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Synthesis, Structure and Cytostatic Activity of a Series of *N*-Substituted 3,4-Diphenyl-1*H*-pyrrole-2,5-diones

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A series of *N*-substituted 3,4-diphenyl-1*H*-pyrrole-2,5-diones (diphenylmaleimides) (IV) were synthesized and tested for cytostatic activity. Compounds IVa—k were prepared from diphenylmaleic anhydride or its dinitro derivative (V or VI) and the corresponding amine. Compounds IVl—n were obtained by reaction of 3-(*p*-nitrophenyl)-4-phenyl-1*H*-pyrrole-2,5-dione potassium salt with the appropriate chloroalkylamine. Hydrogenation of IVl, n gave the the corresponding *cis*-3-(*p*-aminophenyl)-4-phenylsuccinimides (VIIIa, b). The structure–cytostatic activity relationship of these compounds is discussed.

Keywords 3,4-diphenyl-1*H*-pyrrole-2,5-dione; diphenylmaleimide; cytostatic activity; structure–activity relationship

The search for potent antitumor agents based on the benzo[*d*,*e*]isoquinoline-1,3-dione system[1-3] has been an area of considerable interest to us. The best compounds found so far are Mitonafide (Ia) ($X=NO_2$, $n=2$, $Y=N(CH_3)_2$) and Amonafide (Ib) ($X=NH_2$, $n=2$, $Y=N(CH_3)_2$), which inhibit deoxyribonucleic acid (DNA) synthesis[2] by intercalation[4,5] and have been selected as candidate antitumor agents by the National Cancer Institute. Compound Ib is now in clinical trial (as NSC 308847). In connection with this work we have synthesized[6] and determined the cytotoxic activity[6] of molecules II of similar topology to I, based on the perimidine skeleton. In a preliminary screening of IIa ($X=H$, $R=CH_2N(CH_3)_2$) with P388 leukemia, however, the compound showed no *in vivo* activity.

On the other hand, we have been interested in the synthesis of non-bioisosteric analogues related to I. So, we have synthesized[7] and evaluated the cytostatic activity[7] of a series of *N*-substituted 3-diphenylmethylene-2,5-pyrrolidinediones (III), which were inactives as antitumor agents. In the present work we have considered the 3,4-diphenyl-1*H*-pyrrole-2,5-dione skeleton (IV), which contains a cyclic imide as in I and a conjugated alkene-carbonyl system. It is noteworthy that according to Kupchan *et al.*,[8] this system may exhibit cytostatic activity due to the ability to react with the SH groups of proteins by Michael addition.

Chemistry The *N*-substituted 3,4-diphenyl-1*H*-pyrrole-2,5-diones (IVa—i) were prepared by reaction of diphenylmaleic anhydride (V) with the corresponding amine in ethanol. Similarly, compounds IVj, k were obtained from 3,4-bis-(*p*-nitrophenyl)maleic anhydride (VI) and the appropiate amine (Chart 2, Table I).

The *N*-substituted 3-(*p*-nitrophenyl)-4-phenyl-1*H*-pyrrole-2,5-diones[9] (IVl—n) (Table I) were prepared by reaction of the 3-(*p*-nitrophenyl)-4-phenyl-1*H*-pyrrole-2,5-dione potassium salt (VII) with the corresponding chloroalkylamine. The synthesis of VII was carried out by condensation of benzoylformic acid with *p*-nitro-phenylacetonitrile in the presence of piperidine.[9] Hydrogenation of IVl, n over 10% palladium on charcoal gave the corresponding *cis*-3-(*p*-aminophenyl)-4-phenylsuccinimides (VIIIa, b) (Chart 3, Table I).

Pharmacology and Structure–Activity Relationship ID_{50}, the concentration of a drug (in μM) required to inhibit by 50% the growth of a Hela cell culture, has been used as a biological parameter. The ID_{50} values of each product are reported in Table I.

Figure 1 shows the effect of several concentrations of 3,4-

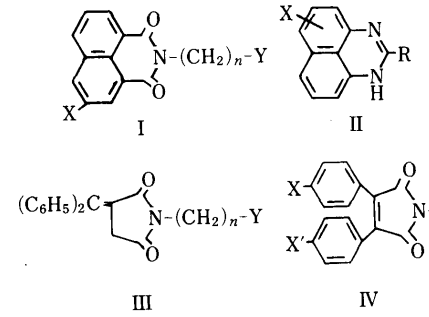


Chart 1

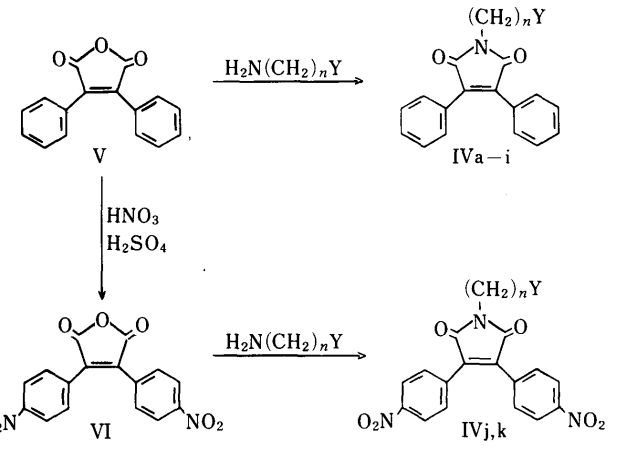


Chart 2

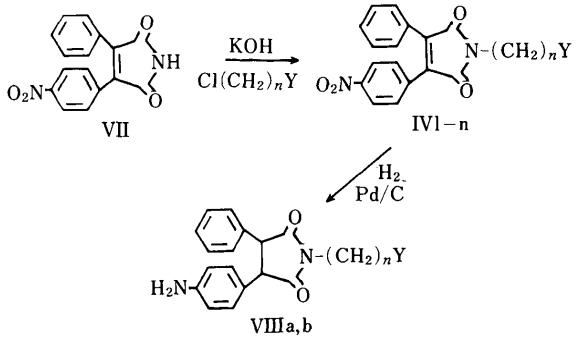
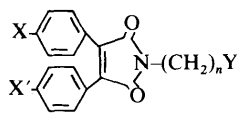
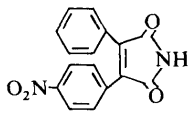


Chart 3

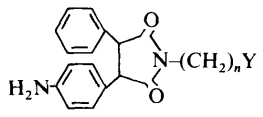
TABLE I. *N*-Substituted 3,4-Diphenyl-1*H*-pyrrole-2,5-diones



IVa—n



VII



VIIIa, b

Compd. No.	X	X′	Y	*n*	Formula	mp (°C)	Solvent	ID_{50}[a]
IVa	H	H	$N(CH_3)_2$	2	$C_{20}H_{20}N_2O_2$	99	Petroleum ether	31.2
IVb	H	H	$N(CH_2CH_3)_2$	2	$C_{22}H_{24}N_2O_2$	51—52	Ethanol–water	86.1
IVc	H	H	$N(CH_2)_4$	2	$C_{22}H_{22}N_2O_2$	150	Cyclohexane	21.6
IVd	H	H	$N(CH_2)_5$	2	$C_{23}H_{24}N_2O_2$	85—86	DMF–water	83.2
IVe	H	H	$N(CH_2CH_2)_2NH$	2	$C_{22}H_{23}N_3O_2$	149—150	Petroleum ether	83.0
IVf	H	H	$N(CH_2CH_2)_2O$	2	$C_{22}H_{22}N_2O_3$	92	Petroleum ether	82.8
IVg	H	H	$N(CH_2CH_2)_2NCH_3$	3	$C_{24}H_{27}N_3O_2$	66—67	Petroleum ether	25.7
IVh	H	H	$N(CH_3)_2$	3	$C_{21}H_{22}N_2O_2$	75	Petroleum ether	89.7
IVi	H	H	$N(CH_2CH_3)_2$	3	$C_{23}H_{26}N_2O_2$	68	Petroleum ether	82.8
IVj	NO_2	NO_2	$N(CH_3)_2$	2	$C_{20}H_{18}N_4O_6$	160	DMF–water	73.1
IVk	NO_2	NO_2	$N(CH_2CH_2)_2O \cdot HCl$	2	$C_{22}H_{21}ClN_4O_7$	>260	Methanol	65.4
VII	—	—	—	—	$C_{16}H_{10}N_2O_4$	203—204	$CHCl_3$–cyclohexane	135.9
IVl	H	NO_2	$N(CH_2)_5$	2	$C_{23}H_{23}N_3O_4$	86—88	Cyclohexane	118.4
IVm	H	NO_2	$N(CH_3)_2$	3	$C_{21}H_{21}N_3O_4$	114—116	Petroleum ether	126.5
IVn	H	NO_2	$N(CH_2)_5$	3	$C_{24}H_{25}N_3O_4$	104	Petroleum ether	76.2
VIIIa[b]	—	—	$N(CH_2)_5$	2	$C_{23}H_{27}N_3O_2$	Oil	—	10.5
VIIIb[c]	—	—	$N(CH_2)_5$	3	$C_{24}H_{29}N_3O_2$	84—86	Cyclohexane	10.2
Mitonafide								0.5
Amonafide								8.8

a) Drug concentration (μM) which reduces cell growth to 50% of the control. *b*) (*Z*)-3-(*p*-Aminophenyl)-4-phenyl-1-(2-piperidinoethyl)succinimide. *c*) (*Z*)-3-(*p*-Aminophenyl)-4-phenyl-1-(3-piperidinopropyl)succinimide.

diphenyl-1-[2-(1-pyrrolidinyl)ethyl]-1*H*-pyrrole-2,4-dione (IVc) on HeLa cell growth. A severe growth inhibition was observed at the three tested concentrations. Total growth inhibition was achieved 48 h after applying the compound. The cells treated with 4.32 μM IVc showed a recovery of growth after a few hours, which indicates a reversible action of IVc. In addition to growth inhibition, an increase in cellular mortality was observed in cells treated with 21.64 and 108.24 μM, 48 h after the compound addition. In these cases the cellular growth did not recover.

Although no clear structure–activity relationship (SAR) can be deduced in the 3,4-diphenyl-1*H*-pyrrole-2,5-dione series, the volume of the dialkylamino group (Y) in compounds with two methylene groups in the side chain seems to be important for cytostatic activity. Compound IVa ($Y = N(CH_3)_2$) was approximately two and a half times more potent than IVb, d—f. Comparing compounds IVa and IVh, an increase in the number of methylene groups caused a decrease in activity. However, this tendency was not observed when the volume of the dialkylamino group was increased (compounds IVb and IVi). These facts seem to indicate an important role of the side chain in the activity.

The introduction of a nitro group in the benzene ring decreased the cytostatic activity.

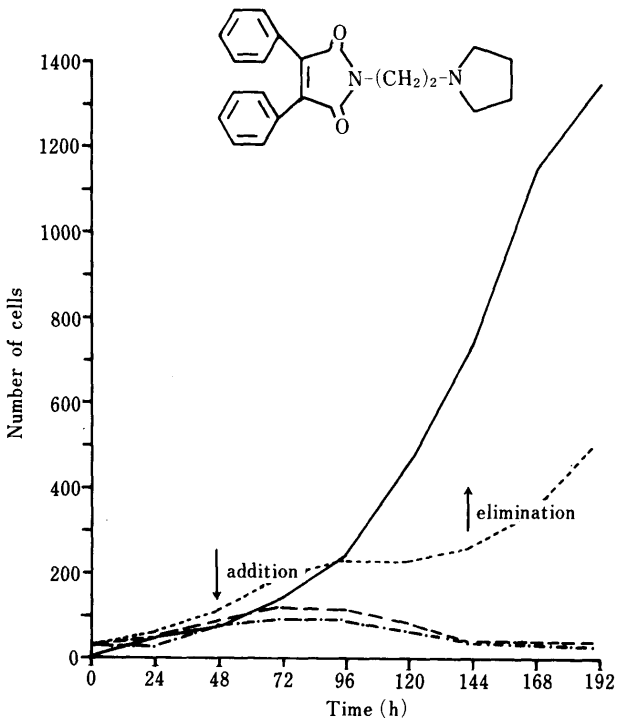


Fig. 1. Growth Curve of Hela Cells. Effect of IVc

Final concentration in the culture medium. ——, growth control; ------, 4.32 μM; – – – –, 21.64 μM; – · – · –, 108.24 μM.

Experimental

Melting points were measured with a Büchi apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian T-60A (60 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard.

General Procedure for the Preparation of *N*-Substituted 3,4-Diphenyl-1*H*-pyrrole-2,5-diones (IVa—i) A suspension of diphenylmaleic anhydride (V) (1.25 g, 0.0005 mol) and the corresponding amine (0.005 mol) in ethanol (30 ml) was stirred at room temperature for 2 h. Evaporation of the solvent under reduced pressure yielded the title compounds.

1-(2-Dimethylaminoethyl)-3,4-diphenyl-1*H*-pyrrole-2,5-dione (IVa) 79% yield, mp 99 °C (petroleum ether). IR (KBr): 3040, 2930, 2810, 2740, 1750, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.2 (6H, s, $N(CH_3)_2$), 2.6 (2H, t, $J = 6$ Hz, CH_2-N), 3.6 (2H, t, $J = 6$ Hz, $(CO)_2N$-CH_2), 7.0—7.3

(10H, m, ArH). *Anal.* Calcd for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.74. Found: C, 75.22; H, 6.09; N, 8.89.

1-(2-Diethylaminoethyl)-3,4-diphenyl-1*H*-pyrrole-2,5-dione (IVb) 87% yield, mp 51—52 °C (ethanol–water). IR (KBr): 3040, 2960, 2940, 2800, 1760, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0 (6H, t, J=6 Hz, $2CH_3$), 2.3—2.7 (6H, m, CH_2N-$(CH_2)_2$), 3.6 (2H, t, J=6 Hz, $(CO)_2N$-CH_2), 7.0—7.3 (10H, m, ArH). *Anal.* Calcd for $C_{22}H_{24}N_2O_2$: C, 75.86; H, 6.89; N, 8.04. Found: C, 75.72; H, 7.13; N, 7.92.

3,4-Diphenyl-1-[2-(1-pyrrolidinyl)ethyl]-1*H*-pyrrole-2,5-dione (IVc) 42% yield, mp 105 °C (cyclohexane). IR (KBr): 3040, 2920, 2860, 2780, 2740, 1760, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8 (4H, m, C-CH_2-CH_2-C), 2.4—2.6 (4H, m, -$N(CH_2)_2$), 2.7 (2H, t, J=6 Hz, -CH_2-N), 3.7 (2H, t, J=6 Hz, $(CO)_2N$-CH_2), 7.0—7.3 (10H, m, ArH). *Anal.* Calcd for $C_{22}H_{22}N_2O_2$: C, 76.27; H, 6.40; N, 8.08. Found: C, 76.31; H, 6.34; N, 8.35.

3,4-Diphenyl-1-(2-piperidinoethyl)-1*H*-pyrrole-2,5-dione (IVd) 51% yield, mp 85—86 °C (*N*,*N*-dimethylformamide (DMF)–water). IR (KBr): 3050, 2920, 2850, 2790, 1760, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5 (6H, m, C-$(CH_2)_3$-C), 2.3—2.6 (6H, m, $CH_2N(CH_2)_2$), 3.7 (2H, t, J=6 Hz, $(CO)_2N$-CH_2), 7.0—7.3 (10H, m, ArH). *Anal.* Calcd for $C_{23}H_{24}N_2O_2$: C, 76.63; H, 6.71; N, 8.77. Found: C, 76.77; H, 6.69; N, 8.18.

3,4-Diphenyl-1-[2-(1-piperazinyl)ethyl]-1*H*-pyrrole-2,5-dione (IVe) 95% yield, mp 149—150 °C (petroleum ether). IR (KBr): 3040, 2940, 2830, 2810, 1760, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.7 (1H, s-br, NH), 2.4—3.0 (10H, m, $5CH_2$), 3.7 (2H, t, J=6 Hz, $(CO)_2N$-CH_2), 7.0—7.3 (10H, m, ArH). *Anal.* Calcd for $C_{22}H_{23}N_3O_2$: C, 73.10; H, 6.41; N, 11.62. Found: C, 72.90; H, 6.20; N, 11.67.

1-(2-Morpholinoethyl)-3,4-diphenyl-1*H*-pyrrole-2,5-dione (IVf) 81% yield, mp 92 °C (petroleum ether). IR (KBr): 3040, 2960, 2940, 2820, 1760, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.3—2.6 (6H, m, CH_2N-$(CH_2)_2$), 3.4—3.8 (6H, m, CH_2-O-CH_2 and $(CO)_2N$-CH_2), 7.0—7.3 (10H, m, ArH). *Anal.* Calcd for $C_{22}H_{22}N_2O_3$: C, 72.90; H, 6.11; N, 7.73. Found: C, 73.10; H, 6.18; N, 7.83.

1-[3-(4-Methyl-1-piperazinyl)propyl]-3,4-diphenyl-1*H*-pyrrole-2,5-dione (IVg) 44% yield, mp 66—67 °C (petroleum ether). IR (KBr):3060, 2935, 2800, 2760, 1760, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8 (2H, m, C-CH_2-C), 2.2 (3H, s, N-CH_3), 2.3 (10H, m, CH_2-$N(CH_2$-$CH_2)_2$-N), 3.6 (2H, t, J=6 Hz, $(CO)_2N$-CH_2), 7.0—7.3 (10H, m, ArH). *Anal.* Calcd for $C_{24}H_{27}N_3O_2$: C, 74.00; H, 6.98; N, 10.78. Found: C, 73.86; H, 7.03; N, 10.94.

1-(3-Dimethylaminopropyl)-3,4-diphenyl-1*H*-pyrrole-2,5-dione (IVh) 65% yield, mp 75 °C (petroleum ether). IR (KBr): 3040, 2940, 2820, 1760, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8 (2H, m, C-CH_2-C), 2.2 (6H, s, $2CH_3$), 2.3 (2H, t, J=6 Hz, CH_2-N), 3.6 (2H, t, J=6 Hz, $(CO)_2N$-CH_2), 7.0—7.3 (10H, m, ArH). *Anal.* Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.37. Found: C, 75.75; H, 6.56; N, 8.30.

1-(3-Diethylaminopropyl)-3,4-diphenyl-1*H*-pyrrole-2,5-dione (IVi) 45% yield, mp 68 °C (petroleum ether). IR (KBr): 3070, 2940, 2820, 2780, 1760, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8 (6H, t, J=6 Hz, $2CH_3$), 1.5—1.9 (2H, m, C-CH_2-C), 2.2—2.6 (6H, m, CH_2N-$(CH_2)_2$), 3.5 (2H, t, J=6 Hz, $(CO)_2N$-CH_2), 7.0—7.3 (10H, m, ArH). *Anal.* Calcd for $C_{23}H_{26}N_2O_2$: C, 76.24; H, 7.18; N, 7.73. Found: C, 76.16; H, 6.87; N, 7.95.

Bis(*p*-nitrophenyl)maleic Anhydride (VI) This compound was obtained according to the reported method[10] in 96% yield. mp 194—196 °C (EtOH).

1-(2-Dimethylaminoethyl)-3,4-bis(*p*-nitrophenyl)-1*H*-pyrrole-2,5-dione (IVj) A suspension of VI (0.34 g, 0.001 mol) and *N*,*N*-dimethylethylenediamine (0.08 g, 0.001 mol) in EtOH (30 ml) was stirred at room temperature for 2 h. The solvent was evaporated off and the solid was crystallized from DMF–H_2O to give 0.26 g (63%) of IVj, mp 160 °C. IR (KBr): 3920, 3880, 2940, 2840, 2820, 1770, 1700, 1520, 1350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.2 (6H, s, $2CH_3$), 2.5 (2H, t, J=6 Hz, CH_2-N), 3.7 (2H, t, J=6 Hz, $(CO)_2N$-CH_2), 7.4 (4H, d, J=4 Hz, $2H_2$ and $2H_6$-phenyl), 8.0 (4H, d, J=4 Hz, $2H_3$ and $2H_5$-phenyl). *Anal.* Calcd for $C_{20}H_{18}N_4O_6$: C, 58.53; H, 4.39; N, 13.65. Found: C, 58.35; H, 4.51; N, 13.92.

1-(2-Morpholinoethyl)-3,4-bis(*p*-nitrophenyl)-1*H*-pyrrole-2,5-dione Hydrochloride (IVk) A suspension of VI (2.04 g, 0.006 mol) and *N*-(2-aminoethyl)morpholine (0.78 g, 0.006 mol) in EtOH (30 ml) was stirred at room temperature for 2 h. The solvent was evaporated off under reduced pressure and the resulting oil was treated with a current of dry hydrogen chloride for 2 h. The reaction mixture was evaporated *in vacuo* and the resulting oil was treated with AcOEt to give a precipitate of (*N*-(2-aminoethyl)morpholine hydrochloride). The solvent was evaporated off and the solid was crystallized from MeOH to give 1.9 g (67%) of IVk, mp 260 °C. IR (KBr): 3400, 2840, 2520, 2460, 1750, 1700, 1520, 1350 cm^{-1}. ^{1}H-NMR (CF_3CO_2H) δ: 3.6—4.4 (12H, m, $6CH_2$), 7.4 (4H, d, J=4 Hz, $2H_2$ and $2H_6$-phenyl), 8.1 (4H, d, J=4 Hz, $2H_3$ and $2H_5$-phenyl). *Anal.* Calcd for $C_{22}H_{21}ClN_4O_7$: C, 54.04; H, 4.33; Cl, 7.25; N, 11.46. Found: C, 54.11; H, 4.68; Cl, 7.05; N, 11.45.

3-(*p*-Nitrophenyl)-4-phenyl-1*H*-pyrrole-2,5-dione (VII) A suspension of benzoylformic acid (1.5 g, 0.01 mol) and *p*-nitrophenylacetonitrile (1.62 g, 0.01 mol) in piperidine (15 ml) was stirred at room temperature for 2 h. The solvent was evaporated off and the residue was dissolved in ethyl ether, washed with 5% HCl and H_2O, dried over $MgSO_4$ and evaporated to dryness. The solid was crystallized from $CHCl_3$–cyclohexane to give 1.3 g (45%) of VII, mp 203—205 °C (lit.[9] mp 204—206 °C).

General Procedure for the Preparation of *N*-Substituted 3-(*p*-Nitrophenyl)-4-phenyl-1*H*-pyrrole-2,5-diones (IVl—n) A suspension of 3-(*p*-nitrophenyl)-4-phenyl-1*H*-pyrrole-2,5-dione potassium salt (1.28 g, 0.004 mol) and the corresponding chloroalkylamine (0.004 mol) in DMF (50 ml) was refluxed for 6 h. The solvent was evaporated off under reduced pressure and the resulting oil was treated with H_2O and $CHCl_3$ and dried over $MgSO_4$. The solvent was removed to yield the corresponding compounds.

3-(*p*-Nitrophenyl)-4-phenyl-1-(2-piperidinoethyl)-1*H*-pyrrole-2,5-dione (IVl) 55% yield, mp 86—88 °C (cyclohexane) (lit.[9] mp 87—89 °C).

1-(3-Dimethylaminopropyl)-3-(*p*-nitrophenyl)-4-phenyl-1*H*-pyrrole-2,5-dione (IVm) 56% yield, mp 114—116 °C (petroleum ether) (lit.[9] mp 115—117 °C).

3-(*p*-Nitrophenyl)-4-phenyl-1-(3-piperidinopropyl)-1*H*-pyrrole-2,5-dione (IVn) 47% yield, mp 104 °C (petroleum ether) (lit.[9] mp 105 °C).

***cis*-3-(*p*-Aminophenyl)-4-phenyl-1-(2-piperidinoethyl)succinimide (VIIIa)** A solution of IVl (1.5 g, 0.004 mol) in DMF (100 ml) containing 90 mg of 10% Pd–C was shaken for 6 h in a Parr apparatus. After filtration and concentration, an oil was obtained which was purified by column chromatography with benzene–ethanol (9 : 1) as an eluent to give 1.1 g of VIIIa. IR (KBr): 3430, 3330, 3070, 3040, 2940, 2800, 1775, 1700, 800, 740, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5 (6H, m, C-$(CH_2)_3$-C), 2.5 (6H, m, CH_2N-$(CH_2)_2$-), 3.6 (6H, m, 2CH, $1NH_2$ and $(CO)_2N$-CH_2), 6.3 (2H, d, J=4 Hz, H_2 and H_6-phenyl), 6.7 (2H, d, J=4 Hz, H_3 and H_5-phenyl), 7.1 (5H, br s, ArH). *Anal.* Calcd for $C_{23}H_{37}N_3O_2$: C, 73.17; H, 7.21; N, 11.14. Found: C, 73.04; H, 7.44; N, 11.03.

***cis*-3-(*p*-Aminophenyl)-4-phenyl-1-(3-piperidinopropyl)succinimide (VIIIb)** A solution of IVn (1.55 g, 0.003 mol) in DMF (100 ml) containing 90 mg of 10% Pd–C was shaken for 6 h in a Parr apparatus. After filtration and concentration was isolated 1.2 g (87%) of VIIIb, mp 84—86 °C (cyclohexane). IR (KBr): 3430, 3330, 3065, 3040, 2940, 2800, 1770, 1700, 820, 750, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5 (8H, m, C-$(CH_2)_3$-C and C-CH_2-C), 2.3 (6H, m, CH_2-$N(CH_2)_2$-), 3.8 (6H, m, NH_2, CH-CH and $(CO)_2N$-CH_2), 6.5 (2H, d, J=4 Hz, H_2 and H_6-phenyl), 6.8 (2H, d, J=4 Hz, H_3 and H_5-phenyl), 7.1 (5H, br s, ArH). *Anal.* Calcd for $C_{24}H_{29}N_3O_2$: C, 73.62; H, 7.46; N, 10.73. Found: C, 73.44; H, 7.51; N, 10.65.

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