Tetrahedron Vol. 43, No. 6, pp. 1147 to 1156, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00
Pergamon Journals Ltd.

STEREOCONTROLLED FORMATION OF 1,2-DIHYDROINDOLES

S.J. Veenstra, H.P. Fortgens, R.J. Vijn, B.S. de Jong and W.N. Speckamp*,

Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam (The Netherlands).

(*Received in UK* 11 *February* 1987)

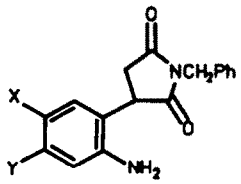
Abstract - Imines 4 cyclize stereoselectively to dihydroindoles 2 upon use of a Li or Na alkoxide-alcohol combination. Depending on the type of alcohol applied either cis (2C) or trans (2T) spiroindolines 2 are formed. In case of imines 4 derived from electron-rich aromatic aldehydes the formation of 2 occurs also thermally. With Lewis acid/catalysis cyclization 4 → 2 proceeds in a less stereoselective manner. The stereochemistry of 2 follows from characteristic ^1H and ^{13}C NMR data.

INTRODUCTION

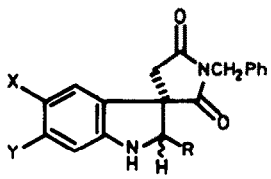
Aiming at the synthesis of indole alkaloids through N-acyliminium ion cyclizations[1] we were looking for a synthesis of compounds of type 2 from aminoaryl imide 1. The route to be developed had to satisfy two major requirements: (i) rather than the indole unit for which a vast array of novel approaches have been reported in the last decade[2] the required structure should contain an indoline skeleton; (ii) the synthetic pathway should lead to the indoline stereochemistry found in the natural products. Our attention was initially focussed on an adaption of the Madelung reaction[3]. It was anticipated that due to the presence of anion-stabilizing carbonyl groups in 1 the harsh experimental conditions of the indole formation possibly could be alleviated in order to arrive at spiroindolenines 3 which upon stereoselective hydrogenation would lead to the desired type of material. Although the latter approach never worked satisfactorily it was discovered that imines of type 4 generally cyclized to dihydroindoles 2[4] upon base or acid catalysis. In case of an electron-rich substituent R in 4 reflux in an inert solvent sufficed to form the indoline 2. The same observation was made for certain aryl substituents X and Y in the starting imine 4[5a,b].

RESULTS AND DISCUSSION

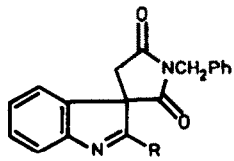
The ring closure of imines 4 to indolines 2 can be viewed upon as a 1,5-electrocyclization[6] the ease of which is primarily governed by the nature of the group R and aromatic substituents X and Y. When 4b is refluxed in xylene for 18 h the isomerically pure cis spiroindoline 2bC is formed in 50% yield no trace of the trans stereoisomer 2bT being detected (Table 1, entry 4). Analogous results were obtained by refluxing imines 4k, 4l and 4m, derived from electron-rich aromatic and heteroaromatic aldehydes and affording 2kC, 2lC and 2mC (Table 1, entries 6-8). In all cases the relative orientation of the imide-carbonyl at C-3 with respect to the C-2 substituent (See Fig. 2) appeared to be cis[7]. Imines of other aromatic aldehydes e.g. 4a and 4d (Table 1, entries 1 and 5) and non-enolizable aliphatic aldehydes failed to cyclize thermally. Imines of enolizable aldehydes upon prolonged heating gave only imine-enamine dimerization products. The influence of the substituents X and Y in the phenyl ring of the imine appears from the results in entries 10-12 (Table 1). Imine 8a quantitatively cyclized after 21 days of reflux in toluene. Interestingly, a 7:3 mixture of the cis and trans stereoisomers 10cC and 10aT was obtained. Similarly, imine 9a



1 X = Y = H
6 X = Cl Y = H
7 X = H Y = OMe

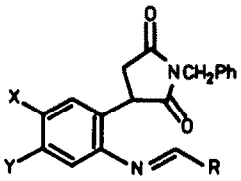


2 X = Y = H
10 X = Cl Y = H
11 X = H Y = OMe

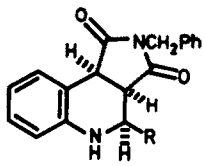


3

a R = C_6H_5
b R = 4-OMe-C_6H_4
c R = 4-NO_2-C_6H_4
d R = 4-CN-C_6H_4
e R = 3-C_5H_4N
f R = (E)-CH=CHC_6H_5
g R = C_3H_7
h R = $C(CH_3)_3$
i R = $CH_2CH_2C{\equiv}CCH_2CH_2OCH_2Ph$
j R = 
k R = 4-NMe_2-C_6H_4
l R = 3-(N-benzyl)-indolyl
m R = 2-pyrrolyl



4 X = Y = H
8 X = Cl Y = H
9 X = H Y = OMe



5

afforded the cyclized product 11aC upon refluxing in toluene (entries 11 and 12) as the sole isomer together with starting imine. These observations point to the existence of a pivotal 1,5-dipole A as intermediate (Fig. 1), since both the formation and the mode of reaction of such an intermediate will be influenced by the nature of R and the aromatic substituents X and Y[5b].

A strong rate-accelerating effect was noted upon addition of a catalytic amount of a tertiary amine to the toluene solution of the phenyl imine 4a; complete conversion (18 h, reflux) to a

Table 1. 2,3-Dihydroindoles 2 from imines 4 by refluxing in inert aromatic solvent

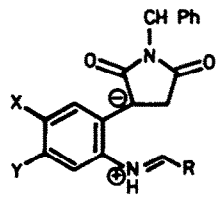
Entry	Imine	Solvent	Time h	Product[a]	Yield %[b]	Starting imine %[b]
1	4a	toluene	168	-	-	100[c]
2	4a	toluene + NEt_3[d]	18	2aC	100[c]	-
3	4b	benzene	504	2bC	17	70
4	4b	xylene	18	2bC	50	25
5	4d	benzene	768	-	-	97
6	4k	benzene	504	2kC	20	-
7	4l	benzene	168	2lC	40	40
8	4m	toluene	96	2mC	59	-
9	4h	toluene + NEt_3[d]	18	-	-	100[c]
10	8a	toluene	504	10aC	70[c]	-
				10aT	30[c]	-
11	9a	toluene	120	11aC	40	60
12	9a	toluene	720	11aC	90	10

[a] C (Cis) and T (Trans) refer to C-2 stereochemistry[4]

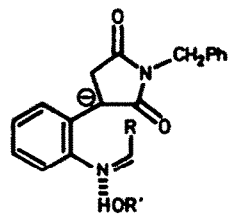
[b] All values refer to isolated yields unless otherwise indicated

[c] Determined from ^1H NMR of the crude reaction mixture

[d] 3-5 equiv. NEt_3 were used.



1,5 - dipole A



(Z)-imine B

Fig. 1

Table 2. Reaction of imines 4 in presence of strong base

Entry	Starting imine	Conditions[a]	Product[c]	Yield[b] %	m.p. °C	Other products
1	4a	D	2aC	71	217-219	-
2	4a	G	2aT	90	158-160	-
3	4a	H	2aT	36		5a (46%)[d] + 2aC (18%)[d]
4	4b	E	2bC	81	219-222	-
5	4b	G	2bT	45	181-183	2bC (5%)[d]
6	4c	E	2cC	62	276-284	-
7	4c	G	2cT	60	190-203	-
8	4d	E	2dC	47	160.5-162	-
9	4e	E	2eC	49	184-186	-
10	4f	D	2fC	80	216-219	-
11	4f	G	2fT	66[e]	155-156	-
12	4f	H	2fT	47		2fC (7%)[d]
13	4g	E	2gC	83	125-126	-
14	4g	G	2gT	21	148.5-149.5	5g (52%)[b]
15	4h	E	2hC	81	159-160	-
16	4h	G	2hT	20[f]	173-174	-
17	4i	D	2iC	55	oil	-
18	4i	H	2iT	73	82-83	5i (5%)[b] + 2iC (7%)[d]
19	4j	D	2jC	60	132-134	-
20	4j	H	2jT	43	115-117	-
21	8a	D	10aC	86	243-246	-
22	8a	G	10aT	59	150-152	10aC (10%)
23	9a	-[g]	11aC	75	202-204	-

[a] D $NaOBu^t/HOBu^t$ 25°C E $NaOBu^t/HOBu^t$/THF 0°C
G NaOEt/HOEt 25°C H NaOMe/DMSO 0°C

[b] All values refer to isolated yields unless otherwise indicated

[c] C (Cis) and T (Trans) refer to C-2 H stereochemistry

[d] Determined from ^1H NMR of the crude reaction mixture

[e] Corrected for recovered imine

[f] Not optimized

[g] See experimental.

single stereoisomer 2aC was observed (Table 1, entry 2). The ring closure was also expedited by a catalytic amount of strong base. Upon use of EtOH/EtONa a single stereoisomer 2aT was formed which, however, possessed the undesired trans stereochemistry. Quite unexpectedly, a dramatic solvent effect was noted upon use of Bu^tOH/Bu^tOM (M=Li or Na), which afforded the cis stereoisomer 2aC. The decisive role of the structure of the base on the stereochemistry of the imine cyclization was verified for a number of other imines as shown in Table 2. The cyclization could also be induced by other bases, which, in general, gave less stereoselective results (e.g. $NaOCH_3$/DMSO: entries 3, 12, 18 and 20, Table 2). Sometimes, byproducts of the tetrahydroquinoline type 5 were formed also (entries 3, 14 and 18).

From the results of Table 2 it can be inferred that imines 4, 8 and 9 derived from both aromatic and aliphatic aldehydes under the influence of strong base consistently give rise to the following cyclization pattern. In EtOH and DMSO as solvents indolines 2T are formed possessing the - unnatural - trans stereochemistry. In Bu^tOH as solvent the opposite stereochemical result is obtained affording the desired cis products. Neither steric crowding in the imine (entry 15), nor the presence of functional groups (entries 17-20) interfere with this generally observed trend.

In order to assess the importance of the structure of the alcoholic solvent molecule as well as its relative proportion needed for complete conversion of starting imine into cis cyclization product 2C a number of secondary and tertiary alcohols were investigated (Table 3). From the results of entries 1-4 the effect of the amount of Bu^tOH on the C/T ratio is apparent. That LDA is less satisfactory as a base (entries 1-3) as compared to BuLi (entry 4) is due to a - independently controlled - detrimental effect of a secondary amine on the yield of cyclization. Various structurally different alcohols gave satisfactory yields (Table 3, entries 8-12). In presence of at least 3.0 eq of alcohol yields of 60-80% of the cis products were obtained.

Table 3. Effect of alcohol R'OH on stereochemistry of 1,5-electrocyclization

Entry	Imine	Equiv. of R'OH[a]	Equiv. of base[b]	Time[b] h	Product	Yield[c] %
1	4h	-	1.0 LDA	3	2hC (1)	20
		-			+2hT (25	
2	4h	1.5 B	1.0 LDA	3	2hC(1) + 2hT (1)	30
3	4h	3.0 B	1.0 LDA	3	2hC (2) + 2hT (1)	30
4	4h	3.0 B	1.0 BuLi	3	2hC (7) + 2hT (1)	80
5	4h	1.0 M	0.8 BuLi	3	2hC	20
6	4h	3.0 BOR	0.5 BuLi	3	2hC	73
7	4h	3.0 C	0.9 BuLi	2.5	2hC (1) + 2hT (2)	72
8	4g	3.0 M	1.0 BuLi	0.25	2gC	40
9	4g	15.0 M	1.0 BuLi	0.5	2gC	82
10	4g	3.0 BOR	0.5 BuLi	0.25	2gC	70
11	4g	4.0 C	1.2 BuLi	4	2gC	70
12	4g	2.5 V	1.4 BuLi	0.5	2gC	60
13	4g	3.0 O	1.0 BuLi	0.5	2gC	67
14	4a	3.2 M	1.2 BuLi	d	2aC	64

a B: t-Butanol; M: (1R)-(-)Menthol; BOR: (2R)-(-)Borneol;
C: (1R)-(+)Cedrol; V: (2S)-(+)Viridoflorol; O: (2R)-(-)Octanol

b Addition of base and alcohol to imine in THF at -78°C mixture allowed to warm to 0°C and stirred for the time indicated. Work-up by quenching with H_2O (see experimental part, procedure F)

c Determined after purification. Accuracy ± 5%

d After addition at -78°C the mixture was allowed to warm to -40°C and then quenched with H_2O.

An excess amount of 15.0 eq - entry 9 - gave the best result. Interestingly, upon reaction of the imine 4h derived from pivaldehyde in the presence of cedrol, the selectivity of the reaction was lost (entry 7). This result markedly contrasts with the high stereoselection observed with Bu^tOH (entry 15, Table 2) and supports the earlier given rationale[5b] of a solvent-association complex B (Fig. 1) playing a role in the imine (E) → (Z)isomerization. A relatively simple secondary alcohol, 2-octanol, also afforded acceptable yields of cis product (entry 13). The imine of an aromatic aldehyde e.g. 4a reacted analogously (entry 14). The enantioselectivity of the cyclization reaction resulting from the use of an optically active alcohol, can be very high in certain cases. This has been described elsewhere[15,16].

Upon refluxing 4a in toluene in the presence of one eq of $Zn(OAc)_2$ ring closure also took place albeit in a less stereoselective manner. In addition to 46% of 2aC and 16% of 2aT also 8% of 3a was formed while 8% of 4a was recovered. Other Lewis catalysts effected similar outcomes except for the amount of oxidized product 3a which was 40% upon use of $FeCl_3$ and 35% with $Pd(OAc)_2$. Protic acids also catalyzed the cyclization; for instance, both HOAc and CF_3COOH gave rise to the formation of 2aC from 4a in addition to considerable amounts of 3a. The latter material was formed by air oxidation of 2aC under acid catalysis which was controlled independently. A CF_3COOH solution of 2aC in toluene afforded 70% of 3a after heating to 80°C for one hour. Hydrogenation (Pd/C-H_2) of 3a gave a 85:15 mixture of 2aC and 2aT.

Structure determination of cis and trans isomers of spirocyclic product 2 was accomplished by ^1H- and ^{13}C NMR analysis. In Table 4 a survey of the parameters is given in which $\delta H_{AB}=\frac{1}{2}(\delta H_{4',A}+\delta H_{4',B})$ and $\Delta H_{AB}=\delta H_{4',A}-\delta H_{4',B}$. Characteristic differences are found for δH_{AB} (aromatic series 2a-2c), ΔH_{AB} (aliphatic series 2f-2j), δH_2 (all compounds) and δC-2 values (all compounds). The observed trends most likely follow from anisotropy effects in the preferred conformation of the trans isomer as indicated in Fig. 2. The most notable features are (i) the proximity of the C-2' carbonyl to H-2 and (ii) the position of the C-4' H_AH_B with respect to the C-2 substituent.

Table 4. ^1H NMR and ^{13}C NMR parameters of indolines 2

Compound[a]	δH_{AB} C[c]	δH_{AB} T[c]	ΔH_{AB} C	ΔH_{AB} T	δH_2 C	δH_2 T	$\delta C\text{-}2^b$ C	$\delta C\text{-}2^b$ T
2a	3.17; 2.43		0.27; 0.23		5.07; 5.47		74.9; 69.0	
2b	3.08; 2.48		0.26; 0.18		4.91; 5.48		n.d.	
2c	3.47; 2.40		0 ; 0		5.26; 5.55		n.d.	
2f	3.03; 2.88		0.32; 0.66		4.48; 4.91		n.d.	
2g	2.93; 2.82		0.47; 0.68		3.85; 4.28		70.4; 64.4	
2h	3.04; 3.02		0.25; 0.98		3.65; 4.28		n.d.	
2i	2.92; 2.78		0.34; 0.64		4.01; 4.33		68.4; 63.7	
2j	2.92; 2.81		0.34; 0.70		3.97; 4.50		65.1; 59.8	

[a] Determined in $CDCl_3$ except for 2c (DMSO)

[b] ^{13}C NMR values

[c] C and T denote cis and trans series.

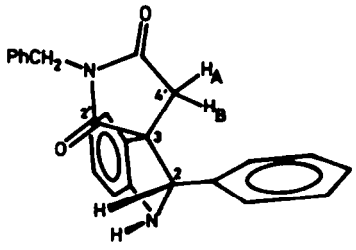


Fig. 2 Stereochemistry of 2aT

In conclusion the 1,5-electrocyclization of C-substituted o-aminoaryl succinimides is a versatile pathway for arriving at spiro-dihydroindoles in a highly stereocontrolled fashion. Further results in the synthesis of indoles and applications of the method in the total synthesis of alkaloids will be reported in due course.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer. The absorptions are given in cm^{-1} and all spectra are taken in $CHCl_3$. PMR spectra were run on a Varian Associates Model A-60-D and XL-100 or Bruker WM 250 instruments, using TMS as an internal standard. Mass spectra were obtained with a Varian Mat-711 spectrometer.

Thermal cyclizations. Procedures A, B and C.

The imine (0.1 mmol) was refluxed in 5 ml of an aromatic solvent for the time indicated. After evaporation of the solvent the residue was crystallized from ethanol (procedure A).
In presence of triethylamine the work-up was similar (procedure B).
In presence of 1-3 eq of acid the solution was washed with Na_2CO_3 aq and water, dried upon $MgSO_4$ and evaporated (procedure C).

General methods for spirocyclization of imines 4 with base

Procedure D: About 15 mg (0.6 mmol) clean sodium chips were added to 10 ml freshly distilled t-BuOH (from CaO) in a three-necked flask of 50 ml equipped with a reflux condenser under dry nitrogen atmosphere. The mixture was stirred magnetically and refluxed for several hours till the sodium was dissolved. The solution was cooled to 25-30°C and a toluene solution of 1 mmol of the appropriate imine was added at once and the mixture was stirred for 15 minutes. The reactions were monitored on TLC (silicagel with an appropriate EtOAc/LP 60-80 mixture as eluent). Too long reaction times led to decreasing yields of cyclization products. The reaction mixture was poured into 100 ml of water and extracted twice with $CHCl_3$. Drying with Na_2SO_4 and evaporation of the solvent under reduced pressure furnished the crude reaction products.

Procedure E: About 15 mg clean sodium chips were dissolved in 10 ml of freshly distilled t-BuOH as in procedure D. 10 ml of THF (distilled from $LiAlH_4$) was added and the flask was cooled in an ice bath to 0°C. A toluene solution of the imine (1 mmol) was added at once. Reaction time and work-up see procedure D.

Procedure F: To 30 eq of alcohol in 10 ml of THF at -78°C 1.0 eq of BuLi in hexane was added. After warming to 0°C 1.0 mmol of imine in 1 ml of toluene was added at once and the mixture stirred for the time indicated in table III. Work-up as under D.

Procedure G: 9 mg (0.4 mmol) of clean sodium chips were dissolved in 10 ml of dry EtOH (distilled from magnesium) in a round bottomed flask of 50 ml under N_2. The solution was stirred magnetically. A toluene solution of 1 mmol of the imine was added at once. After 10 minutes the reaction mixture was poured into 100 ml of water. Chloroform extraction (two times) and work-up afforded the crude reaction products.

Procedure H: 9 mg (0.4 mmol) of clean sodium chips were dissolved in 0.5 ml dry MeOH in a three-necked flask of 50 ml under N_2. The methanol was evaporated at 0.1 mm Hg, while the flask was heated to 100°C. After cooling 10 ml of dry DMSO (distilled from CaH_2) and stored over mol sieves 4Å) was added to the dry NaOMe. The mixture was stirred magnetically and a toluene solution of 1 mmol of the imine was added at once. After 10 minutes the reaction was quenched with 100 ml of water. Extraction with diethyl ether (two times) and work-up afforded the crude reaction products.

N-benzyl-3(o-amino)phenyl pyrrolidine-2,5-dione 1:

10 g (45.5 mmol) of 3(o-nitro)phenyl-pyrrolidine-2,5-dione[8] and 30 g (210 mmol) of anhydrous K_2CO_3 were suspended in 200 ml of acetone. The mixture was vigorously stirred and 8.55 g (50 mmol) of benzylbromide was added at once. The reaction was monitored on TLC (silicagel/EtOAc/LP 60-80). When all the starting material was converted, 500 ml of water was added. The mixture was extracted six times with 30 ml portions of $CHCl_3$. The combined organic layers were washed with water and dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residual solid was recrystallized from acetone/EtOH.
Yield: 14.1 g (4.55 mmol, 85%) white crystals. M.p. 147-148°C (EtOH). IR(KBr): 1775 and 1705 cm^{-1} (C=O, imide), 1520 cm^{-1} (NO_2). ^1H NMR δ($CDCl_3$): 8.05 (m, 1H), 7.65-7.10 (m, 8H), 4.74 (s, 2H, CH_2Ph), 4.43 (d of d, J=6 and 8 Hz, CHAr), 3.5-2.5 (m, 2H, CH_2CHAr, ABX).

10 g (32.3 mmol) of the N-benzyl imide was suspended in 150 ml of toluene containing 1 ml of EtOH. 300 Mg of the catalyst (10% palladium on charcoal) was added and the mixture hydrogenated for 18 hr at 1 atm. The catalyst was filtered off over high-flow. Eventually crystallized material was taken up in CH_2Cl_2 and also filtered over high-flow. The toluene/CH_2Cl_2 solution of 1 was concentrated under reduced pressure to about 50 ml, which was triturated with light petroleum b.p. 60-80°C. 1 Crystallized almost immediately.
Yield: 8.123 g (29.0 mmol) of 1. M.p. 110-113°C. By concentrating the mother liquor another batch of 0.632 g (2.26 mmol) of 1 was obtained, m.p. 105-111°C, sufficiently pure for further use. Total yield 97%. Recrystallization from EtOH afforded an analytical pure sample; m.p. 112-114°C. IR(KBr): 3390 and 3330 cm^{-1} (NH_2), 1760 and 1685 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.4-6.7 (m, 9H), 4.67 (s, 2H, CH_2Ph), 4.21 (d of d, J=6 and 8 Hz, CHAr), 3.91 (br 1H, NH), 3.05 (m, 2H, CH_2-CHAr, ABX). Found: C, 72.8; H, 5.8; N, 9.9; $C_{17}H_{16}N_2O_2$ requires: C, 72.84; N, 5.75; N, 9.99.

Cis-2-phenyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2aC:

280 mg (1 mmol) of amine 1 and 117 mg (1.1 mmol) of benzaldehyde were refluxed in toluene (10 ml) for one hour. The crude reaction product was crystallized from EtOH. M.p. 4a 94-97°C.
368 mg (1 mmol) of imine 4a was dissolved in 5 ml of toluene and cyclized with NaOtBu according to procedure D. Yield: 261 mg (0.71 mmol, 71%) of 2aC as colorless white needles. M.p. 217-219°C (i-PrOH). IR(KBr): 3320 cm^{-1} (NH), 1770 and 1700 cm^{-1} (C=O, imide). ^1H NMR δ(CD_2Cl_2): 7.54-6.68 (m, 14H), 5.07 (s, 1H, CHPh), 4.27 (s, 3H, CH_2Ph and NH), 3.31 (d, 1H, J=18 Hz, C-4'H_a), 3.04 (d, 1H, J=18 Hz, C-4'H_b). C-NMR δ(CD_2Cl_2): 178.7 (C=O), 174.7 (C=O), 74.9 (C-2), 58.5 (C-3), 42.4 (CH_2Ph), 4.16 (C-4'). Found: C, 78.2; H, 5.5; N, 7.6; $C_{24}H_{20}N_2O_2$ requires: C, 78.24, H, 5.47, N, 7.60.

Trans-2-phenyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2aT

200 mg (0.54 mmol) of imine 4a was dissolved in 2 ml of dry toluene and added to a stirred solution of NaOEt in EtOH (procedure G). Work-up afforded 180 mg (0.49 mmol, 90%) of 2aT as white crystals. M.p. 158-160°C (EtOH). IR(KBr): 3320 cm^{-1} (NH), 1760 and 1690 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.4-7.0 (m, 1H), 6.73 (m, 3H), 5.47 (d, 1H, J=3 Hz, NCH), 4.71 (br s, 2H, CH_2Ph), 4.14 (d, 1H, NH, J=3 Hz), 2.55 (d, 1H, J=18.5 Hz, C-4'H_a), 2.32 (d, 1H, J=18.5 Hz, C-4'H_b). ^{13}C NMR δ($CDCl_3$): 178.9 (s, C=O), 174.4 (s, C=O), 69.0 (d, C-2), 58.0 (s, C-3), 42.7 (t, CH_2Ph), 39.0 (t, C-4'). Found: C, 78.2; H, 5.5; N, 7.7; $C_{24}H_{20}N_2O_2$ requires: C, 78.24; H, 5.47; N, 7.60.

Cis-2(4-methoxy)phenyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2bC

A toluene solution (5 ml) of the imine 4b (200 mg, 0.5 mmol) was added at once to a solution of NaOtBu in t-BuOH/THF (procedure E). Work-up and crystallization from EtOH afforded 162 mg (0.41 mmol, 81%) of 2bC as white crystals. M.p. 219-222°C. IR(KBr): 3340 cm^{-1} (NH), 1770 and 1700 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.77 (d, 2H, J=9 Hz, pOMeAr), 6.94 (d, 2H, J=9 Hz, pOMeAr), 7.43-6.55 (m, 9H), 4.91 (s, NCHAr), 4.28 (s, 2H, CH_2Ph), 4.13 (br, 1H, NH), 3.72 (s, 3H, OCH_3), 3.23 (d, 1H, J=19 Hz, C-4'H_a), 2.93 (d, 1H, J=19 Hz, C-4'H). Found: C, 75.3; H, 5.6; N, 7.0; $C_{25}H_{22}N_2O_3$ requires: C, 75.35; H, 5.57; N, 7.03.

Trans-2(4-methoxy)phenyl-2,3-dihydro-indole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2bT

A toluene solution (2 ml) of imine 4b (200 mg, 0.50 mmol) was added at once to a solution of 3.0 mmol of NaOEt in 10 ml of EtOH (procedure G). Work-up afforded 110 mg (0.28 mmol, 55%) of compound 2bT with 10% contamination of the cis isomer 2bC as an oil. Repeated crystallization from MeOH furnished the pure trans isomer 2bT. M.p. 181-183°C. Found: C, 75.3, H, 5.6; $C_{25}H_{22}N_2O_3$ requires: C, 75.35; H, 5.57.

Cis-2(o-nitro)phenyl-2,3-dihydro-indole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2cC

Imine 4c was prepared from 280 mg (1.0 mmol) amine 1 and 166 mg (1.1 mmol) p-nitrobenzaldehyde. The crude imine 4c was cyclized according to procedure E. Work-up and crystallization of the crude reaction product from EtOH afforded 247 mg (0.62 mmol, 62%) of 2cC as a yellow crystalline compound, M.p. 276-284°C (subl.). IR(KBr): 3380 cm^{-1} (NH), 1770 and 1700 cm^{-1} (C=O, imide), 1520 cm^{-1} (NO_2). ^1H NMR δ(DMSO-d_6): 7.97 (d, 2H, J=8 Hz, pNO_2Ar), 7.70 (d, 2H, J=8 Hz, pNO_2Ar), 7.3-6.15 (m, 9H), 6.30 (d, 1H, J=3 Hz, NH), 5.26 (d, 1H, J=3 Hz, NCHAr), 4.20 (br s, 2H, CH_2Ph), 3.47 (s, 2H, CH_2CO). Found: C, 69.3; H, 4.8; N, 9.9; $C_{24}H_{19}N_3O_4$ requires: C, 69.72; H, 4.63; N, 10.16.

Trans-2(4-nitro)phenyl-2,3-dihydro-indole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2cT

100 mg (0.25 mmol) of imine 4c was dissolved in 1 ml of toluene and spiro cyclized according to procedure C. Work-up afforded 60 mg (0.15 mmol, 60%) of 2cT as a yellow crystalline compound. M.p. 190-203 (dec)°C (EtOH). IR($CHCl_3$): 3400 cm^{-1} (NH), 1775 and 1705 cm^{-1} (C=O, imide), 1520 cm^{-1} ($-NO_2$). ^1H NMR δ($CDCl_3$): 8.0 (d, 2H, J=9 Hz, pNO_2Ar), 7.35 (s, 5H), 7.32 (d, 2H, J=9 Hz, pNO_2Ar), 7.3-7.0 (m, 1H), 6.75 (m, 3H), 5.55 (d, 1H, J=3 Hz, NCH), 4.73 (s, 2H, CH_2Ph), 4.27 (br, 1H, NH), 2.40 (s, 2H, $-CH_2CO$). Found: C, 69.9; H, 4.7; N, 10.0; $C_{24}H_{19}N_3O_4$ requires: C, 69.72; H, 4.63; N, 10.16.

Cis-2(4-cyano)phenyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2dC

The imine 4d was prepared from 280 mg (1.0 mmol) amine 1 and 144 mg (1.1 mmol) p-cyanobenzaldehyde. The crude imine 4d was cyclized according to procedure E. Work-up and crystallization of the reaction mixture from EtOH afforded 185 mg (0.47 mmol, 47%) of 2dc as a white crystalline compound. M.p. 160.5-162°C. IR(KBr): 3400 cm^{-1} (NH), 2220 cm^{-1} (CN), 1780 and 1700 cm^{-1} (C=O, imide). ^1H NMR δ(pyridine-d_5): 7.79 (d, 2H, J=8 Hz, pCN), 7.42 (d, 2H, J=8 Hz, pONAr), 7.21 (s, 5H), 7.3-6.75 (m, 5H, 4 indole H and NH), 5.32 (d, 1H, J=3 Hz, NCH), 4.41 (br s, 2H, CH_2Ph), 3.67 (d, 1H, J=19 Hz, C-4'H_a), 3.45 (d, 1H, J=19 Hz, C-4'H_b). Found: C, 75.8; H, 5.0; N, 10.5; $C_{25}H_{19}N_3O_2$ requires: C, 76.32; H, 4.87; N, 10.68.

Cis-2(3-pyridyl)2,3-dihydro-indole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2eC

Imine 4e was prepared from 280 mg (1.0 mmol) of amine 1 and 103 mg (1.1 mmol) of pyridine-3-carboxaldehyde. A toluene solution of the crude imine was added at once to a solution of NaOtBu in t-BuOH/THF (procedure E). Work-up and crystallization of the crude product from EtOH afforded 180 mg (0.49 mmol, 49%) of 2eC. M.p. 184-186°C. IR(KBr): 3380 cm^{-1} (NH), 1770 and 1700 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.3-6.8 (m, 10H), 5.06 (s, 1H, NCH), 4.38 (s, 2H, CH_2Ph), 4.32 (br, 1H, NH_2), 3.34 (d, 1H, J=18.5 Hz, C-4'H_a), 3.04 (d, 1H, J=18.5 Hz, C-4'H_b). Found: C, 74.6; H, 5.2; N, 11.4; $C_{23}H_{29}N_3O_2$ requires: C, 74.78; H, 5.18; N, 11.38.

Cis-2-styryl-2,3-dihydro-indole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2fC

200 mg (0.51 mmol) of imine 3r was spiro cyclized according to procedure D. Work-up and crystallization of the crude reaction product gave 160 mg (0.41 mmol, 80%) of compound 2fc as white crystals M.p. 216-219°C (EtOH). IR(KBr): 3400 and 3330 cm^{-1} (NH), 1765 and 1690 cm^{-1} (C=O, imide). ^1H NMR δ(CD_2Cl_2): 7.29 (s, 5H), 7.3-6.7 (m, 9H), 6.78 and 6.62 (d, 1H, J=16 Hz, =CHPh), 6.41, 6.33, 6.25 and 6.17 (d of d, 1H, J=8 and 16 Hz, CH=CHPh), 4.59 (s, 2H, CH_2Ph), 4.48 (d, 1H, J=8 Hz, H-2), 4.14 (br, 1H, NH), 3.19 (d, 1H, J=18.5 Hz, C-4'H_a), 2.87 (d, 1H, J=18.5 Hz, C-4'H_b).

Trans-2-styryl-2,3-dihydro-indole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2fT

100 mg (0.254 mmol) of imine 4f was spiro cyclized according to procedure G. Work-up and column chromatography of the crude reaction product afforded two fractions: compound 2fT (38 mg) and imine 4f (42 mg). M.p. 155-156°C (EtOH). IR($CHCl_3$): 3400 cm^{-1} (NH), 1770 and 1700 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.5-7.0 (m, 11H), 6.74 (m, 3H), 6.64 (d, 1H, J=16 Hz, C=CHPh), 4.91 (d, 1H, J=6.5 Hz, H-2), 4.75 (s, 2H, CH_2Ph), 4.04 (br, 1H, NH), 3.21 (d, 1H, J=18.5 Hz, C-4'H_a), 2.55 (d, 1H, J=18.5 Hz, C-4'H_b). Found: C, 79.2; H, 5.7; N, 7.0; $C_{26}H_{22}N_2O_2$ requires: C, 79.17; H, 5.62; N, 7.10.

Cis-2-propyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2'-5'-dione 2gC

The imine 4g was prepared from 560 mg (2.0 mmol) amine 1 and 500 mg (6.9 mmol) of butyraldehyde. 335 mg (1.0 mmol) of imine 4g was dissolved in 2 ml of toluene and treated with NaOtBu according to procedure E. Work-up and crystallization of the crude reaction product from EtOAc/hexane furnished 278 mg (0.83 mmol, 83%) of 2gC as white needles. M.p. 125-126°C. IR(KBr): 3440 and 3340 cm^{-1} (NH), 1770 and 1695 cm^{-1} (C=O imide). ^1H NMR δ($CDCl_3$): 7.45-6.65 (m, 9H), 4.70 (d, 1H, J=14 Hz, CH_aH_bPh), 4.61 (d, 1H, J=14 Hz, CH_aH_bPh), 4.03-3.67 (m, 2H, NH and H-2), 3.17 (d, 1H, J=19 Hz, C-4'H_a), 2.70 (d, 1H, J=19 Hz, C-4'H_b), 1.7-1.1 (m, 4H, CH_2CH_2), 0.79 (t, 3H, CH_3). ^{13}C NMR δ($CDCl_3$): 176.0 (C=O), 174.7 (C=O), 70.0 (d, C-2), 55.7 (s, C-3), 42.4 (t, CH_2Ph), 41.6 (t, C-4'), 32.1, 20.5 and 13.9 (t, t and q, $CH_2CH_2CH_3$). Found: C, 75.4; H, 6.6; N, 8.4; $C_{21}H_{22}N_2O_2$ requires: C, 75.42; H, 6.63; N, 8.38.

Cyclization of imine 4g with NaOEt

335 mg (10 mmol) of imine 4g was dissolved in 2 ml of dry toluene and added at once to a stirred solution of NaOEt in EtOH (procedure G). Work-up and column chromatography of the crude reaction product on silicagel afforded two fractions:

2-Benzyl-3a,4,5,9b-tetrahydro-4-propyl-1H-pyrrolo[3,4-c]quinoline-1,3(2H)-dione 5g

Fraction I: 174 mg (0.52 mmol) of compound 5g as a solidifying oil. M.p. 119-120°C (CCl_4, hexane). IR($CHCl_3$): 3420 cm^{-1} (NH), 1770 and 1700 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.6-6.9 (m, 9H), 4.64 (s, 2H, CH_2Ph), 3.91 (d, 1H, J=9 Hz, H-4), 3.62 (t of d, 1H, J=7.7 and 3.5 Hz, H-2), 3.7-3.5 (br, 1H, NH), 3.09 (d of d, J=9 and 3.5 Hz, H-3), 1.7-1.1 (m, 4H, CH_2CH_2), 0.90 (m, 3H, CH_3). ^{13}C NMR δ($CDCl_3$): 177.5 (C=O), 176.3 (C=O), 50.2 (d, C-2), 46.8 (d, C-4), 42.4 (t, CH_2Ph), 40.3 (d, C-3), 34.6 (19.0 and 13.7 (t, t and q, $CH_2CH_2CH_3$). MS: m/z 334 (M^+). Found: C, 75.5; H, 6.6; N, 8.4; $C_{21}H_{22}N_2O_2$ requires: C, 75.42; H, 6.63; N, 8.38.

Trans-2-propyl-2,3-dihydroindole-3-spiro-3'(N'-benzyl)pyrrolidine-2',5'-dione 2gT

Fraction II: 70 mg (0.21 mmol, 21%) of compound 5i as a solidifying oil. M.p. 148.5-149.5°C (EtOAc, hexane). IR(KBr): 3430 and 3320 cm^{-1} (NH), 1765 and 1685 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.5-7.2 (m, 5H), 7.15-7.0 (m, 1H), 6.73-6.58 (m, 3H), 4.79 (s, 2H, CH_2Ph), 4.28 (d of d, 1H, J=5 and 7 Hz, H-2), 4.02 (br, 1H, NH), 3.16 (d, 1H, J=18.5 Hz, C-4'H_a), 2.48 (d, 1H, J=18.5 Hz, C-4'-

H_b), 1.7-1.0 (m, 4H, CH_2CH_2-), 0.89 (m, 3H, CH_3). ^{13}C NMR δ($CDCl_3$): 84.4 (d, C-2), 58.2 (s, C-3), 42.9 (t, CH_2Ph), 37.8 (t, C-4'), 33.3 (t), 19.8 (t) and 14.0 (q). MS: m/z 334 (M^+). Found: C, 75.3; H, 6.6; N, 8.4; $C_{21}H_{22}N_2O_2$ requires: C, 75.42; H, 6.63; N, 8.38.

Cis-2-t-butyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2hC

280 mg (1.0 mmol) of amine 1 and 190 mg (2.2 mmol) of pivaldehyde were refluxed for 3 hr in toluene and afforded 4h in quantitative yield.
200 mg of 4h (0.57 mmol) were dissolved in 1 ml of toluene and added at once to a solution of NaOtBu in t-BuOH/THF (procedure E). The reaction was stirred for 3 hr at 0°C. Work-up and crystallization of the crude reaction product from EtOH/hexane furnished 166 mg (0.48 mmol, 83%) of compound 2hC as white crystals. M.p. 159-160°C. IR($CHCl_3$): 3350 cm^{-1} (NH), 1770 and 1700 cm^{-1} (C=O, imide). ^{1}H NMR δ($CDCl_3$): 7.4 (m, 2H), 7.28 (m, 3H), 7.12 (t, 1H, J=8 Hz), 6.76 (m, 3H), 4.77 (d, 1H, J=14 Hz, CH_aH_bPh), 4.60 (d, 1H, J=14 Hz, CH_aH_bPh), 3.92 (br, 1H, NH), 3.65 (s, 1H, H-2), 3.17 (d, 1H, J=19 Hz, C-4'H_a), 2.92 (d, 1H, J=19 Hz, C-4'H_b), 0.87 (s, 9H, t-Bu). Found: C, 75.9; H, 7.1; N, 7.8; $C_{22}H_{24}N_2O_2$ requires: C, 75.83; H, 6.94; N, 8.04.

Trans-2-t-butyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2hT

200 mg (0.57 mmol) of imine 4h was cyclized according to procedure G. Work-up afforded 100 mg of an oil which was purified via column chromatography. Yield 40 mg (0.11 mmol, 20%) of compound 2hT. M.P. 173-174°C (EtOAc/i-propylether). IR($CHCl_3$): 7.5-6.5 (m, 9H), 4.80 (s, 2H, CH_2Ph), 4.28 (s, 1H, H-2), 4.1-3.8 (br, 1H, NH) 3.51 (d, 1H, J=18 Hz, C-4'H_a), 2.53 (d, 1H, J=18 Hz, C-4'H_b), 1.02 (s, 9H, t-Bu). Found: C, 75.9; H, 7.0; N, 8.2; $C_{22}H_{24}N_2O_2$ requires: C, 75.83; H, 6.94; N, 8.04.

Trans-2(6-benzyloxy)hex-3-ynyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2iT

200 mg (0.42 mmol) of imine 4i[9] was dissolved in 1 ml of toluene and added to a stirred suspension of NaOMe in dry DMSO under N_2 according to procedure H. Work-up and column chromatography of the crude reaction product afforded two fractions:
I : 10 mg (0.01 mmol, 5%) of compound 5i as an oil.
II: 146 mg (0.31 mmol, 73%) of compound 2iT as an air sensitive oil, which was contaminated with the cis product 2iC for 7%. Crystallization of the product from MeOH furnished the pure trans isomer 2iT. M.p. 82-83°C. IR(KBr): 3325 cm^{-1} (NH), 1770 and 1690 cm^{-1} (C=O, imide). ^{1}H NMR δ($CDCl_3$): 7.28 (m, 10H), 7.01 (m, 1H), 6.57 (m, 3H), 4.71 (s, 2H, NCH_2Ph), 4.50 (s, 2H, OCH_2Ph), 4.33 (m, 2H, NH and H-2), 3.52 (t, 2H, OCH_2), 3.10 (d, 1H, J=18.5 Hz, C-4'H_a), 2.46 (d, 1H, J=18.5 Hz, C-4'H_b), 2.53-2.12 (m, 4H, $CH_2C{\equiv}CCH_2$)-1.88-1.46 (m, 2H). ^{13}C-NMR δ($CDCl_3$): 178.6 (C=O), 174.7 (C=O), 79.4 and 78.6 (C≡C), 72.7 (OCH_2Ph), 68.5 (OCH_2), 63.7 (C-2), 56.5 (C-3), 42.7 (NCH_2Ph), 38.0 (C-4'), 30.2, 20.1 and 16.5. Found: C, 77.8; H, 6.3; N, 5.8; $C_{31}H_{30}N_2O_3$ requires: C, 77.80; H, 6.32; N, 5.85.

Cis-2(6-benzyloxy)hex-3-ynyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2'5'-dione 2iC

The imine 4i[9] was prepared from 560 mg (2.0 mmol) of amine 1 and 480 mg (2.2 mmol) of aldehyde 12[10]. Spirocyclization was carried out with NaOtBu as base according to procedure D. Work-up and column chromatography over silica gel afforded 308 mg (0.64 mmol) of compound 2iC as an air sensitive oil. IR($CHCl_3$): 3400 cm^{-1} (NH), 1770 and 1700 cm^{-1} (C=O, imide). ^{1}H NMR δ($CDCl_3$): 7.43-7.00 (m, 1H), 6.72 (m, 3H), 4.67 (d, 1H, J=14 Hz, NCH_aH_bPh), 4.59 (d, 1H, J=14 Hz, NCH_aH_bPh), 4.49 (s, 2H, OCH_2Ph), 4.01 (d of d, 1H, J=4 and 9 Hz, H-2), 4.2-3.7 (br, 1H, NH), 3.50 (t, 2H, OCH_2), 3.09 (d, 1H, J=18.5 Hz, C-4'H), 2.75 (d, 1H, J=18.5 Hz, C-4'H), 2.41 (m, 2H, CH_2CH_2O-), 2.19 (m, 2H, $NCHCH_2CH_2$), 2.00-1.40 (m, 2H, $NCHCH_2CH_2$). ^{13}C NMR δ($CDCl_3$): 176.1 (C=O, 174.8 (C=O), 79.3 and 78.9 (C-C), 72.9 (OCH_2Ph), 68.6 (OCH_2), 68.4 (C-2), 55.7 (C-3), 42.5 (CH_2Ph), 41.6 (C-4'), 28.7, 20.2 and 16.7.

Cis-2(2,2-ethylenedioxy)propyl-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2jC

The imine 4j[11] was prepared according to procedure A from 560 mg (20 mmol) of amine 1 and 290 mg (2.2 mmol) of 3,3-ethylenedioxy butanal 13. Spiro cyclization was carried out with NaOtBu according to procedure D. Work-up and column chromatography on silica gel afforded 470 mg (2.55 mmol), 60%) of compound 2jC as a solidifying oil. M.p. 132-134°C (EtOAc, i-propyl ether). IR(KBr): 3380 cm^{-1} (NH), 1765 and 1690 cm^{-1} (C=O, imide). ^{1}H NMR δ($CDCl_3$): 7.45-6.58 (m, 8H), 4.69 (d, 1H, J=14 Hz, CH_aH_bPh), 4.61 (d, 1H, J=14 Hz, CH_aH_bPh), 3.97 (m, 1H, H-2), 3.88 (m, 4H, OCH_2CH_2O), 3.09 (d, 1H, J=18.5 Hz, C-4'H_a), 2.75 (d, 1H, J=18.5 Hz, C-4'H_b), 2.22-1.65 (m, 2H, ABX, $NCHCH_2$), 1.21 (s, 3H, CH_3). ^{13}C NMR δ($CDCl_3$): 176.1 (s, C=O), 174.9 (C=O), 108.8 (s, O-C-O), 65.1 (d, C-2), 64.4 (t, 2C, OCH_2CH_2O, 42.4 (t, CH_2Ph), 41.7 (t, C-4'), 38.8 (t, C-8), 24.0 (q, CH_3). Found: C, 70.4; H, 6.1; N, 7.6; $C_{23}H_{24}N_2O_4$ requires: C, 70.41; H, 6.12; N, 7.14.

Cis-2(4-dimethylamino)phenyl-2,3-dihydro-indole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2kC

280 mg (1.0 mmol) of amine 1 and 1.64 mg (1.1 mmol) of p-dimethylamino benzaldehyde were refluxed in benzene for 21 days. Evaporation of the solvent under reduced pressure and crystallization of the reaction mixture from EtOH furnished 82 mg (0.20 mmol, 20%) of spiro imide 2kC. M.p. 203-204°C (EtOH). IR(KBr): 3340 cm^{-1} (NH), 1770 and 1700 cm^{-1} (C=O, imide). ^{1}H NMR δ($CDCl_3$): 7.33 (d, 2H, J=9 Hz, pNMe_2Ar), 7.3-6.8 (m, 9H), 6.58 (d, 2H, J=9 Hz, pNMe_2Ar), 4.94 (br, NCHAr), 4.35 (br s, 2H, CH_2Ph), 4.1 (br, 1H, NH), 3.26 (d, 1H, J=18 Hz, C-4'H_a), 2.96 (d, 1H, J=18 Hz, C-4'H_b), 2.97 (s, 6H, $N(CH_3)_2$). Found: C, 75.8; H, 6.2; N, 10.0; $C_{26}H_{25}N_3O_2$ requires: C, 75.89; H, 6.12; N, 10.21.

Cis-2[3-N-benzyl)indole]2,3-dihydro-indole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2lC

280 mg (1 mmol) of amine 1 and 235 mg (1 mmol) of N-benzyl-indole-3-carboxaldehyde were refluxed in benzene for 168 hr. The solvent was evaporated under reduced pressure. The crude mixture

showed three spots on TLC (silicon gel, EtOAc/LP 60-80). Crystallization of the crude reaction product from EtOAc afforded 200 mg (0.40 mmol) of white crystals 21C. M.p. 188-192°C. The mother liquor was concentrated and subjected to column chromatography, which in addition gave: 70 mg (0.14 mmol) of 21C. Total yield: 270 mg (54%). M.p. 191-194°C (EtOAc). IR($CHCl_3$): 3400 cm^{-1} (NH), 1775 and 1700 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.70 (m, 1H), 7.4-6.7 (m, 18H), 5.49 br s, 1H, NCH), 5.12 (br s, 2H, CH_2Ph, indole), 4.28 (s, 2H, CH_2Ph, imide), 4.2 (br s, 1H, NH), 3.34 (d, 1H, J=18 Hz, C-4'H_a), 3.14 (d, 1H, J=18 Hz, C-4'H_b).

Cis-2(2-pyrrolyl)2,3-dihydro-indole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 2mC

280 mg (1 mmol) of amine 1 and 100 mg (1.05 mmol) of pyrrole-2-carboxaldehyde were refluxed in toluene for 96 hr. Work-up, treatment with charcoal and column chromatography of the crude reaction product followed by crystallization from EtOAc/hexane afforded 211 mg (0.59 mmol, 59%) of 2mC as white crystals. M.p. 170-173°C. IR(KBr): 3320 cm^{-1} (NH), 1770 and 1690 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 8.9 (br, 1H, NH pyrrole), 7.3-7.1 (m, 4H), 7.0-6.75 (m, 5H), 6.65 (m, 1H, NCH=), 6.22-6.05 (m, 2H, =CH-CH=), 5.03 (s, 1H, NCH), 4.46 (s, 2H, CH_2Ph), 4.18 (br, 1H, NH, indole), 3.22 (d, 1H, J=19 Hz, C-4'H_a), 2.90 (d, 1H, J=19 Hz, C-4'H_b). Found: C, 73.9; H, 5.3; N, 11.6; $C_{22}H_{19}N_3O_2$ requires: C, 73.93; H, 5.36; N, 11.76.

Cis-2-phenyl-5-chloro-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 10aC

50 mg (0.125 mmol) of imine 8a[13] was spiro cyclized according to procedure D. Work-up afforded 43 mg (86%) of compound 10aC as a white solid. M.p. 243-246°C (MeOH). IR($CHCl_3$): 3400 and 3320 cm^{-1} (NH), 1780 and 1710 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.5-6.5 (m, 13H), 5.62 (br, 1H, NH), 5.08 (d, 1H, J=18.5 Hz, C-4'H_b). Found: C, 70.8; H, 4.9; N, 6.5; Cl, 8.7; $C_{24}H_{19}N_2O_2Cl$ requires: C, 71.54; H, 4.75; N, 6.95; Cl, 8.81.

Trans-2-phenyl-5-chloro-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 10aT

26 mg (0.064 mmol) of imine 8a[13] was spiro cyclized according to procedure G. The oily crude reaction product was crystallised from MeOH. Yield: 18 mg (0.045 mmol, 69%) of white crystals, which consisted of 85% trans isomer 10aT and 15% cis product 10aC. Repeated crystallizations from MeOH yielded the pure trans isomer 10aT; m.p. 150-152°C. IR($CHCl_3$): 3400 cm^{-1} (NH), 1775 and 1705 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.5-7.0 (m, 11H), 6.7 (m, 2H), 5.49 (s, 1H, H-2), 4.73 (s, 2H, CH_2Ph), 4.2 (br, 1H, NH), 2.56 (d, 1H, J=18.5 Hz, C-4'H_a), 2.32 (d, 1H, J=18.5 Hz, C-4'H_b). Found: C, 71.1; H, 4.8; N, 6.7; Cl, 8.8; $C_{24}H_{19}N_2O_2Cl$ requires: C, 71.54: H, 4.75; N, 6.95; Cl, 8.81.

Cis-2-phenyl-6-methoxy-2,3-dihydroindole-3-spiro-3'(N'benzyl)pyrrolidine-2',5'-dione 11aC

To a soln of 0.25 equiv of BuLi (0.22 ml of 15% soln) in 5 ml ButOH and 5 ml THF a soln of 0.5 mmol of imine 9a[14] in 2.5 ml of toluene was added at 0°C. After 25 min the soln was quenched with NaCl sat aq and extracted with $CHCl_3$. Crystallization from EtOH; m.p. 11aC 202-204°C. IR($CHCl_3$): 3390 (NH), 1770 and 1700 cm^{-1} (C=O, imide). ^1H NMR δ($CDCl_3$): 7.52-6.30 (m, 13H), 5.02 (d, 1H, J=4 Hz, H_2), 4.27 (s, 2H, CH_2Ph), 4.20 (m, 1H, NH), 3.79 (s, 3H, OCH_3), 3.24 (d, 1H, J=19.0 $H_{4a'}$), 2.99 (d, 1H, J=19.0 $H_{4'b}$).

2-Phenyl-indolenine-3-spiro(N'benzyl)pyrrolidine-2'5'-dione 3a

A soln of 37 mg (0.1 mmol) 2a, 34 mg of trifluoroacetic acid in 10 ml of toluene was stirred for 2 h at 110°C. After repeated washings with Na_2CO_3 aq the residue was column chromatographed over silica gel. Yield 22 mg (60%). M.p. 3: 135-140°C (yellow crystals. ^1H NMR δ($CDCl_3$): 3.00 (d, 1H, J=18.0 Hz, C-4'H_b) 3.31 (d, 1H, J=11.0 Hz, C-4'H_a), 4.78 (d, 1H, J=14.0 Hz, CH_aH_bPh, 5.12 (d, 1H, J=14.0 Hz, CH_aH_bPh), 7.1-7.9 (m, 14H, ArH).
Upon hydrogenation of 3 over Pd/C a 85:15 mixture of 2aC and 2aT was obtained.

7-Benzyloxy-hept-4-ynal 12

To a soln of 55 mg of Li, and a trace of $Fe(NO_3)_3$ in 50 ml of NH_3 1 g of benzyloxybut-3-yne in 10 ml of DMSO was added. After 1 h 1.13 g of 1,1-ethylenedioxy-3-bromopropane[10] in 5 ml of DMSO was added. After 1 h stirring at r.t. the soln was poured upon NH_4Cl aq and extracted with ether. Distillation of the resulting oil (Kugelrohr 200°C/0.01 mm Hg) gave 1 g of 1,1-ethylenedioxy-7--benzyloxy hept-4-yne. ^1H NMR δ($CDCl_3$): 7.34 (s, 5H), 4.97 (t, 1H, J=4.5 Hz), 4.54 (s, 2H, CH_2Ph), 3.88 (m, 4H, OCH_2CH_2O), 3.57 (t, 2H, CH_2O), 2.63-2.15 (m, 4H), 2.04-1.63 (m, 2H).
1 g of the acetal was refluxed in 20 ml acetic acid and 10 ml of water. After 2 h the acetic acid was evaporated under reduced pressure and the residue was taken up in ether and washed with sat aq $NaHCO_3$. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The residual brownish oil was distilled in a Kugelrohr at 160°C/0.01 mm Hg. Yield 740 mg (3.42 mmol, 89%) of 12 as a colourless oil. ^1H NMR δ($CDCl_3$): 9.79 (s, 1H), 7.34 (s, 5H), 5.54 (s, 2H, CH_2Ph), 3.56 (t, 2H, OCH_2), 2.64-2.30 (m, 6H).

ACKNOWLEDGEMENT: We thank P. Seignette and H. Schenk for the X-ray analysis of compound 2aT. The present investigation was carried out under the auspices of the Netherlands Foundation for Chemical Research (SON) and with financial support from the Netherlands Organization for Advancement of Pure Research (ZWO).

REFERENCES AND FOOTNOTES

1. W.N. Speckamp and H. Hiemstra, Tetrahedron, 41, 4367 (1985).
2a. U. Hengartner, A.D. Batcho, J.F. Blount, W. Leimgruber, M.E. Larscheid and J.W. Scott, J.Org.Chem., 44, 3748 (1979);
b. J.T. Carlock, J.S. Bradshaw, B. Stanovnik and M. Tisler, J.Org.Chem., 42, 1883 (1977);

c. U. Hengartner, D. Valentine, Jr., K.K. Johnson, M.E. Larscheid, F. Pigott, F. Scheidl, J.W. Scott, R.C. Sun, J.M. Townsend and T.H. Williams, J.Org.Chem., 44, 3741 (1979);
d. Y. Ito, K. Kobayashi and T. Saegusa, J.Org.Chem., 44, 2030 (1979);
e. Y. Ito, K. Kobayashi and T. Saegusa, Tetrahedron Lett., 1039 (1979);
f. M. Mori, K. Chiba and Y. Ban, Tetrahedron Lett., 1037 (1977);
g. H. Person, M.D.A. Pardo and A. Founcaud, Tetrahedron Lett., 281 (1980);
h. J. Kökösi, I. Herwecz, G. Szász and Z. Mészáros, Tetrahedron Lett., 4861 (1981);
i. W. Wierenga, J. Griffin and M.A. Warpehoski, Tetrahedron Lett., 2437 (1983);
j. R.M. Coates and C.W. Hutchins, J.Org.Chem., 44, 4742 (1979);
k. R.R. Bard and J.F. Bunnett, J.Org.Chem., 45, 1546 (1980);
l. L.S. Hegedus, G.F. Allen and E.L. Waterman, J.Am.Chem.Soc., 98, 2674 (1976);
m. J.F. Wolfe, M.C. Sleevi and R.R. Goehring, J.Am.Chem.Soc., 102, 3646 (1980).
3. "Indoles ed. by W.J. Houlihan, Wiley-Interscience, New York (1972), Parts 1 and 2, and (1979), Part 3.
4. The stereochemistry of 2 is referred to as cis in case the C-2 R substituent and the C-2' carbonyl group (See Figure 2) have a cis relationship. Correspondingly the second isomer of 2 is denoted as trans.
5a. S.J. Veenstra and W.N. Speckamp, Preliminary communication: J.Am.Chem.Soc., 103, 4647 (1981).
b. W.N. Speckamp, Heterocycles, 21, 211 (1984).
6. R. Huisgen, Angew.Chem., 92, 979 (1980).
7. The stereochemistry of cis and trans series followed from an X ray of trans 2a. P. Seignette and H. Schenk, Laboratory for Crystallography, University of Amsterdam.
8. J.B.P.A. Wijnberg and W.N. Speckamp, Tetrahedron, 34, 2399 (1978).
9. The imine was prepared from imide 1 and aldehyde 12[10].
10. G. Büchi and H. Wüest, J.Org.Chem., 34, 1122 (1969).
11. The aldehyde was prepared according to Ban[12] (See experimental).
12. T. Oishi, M. Nagai and Y. Ban, Tetrahedron Lett., 491 (1968).
13. The amine 6 was prepared according to the procedure described in ref. 8.
14. The synthesis of amine 7 will be reported separately (L.C. Niemann, to be published).
15. S.J. Veenstra and W.N. Speckamp, J.Chem.Soc.,Chem.Commun., 369 (1982).
16. R.J. Vijn, W.N. Speckamp, B.S. de Jong, and H. Hiemstra, Angew.Chem.Int.Ed.Engl., 23, 165 (1984).