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SYNTHESIS OF 3-SUBSTITUTED INDOLES VIA A MODIFIED MADELUNG REACTION

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Abstract-Anilides **4a-c,e-k**, **11a-d** in which the amide function is benzylated, or silylated and having different electron-withdrawing groups (EWG) at the methyl moiety in the ortho position of the amide function, cyclize under the influence of potassium tert-butoxide to the corresponding indole derivatives **5a-c,e-k** and **9a-d**, respectively. Under these conditions the chloroacetamides **4d,n** and **11e** are converted into the tetrahydroquinolines **6a,b** and **12**, respectively. Treatment of chloroacetamide **4m** with KOt-Bu gave, in addition to starting material, indole **5m**, tetrahydroquinoline **6c** and 2(1H)-quinolinone **7**. When 3-indolecarbonitrile **5a** is treated with sodium in liquid ammonia debenzylation takes place, while after catalytic hydrogenation with 5% Pd/C the corresponding 2,3-dimethylindole **8** is formed.

The development of new synthetic methods for the construction of the indole nucleus remains of great importance. This is due to the fact that the indole ring system constitutes part of a large variety of natural products.[1] Specifically, many 3-substituted indoles are well known to have a biological function, either as intermediates or as natural drugs.[1]

One of the approaches to this class of heterocycles is the Madelung indole synthesis,[2] which involves the intramolecular condensation of an N-acylated-ortho-alkylaniline using a strong base at temperatures of 200-400°. Although Houlihan et al.[3] performed the reaction at lower temperatures, the excess of n-butyllithium or lithium diisopropylamide required, restricts the use of this reaction. Among related methods for the synthesis of indoles we can enumerate those of Schulenberg,[4] Bergman et al.,[5] Le Corre et al.,[6] and Makosza et al..[7]

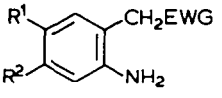
Recently we have published a modified Madelung indole synthesis for the preparation of 2,3-dihydro-1H-pyrrolo[1,2-a]indoles and 6,7,8,9-tetrahydropyrido[1,2-a]indoles.[8] In the present paper we describe the results of our work on the modified Madelung indole synthesis under mild conditions of N-monoacylated-ortho-alkylanilines in which the nitrogen is also benzylated, or in which the amide function is also silylated and carrying different electron-withdrawing groups (EWG) at the methyl moiety in the ortho position of the amide function to give the 3-EWG-substituted-N-benzylindoles **5** or the indoles **9**.

RESULTS AND DISCUSSION

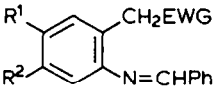
The starting amides **4** for the intramolecular condensation were synthesized in good overall yields by reductive alkylation of the anilines **1**, via formation of the imines **2** and subsequent reduction to the N-benzylanilines **3**, followed by acylation to afford the amides **4**.

The anilines **1a**,[9] **1b**,[10] **1c**,[7] and **1e**,[11] were obtained according to the literature. The cor-

responding imines **2a–c,e** could be easily synthesized using benzaldehyde in benzene under azeotropic removal of water. Selective reduction of the imines **2** using $NaCNBH_3$[12] in methanolic HCl gave the N-benzylated anilines **3** in good overall yields from **1** (75–86%). The aniline derivatives **3** were converted into the amides **4** using different conditions, dependent on the EWG. In most cases the amides **4** were formed under acid catalysis (p-TosOH). However, when a tert-butyl ester is applied as EWG (**4b** and **4i**) these conditions would result in the loss of the tert-butyl group.



1a-c,e



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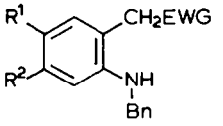
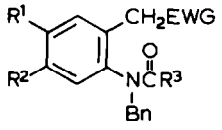


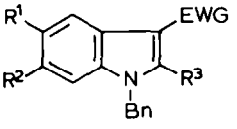
3a-c,e

	R^1	R^2	EWG
a	OCH_3	OCH_3	CN
b	H	H	CO_2t-Bu

	R^1	R^2	EWG
c	Cl	H	SO_2Ph
e	H	H	CN



4a-j,m,n



5a-c, e-m

	R^1	R^2	R^3	EWG
a	OCH_3	OCH_3	CH_3	CN
b	H	H	CH_3	CO_2t-Bu
c	Cl	H	CH_3	SO_2Ph
d	H	H	CH_2Cl	CN
e	OCH_3	OCH_3	H	CN
f	OCH_3	OCH_3	CF_3	CN
g	OCH_3	OCH_3	Ph	CN

	R^1	R^2	R^3	EWG
h	OCH_3	OCH_3	CH_2OCH_3	CN
i	H	H	Ph	CO_2t-Bu
j	Cl	H	Ph	SO_2Ph
k	OCH_3	OCH_3	CH_3	CO_2CH_3
m	Cl	H	CH_2Cl	SO_2Ph
n	OCH_3	OCH_3	CH_2Cl	CN

Therefore these amides were synthesized under basic conditions [ethyldiisopropylamine ($EtiPr_2N$), dimethylaminopyridine (DMAP), CH_2Cl_2].

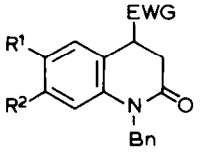
The formylation reaction to give **4e** was carried out with a mixed anhydride formed from formic acid and acetic anhydride.[13] The methoxyacetyl group was introduced using the acid chloride of methoxyacetic acid,[14] while the other amides were synthesized using commercially available acid anhydrides or acid chlorides.

In order to examine the behaviour of a different ester function as EWG on the intramolecular condensation we decided to transform the 2-(cyanomethyl)anilide **4a** into **4k** using a Pinner synthesis.[15] When a solution of **4a** in methanol was exposed to a continuous stream of HCl gas and subsequently refluxed for 2 hr **4k** was obtained in a yield of 79%.

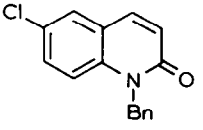
In most cases the compounds **4** displayed hindered rotation around the amide bond as can be deduced from their ^{1}H-NMR spectra, viz. the NCH_2 and the CH_2EWG signals are present as AB quartets. Compound **4e** even consisted of two conformers (3:7) as was revealed by the spectral data. In this case of steric hindrance the C=O moiety of the minor conformer is located in the vicinity of the aromatic ring. This is revealed in the ^{1}H-NMR spectrum by an upfield shift of the CHO absorption of the minor conformer at δ 8.55 as compared with a value of δ 8.13 for the main conformer. In addition the ^{13}C-NMR spectrum shows double absorptions, e.g. for the CHO doublets at

δ 162.4 (main conformer) and δ 161.9 (minor conformer).

The intramolecular condensation reaction of the amides **4a-c,e-k** was carried out by treatment with 1 equivalent of potassium tert-butoxide (KOt-Bu) in THF at room temperature to yield the corresponding indoles **5a-c,e-k** within 10 min (Table 2). Proof for the structures of the indoles **5** was obtained from the spectral data. The molecular ion (M^+) value in the mass spectra of the indoles **5** is found 18 daltons lower than the M^+ value of the starting anilides **4**. In the ^{1}H-NMR spectra the original CH_2EWG signals are missing. The NC=O absorptions are lacking in both the IR and ^{13}C-NMR spectra. In addition the ^{13}C-NMR spectra reveal the presence of a C=C bond (Table 2). The 5,6-dimethoxyindoles **5a,e-h,k** were found to be sensitive to oxidation and therefore stored under argon.[16]



6 a-c



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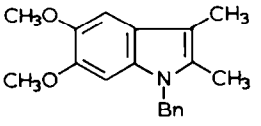


8

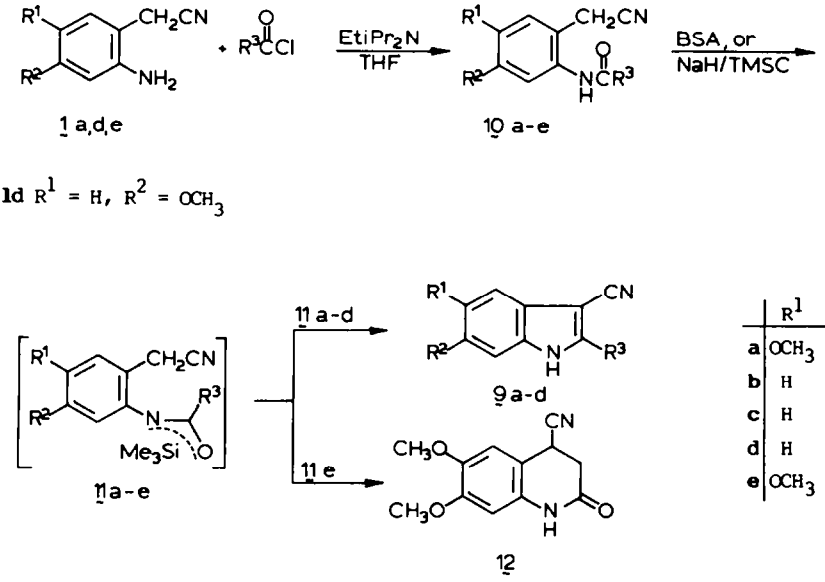
	R^1	R^2	EWG
a	H	H	CN
b	OCH_3	OCH_3	CN
c	Cl	H	SO_2Ph

When the chloroacetamides **4d,m,n** were treated with 1 equivalent of KOt-Bu a deviation of the intramolecular condensation reaction was observed. Under these conditions the chloroacetamide **4d** gave 2-oxo-1,2,3,4-tetrahydroquinoline **6a** as a single product in a yield of 78%. Proof for the structure of **6a** was obtained from the spectroscopic data. The M^+ value of the quinoline **6a** is 36 daltons lower than that of the starting amide **4d**. In the ^{1}H-NMR spectrum a doublet at δ 2.84 (J = 7.8 Hz; H-3) and a triplet at δ 3.98 (J = 7.8 Hz; H-4) are present. The NC=O bond is still present as revealed by the IR and ^{13}C-NMR spectra. Apparently in this case substitution of the activated chlorine atom is preferred over the intramolecular condensation reaction. In the same way **4n** could be converted into the corresponding tetrahydroquinoline **6b**. Starting from chloroacetamide **4m**, in addition to starting material (15%), three products could be isolated, viz. the indole **5m** (16%), the tetrahydroquinoline **6c** (29%), and the known 2(1H)-quinolinone **7**[17] (17%). The latter product is derived from **6c** by a thermal elimination reaction of benzenesulfinic acid, as could be confirmed by stirring **6c** in THF at room temperature. With the exception of the chloroacetamide **4m**, the quinolines **6** derived from the corresponding chloroacetamides **4** could be obtained in good yields (Table 3). To the best of our knowledge this methodology can be considered a new synthetic approach for the construction of 2-oxo-1,2,3,4-tetrahydroquinoline systems containing an EWG at position 4. Similar quinoline derivatives have also been obtained via different routes.[18a,b]

In principle, starting from N-benzylated indoles, also the corresponding N-unprotected indoles are accessible. It is known from the literature[1] that debenzylation of indolic nitrogen can be accomplished by treatment with sodium in liquid ammonia or using hydrogen over 10% palladium-charcoal. However, a similar substituted indole, viz. ethyl 2-methyl-1-(phenylmethyl)-1H-indole-3-carboxylate, could not be transformed into the corresponding unblocked indole derivative in these ways.[19] We therefore decided to study the removal of the protecting group using 3-indolecarbonitrile **5a** as an example. When **5a** was subjected to catalytic hydrogenation with 5% Pd/C during 1 week, 5,6-dimethoxy-2,3-dimethyl-1-(phenylmethyl)-1H-indole (**8**) was obtained in a yield of 85%. The structure of **8** is clearly shown by the spectral data. The mass spectrum exhibits a molecular ion value of 295.156 ($C_{19}H_{21}NO_2$). In the IR spectrum the CN absorption is missing, while the ^{1}H-NMR spectrum shows the presence of 2 CH_3 groups at δ 2.24 (s, 6H). In

addition the ^{13}C-NMR spectrum also reveals 2 CH_3 quartets at δ 10.2 and 9.0. Apparently, under these conditions the nitrile moiety is reduced to an aminomethyl group, which undergoes elimination of the amino part with assistance of the indolic nitrogen lone pair, followed by reduction of the resulting methylene function to a methyl group. However, the desired indole **9a** could be obtained by treatment of **5a** with sodium in liquid ammonia in a yield of 85%.

Although we were able to perform the desired transformation we reasoned that the whole operation, e.g. protection and later deprotection is laborious. Therefore we decided to examine the use of a potentially more easily removable group, *viz.* the trimethylsilyl group. In this case it was even possible to perform our modified Madelung reaction in a one pot process starting from the anilides **10** (Scheme 1). The starting anilines **1a,d,e** were converted into the corresponding amides **10** by reaction with the appropriate acid chloride in THF in the presence of $EtiPr_2N$ at room temperature for 0.5 hr in good yields (81-95%).



	R^1	R^2	R^3
a	OCH_3	OCH_3	CH_3
b	H	H	CH_3
c	H	H	Ph
d	H	OCH_3	CH_3
e	OCH_3	OCH_3	CH_2Cl

Scheme 1

A solution of the anilides **10a-d** in THF was treated either with excess of bis(trimethylsilyl)acetamide[20] (BSA) for 45 min at 40°, or with trimethylsilyl chloride (TMSC) after the addition of 1 equivalent of NaH, followed by adding 1 equivalent of KO*t*-Bu at room temperature to give the corresponding indoles **9** after work up. The silylated amide may undergo an intramolecular modified Peterson type reaction[21] to afford a 3*H*-indole, which undergoes tautomerization to give the corresponding 1*H*-indole. When BSA was used as silylating agent, even in excess (2-4 equivalents) the indoles **9a-d** were obtained in moderate yields (50-58%), probably the equilibrium for the transfer of a silyl group to the anilide **10** is unfavourable. However, treatment with NaH/TMSC gave the desired indoles **9a-d** in good yields (80-89%). Proof for the structure of the indoles was obtained from the spectral data (Table 2). When anilide **10e** was treated with 2 equivalents of BSA, followed by 1 equivalent of KO*t*-Bu the known tetrahydroquinoline **12**[18a] could be obtained in a yield of 51%.

In summary we can conclude that our modified Madelung reaction represents a very useful and simple synthetic method for the preparation of indoles and *N*-alkylindoles containing an EWG at position 3. In general we can state that our method is highly competitive with other routes to this type of indoles.[7,19,22-30]

The indoles **5** and **9** are useful synthetic intermediates, since the ester or nitrile group at position 3 can be easily converted into a variety of other functionalities. The easy availability of the starting materials and the mild conditions used for transforming the amides into the corresponding indoles, provides a convenient access to highly functionalized indoles, that may serve as starting materials for the synthesis of biological active compounds. Further studies for applying our method are in progress.

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 A. Christenhusz of the Laboratory of Chemical Analysis of the University of Twente.

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

Column chromatography was performed with silica gel, unless otherwise stated.

All reactions were carried out under a nitrogen atmosphere.

P.e. is the abbreviation of petroleum ether (b.p. 60–80°).

2-Amino-4-methoxybenzeneacetonitrile (**1d**) was prepared analogously to 2-amino-5-methoxybenzeneacetonitrile.[31] Starting from 2-chloro-5-methoxy-1-nitrobenzene the chlorine atom is substituted with ethyl cyanoacetate, followed by decarboxylation of the resulting product and reduction of the nitro group.

M.p. 83–84° (diisopropyl ether). ^{1}H-NMR δ : 7.08 (d, 1H, J = 7.8 Hz, H-6), 6.35 (dd, 1H, J = 7.8 and 2.2 Hz, H-5), 3.8–3.1 (br s, 2H, NH_2), 3.76 (s, 3H, OCH_3), 3.50 (s, 2H, CH_2CN). ^{13}C-NMR δ : 160.7 (C-4), 145.3 (s, C-2), 130.5 (d, C-6), 117.5 (s, CN), 107.4 (s, C-1), 104.9 (d, C-5), 102.3 (d, C-3), 55.2 (q, OCH_3), 19.2 (t, CH_2CN). IR (KBr) cm^{-1}: 2250 (CN). MS: m/e 162.079 (M^+, calc. 162.079). (Found: C, 66.40; H, 6.25; N, 17.32. Calc. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27.)

General procedure for the synthesis of the N-(phenylmethyl)anilines **3a–d**

To a soln of the aniline **1** (10.7 mmol) in benzene (200 ml) was added benzaldehyde (1.17 ml, 11.5 mmol) and a catalytic amount of p-TosOH, subsequently water was removed by azeotropic distillation, using a Dean-Stark trap. After 16 hr the reaction mixture was evaporated. The resulting crude imine **2** (10.7 mmol) was suspended in MeOH (200 ml) and a small quantity of the indicator bromocresol green was added. To this soln was added a small portion of a 3M methanolic HCl solution followed by a portion of $NaCNBH_3$ until the soln turned blue, then the whole sequence was repeated several times until the yellow colour persisted. Usually, the entire reaction requires 1 equivalent of $NaCNBH_3$. During the reduction product **3c** precipitated and could be collected by filtration, while the others were worked up as follows: the MeOH was removed and the residue was taken up in $CHCl_3$ (150 ml) and water (150 ml). The water layer was extracted once more with $CHCl_3$ (150 ml). The combined extracts were dried ($MgSO_4$) and evaporated. The crude products **3** were purified by recrystallization.

4,5-Dimethoxy-2-[(phenylmethyl)amino]benzeneacetonitrile (**3a**)

Yield 76%, m.p. 74–78° (MeOH). ^{1}H-NMR δ : 7.5–7.25 (m, 5H, PhH), 6.80 and 6.35 (s, 1H, ArH), 4.82 and 4.77 (s, 3H, OCH_3), 4.35 (br s, 2H, CH_2), 3.53 (s, 2H, CH_2CN). ^{13}C-NMR δ : 150.0 (s, C-4 and C-5), 141.7 (s, C-2), 117.5 (s, CN), 57.0 and 56.0 (q, OCH_3), 49.5 (t, CH_2), 20.0 (t, CH_2CN). IR (KBr) cm^{-1}: 2250 (CN). MS: m/e 282.137 (M^+, calc. 282.136). (Found: C, 72.25; H, 6.39; N, 9.89. Calc. for $C_{17}H_{18}NO_2$: C, 72.32; H, 6.43; N, 9.92.)

1,1-Dimethylethyl 2-[(phenylmethyl)amino]benzeneacetate (**3b**)

Yield 75%, m.p. 63–64.5° (p.e.). ^{1}H-NMR δ : 7.4–7.0 and 6.8–6.55 (m, 9H, ArH and PhH), 5.2–4.8 (br s, 1H, NH), 4.37 (br s, 2H, NCH_2), 3.48 (s, 2H, $CH_2C{=}O$), 1.38 [s, 9H, $C(CH_3)_3$]. ^{13}C-NMR δ : 171.1 (s, C=O), 146.6 (s, C-2), 139.4 (s, C-1), 81.3 (s, $\underline{C}Me_3$), 48.0 (t, NCH_2), 40.2 (t, $\underline{CH_2}C{=}O$), 28.0 (q, CH_3). IR (KBr) cm^{-1}: 1700 (C=O). MS: m/e 297.173 (M^+, calc. 297.169). (Found: C, 76.70; H,

7.74; N, 4.74. Calc. for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71.)

4-Chloro-N-(phenylmethyl)-2-(phenylsulfonylmethyl)benzenamine (**3c**)

Yield 85%, m.p. 169-170° (MeOH). ^{1}H-NMR δ : 7.8-7.2 (m, 5H, PhH), 7.08 (dd, 1H, J = 8.8 and 2.5 Hz, H-5), 6.61 (d, 1H, J = 8.8 Hz, H-6), 6.51 (d, 1H, J = 2.5 Hz, H-3), 4.35 (d, 2H, J = 4.3 Hz, NCH_2), 4.34 (s, 2H, CH_2S). ^{13}C-NMR δ : 146.3 (s, C-1), 138.5 (s, C-2), 137.4 (s, ArCS), 115.5 (s, C-4), 59.9 (t, CH_2S), 48.1 (t, NCH_2). IR (KBr) cm^{-1}: 1325 and 1145 (SO_2). MS: m/e 371.075 (M^+, calc. 371.072). (Found: C, 64.55; H, 4.85; N, 3.74. Calc. for $C_{20}H_{18}ClNO_2S$: C, 64.60; H, 4.88; N, 3.77.)

2-[(Phenylmethyl)amino]benzeneacetonitrile (**3e**)

Yield 76%, m.p. 101-102° (MeOH). ^{1}H-NMR δ : 7.5-7.1 and 6.8-6.6 (m, 9H, ArH and PhH), 4.36 (s, 2H, NCH_2), 3.9-3.7 (br s, 1H, NH) 3.51 (s, 2H, $CH_2C{=}O$). ^{13}C-NMR δ : 145.2 (s, C-2), 138.6 (s, C-1), 117.2 (s, CN), 48.0 (t, NCH_2), 20.1 (t, CH_2CN), 28.0 (q, CH_3). IR (KBr) cm^{-1}: 2250 (CN). MS: m/e 222.116 (M^+, calc. 222.116). (Found: C, 81.25; H, 6.36; N, 12.57. Calc. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60.)

General procedure for the synthesis of the N-(phenylmethyl)amides **4a,c-h,j,m,n**

To the acid anhydride, acid chloride or mixed anhydride[32] (50 mmol) was added the N-(phenylmethyl)aniline **3a-c,e** (5 mmol) and a catalytic amount of p-TosOH. The mixture was refluxed and when the reaction was complete as followed from TLC (EtOAc/p.e. 1:1), the excess of reagent was removed under reduced pressure and the residue taken up in EtOAc (200 ml) and water (100 ml). The water layer was carefully neutralized using sat $NaHCO_3$ aq, the layers were separated and the organic soln dried ($MgSO_4$) and evaporated to give the crude N-(phenylmethyl)amides **4a,c-h,j,m,n.** The compounds **4c,f,m,n** were recrystallized from MeOH, while the others were purified by chromatography using EtOAc/p.e. 1:1 as eluent. The yields, melting points, characteristic NMR data and molecular ion values (M^+) are given in Table 1.

General procedure for the synthesis of the N-(phenylmethyl)amides **4b,i**

To a soln of the N-(phenylmethyl)aniline **3b** (1.40 g, 4.7 mmol), DMAP (0.24 g, 2 mmol), and $EtiPr_2N$ (1.16 g, 9 mmol) in CH_2Cl_2 (100 ml) was added acetic anhydride or benzoyl chloride (5 mmol) and the resulting soln was refluxed for 3 days. The reaction mixture was washed with sat NH_4Cl aq (100 ml) and dried ($MgSO_4$). Evaporation afforded the crude N-(phenylmethyl)amides **4b,i**, of which **4i** was purified by recrystallization from Et_2O/p.e., while **4b** was purified by chromatography (EtOAc). The yields, melting points, characteristic NMR data and molecular ion values (M^+) are presented in Table 1.

Methyl 4,5-dimethoxy-2-N-[acetyl(phenylmethyl)amino]benzeneacetate (**4k**)

Hydrogen chloride was bubbled through a soln of N-(phenylmethyl)amide **4a** (0.97 g, 3 mmol) in MeOH (50 ml) and the mixture was refluxed for 2 hr. The resulting soln was poured into water (75 ml), carefully neutralized ($NaHCO_3$) and extracted with EtOAc (3 x 100 ml). The combined extracts were washed with brine (1 x 200 ml), dried ($MgSO_4$) and evaporated to give **4k** (79%) as an oil which could not be crystallized. The characteristic NMR data and molecular ion value (M^+) are given in Table 1.

General procedure for the synthesis of the amides **10a-e**

To a soln of $EtiPr_2N$ (1.16 g, 9 mmol) and the aniline **1a,d,e** (8 mmol) in THF (25 ml) was added a soln of the acid chloride or acetic anhydride (8 mmol) in THF (5 ml) at room temp. After stirring for 1 hr the reaction mixture was concentrated, EtOAc (100 ml) added and the resulting soln washed with sat NH_4Cl aq (2 x 75 ml). Drying ($MgSO_4$) and evaporation of the solvent afforded the crude products **10**, which were purified by trituration. Compound **10a** could be obtained as a very oxidation-sensitive solid after trituration with EtOAc in a yield of 89%, m.p. 179.5-180.5° (ref. 16: 179-180°). The amide **10b** was isolated after recrystallization from benzene in a yield of 81%, m.p. 119-120° (ref. 33: 120°). The anilides **10c-e** were purified by trituration with MeOH. The yields, melting points, characteristic NMR data and molecular ion values (M^+) of the amides **10c-e** are given in Table 1.

General procedure for the synthesis of the 1-(phenylmethyl)indoles **5a-c,e-m**, the tetrahydro-2-oxo-1-(phenylmethyl)quinolines **6a-c** and 6-chloro-1-(phenylmethyl)-2(1H)-quinolinone (**7**)

To a soln of the amide **4a-n** (2.6 mmol) in THF (100 ml) was added KO*t*-Bu (0.3 g, 2.7 mmol). After 10 min the reaction was quenched with water (2 ml) whereupon the reaction mixture was concentrated. EtOAc (100 ml) was added and the resulting soln was washed with sat NH_4Cl aq (2 x 100 ml) and dried ($MgSO_4$). Evaporation afforded the crude 1-(phenylmethyl)indoles **5a-c,e-k** or the tetrahydro-2-oxo-1-(phenylmethyl)quinolines **6a,b**, which were purified by chromatography using

Table 1. Yields, Melting points, Selected Spectroscopic Data of the Amides **4** and **10**[a]

	Yield (%)	m.p. (°C) (solvent)	^{1}H-NMR,[b] δ NCH_2 (AB q, J)	CH_2EWG (AB q, J)	ArH (s, 1H)	R^3 (s)	^{13}C-NMR,[b] δ NC=O (s)	CH_2EWG (t)	MS(M^+) found (calc.)
4a	79	108-110 (Et_2O)	4.92, 4.67 (13.8)	3.32, 3.02 (18.3)	6.90 6.30	1.81 (3H)	170.4	18.9	324.147 (324.146)
4b	94	94-96 (p.e.)	5.40, 4.19 (13.9)	3.37 c	7.45-6.65 d	1.79 (3H)	170.7	37.2	339.183 (339.184)
4c	82	138-139 (MeOH)	5.41, 3.99 (14.0)	4.12 (s)	8.0-7.0 6.64 e 6.54	1.71 (3H)	170.7	56.4	413.088 (413.085)
4d	83	57-58 (MeOH)	4.96, 4.71 (13.8)	3.47, 3.18 (18.6)	7.6-6.9 (m)[d]	3.72 (2H)	166.3	19.7	298.087 (298.087)
4e	98	oil[f]	4.80, 4.71 (s) (s)	3.23 (s)	6.90 6.38 6.29	8.13 8.55	162.4 161.9	19.7 19.2	310.131 (310.132)
4f	79	110-111 (Et_2O)	5.09, 4.61 (13.7)	3.43, 3.10 (15.5)	6.93 6.25	-	157.2 g	19.2	378.119 (378.120)
4g	98	59-61 (Et_2O)	5.00 (s)	2.95 (s)	6.68 6.53	7.4-7.1 (m)[d]	169.7	19.2	386.163 (386.162)
4h	88	125-126 (MeOH)	4.97, 4.64 (13.7)	3.48, 3.04 (18.4)	6.91 6.25	3.66[h] (2H)	169.0	19.0	354.158 (354.158)
4i	81	92-94 i	5.70, 4.32 (13.9)	3.43 j	7.3-6.55 (m)[c]		170.0	37.6	401.199 (401.202)
4j	95	134-137 (MeOH)	5.79, 4.37 (14.3)	3.90, 3.77 (14.2)	6.60 6.56	8.2-7.0 (m)[e]	171.5	56.9	475.100 (475.101)
4k	79	oil	5.38, 4.18 (13.8)	3.36 (s)	6.82 6.08	1.80 (3H)	171.5	35.4	357.148 (357.150)
4m	85	147-148 (MeOH)	5.38, 4.22 (13.9)	4.07 (s)	8.0-7.0 6.81 e 6.70	3.79 (2H)	167.2	56.8	447.049 (447.046)
4n	91	135-136 (MeOH)	5.06, 4.60 (13.7)	3.43, 3.11 (18.5)	6.92 6.29	3.75 (2H)	167.1	19.3	358.108 (358.110)
10c	95	174-175 (EtOAc)	-	3.96 (s)	8.1-7.75 7.6-7.1		165.5	19.9	236.094 (236.095)
10d	92	161-163 (MeOH)	-	3.64 (s)	7.27 6.9-6.7 (d)[k] (m, 2H)	2.21 (3H)	169.4	19.9	204.087 (204.090)
10e	81	161-162 (MeOH)	-	3.63 (s)	6.89 6.86	4.22 (2H)	165.1	20.3	268.061 (268.062)

a) Satisfactory elemental analyses (±0.4% for C, H and N) were obtained for all crystalline amides **4** and **10**. b) The NMR spectra of **10c** were recorded in DMSO-d_6. c) d, J = 1.5 Hz. d) Overlap with Ph signals. e) Overlap with Ph and SO_2Ph signals. f) Mixture of 2 isomers. g) q, J = 35.9 Hz. h) Also δ 3.34 (s, 3H, OCH_3). i) Recrystallized from Et_2O/p.e.. j) d, J = 4.9 Hz. k) H-6, J_{ortho} = 8.0 Hz. The NCH_2 absorptions in the ^{13}C-NMR spectra were found at δ 50.1 - 55.1.

EtOAc/p.e. 1:1 as eluent. Starting from amide **4m** the reaction mixture consisted of starting material (15%), indole **5m** (16%), tetrahydroquinoline **6c** (29%) and 2(1H)-quinolinone **7**[17] (17%), which could be separated by chromatography using CH_2Cl_2 as eluent. Compound **7** was recrystallized from MeOH, m.p. 127-128° (ref. 17: m.p. 129°). The yields, melting points, characteristic NMR data and molecular ion values (M^+) of the 1-(phenylmethyl)indoles **5a-c,e-m** and of the tetrahydro-2-oxo-1-(phenylmethyl)quinolines **6a-c** are summarized in Tables 2 and 3, respectively.

General procedure for the synthesis of the indoles **9** and 1,2,3,4-tetrahydro-6,7-dimethoxy-2-oxo-4-quinolinecarbonitrile (**12**)

a) Using BSA. To a soln of the amide **10** (5 mmol) in THF (50 ml) was added BSA (10-20 mmol) and the reaction mixture was heated for 45 min at 40°, after which the soln was allowed to cool to room

Table 2. Yields, Melting points, Selected Spectroscopic Data of the 1-(Phenylmethyl)indoles **5** and the Indoles **9**[a]

	Yield (%)	m.p. (°C) (solvent)	^{1}H-NMR, δ NCH_2 (s)	ArH (s, 1H)	R^3 (s)	C-2 (s)	^{13}C-NMR, δ C-3 (s)	NCH_2 (t)	MS(M^+) found (calc.)
5a	79	168-169 (MeOH)	5.27	7.13 6.70	2.50 (3H)	143.5	85.3	47.4	306.135 (306.137)
5b	79	120-121 (MeOH)	5.33	7.3 - 6.9 b	2.71 (3H)	144.7	116.2	46.4	321.174 (321.173)
5c	74	141-142 (MeOH)	5.28	8.2 - 7.9 7.6 - 6.9[c]	2.68 (3H)	144.0	100.3	47.1	395.075 (395.075)
5e	79	156-157 (MeOH)	5.30	d 6.75	d	133.0	85.8	51.1	292.122 (292.121)
5f	81	139-141 (MeOH)	5.47	e 6.61	-	131.6	89.0	49.3	360.107 (360.109)
5g	90	153-154 (MeOH)	5.31	f 6.64	7.46 (5H)	146.5	86.0	48.5	368.152 (368.153)
5h	84	120-121 (Et_2O)	5.43	7.15 6.68	4.63[g] (2H)	141.1	87.0	47.9	336,148 (336.147)
5i	83	130-131 (MeOH)	5.15	7.5 - 6.75[b]		146.0	107.2	47.5	383.190 (383.189)
5j	73	157-158 (MeOH)	5.07	8.5 - 8.3[h] 7.8 - 6.7[h]		143.6	114.8	47.9	457.091 (457.091)
5k	72	149-150 (MeOH)	5.30	7.67 6.69	2.67 (3H)	142.9	103.0	46.7	339.147 (339.147)
5m	16	135-136 (MeOH)	5.48	8.2 - 8.0[h] 7.6 - 6.9[h]	5.22 (2H)	142.7	113.6	47.5	429.028 (429.036)
9a	80[i] 56[j]	150-155 k	-	7.07 6.84	2.57 (3H)	142.4	83.5	-	216.090 (216.090)
9d	88[i] 57[j]	168-169 (MeOH)	-	7.5 - 7.3[h] 6.9 - 6.7[h]	2.55 (3H)	144.4	83.9	-	186.080 (186.079)

a) Satisfactory elemental analyses (±0.4% for C, H and N) were obtained for the indoles **5** and **9d**; indole **9a** was found to be very unstable. b) m, overlap with Ph signals. c) m, overlap with Ph and SO_2Ph absorptions. d) m, overlap with Ph signals δ 7.7 - 7.0. e) m, overlap with Ph signals δ 7.4 - 6.9. f) m, overlap with Ph signals δ 7.35 - 6.8. g) Also δ 3.36 (s, 3H, OCH_3). h) m. i) With NaH/TMSC. j) With BSA. k) Compound **9a** could not be recrystallized, due to its sensitivity to oxidation.

temp. Subsequently KOt-Bu (0.6 g, 5.5 mmol) was added and after stirring for 1 hr water (2 ml) was added whereupon the reaction mixture was concentrated. EtOAc (100 ml) was added and the resulting soln washed with sat NH_4Cl aq (2 x 100 ml) and dried ($MgSO_4$). Evaporation afforded the crude indoles **9** or the 2-oxo-tetrahydroquinoline **12**, which were purified by trituration or chromatography. Tetrahydroquinoline **12** could be isolated after chromatography [neutral Al_2O_3 90 (II-III), EtOAc/benzene 4:1] in a yield of 51%, m.p. 199-201° (ref. 18a: 200-202°) and compounds **9a,d** by chromatography using EtOAc as eluent. Compound **9b** was obtained after trituration with $CHCl_3$ in a yield of 58%, m.p. 204-205.5° (ref. 34: 204-206°, ref. 35: 205-208°), while indole **9c** was isolated after trituration with MeOH in a yield of 50%, m.p. 246.5-248° (ref. 34: 246-248°, ref. 36: 240°).

b) Using NaH/TMSC. To a suspension of 80% NaH (0.12 g, 5 mmol) in THF (100 ml) was added the amide **10a-d** (5 mmol) at 0° and when no more hydrogen gas evolved, TMSC (0.55 g, 5 mmol) was added. The reaction mixture was stirred for 15 min at room temp and then KOt-Bu (0.56 g, 5 mmol) was added. After 30 min the reaction was worked up as above. The indoles **9b,c** could be obtained in yields of 89% and 80%, respectively. The yields, melting points, characteristic NMR data and molecular ion values (M^+) of the indoles **9a,d** are summarized in Table 2.

5,6-Dimethoxy-2,3-dimethyl-1-(phenylmethyl)-1H-indole (**8**)

Indole **5a** (0.05 g, 0.16 mmol) was hydrogenated in EtOAc/EtOH (1:1, 10 ml) containing a catalytic amount of 5% Pd/C for 7 days. The reaction mixture was filtered over hyflo and the solvent evaporated. After chromatography (EtOAc/p.e. 1:1) **8** could be isolated in a yield of 85%, m.p. 83-86°. This indole was very sensitive to oxidation and therefore no satisfactory elemental analysis could be obtained. ^{1}H-NMR δ : 7.4-6.75 (m, 6H, Ph and H-4), 6.68 (s, 1H, H-7), 5.22 (s, 2H, NCH_2), 3.92 and 3.82 (s, 3H, OCH_3), 2.24 (s, 6H, CH_3). ^{13}C-NMR δ : 146.3 and 144.7 (s, C-5 and C-6), 138.3 and 138.2 (s, C-2 and C-7a), 121.5 (s, C-3a), 106.6 (s, C-3), 56.6 (q, OCH_3), 46.7 (t, NCH_2), 10.2 and 9.0 (q, CH_3). MS: m/e 259.156 (M^+, calc. for $C_{12}H_{12}N_2O_2$: 259.157).

Table 3. Yields, Melting points, Selected Spectroscopic Data of the Quinolines **6**[a]

			^{1}H-NMR, δ			^{13}C-NMR, δ			MS(M^+)
	Yield (%)	m.p. (°C) (solvent)	NCH_2 (AB q, J)	H-3 (d, J)	H-4 (t, J)	NC=O (s)	C-3 (t)	C-4 (d)	found (calc.)
6a	78	130-131 (MeOH)	5.07, 4.81 (16.3)	2.84 (7.8)	3.98 (7.8)	166.2	34.9	28.5	262.110 (262.111)
6b	74	172-173 (MeOH)	5.35, 5.02 (16.1)	3.07 (7.4)	4.15 (7.4)	166.1	35.2	28.1	322.132 (322.132)
6c	29	181-182 (Et_2O)	5.53 (s)	5.35 (18.0)	2.84 (18.0)	162.0	47.6	63.7	411.070 (411.070)

a) Satisfactory elemental analyses (±0.4% for C, H and N) were obtained for all quinolines **6**.

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