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Dedicated to Professor Dr. W. Wiegreb (Regensburg, Germany) on the occasion of his 65th birthday.

The preparation of 3-amino- and 3-dialkylamino-4-cyanoazepino[3,4-*b*]indoles bearing substituents on the aromatic nucleus and N¹⁰ is outlined. Starting from suitable substituted ethyl 3-formylindole-2-carboxylates **2**, condensation with malononitrile (**3**) and subsequent sodium borohydride-reduction yielded ethyl 3-(2,2-dicyanoethyl)indole-2-carboxylates **5** and **19**, respectively, which were cyclized in boiling alkoxides to 3-alkoxy-4-cyanoazepino[3,4-*b*]indoles **10,11,20** and **21**. This sequence constitutes a novel and flexible route to functional azepino[3,4-*b*]indoles. The aminolysis of **10,11,20** and **21** with different amines and ammonia yielded the title compounds which were screened for their possible biological activity.

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In the course of the synthesis of rigid analogues of folate antagonists, we have found that methyl 2-(2,2-dicyanoethyl)benzoates can be cyclized to 3-alkoxy-4-cyano-1-oxo-1,2-dihydro-5*H*-2-benzazepines in good yields [1]. In order to find out the limitation of this reaction, we attempted to investigate the cyclisation reaction of heteroaromatic *o*-(2,2-dicyanoethyl) esters, for example ethyl 3-(2,2-dicyanoethyl)indole-2-carboxylate (**5a**). Indole was selected as the heterocyclic moiety because derivatives of this system are used as drugs and the new 3,4-functional 1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indoles could serve as compounds of medicinal interest.

The present paper reports on the synthesis of suitable indoles as the starting material and on cyclisation to azepino[3,4-*b*]indoles and their aminolysis to 3-amino- and 3-alkylaminoazepino[3,4-*b*]indoles.

Besides the known starting substances **2a**, **2b**, **2d** and **2f** we prepared the new ethyl 3-formylindole-2-carboxylates **2c** and **2e** in good yields from ethyl indole-2-carboxylates **1c** and **1e** by Vilsmeier formylation with phosphoryl chloride and *N*-methylformanilide (see Scheme 1).

According to our cyclisation methodology [1], the aldehydes **2b-e** were first reacted with malononitrile (**3**) in ethanol using β -alanine as a catalyst. The new ylidene malononitriles **4b-e** were obtained in excellent yields (75–91%). Compound **4a** was previously prepared on a similar route by Röder and Pigulla [2]. The activated ylidene double bond in **4a-e** was then easily reduced with sodium borohydride in methanol at -5° to give the starting material for our cyclisation reaction.

By treatment of **5a** and **5e** in boiling sodium methylate over four hours the sodium salts of the azepino[3,4-*b*]indole derivatives **8a** and **8e** were obtained. After evaporation of the solvent (methanol), the residues were immediately dissolved in water. Acidification with diluted 2*N* sulfuric acid

caused the precipitation of the 3-methoxyazepino[3,4-*b*]indoles **10a** and **10e**. Compounds **5a-d** were treated analogously with sodium ethylate to yield 3-ethoxyazepino[3,4-*b*]indoles **11a-d** ($R^3 = \text{Et}$).

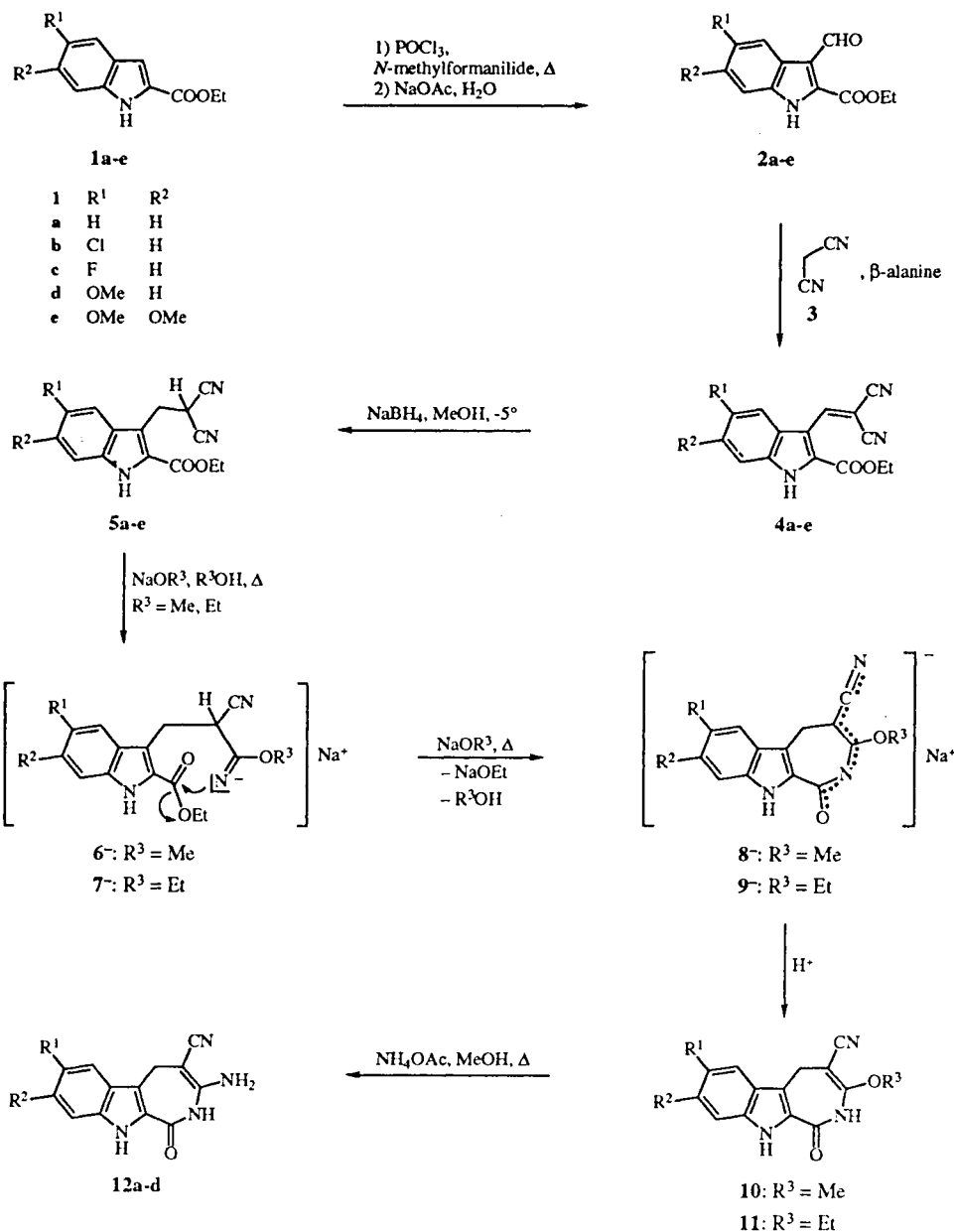
For this cyclisation reaction the following pathway seems to be plausible (see Scheme 1): a methoxide-ion first attacks a nitrile group in **5**, thus generating the nucleophilic imidate anion **6⁻** [3]. Intramolecular attack of this nucleophilic imidate at the ester function leads to a neutral azepino[3,4-*b*]indole derivative **8** by splitting off ethoxide. As an NH-acidic derivative compound **8** is expected to be immediately deprotonated in the presence of alkoxides to yield the sodium salt **8⁻**. In this salt, the negative charge is delocalized over C-1, N-2, C-3, C-4 as well as the cyano group. Spectroscopic proof is the downfield shifts of the ¹³C-signals of C-1, C-3 and the cyano group of the isolated salt of the *N*-benzyl substituted derivative **21⁻** compared to the signals of the neutral molecule **21**. The signal of C-4 in the anion **21⁻** shows a shift to higher field (see Table 1). Further spectroscopic proof of the cyclisation is the intense band of the cyano group at 2200 cm⁻¹ in the ir-spectrum of **10,11,20** and **21**, caused by a β -cyanoenol ether structure. In contrast the intensity of the CN-band in the starting compounds **5** and **19** is very low.

Table 1

	21	21⁻
C-1	161.4	180.4
C-3	158.8	171.2
C-4	79.3	61.5
CN	121.3	129.0

¹³C nmr data of **21** and **21⁻** (ppm), (**21** [D₆]DMSO, **21⁻** deuterium oxide).

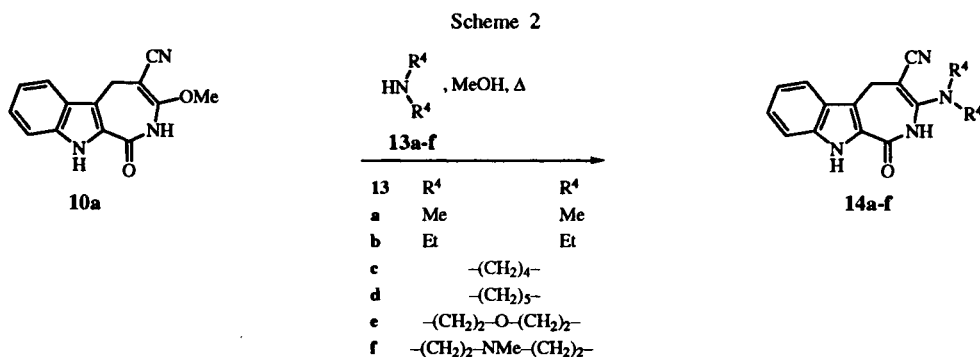
Scheme 1



Azepino[3,4-*b*]indoles **10** or **11** exhibit a partial structure of a β -cyanoenol ether. This type of enol ether was expected to react easily with *N*-nucleophiles, such as, e.g., ammonia or amines, to give β -cyanoenamines. This assumption was confirmed by refluxing **10** or **11** in methanol in the presence of ammonium acetate to give rise to the 3-aminoazepino[3,4-*b*]indole-4-nitriles **12a-d** (see Scheme 1). The latter can be regarded as a versatile starting material for heteroannellated azepinoindoles such as pyrimido[5',4':6,7]azepino[3,4-*b*]indoles which are subjects of a following publication. In order to prepare substituted 3-aminoazepino[3,4-*b*]indoles for pharmacological tests, **10a** was treated with aliphatic or

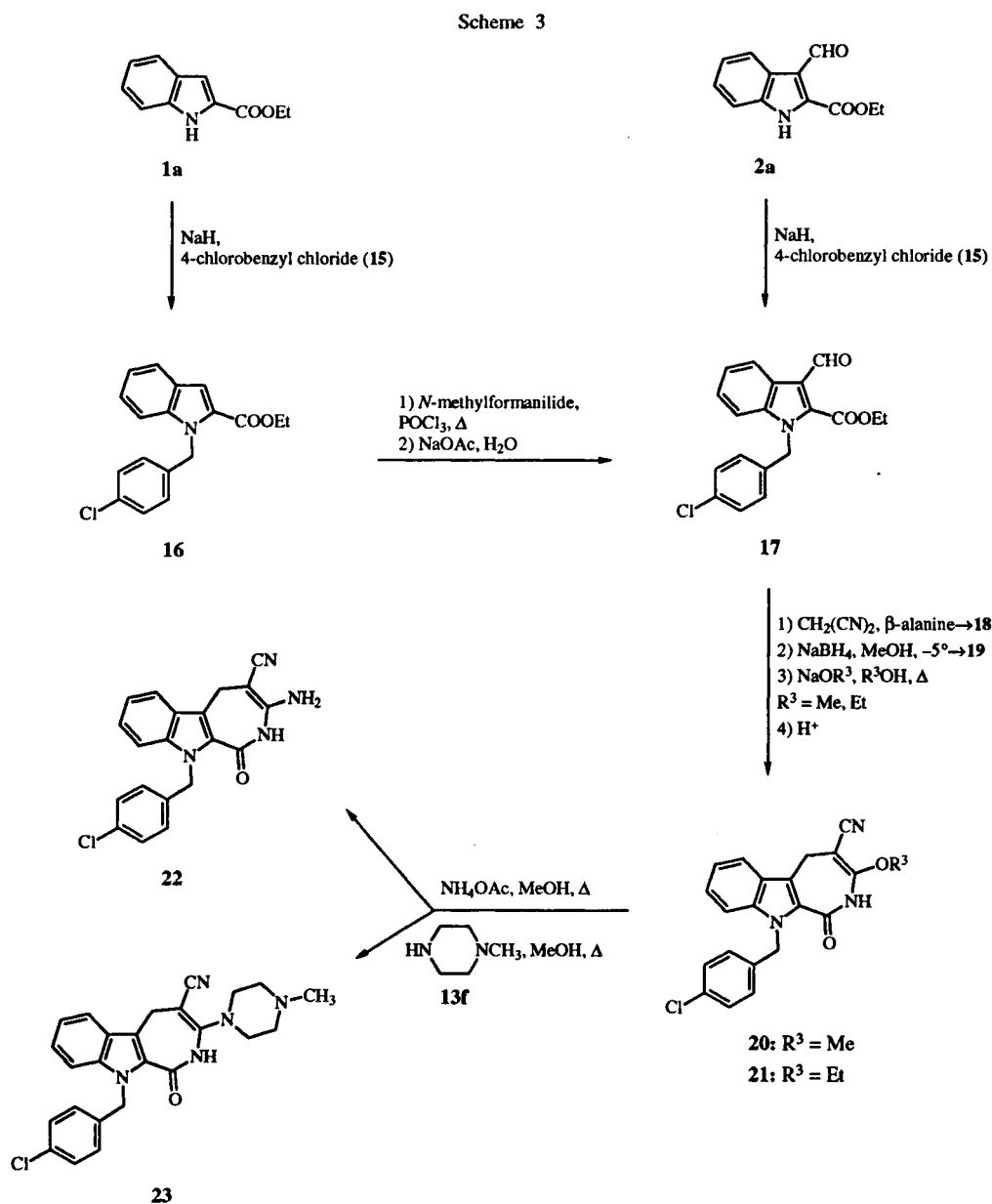
cycloaliphatic amines **13a-f** in boiling methanol to yield the 4-cyano-3-dialkylaminoazepino[3,4-*b*]indoles **14a-f** in good yields (see Scheme 2).

Since Mebhydroline, an antiallergic agent and a [b]-heteroannellated indole derivative is substituted on N-1 with a 4-chlorobenzyl group, we decided to prepare azepino[3,4-*b*]indoles with the same substitution pattern on N-10 as potential antiallergic agents. Starting from ethyl indole-2-carboxylate (**1a**), *N*-benzylation was easily performed with sodium hydride and 4-chlorobenzyl chloride (**15**) [4]. Reaction product **16** was formylated to give the *o*-formylcarboxylate **17** in 85% yield. In an alternative route, **17** could be prepared by alkylation of **2a** with sodium



hydride and 4-chlorobenzyl chloride (15). Due to the low yield (20%), the first reaction sequence is preferred.

The following reaction sequence with aldehyde 17 (condensation with malononitrile, reduction with sodium



borohydride and cyclisation in boiling sodium methylate or sodium ethylate, followed by acidic work up) gave rise to the N-10 4-chlorobenzyl substituted azepino[3,4-*b*]-indoles **20** and **21**. Subsequent aminolysis of **20** ($R^3 = \text{Me}$) with ammonium acetate or *N*-methylpiperazine (**13f**) in boiling methanol yielded the target compounds **22** and **23** (see Scheme 3).

Biological Activity.

The azepino[3,4-*b*]indoles **10a**, **10e** and **23** showed an activity of 50-80% compared to podophyllotoxine in a bioassay on cytotoxic effects, utilizing the so-called brine shrimp test [5]. Derivatives **10a**, **12a** and **14f** exhibited no significant antiallergic activity in a lipoxigenase-bioassay. The effects of **10a** and **12a** in an anticholinergic antiasthmatic screening were not significant. Using another test model for antiasthmatic activity, compounds **10a**, **12a**, **14f**, **20**, **22** and **23** were not able to obstruct the production of interleucine 4 and 5. Moreover **14f** had no affinity to benzodiazepine receptors in the central nervous system. Finally, compounds **10a** and **14f** showed no effects in an NCI anti HIV-screening.

EXPERIMENTAL

All melting points were determined using a Büchi-530 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer-Lambda 5 instrument. The ^1H and ^{13}C nmr spectra were obtained with a Bruker-BZH-360/52 instrument with tetramethylsilane as the internal standard. The mass spectra were recorded on a Finnigan-4500 instrument at 70eV.

Ethyl 5-Fluoro-3-formylindole-2-carboxylate (**2c**).

A mixture of phosphoryl chloride (11.50 g, 75 mmol) and *N*-methylformanilide (10.10 g, 75 mmol) was stirred at room temperature for 15 minutes. After the addition of a solution of **1c** (10.40 g, 50 mmol) and 250 ml of 1,2-dichloroethane the mixture was heated at reflux for 3 hours. After pouring the warm mixture into a solution of 40 g of sodium acetate and 400 ml of ice water, stirring was continued for 15 minutes. The mixture was extracted with chloroform. The organic layer was dried (sodium sulfate) and evaporated *in vacuo*. Crystallization from ethanol yielded 8.6 g (73%) of **2c**, mp 236-239°; ir (potassium bromide): ν 3159 cm^{-1} (NH), 3065 and 2991 (CH), 1723 (CO); uv (methanol): λ max 218 nm (log ϵ 4,393), 247 (4,198), 255 (4,182), 315 (4,138); (pH 11): 275 (4,367), 352 (4,121); ^1H nmr (DMSO- d_6): δ 1.41 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 4.47 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 7.29 (ddd, 1H, 6-H, $J = 2.5, 9.5$ Hz), 7.60 (dd, 1H, 7-H, $J = 4.5, 9.5$ Hz), 7.90 (dd, 1H, 4-H, $J = 2.5, 9.5$ Hz), 10.57 (s, 1H, CHO), 12.95 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.2 (OCH_2CH_3), 62.2 (OCH_2CH_3), 107.0 (C-7), 114.9 (C-3), 114.9 (C-4), 115.1 (C-6), 118.4 (C-3a), 125.1 (C-2), 132.4 (C-7a), 157.6 (C-5), 161.4 (COOEt), 187.6 (CHO); ms: m/z 235 (M^+), 206 ($\text{M}^+ - \text{C}_2\text{H}_5$), 188 ($\text{M}^+ - \text{C}_2\text{H}_7\text{O}$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{FNO}_3$: C, 61.3; H, 4.3; N, 6.0. Found: C, 61.3; H, 4.5; N, 6.0.

Ethyl 3-Formyl-5,6-dimethoxyindole-2-carboxylate (**2e**).

The preparation as for **2c** from phosphoryl chloride (2.90 g, 18.8 mmol), *N*-methylformanilide (2.50 g, 18.8 mmol) and **1e** (3.10 g, 12.5 mmol) gave 3.3 g (95%) of **2e**, mp 228-230°; ir (potassium bromide): ν 3152 cm^{-1} (NH), 2998, 2979, 2937, 2907 and 2842 (CH), 1713 (CO); uv (methanol): λ max 221 nm (log ϵ 4,369), 246 (4,223), 253 (4,277), 347 (4,077); (pH 11): 284 (4,095), 364 (4,146); ^1H nmr (DMSO- d_6): δ 1.39 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.43 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 6.98 (s, 1H, 7-H), 7.65 (s, 1H, 4-H), 10.58 (s, 1H, CHO), 12.56 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.1 (OCH_2CH_3), 55.5 (OCH_3), 55.5 (OCH_3), 61.4 (OCH_2CH_3), 94.7 (C-7), 102.3 (C-4), 118.0 (C-3), 118.6 (C-3a), 130.2 (C-2), 130.8 (C-7a), 148.1 (C-5), 149.8 (C-6), 160.1 (COOEt), 187.6 (CHO); ms: m/z 277 (M^+), 248 ($\text{M}^+ - \text{C}_2\text{H}_5$), 230 ($\text{M}^+ - \text{C}_2\text{H}_7\text{O}$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_5$: C, 60.6; H, 5.5; N, 5.1. Found: C, 60.5; H, 5.4; N, 5.0.

Ethyl 5-Chloro-3-(2,2-dicyanoethenyl)indole-2-carboxylate (**4b**).

Ethyl 5-chloro-3-formylindole-2-carboxylate (**2b**) (1.08 g, 5 mmol), malononitrile (**3**) (0.66 g, 10 mmol) and β -alanine (0.01 g, 0.15 mmol) were stirred in 50 ml of ethanol at room temperature for 2 hours. The yellow precipitate was collected by filtration and crystallized from ethanol to yield 1.3 g (87%) of **4b**, mp 227-230°; ir (potassium bromide): ν 3289 cm^{-1} (NH), 3071, 2993, 2981, 2938 and 2870 (CH), 2225 (CN), 1696 (CO); uv (methanol): λ max 206 nm (log ϵ 4,596), 225 (4,362), 287 (4,169), 381 (4,162); (pH 11): 304 (4,136), 440 (4,487); ^1H nmr (DMSO- d_6): δ 1.39 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 4.43 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 7.46 (dd, 1H, 6-H, $J = 2.0, 9.0$ Hz), 7.62 (d, 1H, 7-H, $J = 9.0$ Hz), 8.07 (d, 1H, 4-H, $J = 2.0$ Hz), 8.82 (s, 1H, 1'-H), 13.36 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.0 (OCH_2CH_3), 62.0 (OCH_2CH_3), 81.3 (C-2'), 111.9 (C-3), 114.0 (CN), 114.8 (CN), 115.4 (C-7), 121.7 (C-4), 125.0 (C-3a), 126.7 (C-6), 127.2 (C-5), 131.0 (C-2), 135.0 (C-7a), 154.5 (C-1'), 159.8 (COOEt); ms: m/z 301/299 (M^+), 255/253 ($\text{M}^+ - \text{C}_2\text{H}_6\text{O}$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{10}\text{ClN}_3\text{O}_2$: C, 60.1; H, 3.4; N, 14.0. Found: C, 60.3; H, 3.4; N, 14.1.

Ethyl 5-Fluoro-3-(2,2-dicyanoethenyl)indole-2-carboxylate (**4c**).

The preparation described for **4b** from **2c** (7.06 g, 30 mmol), malononitrile (**3**) (3.96 g, 60 mmol) and β -alanine (0.05 g, 0.75 mmol) provided 6.4 g (75%) of **4c**, mp 228-231°; ir (potassium bromide): ν 3275 cm^{-1} (NH), 3075, 3044, 2989, 2969, 2939 and 2906 (CH), 2226 (CN), 1697 (CO); uv (methanol): λ max 216 nm (log ϵ 4,132), 275 (4,214), 285 (4,246), 382 (4,223); (pH 11): 296 (4,197), 436 (4,539); ^1H nmr (DMSO- d_6): δ 1.39 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 4.44 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 7.33 (ddd, 1H, 6-H, $J = 2.5, 9.5$ Hz), 7.63 (dd, 1H, 7-H, $J = 4.5, 9.0$ Hz), 7.78 (dd, 1H, 4-H, $J = 2.5, 9.5$ Hz), 8.83 (s, 1H, 1'-H), 13.32 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.2 (OCH_2CH_3), 62.4 (OCH_2CH_3), 81.1 (C-2'), 107.4 (C-3), 107.9 (C-7), 112.7 (CN), 112.8 (CN), 115.1 (C-4), 115.7 (C-6), 124.8 (C-3a), 131.3 (C-2), 133.2 (C-7a), 155.1 (C-1'), 156.7 (C-5), 160.5 (COOEt); ms: m/z 283 (M^+), 237 ($\text{M}^+ - \text{C}_2\text{H}_6\text{O}$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{10}\text{FN}_3\text{O}_2$: C, 63.6; H, 3.6; N, 14.8. Found: C, 63.8; H, 3.7; N, 14.7.

Ethyl 3-(2,2-Dicyanoethyl)-5-methoxyindole-2-carboxylate (4d).

The preparation as for 4b from 2d (6.18 g, 25 mmol), malononitrile (3) (3.30 g, 50 mmol) and β -alanine (0.04 g, 0.60 mmol) yielded 6.4 g (87%) of 4d, mp 204–206°; ir (potassium bromide): ν 3294 cm^{-1} (NH), 3009, 2990, 2966, 2943, and 2841 (CH), 2227 (CN), 1708 (CO); uv (methanol): λ max 205 nm (log ϵ 4,263), 218 (4,218), 279 (4,157), 381 (4,038); (pH 11): 303 (4,139), 441 (4,352); ^1H nmr (DMSO- d_6): δ 1.39 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.84 (s, 3H, OCH_3), 4.42 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 7.09 (dd, 1H, 6-H, $J = 2.5, 9.0$ Hz), 7.42 (d, 1H, 4-H, $J = 2.5$ Hz), 7.52 (d, 1H, 7-H, $J = 9.0$ Hz), 8.84 (s, 1H, 1'-H), 13.18 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.5 (OCH_2CH_3), 55.8 (OCH_3), 61.3 (C-2', OCH_2CH_3), 101.2 (C-7), 114.0 (CN), 114.6 (C-3), 114.7 (C-4), 117.5 (C-6), 125.4 (C-3a), 127.6 (C-2), 131.6 (C-7a), 154.5 (C-1', C-5), 161.8 (COOEt); ms: m/z 295 (M^+), 249 ($\text{M}^+ - \text{C}_2\text{H}_6\text{O}$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_3$: C, 65.1; H, 4.4; N, 14.2. Found: C, 64.8; H, 4.6; N, 14.0.

Ethyl 3-(2,2-Dicyanoethyl)-5,6-dimethoxyindole-2-carboxylate (4e).

The preparation by the method for 4b from 2e (11.09 g, 40 mmol), malononitrile (3) (5.28 g, 80 mmol) and β -alanine (0.04 g, 0.60 mmol) gave 11.9 g (91%) of 4e, mp 255–258°; ir (potassium bromide): ν 3269 cm^{-1} (NH), 3005, 2968, 2944 and 2841 (CH), 2224 (CN), 1709 (CO); uv (methanol): λ max 205 nm (log ϵ 4,314), 282 (4,196), 296 (4,193), 396 (4,173); (pH 11): 318 (4,236), 447 (4,419); ^1H nmr (DMSO- d_6): δ 1.38 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.84 (s, 6H, OCH_3), 4.40 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 7.01 (s, 1H, 7-H), 7.41 (s, 1H, 4-H), 8.82 (s, 1H, 1'-H), 9.63 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.4 (OCH_2CH_3), 56.0 (OCH_3), 56.0 (OCH_3), 62.0 (OCH_2CH_3), 78.9 (C-2'), 95.5 (C-7), 103.8 (C-4), 113.5 (C-3), 114.8 (CN), 115.8 (CN), 117.7 (C-3a), 128.1 (C-2), 131.8 (C-7a), 147.5 (C-5), 150.3 (C-6), 155.1 (C-1'), 160.2 (COOEt); ms: m/z 325 (M^+), 279 ($\text{M}^+ - \text{C}_2\text{H}_6\text{O}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4$: C, 62.8; H, 4.6; N, 12.9. Found: C, 62.9; H, 4.7; N, 12.6.

Ethyl 3-(2,2-Dicyanoethyl)indole-2-carboxylate (5a).

Ethyl 3-(2,2-dicyanoethyl)indole-2-carboxylate (4a) (1.06 g, 4 mmol) was suspended in 50 ml of methanol and cooled to -5°. Sodium borohydride (0.17 g, 4.4 mmol) was added in portions and after 15 minutes the mixture was hydrolyzed with 50 ml of water and 50 ml of 2N hydrochloric acid and the white precipitate obtained was collected by filtration and crystallized from ethanol to yield 1.0 g (89%) of 5a, mp 170–173°; ir (potassium bromide): ν 3322 cm^{-1} (NH), 3062, 2999, 2942 and 2914 (CH), 2253 (CN), 1679 (CO); uv (methanol): λ max 209 nm (log ϵ 4,371), 220 (4,377), 229 (4,427), 297 (4,322); ^1H nmr (DMSO- d_6): δ 1.39 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.84 (d, 2H, 1'-H, $J = 7.5$ Hz), 4.37 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 5.05 (t, 1H, 2'-H, $J = 7.5$ Hz, deuterium oxide-exchangeable), 7.13 (dd, 1H, 5-H, $J = 8.0$ Hz), 7.30 (dd, 1H, 6-H, $J = 8.0$ Hz), 7.46 (d, 1H, 7-H, $J = 8.0$ Hz), 7.89 (d, 1H, 4-H, $J = 8.0$ Hz), 11.97 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.5 (OCH_2CH_3), 23.9 (C-2'), 25.5 (C-1'), 61.6 (OCH_2CH_3), 113.2 (C-7), 114.7 (CN), 115.2 (CN), 121.0 (C-3, C-4, C-5), 125.3 (C-3a), 126.1 (C-6), 127.3 (C-2), 136.4 (C-7a), 162.0 (COOEt); ms: m/z 267 (M^+), 202 ($\text{M}^+ - \text{C}_3\text{HN}_2$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$: C, 67.4; H, 4.9; N, 15.7. Found: C, 67.1; H, 5.1; N, 15.3.

Ethyl 5-Chloro-3-(2,2-dicyanoethyl)indole-2-carboxylate (5b).

The preparation as for 5a from 4b (1.20 g, 4 mmol) and sodium borohydride (0.17 g, 4.4 mmol) provided 1.1 g (91%) of 5b, mp 200–203°; ir (potassium bromide): ν 3354 cm^{-1} (NH), 2982 and 2904 (CH), 2265 (CN), 1703 (CO); uv (methanol): λ max 211 nm (log ϵ 4,354), 229 (4,487), 297 (4,220); ^1H nmr (DMSO- d_6): δ 1.38 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.84 (d, 2H, 1'-H, $J = 7.5$ Hz), 4.37 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 5.05 (t, 1H, 2'-H, $J = 7.5$ Hz, deuterium oxide-exchangeable), 7.30 (dd, 1H, 6-H, $J = 2.0, 9.0$ Hz), 7.47 (d, 1H, 7-H, $J = 9.0$ Hz), 8.05 (d, 1H, 4-H, $J = 2.0$ Hz), 12.17 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.5 (OCH_2CH_3), 24.3 (C-2'), 25.3 (C-1'), 61.8 (OCH_2CH_3), 114.7 (C-7), 114.8 (CN), 114.9 (CN), 120.3 (C-3, C-4), 125.8 (C-6), 126.2 (C-5), 126.8 (C-3a), 128.4 (C-2), 134.8 (C-7a), 161.7 (COOEt); ms: m/z 303/301 (M^+), 238/236 ($\text{M}^+ - \text{C}_3\text{HN}_2$), 192/190 ($\text{M}^+ - \text{C}_5\text{H}_7\text{N}_2\text{O}$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{ClN}_3\text{O}_2$: C, 59.7; H, 4.0; N, 13.9. Found: C, 59.9; H, 4.2; N, 13.6.

Ethyl 3-(2,2-Dicyanoethyl)-5-fluoroindole-2-carboxylate (5c).

The preparation described for 5a from 4c (3.40 g, 12 mmol) and sodium borohydride (0.50 g, 19.2 mmol) gave 2.5 g (73%) of 5c, mp 193–195°; ir (potassium bromide): ν 3337 cm^{-1} (NH), 2998 and 2914 (CH), 2252 (CN), 1680 (CO); uv (methanol): λ max 218 nm (log ϵ 4,320), 294 (4,243); ^1H nmr (DMSO- d_6): δ 1.39 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.83 (d, 2H, 1'-H, $J = 7.5$ Hz), 4.37 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 5.04 (t, 1H, 2'-H, $J = 7.5$ Hz, deuterium oxide-exchangeable), 7.18 (ddd, 1H, 6-H, $J = 2.5, 9.0$ Hz), 7.47 (dd, 1H, 7-H, $J = 4.5, 9.5$ Hz), 7.73 (dd, 1H, 4-H, $J = 2.5, 9.5$ Hz), 12.09 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.3 (OCH_2CH_3), 23.2 (C-2'), 25.3 (C-1'), 61.4 (OCH_2CH_3), 105.1 (C-7), 113.8 (CN), 114.4 (CN), 114.5 (C-4), 114.9 (C-3), 115.0 (C-6), 126.7 (C-3a), 127.3 (C-2), 132.9 (C-7a), 155.8 (C-5), 161.4 (COOEt); ms: m/z 285 (M^+), 220 ($\text{M}^+ - \text{C}_3\text{HN}_2$), 174 ($\text{M}^+ - \text{C}_5\text{H}_7\text{N}_2\text{O}$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{FIN}_3\text{O}_2$: C, 63.2; H, 4.2; N, 14.7. Found: C, 63.2; H, 4.5; N, 14.4.

Ethyl 3-(2,2-Dicyanoethyl)-5-methoxyindole-2-carboxylate (5d).

The preparation by the method for 5a from 4d (5.02 g, 17 mmol) and sodium borohydride (0.71 g, 18.7 mmol) yielded 4.8 g (95%) of 5d, mp 164–166°; ir (potassium bromide): ν 3318 cm^{-1} (NH), 3061, 2985, 2960, 2938 and 2835 (CH), 2254 (CN), 1689 (CO); uv (methanol): λ max 211 nm (log ϵ 4,295), 299 (4,167); ^1H nmr (DMSO- d_6): δ 1.38 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.79 (s, 3H, OCH_3), 3.83 (d, 2H, 1'-H, $J = 7.5$ Hz), 4.35 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 5.02 (t, 1H, 2'-H, $J = 7.5$ Hz, deuterium oxide-exchangeable), 6.95 (dd, 1H, 6-H, $J = 2.5, 9.0$ Hz), 7.35 (d, 1H, 7-H, $J = 9.0$ Hz), 7.39 (d, 1H, 4-H, $J = 2.5$ Hz), 9.44 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.0 (OCH_2CH_3), 23.5 (C-2'), 25.2 (C-1'), 55.3 (OCH_3), 60.6 (OCH_2CH_3), 100.8 (C-7), 113.5 (CN), 114.2 (CN), 114.3 (C-3, C-4), 116.9 (C-6), 125.0 (C-3a), 127.2 (C-2), 131.3 (C-7a), 154.0 (C-5), 161.2 (COOEt); ms: m/z 297 (M^+), 232 ($\text{M}^+ - \text{C}_3\text{HN}_2$), 186 ($\text{M}^+ - \text{C}_5\text{H}_7\text{N}_2\text{O}$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3$: C, 64.6; H, 5.1; N, 14.1. Found: C, 64.2; H, 5.1; N, 13.6.

Ethyl 3-(2,2-Dicyanoethyl)-5,6-dimethoxyindole-2-carboxylate (5e).

The preparation as for 5a from 4e (9.76 g, 30 mmol) and sodium borohydride, (1.25 g, 33.0 mmol) provided 9.4 g (96%) of 5e, mp 246–248°; ir (potassium bromide): ν 3320 cm^{-1} (NH), 3085, 3005, 2964, 2937, 2903 and 2841 (CH), 2255, 2224 (CN), 1662 (CO); uv (methanol): λ max 213 nm (log ϵ 4,354), 322 (4,179); ^1H nmr (DMSO- d_6): δ 1.36 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.79 (s, 6H, OCH_3), 3.80 (d, 2H, 1'-H, $J = 7.5$ Hz), 4.33 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 5.00 (t, 1H, 2'-H, $J = 7.5$ Hz, deuterium oxide-exchangeable), 6.87 (s, 1H, 7-H), 7.38 (s, 1H, 4-H), 11.64 (s, 1H, 1-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.4 (OCH_2CH_3), 23.9 (C-2'), 25.5 (C-1'), 55.9 (OCH_3), 56.1 (OCH_3), 60.8 (OCH_2CH_3), 94.6 (C-7), 101.6 (C-4), 114.6 (CN), 115.3 (C-3), 120.3 (C-3a), 123.1 (C-2), 131.5 (C-7a), 146.1 (C-5), 150.3 (C-6), 161.6 (COEt); ms: m/z 327 (M^+), 262 ($\text{M}^+ - \text{C}_3\text{H}_5\text{N}_2$), 216 ($\text{M}^+ - \text{C}_5\text{H}_7\text{N}_2\text{O}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_4$: C, 62.4; H, 5.2; N, 12.8. Found: C, 62.1; H, 5.3; N, 12.5.

4-Cyano-3-methoxy-1-oxo-1,2,5,10-tetrahydroazepino-[3,4-*b*]indole (10a).

A solution of sodium (1.15 g, 50 mmol) in 60 ml of methanol and ethyl 3-(2,2-dicyanethyl)indole-2-carboxylate (5a) (2.67 g, 10 mmol) was heated at reflux for 4 hours. The solution was evaporated *in vacuo* and the residue was dissolved in 100 ml of water. After acidification with 2N sulfuric acid a brown precipitate was formed which was purified by flush-chromatography on silica gel under reduced pressure (toluene:ethyl acetate 7:3 v/v). Crystallization from methanol/water (9:1) yielded 0.9 g (35%) of 10a, mp 242–243°; ir (potassium bromide): ν 3386 cm^{-1} and 3199 (NH), 3088, 2970 and 2927 (CH), 2207 (CN), 1670 and 1646 (CO); uv (methanol): λ max 210 nm (log ϵ 4,468), 221 (4,519), 300 (4,168); (pH 11): 264 (4,193); ^1H nmr (DMSO- d_6): δ 3.63 (s, 2H, 5-H), 3.83 (s, 3H, OCH_3), 7.11 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.30 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.43 (d, 1H, 9-H, $J = 8.0$ Hz), 7.81 (d, 1H, 6-H, $J = 8.0$ Hz), 10.54 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.79 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 21.0 (C-5), 60.2 (OCH_3), 75.5 (C-4), 113.0 (C-9), 119.8 (CN), 120.8 (C-7), 121.0 (C-5a), 121.1 (C-6), 125.0 (C-5b), 126.2 (C-10a), 126.4 (C-8), 137.4 (C-9a), 160.4 (C-3), 161.2 (C-1); ms: m/z 253 (M^+), 238 ($\text{M}^+ - \text{CH}_3$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_2$: C, 66.4; H, 4.4; N, 16.6. Found: C, 66.0; H, 4.5; N, 16.5.

4-Cyano-1-oxo-3,7,8-trimethoxy-1,2,5,10-tetrahydroazepino-[3,4-*b*]indole (10e).

This compound was prepared as described for 10a from 5e (3.93 g, 12 mmol) and sodium (1.38 g, 60 mmol). The brown precipitate was purified by mpic on silica gel (toluene:ethyl acetate 6:4 v/v). Crystallization from methanol/water (9:1) yielded 0.8 g (22%) of 10e, mp 229–231°; ir (potassium bromide): ν 3279 cm^{-1} (NH), 3093, 2954 and 2845 (CH), 2205 (CN), 1642 and 1627 (CO); uv (methanol): λ max 211 nm (log ϵ 4,452), 329 (4,128); ^1H nmr (DMSO- d_6): δ 3.60 (s, 2H, 5-H), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.84 (s, 1H, 9-H), 7.27 (d, 1H, 6-H), 10.32 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.49 (s, 1H, 10-NH, deuterium oxide-exchangeable); ms: m/z 313 (M^+), 298 ($\text{M}^+ - \text{CH}_3$).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_4$: C, 61.3; H, 4.8; N, 13.4. Found: C, 61.5; H, 4.9; N, 13.5.

4-Cyano-3-ethoxy-1-oxo-1,2,5,10-tetrahydroazepino-[3,4-*b*]indole (11a).

A solution of sodium (0.45 g, 15 mmol) in 40 ml of ethanol and ethyl 3-(2,2-dicyanethyl)indole-2-carboxylate (5a) (0.80 g, 3 mmol) was heated at reflux for 4 hours. The solution was evaporated *in vacuo* and the residue was dissolved in 100 ml of water. After acidification with 2N sulfuric acid a brown precipitate formed which was purified by flush-chromatography on silica gel under reduced pressure (toluene:ethyl acetate 7:3 v/v). Crystallization from methanol/water (9:1) yielded 0.14 g (18%) of 11a, mp 232–234°; ir (potassium bromide): ν 3307 cm^{-1} and 3120 (NH), 2987 and 2928 (CH), 2197 (CN), 1656 and 1631 (CO); uv (methanol): λ max 208 nm (log ϵ 4,526), 220 (4,485), 233 (4,477), 252 (4,291), 304 (4,325); (pH 11): 256 (4,349); ^1H nmr (DMSO- d_6): δ 1.19 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.64 (s, 2H, 5-H), 4.15 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 7.11 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.30 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.43 (d, 1H, 9-H, $J = 8.0$ Hz), 7.81 (d, 1H, 6-H, $J = 8.0$ Hz), 10.54 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.78 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 15.0 (OCH_2CH_3), 21.1 (C-5), 69.2 (OCH_2CH_3), 77.3 (C-4), 113.2 (C-9), 120.1 (CN), 121.0 (C-7), 121.0 (C-5a), 121.4 (C-6), 126.1 (C-5b), 126.2 (C-10a), 126.5 (C-8), 137.5 (C-9a), 159.1 (C-3), 161.4 (C-1); ms: m/z 267 (M^+), 238 ($\text{M}^+ - \text{C}_2\text{H}_5$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2$: C, 67.4; H, 4.9; N, 15.7. Found: C, 67.6; H, 5.0; N, 15.8.

7-Chloro-4-cyano-3-ethoxy-1-oxo-1,2,5,10-tetrahydroazepino-[3,4-*b*]indole (11b).

The preparation as for 11a from 5b (3.02 g, 10 mmol) and sodium (1.15 g, 50 mmol) in 60 ml of ethanol yielded 0.41 g (14%) of 11b, mp 244–247°; ir (potassium bromide): ν 3308 cm^{-1} and 3119 (NH), 2922 and 2851 (CH), 2202 (CN), 1635 (CO); uv (methanol): λ max 226 nm (log ϵ 4,501), 307 (4,077); ^1H nmr (DMSO- d_6): δ 1.20 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.65 (s, 2H, 5-H), 4.15 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 7.29 (dd, 1H, 8-H, $J = 2.0$, 9.0 Hz), 7.44 (d, 1H, 9-H, $J = 9.0$ Hz), 7.98 (d, 1H, 6-H, $J = 2.0$ Hz), 10.61 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.99 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.5 (OCH_2CH_3), 20.2 (C-5), 68.2 (OCH_2CH_3), 76.7 (C-4), 114.1 (C-9), 119.1 (CN), 119.9 (C-5a), 119.9 (C-6), 124.6 (C-5b), 125.6 (C-10a), 125.6 (C-8), 127.3 (C-7), 135.3 (C-9a), 158.3 (C-3), 160.5 (C-1); ms: m/z 303/301 (M^+), 274/272 ($\text{M}^+ - \text{C}_2\text{H}_5$).

Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{ClN}_3\text{O}_2$: C, 59.7; H, 4.0; N, 13.9. Found: C, 59.9; H, 4.0; N, 14.0.

4-Cyano-ethoxy-7-fluoro-1-oxo-1,2,5,10-tetrahydroazepino-[3,4-*b*]indole (11c).

The preparation as described for 11a from 5c (1.14 g, 4 mmol) and sodium (0.46 g, 20 mmol) in 60 ml of ethanol provided 0.30 g (26%) of 11c, mp 243–244°; ir (potassium bromide): ν 3307 cm^{-1} and 3186 (NH), 3078 and 2926 (CH), 2214 and 2205 (CN), 1727, 1662 and 1636 (CO); uv (methanol): λ max 207 nm (log ϵ 4,255), 220 (4,260), 305 (3,970); (pH 11): 265 (4,170); ^1H nmr (DMSO- d_6): δ 1.19 (t, 3H, OCH_2CH_3 , $J = 7.0$ Hz), 3.63 (s, 2H, 5-H), 4.15 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 7.17 (ddd, 1H, 8-H, $J = 2.5$, 9.5 Hz), 7.42 (dd, 1H, 9-H, $J = 4.5$, 9.5 Hz), 7.68 (dd, 1H, 6-H, $J = 2.5$, 9.5 Hz), 10.59 (s, 1H, 2-NH,

deuterium oxide-exchangeable), 11.90 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.7 (OCH₂CH₃), 20.6 (C-5), 68.6 (OCH₂CH₃), 77.0 (C-4), 104.9 (C-9), 114.1 (CN), 114.7 (C-5a), 115.4 (C-6), 119.5 (C-8), 120.6 (C-5b), 124.8 (C-10a), 133.8 (C-9a), 155.6 (C-7), 158.6 (C-3), 160.7 (C-1); ms: m/z 285 (M⁺), 256 (M⁺-C₂H₅).

Anal. Calcd. for C₁₅H₁₂FN₃O₂: C, 63.2; H, 4.2; N, 14.7. Found: C, 63.4; H, 4.8; N, 14.5.

4-Cyano-3-ethoxy-7-methoxy-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (11d).

The preparation as for 11a from 5b (4.16 g, 14 mmol) and sodium (1.61 g, 70 mmol) in 60 ml of ethanol yielded 0.87 g (21%) of 11d, mp 235-237°; ir (potassium bromide): ν 3395 cm⁻¹, 3332 and 3178 (NH), 3067, 2987 and 2932 (CH), 2197 (CN), 1669 and 1625 (CO); uv (methanol): λ max 210 nm (log ϵ 4,253), 222 (4,286), 300 (3,896); (pH 11): 264 (3,880), 340 (3,757); ^1H nmr (DMSO- d_6): δ 1.20 (t, 3H, OCH₂CH₃, J = 7.0 Hz), 3.63 (s, 2H, 5-H), 3.80 (s, 3H, OCH₃), 4.15 (q, 2H, OCH₂CH₃, J = 7.0 Hz), 6.95 (dd, 1H, 8-H, J = 2.5, 9.0 Hz), 7.29 (d, 1H, 6-H, J = 2.5 Hz), 7.31 (d, 1H, 9-H, J = 9.0 Hz), 10.47 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.64 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.4 (OCH₂CH₃), 20.5 (C-5), 55.4 (OCH₃), 68.1 (OCH₂CH₃), 76.5 (C-4), 100.5 (C-9), 113.4 (CN), 117.3 (C-6), 119.4 (C-5a), 119.8 (C-5b), 124.8 (C-8), 126.2 (C-10a), 132.4 (C-9a), 153.9 (C-7), 158.4 (C-3), 160.6 (C-1); ms: m/z 297 (M⁺), 268 (M⁺-C₂H₅).

Anal. Calcd. for C₁₆H₁₅N₃O₃: C, 64.6; H, 5.1; N, 14.1. Found: C, 65.1; H, 5.4; N, 14.4.

3-Amino-4-cyano-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (12a).

Method A.

A solution of 4-cyano-3-methoxy-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (10a) (1.01 g, 4 mmol) and ammonium acetate (6.17 g, 80 mmol) in 50 ml of methanol was heated at reflux for 2 hours. After cooling to room temperature the white precipitate was collected by filtration and crystallized from acetone/water (1:1) to yield 0.80 g (84%) of 12a, mp 282-285°; ir (potassium bromide): ν 3448 cm⁻¹, 3427, 3344 and 3327 (NH), 2959, 2919 and 2850 (CH), 2197 and 2172 (CN), 1661 and 1609 (CO); uv (methanol): λ max 209 nm (log ϵ 4,189), 221 (4,233), 302 (3,959); (pH 11): 263 (3,990); ^1H nmr (DMSO- d_6): δ 3.51 (s, 2H, 5-H), 5.93 (s, 2H, 3-NH₂, deuterium oxide-exchangeable), 7.09 (dd, 1H, 7-H, J = 8.0 Hz), 7.28 (dd, 1H, 8-H, J = 8.0 Hz), 7.41 (d, 1H, 9-H, J = 8.0 Hz), 7.77 (d, 1H, 6-H, J = 8.0 Hz), 9.54 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.70 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 21.3 (C-5), 60.9 (C-4), 112.8 (C-9), 120.4 (CN), 120.8 (C-7), 122.5 (C-5a), 122.8 (C-6), 124.7 (C-5b), 125.9 (C-8), 126.3 (C-10a), 137.2 (C-9a), 153.2 (C-3), 161.9 (C-1); ms: m/z 238 (M⁺).

Anal. Calcd. for C₁₃H₁₀N₄O: C, 65.5; H, 4.2; N, 23.5. Found: C, 65.5; H, 4.4; N, 23.1.

Method B.

Using the preparation as described in Method A, 11a (0.27 g, 1 mmol) and ammonium acetate (1.54 g, 20 mmol) in 20 ml of methanol afforded 0.12 g (50%) of 12a.

3-Amino-4-cyano-7-chloro-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (12b).

The preparation as for 12a from 11b (0.60 g, 2 mmol) and ammonium acetate (3.08 g, 40 mmol) in 40 ml of methanol provided 0.36 g (66%) of 12b, mp 280°; ir (potassium bromide): ν 3402 cm⁻¹, 3322 and 3203 (NH), 3084, 2965 and 2851 (CH), 2199 (CN), 1669 and 1655 (CO); uv (methanol): λ max 210 nm (log ϵ 4,135), 227 (4,136), 307 (3,856); (pH 11): 263 (3,905); ^1H nmr (DMSO- d_6): δ 3.50 (s, 2H, 5-H), 5.95 (s, 2H, 3-NH₂, deuterium oxide-exchangeable), 7.27 (dd, 1H, 8-H, J = 2.0, 9.0 Hz), 7.41 (d, 1H, 9-H, J = 9.0 Hz), 7.93 (d, 1H, 6-H, J = 2.0 Hz) 9.63 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.92 (s, 1H, 10-NH, deuterium oxide-exchangeable); ms: m/z 274/272 (M⁺).

Anal. Calcd. for C₁₃H₉ClN₄O: C, 57.3; H, 3.3; N, 20.5. Found: C, 57.4; H, 3.4; N, 20.6.

3-Amino-4-cyano-7-fluoro-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (12c).

The preparation described for 12a from 11c (0.57 g, 2 mmol) and ammonium acetate (3.08 g, 40 mmol) in 40 ml of methanol gave 0.30 g (59%) of 12c, mp 280°; ir (potassium bromide): ν 3402 cm⁻¹, 3314 and 3205 (NH), 3088, 2966 and 2850 (CH), 2199 (CN), 1669 and 1602 (CO); uv (methanol): λ max 207 nm (log ϵ 4,299), 219 (4,263), 261 (4,057), 304 (4,093); ^1H nmr (DMSO- d_6): δ 3.49 (s, 2H, 5-H), 5.94 (s, 2H, 3-NH₂, deuterium oxide-exchangeable), 7.14 (ddd, 1H, 8-H, J = 2.5, 9.5 Hz), 7.40 (dd, 1H, 9-H, J = 4.5, 9.5 Hz), 7.63 (dd, 1H, 6-H, J = 2.5, 4.5 Hz) 9.60 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.82 (s, 1H, 10-NH, deuterium oxide-exchangeable); ms: m/z 256 (M⁺).

Anal. Calcd. for C₁₃H₉FN₄O: C, 60.9; H, 3.5; N, 21.9. Found: C, 60.5; H, 3.6; N, 21.9.

3-Amino-4-cyano-7-methoxy-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (12d).

The preparation by the procedure described for 12a from 11d (0.60 g, 2 mmol) and ammonium acetate (3.08 g, 40 mmol) in 40 ml of methanol, afforded 0.37 g (69%) of 12d, mp 269-273°; ir (potassium bromide): ν 3313 cm⁻¹ and 3220 (NH), 2989, 2949 and 2843 (CH), 2194 (CN), 1669 and 1656 (CO); uv (methanol): λ max 211 nm (log ϵ 4,626), 261 (4,193), 304 (4,327); ^1H nmr (DMSO- d_6): δ 3.49 (s, 2H, 5-H), 3.80 (s, 3H, OCH₃), 5.91 (s, 2H, 3-NH₂, deuterium oxide-exchangeable), 6.93 (dd, 1H, 8-H, J = 2.5, 9.0 Hz), 7.24 (d, 1H, 6-H, J = 2.5 Hz), 7.29 (d, 1H, 9-H, J = 9.0 Hz) 9.48 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.56 (s, 1H, 10-NH, deuterium oxide-exchangeable); ms: m/z 268 (M⁺).

Anal. Calcd. for C₁₄H₁₂N₄O₂: C, 62.7; H, 4.5; N, 20.9. Found: C, 62.8; H, 4.9; N, 20.9.

4-Cyano-3-dimethylamino-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (14a).

A solution of 4-cyano-3-methoxy-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (10a) (0.25 g, 1 mmol) and a 30% aqueous solution of dimethylamine (13a) (0.75 g, 5 mmol) in 25 ml of methanol was heated at reflux for 3 hours. After cooling to room temperature the white precipitate was collected by filtration and crystallized from methanol to yield 0.14 g (53%) of 14a, mp 260-261°; ir (potassium bromide): ν 3288 cm⁻¹ and 3198 (NH), 3080, 2937, 2880 and 2831 (CH), 2178 (CN), 1656 and 1606 (CO); uv (methanol): λ max 209 nm (log ϵ 4,652), 220 (4,637), 233 (4,561), 272 (4,535), 307 (4,480); (pH 2): 313 (4,359); ^1H nmr (DMSO- d_6): δ 2.96 (s, 6H, NCH₃), 3.43 (s, 2H, 5-H), 7.10 (dd, 1H, 7-H, J = 8.0 Hz), 7.28 (dd, 1H, 8-H, J = 8.0

Hz), 7.42 (d, 1H, 9-H, $J = 8.0$ Hz), 7.79 (d, 1H, 6-H, $J = 8.0$ Hz), 9.83 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.74 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 22.7 (C-5), 41.5 (CH_3), 67.9 (C-4), 112.9 (C-9), 120.4 (CN), 120.7 (C-7), 122.5 (C-5a), 124.5 (C-6), 125.1 (C-5b), 125.8 (C-8), 126.7 (C-10a), 137.3 (C-9a), 155.4 (C-3), 162.3 (C-1); ms: m/z 266 (M^+).

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}$: C, 67.7; H, 5.3; N, 21.0. Found: C, 67.3; H, 5.2; N, 21.1.

4-Cyano-3-diethylamino-1-oxo-1,2,5,10-tetrahydroazepino-[3,4-*b*]indole (14b).

The preparation described for 14a from 10a (0.25 g, 1 mmole) and a 30% aqueous solution of diethylamine (13b) (3.0 g, 20 mmoles) afforded 0.12 g (41%) of 14b, mp 180–182°; ir (potassium bromide): ν 3270 cm^{-1} (NH), 2975 and 2930 (CH), 2185 (CN), 1655 and 1606 (CO); uv (methanol): λ max 211 nm (log ϵ 4.392), 276 (4.107), 305 (4.109); ^1H nmr (DMSO- d_6): δ 1.03 (t, 6H, NCH_2CH_3 , $J = 7.0$ Hz), 3.32 (q, 4H, NCH_2CH_3 , $J = 7.0$ Hz), 3.46 (s, 2H, 5-H), 7.11 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.29 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.43 (d, 1H, 9-H, $J = 8.0$ Hz), 7.80 (d, 1H, 6-H, $J = 8.0$ Hz), 9.79 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.74 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 13.6 (NCH_2CH_3), 22.8 (C-5), 45.4 (NCH_2CH_3), 72.8 (C-4), 113.0 (C-9), 120.2 (CN), 120.5 (C-7), 120.8 (C-5a), 122.2 (C-6), 124.6 (C-5b), 125.0 (C-8), 126.0 (C-10a), 137.4 (C-9a), 154.3 (C-3), 162.6 (C-1); ms: m/z 294 (M^+), 265 ($\text{M}^+ - \text{C}_2\text{H}_5$), 240 ($\text{M}^+ - \text{C}_3\text{H}_4\text{N}$).

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}$: C, 69.4; H, 6.2; N, 19.0. Found: C, 69.1; H, 6.2; N, 19.1.

4-Cyano-1-oxo-3-pyrrolidino-1,2,5,10-tetrahydroazepino-[3,4-*b*]indole (14c).

The preparation as for 14a from 10a (0.25 g, 1 mmole) and pyrrolidine (13c) (0.36 g, 5 mmoles) in 25 ml of methanol provided 0.15 g (51%) of 14c, mp 256–258°; ir (potassium bromide): ν 3290 cm^{-1} , 3230 and 3117 (NH), 3057, 2951 and 2874 (CH), 2178 (CN), 1656 (CO); uv (methanol): λ max 208 nm (log ϵ 4.511), 221 (4.451), 233 (4.366), 276 (4.395), 308 (4.511); (pH 2): 245 (4.281), 333 (4.194); ^1H nmr (DMSO- d_6): δ 1.86 (t, 4H, 3'-H, 4'-H, $J = 6.5$ Hz), 3.44 (s, 2H, 5-H), 3.53 (t, 4H, 2'-H, 5'-H, $J = 6.5$ Hz), 7.10 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.28 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.42 (d, 1H, 9-H, $J = 8.0$ Hz), 7.79 (d, 1H, 6-H, $J = 8.0$ Hz), 9.56 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.74 (s, 1H, 10-NH, deuterium oxide-exchangeable); ms: m/z 292 (M^+).

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}$: C, 69.8; H, 5.5; N, 19.2. Found: C, 69.5; H, 5.5; N, 18.8.

4-Cyano-1-oxo-3-piperidino-1,2,5,10-tetrahydroazepino-[3,4-*b*]indole (14d).

The preparation by the method for 14a from 10a (0.25 g, 1 mmole) and piperidine (13d) (0.43 g, 5 mmoles) in 20 ml of methanol yielded 0.24 g (78%) of 14d, mp 248°; ir (potassium bromide): ν 3298 cm^{-1} and 3257 (NH), 3054, 2941 and 2852 (CH), 2182 (CN), 1652 (CO); uv (methanol): λ max 207 nm (log ϵ 4.698), 221 (4.622), 236 (4.514), 275 (4.469), 306 (4.441); ^1H nmr (DMSO- d_6): δ 1.57 (s, 6H, 3'-H, 4'-H, 5'-H), 3.27 (s, 4H, 2'-H, 6'-H), 3.44 (s, 2H, 5-H), 7.10 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.29 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.42 (d, 1H, 9-H, $J = 8.0$ Hz), 7.80 (d, 1H, 6-H, $J = 8.0$ Hz), 9.81 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.75 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 22.8 (C-5), 24.0 (C-4'),

25.9 (C-3', C-5'), 51.1 (C-2', C-6'), 69.7 (C-4), 112.8 (C-9), 120.3 (CN), 120.7 (C-7), 122.3 (C-5a), 124.5 (C-6), 124.8 (C-5b), 125.8 (C-8), 126.7 (C-10a), 137.3 (C-9a), 155.3 (C-3), 162.6 (C-1); ms: m/z 306 (M^+).

Anal. Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}$: C, 70.6; H, 5.9; N, 18.3. Found: C, 70.3; H, 5.8; N, 18.1.

4-Cyano-3-morpholino-1-oxo-1,2,5,10-tetrahydroazepino-[3,4-*b*]indole (14e).

This compound was prepared as described for 14a and from 10a (0.25 g, 1 mmole), morpholine (13e) (2.61 g, 30 mmoles) and glacial acetic acid (1.80 g, 30 mmoles) in 20 ml of methanol afforded 0.18 g (58%) of 14e, mp 263–264°; ir (potassium bromide): ν 3411 cm^{-1} , 3292 and 3180 (NH), 3072, 2974, 2954, 2930, 2900 and 2860 (CH), 2193 (CN), 1646 (CO); uv (methanol): λ max 207 nm (log ϵ 4.605), 272 (4.022), 300 (3.936); ^1H nmr (DMSO- d_6): δ 3.28 (t, 4H, 2'-H, 6'-H, $J = 4.5$ Hz), 3.46 (s, 2H, 5-H), 3.65 (t, 4H, 3'-H, 5'-H, $J = 4.5$ Hz), 7.10 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.28 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.42 (d, 1H, 9-H, $J = 8.0$ Hz), 7.79 (d, 1H, 6-H, $J = 8.0$ Hz), 9.95 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.76 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 22.8 (C-5), 50.2 (C-2', C-6'), 66.6 (C-3', C-5'), 70.6 (C-4), 113.0 (C-9), 120.6 (CN), 120.8 (C-5a, C-7), 122.2 (C-6), 124.6 (C-5b), 126.1 (C-8), 126.8 (C-10a), 137.5 (C-9a), 155.0 (C-3), 162.6 (C-1); ms: m/z 308 (M^+).

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_2$: C, 66.2; H, 5.2; N, 18.2. Found: C, 66.4; H, 5.4; N, 18.2.

4-Cyano-3-(*N*-methylpiperazino)-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (14f).

The preparation as for 14a from 10a (1.01 g, 4 mmoles) and *N*-methylpiperazine (13f) (4.01 g, 40 mmoles) in 40 ml of methanol gave 0.32 g (25%) of 14f, mp 246°; ir (potassium bromide): ν 3301 cm^{-1} and 3264 (NH), 2944, 2888, 2852 and 2801 (CH), 2182 (CN), 1651 (CO); uv (methanol): λ max 208 nm (log ϵ 4.317), 221 (4.309), 239 (4.197), 271 (4.147), 305 (4.147); ^1H nmr (DMSO- d_6): δ 2.20 (s, 3H, NCH_3), 2.40 (t, 4H, 3'-H, 5'-H, $J = 5.0$ Hz), 3.29 (t, 4H, 2'-H, 6'-H, $J = 5.0$ Hz), 3.31 (s, 2H, 5-H), 7.11 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.29 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.42 (d, 1H, 9-H, $J = 8.0$ Hz), 7.80 (d, 1H, 6-H, $J = 8.0$ Hz), 9.87 (s, 1H, 2-NH, deuterium oxide-exchangeable), 11.76 (s, 1H, 10-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 23.0 (C-5), 46.0 (NCH_3), 49.6 (C-3', C-5'), 54.9 (C-2', C-6'), 70.4 (C-4), 113.1 (C-9), 120.8 (CN), 121.0 (C-7), 122.5 (C-5a), 124.7 (C-6), 125.1 (C-5b), 126.3 (C-8), 126.9 (C-10a), 137.6 (C-9a), 155.0 (C-3), 162.8 (C-1); ms: m/z 321 (M^+).

Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}$: C, 67.3; H, 6.0; N, 21.8. Found: C, 66.9; H, 5.5; N, 21.6.

Ethyl 1-(4-Chlorobenzyl)indole-2-carboxylate (16).

A solution of ethyl indole-2-carboxylate (1a) (1.95 g, 10 mmoles) and an 80% suspension of sodium hydride in petroleum (0.30 g, 11 mmoles) in 200 ml of dimethyl sulfoxide was stirred at 50° for 30 minutes. After the addition of 4-chlorobenzyl chloride (15) (1.60 g, 10 mmoles) and stirring at 80° for an additional 30 minutes the mixture was poured into 300 ml of water and extracted with toluene (3 x 300 ml). The organic layer was washed with 300 ml of 2*N* hydrochloric acid, dried over sodium sulfate and evaporated *in vacuo*. Purification by mp on silica gel (cyclohexane:ethyl acetate 8:2 v/v) and crystallization from ethanol yielded 1.50 g (48%), mp 93–95°; ir (potassium

bromide): ν 3064 cm^{-1} , 3051, 2985, 2940 and 2911 (CH), 1786 (CO); uv (methanol): λ max 206 nm (log ϵ 4,533), 220 (4,568), 292 (4,331); ^1H nmr (DMSO- d_6): δ 1.28 (t, 3H, OCH_2CH_3 , J = 7.0 Hz), 4.28 (q, 2H, OCH_2CH_3 , J = 7.0 Hz), 5.84 (s, 2H, 1'-H), 7.03 (d, 2H, 2''-H, 6''-H, J = 8.5 Hz), 7.15 (dd, 1H, 5-H, J = 8.0 Hz), 7.32 (dd, 1H, 6-H, J = 8.0 Hz), 7.33 (d, 2H, 3''-H, 5''-H, J = 8.5 Hz), 7.46 (s, 1H, 3-H), 7.57 (d, 1H, 7-H, J = 8.0 Hz), 7.73 (d, 1H, 4-H, J = 8.0 Hz); ^{13}C nmr (DMSO- d_6): δ 14.1 (OCH_2CH_3), 46.5 (C-1'), 60.5 (OCH_2CH_3), 110.8 (C-3), 111.2 (C-7), 120.9 (C-4), 122.5 (C-5), 125.3 (C-6), 125.5 (C-3a), 128.1 (C-3''), 128.4 (C-2''), 128.6 (C-2), 130.7 (C-4''), 137.5 (C-1''), 139.0 (C-7a), 161.2 (COOEt); ms: m/z 315/313 (M^+), 127/125 ($\text{C}_7\text{H}_6\text{Cl}^+$).

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{ClNO}_2$: C, 68.9; H, 5.1; N, 4.5. Found: C, 69.0; H, 5.2; N, 4.5.

Ethyl 1-(4-Chlorobenzyl)-3-formylindole-2-carboxylate (17).

Method A.

The preparation as for 2c from phosphoryl chloride (5.80 g, 37.5 mmol), *N*-methylformanilide (5.10 g, 37.5 mmol) and 16 (7.80 g, 25 mmol) gave 3.60 g (42%) of 17, mp 94°; ir (potassium bromide): ν 3064 cm^{-1} , 2995, 2980, 2937 and 2904 (CH), 1713 (CO); uv (methanol): λ max 219 nm (log ϵ 4,509), 249 (4,208), 254 (4,191), 318 (4,075); ^1H nmr (DMSO- d_6): δ 1.30 (t, 3H, OCH_2CH_3 , J = 7.0 Hz), 4.41 (q, 2H, OCH_2CH_3 , J = 7.0 Hz), 5.84 (s, 2H, 1'-H), 7.12 (d, 2H, 2''-H, 6''-H, J = 8.5 Hz), 7.36 (dd, 1H, 5-H, J = 8.0 Hz), 7.37 (d, 2H, 3''-H, 5''-H, J = 8.5 Hz), 7.41 (dd, 1H, 6-H, J = 8.0 Hz), 7.68 (d, 1H, 7-H, J = 8.0 Hz), 8.34 (d, 1H, 4-H, J = 8.0 Hz), 10.50 (s, 1H, CHO); ^{13}C nmr (DMSO- d_6): δ 13.8 (OCH_2CH_3), 47.5 (C-1'), 62.3 (OCH_2CH_3), 111.9 (C-7), 119.1 (C-3), 122.5 (C-4), 123.8 (C-3a), 124.1 (C-5), 126.3 (C-6), 128.2 (C-3''), 128.4 (C-2), 128.6 (C-2''), 132.0 (C-4''), 136.3 (C-1''), 137.4 (C-7a), 160.2 (COOEt), 187.8 (CHO); ms: m/z 343/341 (M^+), 127/125 ($\text{C}_7\text{H}_6\text{Cl}^+$).

Anal. Calcd. for $\text{C}_{19}\text{H}_{16}\text{ClNO}_3$: C, 66.8; H, 4.7; N, 4.1. Found: C, 66.9; H, 4.7; N, 4.2.

Method B.

Using the preparation as described for 16, 2a (6.50 g, 30 mmol), an 80% suspension of sodium hydride in petroleum (1.00 g, 33 mmol) and 4-chlorobenzyl chloride (15) afforded 17 (5.30 g, 33 mmol). Purification by mpc on silica gel (cyclohexane:ethyl acetate 7:3 v/v) and crystallization from ethanol yielded 9.70 g (95%) of compound 17.

Ethyl 1-(4-Chlorobenzyl)-3-(2,2-dicyanoethenyl)indole-2-carboxylate (18).

The preparation as for 4b from 17 (0.68 g, 2 mmol), malononitrile (3) (0.26 g, 4 mmol) and β -alanine (0.01 g, 0.15 mmol) provided 0.53 g (68%) of 18, mp 102-104°; ir (potassium bromide): ν 3054 cm^{-1} , 2986 and 2941 (CH), 2231 (CN), 1703 (CO); uv (methanol): λ max 206 nm (log ϵ 4,571), 220 (4,591), 279 (4,268), 284 (4,288), 387 (4,317); (pH 11): 319 (4,112); (pH 2): 321 (4,086); ^1H nmr (DMSO- d_6): δ 1.28 (t, 3H, OCH_2CH_3 , J = 7.0 Hz), 4.36 (q, 2H, OCH_2CH_3 , J = 7.0 Hz), 5.88 (s, 2H, 1'-H), 7.11 (d, 2H, 2''-H, 6''-H, J = 8.5 Hz), 7.38 (d, 2H, 3''-H, 5''-H, J = 8.5 Hz), 7.39 (dd, 1H, 5-H, J = 8.0 Hz), 7.48 (dd, 1H, 6-H, J = 8.0 Hz), 7.75 (d, 1H, 7-H, J = 8.0 Hz), 7.98 (d, 1H, 4-H, J = 8.0 Hz), 8.87 (s, 1H, 1'-H); ^{13}C nmr (DMSO- d_6): δ 13.6 (OCH_2CH_3), 47.7 (C-1'), 62.3 (OCH_2CH_3), 82.0 (C-2'), 112.4 (C-7), 113.6 (C-3), 113.6 (CN), 114.5 (CN),

122.2 (C-4), 123.1 (C-5), 123.1 (C-3a), 126.5 (C-6), 128.2 (C-3''), 128.6 (C-2''), 130.3 (C-2), 132.0 (C-4''), 136.2 (C-1''), 137.8 (C-7a), 156.1 (C-1'), 159.9 (COOEt); ms: m/z 391/389 (M^+), 127/125 ($\text{C}_7\text{H}_6\text{Cl}^+$).

Anal. Calcd. for $\text{C}_{22}\text{H}_{16}\text{ClN}_3\text{O}_2$: C, 67.8; H, 4.1; N, 10.8. Found: C, 68.2; H, 4.4; N, 10.7.

Ethyl 1-(4-Chlorobenzyl)-3-(2,2-dicyanoethyl)indole-2-carboxylate (19).

The preparation described for 5a from 18 (0.78 g, 2 mmol) and sodium borohydride, (0.083 g, 2.2 mmol) afforded 0.76 g (97%) of 19, mp 118°; ir (potassium bromide): ν 2984 cm^{-1} , 2962 and 2931 (CH), 2259 (CN), 1703 (CO); uv (methanol): λ max 206 nm (log ϵ 4,258), 220 (4,271), 234 (4,135), 296 (4,037), 331 (3,468); ^1H nmr (DMSO- d_6): δ 1.32 (t, 3H, OCH_2CH_3 , J = 7.0 Hz), 3.90 (d, 2H, 1'-H, J = 7.5 Hz), 4.31 (q, 2H, OCH_2CH_3 , J = 7.0 Hz), 5.10 (t, 1H, 2''-H, J = 7.5 Hz, deuterium oxide-exchangeable), 5.84 (s, 2H, 1''-H), 7.01 (d, 2H, 2''-H, 6''-H, J = 8.5 Hz), 7.21 (dd, 1H, 5-H, J = 8.0 Hz), 7.32 (d, 2H, 3''-H, 5''-H, J = 8.5 Hz), 7.37 (dd, 1H, 6-H, J = 8.0 Hz), 7.59 (d, 1H, 7-H, J = 8.0 Hz), 7.99 (d, 1H, 4-H, J = 8.0 Hz); ^{13}C nmr (DMSO- d_6): δ 14.1 (OCH_2CH_3), 23.9 (C-2'), 25.9 (C-1'), 47.5 (C-1''), 61.6 (OCH_2CH_3), 111.6 (C-7), 114.6 (CN), 117.3 (CN), 121.4 (C-4), 121.6 (C-5), 125.9 (C-3), 126.4 (C-3a), 126.6 (C-6), 128.3 (C-3''), 128.9 (C-2''), 130.9 (C-2), 132.1 (C-4''), 137.8 (C-1''), 138.2 (C-7a), 161.6 (COOEt); ms: m/z 393/391 (M^+), 328/326 ($\text{M}^+ - \text{C}_3\text{HN}_2$), 127/125 ($\text{C}_7\text{H}_6\text{Cl}^+$).

Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{ClN}_3\text{O}_2$: C, 67.4; H, 4.6; N, 10.7. Found: C, 66.9; H, 4.7; N, 10.6.

10-(4-Chlorobenzyl)-4-cyano-3-methoxy-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (20).

The preparation as for 10a from 19 (4.70 g, 12 mmol) and sodium (1.38 g, 60 mmol) in 100 ml of methanol yielded 2.89 g (64%) of 20, mp 227-229°; ir (potassium bromide): ν 3182 cm^{-1} (NH), 3071, 2954 and 2927 (CH), 2207 (CN), 1665 and 1636 (CO); uv (methanol): λ max 208 nm (log ϵ 4,629), 222 (4,656), 235 (4,508), 305 (4,209); (pH 11): 266 (3,950); ^1H nmr (DMSO- d_6): δ 3.61 (s, 2H, 5-H), 3.74 (s, 3H, OCH_3), 5.71 (s, 2H, 1'-H), 7.08 (d, 2H, 2''-H, 6''-H, J = 8.5 Hz), 7.19 (dd, 1H, 7-H, J = 8.0 Hz), 7.34 (d, 2H, 3''-H, 5''-H, J = 8.5 Hz), 7.35 (dd, 1H, 8-H, J = 8.0 Hz), 7.55 (d, 1H, 9-H, J = 8.0 Hz), 7.90 (d, 1H, 6-H, J = 8.0 Hz), 10.68 (s, 1H, 2-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 20.7 (C-5), 46.8 (C-1'), 59.7 (OCH_3), 77.0 (C-4), 111.4 (C-9), 121.1 (CN), 121.3 (C-7), 121.7 (C-5a), 124.0 (C-6), 124.4 (C-5b), 126.1 (C-10a), 126.6 (C-8), 128.7 (C-3''), 128.8 (C-2''), 132.2 (C-4''), 137.9 (C-1''), 138.8 (C-9a), 160.2 (C-3), 161.2 (C-1); ms: m/z 379/377 (M^+), 252 ($\text{M}^+ - \text{C}_7\text{H}_6\text{Cl}$), 127/125 ($\text{C}_7\text{H}_6\text{Cl}^+$).

Anal. Calcd. for $\text{C}_{21}\text{H}_{16}\text{ClN}_3\text{O}_2$: C, 66.8; H, 4.3; N, 11.1. Found: C, 67.3; H, 4.6; N, 10.8.

10-(4-Chlorobenzyl)-4-cyano-3-ethoxy-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (21).

The preparation by the method for 10a from 19 (0.98 g, 2.5 mmol) and sodium (0.29 g, 12.5 mmol) in 40 ml of ethanol afforded 0.43 g (44%) of 21, mp 207-210°; ir (potassium bromide): ν 3190 cm^{-1} (NH), 3079 and 2953 (CH), 2197 (CN), 1660 and 1631 (CO); uv (methanol): λ max 208 nm (log ϵ 4,6569), 223 (4,683), 305 (4,244); (pH 11): 264 (4,331); ^1H nmr (DMSO- d_6): δ 1.00 (t, 3H, OCH_2CH_3 , J = 7.0 Hz), 3.61 (s, 2H,

5-H), 4.03 (q, 2H, OCH_2CH_3 , $J = 7.0$ Hz), 5.74 (s, 2H, 1'-H), 7.02 (d, 2H, 2"-H, 6"-H, $J = 8.5$ Hz), 7.20 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.31 (d, 2H, 3"-H, 5"-H, $J = 8.5$ Hz), 7.37 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.62 (d, 1H, 9-H, $J = 8.0$ Hz), 7.91 (d, 1H, 6-H, $J = 8.0$ Hz), 10.66 (s, 1H, 2-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 14.6 (OCH_2CH_3), 20.7 (C-5), 46.8 (C-1'), 68.4 (OCH_2CH_3), 79.3 (C-4), 111.5 (C-9), 121.3 (CN), 121.5 (C-7), 121.8 (C-5a), 124.0 (C-6), 125.2 (C-5b), 126.9 (C-8), 128.5 (C-10a), 128.8 (C-3", C5"), 129.0 (C-2", C-6"), 132.4 (C-4"), 137.9 (C-1"), 139.1 (C-9a), 158.8 (C-3), 161.4 (C-1); ms: m/z 393/391 (M^+), 266 ($\text{M}^+ - \text{C}_7\text{H}_6\text{Cl}$), 127/125 ($\text{C}_7\text{H}_6\text{Cl}^+$).

Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{ClN}_3\text{O}_2$: C, 67.4; H, 4.6; N, 10.7. Found: C, 67.7; H, 5.1; N, 10.6.

3-Amino-10-(chlorobenzyl)-4-cyano-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (22).

The preparation as for 12a from 20 (0.76 g, 2 mmol) and ammonium acetate (3.08 g, 40 mmol) in 40 ml of methanol gave 0.43 g (59%) of 22, mp 231–233°; ir (potassium bromide): ν 3425 cm^{-1} , 3334, 3224 and 3122 (NH), 3054 and 2960 (CH), 2179 (CN), 1661 and 1645 (CO); uv (methanol): λ max 209 nm ($\log \epsilon$ 4.472), 221 (4.452), 238 (4.306), 267 (4.052), 305 (4.082), 338 (3.674); ^1H nmr (DMSO- d_6): δ 3.49 (s, 2H, 5-H), 5.74 (s, 2H, 1'-H), 5.99 (s, 2H, 3-NH₂, deuterium oxide-exchangeable), 7.06 (d, 2H, 2"-H, 6"-H, $J = 8.5$ Hz), 7.06 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.33 (d, 2H, 3"-H, 5"-H, $J = 8.5$ Hz), 7.34 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.50 (d, 1H, 9-H, $J = 8.0$ Hz), 7.86 (d, 1H, 6-H, $J = 8.0$ Hz), 9.66 (s, 1H, 2-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 21.2 (C-5), 46.7 (C-1'), 62.6 (C-4), 111.3 (C-9), 121.1 (C-7, CN), 122.3 (C-5a), 123.8 (C-6), 125.8 (C-5b), 126.1 (C-10a), 126.5 (C-8), 128.7 (C-3", C-5"), 128.8 (C-2", C-6"), 132.1 (C-4"), 137.9 (C-1"), 138.8 (C-9a), 153.3 (C-3), 162.1 (C-1); ms: m/z 364/362 (M^+), 237 ($\text{M}^+ - \text{C}_7\text{H}_6\text{Cl}$), 127/125 ($\text{C}_7\text{H}_6\text{Cl}^+$).

Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{ClN}_4\text{O}$: C, 66.2; H, 4.2; N, 15.4. Found: C, 66.1; H, 4.6; N, 15.1.

10-(4-Chlorobenzyl)-4-cyano-3-(*N*-methylpiperazino)-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indole (23).

The preparation as described for 14f from 20 (0.76 g, 2 mmol) and *N*-methylpiperazine (13f) (2.00 g, 20 mmol) in

40 ml of methanol provided 0.58 g (65%) of 23, mp 214–216°; ir (potassium bromide): ν 3215 cm^{-1} and 3117 (NH), 3054, 2969, 2934 and 2839 (CH), 2185 (CN), 1670 (CO); uv (methanol): λ max 210 nm ($\log \epsilon$ 4.453), 275 (4.132), 305 (4.077); ^1H nmr (DMSO- d_6): δ 2.18 (s, 3H, CH₃), 2.35 (s, 4H, 3"-H, 5"-H), 3.22 (s, 4H, 2"-H, 6"-H), 3.46 (s, 2H, 5-H), 5.69 (s, 2H, 1'-H), 7.09 (d, 2H, 2"-H, 6"-H, $J = 8.5$ Hz), 7.17 (dd, 1H, 7-H, $J = 8.0$ Hz), 7.32 (d, 2H, 3"-H, 5"-H, $J = 8.5$ Hz), 7.34 (dd, 1H, 8-H, $J = 8.0$ Hz), 7.55 (d, 1H, 9-H, $J = 8.0$ Hz), 7.87 (d, 1H, 6-H, $J = 8.0$ Hz), 10.01 (s, 1H, 2-NH, deuterium oxide-exchangeable); ^{13}C nmr (DMSO- d_6): δ 22.9 (C-5), 45.9 (CH₃), 46.6 (C-1'), 49.3 (C-3", C-5"), 54.7 (C-2", C-6"), 72.2 (C-4), 111.3 (C-9), 120.9 (CN), 121.0 (C-7), 121.7 (C-5a), 123.7 (C-6), 126.2 (C-5b), 126.4 (C-10a), 127.2 (C-8), 128.7 (C-3", C-5"), 128.9 (C-2", C-6"), 132.1 (C-4"), 137.8 (C-1"), 138.7 (C-9a), 154.3 (C-3), 162.5 (C-1); ms: m/z 447/445 (M^+), 127/125 ($\text{C}_7\text{H}_6\text{Cl}^+$).

Anal. Calcd. for $\text{C}_{25}\text{H}_{24}\text{ClN}_5\text{O}$: C, 67.3; H, 5.4; N, 15.7. Found: C, 67.5; H, 5.8; N, 15.5.

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