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SYNTHESIS OF DIHYDRO-1H-PYRROLO- AND TETRAHYDROPYRIDO[1,2-a]INDOLES VIA A MODIFIED MADELUNG REACTION

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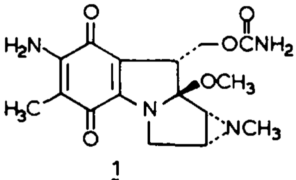
Abstract-1-(2-Methylphenyl)lactams **9**, having different electron-withdrawing groups at the benzylic position, cyclize under the influence of sodium hydride or potassium tert-butoxide. Depending on the ring size of the lactam moiety dihydropyrrolo- (**10**), tetrahydropyrido[1,2-a]indole (**11**), or dihydro-1H-1-benzazepine (**12**) derivatives are formed. Pyrrolo[1,2-a]indole **10c** has been converted into the corresponding quinone **15b**. Starting from naphthaleneacetonitrile **20**, prepared in 5 steps from 2,3-dichloronaphthoquinone, the 5,10-dioxo-1H-pyrrolo[1,2-a]benz[f]indole **22** is obtained upon treatment with base and subsequent oxidation of the protected hydroquinone function with ceric ammonium nitrate.

The interest in pyrrolo[1,2-a]indoles remains high because a 2,3,9,9a-tetrahydro-5,8-dioxo-1H-pyrrolo[1,2-a]indole constitutes the basic skeleton of the mitomycins, an important class of heterocyclic anti-tumour antibiotics.[1,2] In spite of the relative high toxicity mitomycin C (**1**) is currently employed clinically for the treatment of solid tumours.[2] Mitosenes (**2**), which arise from mitomycins by elimination of the functionality at C-9a,[2] generally also exhibit anti-tumour activity.[3]



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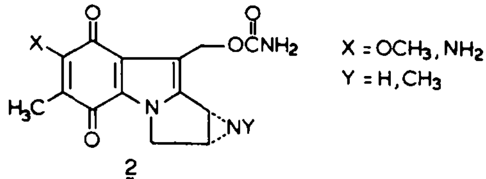

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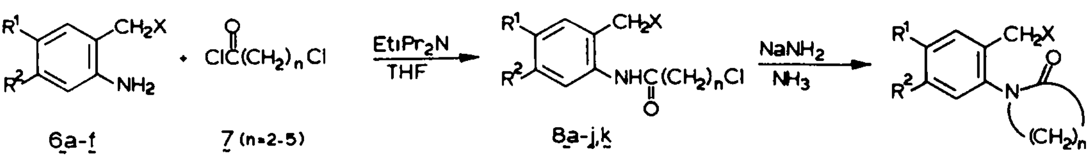
Synthetic methods for the synthesis of pyrrolo[1,2-a]indoles have been thoroughly reviewed.[4] Recently we have published a synthesis of 2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a]indoles based on the principle of the "tertiary amino effect" in heterocyclic chemistry.[5] In the present paper we wish to describe our approach to the synthesis of 2,3-dihydro-1H-pyrrolo[1,2-a]indoles (potential mitosenes) which represents a modification of the Madelung indole synthesis; the intramolecular condensation of N-acylated-ortho-alkylanilines.[6] The original reaction as developed by Madelung suffers from the drawback that drastic conditions e.g. 200-400° and strong bases, are required.[7] More recently Houlihan et al.[8] performed the reaction at lower temperatures but the excess of n-butyllithium or lithium diisopropylamide required, restricts the use of this reaction. A related method for the synthesis of indoles has been developed by Bergman et al.[9] Starting from 2-methyl-3-nitroanilines or the corresponding imino ether derivatives, 4-nitroindoles were obtained by reaction with diethyl oxalate under the influence of potassium ethoxide. In this reaction the nitro group stabilizes the intermediate carbanion at the adjacent ring carbon atom. A variation of the Madelung reaction was found by Schulenberg[10] 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-acylaminobenzylidenephosphoranes 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 Sand[15] 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.

RESULTS[17] 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.



6a-f 7 (n=2-5) 8a-j,k 9a-j,m

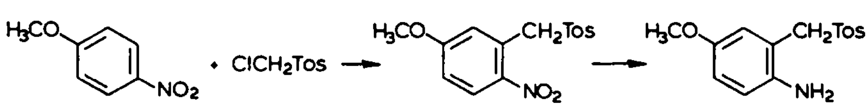
	n	R^1	R^2	X
a	3	H	H	CN
b	3	OCH_3	OCH_3	CN
c	3	OCH_3	H	CN
d	3	OCH_3	CH_3	CN

	n	R^1	R^2	X
e	3	OCH_3	OCH_3	Tos
f	3	H	H	CO_2t-Bu
g	4	OCH_3	OCH_3	CN
h	4	OCH_3	H	CN

	n	R^1	R^2	X
i	4	OCH_3	CH_3	CN
j	2	OCH_3	OCH_3	CN
k	5	OCH_3	OCH_3	CN
m	3	H	H	CO_2Me

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 nucleofilic substitution reaction[20] 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 (KOt-Bu) afforded the nitrobenzene 5 in a yield of 89%. Subsequent reduction of the nitro group with iron metal in ethanol[22] gave the aniline 6e (60%) (Scheme 2).



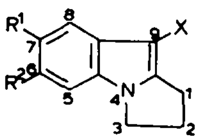
3 4 5 6e

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

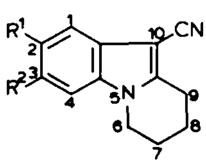
2). Subsequent cyclization of the amides **8** according to Manhas and Jeng[23] with 1.5 equivalents of sodium amide ($NaNH_2$) in liquid ammonia gave the lactams **9a–j** (Table 3). Compound **8k** failed to undergo cyclization under different reaction conditions used. This result is in line with the work of Manhas and Jeng[23] 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 triamide[24] 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 acid[26] 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**.



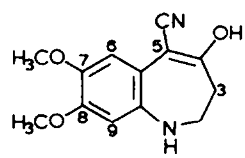
10

	R^1	R^2	X
a	H	H	CN
b	OCH_3	OCH_3	CN
c	OCH_3	H	CN
d	OCH_3	CH_3	CN
e	OCH_3	H	Tos
f	H	H	CO_2t-Bu
g	H	H	CO_2Me

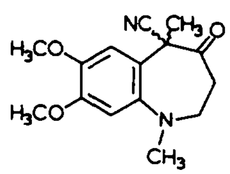


11

	R^1	R^2
a	OCH_3	OCH_3
b	OCH_3	H
c	OCH_3	CH_3



12



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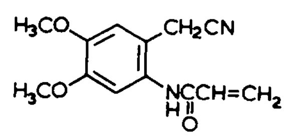


14

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-azetidinyl)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-i**.

Product	m.p. (°C) (solvent)	Method A Time (hr)	Method A Temp (°C)	Method A Yield (%)	Method B Time (min)	Method B 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

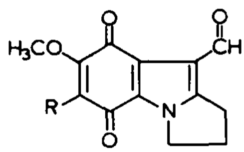
a) Decomposes. b) Ref. 27 m.p. 203-203.5°. c) Ref. 28 m.p. 173-173.5°, Ref. 27 m.p. 174-174.5°. d) Could not be recrystallized. e) Only polymeric material was obtained. f) Yields **10f** in 58%.

The ^{13}C-NMR spectrum of benzazepine **12** exhibits =$\underline{C}$CN and =COH absorptions at δ 88.6 and 170.4, respectively, while the ^{1}H-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-1$\underline{H}$-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}. ^{13}C-NMR spectroscopy shows in addition to a C=O signal at δ 202.4, the NCH_3 and $\underline{C}CH_3$ absorptions at δ 41.8 (q) and 23.6 (q), respectively. In the ^{1}H-NMR spectrum both the NH and OH signals are missing and the NCH_3 and CCH_3 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$\underline{t}$-Bu were added resulting in the formation of the desired pyrrolo[1,2-$\underline{a}$]indoles **10** or the pyrido[1,2-$\underline{a}$]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$\underline{t}$-Bu caused dehydrohalogenation of the intermediate propanamide **8j** leading to $\underline{N}$-[2-(cyanomethyl)-4,5-dimethoxyphenyl]propenamide (**14**; 77%).

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

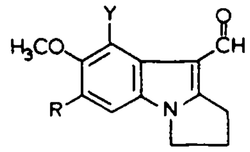
10d has previously been converted into quinone **15a** by the sequence: reduction of the cyano to an aldehyde group (**16a**), nitration (**16b**), reduction of the nitro group and subsequent oxidation of the resulting aniline derivative (**16c**) by Fremy's salt.[27] In a similar way we have converted 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**).



15

a R= CH_3

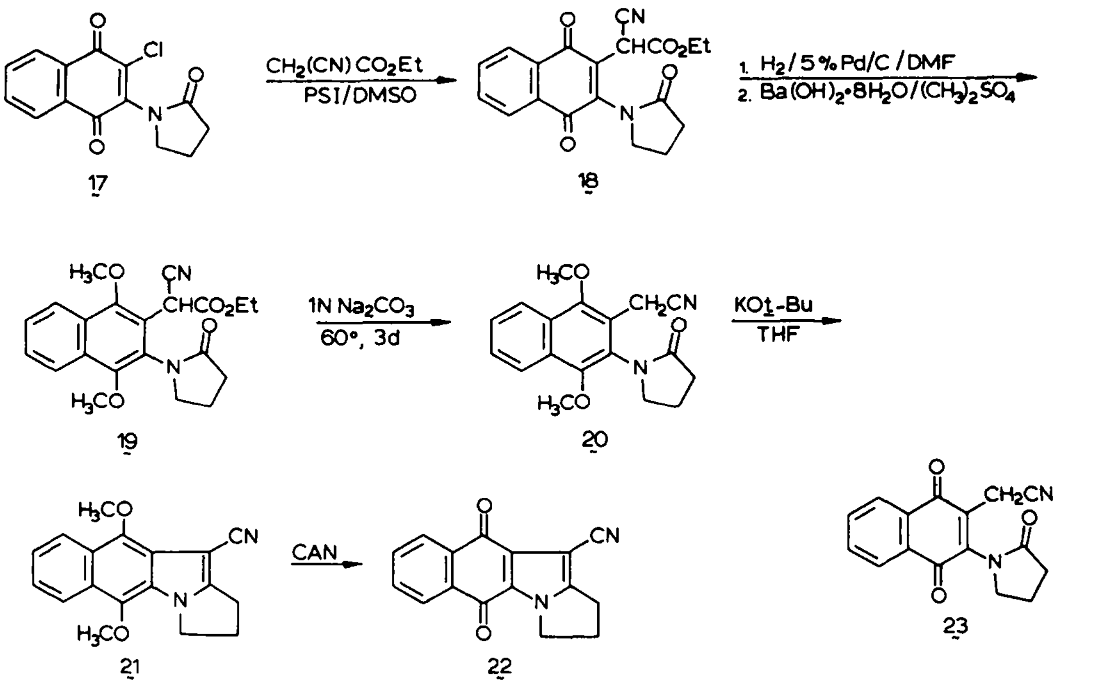
b R= H



16

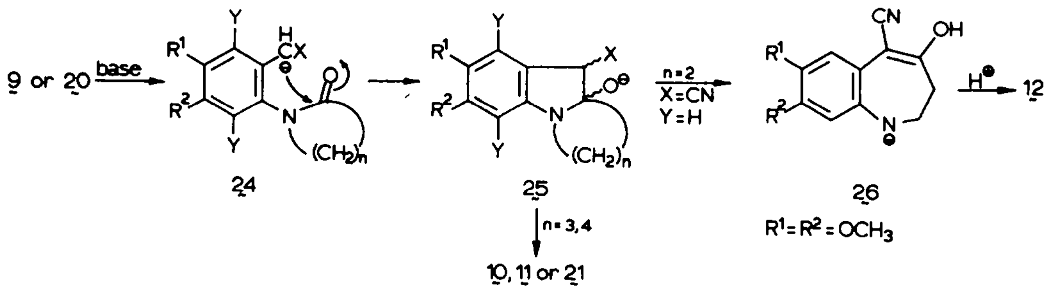
	R= CH_3		R= H
a	Y= H	**d**	Y= H
b	Y= NO_2	**e**	Y= NO_2
c	Y= NH_2	**f**	Y= NH_2

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 KOt-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 methylation[32] of quinone **18** by catalytic hydrogenation in the presence of dimethyl sulfate and $Ba(OH)_2 \cdot 8H_2O$ 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 KO*t*-Bu in THF at room temperature afforded the 1*H*-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.



Scheme 4

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 KO*t*-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-i 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-1*H*-pyrrolo[1,2-*a*]indoles (10,21) and 6,7,8,9-tetrahydro-1*H*-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.ps were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Bruker WP-80 spectrometer and ^{13}C-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-methylphenyl)sulfonyl]methyl]-1-nitrobenzene (5)

To a soln of KO*t*-Bu (12.5 g, 112 mmol) in THF (1 l) was added dropwise a soln of 1-[(chloromethyl)sulfonyl]-4-methylbenzene[21] (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 CH$_2$X (s)	CH$_2$Cl (m)	ArH	^{13}C-NMR ($CDCl_3$), δ NC=O (s)	CH$_2$Cl (t)	R^1 (q)	R^2 (q)	MS(M$^+$) found (calcd)
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 (s,1H) 6.79 (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 (s,1H) 6.81 (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 (m,2H) 6.3-6.2 (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 (s,1H) 6.78 (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] (d,H-6) 7.0-6.7 (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 (s,1H) 6.77 (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 (s,1H) 6.88 (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 (s,1H) 6.79 (s,1H)	172.0	44.8	56.2	56.1	324.124 (324.123)

a) Satisfactory elemental analyses (±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°)/$CHCl_3$. 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 NH_4Cl aq (250 ml) and extracted with Et_2O (3 x 200 ml). After drying ($MgSO_4$) 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). ^{1}H-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, CH_2Ar), 3.90 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3Ph). ^{13}C-NMR δ: 162.9 (s, C-4), 142.2 (s, C-1), 135.0 (s, Ar<u>C</u>S), 125.9 (s, C-2), 59.0 (t, CH_2Ar), 56.0 (q, OCH_3), 21.7 (q, CH_3Ph). IR (KBr) cm^{-1}: 1340 and 1140 (SO_2). MS: <u>m/e</u> 321.065 (M$^+$, calc.: 321.067). (Found: C, 56.23; H, 4.75; N, 4.37. Calc. for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.71; N, 4.36%.)

<u>4-Methoxy-2-[[(4-methylphenyl)sulfonyl]methyl]benzenamine</u> (**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 Na_2CO_3 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). ^{1}H-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, CH_2Ar), 3.93 (br s, 2H, NH_2), 3.54 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3Ph). ^{13}C-NMR δ: 158.4 (s, C-4), 152.8 (s, C-1), 134.9 (s, Ar<u>C</u>S), 127.6 (s, C-2), 60.0 (t, CH_2Ar), 55.6 (q, OCH_3), 21.6 (q, CH_3Ph). IR (KBr) cm^{-1}: 3460 and 3380 (NH_2). MS: <u>m/e</u> 291.093 (M$^+$, calc.: 291.093). (Found: C, 61.75; H, 5.90; N, 4.84. Calc. for $C_{15}H_{17}NO_3S$: 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] CH$_2$X (s)	CH$_2$N (m)	ArH	^{13}C-NMR ($CDCl_3$), δ[e] NC=O (s)	CH$_2$N (t)	R^1 (q)	R^2 (q)	MS(M$^+$) found (calcd)
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 ^{1}H-NMR and ^{13}C-NMR spectra of 9j were recorded in DMSO-d_6. 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 Et*i*-Pr_2N (4.7 ml, 27.5 mmol) and amine 6 (25 mmol) in THF (70 ml) was added a soln of the acid chloride 7[33] (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 NH_4Cl aq (2 x 250 ml). Drying ($MgSO_4$) 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 triturated with EtOAc; 8b-d,h,i,k with diisopropyl ether and 8e with MeOH. Compd 8f was purified by chromatography using $CHCl_3$ 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 $NaNH_2$ (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 NH_3, $CHCl_3$ (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 $MgSO_4$. Evaporation afforded the crude 9a-j, which were purified as follows: 9a,d,i were triturated with diisopropyl ether; 9b,j with EtOH; 9e with benzene and 9c,f-h by chromatography (EtOAc/$CHCl_3$ 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 CF_3COOH (500 mg, 4.4 mmol) in CH_2Cl_2 (15 ml) was refluxed for 4 hr. The reaction mixture was washed twice with water, dried ($MgSO_4$) 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 CH_2N_2 [prepared from diazald (3.0 g, 13.7 mmol)] in Et_2O (30 ml) at 0°. After stirring for 15 min the excess of CH_2N_2 was destroyed using some drops of AcOH. After removal of the solvents the residue was dissolved in CH_2Cl_2 (30 ml), and the resulting soln washed with 2 N NaOH (2 x 20 ml). After drying ($MgSO_4$) 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 NH_4Cl aq (75 ml) and dried ($MgSO_4$). Evaporation of the toluene afforded the crude products **10a-g** and **11a**.

Method B (KO*t*-Bu/THF).

To a soln of KO*t*-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 NH_4Cl aq (2 x 100 ml) and dried ($MgSO_4$). 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/$CHCl_3$ 1:1 as eluent and **11c** using $CHCl_3$ 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°.[34] ^{1}H-NMR (DMSO-*d*$_6$) 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, OCH_3), 3.2-3.1 (m, 2H, NCH_2), 2.7-2.6 (m, 2H, CH_2C=). ^{13}C-NMR (DMSO-*d*$_6$) 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 $C_{13}H_{14}N_2O_3$: 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 K_2CO_3 (275 mg, 2 mmol) and CH_3I (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 NH_4Cl aq (2 x 100 ml), dried ($MgSO_4$) and evaporated. The crude residue was subjected to chromatography (EtOAc/MeOH 95:5) to give **13** as an oil (37%). ^{1}H-NMR δ: 7.07 and 6.73 (s, 1H, ArH), 3.92 and 3.91 (s, 3H, OCH_3), 3.3-2.5 (m, 4H, NCH_2 and CH_2CO), 2.74 (s, 3H, NCH_3), 1.77 (s, 3H, CH_3). ^{13}C-NMR δ: 202.4 (s, C=O), 56.6 (t, C-2), 52.3 (s, C-5), 41.8 (q, NCH_3), 38.5 (t, C-3), 23.6 (q, CH_3). IR (KBr) cm^{-1}: 2240 (CN), 1730 (C=O). MS: m/e 274.131 (M^+, calc. for $C_{15}H_{18}N_2O_3$: 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 $CHCl_3$ (2 x 100 ml). The combined extracts were washed with sat $NaHCO_3$ aq (4 x 100 ml), water and dried with $MgSO_4$. After removal of the solvent the residue was purified by chromatography ($CHCl_3$/EtOAc 1:1) to give pure **16a** (80%), m.p. 150-153° (MeOH). ^{1}H-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, NCH_2), 3.88 (s, 3H, OCH_3), 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^+)
	=C-CH_2 (m)	CH_2N (m)	ArH (m)	eR^1 (s)	eR^2 (s)	CH_2N (t)	R^1 (q)	R^2 (q)	C-X (s)	found (calcd)
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 6.75 (s,1H) (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 7.03 (s,H-4)(s,H-1)	3.88	2.32	42.5	55.7	17.1	144.8	240.126 (240.126)

a) Satisfactory elemental analyses (±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) R^1, R^2 = H. f) The C-9 signals of the pyrrolo[1,2-a]indoles 10a-g were situated with small intensities in the region of δ100-109, while the C-10 signals of 11a-c were located at δ82.2, 82.2 and 81.8, respectively.

^{13}C-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, OCH_3), 44.7 (t, NCH_2). 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 $C_{13}H_{13}NO_2$: 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 CH_2Cl_2 (75 ml) was added a soln of 65% HNO_3 (1.0 g) in CH_2Cl_2 (15 ml). After stirring for 15 min the reaction mixture was washed with sat $NaHCO_3$ aq (2 x 50 ml) and dried with $MgSO_4$. 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 $CHCl_3$ (3 x 75 ml). The combined extracts were washed with sat $NaHCO_3$ aq (2 x 75 ml), water and dried with $MgSO_4$. After removal of the solvent the residue was separated by chromatography (EtOAc) to afford pure 16f (42%), m.p. 177-178.5° (EtOAc). ^{1}H-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, NH_2), 4.1-3.8 (m, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.3-3.0 (m, 2H, H-1), 2.8-2.5 (m, 2H, H-2). ^{13}C-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, OCH_3), 44.6 (t, NCH_2). IR (KBr) cm^{-1}: 3460 (NH_2), 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 $C_{13}H_{14}N_2O_2$: 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 $CHCl_3$

(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). ^{1}H-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). ^{1}H-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°. ^{1}H-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). ^{1}H-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}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, $=CCH_2$), 2.9-2.6 (m, 2H, $=CCCH_2$). 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 $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68%.)[35]

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