Pergamon

Tetrahedron Vol. 51, No. 26, pp. 7263-7276, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00350-9

Synthesis of 1,3,4,5-Tetrahydropyrrolo-[4,3,2-*de*]quinolines *via* the Vicarious Nucleophilic Substitution of Hydrogen

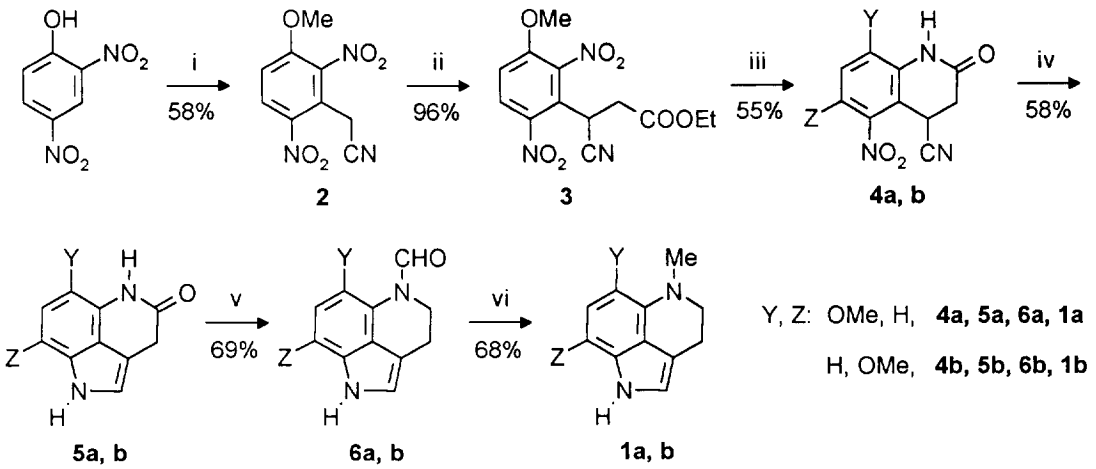
Mieczysław Mąkosza* and Jacek Stalewski

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44, 01-224 Warsaw, Poland

Abstract: The VNS reaction was used as key steps in synthesis of *O*-methylnordehydrobufotenine and its 8-methoxy isomer starting from simple benzene derivatives. Attempts to use nitrobenzoxazole derivatives as a starting material were made. Several approaches were developed but all of them failed to produce the desired ring system on various stages of synthesis.

Many alkaloids contain the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system. It is present for example in dehydrobufotenine - a component of the toad poison which was isolated and identified many years ago.[1] Although first syntheses of this ring system, including dehydrobufotenine itself, were already completed in the sixties[2] there is growing interest in this chemistry because it was shown that many recently isolated marine alkaloids, such as batzellines, isobatzellines, damirones, as well as more complex molecules such as the discorhabdines, prianosines, wayakin, the makaluvamines, and the fungal substance, haematopodin, contain the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline moiety.[3] There are two main approaches to synthesis of this skeleton: construction of the six-membered nitrogen-containing heterocyclic ring starting from an indole derivative and first preparation of the desired quinoline framework to which a pyrrole ring is subsequently attached.[3, 4, 5]

Our study of the Vicarious Nucleophilic Substitution of Hydrogen, VNS[6] and its application in synthesis of heterocyclic compounds,[7] particularly indoles and quinolines, suggest that this reaction could be a useful and efficient tool in the chemistry of these alkaloids. In order to show potential applicability of the VNS reaction in synthesis of tetrahydropyrroloquinoline alkaloids we have chosen *O*-methylnordehydrobufotenine **1a**[2] as the synthetic target. Our approach was based on use of the VNS reaction for simple synthesis of polysubstituted nitrobenzene derivatives which would be subsequently converted into desired tricyclic framework *via* selective transformations of the substituents. The simplest planned approach to the synthesis of **1a** is shown on Scheme 1. We have shown earlier that the VNS reaction in 2,4-dinitrophenol with chloromethyl phenyl sulfone carbanion proceeds exclusively in position 3,[8] hence the same orientation of the VNS cyanomethylation was expected. The second crucial step in scheme 1 - the selective reduction of 2-nitro group - was planned on the basis of recently reported selective reduction of 2-NO_2 in 2,4-dinitroanisole.[9]



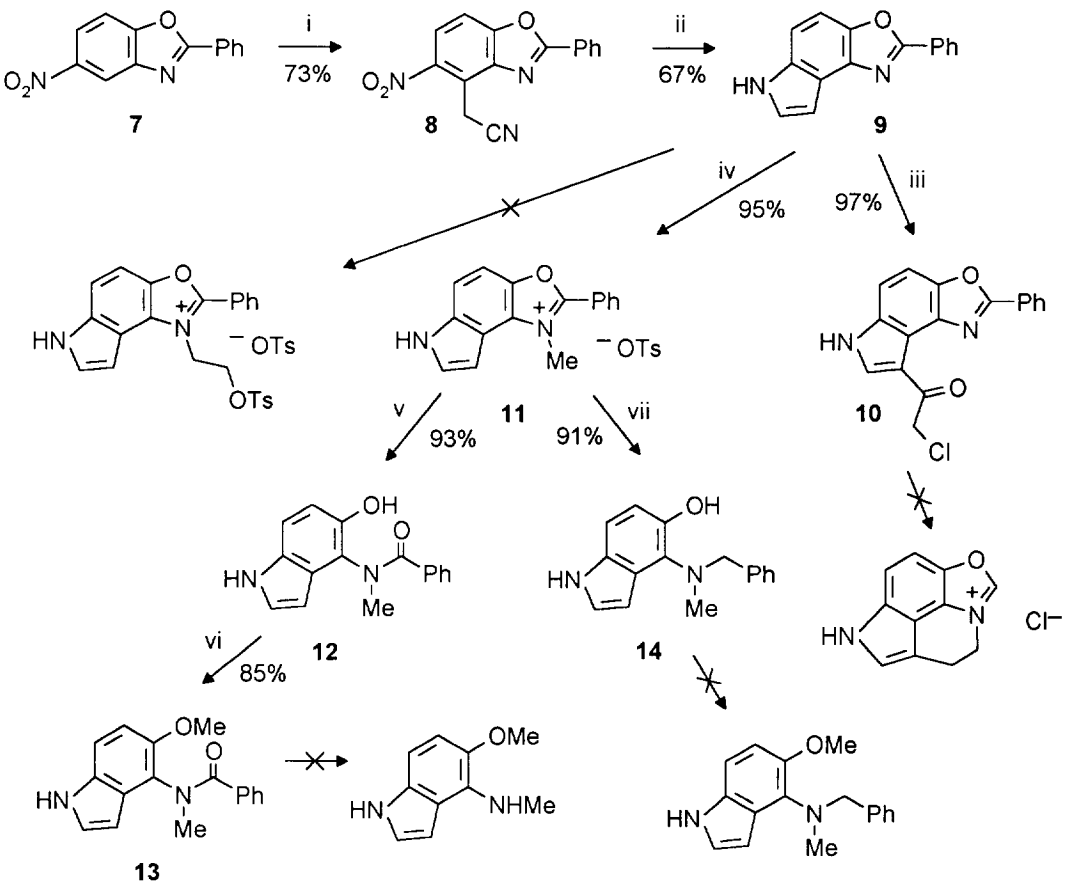
i: $PhOCH_2CN$, t-BuOK, DMF, then Me_2SO_4, $NaHCO_3$, acetone; ii:$BrCH_2COOEt$, K_2CO_3, MeCN; iii: H_2/ $PdCl_2$, Fe, i-PrOH, AcOH; iv: H_2/ Pd/C, EtOH, AcOH; v: $BH_3{\cdot}Me_2S$, THF, then MeOH and $HCOOCOCH_3$ vi: $BH_3{\cdot}Me_2S$, THF.

Scheme 1

This method consists in catalytic hydrogenation with $PdCl_2$/Fe catalytic system in a mixture of ethanol and acetic acid. The aniline produced *via* such selective reduction should cyclize easily to produce lactam **4a**, so this crucial intermediate should be readily available from simple starting materials and its standard transformations should produce **1a**. Indeed, the cyanomethylation of 2,4-dinitrophenol proceeded in position 3, as expected. The product was *O*-methylated and the product anisole **2** alkylated with ethyl bromoacetate to give **3** which was subjected to the selective reduction under slightly changed conditions compared to those reported. Only one of the nitro groups was reduced to produce a lactam which was hydrogenated in the presence of Pd/C in EtOH-AcOH mixture to give the indole ring. Reduction of the lactam group with $BH_3{\cdot}Me_2S$ provided a secondary amine which was unstable hence it was directly *N*-formylated and then the formyl group reduced to the final *N*-methyl derivative. However, the physical and spectral properties of this product differed from those described for **1a**.[2] We obtained an oil, whereas **1a** was reported to be a crystalline material. Moreover, the chemical shifts in the ^1H NMR spectra of our product differed substantially from those described, thus it was identified as **1b**, an isomer of **1a**. Recently two syntheses of **1b** were reported [3, 4] and physical as well as spectral properties of our product turned out to be identical to those of the published compounds.

Obviously the synthesis of **1a** according to scheme 1 went into another direction on the step of the first nitro group reduction. Instead of expected reduction of 2-NO_2 - 4-NO_2 was reduced furnishing **4b** instead of **4a**. Further synthesis went according to our expectation but with the isomeric compounds, giving finally **1b**. Routine spectral analysis of **4b**, **5b** and **6b** did not allow differentiation with the isomeric series of **4a**, **5a** and **6a**. The different course of the reduction of **3** was perhaps due to steric hindrance created by two substituents. Since this scheme for synthesis of **1a** gave the

isomeric product **1b** and a few attempts of synthesis of **4a** *via* modification of this scheme were not promising, we have tested other possibilities. First we tried to use readily available 5-nitrobenzoxazole, in which the VNS reaction should proceed in position 4, giving the desired substitution pattern. It turns out however, that for the VNS reaction to occur in the carbocyclic ring of 5-nitrobenzoxazole it was neccessary to protect position 2- against nucleophilic attack with phenyl or methylthio group.[10] Thus 2-phenyl-5-nitrobenzoxazole **7** was reacted with *p*-chlorophenoxyacetonitrile giving the expected product of the VNS of hydrogen in position 4, **8** (Scheme 2). Such an orientation was in full agreement with that observed earlier for the VNS reaction in bicyclic nitroarenes such as 2-nitronaphthalene,[11]

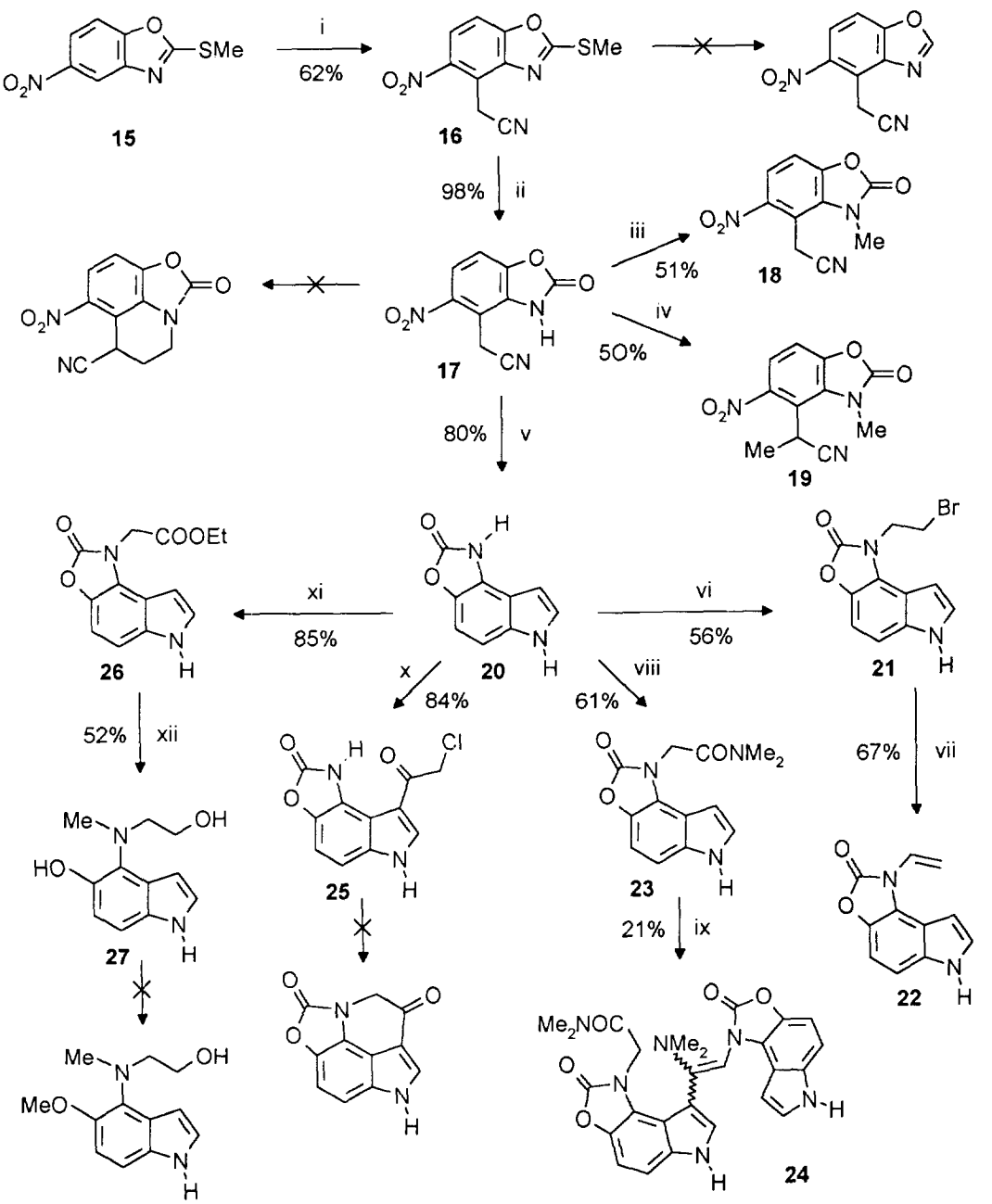


i: 4-$ClC_6H_4OCH_2CN$, NaOH, DMSO; ii: H_2/ Pd/C, EtOH, AcOH; iii: $ClCH_2CONMe_2$, $POCl_3$, dioxane; iv: CH_3OTs; v: NaOH, H_2O, MeOH; vi: MeI, K_2CO_3, acetone; vii: $NaBH_4$, EtOH.

Scheme 2

6-nitroquinoline[12] or 5-nitroindole.[13] Compound **8** was subsequently hydrogenated to a pyrrolobenzoxazole **9** , which became a starting point for further transformations. Our intention was to construct the 6-membered ring taking advantage of the reactive indolic C-3 and the benzoxazole ring nitrogen atom to make the two carbon atoms connection between these sites. However our attempts to quaternize **9** with ethylene glycol ditosylate failed even under high pressure conditions (10 kbar), which are known to promote quaternization reactions.[14] Probably the bifunctional alkylating agent is insufficiently active since analogous reaction of **9** with methyl tosylate smoothly produced corresponding benzoxazolium salt **11**. Another approach consisted in introducing a two carbon unit at the indolic C-3 *via* the Vilsmeier reaction[15] of **9** with *N,N*-dimethylchloroacetamide to give chloroketone **10**. The latter, however, failed to cyclize to the corresponding benzoxazolium salt. Some attempts to utilize benzoxazolium salt **11** for synthesis of the desired system failed too. Degradation of the oxazole ring *via* hydrolysis or reduction afforded benzamide **12** and benzylamine **14** respectively. The benzamide was *O*-methylated but resulting anisole **13** appeared to be resistant to hydrolysis. We were also unable to achieve *O*-methylation of the phenolic aniline **14**, which decomposed when exposed to basic conditions necessary to generate phenolate.

At this point another approach was tested, in which 2-methylthio-5-nitrobenzoxazole **15** (Scheme 3) was the starting compound. First the VNS reaction was used for selective introduction of cyanomethyl group in position 4 of **15** to give **16**.[10] The next question was how to remove the SMe substituent from the molecule and how to construct the desired 6-membered ring on the basis of the product **16**. Initial attempts to desulfurize this compound by means of Raney nickel resulted only in decomposition. Therefore the sulfur atom in **16** was oxidised with hydrogen peroxide in acetic acid in order to convert the sulfur-containing moiety into a better leaving group. The oxidation gave benzoxazolone **17**, apparently resulting from an initial oxidation and subsequent hydrolysis. Benzoxazolone **17** seemed to be a very promising intermediate since two suitably located potential nucleophilic sites *N* and *C* can be generated upon deprotonation and hopefully connected *via* alkylation with an appropriately substituted ethane derivative, thus creating the desired six-membered ring. Indeed, an initial attempt to alkylate **17** with excess of methyl iodide produced *N, C* - dimethyl derivative **19**. It was also possible to obtain monomethyl derivative **18** when stoichiometric amount of dimethyl sulfate as an alkylating agent was used, the alkylation proceeded at the more acidic N-hydrogen atom. However, when **17** was reacted with 1,2-difunctionalized ethanes no definite products were observed, slow decomposition of **17** took place instead. Apparently, again only very active alkylating agents are able to react with **17**. In another attempt **17** was hydrogenated to the corresponding indole **20**, which was succesfully alkylated with 1,2-dibromoethane at the oxazolone nitrogen atom to give **21**. It was our intention now to form the six-membered ring *via* intramolecular alkylation of indolic C-3 upon formation of the indolyl anion. Unfortunately, treatment of **21** with a range of bases, such as K_2CO_3, *t*-BuOK, NaH, BuLi, resulted invariably in elimination of HBr to give **22**. In this situation we attempted to achieve 6-membered ring formation *via* the intramolecular Vilsmeier acylation. Upon alkylation of **20** with *N,N*-dimethylchloroacetamide a suitable intermediate **23** was obtained. However **23**, when subjected to reaction with $POCl_3$, yielded only the product of the intermolecular reaction **24** in a rather low yield, accompanied by some polymeric material.

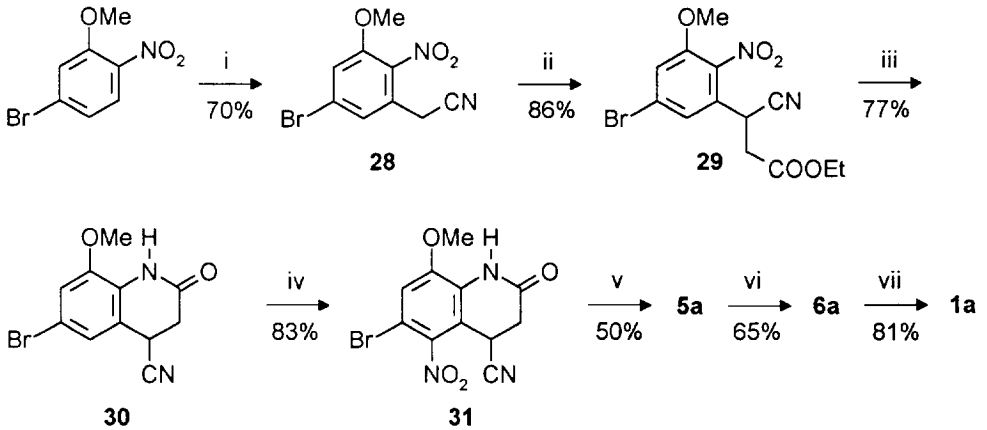


i: 4-$ClC_6H_4OCH_2CN$, NaOH, DMSO; ii: H_2O_2, AcOH; iii: Me_2SO_4, K_2CO_3, acetone; iv: CH_3I, K_2CO_3, DMF; v: H_2/ Pd/C, EtOH, AcOH; vi: $BrCH_2CH_2Br$, K_2CO_3, MeCN; vii: *t*-BuOK, DMF; viii: $ClCH_2CONMe_2$, K_2CO_3, MeCN; ix: $POCl_3$; x: $ClCH_2CONMe_2$, $POCl_3$, dioxane; xi: ICH_2COOEt, K_2CO_3, MeCN; xii: $LiAlH_4$, THF.

Scheme 3

The reverse order of events, i.e. first the Vilsmeier reaction of **20** with *N,N*- dimethylchloroacetamide to form **25**, followed with intramolecular alkylation of the oxazolone nitrogen atom also failed to produce desired tetracyclic product, this time at the alkylation step. Apparently, steric reasons are responsible for failure of the approach utilizing the Vilsmeier reaction. Yet another chance was tried: **20** was alkylated with ethyl iodoacetate and the product **26** was treated with lithium aluminium hydride. As expected, the oxazole ring was destroyed and the COOEt group was reduced to give aminophenol **27**. However all attempts to achieve methylation of the phenolic oxygen atom in the latter compound failed - **27** decomposed rapidly when exposed to basic conditions just as did analogous indolic aminophenol **14**. No reaction occured when **27** was treated with diazomethane.

Thus in our hands benzoxazole derivatives failed to be suitable intermediates in the synthesis of *O*-methylnordehydrobufotenine. In this situation a completely different approach was developed. We intended to obtain first a suitably substituted tetrahydroquinoline starting from a simple benzene derivative and convert it subsequently to the tricyclic system by means of the hydrogenation procedure. This plan was succesfully executed (Scheme 4).



i: 4-ClPhOCH$_2$CN, t-BuOK, DMF; ii: BrCH$_2$COOEt, K_2CO_3, MeCN; iii: Sn, HCl_{aq}, MeOH; iv: 65% HNO_3; v: H_2/ Pd/C, EtOH, AcOH; vi: BH_3·Me_2S, THF, then MeOH and $HCOOCOCH_3$; vii: BH_3 Me_2S, THF.

Scheme 4

5-Bromo-2-nitroanisole (prepared *via* VNS hydroxylation of p-bromonitrobenzene,[16] followed by *O*-methylation) was VNS-cyanomethylated, yielding **28**. The presence of a bromine in the starting material was necessary to assure selective *ortho* orientation and activation of the ring in the VNS reaction. Nitrile **28** was alkylated with ethyl bromoacetate to give cyanoester **29**, accompanied by a small amount (ca. 10%) of the dialkylation product, as it appears from the ^{1}H NMR and MS spectra. This product was not further purified but directly subjected to reduction with tin in hydrochloric acid to give lactam **30**, which contained no impurities as it was the only product insoluble in the reaction media. Nitration of **30** yielded exclusively **31**, which was hydrogenated to give the indole ring,

whereupon the bromine atom was removed from the molecule. Resulting lactamoindol **5a** was converted to **1a** in a similar way as **5b** to **1b**.

Our syntheses of the two isomeric methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinolines, based on the VNS reaction, proves the reaction to be useful and flexible tool in preparation of this important ring system.

Acknowledgment: This work was supported by Grant No. 300609101 provided by the State Committee for Scientific Research (KBN).

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on Varian Gemini (200 MHz) or Bruker AMX (500 MHz) instruments; chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz; assignments marked with asterisk (*) may be interchanged. Mass spectra were recorded on AMD 604 spectrometer. IR spectra were taken with Perkin Elmer 1640 and only noteworthy absorptions are listed. Column chromatography was performed on silica gel 70-230 or 230-400 mesh (Merck) using hexane - ethyl acetate mixtures as eluents unless indicated otherwise. Organic extracts were dried with anhydrous $MgSO_4$. 4-Chlorophenoxyacetonitrile, **7** and **15** were obtained according to described procedures;[10] other reagents were commercially available.

(3-Hydroxy-2,6-dinitrophenyl)acetonitrile: To a solution of *t*-BuOK (400 mmol, 44.88 g) in DMF (250 ml), a solution of 2,4-dinitrophenol (100 mmol, 18.4 g) and phenoxyacetonitrile (105 mmol, 13.97 g) in DMF was added dropwise at -20°C. The reaction mixture was stirred at this temperature for 30 min and poured into ice-cold diluted hydrochloric acid (2 l). The product was extracted with CH_2Cl_2 , the extract was washed with water, dried and the solvent was removed *in vacuo*. Brown oil (27 g) was obtained which slowly crystallized on standing. Analytical sample was obtained by recrystallization from ether to give (3-hydroxy-2,6-dinitrophenyl)acetonitrile as a yellow solid, which appeared to be a complex with one molecule of DMF. M.p.: 63-65°C. δ_H (acetone-d_6): 2.84 (3H, s, DMF NCH_3), 3.00 (3H, s, DMF NCH_3), 4.14 (2H, s, CH_2CN), 7.45 (1H, d, *J*=9.3, H-4), 8.03 (1H, s, $\underline{H}CONMe_2$), 8.36 (1H, d, *J*=9.3, H-5). Elemental analysis: C 44.61, H 3.84, N 18.74; calc. for $C_{11}H_{12}N_4O_6$: C 44.60, H 4.08, N 18.91.

(3-Methoxy-2,6-dinitrophenyl)acetonitrile (2): The crude product from the previous reaction (27 g) and dimethyl sulfate (100 mmol, 12.6 g) were dissolved in acetone and sodium hydrogen carbonate (0.3 mol, 25 g) was added. The mixture was stirred vigorously at r.t. for 24 h. Inorganic salts were filtered off and washed with acetone. The filtrate was evaporated and the residue was dissolved in ethyl acetate and washed with 10% K_2CO_3. The organic layer was dried and evaporated and the residue was recrystallized from isopropanol to give **2** (13.7 g, 58% from 2,4-dinitrofenol) as a brownish solid. M.p.: 120°C. δ_H (acetone-d_6): 4.14 (2H, s, CH_2CN), 4.16 (3H, s, OCH_3), 7.67 (1H, d, *J*=9.4, H-4), 8.50 (1H, d, *J*=9.4, H-5). Elemental analysis: C 45.56, H 2.79, N 17.53; calc. for $C_9H_7N_3O_5$: C 45.58, H 2.98, N 17.72.

Ethyl 3-cyano-3-(3-methoxy-2,6-dinitrophenyl)propionate (3): To a solution of **2** (50 mmol, 11.85 g) and ethyl bromoacetate (8.35 g, 50 mmol) in acetonitrile, potassium carbonate (138 g, 100 mmol) was added and the mixture was stirred vigorously for 4 h. Inorganic solids were filtered off and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and washed with diluted hydrochloric acid and water. The organic layer was dried and evaporated, and the residue was purified by passing through a short silica-gel column to give **3** (15.5 g, 96%) as a pale yellow oil: δ_H (acetone-d_6): 1.25 (3H, t, *J*=7.1, $OCH_2C\underline{H}_3$), 3.11 and 3.43 (2H, AB part of ABX system, J_{AB}=17.3,

$|J_{AX}|$=4.4, $|J_{BX}|$=9.8, CH_2CO_2Et), 4.16 (3H, s, OCH_3), 4.20 (2H, q, J=7.1, OCH_2CH_3), 4.99 (1H, X part of ABX system, CHCN), 7.68 (1H, d, J=9.4, H-4), 8.40 (1H, d, J=9.4, H-5). Elemental analysis: C 48.23, H 4.13, N 12.71; calc. for $C_{13}H_{13}N_3O_7$: C 48.30, H 4.05, N 13.00.

1,2,3,4-Tetrahydro-6-methoxy-5-nitro-2-oxo-4-quinolinecarbonitrile (4): A catalyst was prepared by grinding $PdCl_2$ (0.33 g) and iron powder (1.50 g) in a mortar. The catalyst was added to a solution of **3** (12.65 g, 39.2 mmol) in isopropanol (250 ml) and acetic acid (50 ml), and the mixture was stirred under slight positive pressure of hydrogen for 4h until all the substrate was consumed (TLC control, the reaction time depended on scale). A precipitate of product was formed during this time. The reaction mixture was filtered through celite, the filtrate was discarded and the crystalline product together with the catalyst were treated with acetone, the resulting solution of the product once again was filtered through celite, and the filtrate was evaporated. The residue was boiled in isopropanol. After cooling, the product was filtered to give **4b** (5.3 g, 55%) as a colorless solid. M.p. 228-230°C (dec.). δ_H (acetone-d_6): 2.91 and 3.05 (2H, AB part of ABX system, J_{AB}=13.0, $|J_{AX}|$=2.1, $|J_{BX}|$=6.36, CH_2), 3.95 (3H, s, OCH_3), 4.47 (1H, X part of ABX system, CHCN), 7.33, 7.40 (2H, AB system, J=9.1, H-7 and H-8), 9.78 (1H, br. s, NH). Elemental analysis: C 53.51%, H 3.55%, N 16.76%; calc. for $C_{11}H_9N_3O_4$: C 53.44, H 3.67, N 17.00.

8-Methoxy-2-oxo-1,3,4,5-tetrahydropyrrolo[4,3,2-*d,e*]quinoline (5b): A suspension of **4b** (1.1 g, 4.45 mmol) and 10% Pd/C (250 mg) in ethanol (100 ml) and acetic acid (20 ml) was hydrogenated (45 psi, 60°C) for 8h. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in ethyl acetate and washed with 10% K_2CO_3 solution to remove remaining acetic acid. The organic layer was dried and evaporated to give **5b** (522 mg, 58%) as a colorless solid. M.p. not determined; decomposition over 200°C. δ_H (acetone-d_6 + dmso-d_6): 3.78 (2H, d, J=1.4, CH_2), 3.86 (3H, s, OCH_3), 6.24 (1H,d, J=7.7, H-6)*, 6.43 (1H, d, J=7.7, H-7)*, 6.88 (1H, br. d, J=1.4, H-2), 9.90 (1H, broad s, lactam NH), 10.87 (1H, broad s, indole NH). Elemental analysis: C 65.40, H 5.27, N 13.69; calc. for $C_{11}H_{10}N_2O_2$: C 65.34, H 4.98, N 13.85.

8-Methoxy-5-formyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*d,e*]quinoline (6b): To a solution of **5b** (404 mg, 2 mmol) in THF (15 ml), $BH_3{\cdot}Me_2S$ was added dropwise under argon. The mixture was stirred for 1 h and methanol (1 ml) was added at 0°C, after 15 minutes followed by freshly prepared formic-acetic anhydride. The mixture was stirred overnight, then it was diluted with water and extracted with CH_2Cl_2. The organic extract was washed with an ammonia solution, dried and evaporated. The residue was recrystallized (ethanol-water) to give **6b** (300 mg, 69%) as a colorless solid. M.p. 183-185°C. δ_H ($CDCl_3$): 2.75 (2H, "t", AA' part of AA'XX' system, H-3), 3.68 (3H, s, OCH_3), 3.79 (2H, "t", XX' part of AA'XX' system, H-4), 6.26 (1H, d, J=7.9, H-6)*, 6.45 (1H, d, J=7.9, H-7)*, 6.64 (1H, br. s, H-2), 10.05 (1H, br. s, NH). Elemental analysis: C 66.86, H 5.79, N 12.58; calc. for $C_{12}H_{12}N_2O$: C 66.65, H 5.59, N 12.96.

8-Methoxy-5-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*d,e*]quinoline (1b): To a solution of **6b** (150 mg, 0.7 mmol) in THF (6 ml), $BH_3{\cdot}Me_2S$ was added under argon and the mixture was stirred overnight. Methanol (0.5 ml) was added at 0°C followed with a solution of NaCl and NH_3, and the product was extracted with CH_2Cl_2. The organic extract was dried and evaporated. The residue was purified by passing through a short silica-gel column to give **1b** (95 mg, 68%) as a colorless oil slowly turning pale blue on the air: δ_H ($CDCl_3$) 2.91 (3H, s, NCH_3), 3.05 (2H, br. "t", AA' part of AA'XX' system, H-3), 3.22 (2H, "t", AA' part of AA'XX' system, H-4), 3.88 (3H, s, OCH_3), 6.10 (1H, d, J=7.9, H-6), 6.51 (1H, d, J=7.9, H-7), 6.70 (1H, br. s, H-2), 8.08 (1H, broad s, NH). Elemental analysis: C 70.85, H 6.84, N 13.04; calc. for $C_{12}H_{14}N_2O$: C 71.26, H 6.95, N 13.85.

(5-Nitro-2-phenylbenzoxazol-4-yl)acetonitrile (8): 7 (17g, 70.8 mmol) and *p*-chlorophenoxyacetonitrile (12.45 g, 74.3 mmol) were mixed with DMSO (200 ml) and to the resulting suspension powdered KOH (16.8 g, 350 mmol)

was added. The mixture was stirred for 2 h and poured into a diluted ice-cold hydrochloric acid. The precipitate formed was collected by filtration and recrystallized from EtOH to give **8**[10] (14.5 g, 73%) as a colorless solid.

2-Phenyl-6*H*-pyrrolo[3,2-*e*]benzoxazole (9): **8** (3.25 g, 11.65 mmol) and 10% Pd/C were suspended in a mixture of ethanol (100 ml) and acetic acid (20 ml) and the mixture was hydrogenated (40 psi, r.t.) for 6 h. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 and washed with 10% K_2CO_3 solution. The extract was dried and evaporated and the residue was recrystallized (toluene - hexane 1:1) to give **9** (1.83 g, 67%) as a colorless solid. M.p. 215-216°C. δ_H ($CDCl_3$, 500 MHz): 7.03 (1H, ddd, J=3.1, J=2.0, J=0.9, H-8), 7.34 (1H, dd, J=3.1, J=2.5, H-7), 7.38 (1H, part A of AB system, dd, J_{AB}=8.7, J=0.9, H-5), 7.44 (1H, part B of AB system, d, J_{AB}=8.7, H-4), 7.47-7.54 (3H, m, Ph), 8.29-8.32 (2H, m, Ph), 9.86 (1H, br. s). Elemental analysis: C 76.76, H 4.03, N 11.95; calc. for $C_{15}H_{10}N_2O$: C 76.91, H 4.30, N 11.96.

8-Chloroacetyl-2-phenyl-6*H*-pyrrolo[3,2-*e*]benzoxazole (10): To an ice-cooled solution of *N,N*-dimethylochloroacetamide (243 mg, 2 mmol) in dioxane (0.5 ml), a solution of $POCl_3$ (153 mg, 1 mmol) in dioxane (0.5 ml) was added dropwise. The resulting solution was stirred for 1 h at r.t. and **9** (117 mg, 0.5 mmol) was added. The reaction mixture was heated at 80°C for 1 h. After cooling the red solution was poured into water. NaOH solution was added to the resulting suspension until pH reached 8, then the mixture was warmed to boiling and allowed to cool. The crystalline product was collected by filtration, washed with water and air-dried. Finally it was suspended in *i*-PrOH, warmed to boiling, allowed to cool and collected to give **10** (151 mg, 97%) as a pale yellow solid. M.p. 242-4°C (DMF-EtOH). δ_H (dmso-d_6): 5.52 (2H, s, CH_2), 7.61, 7.70 (2H, AB system, J_{AB}=8.8, H-4 and H-5), 7.63-7.68 (3H, m, Ph), 8.21-8.28 (2H, m, Ph), 8.39 (1H, d, J=3.2, H-7). IR (KBr, cm^{-1}): 1640 (C=O), 3238 (N-H). MS, m/z (%): 312, 310 (M^+, 8, 24 respectively), 276 (11), 261 (100), 247 (3), 233 (10), 205 (7), 178 (3), 158 (10), 151 (4), 130 (13). HRMS (EI), m/z: 310.05093. $C_{17}H_{11}ClN_2O_2$ requires 310.0509.

1-Methyl-6*H*-pyrrolo[3,2-*e*]benzoxazolium *p*-toluenosulfonate (11): **9** (1.17 g, 5 mmol) and methyl *p*-toluenosulfonate (25 mmol) were stirred at 125°C for 45 min under argon. After cooling, the reaction mixture was dissolved in methanol and ether was added to the resulting solution. The crystalline product formed was collected by filtration and dried *in vacuo* to give **11** (2 g, 95%) as a pale yellow solid. M.p. 216-8°C. δ_H (dmso-d_6): 2.28 (3H, s, $SO_3C_6H_4C\underline{H}_3$), 4.38 (3H, s, NCH_3), 7.06-7.14 (2H, br. d, AA' part of AA'XX' system, aromatic protons of $^-$OTs), 7.22 (1H, br. "t", H-7), 7.42-7.50 (2H, br. d, XX' part of AA'XX' system, aromatic protons of $^-$OTs), 7.76-7.86 (6H, m, H-4, H-5, H-7, Ph), 8.18-8.26 (2H, m, Ph), 12.28 (1H, br.s, NH). Elemental analysis: C 65.60, H 4.49, N 6.58; calc. for $C_{23}H_{20}N_2O_4S$: C 65.70, H 4.79, N 6.66.

4-(Benzoylmethylamino)-1*H*-indol-5-ol (12): To a solution of NaOH (120 mg, 3 mmol) in a 1:1 mixture of methanol and water (6 ml) benzoxazolium sait **11** (420 mg, 1 mmol) was added and the mixture was stirred for 1h at r.t. to form a clear solution. Then it was diluted with water, acidified with hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was purified by passing through a short silica-gel column to give **12** (248 mg, 93%) as a colorless solid. M.p. 196-7°C. δ_H (acetone-d_6) 3.34 (3H, s, NCH_3), 6.34 (1H, ddd, J=3.1, J=2.1, J=0.9, H-3), 6.67 (1H, d, J=8.6, H-6), 6.96-7.13 (3H, m, Ph), 7.12 (1H, dd, J=8.6, J=0.9, H-7), 7.25 (1H, "t", H-2), 7.38-7.45 (2H, m, Ph), 8.02 (1H, s, OH), 10.13 (1H, br. s, NH). Elemental analysis: C 72.07, H 5.07, N 10.54; calc. for $C_{16}H_{14}N_2O_2$: C 72.17, H 5.30, N 10.52.

4-(Benzoylmethylamino)-5-methoxy-1*H*-indole (13): To a solution of **12** (133 mg, 0.5 mmol) and methyl iodide (142 mg, 1 mmol) in acetone (5ml), K_2CO_3 (200 mg) was added and the mixture was gently refluxed with vigorous stirring for 6 h. The solvent together with excess methyl iodide were removed under reduced pressure, water was added to the residue and the product was extracted with ethyl acetate. The extract was dried and evaporated and the residue recrystallized from ethyl acetate - hexane to give **13** (119 mg, 85%) as a colorless solid. M.p. 213-5°C. δ_H

($CDCl_3$, 500 MHz): 3.44 (3H, s, NCH_3), 3.61 (1H, s, OCH_3), 6.47 (1H, ddd, *J*=3.1, *J*=2.1, *J*=0.9, H-3), 6.65 (1H, d, *J*=8.8, H-6), 6.97-7.01 (2H, m, Ph), 7.07-7.11 (1H, m, Ph), 7.13 (1H, dd, *J*=8.8, *J*=0.9, H-7), 7.17 (1H, "t", H-2), 7.31-7.35 (2H, m, Ph), 8.70 (1H, br. s, NH). Elemental analysis: C 72.77, H 5.65, N 10.00; calc. for $C_{17}H_{16}N_2O_2$: C 72.84, 5.75, N 9.99.

4-(Benzylmethylamino)-1*H*-indol-5-ol (14): To an ice-cooled solution of $NaBH_4$ (113 mg, 3 mmol) in EtOH (5 ml), **11** (420 mg, 1 mmol) was added and the mixture was stirred with ice cooling for 20 min. and then at r.t. for 10 min.. Water was added, followed by hydrochloric acid. After the excess sodium borohydride was destroyed, the resulting homogenous solution was made slightly alkaline with ammonia solution and extracted with ethyl acetate. The extract was dried and evaporated and the residue purified by passing through a short silica-gel column to give **13** (229 mg) as an unstable greenish oil: δ_H ($CDCl_3$): 2.82 (3H, s, NCH_3), 4.24 (2H, s, CH_2), 6.60 (1H, ddd, *J*=3.2, *J*=2.0, *J*=0.9, H-3), 6.86 (1H, d, *J*=8.6, H-6), 7.12 (1H, dd, *J*=8.6, *J*=0.9, H-7), 7.17 (1H, "t", H-2), 7.24-7.35 (5H, m, Ph), 8.12 (1H, br. s, NH). MS, m/z (%): 252 (M^+, 17), 161 (100), 134 (43), 116 (8), 91 (7). HRMS (EI), m/z: 252.1263; $C_{16}H_{16}N_2O$ requires 252.12626. Elemental analysis: C 75.90, H 6.31, N 10.95; calc. for $C_{16}H_{16}N_2O$ C 76.16, H, 6.39, N 11.10.

[(2-(Methylthio)-5-nitro-benzoxazol-4-yl]acetonitrile (16): To a solution of **15** (6.3 g, 30 mmol) and p-chlorophenoxyacetonitrile (5.53 g, 33 mmol) in DMSO (300 ml), powdered NaOH (6 g, 150 mmol) was added. The mixture was stirred for 4h and poured into water. The product was collected by filtration and purified by boiling in ethanol to give **16**[10] (4.61 g, 62%) as a pale yellow solid.

17: see ref.[10]

(3-Methyl-5-nitro-2-oxo-2,3-dihydrobenzoxazol-4-yl)acetonitrile (18): **17** (110 mg, 0.5 mmol) and methyl sulfate (70 mg, 0.55 mmol) were dissolved in acetone (5 ml). K_2CO_3 (200 mg) was added to the solution and the mixture was stirred at r.t. overnight. The solvent was evaporated, water was added to the residue and the resulting suspension was extracted with ethyl acetate. The extract was dried and evaporated and the residue was purified by passing through a short silica-gel column to give **18** (60 mg, 51%) as a colorless solid. M.p. 193°C (acetone - ethanol). δ_H (acetone): 3.84 (3H, s, NCH_3), 4.44 (2H, s, CH_2CN), 7.51 (1H, d, *J*=8.8, H-7), 7.97 (1H, d, *J*=8.8, H-6). Elemental analysis: C 51.49, H 2.86, N 17.74; calc. for $C_{10}H_7N_3O_4$: C 51.51, H 3.03, N 18.02.

2-(3-Methyl-5-nitro-2-oxo-2,3-dihydrobenzoxazol-4-yl)propionitrile (19): **17** (55 mg, 0.25 mmol) and methyl iodide (142 mg, 1 mmol) were dissolved in DMF (3 ml). K_2CO_3 (200 mg) was added to the solution and the mixture stirred at r.t. overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was dried and evaporated and the residue was purified by passing through a short silica-gel column to give **19** (30 mg, 51%) as a colorless solid. M.p. 137-8°C (ethanol). δ_H (acetone): 1.96 (3H, d, *J*=7.1, $CHC\underline{H}_3$) 3.83 (3H, s, NCH_3), 5.08 (1H, q, *J*=7.1, $C\underline{H}CH_3$), 7.50 (1H, d, *J*=8.7, H-7), 7.84 (1H, d, *J*=8.7, H-6). MS, m/z (%): 247 (M^+, 20), 230 (100), 215 (17), 202 (7), 173 (32), 157 (8), 131 (11), 116 (8). HRMS (EI), m/z: 247.0593; $C_{11}H_9N_3O_4$ requires 247.0593.

(1*H*, 6*H*)-Pyrrolo[3,2-*e*]benzoxazol-2-one (20) A suspension of **17** (920 mg, 4.2 mmol) and 10% Pd/C (300 mg) in ethanol (80 ml) and acetic acid (20 ml) was hydrogenated (40 psi, r.t.) for 5 h. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in ethyl acetate and washed with water. The extract was dried and evaporated and the residue was purified by passing through a short silica-gel column to give **20** (582 mg, 80%) as a colorless solid. M.p. 253-5°C (dec.). δ_H ($CDCl_3$+dmso-d_6): 6.52 (1H, m, H-8), 7.01, 7.11 (2H, AB system, J_{AB}=8.8, H-4 and H-5), 7.24 (1H, "t", H-7), 10.33 (1H, br. s, oxazolone NH), 11.24 (br. s, indole NH) . Elemental analysis: C 61.94, H 3.63, N 15.81; calc. for $C_9H_6N_2O_2$: C 62.07, H 3.47, N 16.09.

1-(2-bromoethyl)-(1*H*, 6*H*)-pyrrolo[3,2-*e*]benzoxazol-2-one (21): To a solution of **20** (1.055 g, 6.1 mmol) and 1,2-dibromoethane (1.316 g, 7 mmol) in acetonitrile (30 ml), K_2CO_3 (2 g) was added and the mixture was gently refluxed

with vigorous stirring for 1 h. Inorganic salts were filtered off, the filtrate was evaporated and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic layer was dried and evaporated and the residue recrystallized from ethanol to give **21** (957 mg, 56%) as a colorless solid. M.p. 183-5°C. δ_H (dmso-d_6): 3.86 (2H, t, J=6.0, $NCH_2\underline{CH_2}Br$), 4.45 (2H, t, J=6.0, $NC\underline{H_2}CH_2Br$), 6.64 (1H, m, H-8), 7.13, 7.18 (2H, AB system, J_{AB}=8.7, H-4 and H-5), 7.49 (1H, "t", H-7), 11.42 (1H, br. s, NH). Elemental analysis: C 47.34, H 2.98, N 9.96; calc. for $C_{11}H_9BrN_2O_2$: C 47.00, H 3.23, N 9.97.

1-Ethenyl-(1*H*, 6*H*)-pyrrolo[3,2-*e*]benzoxazol-2-one (22): To a solution of **21** (84 mg, 0.3 mmol) in DMF (2 ml), a solution of *t*-BuOK (0.6 mmol) in DMF (2ml) was added at 0°C. The reaction mixture was stirred for 1 h at r.t., poured into diluted hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was purified by passing through a short silica-gel column to give **22** (40 mg, 67%) as a colorless solid. M.p. 180°C. δ_H (dmso-d_6): 5.21 (1H, d, J=9.2, $NCH{=}CH_{cis}\underline{H}_{trans}$), 5.91 (1H, d, J=15.6, $NCH{=}C\underline{H}_{cis}H_{trans}$), 6.75 (1H, m, H-8), 7.15, 7.25 (2H, AB system, J_{AB}=8.7, H-4 and H-5), 7.26 (1H, dd, J=15.6, J=9.2, $NC\underline{H}{=}CH_2$), 7.50 (1H, "t", H-7), 11.50 (br. s, NH). MS, m/z (%): 200 (M^+, 100), 172 (17), 155 (8), 143 (10), 129 (11), 117 (8). HRMS (EI), m/z: 200.05858; $C_{11}H_8N_2O_2$ requires 200. 05858.

***N*, *N*-dimethyl (2-oxo-1,2-dihydro-6*H*-pyrrolo[3,2-*e*]benzoxazol-1-yl)acetamide (23)**: **20** (174 mg, 1 mmol), *N*,*N*-dimethylochloroacetamide (122 mg, 1 mmol) and K_2CO_3 (200 mg) were refluxed in acetonitrile (8 ml) with vigorous stirring for 2 h. After cooling the solvent was removed under reduced pressure. Water was added to the residue and the resulting suspension was extracted with ethyl acetate. The extract was dried and evaporated and the crude product boiled in ethanol. After cooling **23** (157 mg, 61%, colorless solid) was collected by filtration. M.p. 270-1°C. δ_H (acetone-d_6): 2.92 (3H, s, NCH_3), 3.27 (3H, s, NCH_3), 4.97 (2H, s, CH_2), 6.50 (1H, ddd, J=3.2, J=2.0, J=0.9, H-8), 7.05 (1H, d, J=8.7, H-4), 7.18 (1H, dd, J=8.7, J=0.9, H-5), 7.36 (1H, "t", H-7). MS, m/z (%): 259 (M^+, 100), 187 (71), 214 (7), 173 (4), 159 (8), 143 (59), 132 (3), 116 (28). HRMS (EI), m/z: 259.0957; $C_{13}H_{13}N_3O_3$ requires 259.09569.

***N*, *N*-dimethyl 8-{[1-dimethylamino-2-(2-oxo-1,2-dihydro-6*H*-pyrrolo[3,2-*e*]benzoxazol-1-yl)ethenyl]-2-oxo-1,2-dihydro-6*H*-pyrrolo[3,2-*e*]benzoxazol-1-yl}acetamide (24)**: **23** (50 mg, 0.19 mmol) was suspended in $POCl_3$ (3ml) and the mixture was heated to 85-90°C for 1.5 h to form a clear red solution. After cooling as much as possible of $POCl_3$ was removed under reduced pressure and water was added to the residue, which induced its crystallization. 1*M* NaOH was added to the resulting suspension until pH 8 was reached, the mixture was heated to boiling and allowed to cool. The crystalline material was collected by filtration, air dried and purified by passing through a short silica-gel column (ethyl acetate) to give **24** (10 mg, 21%) as a colorless solid. M.p. 289°C. δ_H (dmso-d_6): 2.60 (6H, br. s, enamine NCH_3), 2.92 (3H, s, amide NCH_3), 3.15 (3H, s, amide NCH_3), [4.75, (1H, d, J=17.3), 5.45 (1H, d, J=17.3), CH_2], 5.70 (1H, s, HC=C), 6.70 (1H, d, J=2.6, H-7), 6.78 (1H, m, H-8'), 6.92 (1H, d, J=8.7, H-4'), 7.07 (1H, dd, J=8.7, J=0.7, H-5'), 7.06, 7.17 (2H, AB system, H-4 and H-5), 7.51 (1H, "t", H-7), 11.20 (1H, br. s, NH), 11.37 (1H, br. s, NH); each of the heterocyclic systems is numbered independently; protons of the system not connected with acetamide moiety are marked with prims ('). MS, m/z (%): 500 (58), 327 (17), 313 (20), 284 (39), 269 (13), 254 (47), 241 (17), 229 (45), 211 (16), 187 (13), 174 (100), 118 (45). LSIMS, m/z: 501 $(M+H)^+$. HRMS (EI), m/z: 500.18082; calc. for $C_{26}H_{24}N_6O_5$: 500.18081.

8-Chloroacetyl-(1*H*, 6*H*)-pyrrolo[3,2-*e*]benzoxazol-2-one (25): To an ice-cooled solution of *N*,*N*-dimethylochloroacetamide (243 mg, 2 mmol) in dioxane (0.5 ml), a solution of $POCl_3$ (153 mg, 1 mmol) in dioxane (0.5 ml) was added dropwise. The resulting solution was stirred for 1 h at r.t. and **20** (87 mg, 0.5 mmol) was added. The reaction mixture was heated at 60°C for 1 h. After cooling, the red solution was poured into water. NaOH solution was added to the resulting suspension until pH reached 8, then the mixture was warmed to boiling and

allowed to cool. The crystalline product was collected by filtration, washed with water and air-dried. Finally it was suspended in EtOH, warmed to boiling, allowed to cool and collected to give **25** (84%) as a yellow solid. M.p. not determined; decomposition over 280°C . δ_H (dmso-d_6): 4.95 (2H, s, CH_2), 7.23 (2H, s, H-4 and H-5), 8.50 (1H, d, J=2.7, H-7), 10.19 (1H, s, oxazolone NH), 12.40 (1H, br. s, indole NH). IR (KBr, cm^{-1}): 1644 (ketone C=O), 1765 (oxazolone C=O), 3365, 3425 (indole and oxazolone NH). Elemental analysis: C 52.50, H 2.66, N 10.73; calc. for $C_{11}H_7ClN_2O_3$: C 52.71, H 2.82, N 11.18.

Ethyl (2-oxo-1,2-dihydro-6*H*-pyrrolo[3,2-*e*]benzoxazol-1-yl)acetate (26): **20** (174 mg, 1 mmol), ethyl iodoacetate (257 mg, 1.2 mmol), K_2CO_3 (200 mg) were stirred in acetonitrile (5 ml) for 3 h. Inorganic salts were filtered off, the solvent was evaporated, the residue was mixed with water and extracted with ethyl acetate. The extract was dried and evaporated and the residue recrystallized from EtOH to give **26** (220 mg, 85%) as a colorless solid. M.p. 163°C. ($CDCl_3$ + dmso-d_6): 1.18 (3H, t, J=7.1, $OCH_2\underline{CH_3}$), 4.14 (2H, q, J=7.1, $O\underline{CH_2}CH_3$), 4.72 (2H, s, NCH_2CO_2Et), 6.29 (1H, m, H-8), 6.96, 7.12 (2H, AB system, J_{AB}=8.8, H-4 and H-5), 7.2 (1H, "t", H-7), 10.81 (1H, br. s, NH). Elemental analysis: C 59.84, H 4.48, N 10.64; calc. for $C_{13}H_{12}N_2O_4$: C 60.00, H 4.65, N 10.76.

4-[(2-hydroxyethyl)methylamino)-1*H*-indol-5-ol (27): To a suspension of $LiAlH_4$ (5 mmol) in THF (10 ml), a solution of **26** (260 mg, 1 mmol) in THF (2 ml) was added dropwise, the mixture was refluxed for 3 h, carefully diluted with water, and neutralized. The resulting suspension of insoluble inorganic salts was extracted with several portions of ethyl acetate. The joined extracts were dried and evaporated and the residue purified by passing through a short silica-gel column , to give **27** (108 mg, 52%) as an unstable bluish oil: δ_H ($CDCl_3$): 2.92 (3H, s, NCH_3), 3.29 (2H, "t", AA' part of AA'XX' system, $NC\underline{H_2}CH_2OH$), 3.58 (2H, "t" XX' part of AA'XX' system, $NCH_2C\underline{H_2}OH$), 6.48 (1H, m, H-3), 6.86 (1H, d, J=8.6, H-6), 7.08-7.16 (2H, m, H-2 and H-7), 8.25 (1H, br. s, NH). MS, m/z (%): 206 (M+, 57), 175 (100), 159 (9), 146 (7), 134 (91), 116 (8), 104 (8). Elemental analysis: C 63.92, H 6.80 , N 13.23; calc. for $C_{11}H_{14}N_2O_2$: C, 64.06, H, 6.84, N 13.58

(5-Bromo-3-methoxy-2-nitrophenyl)acetonitrile (28): To a solution of *t*-BuOK (11.2 g, 100 mmol) in DMF (80 ml), a solution of 2-nitro-5-bromoanisole and *p*-chlorophenoxyacetonitrile in DMF (30 ml) was added dropwise at -20°C. The mixture was stirred at this temperature for 15 min. and poured into an ice-cold diluted hydrochloric acid. The precipitate formed was collected by filtration, washed with water, air-dried and recrystallized from EtOH to give **28** (7.62 g, 70%) as a brownish solid. M.p. 120-1°C. δ_H ($CDCl_3$): 3.75 (2H, s, CH_2CN), 3.93 (3H, s, OCH_3), 7.22 (1H, d, J=1.1, H-4)*, 7.35 (1H, d, J=1.1, H-6)*. Elemental analysis: C 40.03, H 2.46, N 10.33; calc. for $C_9H_7BrN_2O_3$: C 39.88, H 2.60, N 10.33.

Ethyl 3-cyano-3-(5-Bromo-3-methoxy-2-nitrophenyl)propionate (29): **28** (7.62 g, 28.1 mmol), ethyl bromoacetate (4.84 g, 29 mmol), and K_2CO_3 (10 g) were stirred in acetonitrile (60 ml) overnight. Inorganic salts were filtered off, the filtrate was evaporated, the residue was dissolved in chloroform and washed with diluted HCl. The organic layer was dried and boiled with charcoal. The charcoal was filtered off and the filtrate was evaporated to give a pale yellow oil (9.86 g). This material contained **29** (90 mol%, 88 % by weight, 86 % yield) together with the dialkylation product, as revealed by MS and ^1H NMR spectra. Given below spectral data correspond to the major product. δ_H ($CDCl_3$): 1.27 (3H, t, J=7.1, $OCH_2\underline{CH_3}$), 2.91-2.97 (2H, m, CH_2CO_2Et), 3.93 (3H, s, OCH_3), 4.09-4.31 (3H, m, $O\underline{CH_2}CH_3$ and CHCN), 7.22 (1H, d, J=1.7, H-4)*, 7.40 (1H, d, J=1.7, H-6)*. LSIMS m/z: 357, 359 $(M+H)^+$.

1,2,3,4-Tetrahydro-6-bromo-8-methoxy-2-oxo-4-quinolinecarbonitrile (30): To a solution of crude **29** (8.36 g, 7.36 g, 20.6 mmol of the pure compound) in methanol (90 ml), tin (5.58 g, 47 mmol) was added followed by a hydrochloric acid solution in methanol (1:1, 10 ml, all at once). Upon addition temperature rose to 40 °C and then gradually dropped. After 2h stirring the crystalline product was collected by filtration, washed thoroughly with methanol and air-dried to give **30** (4.48 g, 77%) as a colorless solid. M.p. 233-4 °C. δ_H (dmso-d_6): 2.83, 2.91 (2H,

AB part of ABX system, J_{AB}=16.1, $|J_{AX}|$=6.7, $|J_{BX}|$= 5.7, CH_2), 3.86 (3H, s, OCH_3), 4.69 (1H, part X of ABX system, CHCN), 7.22 (1H, d, *J*=1.6, H-5)*, 7.26 (1H, d, *J*=1.6, H-7)*). Elemental analysis: C 47.02, H 3.14, N 9.99; calc. for $C_{11}H_9BrN_2O_2$: C 47.00, H 3.23, N 9.97.

1,2,3,4-Tetrahydro-6-bromo-8-methoxy-5-nitro-2-oxo-4-quinolinecarbonitrile (31): A suspension of **30** (1.967 g, 7 mmol) in 65% nitric acid (15 ml) was stirred at r.t. for 3 h and poured into water with ice. The precipitate formed was collected by filtration, washed thoroughly with water until washing was neutral, and air dried to give **31** (1.894 g, 83%) as a colorless solid. M.p. 197-8°C (dec.). δ_H (acetone): 2.72, 3.03 (2H, AB part of ABX system, J_{AB}=16.7, $|J_{AX}|$=2.1, $|J_{BX}|$= 6.3, CH_2), 3.95 (3H, s, OCH_3), 4.58 (1H, X part of ABX system, CHCN), 7.55 (1H, s, H-7), 10.37 (br. s, NH). MS (EI) m/z (%): 327, 325 (M^+, 90,100 respectively), 270 (12), 268 (17), 229 (17), 157 (32), 129 (26). Elemental analysis: C 40.52, H 2.45, N 13.17; calc. for $C_{11}H_8BrN_3O_4$: C 40.51, H, 2.47, N 12.89.

6-Methoxy-4-oxo-1,3,4,5-tetrahydropyrrolo[4,3,2-*d,e*]quinoline (5a): A suspension of **31** (326 mg, 1 mmol) and 10% Pd/C (120 mg) in a mixture of 10 ml of EtOH and 2 ml of acetic acid was refluxed under hydrogen for 12 h. After cooling the catalyst was filtered off and the filtrate was evaporated. Water was added to the residue and the resulting mixture was extracted with ethyl acetate . The extract was washed with 10% K_2CO_3 dried and evaporated. The residue was purified by passing through a short silica-gel column to give **5a** as a colorless solid. M.p. 164-6°C. δ_H ($CDCl_3$): 3.86 (3H, s, OCH_3), 4.00 (1H, d, *J*=1.6, CH_2), 6.85, 6.89 (2H, AB system, J_{AB}=8.7, H-7 and H-8), 6.84-6.86 (1H, overlapping with the AB system, H-2), 7.82 (br. s, lactam NH), 8.02 (br. s, indole NH). MS, m/z (%): 202 (M^+, 100), 187 (82), 173 (12), 159 (89), 145 (10), 131 (20). Elemental analysis: C 65.24, H 4.82, N 13.71; calc. for $C_{11}H_{10}N_2O_2$: C 65.34, H, 4.98, N 13.85.

5-Formyl-6-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*d,e*]quinoline (6a): To a solution of **5a** (110 mg, 0.54 mmol) in THF (5 ml), $BH_3{\cdot}Me_2S$ (0.1 ml, 1.12 mmol) was added dropwise at r.t. under argon and the mixture was stirred for 4 h. Methanol (0.2 ml) was added dropwise at 0°C and the mixture was stirred for 1 h at r.t. Then it was cooled to 0°C again and formic - acetic anhydride (3 ml) was added dropwise. After 15 min. stirring at 0°C the reaction mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with ammonia solution, dried and evaporated. The residue was purified by passing through a short silica-gel column to give **6a** (76 mg, 65%) as a colorless solid. M.p. 140-1 °C ; ref.[2]: 145-6°C. δ_H ($CDCl_3$): 3.00 (2H, br. "t", AA' part of AA'XX' system, H-3), 3.87 (3H, s, NCH_3), 4.11 (2H, "t", XX' part of AA'XX' system, H-4), 6.95, 7.07 (2H, AB system, J_{AB}=8.7, H-7 and H-8), 6.90 (1H, m, H-2), 8.02 (1H, br. s, NH), 9.20 (1H, s, HCO). MS, m/z (%): 244 (M^+, 78), 216 (39), 201 (100), 173 (45), 155 (13), 146 (8), 128 (3), 118 (10). Elemental analysis: C 66.58, H 5.52, N 12.98; calc. for $C_{12}H_{12}N_2O_2$: C 66.65, H 5.59, N 12.96.

5-Methyl-6-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*d,e*]quinoline (*O*-methylnordehydrobufotenine) (1a): To a solution of **6a** (60 mg, 0.28 mmol) in THF (5 ml), $BH_3{\cdot}Me_2S$ was added at r.t. under argon. The mixture was stirred for 1 h at r.t. and finally was warmed to boiling. After cooling, MeOH (0.5 ml) was added, the resulting mixture was stirred for 30 min. at r.t., diluted with 10% NaOH solution and extracted with CH_2Cl_2. The extract was dried and evaporated. The residue was purified by passing through a short silica-gel column to give **33** (46 mg, 81%) as a colorless solid. M.p. 94-5°C (hexane); ref.[2]: 84-5°C. δ_H ($CDCl_3$): 2.96 (2H, br. "t", AA' part of AA'XX' system, H-3), 3.15 (3H, s, NCH_3), 3.32 (2H, "t", XX' part of AA'XX' system H-4), 3.86 (3H, s, OCH_3), 6.79, 6.87 (2H, AB system, J_{AB}=8.8, H-7 and H-8), 6.75-6,76 (1H, overlapping with the AB system, H-2). MS, m/z (%): 202 (M^+, 73), 187 (100), 170 (20), 160 (8), 146 (9), 130 (8), 115 (7), 101 (7). HRMS (EI), m/z: 202.11102; $C_{12}H_{14}N_2O$ requires 202.110613. Elemental analysis: C 71.18, H 6.98, N 13.75; calc.: C 71.26, H 6.98, N 13.85.

References

1. Marki, F.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1961**, *83*, 3341.
2. Lee, F. G. H.; Daly, J. W.; Manian A. A. *J. Med. Chem.* **1969**, *12*, 321, and the references cited therein.
3. Joule, J. A.; Alvarez, M.; Venemalm, L., Esteves, C., *Tetrahedron* **1994**, *50*, 7879 and the references cited therein.
4. Balczewski, P.; Joule, J. A.; Estévez, C.; Alvarez, M. *J. Org. Chem.* **1994**, *59*, 4571.
5. Roberts, D.; Venemalm, L.; Alvarez, M.; Joule J. A. *Tetrahedron Lett.* **1994**, *42*, 7857.
6. Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 272.
7. Mąkosza, M. *Synthesis* **1991**, 103. (b) Wojciechowski, K.; Mąkosza, M. *Synthesis* **1986**, 651. (c) Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1988**, *203*, 203
8. Mąkosza, M.; Ludwiczak, S. *J. Org. Chem.* **1984**, *49*, 4562.
9. Theodoridis, G.; Manfredi, M. C.; Krebs, J. D. *Tetrahedron Lett.* **1990**, *31*, 6141.
10. Mąkosza, M.; Stalewski, J. *Tetrahedron*, this issue.
11. Mąkosza, M.; Danikiewicz W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1987**, 711.
12. Mąkosza, M.; Glinka, T.; Ostrowski, S.; Rykowski, A. *Chem. Lett.* **1987**, 611.
13. Wojciechowski, K.; Mąkosza, M. *Synthesis* **1989**, 106.
14. Pietraszkiewicz, M.; Sałański, P.; Ostaszewski, R.; Jurczak, J. *Heterocycles* **1986**, *24*, 1203.
15. Remers, W. A. in *The Chemistry of Heterocyclic Compounds* (Weissberger, A.; Taylor, E. C., Ed.), Vol.25 Part III: *Indoles* (Houlihan, W. J., Ed.), Wiley, New York 1979, p. 392.
16. Mąkosza, M.; Sienkiewicz, K. *J. Org. Chem.* **1990**, *55*, 4979.

(*Received in UK* 28 *March* 1995; *revised* 2 *May* 1995; *accepted* 5 *May* 1995)