (2 ml) in chloroform (5 ml). This mixture was then refluxed for 2 h and then stirred at RT for another 20 h. The chloroform with the excess oxalyl chloride was removed under reduced pressure. The crude acid chloride was redissolved in chloroform (20 ml) and piperidine (0.17 g, 2 mmol) was added dropwise. The resulting mixture was then refluxed for 2 h. Again the chloroform was removed under reduced pressure and the crude product chromatographed on a silica gel column with ethyl acetate as the eluent. This procedure afforded (R_f=0.40) 0.35 g (79%) of **18**. M.p. 104 °C. IR (KBr): 1719, 1637, 1532, 1442, 1343, 1231 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.57 (1 H, s), 8.40 (1 H, d), 7.60 (1 H, d), 3.55–3.37 (6 H, m), 3.12–2.89 (3 H, m), 1.68–1.55 (2 H, m), 1.54–1.45 (4 H, m). ^{13}C NMR ($CDCl_3$): δ 168.2 (s), 159.5 (s), 147.8 (s), 138.1 (s), 128.6 (d), 127.5 (d), 119.1 (d), 46.60 (t), 44.5 (d), 42.9 (t), 34.3 (t), 33.7 (t), 26.4 (t), 25.5 (t), 24.4 (t).

7-Nitro-3-(2-oxo-2-piperidin-1-ylethyl)-3,4-dihydroquinoline-2(1H)-one (**7**). To a stirred mixture of 6-nitro-2-(2-oxo-2-piperidin-1-ylethyl)indan-1-one (**18**, 0.30 g, 1 mmol), benzene (15 ml) and sulfuric acid (98%, 2 ml) was added sodium azide (0.070 g, 1.1 mmol). The stirred mixture was gently heated to 40–45 °C for 15 min (evolution of gas was observed) and then left to cool. The sulfuric acid fraction separated out and was poured

into water (50 ml). Filtration gave 0.20 g (63%) **7**. M.p. 227–228 °C. IR (KBr): 1677, 1634, 1525, 1446, 1345 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.53 (1 H, s), 8.31 (1 H, d), 8.10 (1 H, s), 7.62 (1 H, d), 4.10 (1 H, m), 3.38 (2 H, m), 3.32 (4 H, m), 2.95 (1 H, dd, J=8.16 Hz, J'= 16.8 Hz), 2.61 (2 H, q), 1.55 (2 H, m), 1.43 (4 H, m). ^{13}C NMR (DMSO-d_6): δ 167.5 (s), 162.3 (s), 146.7 (s), 145.6 (s), 130.1 (d), 129.9 (s), 126.6 (d), 121.6 (d), 47.3 (d), 45.8 (t), 41.9 (t), 37.4 (t), 32.9 (t), 26.0 (t), 25.2 (t), 24.0 (t).

Acknowledgements. This work was supported by the Swedish Natural Science Research Council. We also thank Prof. G. Cignarella and Dr. P. Vianello at the University of Milan for provision of samples of 1-oxoindan-3-ylacetic acid and 6-nitro-1-oxoindan-3-ylacetic acid for comparison and Prof. C. Stålhandske at the University of Lund for the determination of the structure **13a**.

References

1. Bergman, J. and Sand, P. *Tetrahedron 46* (1990) 6085.
2. Bergman, J. *Unpublished results.*
3. Madelung, W. *Berichte 45* (1912) 1128.
4. Allen, C. F. H. and Van Allan, J. *The Madelung Indole Synthesis.* In: Horning, E. C., Ed., *Org. Synth., Coll. Vol. III*, Wiley, New York 1955, pp. 597–599.
5. Joule, J. A., Mills, K. and Smith, G. F. *Heterocyclic Chemistry*, Chapman & Hall, London 1995, pp. 335–336.
6. Patel, M. V., Balasubramaniyan, P. and Balasubramaniyan, V. *Ind. J. Chem. 18B* (1979) 245.
7. Ashraf, S. A., Hill, J., M'Hamedi, A. and Zerizer, H. *Tetrahedron 48* (1992) 6747.
8. Cignarella, G., Barlocco, D., Landriano, L., Folloni, M., Pinna, G. A., Sala, F. and Germini, M. *Farmaco Ed. Sci. 43* (1988) 169.
9. Ravina, E., Fueyo, J., Masaguer, C. F., Negreira, J., Cid, J., Loza, I., Honrubia, A., Tristan, H., G-Ferreiro, T., Fontenla, J. A., Rosa, E., Calleja, J. M. and De Cebballos, M. L. *Chem. Pharm. Bull. 44* (1996) 534.
10. Wolff, H. *Org. React. 3* (1964) 307.
11. Tomita, M., Minami, S. and Uyeo, S. *J. Chem. Soc. C* (1969) 183.
12. Briepe, J.-F., Charpentier, P., Dupas, G., Quéguiner, G. and Bourguignon, J. *Tetrahedron 53* (1997) 2075.
13. Joseph-Nathan, P., Mendoza, V. and García, E. G. *Can. J. Chem. 52* (1974) 129.
14. Medion-Simon, M. and Pindur, U. *Helv. Chim. Acta 74* (1991) 430.
15. Ahmed, Q., Wagner-Jauregg, T., Pretsch, E. and Seibl, J. *Helv. Chim. Acta 56* (1973) 1646.
16. Rangnekar, V. M., Bhamaria, R. P. and Khadse, B. G. *Ind. J. Pharm. Sci. 46* (1984) 196.
17. Kishikawa, K., Tsuru, I., Kohmoto, S. and Yamamoto, M. *Chem. Lett.* (1994) 1605.
18. Sharpless, N. E. and Flavin, M. *Biochemistry 5* (1966) 2963.
19. Lubineau, A., Bouchain, G. and Queneau, Y. *J. Chem. Soc., Perkin Trans. 1* (1995) 2433.
20. Mustafa, A., Asker, W., Khattab, S. and Zayed, S. M. A. D. *J. Org. Chem. 26* (1961) 787.
21. Rudolf, B. and Zakrzewski, J. *J. Organomet. Chem. 522* (1996) 313.
22. Pastor, S. D. and Hesse, E. T. *J. Org. Chem. 53* (1988) 5776.
23. Cremlyn, R. and Nunes, R. *Phosporus Sulfur 31* (1987) 245.
24. Sondheimer, E. and Holley, R. W. *J. Am. Chem. Soc. 76* (1954) 2467.
25. Roy, R. B. and Swan, G. A. *J. Chem. Soc. C* (1969) 1886.
26. Joseph-Nathan, P., Mendoza, V. and Garcia, E. *J. Org. Chem. 37* (1972) 3950.
27. Oki, M. *The Chemistry of Rotational Isomers*, Springer, Berlin, Heidelberg 1993.
28. Ohno, A., Kunitomo, J. and Kawai, Y. *Tetrahedron 53* (1997) 4601.
29. Ohno, A., Kunitomo, J., Kawai, Y., Kawamoto, T., Tomishima, M. and Yoneda, F. *J. Org. Chem. 61* (1996) 9344.
30. Kitagawa, O., Izawa, H., Sato, K., Dobashi, A. and Taguchi, T. *J. Org. Chem. 63* (1998) 2634.
31. Siddall, T. H., III and Stewart, W. E. *J. Org. Chem. 34* (1969) 233.
32. Soriano-Garcia, M., Toscano, R., Mendoza, V., Garcia, G, E., Guzman, J. A., Aleman, L. O. and Huipe N, E. *Acta Crystallogr., Sect. C 11* (1990) 2263.
33. Bergman, J., Brimert, T. and Stålhandske, C. *Unpublished results.*
34. Huang, X., Luo, X., Roupioz, Y. and Keillor, J. W. *J. Org. Chem. 62* (1997) 8821.
35. Patel, M. V. and Balasubramaniyan, V. *Ind. J. Chem. 15B* (1977) 1142.

Received June 15, 1998.