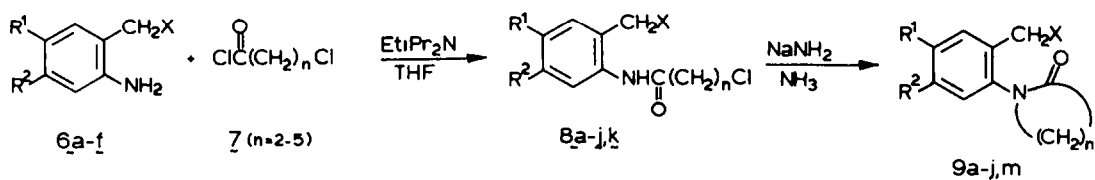


nitro group stabilizes the intermediate carbanion at the adjacent ring carbon atom. A variation of the Madelung reaction was found by Schulenberg¹⁰ who obtained one indole derivative in moderate yield when *N*-benzoyldiphenylamine diester was treated with sodium methoxide. The synthesis of indoles by the Wittig olefination of *ortho*-acylaminobenzylidene phosphoranes may be regarded as a related method.¹¹ Intramolecular Wittig reactions have also been employed for the synthesis of the tricyclic 2,3-dihydropyrrolo[1,2-*a*]indoles.¹²⁻¹⁴ Bergman and Sand¹⁵ have used their method (*vide supra*) for the synthesis of pyrrolo[1,2-*a*]indoles starting from 1-(2-methyl-3-nitrophenyl)-2-pyrrolidinones. Flitsch *et al.*¹⁶ reported that cyclization in the presence of a base of an *N,N*-diacylated-*ortho*-alkylaniline, which contains a *tert*-butyl ester as anion-stabilizing group at the benzylic position, gave the desired 2,3-dihydro-3-oxo-1H-pyrrolo[1,2-*a*]indole derivative only in poor yield.^{16b}

In this paper we describe the results of our work on the modified Madelung reaction under mild conditions of *N*-monoacylated-*ortho*-alkylanilines in which a cyclic amide function is present, with different ring sizes of the lactam moiety and different anion-stabilizing groups at the benzylic carbon atom. This simple synthesis of tricyclic pyrrolo[1,2-*a*]indoles is also studied in the presence of a protected hydroquinone function as a more direct application for the synthesis of mitosenes.

RESULTS¹⁷ AND DISCUSSION

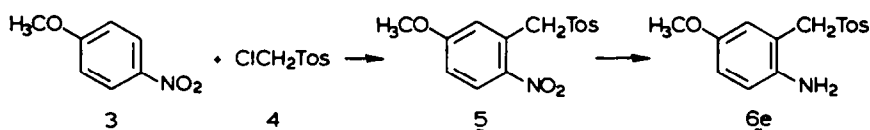
The starting lactams **9** for the intramolecular condensation were synthesized by acylation of the anilines **6** and subsequent cyclization to **9** as depicted in Scheme 1.



	n	R ¹	R ²	X		n	R ¹	R ²	X		n	R ¹	R ²	X
a	3	H	H	CN	e	3	OCH ₃	OCH ₃	Tos	i	4	OCH ₃	CH ₃	CN
b	3	OCH ₃	OCH ₃	CN	f	3	H	H	CO ₂ <i>t</i> -Bu	j	2	OCH ₃	OCH ₃	CN
c	3	OCH ₃	H	CN	g	4	OCH ₃	OCH ₃	CN	k	5	OCH ₃	OCH ₃	CN
d	3	OCH ₃	CH ₃	CN	h	4	OCH ₃	H	CN	l	3	H	H	CO ₂ Me

Scheme 1

The 2-(cyanomethyl)anilines **6a**,¹⁸ **6b**,¹⁹ **6c**,^{5a} **6d**,^{5a} and **6f**¹⁶ were obtained according to the literature. The starting aniline **6e** was prepared via a vicarious nucleophilic substitution reaction²⁰ followed by a Béchamp reduction of the resulting nitro compound. Reaction of 1-methoxy-4-nitrobenzene (**3**) and 1-[(chloromethyl)sulfonyl]-4-methylbenzene (**4**)²¹ in tetrahydrofuran (THF) in the presence of potassium *tert*-butoxide (KO*t*-Bu) afforded the nitrobenzene **5** in a yield of 89%. Subsequent reduction of the nitro group with iron metal in ethanol²² gave the aniline **6e** (60%) (Scheme 2).

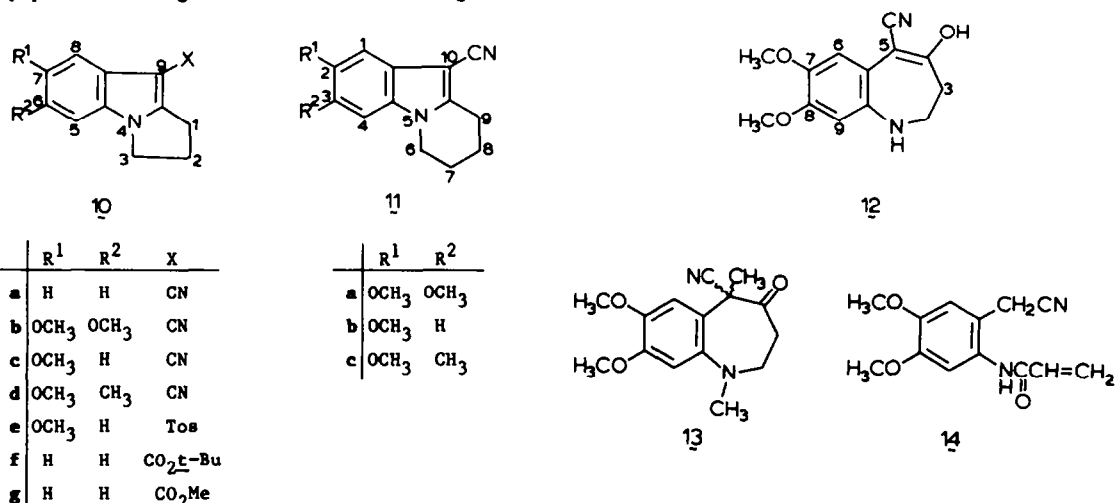


Scheme 2

The anilines **6** were converted into the amides **8** by reaction with the appropriate acid chloride **7** (*n*=2-5) in THF in the presence of ethyldiisopropylamine at room temperature for 0.5 hr (Table

2). Subsequent cyclization of the amides **8** according to Manhas and Jeng²³ with 1.5 equivalents of sodium amide (NaNH_2) in liquid ammonia gave the lactams **9a-j** (Table 3). Compound **8k** failed to undergo cyclization under different reaction conditions used. This result is in line with the work of Manhas and Jeng²³ who also found that *N*-substituted ϵ -caprolactams could not be synthesized in this way. Two other attempts were made to prepare the desired ϵ -caprolactam. Firstly, monoalkylation of **6b** with 1 equivalent of ω -bromocaproic acid methyl ester using either ethyldiisopropylamine in toluene or sodium hydrogencarbonate in hexamethylphosphoric triamide²⁴ gave mainly dialkylated product. The monoalkylated product would be a suitable starting compound for cyclization. The other route involved the formation of an imine by reaction with cyclohexanone and subsequent oxidation of this imine with *meta*-chloroperoxybenzoic acid to the oxaziridine, which is expected to rearrange to the more stable ϵ -caprolactam.²⁵ However, oxidation of the imine under several reaction conditions gave only polymeric material. Compound **9m** was prepared from the *tert*-butyl ester **9f** by reaction with trifluoroacetic acid²⁶ and subsequent esterification of the resulting acid with diazomethane.

The pyrrolidinones **9a-f** could also be synthesized by reaction of **8** in THF using a weaker base *viz.* 1,5-diazabicyclo[4.3.0]non-5-ene. However, this method failed for the synthesis of the piperidinones **9g-i** and the azetidinone **9j**.



The intramolecular condensation reaction of the pyrrolidinones **9a-f,m** and of the piperidinones **9g-i** to the corresponding 2,3-dihydro-1H-pyrrolo[1,2-a]indoles **10** and 6,7,8,9-tetrahydro-1H-pyrido[1,2-a]indoles **11**, respectively, was carried out via two different methods *viz.* treatment with 5 equivalents of sodium hydride (NaH) in toluene at elevated temperatures (method A) and KOt-Bu in THF at room temperature (method B). Pyrrolidinones **9a-f,m** were reacted under the conditions of method A. Except **9a**, they all underwent an intramolecular condensation reaction producing the corresponding pyrrolo[1,2-a]indoles **10**. Under the same conditions piperidinone **9g** yielded pyrido[1,2-a]indole **11a**. Using method A the reaction time appeared to be critical because under these conditions the reaction products polymerized. Reaction with 2 equivalents of KOt-Bu (method B) did not show this drawback. Only for the synthesis of **10g** method B could not be applied because both intramolecular condensation and transesterification took place affording **10f** in a yield of 58%. The results of both methods are summarized in Table 1. The spectral data of both tricyclic systems **10** and **11** are in close agreement with those reported in the literature (Table 4).^{27,28}

Reaction of 4,5-dimethoxy-2-(2-oxo-1-azetidiny)benzeneacetonitrile (**9j**) with KOt-Bu in THF gave only polymeric material at room temperature. However, when the reaction was carried out for 15 min at 5°, trituration of the crude reaction mixture with chloroform gave 2,3-dihydro-4-hydroxy-7,8-dimethoxy-1H-1-benzazepine-5-carbonitrile (**12**) in a yield of 45%. The mass spectrum of benzazepine **12** exhibits the same molecular ion value as the starting azetidinone **9j** and the IR spectrum shows the presence of NH and OH absorptions at 3290 cm^{-1} and 2700-2400 cm^{-1} , respectively.

Table 1. Intramolecular Condensation of the Pyrrolidinones 9a-f,m and the Piperidinones 9g-1.

Product	m.p. (°C) (solvent)	Method A			Method B	
		Time (hr)	Temp (°C)	Yield (%)	Time (min)	Yield (%)
10a	110-133 ^a (toluene)	48	60	<1 ^e	10	88
10b	206-208 ^b (EtOH)	22	110	69	120	83
10c	142-152 ^a (EtOH)	0.75	110	79	90	69
10d	170-172 ^c (EtOH)	2	110	61	90	75
10e	212.5-213.5 (EtOAc)	6	60	75	60	85
10f	158-159.5 (MeOH)	2.5	80	75	90	52
10g	84-86 ^d	6	80	68	- ^f	- ^f
11a	173-174 (EtOAc)	0.75	110	82	20	85
11b	134-139 ^a (EtOH)	-	-	-	15	81
11c	181-182 (EtOH)	-	-	-	10	76

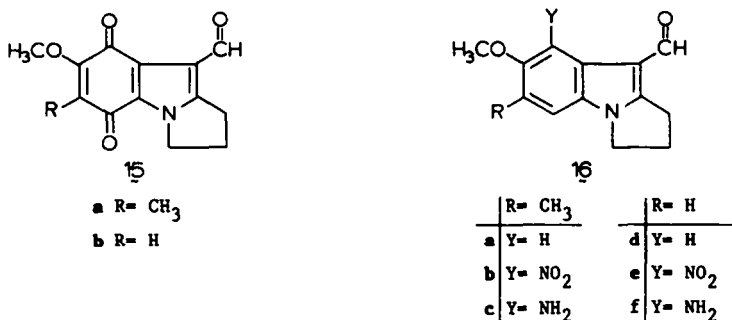
a) Decomposes. b) Ref. 27 m.p. 203-203.5°. c) Ref. 28 m.p. 173-173.5°, Ref. 27 m.p. 174-174.5°. d) Could not be recrystallized. e) Only polymeric material was obtained. f) Yields 10f in 58%.

The ¹³C-NMR spectrum of benzazepine 12 exhibits =CCN and =COH absorptions at δ 88.6 and 170.4, respectively, while the ¹H-NMR spectrum shows the NH and OH signals at δ 10.58 and 5.60, respectively. Additional proof for the structure of 12 was obtained by subsequent methylation with excess of iodomethane in acetone in the presence of potassium carbonate. After purification of the crude product by chromatography 2,3,4,5-tetrahydro-7,8-dimethoxy-1,5-dimethyl-4-oxo-1H-1-benzazepine-5-carbonitrile (13) was obtained (37%) as an oil. The spectral data clearly indicated that both the nitrogen atom and the C-5 position had been methylated and in the mass spectrum the molecular ion value of dimethyl benzazepine 13 is found 28 dalton higher than in the benzazepine 12. The IR spectrum reveals a C=O absorption at 1730 cm⁻¹. ¹³C-NMR spectroscopy shows in addition to a C=O signal at δ 202.4, the NCH₃ and CCH₃ absorptions at δ 41.8 (q) and 23.6 (q), respectively. In the ¹H-NMR spectrum both the NH and OH signals are missing and the NCH₃ and CCH₃ absorptions are found as singlets at δ 2.74 and 1.77, respectively.

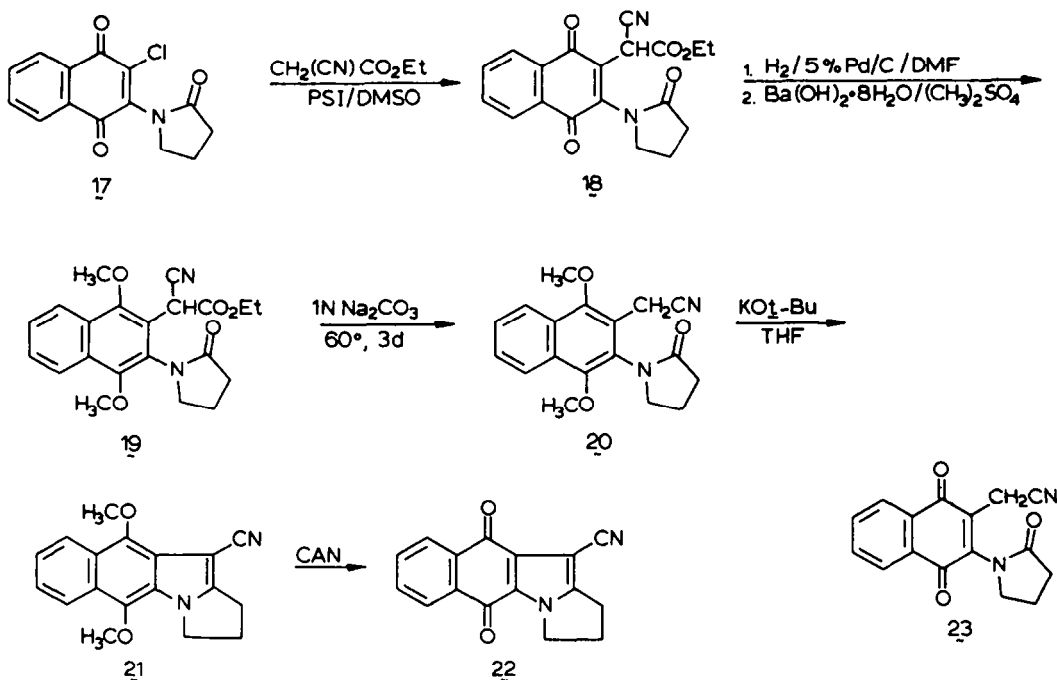
Finally, we found that the entire reaction sequence *viz.* acylation, lactam formation and intramolecular condensation, can be performed without isolation of the intermediate products. A solution of the appropriate ω -chloro acid chloride 7 in THF was added to a solution of the amine 6 and ethyldiisopropylamine in THF and when acylation was complete (0.5 hr), 2.5 equivalents of KO_t-Bu were added resulting in the formation of the desired pyrrolo[1,2-a]indoles 10 or the pyrido[1,2-a]indoles 11. Such a one pot synthesis could not be applied for the preparation of benzazepine 12, because after acylation of aniline 6b with β -chloropropionyl chloride (7, n=2) the excess of KO_t-Bu caused dehydrohalogenation of the intermediate propanamide 8j leading to N-[2-(cyanomethyl)-4,5-dimethoxyphenyl]propenamide (14; 77%).

This new method represents a very useful synthesis of substituted pyrrolo[1,2-a]indoles 10 in which a quinone function can be easily introduced by standard methodology. Pyrrolo[1,2-a]indole

10d has previously been converted into quinone 15a by the sequence: reduction of the cyano to an aldehyde group (16a), nitration (16b), reduction of the nitro group and subsequent oxidation of the resulting aniline derivative (16c) by Fremy's salt.²⁷ In a similar way we have converted pyrrolo[1,2-a]indole 10c into the corresponding 2,3,5,8-tetrahydro-7-methoxy-5,8-dioxo-1H-pyrrolo[1,2-a]indole-9-carboxaldehyde (15b).



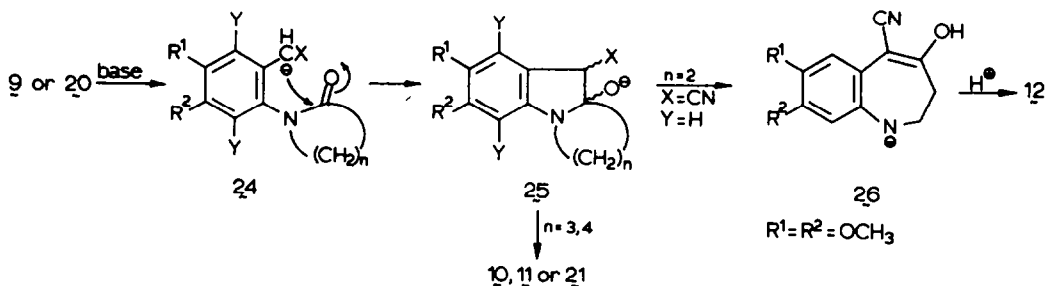
As a more direct application for the synthesis of mitosenes we have also applied our method to a compound in which a protected hydroquinone function is present. The protected quinone 20 smoothly underwent intramolecular condensation in the presence of KO_t-Bu to afford the benz[*f*]pyrrolo[1,2-*a*]indole 21 in a good yield. Deprotection of 21 gave the mitosene 22 in a overall yield of 28% from 17 (Scheme 3).



Scheme 3

The naphthalenedione 17 was prepared from 2,3-dichloro-1,4-naphthoquinone and γ -aminobutyric acid in two steps.²⁹ Reaction of 17 with ethyl cyanoacetate in dimethyl sulfoxide (DMSO) in the presence of potassium succinimidate (PSI)²⁹⁻³¹ gave the light-sensitive naphthaleneacetate 18 in a yield of 73%. The decarboxylation^{5a} of 18 to yield naphthaleneacetonitrile 23, a possible starting material for benz[*f*]pyrrolo[1,2-*a*]indole 22 failed. This negative result may be due to quinone methide formation and led us to protect the quinone 18 as the corresponding dimethyl hydroquinone 19. Reductive methylation³² of quinone 18 by catalytic hydrogenation in the presence of dimethyl sulfate and Ba(OH)₂·8H₂O gave the protected hydroquinone 19 as the major product. This was used without purification, because after decarboxylation of 19 in sodium carbonate solution^{5a} the

naphthaleneacetonitrile **20** precipitated (52% yield from **18**). Treatment of **20** with KOt-Bu in THF at room temperature afforded the 1H-benz[f]pyrrolo[1,2-a]indole **21** after chromatography on alumina in 80% yield. Oxidative demethylation of **21** with ceric ammonium nitrate (CAN)³³ gave the desired indoloquinone **22** in high yield.



A possible mechanism by which the intramolecular condensation can take place is depicted in Scheme 4. The benzylic anion in **24** adds to the carbonyl group leading to the intermediate **25**. In the cases where $n=3$ or 4 dehydration ultimately gives the compounds **10**, **11** ($Y=H$) or **21** ($Y=OCH_3$). When $n=2$, starting from **9j**, elimination of water would lead to a highly strained tricyclic compound. Therefore the reaction proceeds by cleavage of the N-CO bond to give **26**, which after protonation can be isolated as **12**. When NaH is used as a base the protonation can partly take place by unreacted **9** or during the aqueous workup. In the case of KOt-Bu the protonation can also be performed by the *tert*-butanol formed.

As can be seen from Table 1 the reaction time for the formation of the pyrido[1,2-a]indoles **11** is about 6 times smaller than that of the corresponding pyrrolo[1,2-a]indoles **10**. A possible explanation may be the differences in relative torsional strain in the various systems. When the pyrrolidinones **9a-f,m** are converted into **25** ($n=3$) the number of eclipsing interactions increases. A similar conversion of the piperidinones **9g-1** into **25** ($n=4$) would be less unfavourable.

In summary we can conclude that our modified Madelung reaction represents a very useful and simple synthetic method for the construction of tricyclic systems like 2,3-dihydro-1H-pyrrolo[1,2-a]indoles (**10,21**) and 6,7,8,9-tetrahydro-1H-pyrido[1,2-a]indoles (**11**). We have shown that different anion-stabilizing groups and different lactams can be used. In addition the reaction can be performed in the presence of a protected hydroquinone function, as a more direct approach to the synthesis of mitosenes.

EXPERIMENTAL

M.p.s were determined with a Reichert melting point apparatus and are uncorrected. ¹H-NMR spectra were recorded with a Bruker WP-80 spectrometer and ¹³C-NMR spectra were recorded with a Nicolet MT 200 spectrometer, using CDCl_3 as a solvent with Me_4Si as an internal standard, unless otherwise stated. Mass spectra were obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by E. Hoogendam of the Laboratory of Chemical Analysis of the Twente University of Technology.

Solvents were distilled prior to use as follows: CH_3CN , CH_2Cl_2 and toluene from P_2O_5 , THF from sodium/benzophenone ketyl.

Column chromatography was performed with silica gel.

All reactions were carried out under a nitrogen atmosphere.

4-Methoxy-2-[[4-(4-methylphenyl)sulfonyl]methyl]-1-nitrobenzene (**5**)

To a soln of KOt-Bu (12.5 g, 112 mmol) in THF (1 l) was added dropwise a soln of 1-[(chloromethyl)sulfonyl]-4-methylbenzene²¹ (**4**, 10 g, 49 mmol) in THF (200 ml) at -20° . After stirring for 15-30 min at -20° a soln of *p*-methoxynitrobenzene (**3**, 7.5 g, 49 mmol) in THF (300 ml) was added dropwise. Stirring was continued for 45 min at -20° and subsequently for 2 hr at room temp. The

Table 2. Yields, Melting points, Characteristic NMR Data and Molecular Ion Values of the Amides 8.

Compd ^a	Yield (%)	m.p. (°C) (solvent)	¹ H-NMR (CDCl ₃), δ			¹³ C-NMR (CDCl ₃), δ				MS(M ⁺) found (calcd)
			CH ₂ X (s)	CH ₂ Cl (m)	ArH	NC=O (s)	CH ₂ Cl (t)	R ¹ (q)	R ² (q)	
8a	79	98-99 (toluene)	3.68	3.7-3.5	7.5-7.2 (m, 5H) ^f	171.2	44.4	-	-	236.072 (236.072)
8b	96	136-138 (EtOAc)	3.62	3.7-3.6	6.84 6.79 (s, 1H) (s, 1H)	171.1	44.5	56.2	56.1	296.091 (296.093)
8c	83	93-94 (toluene)	3.65	3.8-3.5	7.3-6.75 (m, 4H) ^f	171.5	44.4	55.5	-	266.084 (266.082)
8d	88	144-145 (Dip) ^b	3.65	3.8-3.5	6.97 6.81 (s, 1H) (s, 1H)	171.2	44.4	55.6	15.8	280.098 (280.098)
8e	77	144-145 (MeOH)	4.29	3.8-3.6	6.9-6.8 6.3-6.2 (m, 2H) (m, 1H)	170.7	44.4	55.3	-	395.094 (395.096)
8f	91	64.5-65.5 c	3.53	3.68 ^d	7.4-7.0 (m, 4H)	172.0	44.4	-	-	311.129 (311.129)
8g	94	133-134 (EtOAc)		3.6-3.4 ^e	6.83 6.78 (s, 1H) (s, 1H)	171.7	44.5	56.3	56.2	310.111 (310.108)
8h	89	76-77 (EtOH)	3.61	3.7-3.4	7.08 ^g 7.0-6.7 (d, H-6) (m, 2H)	171.9	44.5	55.5	-	280.097 (280.098)
8i	91	136-137 (EtOH)	3.60	3.7-3.4	6.92 6.77 (s, 1H) (s, 1H)	172.0	44.5	55.6	15.8	294.114 (294.114)
8j	91	165-167 (EtOAc)		4.0-3.7 ^e	6.98 6.88 (s, 1H) (s, 1H)	169.8	42.5	57.3	57.2	282.076 (282.077)
8k	85	99-101 (EtOH)	3.63	3.65-3.35	6.84 6.79 (s, 1H) (s, 1H)	172.0	44.8	56.2	56.1	324.124 (324.123)

a) Satisfactory elemental analyses ($\pm 0.4\%$ for C, H and N) were obtained for all amides 8. b) Dip is the abbreviation of diisopropyl ether. c) Recrystallized from petroleum ether (60-80°)/CHCl₃. d) t, J = 6.2 Hz. e) Overlap of signals. f) Overlap with NH signal. g) d, J = 8.3 Hz.

reaction mixture was neutralized with sat NH₄Cl aq (250 ml) and extracted with Et₂O (3 x 200 ml). After drying (MgSO₄) of the combined extracts and removal of the solvent under reduced pressure, the residue was triturated with diisopropyl ether to afford pure 5 (89%), m.p. 140-141° (MeOH). ¹H-NMR δ: 8.01 (d, 1H, J = 9.7 Hz, ArH), 7.59 (d, 2H, J = 8.5 Hz, PhH), 7.26 (d, 2H, J = 8.1 Hz, PhH), 7.0-6.9 (m, 2H, ArH), 4.95 (s, 2H, CH₂Ar), 3.90 (s, 3H, OCH₃), 2.43 (s, 3H, CH₃Ph). ¹³C-NMR δ: 162.9 (s, C-4), 142.2 (s, C-1), 135.0 (s, ArCS), 125.9 (s, C-2), 59.0 (t, CH₂Ar), 56.0 (q, OCH₃), 21.7 (q, CH₃Ph). IR (KBr) cm⁻¹: 1340 and 1140 (SO₂). MS: m/e 321.065 (M⁺, calc.: 321.067). (Found: C, 56.23; H, 4.75; N, 4.37. Calc. for C₁₅H₁₅NO₅S: C, 56.06; H, 4.71; N, 4.36%.)

4-Methoxy-2-[[[(4-methylphenyl)sulfonyl]methyl]benzenamine (6e)

A suspension of Fe (0.8 g, 14.3 mmol) in EtOH (5 ml) and 4% HCl (1 ml) was refluxed for 30 min whereupon 5 (1.0 g, 3.1 mmol) was added in portions. After refluxing for 2 hr the hot reaction mixture was carefully neutralized with Na₂CO₃ and subsequently filtered. The residue was washed with hot EtOH (2 x 5 ml). Concentration of the combined filtrates and recrystallization of the resulting solid from EtOH gave pure 6e (60%), m.p. 156-157° (EtOH). ¹H-NMR δ: 7.64 (d, 2H, J = 8.6 Hz, PhH), 7.28 (d, 2H, J = 8.5 Hz, PhH), 6.75-6.65 (m, 2H, ArH), 6.2-6.1 (m, 1H, ArH), 4.31 (s, 2H, CH₂Ar), 3.93 (br s, 2H, NH₂), 3.54 (s, 3H, OCH₃), 2.43 (s, 3H, CH₃Ph). ¹³C-NMR δ: 158.4 (s, C-4), 152.8 (s, C-1), 134.9 (s, ArCS), 127.6 (s, C-2), 60.0 (t, CH₂Ar), 55.6 (q, OCH₃), 21.6 (q, CH₃Ph). IR (KBr) cm⁻¹: 3460 and 3380 (NH₂). MS: m/e 291.093 (M⁺, calc.: 291.093). (Found: C, 61.75; H, 5.90; N, 4.84. Calc. for C₁₅H₁₇NO₃S: C, 61.84; H, 5.88; N, 4.81%.)

Table 3. Yields, Melting points, Characteristic NMR Data and Molecular Ion Values of the Lactams 9.

Compd ^a	Yield (%)	m.p. (°C) (solvent)	¹ H-NMR (CDCl ₃), δ ^e			¹³ C-NMR (CDCl ₃), δ ^e				MS(M ⁺) found (calcd)
			CH ₂ X (s)	CH ₂ N (m)	ArH	NC=O (s)	CH ₂ N (t)	R ¹ (q)	R ² (q)	
9a	68	67.5-68.5 (toluene)	3.75	3.9-3.8	7.4-7.1 (m,4H)	174.1	50.7	-	-	200.096 (200.095)
9b	87	158-159 (EtOAc)	3.66	3.9-3.7	6.84 6.70 (s,1H) (s,1H)	174.4	50.7	56.1	56.1	260.116 (260.116)
9c	80	99-100 (EtOAc)	3.70	3.9-3.6	7.25-6.8 (m,3H)	174.4	50.8	55.6	-	230.106 (230.106)
9d	68	164-169 ^c (EtOAc)	3.69	3.95-3.7	6.97 6.79 (s,1H) (s,1H)	174.4	50.8	55.6	15.9	244.119 (244.121)
9e	65	110-112 (EtOH)	4.33	3.8-3.7	7.2-6.6 (m,3H)	174.5	51.2	55.4	-	359.121 (359.119)
9f	96	123.5-125 (MeOH)	3.57	3.78 ^f	7.4-7.1 (m,4H)	174.2	51.1	-	-	275.151 (275.152)
9g	80	116-117 (EtOH)		3.6-3.5	6.85 6.70 (s,1H) (s,1H)	169.8	51.8	56.1	56.1	274.131 (274.132)
9h	83	95-96.5 (EtOAc)	g	3.75-3.45	7.25-6.8 (m,3H)	169.9	51.9	55.6	-	244.121 (244.121)
9i	93	148-149 (EtOH)	h	3.75-3.45	6.98 6.80 (s,1H) (s,1H)	169.9	51.8	55.6	15.9	258.137 (258.137)
9j	82	126-128 (EtOH)		3.9-3.7	6.84 6.68 (s,1H) (s,1H)	165.1	40.8	56.3	56.2	246.100 (246.100)
9m	- ^b	78-80.5 ^d		3.9-3.6	7.5-7.0 (m,4H)	174.3	51.0	-	-	233.106 (233.105)

a) Satisfactory elemental analyses (+0.4% for C,H and N) were obtained for all lactams 9. b) 9m was prepared from 9f. c) Decomposes. d) Could not be recrystallized, but was purified by trituration with diethyl ether. e) The ¹H-NMR and ¹³C-NMR spectra of 9j were recorded in DMSO-d₆. f) t, J = 6.7 Hz. g) Signals at δ 3.77 and 3.45 (AB q, J = 18.3 Hz). h) Signals at δ 3.75 and 3.45 (AB q, J = 18.3 Hz).

General procedure for the synthesis of the ω-chloroalkanamides 8

To a soln of Et₁-Pr₂N (4.7 ml, 27.5 mmol) and amine 6 (25 mmol) in THF (70 ml) was added a soln of the acid chloride 7³³ (n=2-5; 25 mmol) in THF (25 ml) at room temp. After stirring for 1 hr the reaction mixture was concentrated, EtOAc (300 ml) added and the resulting soln washed with sat NH₄Cl aq (2 x 250 ml). Drying (MgSO₄) and evaporation of the solvent afforded the crude ω-chloroalkanamides 8. The amides 8 were purified by trituration or chromatography. Compds 8a,g,j were trituated with EtOAc; 8b-d,h,i,k with diisopropyl ether and 8e with MeOH. Compd 8f was purified by chromatography using CHCl₃ as eluent. The yields, melting points, characteristic NMR data and molecular ion values (M⁺) are given in Table 2.

General procedure for the synthesis of the pyrrolidinones 9a-f, the piperidinones 9g-i and the azetidinone 9j

To a suspension of NaNH₂ (30 mmol; prepared from 690 mg of Na) in liquid ammonia (80 ml) was added the amide 8a-j (20 mmol) in small portions. After evaporation of NH₃, CHCl₃ (200 ml) was added to the residue. The resulting soln was washed with 2 N HCl (2 x 150 ml), water (100 ml) and dried over MgSO₄. Evaporation afforded the crude 9a-j, which were purified as follows: 9a,d,i were trituated with diisopropyl ether; 9b,j with EtOH; 9e with benzene and 9c,f-h by chromatography (EtOAc/CHCl₃ 1:1). The yields, melting points, characteristic NMR data and molecular ion values

(M⁺) are given in Table 3.

Methyl 2-(2-oxo-1-pyrrolidinyl)benzeneacetate (9m)

A soln of 9f (170 mg, 0.6 mmol) and CF₃COOH (500 mg, 4.4 mmol) in CH₂Cl₂ (15 ml) was refluxed for 4 hr. The reaction mixture was washed twice with water, dried (MgSO₄) and evaporated to afford the crude acid (96%), which was used without further purification.

To a soln of the crude acid (1 g, 4 mmol) in dry MeOH (20 ml) was added a soln of CH₂N₂ [prepared from diazald (3.0 g, 13.7 mmol)] in Et₂O (30 ml) at 0°. After stirring for 15 min the excess of CH₂N₂ was destroyed using some drops of AcOH. After removal of the solvents the residue was dissolved in CH₂Cl₂ (30 ml), and the resulting soln washed with 2 N NaOH (2 x 20 ml). After drying (MgSO₄) and evaporation of the solvent, chromatography (EtOAc) afforded pure 9m (58%). The melting point, characteristic NMR data and molecular ion value (M⁺) are given in Table 3.

General procedures for the syntheses of the 2,3-dihydro-1H-pyrrolo[1,2-a]indoles 10 and the 6,7,8,9-tetrahydropyrido[1,2-a]indoles 11

Method A (NaH/toluene).

A suspension of 9a-g,m (5 mmol) and 80% NaH (580 mg, 24 mmol) in toluene (75 ml) was heated (For reaction times and temperatures see Table 1). When the reaction was complete as followed from TLC (EtOAc/MeOH 95:5) water (5 ml) was added. The organic layer was washed with sat NH₄Cl aq (75 ml) and dried (MgSO₄). Evaporation of the toluene afforded the crude products 10a-g and 11a.

Method B (KOt-Bu/THF).

To a soln of KOt-Bu (1.08 g, 10 mmol) in THF (70 ml) was added 9a-i,m (5 mmol). When the reaction was complete as followed from TLC, water (1 ml) was added whereupon the reaction mixture was concentrated. EtOAc (100 ml) was added to the residue and the resulting soln washed with sat NH₄Cl aq (2 x 100 ml) and dried (MgSO₄). Evaporation afforded the crude pyrrolo[1,2-a]indoles 10a-g and the pyrido[1,2-a]indoles 11a-c. The compounds were purified by chromatography: 10a,e and 11a using EtOAc/MeOH 95:5 as eluent; 10c,f,g and 11b using EtOAc/CHCl₃ 1:1 as eluent and 11c using CHCl₃ as eluent. The characteristic NMR data and molecular ion values (M⁺) are summarized in Table 4; melting points are given in Table 1. Data concerning the compounds 10b and 10d are in agreement with those reported in the literature.^{27,28}

2,3-Dihydro-4-hydroxy-7,8-dimethoxy-1H-1-benzazepine-5-carbonitrile (12)

The synthesis of 12 was performed analogously to that of 10 and 11 using method B at 5° starting from azetidinone 9j. Yield 45%, m.p. 159-165°. ¹H-NMR (DMSO-d₆) δ: 10.58 (br s, 1H, NH), 6.89 and 6.43 (s, 1H, ArH), 5.60 (br s, 1H, OH), 3.68 and 3.66 (s, 3H, OCH₃), 3.2-3.1 (m, 2H, NCH₂), 2.7-2.6 (m, 2H, CH₂C=). ¹³C-NMR (DMSO-d₆) δ: 170.4 (s, C-4), 88.6 (s, C-5), 43.5 (t, C-2), 37.9 (t, C-3). IR (KBr) cm⁻¹: 3290 (NH), 2700-2400 (OH), 2200 (CN). MS: m/e 246.100 (M⁺, calc. for C₁₃H₁₄N₂O₃: 246.100).

2,3,4,5-Tetrahydro-7,8-dimethoxy-1,5-dimethyl-4-oxo-1H-1-benzazepine-5-carbonitrile (13)

To a soln of benzazepine 12 (150 mg, 0.6 mmol) in dry acetone (7 ml) was added K₂CO₃ (275 mg, 2 mmol) and CH₃I (430 mg, 3 mmol). After 24 hr the acetone was evaporated and EtOAc (100 ml) added to the residue. The resulting mixture was washed with sat NH₄Cl aq (2 x 100 ml), dried (MgSO₄) and evaporated. The crude residue was subjected to chromatography (EtOAc/MeOH 95:5) to give 13 as an oil (37%). ¹H-NMR δ: 7.07 and 6.73 (s, 1H, ArH), 3.92 and 3.91 (s, 3H, OCH₃), 3.3-2.5 (m, 4H, NCH₂ and CH₂CO), 2.74 (s, 3H, NCH₃), 1.77 (s, 3H, CH₃). ¹³C-NMR δ: 202.4 (s, C=O), 56.6 (t, C-2), 52.3 (s, C-5), 41.8 (q, NCH₃), 38.5 (t, C-3), 23.6 (q, CH₃). IR (KBr) cm⁻¹: 2240 (CN), 1730 (C=O). MS: m/e 274.131 (M⁺, calc. for C₁₅H₁₈N₂O₃: 274.132).

2,3-Dihydro-7-methoxy-1H-pyrrolo[1,2-a]indole-9-carboxaldehyde (16d)

A mixture of nitrile 10c (1.0 g, 4.6 mmol) and nickel aluminum alloy (2.0 g) in 50% aqueous acetic acid (150 ml) was refluxed for 2.5 hr. After filtration, the reaction mixture was extracted with CHCl₃ (2 x 100 ml). The combined extracts were washed with sat NaHCO₃ aq (4 x 100 ml), water and dried with MgSO₄. After removal of the solvent the residue was purified by chromatography (CHCl₃/EtOAc 1:1) to give pure 16a (80%), m.p. 150-153° (MeOH). ¹H-NMR δ: 9.91 [s, 1H, C(O)H], 7.71 (d, 1H, J = 2.3 Hz, H-8), 7.11 (d, 1H, J = 8.5 Hz, H-5), 6.83 (dd, 1H, J = 2.3 and 8.5 Hz, H-6), 4.2-3.9 (m, 2H, NCH₂), 3.88 (s, 3H, OCH₃), 3.4-3.1 (m, 2H, H-1), 2.9-2.5 (m, 2H, H-2).

Table 4. Characteristic NMR Data and Molecular Ion Values of the 2,3-Dihydro-1H-pyrrolo[1,2-a]-indoles 10a,c,e-g and 6,7,8,9-Tetrahydropyrido[1,2-a]indoles 11a-c.

Compd ^a	¹ H-NMR (CDCl ₃), δ					¹³ C-NMR (CDCl ₃), δ ^f				MS(M ⁺) found (calcd)	
	-C-CH ₂ (m)	CH ₂ N (m)	ArH (m)	e _R ¹ (s)	e _R ² (s)	CH ₂ N (t)	R ¹ (q)	R ² (q)	C-X (s)		
10a	3.2-3.0	4.2-4.0	7.7-7.6(1H) 7.3-7.1(3H)	-	-	44.9	-	-	152.7	182.083 (182.084)	
10c	3.3-3.0	4.10 ^b	7.25-7.05(2H) 6.85 ^c (H-6)	3.85	-	45.1	55.8	-	152.6	212.096 (212.095)	
10e	3.4-3.2	4.1-3.9	7.4-6.7(3H)	3.86	-	44.9	55.8	-	150.1	341.109 (341.109)	
10f	3.4-3.1	4.3-3.9	8.2-7.9(1H) 7.4-7.0(3H)	-	-	44.3	-	-	152.4	257.139 (257.142)	
10g	3.4-3.0	4.2-3.8	8.2-7.9(1H) 7.3-7.0(3H)	-	-	44.4	-	-	152.4	215.095 (215.094)	
11a	3.1-3.0	4.1-3.9	7.08 (s,1H)	6.75 (s,1H)	3.93	3.92	42.7	56.4	56.5	144.1	256.121 (256.121)
11b	3.25-3.0	4.15-3.9	7.25-7.05(2H) 6.86 ^d (s,H-3)	3.86	-	42.5	55.8	-	146.0	226.111 (226.111)	
11c	3.2-2.9	4.1-3.8	7.04 (s,H-4)	7.03 (s,H-1)	3.88	2.32	42.5	55.7	17.1	144.8	240.126 (240.126)

a) Satisfactory elemental analyses ($\pm 0.4\%$ for C,H and N) were obtained for all compds. b) t, J = 7.1 Hz. c) d of d, J = 2.7 and 8.55 Hz. d) d of d, J = 2.4 and 8.5 Hz. e) R¹, R² = H. f) The C-9 signals of the pyrrolo[1,2-a]indoles 10a-g were situated with small intensities in the region of δ 100-109, while the C-10 signals of 11a-c were located at δ 82.2, 82.2 and 81.8, respectively.

¹³C-NMR δ : 183.1 [d, C(O)H], 156.6 (s, C-7), 112.6 and 110.6 (d, C-5 and C-6), 110.2 (s, C-9), 103.7 (d, C-8), 55.9 (q, OCH₃), 44.7 (t, NCH₂). IR (KBr) cm⁻¹: 1639 [C(O)H]. MS: m/e 215.095 (M⁺, calc.: 215.095). (Found: C, 72.87; H, 6.35; N, 6.36. Calc. for C₁₃H₁₃N₂O: C, 72.54; H, 6.09; N, 6.51%.)

8-Amino-2,3-dihydro-7-methoxy-1H-pyrrolo[1,2-a]indole-9-carboxaldehyde (16f)

To a soln of 16d (1.0 g, 4.6 mmol) in CH₂Cl₂ (75 ml) was added a soln of 65% HNO₃ (1.0 g) in CH₂Cl₂ (15 ml). After stirring for 15 min the reaction mixture was washed with sat NaHCO₃ aq (2 x 50 ml) and dried with MgSO₄. After removal of the solvent crude 16e was obtained (1.18 g) which was used without purification.

A mixture of the crude nitro compound 16e and iron powder (2 g) in 50% aqueous acetic acid was heated at 85° for 2 hr. After removal of the iron by filtration over hyflo the reaction mixture was extracted with CHCl₃ (3 x 75 ml). The combined extracts were washed with sat NaHCO₃ aq (2 x 75 ml), water and dried with MgSO₄. After removal of the solvent the residue was separated by chromatography (EtOAc) to afford pure 16f (42%), m.p. 177-178.5° (EtOAc). ¹H-NMR δ : 9.52 [s, 1H, C(O)H], 6.80 and 6.38 (d, 1H, J = 8.4 Hz, H-5 and H-6), 5.76 (br s, 2H, NH₂), 4.1-3.8 (m, 2H, NCH₂), 3.85 (s, 3H, OCH₃), 3.3-3.0 (m, 2H, H-1), 2.8-2.5 (m, 2H, H-2). ¹³C-NMR δ : 181.9 [d, C(O)H], 158.0 (s, C-7), 111.0 (s, C-9), 109.6 (d, C-5), 97.0 (d, C-6), 57.1 (q, OCH₃), 44.6 (t, NCH₂). IR (KBr) cm⁻¹: 3460 (NH₂), 1630 [C(O)H]. MS: m/e 230.106 (M⁺, calc.: 230.106). (Found: C, 67.75; H, 6.30; N, 11.81. Calc. for C₁₃H₁₄N₂O₂: C, 67.81; H, 6.13; N, 12.17%.)

2,3,5,8-Tetrahydro-7-methoxy-5,8-dioxo-1H-pyrrolo[1,2-a]indole-9-carboxaldehyde (15b)

To a soln of 16f (0.12 g, 0.5 mmol) in acetone (30 ml) and 0.167 M potassium dihydrogen phosphate (15 ml) was added a soln of Fremy's salt (0.6 g, 2.2 mmol) in water (30 ml). After stirring for 22 hr at room temp the mixture was diluted with water (100 ml) and then extracted with CHCl₃

(3 x 50 ml). The combined extracts were washed with brine (2 x 50 ml) and dried with $MgSO_4$. After removal of the solvent pure **15b** was obtained in quantitative yield, m.p. 247-248° (EtOH). 1H -NMR δ : 10.37 [s, 1H, C(O)H], 5.70 (s, H-6), 4.4-4.15 (m, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.3-3.0 (m, 2H, H-1), 2.85-2.5 (m, 2H, H-2). ^{13}C -NMR δ : 186.7 [d, C(O)H], 178.1 and 177.3 (s, C=O), 160.6 (s, C-7), 149.4 (s, C-9a), 130.8 and 128.8 (s, C-4a and C-8a), 116.0 (s, C-9), 105.6 (d, C-6), 56.7 (q, OCH_3), 47.4 (t, NCH_2), 26.9 and 25.1 (t, C-1 and C-2). IR (KBr) cm^{-1} : 1677 and 1663 (C=O), 1637 [C(O)H]. MS: m/e 245.069 (M^+ , calc.: 245.069). (Found: C, 63.83; H, 4.55; N, 5.65. Calc. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.72%.)

Ethyl α -cyano-1,4-dihydro-1,4-dioxo-3-(2-oxo-1-pyrrolidinyl)-2-naphthaleneacetate (18)

To a yellow suspension of **17**²⁹ (2.75 g, 10 mmol) and ethyl cyanoacetate (1.2 ml, 11 mmol) in dry DMSO (20 ml) was added potassium succinimidate.³¹ After 3 days the resulting purple coloured reaction mixture was diluted with water (20 ml), acidified with 10% HCl and extracted with EtOAc (3 x 100 ml). The combined organic layers were washed once with water and then extracted with sat $NaHCO_3$ aq (10 x 100 ml). The combined $NaHCO_3$ layers were acidified with 10% HCl and then extracted with EtOAc (3 x 500 ml). The combined extracts were washed with brine (50 ml), dried ($MgSO_4$) and evaporated. The crude product was recrystallized from MeOH to give pure **18** (73%), m.p. 178-180° (dec). 1H -NMR δ : 8.25-7.75 (m, 4H, ArH), 5.30 (s, 1H, CHCN), 4.45-3.65 (m, 4H, NCH_2 and OCH_2), 2.75-2.25 (m, 4H, $H_2CC=O$ and $H_2CCC=O$), 1.30 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C -NMR δ : 181.4 and 180.2 (s, C=O), 176.2 (s, NC=O), 162.7 (s, OC=O), 141.4 (s, C-2), 113.9 (s, CN), 63.7 (t, OCH_2), 49.9 (t, NCH_2), 35.2 [d, $CH(CN)$], 30.6 (t, $CH_2C=O$), 13.9 (q, CH_3). IR (KBr) cm^{-1} : 2250 (CN), 1745, 1670 and 1640 (C=O). MS: m/e 352.106 (M^+ , calc.: 352.106). (Found: C, 64.79; H, 4.51; N, 7.92. Calc. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95%.)

1,4-Dimethoxy-3-(2-oxo-1-pyrrolidinyl)-2-naphthaleneacetonitrile (20)

Hydrogen was bubbled through a soln of **18** (1.0 g, 2.8 mmol) in dry DMF (18 ml) to which was added 5% Pd/C (120 mg) until the soln was colourless (3 hr). Then $Ba(OH)_2 \cdot 8H_2O$ (2.76 g, 8.7 mmol) and dimethyl sulfate (1.5 ml, 15.8 mmol) were added and slow hydrogen bubbling was continued. After 24 hr dimethyl sulfate (0.5 ml) was added again; this was repeated once after another 24 hr. After again 24 hr the soln was filtered and evaporated. The residue was taken up in EtOAc (100 ml) and the resulting soln was extracted with 1 N Na_2CO_3 (5 x 100 ml). The combined basic water layers were heated at 60° for 3 days. Upon cooling **20** precipitated. The ppt was collected by filtration, dried and recrystallized from MeOH to afford pure **20** (52%), m.p. 157-158°. 1H -NMR δ : 8.2-8.0 and 7.7-7.5 (m, 2H, ArH), 4.3-4.0 (m, 2H, NCH_2), 3.94 (s, 3H, OCH_3), 3.88 (s, 5H, OCH_3 and CH_2CN), 2.75-2.25 (m, 4H, $H_2CC=O$ and $H_2CCC=O$). ^{13}C -NMR δ : 175.8 (s, C=O), 150.6 and 150.0 (s, C-1 and C-4), 126.6 (s, C-2), 119.6 (s, C-3), 117.9 (s, CN), 62.9 and 62.4 (q, OCH_3), 49.4 (t, NCH_2), 31.0 (t, $CH_2C=O$), 19.6 (t, CH_2CN). IR (KBr) cm^{-1} : 2240 (CN), 1685 (C=O). MS: m/e 310.132 (M^+ , calc.: 310.132). (Found: C, 69.70; H, 5.80; N, 8.99. Calc. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03%.)

2,3-Dihydro-5,10-dimethoxy-1H-benz[f]pyrrolo[1,2-a]indole-11-carbonitrile (21)

A soln of KO^t -Bu (130 mg, 1.1 mmol) in THF (2 ml) was added dropwise to a soln of **20** (150 mg, 0.5 mmol) in THF (5 ml). After stirring for 3 hr some drops of water were added and the reaction mixture was concentrated. EtOAc (200 ml) was added to the residue and the resulting soln washed with sat NH_4Cl aq (2 x 100 ml) and water, dried ($MgSO_4$) and evaporated. The residue was purified by chromatography [neutral Al_2O_3 90 (II-III), CH_2Cl_2] to give **21** (80%), m.p. 196-197° (EtOH). 1H -NMR δ : 8.3-8.1 and 7.5-7.3 (m, 2H, ArH), 4.47 (t, 2H, J = 7.4 Hz, NCH_2), 4.13 and 4.04 (s, 3H, OCH_3), 3.23 (t, 2H, J = 7.3 Hz, $=CCH_2$), 2.72 (m, 2H, $=CCCH_2$). ^{13}C -NMR δ : 157.7 and 157.8 (s, C-5 and C-10), 144.0 (s, C-11a), 136.8 (s, C-10a), 131.3 (s, C-4a), 115.0 (s, CN), 108.2 (s, C-11), 64.1 and 63.5 (q, OCH_3), 47.3 (t, NCH_2). IR (KBr) cm^{-1} : 2220 (CN). MS: m/e 292.123 (M^+ , calc.: 292.121). (Found: C, 74.00; H, 5.51; N, 9.60. Calc. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58%.)

2,3,5,10-Tetrahydro-5,10-dioxo-1H-benz[f]pyrrolo[1,2-a]indole-11-carbonitrile (22)

A soln of CAN (210 mg, 0.38 mmol) in water (1 ml) was added to a soln of **21** (50 mg, 0.17 mmol) in CH_3CN (10 ml) at 0°. After stirring for 30 min at 0° the part of **22** which had precipitated, was filtered off. In addition the filtrate was extracted with $CHCl_3$ (3 x 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated to afford another crop of crude **22**. The combined solids were

recrystallized from EtOH to give pure **22** (91%), m.p. 271–272°. $^1\text{H-NMR}$ δ : 8.2–7.8 and 7.7–7.6 (m, 2H, ArH), 4.44 (t, 2H, $J = 7.2$ Hz, NCH_2), 3.2–3.0 (m, 2H, $=\text{CCH}_2$), 2.9–2.6 (m, 2H, $=\text{CCCH}_2$). IR (KBr) cm^{-1} : 2220 (CN), 1660 (C=O). MS: m/e 262.073 (M^+ , calc.: 262.074). (Found: C, 73.24; H, 3.80; N, 10.69. Calc. for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_2$: C, 73.27; H, 3.84; N, 10.68%.)³⁵

Acknowledgement—We are grateful for the financial support of this work by the "Koningin Wilhelmina Fonds". We express our gratitude to J.M. Visser and J.L.M. Vrieling for recording the NMR- and to T.W. Stevens for recording the mass spectra. The authors are indebted to Prof. Dr. W.N. Speckamp and Dr. E.A. Oostveen (University of Amsterdam) for stimulating discussions and the exchange of information about the preparation of the starting materials.

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