Synthesis of Substituted 3-Amino-4-cyano-1-oxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indoles

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Dedicated to Professor Dr. W. Wiegrebe (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 N^{10} 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 = Et).

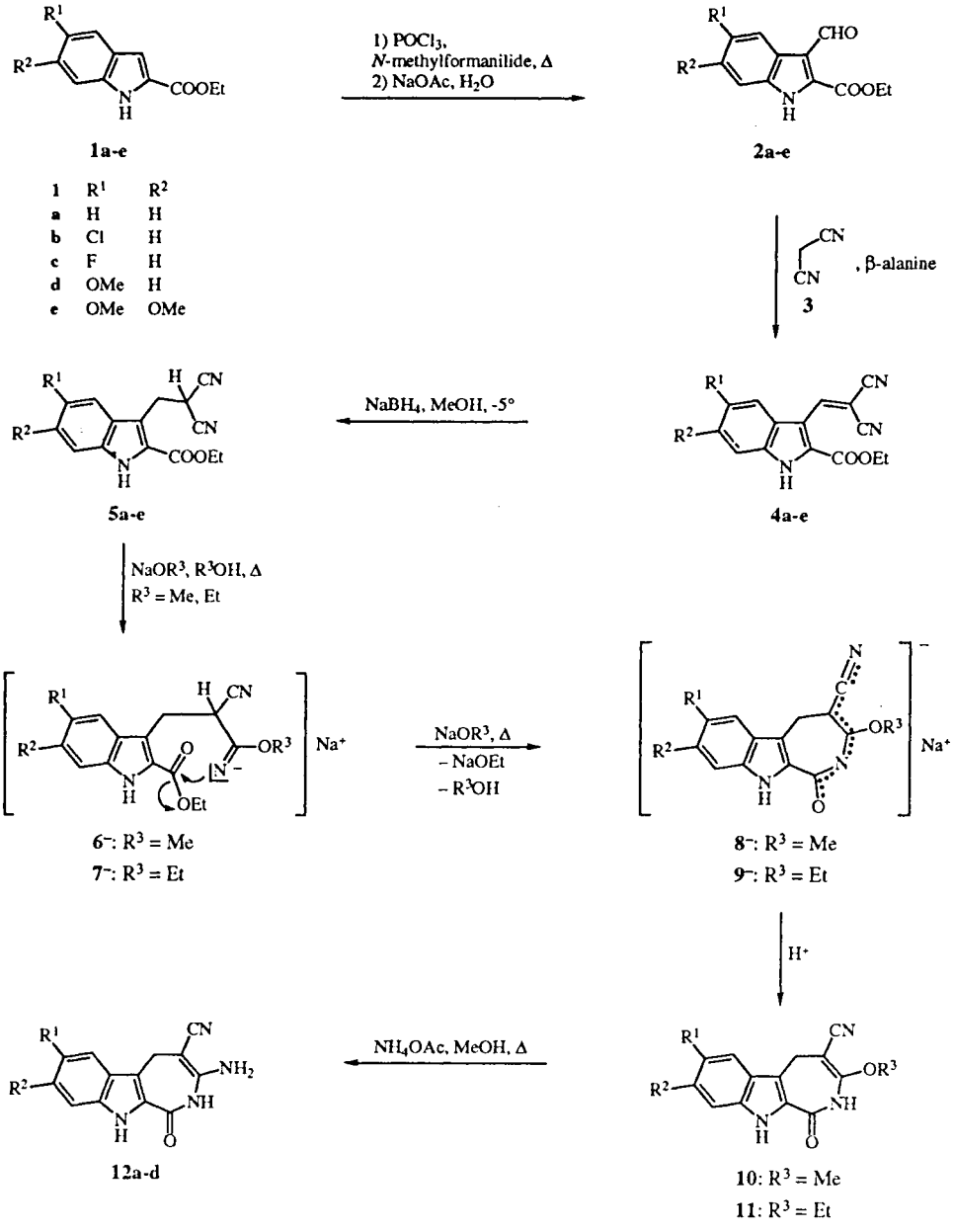
For this cyclisation reaction the following pathway seems to be plausible (see Scheme 1): a methoxide-ion first attacks a nitrile group in **5**, thus generating the nucleophilic imidate anion **6**$^-$ [3]. Intramolecular attack of this nucleophilic imidate at the ester function leads to a neutral azepino[3,4-*b*]indole 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 ^{13}C-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

^{13}C nmr data of **21** and **21**$^-$ (ppm), (**21** [D_6]DMSO, **21**$^-$ deuterium oxide).

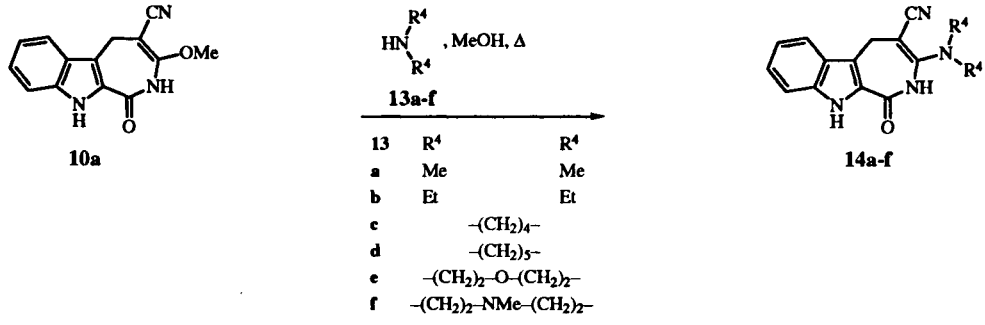
Scheme 1



Azepino[3,4-*b*]indoles **10** or **11** exhibit a partial structure of a β-cyanoenol ether. This type of enolether 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 heteroanellated 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*]-heteroanellated 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

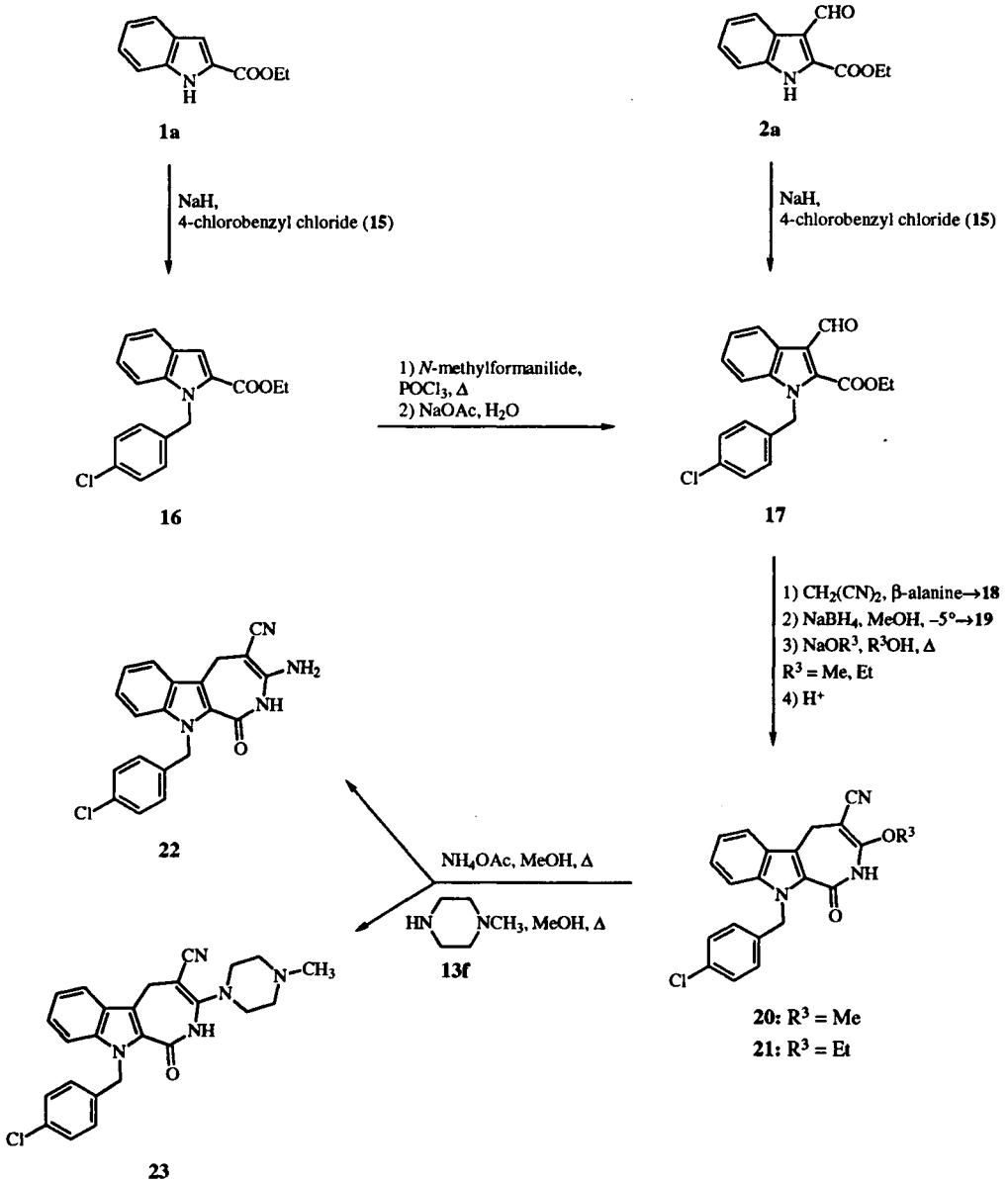
Scheme 2



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

Scheme 3



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 = 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 lipoxygenase-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-Lamda 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 mmoles) and *N*-methylformanilide (10.10 g, 75 mmoles) was stirred at room temperature for 15 minutes. After the addition of a solution of **1c** (10.40 g, 50 mmoles) 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); (*p*H 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 (M^+-C_2H_5), 188 (M^+-C_2H_7O).

Anal. Calcd. for $C_{12}H_{10}FNO_3$: 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 mmoles), *N*-methylformanilide (2.50 g, 18.8 mmoles) and **1e** (3.10 g, 12.5 mmoles) 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); (*p*H 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 (M^+-C_2H_5), 230 (M^+-C_2H_7O).

Anal. Calcd. for $C_{14}H_{15}NO_5$: 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 mmoles), malononitrile (**3**) (0.66 g, 10 mmoles) and β-alanine (0.01 g, 0.15 mmoles) 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); (*p*H 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 (M^+- C_2H_6O).

Anal. Calcd. for $C_{15}H_{10}ClN_3O_2$: 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 mmoles), malononitrile (**3**) (3.96 g, 60 mmoles) and β-alanine (0.05 g, 0.75 mmoles) 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); (*p*H 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 (M^+-C_2H_6O).

Anal. Calcd. for $C_{15}H_{10}FN_3O_2$: C, 63.6; H, 3.6; N, 14.8. Found: C, 63.8; H, 3.7; N, 14.7.

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

The preparation as for **4b** from **2d** (6.18 g, 25 mmoles), malononitrile (**3**) (3.30 g, 50 mmoles) and β-alanine (0.04 g, 0.60 mmoles) 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); (*p*H 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 (M^+-C_2H_6O).

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.1; H, 4.4; N, 14.2. Found: C, 64.8; H, 4.6; N, 14.0.

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

The preparation by the method for **4b** from **2e** (11.09 g, 40 mmoles), malononitrile (**3**) (5.28 g, 80 mmoles) and β-alanine (0.04 g, 0.60 mmoles) 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); (*p*H 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 (M^+-C_2H_6O).

Anal. Calcd. for $C_{17}H_{15}N_3O_4$: 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-dicyanoethenyl)indole-2-carboxylate (**4a**) (1.06 g, 4 mmoles) was suspended in 50 ml of methanol and cooled to -5°. Sodium borohydride (0.17 g, 4.4 mmoles) was added in portions and after 15 minutes the mixture was hydrolized with 50 ml of water and 50 ml of 2*N* 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 (M^+-C_3HN_2).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: 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 mmoles) and sodium borohydride, (0.17 g, 4.4 mmoles) 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 (M^+-C_3HN_2), 192/190 (M^+-$C_5H_7N_2O$).

Anal. Calcd. for $C_{15}H_{12}ClN_3O_2$: 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 mmoles) and sodium borohydride (0.50 g, 19.2 mmoles) 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 (C4), 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 (M^+-C_3HN_2), 174 (M^+-$C_5H_7N_2O$).

Anal. Calcd. for $C_{15}H_{12}FlN_3O_2$: 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 mmoles) and sodium borohydride (0.71 g, 18.7 mmoles) 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 (M^+-C_3HN_2), 186 (M^+-$C_5H_7N_2O$).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: 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 mmoles) and sodium borohydride, (1.25 g, 33.0 mmoles) 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 (COOEt); ms: m/z 327 (M^+), 262 (M^+-C_3HN_2), 216 (M^+-$C_5H_7N_2O$).

Anal. Calcd. for $C_{17}H_{17}N_3O_4$: 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 mmoles) in 60 ml of methanol and ethyl 3-(2,2-dicyanethyl)indole-2-carboxylate (**5a**) (2.67 g, 10 mmoles) 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 2*N* 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); (*p*H 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 (M^+-CH_3).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: 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 mmoles) and sodium (1.38 g, 60 mmoles). The brown precipitate was purified by mplc 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 (M^+-CH_3).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: 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 mmoles) in 40 ml of ethanol and ethyl 3-(2,2-dicyanethyl)indole-2-carboxylate (**5a**) (0.80 g, 3 mmoles) 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 2*N* sulfuric acid a brown precipitate formed which was purified by flush-chromatographie 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); (*p*H 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 (M^+-C_2H_5).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: 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 mmoles) and sodium (1.15 g, 50 mmoles) 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 (M^+-C_2H_5).

Anal. Calcd. for $C_{15}H_{12}ClN_3O_2$: 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 mmoles) and sodium (0.46 g, 20 mmoles) 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); (*p*H 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 (OCH_2CH_3), 20.6 (C-5), 68.6 (OCH_2CH_3), 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^+-C_2H_5).

Anal. Calcd. for $C_{15}H_{12}FN_3O_2$: 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 mmoles) and sodium (1.61 g, 70 mmoles) 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); (*p*H 11): 264 (3,880), 340 (3,757); ^{1}H nmr (DMSO-d_6): δ 1.20 (t, 3H, OCH_2CH_3, J = 7.0 Hz), 3.63 (s, 2H, 5-H), 3.80 (s, 3H, OCH_3), 4.15 (q, 2H, OCH_2CH_3, 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 (OCH_2CH_3), 20.5 (C-5), 55.4 (OCH_3), 68.1 (OCH_2CH_3), 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^+-C_2H_5).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: 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 mmoles) and ammonium acetate (6.17 g, 80 mmoles) 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); (*p*H 11): 263 (3,990); ^{1}H nmr (DMSO-d_6): δ 3.51 (s, 2H, 5-H), 5.93 (s, 2H, 3-NH_2, 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 $C_{13}H_{10}N_4O$: 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 mmole) and ammonium acetate (1.54 g, 20 mmoles) 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 mmoles) and ammonium acetate (3.08 g, 40 mmoles) 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); (*p*H 11): 263 (3,905); ^{1}H nmr (DMSO-d_6): δ 3.50 (s, 2H, 5-H), 5.95 (s, 2H, 3-NH_2, 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 $C_{13}H_9ClN_4O$: 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 mmoles) and ammonium acetate (3.08 g, 40 mmoles) 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); ^{1}H nmr (DMSO-d_6): δ 3.49 (s, 2H, 5-H), 5.94 (s, 2H, 3-NH_2, 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 $C_{13}H_9FN_4O$: 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 mmoles) and ammonium acetate (3.08 g, 40 mmoles) 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); ^{1}H nmr (DMSO-d_6): δ 3.49 (s, 2H, 5-H), 3.80 (s, 3H, OCH_3), 5.91 (s, 2H, 3-NH_2, 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 $C_{14}H_{12}N_4O_2$: 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 mmole) and a 30% aqueous solution of dimethylamine (**13a**) (0.75 g, 5 mmoles) 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); (*p*H 2): 313 (4,359); ^{1}H nmr (DMSO-d_6): δ 2.96 (s, 6H, NCH_3), 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 $C_{15}H_{14}N_4O$: 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); ^{1}H 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 (M^+-C_2H_5), 240 (M^+-C_3H_4N).

Anal. Calcd. for $C_{17}H_{18}N_4O$: 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); (*p*H 2): 245 (4,281), 333 (4,194); ^{1}H 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 $C_{17}H_{16}N_4O$: 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); ^{1}H 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 $C_{18}H_{18}N_4O$: 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 **14c**, 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); ^{1}H 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 (C4), 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 $C_{17}H_{16}N_4O_2$: 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); ^{1}H 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 $C_{18}H_{19}N_5O$: 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 mplc 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", C-5"), 128.4 (C-2", C-6"), 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 ($C_7H_6Cl^+$).

Anal. Calcd. for $C_{18}H_{16}ClNO_2$: 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 mmoles), *N*-methylformanilide (5.10 g, 37.5 mmoles) and **16** (7.80 g, 25 mmoles) 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", C-5"), 128.4 (C-2), 128.6 (C-2", C-6"), 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 ($C_7H_6Cl^+$).

Anal. Calcd. for $C_{19}H_{16}ClNO_3$: 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 mmoles), an 80% suspension of sodium hydride in petroleum (1.00 g, 33 mmoles) and 4-chlorobenzyl chloride (**15**) afforded **17** (5.30 g, 33 mmoles). Purification by mplc 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 mmoles), malononitrile (**3**) (0.26 g, 4 mmoles) and β-alanine (0.01 g, 0.15 mmoles) 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); (*p*H 11): 319 (4,112); (*p*H 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 (C1"), 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"', C-5"'), 128.6 (C-2"', C-6"'), 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 ($C_7H_6Cl^+$).

Anal. Calcd. for $C_{22}H_{16}ClN_3O_2$: 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 mmoles) and sodium borohydride, (0.083 g, 2.2 mmoles) 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"', C-5"'), 128.9 (C-2"', C-6"'), 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 (M^+-C_3HN_2), 127/125 ($C_7H_6Cl^+$).

Anal. Calcd. for $C_{22}H_{18}ClN_3O_2$: 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 mmoles) and sodium (1.38 g, 60 mmoles) 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); (*p*H 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", C-5"), 128.8 (C-2", C-6"), 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 (M^+-C_7H_6Cl), 127/125 ($C_7H_6Cl^+$).

Anal. Calcd. for $C_{21}H_{16}ClN_3O_2$: 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 mmoles) and sodium (0.29 g, 12.5 mmoles) 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); (*p*H 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 (M^+-C_7H_6Cl), 127/125 ($C_7H_6Cl^+$).

Anal. Calcd. for $C_{22}H_{18}ClN_3O_2$: 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 mmoles) and ammonium acetate (3.08 g, 40 mmoles) 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 ε 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-NH_2, 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 (C2", 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 (M^+-C_7H_6Cl), 127/125 ($C_7H_6Cl^+$).

Anal. Calcd. for $C_{20}H_{15}ClN_4O$: 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 mmoles) and *N*-methylpiperazine (**13f**) (2.00 g, 20 mmoles) 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 ε 4,453), 275 (4,132), 305 (4,077); ^1H nmr (DMSO-d_6): δ 2.18 (s, 3H, CH_3), 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 (CH_3), 46.6 (C-1'), 49.3 (C-3"', C-5"'), 54.7 (C-2"', C-6"'), 72.2 (C-4), 111.3 (C9), 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 ($C_7H_6Cl^+$).

Anal. Calcd. for $C_{25}H_{24}ClN_5O$: C, 67.3; H, 5.4; N, 15.7. Found: C, 67.5; H, 5.8; N, 15.5.

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REFERENCES AND NOTES

[1a] R. Troschütz, *Arch. Pharm. (Weinheim)*, **324**, 485 (1991); [b] R. Troschütz and L. Grün, *Arch. Pharm. (Weinheim)*, **326**, 857 (1993).

[2] E. Röder and J. Pigulla, *Arch. Pharm. (Weinheim)*, **311**, 822 (1978).

[3a] F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961); [b] P. Victory and J. Diago, *Afinidad*, **35**, 161 (1978); *Chem. Abstr.*, **89**, 179515j (1978).

[4] Y. Murakami, T. Watanabe, A. Kobayashi and Y. Yokoyama, *Synthesis*, 738, (1984).

[5a] B. N. Mayer, N. R. Ferrigni, J. E. Putnam, L. B. Jacobsen, D. E. Nichols and J. L. McLaughlin, *Planta Med.*, **45**, 31 (1982); [b] K. Hostettman, Methods in Plant Biochemistry, Vol. **6**, Assays for Bioactivity, Academic Press, San Diego, 1991, p 1.