3-AMINO-2(1*H*)-QUINOLONES BY CYCLIZATION OF N-ACYLATED ANTHRANILIC ACID DERIVATIVES

Matthias Rehwald*, Karl Gewald, Hans-Joachim Lankau, and Klaus Unverferth

Institute of Organic Chemistry, Technical University of Dresden, D-01062 Dresden, Germany

Abstract - Reaction of secondary amines with the *N*-(iodoacetyl)anthranilic acid derivatives, 2-(iodoacetylamino)acetophenone and 2-(iodoacetylamino)benzophenone yields 3-amino-2(1*H*)-quinolones in two steps. Analogously heterocondensed 5-amino-6(7*H*)-pyrazolo[5,4-*b*]pyridones were prepared. Hydroxyquinolines were subjected to Cl/OH exchange to give chloroquinolines, which are convenient for consecutive reactions.

4-Hydroxy- and 4-amino-2(1*H*)-quinolones are known as AMPA- and NMDA-receptor antagonists and are considered for the treatment of neurogenerative diseases.[1a,b]

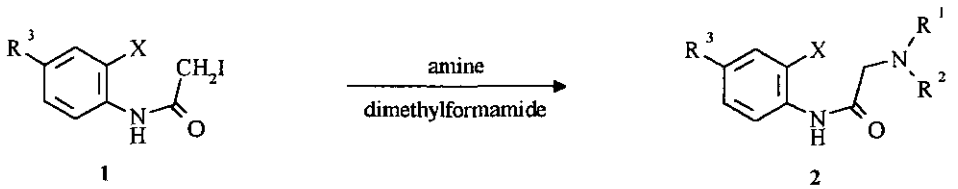
We described the synthesis of 2(1*H*)-quinolones and heterocondensed 2(1*H*)-pyridones accomplished by *Thorpe-Ziegler* cyclization [2,3] and at this we were able to show that various patterns of substitution are obtainable by this way.

RESULTS AND DISCUSSION

The intramoleculare ring closure reaction by *Thorpe-Ziegler* gives rise to amino substituted heterocycles, which otherwise would require a multi-step synthesis. Electron-withdrawing groups usually activate the methylene group for an attack at the nitrile carbon.[4] Now, we established that even electron donor substituted methylene groups undergo the *Thorpe-Ziegler* cyclization when a basic catalytic system like potassium *tert*-butoxide / dimethyl sulfoxide is employed. For our knowledge, such a cyclization under relatively mild conditions was hitherto unreported.

N-Iodoacetylated anthranilic acid derivatives (**1a,b**) and *N*-iodoacetylated o-aminoacetophenone (**1c**) and o-aminobenzophenone (**1d**) were prepared by *Finkelstein* reaction from the respective *N*-chloro-acetylated derivatives.[2] Treatment of *N*-iodoacetylated compounds (**1a-d**) with various secondary amines give the

2-aminoacetyl compounds (**2a-g**), which were subjected to the *Thorpe-Ziegler* cyclization with potassium *tert*-butoxide in dimethyl sulfoxide.



1 **2**

KO*t*Bu / DMSO

3

1,2,3	R^1	R^2	R^3	X	Y
a[a)]	- $(CH_2)_2$ - O - $(CH_2)_2$ -		H	CN	NH_2
b[a)]	- $(CH_2)_2$ - O - $(CH_2)_2$ -		H	CO_2Et	OH
c[a)]	- $(CH_2)_2$ - O - $(CH_2)_2$ -		H	COMe	Me
d	- $(CH_2)_2$ - O - $(CH_2)_2$ -		Cl	COPh	Ph
e	- $(CH_2)_5$ -		H	CN	NH_2
f	- $(CH_2)_2$ - CH(OH) - $(CH_2)_2$ -		H	CN	NH_2
g	Ph	Ph	H	CN	NH_2

a) Preparation of **1** according to lit.[2]

Numbering of C-atoms relates to ^{13}C NMR spectra

Scheme 1

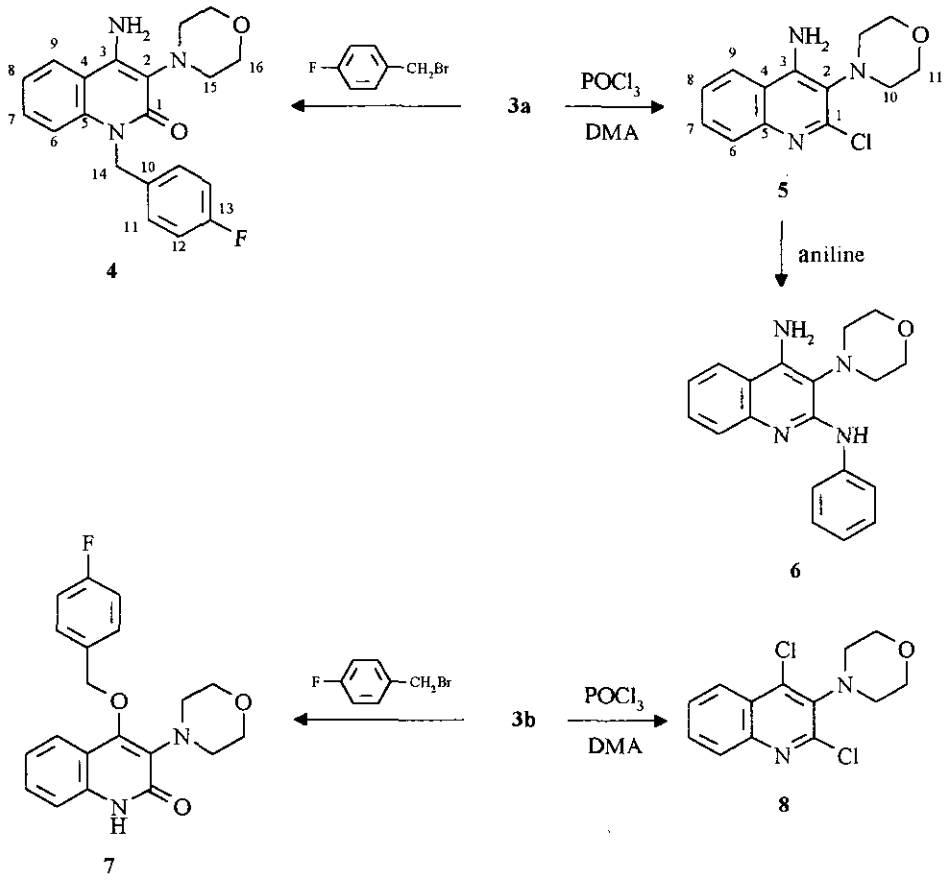
The time and temperature of the reaction have to be carefully controlled in order to reach the recorded yields of 3,4-diamino-2(1*H*)-quinolones (**3a**) and (**3e-g**).

The same reaction conditions were employed to carry out a *Dieckmann* condensation reaction obtaining the 4-hydroxy-3-morpholin-4-yl-2(1*H*)-quinolone (**3b**) from **2b** and to convert **2c,d** into the condensation products (**3c,d**).

4-Amino-3-morpholin-4-yl-2(1*H*)-quinolone (**3a**) can be *N*-alkylated regioselectively to yield the 3,4-diamino-2(1*H*)-quinolone (**4**) with 4-fluorobenzyl bromide under phase-transfer conditions. The position of the 4-fluorobenzyl group is indicated by the missing NH signal at δ = 10.82 ppm in the ^1H NMR spectra of **4**. An *O*-alkylation can be excluded, because it was reported that *O*-alkylation occurs with 2(1*H*)-quinolones only in the case of using silver salts instead of alkali.[5]

4-Amino-2-chloro-3-morpholin-4-ylquinoline (**5**) was obtained by Cl/OH exchange of **3a** with phosphoroxy trichloride. Here, nucleophilic substitution of the Cl by amines is not favoured but under drastic conditions it was possible to introduce the anilino substituent. The resulting 2-anilinoquinoline (**6**)

was earlier reported to exhibit neuro-protective properties and was prepared by reduction of the corresponding nitro derivative.[1]



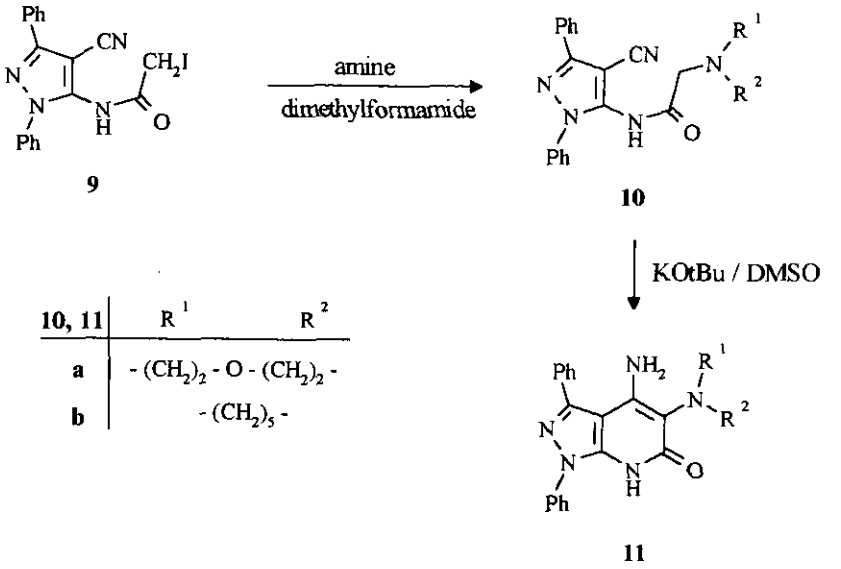
Numbering of C-atoms relates to ^{13}C NMR spectra

Scheme 2

4-Fluorobenzylbromide as alkylating agent reacts with the 4-hydroxyl group of **3b** to give the *O*-alkylation product (**7**). Another simple derivatization of **3b** involving a Cl/OH exchange of both hydroxyl groups was accomplished with phosphoroxy trichloride to yield the 2,4-dichloro-3-morpholin-4-ylquinoline (**8**).

Besides 2(1*H*)-quinolones (**3a-g**), we investigated the possibility to extend our method to synthesis of hetero-condensed 2(1*H*)-pyridones. We established that the nitrile group has to be activated for the *Thorpe-Ziegler* cyclizations with amino substituted methylene groups. This activation can be mediated by an electron-deficient heterocycle or by electron-withdrawing groups attached to heterocycle. The pyrazole derivatives (**10a,b**) proved to be suitable for our experiments and afforded the pyrazolo[5,4-*b*]pyridines

(**11a,b**). In pharmacological studies **3a-g**, **4** and **7** were examined but no significant anticonvulsive activity was found.



10, 11	R^1	R^2
a	$-(CH_2)_2-O-(CH_2)_2-$	
b	$-(CH_2)_5-$	

Scheme 3

Financial support by the BMFT and the Arzneimittelwerk GmbH is gratefully acknowledged.

EXPERIMENTAL

Melting points were measured on a Kofler hot-stage apparatus. ^{1}H NMR spectra and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 using an AC-200 MHz Bruker spectrometer. The IR spectra were recorded on a spectrophotometer Specord 75 (Fa. Carl-Zeiss Jena). Elemental analyses were determined on a EA 1108 (Fa. Carlo Erba Hofheim).

5-Chloro-2-(iodoacetylamino)benzophenone (1d)

This compound was prepared according to a described procedure for **1a**.[2] 5-Chloro-2-(chloro-acetylamino)benzophenone (obtained from 2-amino-5-chlorobenzophenone and chloroacetic acid chloride / dioxane / K_2CO_3, mp 121-123 °C) reacts with potassium iodide in acetone to yield product (**1d**) (87 %), mp 123-126 °C (ethanol).

***N*-(2-Cyanophenyl)-2-morpholin-4-ylacetamide (2a)**

To a stirred solution of **1a** [2] (11,5 g, 40 mmol) in ethanol (40 mL), morpholine (6.96 g, 80 mmol) was added. The reaction mixture was stirred for 30 min at 50 °C and evaporated to dryness under reduced pressure. The residue was treated with water to remove soluble components und the solid was filtered off to yield the product (**2a**) (8.5 g, 87 %), mp 129-131 °C (ethanol); Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.40; H, 6.20; N, 17.08.

***N*-[(Morpholin-4-yl)methylcarbonyl]anthranilic acid ethyl ester (2b)**

To a stirred solution of **1b** [2] (16.65 g, 50 mmol) in dimethylformamide (30 mL), morpholine (8.7 g, 100 mmol) was added at room temperature. After 30 min the reaction mixture was poured into ice-water (300 mL), the solid was filtered off and washed with water to yield the product (**2b**) (14.1 g, 97 %), mp 65-66 °C (ethanol/H_2O); Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.83; H, 7.02; N, 9.69.

***N*-(2-Acetylphenyl)-2-morpholin-4-ylacetamide (2c)**

To a stirred solution of **1c** [2] (15.15 g, 50 mmol) in ethanol (40 mL), morpholine (8.7 g, 100 mmol) was added at room temperature. After 30 min the reaction mixture was poured into ice-water (300 mL), the solid was filtered off and washed with water to yield the product (**2c**) (36.2 g, 92 %), mp 82-84 °C (ethanol); Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.04; H, 6.86; N, 10.67. Found: C, 64.11; H, 6.87; N, 10.61.

***N*-(2-Benzoyl-4-chlorophenyl)-2-morpholin-4-ylacetamide (2d)**

A solution of **1d** (20.0 g, 50 mmol) and morpholine (8.7 g, 100 mmol) in ethanol (20 mL) was refluxed for 1 h. The cooled mixture was poured into water (150 mL) and the precipitate was filtered off to yield the product (**2d**) (17.0 g, 95 %), mp 118-120 °C (ethanol); Anal. Calcd for $C_{19}H_{19}N_2O_3Cl$: C, 63.60; H, 5.34; N, 7.81; Cl, 9.88. Found: C, 63.82; H, 5.36; N, 7.66; Cl, 9.81.

***N*-(2-Cyanophenyl)-2-piperidin-1-ylacetamide (2e)**

To a stirred solution of **1a** [2] (11,5 g, 40 mmol) in ethanol (40 mL), piperidine (6.8 g, 80 mmol) was added. The reaction mixture was stirred for 30 min at 50 °C and evaporated to dryness under reduced pressure. The residue was treated with water to remove soluble components und the solid was filtered off to yield the product (**2e**) (7.0 g, 72 %), mp 104-106 °C (ethanol); IR (KBr): 1692 (CO), 2220 (CN) cm^{-1}; Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.03; H, 7.08; N, 17.24.

***N*-(2-Cyanophenyl)-2-(4-hydroxypiperidin-1-yl)acetamide (2f)**

A solution of **1a** [2] (14.3 g, 50 mmol) and 4-hydroxypiperidine (10.1 g, 100 mmol) in ethanol (20 mL) was refluxed for 1 h. The cooled mixture was poured into water (150 ml) and the precipitate was filtered off to yield the product (**2f**) (10.2 g, 79 %), mp 115-117 °C (ethanol/H_2O); Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.90; H, 6.69; N, 16.13.

***N*-(2-Cyanophenyl)-2-(diphenylamino)acetamide (2g)**

A solution of 2-(bromoacetylamino)benzonitrile (4.8 g, 20 mmol) (obtained from o-aminobenzonitrile and bromoacetic acid chloride in dioxane / K_2CO_3, mp. 119-121 °C) and diphenylamine (3.4 g, 20 mmol) in dimethylformamide (20 mL) was refluxed for 3 h. The reaction mixture was evaporated to dryness under reduced pressure and the residue was treated with saturated aqueous sodium hydrogen carbonate solution. The precipitate was filtered off and washed with water to yield the product **(2g)** (3.7 g, 57 %), mp 146-148 °C (ethanol); Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.83. Found: C, 76.44; H, 5.25; N, 12.82.

3,4-Diamino-2(1*H*)-quinolones (3a, 3c-g), general procedure

To a solution of **2** (10 mmol) in absolute DMSO (5 mL), potassium *tert*-butoxide (2.5 g, 22 mmol) was added at room temperature. Under Exclusion of water the reaction mixture was stirred 30 min at an oil-bath temperature of 120 °C. After cooling, the mixture was poured into ice-water (50 mL) under addition of 3 N HCl (2 mL). The precipitate was filtered off, purified with charcoal and recrystallized with the given solvent.

4-Amino-3-morpholin-4-yl-2(1*H*)-quinolone (3a)

Colorless crystals (1.7 g, 68 %), mp 278-282 °C (ethanol), (lit.,[1a] mp 283-284 °C).

4-Hydroxy-3-(morpholin-4-yl-2(1*H*)-quinolone (3b)

To a solution of **2b** (2.92 g, 10 mmol) in absolute DMSO (5 mL), potassium *tert*-butoxide 3.75 g (33 mmol) was added and the reaction mixture was stirred at 100 °C for 45 min. After cooling, the potassium salt of **3b** was precipitated on addition of ether (200 mL), filtered off and dissolved in water (50 mL). This aqueous solution was neutralized with diluted hydrochloric acid and the precipitate filtered off. After recrystallization with aqueous ethanol (70 %) the product **3b** (1.33 g, 54 %), mp 269 °C (decomp) was obtained. ^{1}H NMR (DMSO-d_6) δ 11.25 (s, 1H, NH), 7.80 (t, J = 7.6 Hz, 1H, benzo-H), 7.30-7.05 (m, 3H, benzo-H), 5.30-4.40 (br s, 1H, OH), 3.80 (m, 4H, $O(CH_2)_2$), 3.10 (m, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR (DMSO-d_6) δ 161.15 (C1), 137.45 (C2), 157.70 (C3), 130.04, 122.98, 120.91, 119.49 (S), 114.71, 114.36 (S) (C4...C9), 66.01 ($O(CH_2)_2$), 49.37 ($N(CH_2)_2$) ppm; Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.43; H, 5.84; N, 11.45.

4-Methyl-3-morpholin-4-yl-2(1*H*)-quinolone (3c)

Colorless crystals (1.7 g, 70 %), mp 248-249 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 11.41 (s, 1H, NH), 7.65 (d, J = 7.7 Hz, 1H, benzo-H), 7.29 (t, J = 7.5 Hz, 1H, benzo-H), 7.18 (d, J = 7.6 Hz, 1H, benzo-H), 7.01 (t, J = 7.5 Hz, 1H, benzo-H), 3.55 (t, J = 4.6 Hz, 4H, $O(CH_2)_2$), 2.95 (t, J = 4.6 Hz, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR (DMSO-d_6) δ 163.13 (C1), 143.95 (C2), 136.74 (C3), 121.12 (C4), 138.45 (C5), 115.85 (C6), 124.99 (C7), 122.15 (C8), 129.28 (C9), 50.25, 67.93 (OCH_2CH_2N), 13.46 (CH_3) ppm; Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.78; H, 6.68; N, 11.65.

6-Chloro-3-morpholin-4-yl-4-phenyl-2(1*H*)-quinolone (3d)

Colorless crystals (2.5 g, 60 %), mp 305-308 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 11.95 (s, 1H, NH), 7.60-6.90 (m, 8H, benzo-H, phenyl-H), 3.31 (t, J = 4.6 Hz, 4H, $O(CH_2)_2$), 2.78 (t, J = 4.6 Hz, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR (DMSO-d_6) δ 160.08 (C1), 139.37 (C2), 138.89 (C3), 121.85 (C4), 134.66 (C5), 116.59 (C6), 123.95 (C7), 125.50 (C8), 127.77 (C9), 50.04, 66.44 (OCH_2CH_2N), 135.36, 128.27, 129.42, 127.77 (phenyl-H) ppm; Anal Calcd for $C_{19}H_{17}N_2O_2Cl$: C, 66.96; H, 5.03; N, 8.22; Cl, 10.40. *Found*: C, 66.71; H, 4.99; N, 8.01; Cl, 10.55.

4-Amino-3-piperidin-1-yl-2(1*H*)-quinolone (3e)

Colorless crystals (1.6 g, 65 %), mp 242-246 °C (ethanol); IR (KBr): 1638 (CO), 3420, 3300, 3330, 3390 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.72 (s, 1H, NH), 7.90 (d, J = 7.6 Hz, 1H, benzo-H), 6.90-7.60 (m, 3H, benzo-H), 6.25 (s, 2H, NH_2), 3.60-3.20 (m, 2H, NCH_2), 2.90-2.40 (m, 2H, NCH_2), 1.90-1.20 (m, 6H, $(CH_2)_3$) ppm; ^{13}C NMR (DMSO-d_6) δ 160.81 (C1), 117.28 (C2), 148.23 (C3), 113.49 (C4), 137.62 (C5), 114.90 (C6), 123.37 (C7), 120.20 (C8), 129.22 (C9), 50.09 ($N(CH_2)_2$), 26.78, 23.99 ($(CH_2)_3$) ppm; Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C, 69.22; H, 7.09; N, 17.26.

4-Amino-3-(4-hydroxypiperidin-1-yl)-2(1*H*)-quinolone (3f)

Colorless crystals (1.8 g, 70 %), mp 234-237 °C (ethanol/H_2O); ^{1}H NMR (DMSO-d_6) δ 10.9 ppm (s, 1H, NH), 7.90 (d, J = 7.6 Hz, 1H, benzo-H), 7.00-7.50 (m, 3H, benzo-H), 6.30 (s, 2H, NH_2), 4.70 (s, 1H, OH), 3.30-3.60, 2.40-2.70, 1.70-1.90, 1.40-1.70 (m, 9H, 4-hydroxypiperidin-1-yl-*H*) ppm; ^{13}C NMR (DMSO-d_6) δ 160.99 (C1), 116.53 (C2), 148.44 (C3), 113.53 (C4), 137.64 (C5), 115.04 (C6), 129.38 (C7), 120.38 (C8), 123.45 (C9), 48.24 ($N(CH_2)_2$), 36.37, 67.93 ($CH_2CH(OH)CH_2$) ppm; Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.25; H, 6.80; N, 16.02.

4-Amino-3-(diphenylamino)-2(1*H*)-quinolone (3g)

Colorless crystals (2.3 g, 70 %), mp 285-287 °C (ethanol/H_2O); ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H, NH), 7.99 (d, J = 7.6 Hz, 1H, benzo-H), 6.70-7.70 (m, 13H, phenyl-H, benzo-H), 6.42 (s, 2H, NH_2) ppm; ^{13}C NMR (DMSO-d_6) δ 160.96 (C1), 110.35 (C2), 150.30 (C3), 113.39 (C4), 138.33 (C5), 115.43 (C6), 130.36 (C7), 120.71 (C8), 123.48 (C9), 146.31, 119.98, 128.64, 121.13 (phenyl-C) ppm; Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.83. Found: C, 76.29; H, 5.26; N, 12.65.

4-Amino-1-(4-fluorophenylmethyl)-3-(morpholin-4-yl)-2(1*H*)-quinolone (4)

A mixture of **3a** (4.92 g, 20 mmol) and potassium hydroxide (2.24 g, 40 mmol) in dimethyl sulfoxide (10 mL) was stirred for 30 min at an oil-bath temperature of 60 °C. Then a solution of 4-fluorobenzyl bromide (3.78 g, 20 mmol) and benzyltriethylammonium chloride (0.5 g) in dimethyl sulfoxide (5 mL) was added dropwise under stirring within 30 min. The solution was stirred for another 1.5 h at 60 °C and then poured into water (200 mL). The precipitate was filtered off and washed with water. The crude product (**4**) (6.4 g) can be purified by two procedures: a) Column chromatography over silica gel 60 (toluene) and elution with

butyl acetate; or b) Recrystallization of the crude product successively with butylacetate and acetone; to yield colorless crystals (4.2 g, 60 %), mp 212-222 °C (acetone); IR (KBr): 3326, 3444 (NH), 1621 (CONH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.05 (d, J = 7.6 Hz, 1H, benzo-H), 7.40 (t, J = 7.5 Hz, 1H, benzo-H), 7.30-7.05 (m, 6H, benzo-H, phenyl-H), 6.60 (s, 2H, NH_2), 5.40 (s, 2H, CH_2), 3.70 (m, 4H, $O(CH_2)_2$), 3.30 (m, 4H, $N(CH_2)_2$) ppm; ^{13}C NMR (DMSO-d_6) δ 160.04 (C1), 114.56 (C2), 148.39 (C3), 115.06 (C4), 137.75 (C5), 114.88 (C6), 130.04 (C7), 120.85 (C8), 124.18 (C9), 134.12, 134.06 (C10, $^4J_{(C-F)}$ = 3 Hz), 128.60, 128.44 (C11, $^3J_{(C-F)}$ = 8 Hz), 115.49, 115.06 (C12, $^2J_{(C-F)}$ = 22 Hz), 163.50, 158.68 (C13, $^1J_{(C-F)}$ = 243 Hz), 43.09 (C14), 49.07 (C15), 67.14 (C16) ppm; Anal Calcd for $C_{20}H_{20}N_3O_2F$: C, 67.97; H, 5.71; N, 11.89. Found: C, 67.74; H, 5.80; N, 11.95.

4-Amino-2-chloro-3-morpholin-4-yl-quinoline (5)

A mixture of **3a** (2.45 g, 10 mmol), phosphoroxy trichloride (9 mL, 0.1 mol) and *N,N*-dimethylaniline (2 g, 16 mmol) was heated to reflux for 30 min at an oil-bath temperature of 170 °C. All volatile components were evaporated under reduced pressure and the residue was dissolved in a mixture of water (100 mL) and petrol ether (30 mL). To this mixture saturated sodium hydrogene carbonate solution was added until the evolution of carbon dioxide has finished. The formed precipitate was filtered off and washed with petrolether and water to yield the product (**5**) (2.3 g, 86 %), mp 197-199 °C (acetonitrile); ^1H NMR (DMSO-d_6) δ 8.25 (d, J = 7.6 Hz, 1H, benzo-H), 7.50-7.70 (m, 2H, benzo-H), 7.35-7.50 (t, J = 7.5 Hz, 1H, benzo-H), 7.05 (s, 2H, NH_2), 3.70-3.90 (m, 4H, $O(CH_2)_2$), 3.40-3.60 (m, 2H, NCH_2), 2.50 (d, J = 4.6 Hz, 2H, NCH_2) ppm; ^{13}C NMR (DMSO-d_6) δ 149.98 (C1), 120.78 (C2), 151.60 (C3), 118.10 (C4), 145.54 (C5), 129.79, 127.67, 124.29, 123.53 (C6, C7, C8, C9), 48.87 (C10), 67.08 (C11) ppm; Anal. Calcd for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; N, 15.93; Cl, 13.44. Found: C, 59.09; H, 5.49; N, 15.82; Cl, 13.69.

4-Amino-2-anilino-3-morpholin-4-ylquinoline (6)

A mixture of **5** (2.64 g, 10 mmol) and aniline (3.72 g, 40 mmol) was stirred for 1 h at an oil-bath temperature of 180-200 °C. The reaction mixture was cooled and water (50 mL) was added. The precipitate was filtered off and recrystallized from ethanol to yield the product (**6**) (2.5 g, 77 %), mp 222-223 °C (ethanol) (lit.,[1] mp 224-225 °C).

4-(4-Fluoro-phenylmethyloxy)-3-(morpholin-4-yl)-2(1*H*)-quinolone (7)

To a stirred mixture of **3b** (2.46 g, 10 mmol) and potassium carbonate (2.76 g, 20 mmol) in dimethylformamide (5 mL), 4-fluorobenzyl bromide (3.78 g, 20 mmol) was added dropwise within 30 min at an oil-bath temperature of 60 °C. The reaction mixture was stirred for 3 h at 60 °C and then poured into water (200 mL) and 10 N sodium hydroxide solution (20 mL) added. The precipitate was washed with water and recrystallized with acetone to yield the product (**7**) (2.9 g, 82 %), mp 198-204 °C (acetone); IR (KBr): 3450 (br) (NH), 1648 (CONH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.60 (s, 1H, NH), 7.75-7.05 (m, 8H,

benzo-H, phenyl-H), 5.40 (s, 2H, CH_2), 3.70-3.60 (m, 4H, $O(CH_2)_2$), 3.20-3.10 (m, 4H, $N(CH_2)_2$) ppm; Anal. Calcd for $C_{20}H_{19}N_2O_3F$: C, 67.77; H, 5.41; N, 7.91. Found: C, 67.93; H, 5.52; N, 7.80.

2,4-Dichloro-3-(morpholin-4-yl)-quinoline (8)

A mixture of **3b** (2.46 g, 10 mmol), phosphoroxy trichloride (9 mL, 0.1 mol) and *N,N*-dimethylaniline (2 g, 16 mmol) was heated to reflux for 30 min at an oil-bath temperature of 170 °C. All volatile components were evaporated under reduced pressure and the residue was dissolved in a mixture of water (100 mL) and petrol ether (30 mL). To this mixture saturated sodium hydrogene carbonate solution was added until the evolution of carbon dioxide has finished. The formed precipitate was filtered off and washed with petrolether and water to yield the product (**8**) (1.6 g, 57 %), mp 113-115 °C (ethanol); ^{1}H NMR (DMSO-d_6) δ 7.70-8.20 (m, 4H, benzo-H), 3.75-3.85 (m, 4H, $O(CH_2)_2$), 3.20-3.30 (m, 4H, $N(CH_2)_2$) ppm; Anal. Calcd for $C_{13}H_{12}N_2OCl_2$: C, 55.14; H, 4.27; N, 9.89; Cl, 25.04. Found: C, 55.13; H, 4.30; N, 9.86; Cl, 25.08.

5-(Iodo-acetylamino)-1,3-diphenyl-1*H*-pyrazol-4-carbonitrile (9)

A mixture of 5-(chloroacetylamino)-1,3-diphenyl-1*H*-pyrazol-4-carbonitrile (6.74 g, 20 mmol) (prepared from 5-amino-1,3-diphenyl-1*H*-pyrazol-4-carbonitrile and chloroacetic acid chloride in nitromethane, 45 min heated to reflux, mp 178-180 °C) and potassium iodide (10 g, 60 mmol) in acetone (150 mL) was heated to reflux for 3 h. The solvent was evaporated under reduced pressure and the residue was triturated with water to remove inorganic salts. The product (**9**) was filtered off and washed with water (8.2 g, 96 %), mp 191-193 °C (ethanol); Anal. Calcd for $C_{18}H_{13}N_4OI$: C, 50.49; H, 3.06; N, 13.08; I, 29.63. Found: C, 50.66; H, 3.07; N, 13.14; I, 29.53.

Pyrazole (10), general procedure

To a stirred solution of **9** (4.28 g, 10 mmol) in dimethylformamide (20 mL), morpholine (3.48 g, 40 mmol) or piperidine (3.4 g, 40 mmol) was added at 40 °C. After 10 min the reaction mixture was poured into water (150 mL), the precipitate filtered off and washed with water.

4-[(4-Cyano-1,3-diphenyl-1*H*-pyrazol-5-yl)aminocarbonylmethyl]morpholine (10a)

Colorless crystals (3.7 g, 96 %), mp 197-199 °C (ethanol); Anal. Calcd for $C_{22}H_{21}N_5O_2$: C, 68.20; H, 5.46; N, 18.08. Found: C, 67.93; H, 5.59; N, 18.21.

1-[(4-Cyano-1,3-diphenyl-1*H*-pyrazol-5-yl)aminocarbonylmethyl]piperidine (10b)

Colorless crystals (2.9 g, 75 %), mp 171-173 °C (ethanol); Anal. Calcd for $C_{23}H_{23}N_5O$: C, 71.67; H, 6.01; N, 18.17. Found: C, 71.97; H, 6.08; N, 18.36.

4-(4-Amino-6,7-dihydro-6-oxo-1,3-diphenyl-1*H*-pyrazolo[5,4-b]pyridin-5-yl)morpholine (11a)

For the preparation of **11a** the general procedure used for the synthesis of 3,4-diamino-2(1*H*)-quinolones (**3**) was employed with a reaction time of 90 min at 110 °C. Colorless crystals (2.8 g, 72 %), mp 248-252 °C (ethanol). IR (KBr): 3486, 3350 (NH), 1620 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.95 (s, 1H,

NH), 8.20 (d, J = 7.7 Hz, 2H, phenyl-H), 7.70 (d, J = 7.6 Hz, 2H, phenyl-H), 7.40-7.60 (m, 5H, phenyl-H), 3.70 (t, J = 7.6 Hz, 1H, phenyl-H), 5.70 (s, 2H, NH_2), 3.75 (d, J = 4.5 Hz, 2H, NCH_2), 3.65 (t, J = 4.5 Hz, 2H, OCH_2), 3.45 (t, 2H, OCH_2), 2.45 (d, 2H, NCH_2) ppm; ^{13}C NMR (DMSO-d_6) δ 161.97 (CO), 128.72, 128.73, 128.54, 128.42, 125.32, 120.66 (d, phenyl-C), 147.46, 147.21, 145.12, 139.19, 133.23, 110.46, 99.58 (s, phenyl-C, pyrazolo[4,5-b]pyridin-C), 67.03 ($O(CH_2)_2$),49.35 ($N(CH_2)_2$) ppm; Anal. Calcd for $C_{22}H_{21}N_5O_2$: C, 68.20; H, 5.46; N, 18.08. Found: C, 68.04; H, 5.60; N, 18.19.

1-(4-Amino-6,7-dihydro-6-oxo-1,3-diphenyl-1*H*-pyrazolo[5,4-b]pyridin-5-yl)piperidine (11b)

For the preparation of **11b** the general procedure used for the synthesis of 3,4-diamino-2(1*H*)-quinolones (**3**) was employed with a reaction time of 90 min at 110 °C. Colorless crystals (1.58 g, 41 %), mp 220-222 °C (ethanol); Anal. Calcd for $C_{23}H_{23}N_5O$: C, 71.67; H, 6.01; N, 18.17. Found: C, 71.66; H, 6.06; N, 18.20.

REFERENCES

1. a) Y. Miura, M. Yoshida, Y. Fujimura, S. Yakaku, Y. Noda, EP 0361489 (28.9.1989) [*Chem. Abstr.*, 1990, **113,** P 115108 k]. b) Ch. F. Bigge, *J. Med. Chem.*, 1995, **38**, 3720.
2. K. Gewald, M. Rehwald and M. Gruner, *Liebigs Ann. Chem.*, 1993, 457.
3. K. Gewald, H. Schäfer and H. Müller, *Chem. Ber.*, 1991, **124,** 1237.
4. E. C. Taylor and A. McKillop, 'The Chemistry of Cyclic Enaminonitriles and o-Aminonitriles', Interscience Publishers, New York, 1970.
5. B. A. Arbusow and S. Bastanowa, *Izv. Akad. S.S.S.R. Otd. Chim.*, 1952, 831.

Received, 22nd November, 1996