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NEW TOTAL SYNTHESIS OF *dl*-PHYSOSTIGMINE (*dl*-ESERINE) VIA REGIOSELECTIVE $NaBH_4$-REDUCTION OF IMIDES[1]

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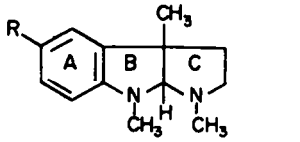
Abstract—The regioselective $NaBH_4/H^+$ reduction of α,α-disubstituted succinimides offers a method for a short and stereoselective total synthesis of *dl*-physostigmine in which the key-step is the formation of the B-ring via amine substitution on a ω-carbinol-lactam.

Physostigmine (eserine) **1a**,[3] the principal alkaloid of the Calabar bean, was synthesized[4] only 70 years after its discovery (1864).[5] To-day a number of syntheses has been reported,[6] all of these starting from an indole type precursor to which ring C is attached. Despite its relatively simple structure, however, the construction of the basis skeleton presents some remarkable difficulties among which the dinitrogen aminal structure is prominent.



1a: R = —O—CO—NH—CH_3
b: R = H
c: R = OH
d: R = OEt

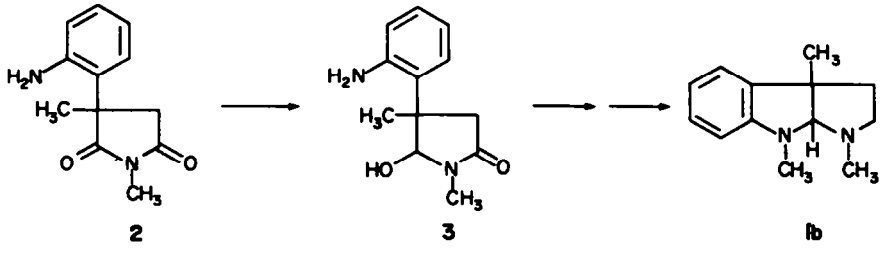
Fig. 1.

As was the case in the syntheses of *dl*-mesembrine and *dl*-(epi)-dihydromaritidine[7] our interest in physostigmine **1a** arose after finding that the $NaBH_4/H^+$ reduction of α,α-disubstituted succinimides proceeds in a highly regioselective manner.[8] Because of the presence of a *cis*-fused pyrrolidine ring in the skeleton of physostigmine **1a** the abovementioned principle could be applied in a new total synthesis of this alkaloid according to a simple pattern outlined below (Scheme 1).

Thus regioselective $NaBH_4/H^+$ reduction of the imide **2**, resulting in the corresponding ω-carbinol-lactam **3** should give after ring-closure, methylation and reduction the physostigmine skeleton **1b**. The planned synthesis in which the B ring of **1** is constructed in a final step constitutes a new procedure in the synthesis of this class of compounds. To test the latter approach the synthesis of *dl*-desoxyeseroline **1b** was chosen as our first target.

As given in Scheme 1 the central compound in the proposed route is 1,3-dimethyl-3-(2-aminophenyl)-succinimide **2** which could possibly be prepared via catalytic hydrogenation of the corresponding NO_2 derivative **9**. A similar transformation **6**→**7** was reported by Askam and Deeks.[9] The synthesis of **9** was realized in the following manner. A Knoevenagel condensation of 2-nitrobenzaldehyde and diethyl malonate by means of $TiCl_4$,[10] followed by cyanide addition and hydrolysis led to the amido-diester **4**.[11] However, acid hydrolysis and decarboxylation of **4** gave in contrast with the results of Loudon and Welling[11] a mixture of dicarboxylic acid **5** and imide **6**. Furthermore the preparation of the imide **8** starting from **5** did not proceed satisfactorily (yield: 10–36%). Presumably because of the presence of the NO_2 group decomposition and resinification was observed at the temperature required for conversion. A more satisfactory result was obtained when the amido-diester **4** was heated in wet DMSO in the presence of NaCl. This adaption of a recently described method for decarboxylation of malonates[12] provided the imide **6** in 61% yield.

N-Methylation leading to **8**, followed by C-methylation or direct dimethylation under the latter circumstances of **6** afforded the desired imide **9** in good yield. The catalytic



Scheme 1.

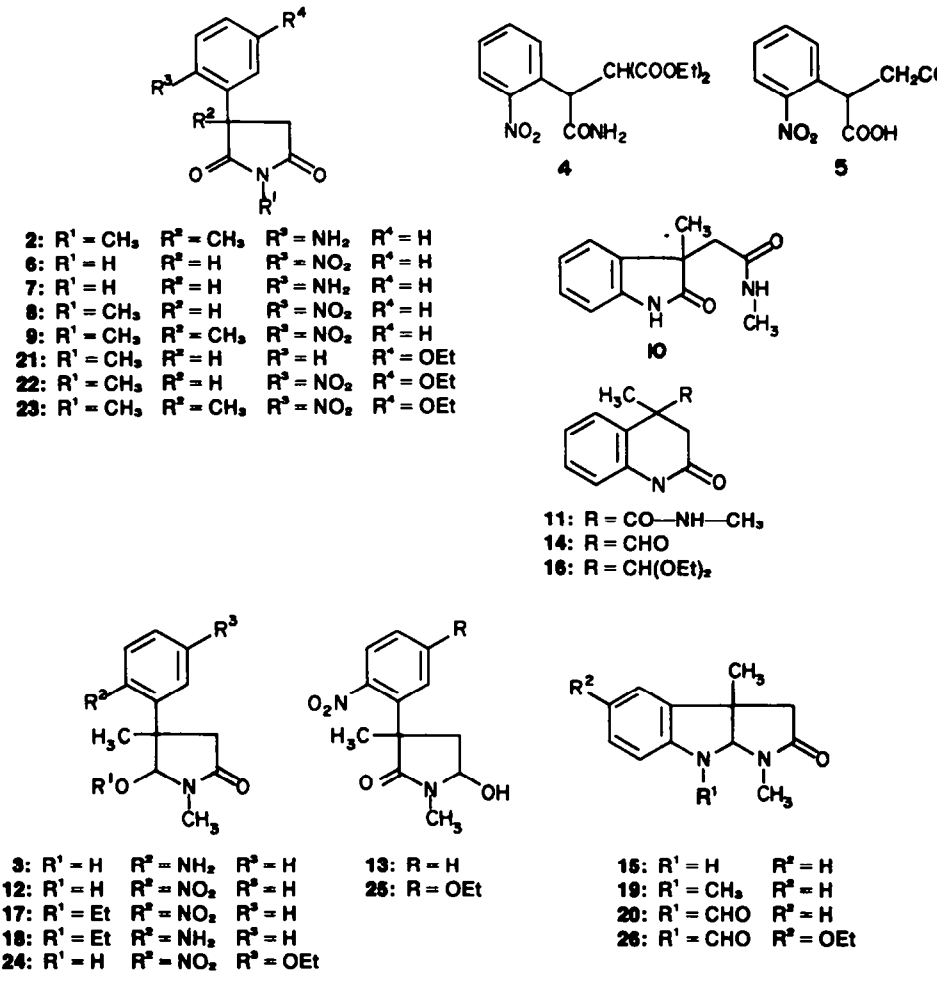


Fig. 2.

hydrogenation of 9→2 however, could not be accomplished. Instead of imide 2 a mixture of 2 compounds in a ratio 1:4, to which the structures 10 and 11 were attributed, was obtained. Its formation could probably result from the attack of the newly formed NH_2 group on both imide CO during the hydrogenation process.

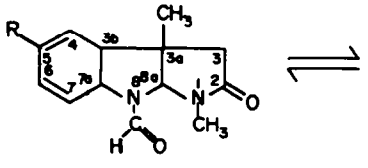
Therefore the $NaBH_4/H^+$ reduction was directly applied to imide 9. As was reported earlier[8] this reduction method proceeded regioselectively and the corresponding ω-carbinol-lactam 12 was isolated in 72% yield. In contrast with the catalytic hydrogenation of imide 9, the analogous reaction applied to 12 showed no ring opening and the desired ω-carbinol-lactam 3 was obtained in quantitative yield. At this stage the crucial step in the synthesis of the physostigmine skeleton, the formation of the B ring, was expected to proceed upon treatment with acid of 3. Because of the possibility that protonation of the NH_2 group in strong acid will retard the B ring formation a weakly acid silica-alumina catalyst[13] was chosen. However, upon treatment at reflux of 3 in a dioxane/H_2O mixture to which the catalyst was added the sole product obtained after chromatography in 65% yield possessed a M^+ peak at $m/e = 189$ in the MS indicating the loss of methylamine during the latter reaction. According to ^1H NMR and IR the latter compound proved to be the aldehyde 14. A slightly different behaviour was noted upon refluxing of 3 in C_6H_6/*p*-TsOH. Work-up and chromatography gave the aldehyde 14 (42%) together with the desired tricyclic compound 15 (30%). Upon treatment of 3 with HCl/EtOH at reflux the yield of 15 decreased (20%), the bulk of the remaining material being a mixture of aldehyde 14 and its diethyl acetal 16. Because of the rather disappointing yield of 15 the procedure was somewhat modified. Instead of 3 the corresponding ethoxy derivative 18 (prepared from 12 via HCl/EtOH treatment at 0°, giving 17 and subsequent catalytic hydrogenation of the latter compound) was used in the ring closure reaction anticipating that this change would suppress the formation of the aldehyde 14. Indeed upon treatment of 18 with HCl/EtOH at reflux the yield of 15 was considerably higher (65%) as compared with 3 as a reference material.

The observed difference in behaviour of 3 and 18 upon treatment with acid is tentatively explained by assuming an interaction between the OH and NH_2 moiety of 3 which renders the elimination of H_2O and thus the formation of the α-acylimmonium intermediate more difficult. Some support for the possible OH–NR_2 interaction was derived from conversion experiments of OH into OEt. In case of 3 and other comparable systems such as 1 - methyl - 4 - phenyl - 4 - (1 - morpholinomethyl) - 5 - hydroxy - 2 - pyrrolidinone[8] the conversion of OH into OEt did not proceed under standard conditions.

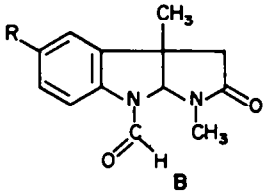
A similar interaction is not possible in case of **18** so that formation of the B ring leading to **15** is preferred.

The synthesis of *dl*-desoxyeseroline **1b** was completed by N_8-methylation[14] of **15**, which afforded **19** in 63% yield, followed by LAH reduction of the latter compound. Although the followed route indeed led to *dl*-desoxyeseroline **1b** the approach was rather lengthy. Therefore a shorter reaction sequence was developed in which the cyclisation step and introduction of the N_8-substituent occurred simultaneously. Thus upon treatment of **3** with acetic formic anhydride at 0° the cyclized N_8-formyl compound **20** was formed in high yield. According to ^{1}H NMR ($CDCl_3$) this compound consisted of a mixture of two rotamers **20A** and **20B** in a ratio 3:1 (Table 1). The signal of the downfield aromatic H (δ = 8.02) integrated for about 25% of 1 proton indicating that **20A** was the predominant configuration. The formyl proton gave rise to signals at δ 8.70 for **20B** and at δ 9.00 for **20A**.

Table 1. Chemical shifts (^{1}H in ppm) of compound **20** and **26**



A



B

20: R = H A:B = 76:24
26: R = OEt A:B = 65:35

	20A†	**20B**†	**26A**†‡	**26B**†‡
CH_3–N(1)	2.96(s)	2.97(s)	2.95(s)	
H_2C(3)	2.56–3.03		2.54–2.95	
CH_2–C(3a)	1.51(s)	1.52(s)	1.51(s)	1.49(s)
aromatic H	7.06–7.40		6.72–7.17	
HC(7)		8.02(m)		7.90(m)
CHO–N(8)	9.00(s)	8.70(s)	8.88(s)	8.62(s)
HC(8a)	5.75(s)	5.29(s)	5.75(s)	5.28(s)

†Measured in $CDCl_3$.

‡The chemical shifts of the protons of the ethoxy-group were found at δ 1.41(t) and δ 4.01(q).

The observations are a consequence of hindered rotation about the N–C bond owing to its partial double bond character which leads to steric interaction. Similar results were reported for the simple 1-formyl-indoline molecule.[15] Further stereochemical proof of **20** was made upon examination of the nuclear Overhauser effect (NOE).[16] Irradiation of the C_{3a}–CH in ^{1}H NMR ($CDCl_3$) increased the integrated area of C_{8a}–H (18.4%) indicating the proximity of C_{3a}–CH_3 and C_{8a}–H and thus proving its *cis* relation. Finally LAH reduction of **20** afforded *dl*-desoxyeseroline **1b** in 77% yield.

The procedure outlined above was also employed in the synthesis of *dl*-physostigmine **1a**. However, contrary to the preparation of **8** the synthesis of the imide **22** possessing the C_5 aromatic substituent was achieved according to standard methods. In order to avoid the difficulties encountered in the preparation of imide **8** the introduction of the 2-NO_2 group was performed in the final step. Thus according to standard methods 3-ethoxybenzaldehyde was transformed to 1 - methyl - 3 - (3 - ethoxyphenyl) - succinimide **21**, which was nitrated with fuming HNO_3 thereby affording a mixture of the required imide **22** and the corresponding 3 - ethoxy - 4 - nitrophenyl derivative in a ratio 65:35, respectively. After chromatography and crystallization imide **22** was obtained in 40% yield. The synthesis of *dl*-physostigmine **1a** was finally completed by methods described previously for the synthesis of *dl*-desoxyeseroline **1b**.

Thus methylation of **22** followed by $NaBH_4/H^+$ reduction of the so-formed imide **23** afforded according to ^{1}H NMR ($CDCl_3$) a mixture of **24** and **25** in a ratio 3:1. After crystallization from EtOAc a 60% yield of pure **24** was obtained. Conversion of **24** into the corresponding tricyclic N_8-formyl compound **26** was achieved in 74% yield after catalytic hydrogenation and subsequent treatment with acetic formic anhydride at 0°. Again the latter compound according to ^{1}H NMR ($CDCl_3$) consisted of a mixture of two rotamers **26A** and **26B** in a ratio 65:35 (Table 1). Completion of the synthesis of *dl*-physostigmine **1a** required a conversion of **26** into *dl*-eserethole **1d** which was accomplished in 75% yield by reduction of **26** with LAH. Having obtained *dl*-eserethole **1d** the total synthesis of **1a** was secured since conversion of **1d** into *dl*-physostigmine **1a** (via *dl*-eseroline **1c**) has been described.[4,17]

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were determined on Unicam SP-200 or Perkin–Elmer 257 instruments. The absorptions are located by their wave numbers (in cm^{-1}). ^{1}H NMR spectra were measured with a Varian A-60D, HA-100 or XL-100 spectrometer using TMS as internal reference. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded on an AEI MS-902 or Varian Mat-711 mass spectrometer. Analyses were performed by Mr. H. Pieters of the Micro-analytical Department of our laboratory. Column chromatography was carried out on silicagel (activity grade II, Woelm). Pre-coated TLC Plates silicagel 60 F254 Merck were used for TLC, the spots being detected by exposure to iodine vapour.

Diethyl α - carbamoyl - α - (2 - nitrobenzyl) - malonate **4** was prepared according to the method described[11] from diethyl 2-nitrobenzylidenemalonate. The latter compound was prepared from 2-nitrobenzaldehyde according to the method described.[10]

2-Nitrophenylsuccinic acid **5**. A soln of **4** (17.00 g, 50.3 mmole) in conc. HCl (500 ml) and HOAc (50 ml) was heated at reflux for 3 hr and concentrated *in vacuo*. The solid separated showed on TLC (silicagel, $CHCl_3$/acetone 4/1) 2 spots with R_f 0.30 and 0.01. Column chromatography on silicagel with $CHCl_3$/acetone 4/1 as an eluent afforded the fraction with R_f 0.30 which consisted of **6**. Crystallization from EtOAc yielded 1.87 g of pure **6** (17%). Further elution gave the fraction with R_f 0.01 as a solid, which was crystallized from H_2O affording 7.19 g of pure **5**, yield: 60%; m.p. 182–184° (H_2O) (lit. 175°,[18] 188°[11]).

3 - (2 - Nitrophenyl) - succinimide **6**. A mixture of **4** (5.82 g, 17.22 mmole), NaCl (1.30 g) and H_2O (1.25 g) in DMSO (25 ml) was heated at 145–148° for 7 hr. The mixture was poured into H_2O (200 ml) and extracted with $CHCl_3$ (4 × 50 ml). The combined organic layers were washed with sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a brown oil, which showed one main spot on TLC (silicagel, $CHCl_3$/acetone 4/1) with R_f 0.30. Column chromatography on silicagel with $CHCl_3$/acetone 4/1 as an eluent afforded the fraction with R_f 0.30 as a yellow solid (2.82 g), which according to ^{1}H NMR ($CDCl_3$) was nearly pure **6**. Crystallization from EtOAc

gave 2.32 g of pure **6**; yield: 61%; m.p. 146–148° (EtOAc) (lit. 142–143°[9]).

1-Methyl-3-(2-nitrophenyl)-succinimide **8**

From **6**. To a mixture of **6** (1.85 g, 8.41 mmole) in CH_2Cl_2 (100 ml) was added an excess of a freshly prepared soln of CH_2N_2 in ether[19] at 0°. The mixture was stirred at 0° for 3 hr and an additional period of 18 hr at r.t. Evaporation of the solvent afforded a yellow solid (1.95 g) which was crystallized from EtOH to give 1.64 g of pure **8**, yield: 83%; m.p. 122–124° (EtOH). IR($CHCl_3$): 1770 (w), 1700 (vs) (imide-CO), 1530 (s), 1350 (s) (NO_2); ^{1}H NMR: δ($CDCl_3$) 2.60–3.40 (2H, $-CH_2-$CO), 3.04 (s, 3H, $-N-CH_3$), 4.41 (1H, $-CO-CH-Ar$), 7.20–7.70 (3H, aromatic H), 8.05 (1H, aromatic H). (Found: C, 56.5; H, 4.4; N, 11.9. Calc. for $C_{11}H_{10}N_2O_4$, M = 234.21: C, 56.41; H, 4.30; N, 11.96%).

From **5**. A mixture of **5** (7.18 g, 30.17 mmole) in $SOCl_2$ (25 ml) was heated at reflux for 1.5 hr. Evaporation to dryness afforded a yellow solid which was dissolved in 35% methylamine soln in H_2O (25 ml). After stirring at r.t. for 30 min. the mixture was diluted with H_2O (25 ml) and acidified with conc HCl. The formed solid was filtered off and dried *in vacuo* (5.71 g) 2.76 g of the latter solid was taken up in xylene (250 ml) and the mixture was refluxed for 17 hr using a Dean and Stark apparatus filled with molecular sieves 4A. Evaporation of the solvent afforded a dark brown oil which was chromatographed on silicagel with $CHCl_3$ as an eluent yielding 1.33 g of crude **8**. Crystallization from EtOH gave 1.07 g of pure **8**.

1,3 - Dimethyl - 3 - (2 - nitrophenyl) - succinimide **9**. To a soln of **6** (2.70 g, 12.27 mmole) in DMF (50 ml) was added K_2CO_3 (5.0 g) at 0°. After 45 min of stirring at 0° a soln of MeI (5 ml) in DMF (10 ml) was added dropwise. The mixture was stirred at 0° for 90 hr, poured into H_2O (250 ml) and extracted with EtOAc (3 × 50 ml). The combined organic layers were washed with sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a yellow solid. Crystallization from EtOH gave 2.58 g of pure **9**, yield: 85%; m.p. 133–135° (EtOH). IR($CHCl_3$): 1770(w), 1700(vs) (imide-CO), 1530(s), 1350(s) (NO_2); ^{1}H NMR: δ($CDCl_3$) 1.78 (s, 3H, $-C-CH_3$), 2.98 (AB system, J = 17.5 Hz, 2H, $-CH_2-$CO), 3.05 (s, 3H, $-N-CH_3$), 7.20–7.99 (4H, aromatic H). (Found: C, 58.1; H, 5.0; N, 11.4. Calc. for $C_{12}H_{12}N_2O_4$, M = 248.23: C, 58.06; H, 4.87; N, 11.29%). With a similar procedure, **8** afforded **9** in about equal yield.

Catalytic hydrogenation of **9**. Compound **9** (0.78 g, 3.15 mmole) was hydrogenated in EtOH (150 ml) over 10% Pd/C (0.10 g) for 2 hr. The catalyst was removed by filtration and the filtrate evaporated. The residual solid (0.68 g) was according to ^{1}H NMR (DMSO-d_6) a mixture of two compounds in a ratio 1:4. Attempts to separate the mixture via chromatography were unsuccessful. Crystallization from acetone afforded one of the compounds in pure form; m.p. 213–218° (acetone). IR(KBr): 3300(s) (NH), 1700(vs), 1650(vs), 1570(s) (amide-CO); ^{1}H NMR: δ(DMSO-d_6) 1.24 (s, 3H, $-C-CH_3$), 2.42 (d, J = 5 Hz, 3H, $-NH-CH_3$), 2.60 (AB system, J = 14.5 Hz, 2H, $-CH_2-$CO), 6.70–7.30 (4H, aromatic H), 7.62 (broad s, 1H, $-NH-$), 10.20 (broad s, 1H, $-NH-$). (Found: C, 66.1; H, 6.5; N, 12.7. Calc. for $C_{12}H_{14}N_2O_2$, M = 218.25: C, 66.03; H, 6.47; N, 12.84%).

1,4 - Dimethyl - 4 - (2 - nitrophenyl) - 5 - hydroxy - 2 - pyrrolidinone **12**. Compound **9** (3.10 g, 12.50 mmole) was reduced in a mixture of EtOH (250 ml) and THF (50 ml) with 3.8 g $NaBH_4$ at 0° for 4.5 hr as described.[8] The crude product was a mixture of **12** and **13** in a ratio 5:1. Purification via crystallization afforded **12** in 72% yield.

1,4 - Dimethyl - 4 - (2 - nitrophenyl) - 5 - ethoxy - 2 - pyrrolidinone **17**. To an ice-cooled soln of **12** (0.22 g, 0.88 mmole) in EtOH (70 ml) 4N HCl/EtOH (1 ml) was added. The mixture was stirred at 0° for 2 hr after which the solvent was evaporated. According to ^{1}H NMR ($CDCl_3$) the residual solid (0.245 g) was pure **17**; yield: 100%; m.p. 113–116° (di-isopropylether). IR($CHCl_3$): 1690(vs) (lactam-CO), 1530(s), 1360(s) (NO_2); ^{1}H NMR: δ($CDCl_3$) 0.98 (t, J = 7 Hz, 3H, $-O-CH_2-CH_3$), 1.51 (s, 3H, $-C-CH_3$), 2.62 (A part AB system, J = 16 Hz, 1H, $-CH-$CO), 2.99 (B part AB system, J = 16 Hz, 1H, $-CH-$CO), 3.04 (s, 3H, $-N-CH_3$), 3.32 (m, J = 7 Hz, 2H, $-O-CH_2-CH_3$), 4.85 (s, 1H, $-N-CH-$OEt), 7.24–7.83 (4H, aromatic H). (Found: C, 60.3; H, 6.4. Calc. for $C_{14}H_{18}N_2O_4$, M = 278.30: C, 60.42; H, 6.52%).

1,4 - Dimethyl - 4 - (2 - aminophenyl) - 5 - hydroxy - 2 - pyrrolidinone **3**. Compound **12** (0.23 g, 0.92 mmole) was hydrogenated in EtOH (100 ml) over 10% Pd/C (0.10 g) for 1 hr. The catalyst was removed by filtration and the filtrate evaporated. The residual solid (0.20 g) was according to ^{1}H NMR nearly pure **3**, yield >95%; m.p. 100–102° (toluene). IR(KBr): 3500(m), 3400(m), 3300(m) (NH and OH), 1680(vs) (lactam-CO); ^{1}H NMR: δ(DMSO-d_6), 1.22 (s, 3H, $-C-CH_3$), 2.64 (AB system, J = 16 Hz, $-CH_2-$CO), 2.66 (s, 3H, $-N-CH_3$), 5.12 (3H, $-NH_2$ and $-N-CH-$OH; becomes a s with D_2O added), 6.37–7.13 (5H, aromatic H and $-OH$; 1H disappears with D_2O added). MS: *m/e* = 78(65%), 160(100), 161(55), 202(64), 220(9) M^+. (Found: C, 65.6; H, 7.5. Calc. for $C_{12}H_{16}N_2O_2$, M = 220.26: C, 65.43; H, 7.32%).

4 - Formyl - 4 - methyl - 1,2,3,4 - tetrahydro - quinolin - 2 - one **14**. Compound **12** (0.32 g, 1.28 mmole) was hydrogenated over 10% Pd/C (0.17 g) as described. The residual oil was dissolved in a mixture of dioxane (10 ml) and H_2O (4 ml). Silica-alumina catalyst[13] (0.15 g) was added after which the mixture was heated at reflux for 1 hr. The mixture was diluted with H_2O (25 ml) and extracted with $CHCl_3$ (3 × 25 ml). The combined organic layers were washed with sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a brown oil (0.27 g) which showed one main spot on TLC (silicagel, EtOAc) with R_f 0.45. Column chromatography on silicagel with EtOAc as an eluent gave 0.16 g of the fraction with R_f 0.45 which consisted of pure **14**: yield: 65%; m.p. 154–156° (EtOAc). IR($CHCl_3$): 1720(vs) (aldehyde-CO), 1680 (vs) (lactam-CO); ^{1}H NMR: δ($CDCl_3$), 1.48 (s, 3H, $-C-CH_3$), 2.49 (A part AB system, J = 16.5 Hz, 1H, $-CH-$CO), 2.95 (B part AB system, J = 16.5 Hz, 1H, $-CH-$CO), 6.90–7.37 (4H, aromatic H), 9.40 (s, 1H, $-CHO$), 9.74 (broad s, 1H, $-NH-$). (Found: C, 69.9; H, 5.9; N, 7.4. Calc. for $C_{11}H_{11}NO_2$, M = 189.21: C, 69.82; H, 5.86; N, 7.40%).

1,3a - Dimethyl - 3,3a,8,8a - tetrahydropyrrolo[2,3-b]- indol - 2 - one **15**. To a soln of **3** (0.19 g, 0.86 mmole) in EtOH (50 ml) 4N HCl/EtOH (1 ml) was added after which the mixture was refluxed for 2 hr. Evaporation of the solvent afforded an oil which was dissolved in $CHCl_3$ (50 ml). The latter soln was washed with sat $NaHCO_3$ aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate gave an oil which showed 2 spots on TLC (silicagel, EtOAc) with R_f 0.45 and 0.13. Column chromatography on silicagel with EtOAc as an eluent afforded the fraction with R_f 0.45 as a white solid (0.11 g) which according to ^{1}H NMR($CDCl_3$) was a mixture of **14** and **16** in a ratio 1:4. Crystallization from EtOAc gave pure **16** (0.052 g); yield: 23%; m.p. 148–151° (EtOAc). IR($CHCl_3$): 3450(w) (NH), 1670(vs) (lactam-CO); ^{1}H NMR: δ($CDCl_3$), 0.96 (t, J = 7 Hz, 3H, $-O-CH_2-CH_3$), 1.04 (t, J = 7 Hz, 3H, $-O-CH_2-CH_3$), 1.29 (s, 3H, $-C-CH_3$), 2.34 (A part AB system, J = 16.5 Hz, 1H, $-CH-$CO), 2.80 (B part AB system, J = 16.5 Hz, 1H, $-CH-$CO), 2.92–3.82 (m, J = 7 Hz, 4H, 2 × $-O-CH_2-CH_3$), 4.21 (s, 1H, $-CH-(OEt)_2$), 6.67–7.53 (4H, aromatic H), 9.20 (broad s, 1H, $-NH-$). (Found: C, 68.5; H, 8.0. Calc. for $C_{15}H_{21}NO_3$, M = 263.33: C, 68.41; H, 8.04%). Further elution gave the fraction with R_f 0.13 as a pink solid (0.035 g) which according to ^{1}H NMR ($CDCl_3$) was pure **15**; yield: 20%; m.p. 123–126° (ether). IR(KBr): 3300(m) (NH), 1660(vs) (lactam-CO); ^{1}H NMR: δ($CDCl_3$), 1.46 (s, 3H, $-C-CH_3$), 2.70 (AB system, J = 17 Hz, 2H, $-CH_2-$CO), 2.85 (s, 3H, $-N-CH_3$), 4.65 (broad s, 1H, $-NH-$), 4.88 (s, 1H, $-N-CH-N-$), 6.58–7.20 (4H, aromatic H). (Found: C, 71.3; H, 7.0. Calc. for $C_{12}H_{14}N_2O$, M = 202.25: C, 71.26; H, 6.98%).

In a similar experiment starting from **17** (0.23 g, 0.83 mmole) hydrogenation over 10% Pd/C (0.11 g), as described for **12**, afforded a colourless oil (0.20 g). Without further purification the oil was dissolved in EtOH (50 ml) and treated with 4N HCl/EtOH (1 ml) at reflux for 2 hr. Work-up as described above gave a mixture of **14**, **15** and **16**. After column chromatography on silicagel with EtOAc as an eluent 0.060 g of a mixture of **14** and **16** in a ratio 1:4 was obtained. Further elution afforded 0.107 g of pure **15**; yield: 65%.

Refluxing of a soln of **3** in C_6H_6, to which 1.1 eq *p*-TsOH was added, for 2 hr and column chromatography afforded **14** and **15** in 42 and 30% yield respectively.

1,3a,8 - Trimethyl - 3,3a,8,8a - tetrahydropyrrolo[2,3-b]- indol - 2 - one **19**. To a soln of **15** (0.224 g, 1.11 mmole) in MeCN (5 ml) was added a soln of 37% formaldehyde in H_2O (1 ml). The

mixture was stirred at r.t. for 30 min after which $NaBH_3CN$ (0.36 g) and HOAc (0.2 ml) was added. After stirring at r.t. for 2 hr again HOAc (0.2 ml) was added and stirring was continued at r.t. for an additional 1.5 hr. The mixture was diluted with ether (75 ml), washed with 5% NaOH soln (25 ml) and sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a pale yellow oil (0.24 g) which was chromatographed on silicagel with EtOAc as an eluent giving 0.152 g of pure **19**; yield: 63%. The analytical data were in all respects identical with those reported.[6]

1,3a - *Dimethyl* - 8 - *formyl* - 3,3a,8,8a - *tetrahydro* - *pyrrolo*[2,3-b]*indol* - 2 - *one* **20**.† Compound **12** (0.496 g, 1.98 mmole) was hydrogenated over 10% Pd/C (0.22 g) as described before. The residual oil (0.44 g) was dissolved in $CHCl_3$ (25 ml) and cooled to 0° after which 5 ml of acetic formic anhydride[20] was added dropwise. The soln was stirred at 0° for 3 hr. Evaporation of the solvent afforded an oil which was dissolved in $CHCl_3$ (60 ml). The soln was washed with 5% Na_2CO_3 (2 × 15 ml) and sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a pale brown oil (0.45 g). Column chromatography on silicagel with EtOAc as an eluent gave 0.35 g of pure **20**; yield: 76%; m.p. 127–129° (CH_2Cl_2/light petroleum (b.p. 80–100°). IR($CHCl_3$): 1690(vs) (lactam-CO); ^{1}H NMR: δ($CDCl_3$) (Table 1). (Found: C, 67.7; H, 6.2; N, 12.1. Calc. for $C_{13}H_{14}N_2O_2$, M = 230.26: C, 67.81; H, 6.13; N, 12.17%).

dl-*Desoxyeseroline* **1b**

(a) *From* **20**. To a soln of **20** (0.156 g, 0.68 mmole) in dry ether (25 ml) LAH (0.20 g) was added. The mixture was refluxed for 2 hr. After cooling the excess of LAH was destroyed by adding H_2O (1 ml), the inorganic substance was removed by filtration. The filtrate was dried over Na_2SO_4, filtered and evaporated giving a yellow oil (0.130 g). Column chromatography on silicagel with $CHCl_3$/acetone 1/1 as an eluent afforded 0.106 g of pure **1b** as an oil; yield: 77%. IR($CHCl_3$): 1600(m), 1500(s) (aromatic); ^{1}H NMR: δ($CDCl_3$), 1.45 (s, 3H, –C–CH_3), 1.98 (m, 2H, –C–CH_2–C–), 2.57 (s, 3H, –N–CH_3), 2.69 (m, 2H, –N–CH_2–), 2.96 (s, 3H, –N–CH_3), 4.12 (s, 1H, –N–CH–N–), 6.35–7.18 (4H, aromatic H). A picrate of m.p. 178–181° (EtOH) (lit. 175°,[6] 179–180°[21]) was analyzed. (Found: C, 53.1; H, 5.0; N, 16.3. Calc. for $C_{19}H_{21}N_5O_7$, M = 431.40: C, 52.90; H, 4.91; N, 16.24%).

(b) *From* **19**. Compound **1b** was prepared from **19** (0.124 g, 0.57 mmole) as described;[6] yield: 63%. The analytical data were identical to those mentioned above.

1 - *Methyl* - 3 - (3 - *ethoxyphenyl*) - *succinimide* **21**. A mixture of ethyl α-cyano-3-ethoxy cinnamate (18.05 g, 73.67 mmole) (prepared in 92% yield from 3-ethoxybenzaldehyde[22] and ethyl cyanoacetate according to the procedure described[23]) and KCN (10.72 g, 165.0 mmole) in MeOH (75 ml) was refluxed for 30 min. The mixture was poured into H_2O (100 ml), slowly acidified with 10% HCl and extracted with ether (3 × 100 ml). The combined extracts were washed with sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a yellow oil which was dissolved in conc HCl (100 ml) and refluxed for 4 hr. The mixture was cooled to 0° and the ppt was filtered off, washed with ice-water and dried *in vacuo* at 80°, yielding 15.5 g of a white solid which was dissolved in AcCl (60 ml) and refluxed for 2 hr. Evaporation to dryness afforded a yellow solid (12.39 g). (IR($CHCl_3$): 1860(w), 1780(vs) (anhydride-CO); yield: 76%), which without further purification was treated with CH_3NH_2 according to the procedure described[24] yielding 11.47 g of pure **21**; m.p. 97–99° (EtOH). IR($CHCl_3$): 1770(w), 1700(vs) (imide-CO): ^{1}H NMR: δ($CDCl_3$), 1.35 (t, J = 7 Hz, 3H, –O–CH_2–CH_3), 2.47–3.41 (2H, –CH_2–CO), 3.00 (s, 3H, –N–CH_3), 3.80–4.20 (q, J = 7 Hz, 2H, –O–CH_2–CH_3 and 1H, –CO–CH–Ar), 6.63–7.42 (4H, aromatic H). (Found: C, 67.0; H, 6.5. Calc. for $C_{13}H_{15}NO_3$, M = 233.26: C, 66.93; H, 6.48%).

1 - *Methyl* - 3 - (2 - *nitro* - 5 - *ethoxyphenyl*) - *succinimide* **22**. To a soln of **21** (4.72 g, 20.27 mmole) in HOAc (20 ml) fuming HNO_3 (d *ca.* 1.5) (10 ml) was added dropwise quickly. The temp. rose to 70°. After stirring for 1 hr the mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with 10% KOH aq and sat NaCl aq, dried over Na_2SO_4 and filtered. Evaporation of the filtrate afforded a pale yellow oil (4.95 g) which according to ^{1}H NMR($CDCl_3$) was a mixture of **22** and the corresponding 3-ethoxy-4-nitrophenyl derivative in a ratio of 65:35. Column chromatography on silicagel with ether as an eluent afforded 2.76 g of pure **22** as a pale yellow oil which solified upon standing. Crystallization from EtOH gave 2.30 g of crystalline **22**; yield: 40% m.p. 127–129° (EtOH). IR($CHCl_3$): 1770(w), 1700(vs) (imide-CO), 1520(s), 1340(s) (NO_2); ^{1}H NMR: δ($CDCl_3$), 1.45 (t, J = 7 Hz, 3H, –O–CH_2–CH_3), 2.62–3.41 (2H, –CH_2–CO), 3.09 (s, 3H, –N–CH_3), 4.11 (q, J = 7 Hz, 2H, –O–CH_2–CH_3), 4.41 (1H, –CO–CH–Ar), 6.77 (d, J = 2.5 Hz, 1H, aromatic H), 6.91 (double d, J = 2.5 and 9 Hz, 1H, aromatic H), 8.18 (d, J = 8 Hz, 1H, aromatic H). (Found: C, 56.0; H, 5.2. Calc. for $C_{13}H_{14}N_2O_5$, M = 278.26: C, 56.11; H, 5.07%).

1,3 - *Dimethyl* - 3 - (2 - *nitro* - 5 - *ethoxyphenyl*) - *succinimide* **23** was prepared from **22** (1.95 g, 70 mmole) according to the procedure described for the synthesis of **9**; yield: 85%; m.p. 107–109° (EtOH). IR($CHCl_3$): 1770(w), 1700(vs) (imide-CO), 1530(s), 1350(s) (NO_2); ^{1}H NMR: δ($CDCl_3$), 1.44 (t, J = 7 Hz, 3H, –O–CH_2–CH_3), 1.73 (s, 3H, –C–CH_3), 2.69 (A part AB system, J = 17.5 Hz, 1H, –CH–CO), 3.04 (s, 3H, –N–CH_3), 3.13 (B part AB system, J = 17.5 Hz, 1H, –CH–CO), 4.11 (q, J = 7 Hz, 2H, –O–CH_2–CH_3), 6.86 (double d, J = 2.5 and 9 Hz, 1H, aromatic H), 7.11 (d, J = 2.5 Hz, 1H, aromatic H), 8.03 (d, J = 9 Hz, 1H, aromatic H). MS: *m/e* = 246(100%), 292(18) M^+. (Found: C, 57.5; H, 5.5. Calc. for $C_{14}H_{16}N_2O_5$, M = 292.28: C, 57.53; H, 5.52%).

1,4 - *Dimethyl* - 4 - (2 - *nitro* - 5 - *ethoxyphenyl*) - 5 - *hydroxy* - 2 - *pyrrolidinone* **24**. Compound **23** (0.79 g, 2.71 mmole) was reduced in a mixture of EtOH (150 ml) and THF (25 ml) with 1.47 g $NaBH_4$ at 0° for 4 hr according to the procedure described.[24] The crude product (0.76 g) was according to ^{1}H NMR ($CDCl_3$) a mixture of **24** and **25** in a ratio 3:1. After crystallization from EtOAc pure **24** (0.48 g) was obtained; yield: 60%; m.p. 176–181° (EtOAc). IR(KBr): 3100(m) (OH), 1650(vs) (lactam-CO); ^{1}H NMR: δ(DMSO-d_6), 1.39 (t, J = 7 Hz, 3H, –O–CH_2–CH_3), 1.44 (s, 3H, –C–CH_3), 2.42 (AB system, J = 16.5 Hz, 2H, –CH_2–CO), 2.71 (s, 3H, –N–CH_3), 4.15 (q, J = 7 Hz, 2H, –O–CH_2–CH_3), 5.25 (d, J = 7 Hz, 1H, –N–CH–OH; becomes a s with D_2O added), 6.88 (d, J = 7 Hz, 1H, –OH); disappears with D_2O added), 6.96–7.80 (3H, aromatic H). (Found: C, 57.2; H, 6.1; N, 9.6. Calc. for $C_{14}H_{18}N_2O_5$, M = 294.30: C, 57.13; H, 6.17; N, 9.52%).

1,3a - *Dimethyl* - 5 - *ethoxy* - 8 - *formyl* - 3,3a,8,8a - *tetrahydro* - *pyrrolo*[2,3-b]*indol* - 2 - *one* **26** was prepared from **24** (0.196 g, 0.67 mmole) according to the procedure described for the synthesis of **20**; yield: 74%; m.p. 149–151° (CH_2Cl_2/ether). IR($CHCl_3$): 1670(vs) (lactam-CO); ^{1}H NMR: δ($CDCl_3$) (Table 1). (Found: C, 65.8; H, 6.7; N, 10.3. Calc. for $C_{15}H_{18}N_2O_3$, M = 274.31: C, 65.67; H, 6.61; N, 10.21%).

dl-*Eserethole* **1d** was prepared from **26** (0.136 g, 0.50 mmole) according to the procedure described for the synthesis of *dl*-**1b**; yield 75%; m.p. 34–37° (lit. 38°[25]). IR($CHCl_3$): 1600(w), 1500(m) (aromatic); ^{1}H NMR: δ($CDCl_3$), 1.36 (t, J = 7 Hz, 3H, –O–CH_2–CH_3), 1.44 (s, 3H, –C–CH_3), 1.95 (m, 2H, –C–CH_2–C–), 2.55 (s, 3H, –N–CH_3), 2.70 (m, 2H, –N–CH_2–), 2.90 (s, 3H, –N–CH_3), 3.95 (q, J = 7 Hz, 2H, –O–CH_2–CH_3), 4.05 (s, 1H, –N–CH–N–), 6.34 (1H, aromatic H), 6.66 (2H, aromatic H). A picrate of m.p. 153–156° (EtOH) (lit. 150–151°,[26] 155°[25]) was analyzed. (Found: C, 52.9; H, 5.3; N, 14.8. Calc. for $C_{21}H_{25}N_5O_8$, M = 475.45: C, 53.05; H, 5.30; N, 14.73%).

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†Compound **20** could be converted into **15** upon refluxing of a soln of the former in EtOH to which a catalytic amount of acid was added in quantitative yield.

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