Synthesis of Vinca Alkaloids and Related Compounds LXXXV. [1]. Studies with Azepino[3,4-*b*]indoles

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The synthesis of some new pyrido[1',2':1,2]azepino[3,4-*b*]indoles starting from indole-3-propanamine **1** is described. Stereochemistry and observed side reactions are discussed.

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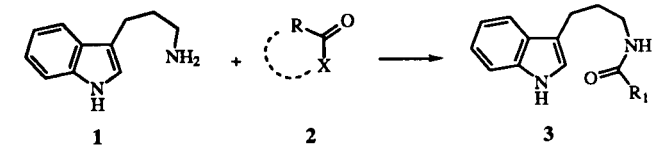
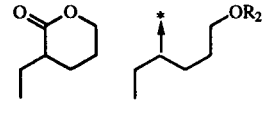
Since vincamine was discovered and proved to be an effective cerebral vasodilator, extensive research was developed to find more and more potent derivatives. The most successful one was Cavinton (vinpocetine) [2]. To synthesize a new class of analogs, our aim was to change ring C of vincamine to an azepine ring and omit ring E. Now we present the results of these investigations.

At first homotryptamine **1** and lactone **2b** were coupled, and some simple derivatives were prepared by acylation. As model compounds for further functionalization, compounds **3** were oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [3] (Scheme 1). The oxidations proceeded chemoselectively, *i.e.* the primary hydroxy group of **3b** remained intact.

Scheme 1



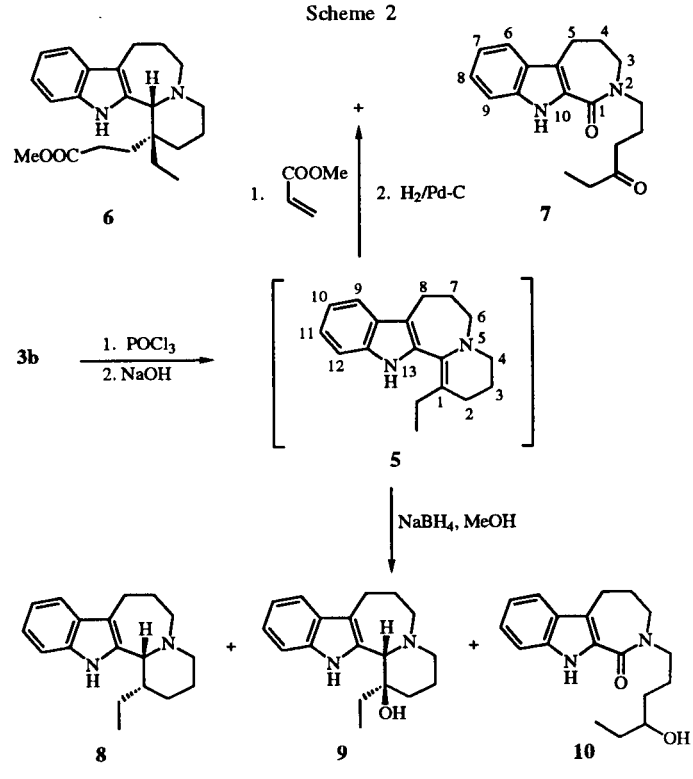
1

2	3	4	RCOX	R_1
a	a	a	Ac_2O	Me
b	b-h	b-g		

3	4	R_2
b	b	H
c	c	Ac
d	d	$ClCH_2CO$
–	e	CH_3CH_2CO
–	f	$3,4,5\text{-}(CH_3O)_3C_6H_2CO$
–	g	$4\text{-}NO_2\text{-}C_6H_4CO$
h	–	Bz

In the second step we carried out the Bischler-Napieralski cyclization from the hydroxycarboxamide **3b** (Scheme 2). Unfortunately, we could isolate neither enamine **5** nor its immonium salt. By-products **7**, **9**, and **10** provided evidence for the sensitivity of enamine **5**, therefore we used crude **5**, without isolation, immediately for further transformations. Compound **6** was obtained stereoselectively as in the course of the synthesis of vincamine [2]. However, yields and reproducibility were low in this case, therefore we focused our attention on the Pictet-Spengler cyclizations.

Scheme 2



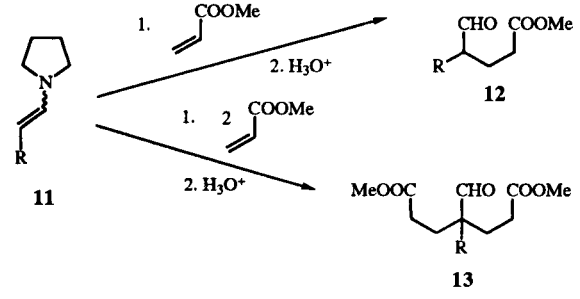
It is known from the literature that homotryptamine **1** can be condensed with levulinic esters [4-8]. We prepared formyl-esters **12** and **13** using enamine chemistry [9-10] (Scheme 3) and reacted them with homotryptamine **1** [11].

The main products of the condensation of **1** and **13** were naphtyridines **14** (Scheme 4). In addition to **14**, the acylhomotryptamine **3a** and the expected **15** and **16** were isolated as minor products.

The Pictet-Spengler reaction has long been an important procedure for the synthesis of both indole and iso-

quinoline alkaloids, and surprisingly few side-reactions have been reported. To rationalize the formation of the dimer **14** in substantial amount in this case we may assume that the formation of the seven-membered ring goes through a much higher energy barrier than in the case of six- or five-membered ring formation. Thus the imine intermediate reacts preferentially with a second molecule of homotryptamine forming the naphtyridines.

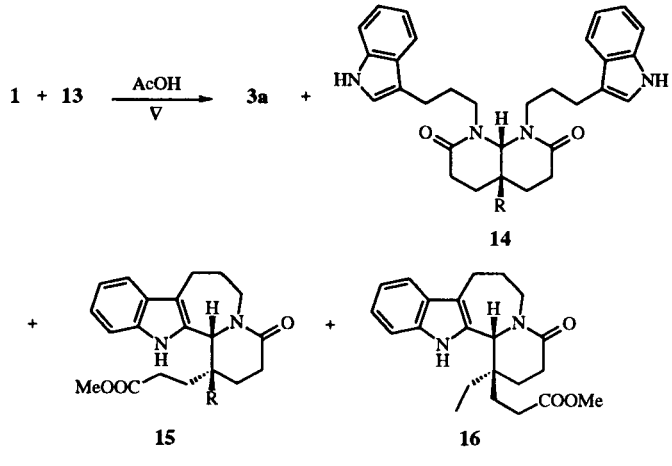
Scheme 3



11	12	13	14	15	16	17	18	19	20	21	R
a	a	a	a	a	–	a	a	a	a	–	Me
b	b	b	b	b	b	b	–	b	–	b	Et
c	c	c	c	–	–	c	c	c	–	–	n-C_5H_{11}

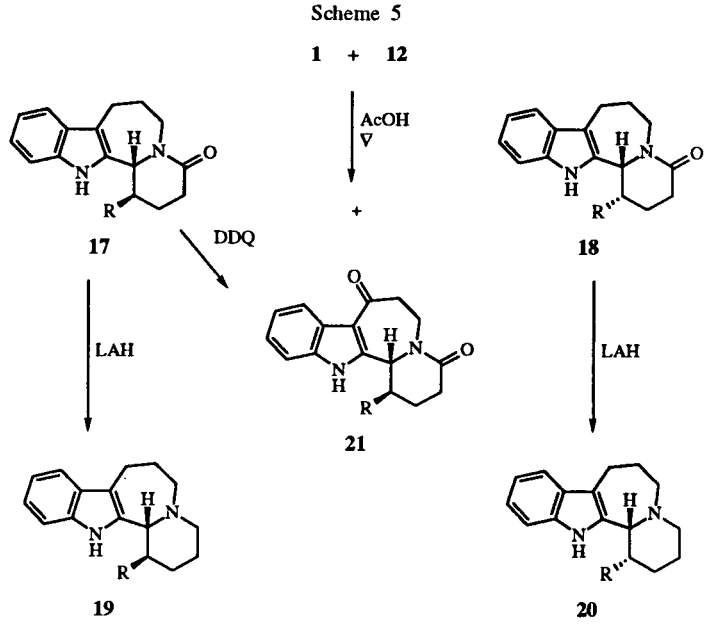
Earlier a similar side-reaction was observed by us with tryptamine when instead of the diester **13**, the corresponding monoester-monocarboxylic acid was used, but the rationalization is different [12].

Scheme 4



The Pictet-Spengler condensation of **1** and **12** proceeded smoothly and stereoselectively: isomers **17** dominated (Scheme 5). Reacting lactam **17b** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone we could functionalize the azepine ring. In contrast, with an amine such as vincamine, this oxidation failed. There is a downfield shift of about 1 ppm for the indole ring proton of position 4 in all oxo compounds **4** and **21** which suggests that the carbonyl group attached to the indole 3 position is coplanar with the ring. This is trivial in the case of the open-chain derivatives **4** but not for **21b**. In the latter case the downfield shift of the indole 4 proton is an evidence for the conformation of the azepine ring.

Scheme 5



We used for the reduction of lactams **17** and **18** lithium aluminium hydride. There is always a problem in these reductions if the product is acid-sensitive or if it is a base, because during the alkaline work-up aluminium hydroxide precipitates and adsorbs some part of the product. To circumvent this difficulty, we developed a new work-up method: the reaction is quenched with excess 40% sodium hydroxide, and the mixture which contains aluminium in the water-soluble form of sodium aluminate is extracted with tetrahydrofuran.

The resulting compounds **19** and **20** were biologically active, especially **19a** [13], concerning data will be published elsewhere.

The chemical shift values of 13b-H, C4, C6, and C13b in **6**, **8**, **9**, and **20** suggest a *trans* C/D ring annelation for these compounds. In addition, in the ir spectrum of **20a** Bohlmann-bands could be detected as well.

The similarity of proton and carbon nmr data of naphthyridine **14b** and a closely related tryptamine analog [12] reflects *cis* ring junction for the naphtyridine moiety.

EXPERIMENTAL

The ir, nmr and mass spectra were recorded on a Karl Zeiss SPECORD-75 IR, a Varian XL-100 (100.1 MHz for protons and 25.16 MHz for carbons) and an AEI MS 902 instrument respectively. Superscripts *a*, *b*, and *c* in ^{13}C-nmr spectra denote interchangeable assignments. Relative configuration is described

according to the CIP rules [14], and also see reference [15] for "l" (like) and "u" (unlike) nomenclature.

N-[3-(1*H*-Indol-3-yl)propyl]acetamide (**3a**).

1*H*-Indole-3-propanamine (**1**, 8 g, 46 mmoles) was stirred in acetic anhydride (10 ml) in a water bath at 25° for 2 hours. The mixture was allowed to stand overnight, the solvent was evaporated *in vacuo*, the residue was distributed between chloroform (50 ml) and saturated sodium hydrogen carbonate solution (50 ml). The organic phase was dried over sodium sulfate, and evaporated to dryness *in vacuo* to yield 8.54 g (86%) oil, which solidified upon standing. The product may be recrystallized from ethyl acetate, mp 97-99°; ir (potassium bromide, cm^{-1}): 3357, 3293, 1626; ^{1}H-nmr (deuteriochloroform, δ, ppm): 1.7-2.1 (m, 2H, propyl 2-H_2), 1.85 (s, 3H, CH_3), 2.78 (t, J = 7 Hz, 2H, propyl 3-H_2), 3.27 (q, J = 7 Hz, 2H, propyl 1-H_2), 5.54 (b, 1H, CONH), 6.94 (d, J = 2 Hz, 1H, indole 2-H), 7.0-7.7 (m, 4H, indole 4-7 protons), 8.25 (b, 1H, indole NH).

Anal. Calcd. for $C_{13}H_{16}N_2O$ (216.29): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.42; H, 7.24; N, 12.73.

2-Ethyl-5-hydroxy-*N*-[3-(1*H*-indol-3-yl)propyl]pentanamide (**3b**).

1*H*-Indole-3-propanamine (**1**, 72.4 g, 0.416 mole) was heated in a 12.5% chlorobenzene solution of 3-ethyltetrahydro-2*H*-pyran-2-one [2] (**2b**, 408 ml) under reflux for 4 hours. The solvent was evaporated *in vacuo*, the residue was triturated with hexane (3 x 100 ml), and recrystallized twice as follows: the crude product was dissolved in a 15-fold hot mixture of benzene and ethyl acetate (9:1), the solution was filtered, cooled to 40° and stirred at this temperature for 2 hours. The separated crystals were filtered at 5°. The mother liquor was chromatographed (column: Φ 56 x 600 mm, adsorbent: silica gel, eluent: ethyl acetate). The combined yield was 99.5 g (79%), mp 49-50°; ir (potassium bromide, cm^{-1}): 3385, 3289, 3095, 1629, 1600; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.84 (t, J = 7 Hz, 3H, CH_3), 1.1-2.1 (m, 7H), 1.89 (m, 2H, ethyl CH_2), 2.28 (s, 1H, OH), 2.78 (t, J = 7 Hz, 2H, propyl 3-H_2), 3.31 (q, J = 6.5 Hz, 2H, propyl 1-H_2), 3.55 (m, 2H, OCH_2), 5.70 (bt, J ≈ 6.5 Hz, 1H, CONH), 6.95 (d, J = 2.4 Hz, 1H, indole 2-H), 6.95-7.65 (m, 4H, indole 4-7 protons), 8.47 (b, 1H, indole NH); ms: [70 eV, 150°, m/z (%)] 302 (63) (M), 201 (1.7), 174 (3.5), 173 (2.0), 157 (100), 144 (35), 143 (8), 131 (40), 130 (58), 117 (9), 100 (7), 114.5 (3).

Anal. Calcd. for $C_{18}H_{26}N_2O_2$ (302.42): C, 71.49; H, 8.67; N, 9.26. Found: C, 71.42; H, 8.84; N, 8.97.

Procedure for the Acylation of **3b** and **4b**.

Compound **3b** or **4b** (0.01 mole) was dissolved in tetrahydrofuran (30 ml), 0.05 mole of acid chloride and 5.3 g of sodium carbonate (or equivalently 0.05 mole of acid anhydride and 10 ml of pyridine) were added, and the mixture was stirred at room temperature for 1 day. The solvent was evaporated *in vacuo*, the residue was distributed between dichloromethane (50 ml) and water (50 ml). The organic phase was dried over sodium sulfate, evaporated to dryness and crystallized from ethyl acetate-hexane.

Procedure for the Oxidation of **3a-c** and **17b**.

Substrate **3a-c** or **17b**, (0.01 mole) was dissolved in a mixture of tetrahydrofuran (144 ml) and water (16 ml), and a solution of 4,5-dichloro-3,6-dioxo-1,4-cyclohexadiene-1,2-dicarbonitrile (4.55 g, 0.02 mole in 50 ml of tetrahydrofuran) was added dropwise under an inert atmosphere at 0-10° using an ice-water bath. After the addition the mixture was stirred at 0-10° for 1 hour, the solvents were removed *in vacuo*, and the residue was distributed between ethyl acetate (50 ml) and a solution of sodium hydroxide (5%, 50 ml). The organic layer was dried over sodium sulfate, the solvent was evaporated *in vacuo* and the residue was chromatographed if necessary (column: Φ 30 x 250 mm, adsorbent: silica gel, eluent: ethyl acetate-acetone 6:4) and crystallized from ethyl acetate. By acidification of the sodium hydroxide layer and extraction with ethyl acetate one can obtain 4,5-dichloro-3,6-dihydroxyphthalonitrile almost quantitatively.

{4-{*N*-[3-(1*H*-Indol-3-yl)propyl]carbamoyl}hexyl} Acetate (**3c**).

This compound was obtained as a white crystalline powder, yield 51%, mp 68-70°; ir (potassium bromide, cm^{-1}): 3381, 3271 (NH), 1711 (COO), 1614, 1592 (CONH); ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.85 (t, J = 7 Hz, 3H, hexyl 6-H_3), 1.2-2.0 (m, 7H), 1.92 (m, 2H, hexyl 5-H_2), 1.98 (s, 3H, acetyl CH_3), 2.81 (t, J = 7 Hz, 2H, propyl 3-H_2), 3.35 (q, J = 6.5 Hz, 2H, propyl 1-H_2), 4.02 (t, J = 6.2 Hz, 2H, hexyl 1-H_2), 5.50 (bt, J ≈ 6 Hz, 1H, CONH), 6.99 (d, J = 2.4 Hz, 1H, indole 2-H), 7.0-7.65 (m, 4H, indole 4-7 protons), 8.22 (b, 1H, indole NH); ms: [70 eV, 150°, m/z (%)] 344 (41) (M), 157 (100), 144 (33.4), 131 (41), 130 (64.3).

Anal. Calcd. for $C_{20}H_{28}N_2O_3$ (344.46): C, 69.73; H, 8.19; N, 8.13. Found: C, 69.78; H, 8.27; N, 7.83.

{4-{*N*-[3-(1H-Indol-3-yl)propyl]carbamoyl}hexyl} Chloroacetate (**3d**).

This compound was obtained from **3b** as colorless prisms, yield 53%, mp 83°; ir (potassium bromide, cm^{-1}): 3390, 3288 (NH), 1754 (COO), 1630 (CONH); ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.84 (t, J = 7 Hz, 3H, Me), 1.1-2.0 (m, 7H, hexyl 2-H_2, 3-H_2, 4-H, propyl 2-H_2), 1.93 (m, 2H, hexyl 5-H_2), 2.80 (t, J = 7 Hz, 2H, propyl 3-H_2), 3.35 (q, J = 6.5 Hz, 2H, propyl 1-H_2), 3.98 (s, 2H, chloroacetate), 4.14 (t, J = 6 Hz, 2H, hexyl 1-H_2), 5.50 (bt, J = 6 Hz, 1H, CONH), 6.99 (d, J = 2.4 Hz, 1H, indole 2-H), 7.0-7.65 (m, 4H, indole 4-7 protons), 8.20 (b, 1H, indole NH).

Anal. Calcd. for $C_{20}H_{27}ClN_2O_3$ (378.90): C, 63.39; H, 7.18; Cl, 9.36; N, 7.39. Found: C, 63.47; H, 7.29; Cl, 9.15; N, 7.38.

{4-{*N*-[3-(1*H*-Indol-3-yl)propyl]carbamoyl}hexyl} Benzoate (**3h**).

This compound was obtained from **3b** as a white crystalline powder, yield 49%, mp 122°; ir (potassium bromide, cm^{-1}): 3393, 3288 (NH), 1700 (COO), 1627 (CONH); ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.85 (t, J = 7 Hz, 3H, Me), 1.2-2.1 (m, 7H, hexyl 2-H_2, 3-H_2, 4-H, propyl 2-H_2), 1.92 (m, 2H, hexyl 5-H_2), 2.80 (t, J = 7 Hz, 2H, propyl 3-H_2), 3.35 (q, J = 6.5 Hz, 2H, propyl 1-H_2), 4.30 (t, J = 6 Hz, 2H, hexyl 1-H_2), 5.50 (bt, J = 6 Hz, 1H, CONH), 6.98 (d, J = 2.4 Hz, 1H, indole 2-H), 7.0-7.7 (m, 7H, indole 4-H, benzoyl 3-5 protons), 8.04 (m, 2H, benzoyl 2-H, 6-H), 8.16 (b, 1H, indole NH).

Anal. Calcd. for $C_{25}H_{31}N_2O_3$ (407.54): C, 73.69; H, 7.67; N, 6.87. Found: C, 73.80; H, 7.51; N, 6.69.

N-[3-(1*H*-Indol-3-yl)-3-oxopropyl]acetamide (**4a**).

This compound was obtained as a white crystalline powder and yielded 56%, mp 170°; ir (potassium bromide, cm^{-1}): 3266, 3215, 3184, 3100, 1648, 1621, 1583; ^{1}H-nmr (deuterio-

chloroform + DMSO-d_6, δ, ppm): 1.87 (s, 3H, CH_3), 3.06 (t, J = 6.6 Hz, 2H, propyl 2-H_2), 3.54 (t, J = 6.6 Hz, 2H, propyl 1-H_2), 7.05-7.3 (m, 2H, indole 5, 6 protons), 7.35-7.55 (m, 1H, indole 7-H), 7.85 (bs, 2H, indole NH, amide NH), 8.07 (s, 1H, indole 2-H), 8.15-8.35 (m, 1H, indole 6-H); ms: [70 eV, 150°, m/z (%)] 230 (33) (M), 212 (1), 187 (3), 171 (27), 159 (6), 144 (100), 130 (4), 117 (13), 116 (12), 89 (11), 86 (10).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$ (230.27): C, 67.81; H, 6.13; N, 12.16. Found: C, 67.86; H, 6.40; N, 12.12.

2-Ethyl-5-hydroxy-*N*-[3-(1*H*-indol-3-yl)-3-oxopropyl]pentanamide (**4b**).

This compound was obtained as colorless prisms, yield 62%, mp 136°; ir (potassium bromide, cm^{-1}): 3215, 3300, 1627, 1600; ^{1}H-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 0.83 (t, J = 7 Hz, 3H, CH_3), 1.2-1.9 (m, 6H), 2.02 (m, 1H, 2-H), 2.63 (b, 1H, OH), 3.10 (t, J = 6 Hz, 2H, propyl 2-H_2), 3.51 (m, 2H, 5-H_2), 3.67 (q, J = 6 Hz, 2H, propyl 1-H_2), 6.82 (bt, J = 6 Hz, 1H, CONH), 7.1-7.6 (m, 3H, indole 5-7 protons), 7.96 (d, J = 3 Hz, 1H, indole 2-H), 8.25-8.45 (m, 1H, indole 4-H), 11.10 (bs, 1H indole NH); ms: [70 eV, 150°, m/z (%)] 317 (4.7), 316 (24) (M), 298 (1.3), 271 (1), 258 (4), 243 (1.8), 215 (3.5), 187 (12), 172 (27), 171 (47), 159 (9), 154 (5.7), 145 (25), 144 (100), 117 (16).

Anal. Calcd. for $C_{18}H_{24}N_2O_3$ (316.40): C, 68.33; H, 7.65; N, 8.85. Found: C, 68.27; H, 7.87; N, 8.59.

{4-{*N*-[3-(1*H*-Indol-3-yl)-3-oxopropyl]carbamoyl}hexyl} Acetate (**4c**).

Compound **4c** was prepared in two ways, by oxidation of **3c** in 67% yield and by acetylation of **4b** in 89% yield. It was a white crystalline powder in both cases, mp 108°; ir (potassium bromide, cm^{-1}): 3413, 3327, 1736, 1641, 1612; ^{1}H-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 0.84 (t, J = 7.3 Hz, 3H, hexyl 6-H_3), 1.2-1.8 (m, 6H), 1.97 (s, 3H, acetyl CH_3), 2.0 (m, 1H, hexyl 4-H), 3.11 (t, J = 6 Hz, 2H, propyl 2-H_2), 3.64 (q, J = 6 Hz, 2H, propyl 1-H_2), 3.97 (t, J = 6 Hz, 2H, hexyl 1-H_2), 7.13 (bt, J = 6 Hz, 1H, CONH), 7.15-7.30 (m, 2H, indole 5, 6 protons), 7.35-7.55 (m, 1H, indole 7-H), 8.03 (d, J = 3 Hz, 1H, indole 2-H), 8.2-8.4 (m, 1H, indole 4-H), 11.34 (bs, 1H, indole NH).

Anal. Calcd. for $C_{20}H_{26}N_2O_4$ (358.44): C, 67.02; H, 7.31; N, 7.81. Found: C, 66.99; H, 7.35; N, 7.58.

{4-{*N*-[3-(1*H*-Indol-3-yl)-3-oxopropyl]carbamoyl}hexyl} Chloroacetate (**4d**).

This compound was obtained from **4b** as a white crystalline powder and yielded 95%, mp 113°; ir (potassium bromide, cm^{-1}): 3300, 3220, 1741, 1617, 1636, 1604; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.85 (t, J = 7 Hz, 3H, hexyl 6-H_3), 1.2-1.8 (m, 6H), 1.98 (m, 1H, hexyl 4-H), 3.14 (t, J = 6 Hz, 2H, propyl 2-H_2), 3.76 (q, J = 6 Hz, 2H, propyl 1-H_2), 3.95 (s, 2H, $ClCH_2CO$), 4.07 (m, 2H, hexyl 1-H_2), 6.56 (bt, J = 6 Hz, 1H, CONH), 7.2-7.7 (m, 3H, indole 5-7 protons), 7.94 (d, J = 3 Hz, 1H, indole 2-H), 8.45-8.65 (m, 1H, indole 4-H), 10.0 (b, 1H, indole NH).

Anal. Calcd. for $C_{20}H_{25}ClN_2O_4$ (392.89): C, 61.14; H, 6.41; Cl, 9.02; N, 7.13. Found: C, 60.89; H, 6.49; Cl, 9.28; N, 6.86.

{4-{*N*-[3-(1*H*-Indol-3-yl)-3-oxopropyl]carbamoyl}hexyl} Propionate (**4e**).

This compound was obtained as a white crystalline powder, yield 76%, mp 108°; ir (potassium bromide, cm^{-1}): 3400, 3309, 3224, 1730, 1636, 1608; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.83 (t, J = 7 Hz, 3H, hexyl 6-H_3), 1.06 (t, J = 7.5 Hz, 3H, propionyl CH_3), 1.2-1.85 (m, 6H), 2.0 (m, 1H, hexyl 4-H), 2.24 (q, J = 7.5 Hz, 2H, propionyl CH_2), 3.11 (t, J = 6 Hz, 2H, propyl 2-H_2), 3.72 (t, J = 6 Hz, 2H, propyl 1-H_2), 4.00 (t, J = 6 Hz, 2H, hexyl 1-H_2), 6.51 (b, 1H, CONH), 7.2-7.55 (m, 3H, indole 5-7 protons), 7.89 (d, J = 3 Hz, 1H, indole 2-H), 8.36 (m, 1H, indole 4-H), 9.82 (b, 1H, indole NH).

Anal. Calcd. for $C_{21}H_{28}N_2O_4$ (372.47): C, 67.71; H, 7.58; N, 7.52. Found: C, 67.65; H, 7.55; N, 7.49.

{4-{*N*-[3-(1*H*-Indol-3-yl)-3-oxopropyl]carbamoyl}hexyl} 3,4,5-Trimethoxybenzoate (**4f**).

This compound was obtained as a white crystalline powder, yield 35%, mp 99°; ir (potassium bromide, cm^{-1}): 3400, 1705, 1636, 1584; ^{1}H-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 0.85 (t, J = 7 Hz, 3H, hexyl 6-H_3), 1.3-1.9 (m, 6H), 2.04 (m, 1H, hexyl 4-H), 3.11 (t, J = 6 Hz, 2H, propyl 2-H_2), 3.69 (bt, J = 6 Hz, 2H, propyl 1-H_2), 3.86 (s, 9H, OCH_3), 4.24 (t, J = 6 Hz, 2H, hexyl 1-H_2), 6.80 (b, 1H, CONH), 7.15-7.35 (m, 2H, indole 5, 6 protons), 7.28 (s, 2H, trimethoxybenzoyl 2, 6 protons), 7.35-7.50 (m, 1H, indole 7-H), 7.95 (d, J = 3 Hz, 1H, indole 2-H), 8.25-8.40 (m, 1H, indole 4-H), 10.94 (b, 1H, indole NH).

Anal. Calcd. for $C_{28}H_{34}N_2O_7$ (510.59): C, 65.87; H, 6.71; N, 5.49. Found: C, 65.57; H, 6.95; N, 5.50.

{4-{*N*-[3-(1*H*-Indol-3-yl)-3-oxopropyl]carbamoyl}hexyl} 4-Nitrobenzoate (**4g**).

This compound was obtained as light yellow prisms, yield 43%, mp 167°; ir (potassium bromide, cm^{-1}): 3400, 3300, 3209, 1706, 1624, 1600, 1513, 1266; ^{1}H-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 0.86 (t, J = 7 Hz, 3H, hexyl 6-H_3), 1.2-1.9 (m, 6H), 2.08 (m, 1H, hexyl 4-H), 3.12 (t, J = 6.5 Hz, 2H, propyl 2-H_2), 3.69 (bt, J = 6 Hz, 2H, propyl 1-H_2), 4.29 (t, J = 6 Hz, 2H, hexyl 1-H_2), 6.92 (b, 1H, CONH), 7.1-7.3 (m, 2H, indole 5, 6 protons), 7.35-7.65 (m, 1H, indole 7-H), 7.94 (d, J = 3 Hz, 1H, indole 2-H), 8.0-8.4 (m, 1H, indole 4-H), 8.11 (d, J = 9.5 Hz, 2H) and 8.23 (d, J = 9.5 Hz, 2H, nitrobenzoyl protons), 11.10 (b, 1H, indole NH).

Anal. Calcd. for $C_{25}H_{27}N_3O_6$ (465.51): C, 64.51; H, 5.85; N, 9.03. Found C, 64.28; H, 5.99; N, 9.10.

Bischler-Napieralski Cyclization of **3b**.

Hydroxycarboxamide **3b** (10 g, 33.2 mmoles) was refluxed in phosphorusoxychloride (90 ml) under argon for 12 hours, the excess of the reagent was removed *in vacuo*, and the residue was diluted with water (100 ml) and dichloromethane (100 ml). With ice-water cooling, the *p*H was adjusted to 11 with a 40% solution of sodium hydroxide. The mixture was stirred under argon for 0.5 hour at room temperature, the organic phase was separated, dried over sodium sulfate and evaporated *in vacuo* to give *ca.* 10 g of a light brown oil which contained enamine **5** and was used immediately for subsequent preparations.

Alkylation of Enamine **5**.

Enamine **5** (*ca.* 10 g) was stirred in methyl acrylate (14 ml, 15.6 mmoles) with one drop of methanol under argon for 2 days at room temperature. Excess methyl acrylate was evaporated *in vacuo*, palladium-charcoal (5%, 1 g) and dimethylformamide (50 ml) were added and the adduct was hydrogenated at room temperature and normal pressure. The calculated amount of hydrogen (0.8 l) was absorbed in 1 day. The catalyst was filtered, the

filtrate was diluted with water (100 ml), extracted with dichloromethane (3 x 50 ml), the extract was dried over sodium sulfate, the solvent was removed *in vacuo* and the residue was chromatographed (column: Φ 40 x 300 mm, overpressure: 0.2 MPa, adsorbent: Reanal Kieselgel G, eluent: toluene-chloroform-ethyl acetate 8:1:1). The first fraction (0.42 g) was crystallized as the hydrochloride salt from ether-methanol and yielded 0.34 g (**6**, 2.6% from **3b**), the second one (1.23 g) was crystallized from ethyl acetate-hexane to give 0.43 g (**7**, 4.3% from **3b**).

Methyl {1-Ethyl-1,2,3,4,6,7,8,13b-octahydro-13*H*-pyrido-[1',2':1,2]azepino[3,4-*b*]indole-1-propionate} (1,13b l) (**6**).

The hydrochloride salt was a white crystalline powder, mp (salt) 160°; ir (salt, potassium bromide, cm^{-1}): 3427 (NH), 2400-2760 (NH), 1717 (COO); ^{1}H-nmr (base, deuteriochloroform, δ, ppm): 1.00 (t, J = 7 Hz, 3H, C-Me), 1.1-3.3 (m, 18H), 3.36 (s, 1H, 13b-H), 3.58 (s, 3H, O-Me), 6.9-7.6 (m, 4H, 9-12 protons), 7.70 (b, 1H, indole NH); ^{13}C-nmr (base, deuteriochloroform, δ, ppm): 8.2 (ethyl CH_3), 18.8 (8), 22.4 (3), 27.3 (propionate α), 28.8 (7^a), 29.0 (propionate β^a) 29.7 (ethyl CH_2), 31.9 (2), 41.1 (1), 51.4 (OMe), 54.2 (6), 57.8 (4), 72.9 (13b), 110.1 (12), 113.4 (8a), 117.8 (9), 118.9 (10), 121.0 (11), 127.9 (8b), 133.5 (13a), 134.9 (12a), 174.9 (CO); ms: [base, 70 eV, 150°, m/z (%)] 354 (31.6) (M), 281 (100), 198 (14.7), 184 (17.8), 156 (13.8), 130 (5.6).

Anal. Calcd. for $C_{22}H_{30}N_2O_2$•HCl (390.96): C, 67.58; H, 7.99; Cl, 9.07; N, 7.16. Found: C, 67.31; H, 7.77; Cl, 8.98; N, 7.42.

1,2,3,4,5,10-Hexahydro-2-(4-oxohexyl)azepino[3,4-*b*]indol-1-one (**7**).

This compound was obtained as a white crystalline powder, mp 146°, ir (potassium bromide, cm^{-1}): 3288 (NH), 1712 (CO), 1605 (CON); ^{1}H-nmr (deuteriochloroform, δ, ppm): 1.03 (t, J = 7.5 Hz, 3H, Me), 1.75-2.3 (m, 4H, 4-H_2, hexyl 2-H_2), 2.42 (q, J = 7.5 Hz, 2H, hexyl 5-H_2), 2.50 (t, J = 7 Hz, 2H, hexyl 3-H_2), 3.08 (t, J = 6.5 Hz, 2H, 5-H_2), 3.5-3.7 (m, 4H, 3-H_2, hexyl 1-H_2) 7.0-7.4 (m, 4H, 6-9 protons), 9.27 (b, 1H, indole NH); ^{13}C-nmr (deuteriochloroform, δ, ppm): 7.8 (Me), 22.0 (hexyl 2), 25.3 (5), 26.9 (4), 36.0 (hexyl 5), 39.2 (hexyl 3), 48.6 (hexyl 1^a), 49.1 (3^a), 111.8 (9), 117.6 (5a), 118.5 (6), 120.1 (7), 124.7 (8), 127.4 ($5b^b$), 128.0 ($10a^b$), 135.9 (9a), 163.5 (1), 210.8 (hexyl 4); ms: [70 eV, 150°, m/z (%)] 298 (100) (M), 241 (27), 227 (43), 226 (56), 213 (51), 201 (5), 200 (18), 185 (17), 183 (10), 171 (10), 170 (31), 158 (32), 157 (10), 156 (18), 144 (17), 143 (15), 130 (18), 129 (10), 128 (10).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$ (298.39): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.39; H, 7.56; N, 9.47.

Reduction of Enamine **5**.

Enamine **5** (*ca.* 10 g) was dissolved in the mixture of methanol (80 ml) and dichloromethane (20 ml) under argon, sodium borohydride (2 g) was added, and the mixture was stirred at room temperature for 1 hour. The solvents were removed *in vacuo*, and the residue was distributed between water (100 ml) and dichloromethane (100 ml). The organic layer was washed with brine (50 ml), dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed (column: Φ 40 x 300 mm, overpressure: 0.2 MPa, adsorbent: Reanal Kieselgel G, eluent: 500 ml of toluene-chloroform-ethyl acetate 8:1:1, 250 ml of toluene-ethyl acetate 1:1, then ethyl acetate). Three fractions were collected: 0.47 g, 0.69 g, and 0.73 g respectively. The first one was crystallized as the hydrochloride salt from ether-methanol to yield 0.26 g (2.4%) of **9**. The second one in the same manner gave 0.49 g (4.8%) of **8** as the hydrochloride salt. The third one was crystallized from carbon tetrachloride and yielded 0.52 g (5.2%) of **10**.

1-Ethyl-1,2,3,4,6,7,8,13b-octahydro-13*H*-pyrido[1',2':1,2]-azepino[3,4-*b*]indole (1,13b u) (**8**).

The hydrochloride salt was a white crystalline powder, mp (salt) 290°; ir (salt, potassium bromide, cm^{-1}): 3300 (NH), 2400-2764 (NH); ^{1}H-nmr (base, deuteriochloroform, δ, ppm): 0.72 (t, J = 7 Hz, 3H, Me), 1.0-3.3 (m, 15H), 3.70 (b [J ≈ 2.0-2.5 Hz], 1H, 13b-H), 7.0-7.6 (m, 4H, 9-12 protons), 7.7 (b, 1H, indole NH); ^{13}C-nmr (base, deuteriochloroform, δ, ppm): 12.3 (Me), 19.2 (8^a), 19.7 (ethyl $CH_2{}^a$), 22.2 (3), 26.4 (2), 28.0 (7), 43.0 (1), 55.8 (6), 57.0 (4), 69.8 (13b), 110.3 (12), 112.2 (8a), 117.6 (9), 118.8 (10), 120.7 (11), 128.2 (8b), 135.1 (13a), 138.9 (12a); ms: [base, 70 eV, 150°, m/z (%)] 268 (100) (M), 253 (26.9), 239 (10.0), 198 (54.7), 184 (31.6), 156 (17.8), 130 (5.6), 36 (17.8).

Anal. Calcd. for $C_{18}H_{24}N_2$•HCl (304.87): C, 70.92; H, 8.27; Cl, 11.63; N, 9.19. Found: C, 70.65; H, 7.98; Cl, 11.82; N, 9.21.

1-Ethyl-1,2,3,4,6,7,8,13b-octahydro-13*H*-pyrido[1',2':1,2]-azepino[3,4-*b*]-indol-1-ol (1,13b u) (**9**).

The hydrochloride salt was a white crystalline powder, mp (salt) 215°; ir (salt, potassium bromide, cm^{-1}): 3331, 3241 (OH, NH), 2700, 2623, 2574 (NH); ^{1}H-nmr (base, deuteriochloroform, δ, ppm): 0.75 (t, J = 7 Hz, 3H, Me), 0.9-3.3 (m, 15H), 3.48 (s, 1H, 13b-H), 7.0-7.6 (m, 4H, 9-12 protons), 8.4 (b, 1H, indole NH); ^{13}C-nmr (base, deuteriochloroform, δ, ppm): 6.5 (Me), 19.0 (8), 23.3 (3), 25.2 (ethyl CH_2), 28.2 (7), 33.9 (2), 54.9 (6), 56.2 (4), 74.8 (1), 75.3 (13b), 110.5 (12), 112.9 (8a), 117.6 (9), 118.8 (10), 120.9 (11), 128.0 (8b), 133.5 (13a), 135.2 (12a); ms: [base, 70 eV, 150°, m/z (%)] 284 (35.5) (M), 212 (6.3), 199 (8.6), 185 (100), 169 (9.4), 156 (18.6), 128 (18.8).

Anal. Calcd. for $C_{18}H_{24}N_2O$•HCl (320.86): C, 67.38; H, 7.85; Cl, 11.05; N, 8.73. Found: C, 67.57; H, 7.60; Cl, 10.93; N, 8.92.

1,2,3,4,5,10-Hexahydro-2-(4-hydroxyhexyl)azepino[3,4-*b*]indol-1-one (**10**).

This compound was obtained as a white crystalline powder, mp 143°; ir (potassium bromide, cm^{-1}): 3340 (OH), 3281 (NH), 1595 (CON); ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.94 (t, J = 7 Hz, 3H, Me), 1.3-2.3 (m, 9H, 4-H_2, hexyl 2-H_2, hexyl 3-H_2, hexyl 5-H_2, OH), 3.06 (t, J = 6.5 Hz, 2H, 5-H_2), 3.4-3.9 (m, 5H, 3-H_2, hexyl 1-H_2, 4-H), 7.0-7.7 (m, 4H, 6-9 protons), 9.37 (b, 1H, indole NH); ^{13}C-nmr (deuteriochloroform, δ, ppm): 10.0 (Me), 24.3 (hexyl 2), 25.2 (5), 26.8 (4), 30.4 (hexyl 5), 33.7 (hexyl 3), 49.2 (hexyl 1^a), 49.5 (3^a), 72.8 (hexyl 4), 111.7 (9), 117.6 (5a), 119.5 (6), 120.0 (7), 124.7 (8), 127.4 ($5b^b$), 128.0 ($10a^b$), 135.7 (9a), 163.4 (1); ms: [70 eV, 150°, m/z (%)] 300 (96) (M), 282 (6), 271 (26), 241 (10), 228 (10), 227 (10), 213 (100), 201 (26), 200 (50), 185 (16), 183 (10), 171 (10), 170 (32), 158 (32), 157 (14), 156 (18), 144 (18), 143 (16), 130 (26), 129 (16), 128 (10).

Anal. Calcd. for $C_{18}H_{24}N_2O_2$ (300.40): C, 71.97; H, 8.05; N, 9.32. Found: C, 72.19; H, 7.75; N, 9.48.

Methyl (4-Formylnonanoate) (**12c**).

Freshly prepared enamine **11c** (16.7 g, 0.1 mole) was added dropwise under argon to the solution of methyl acrylate (9.0 ml, 0.1 mole) in abs. methanol (75 ml) at 0-5°. After the addition the

reactants were stirred at room temperature for 5 hours, then acetic acid (9 ml, 0.15 mole) and water (45 ml) were added and the mixture was refluxed for 8 hours. After cooling, it was diluted with water (400 ml), and extracted with dichloromethane (4 x 50 ml). The extract was washed with water (150 ml), neutralized with a saturated solution of sodium hydrogen carbonate, dried over sodium sulfate and fractionated at reduced pressure, bp 80-96°/27 Pa, 13.4 g (67%); ir (film, cm^{-1}): 2717, 1727.

Anal. Calcd. for $C_{11}H_{20}O_3$ (200.28): C, 65.97; H, 10.07. Found: C, 66.14; H, 9.93.

General Procedure for the Preparation of **13**.

Freshly prepared enamine **11** (0.1 mole) was added dropwise under argon to a solution of methyl acrylate (20 ml, 0.22 mole) in abs. methanol (75 ml) at 0-5°. After stirring at room temperature for 5 hours, the mixture was boiled for 48 hours. Acetic acid (9 ml, 0.15 mole) and water (45 ml) were added and the boiling was continued for 8 hours. The mixture was cooled, diluted with water (400 ml), and extracted with dichloromethane (4 x 50 ml). The extract was washed with water (150 ml), neutralized with a saturated solution of sodium hydrogen carbonate, dried over sodium sulfate and fractionated at reduced pressure.

Dimethyl (4-Formyl-4-methylheptanedioate) (**13a**).

This compound was obtained as a colorless oil, yield 37%, bp 110-116°/27 Pa; ir (film, cm^{-1}): 2700, 1730.

Anal. Calcd. for $C_{11}H_{18}O_5$ (230.27): C, 57.38; H, 7.88. Found: C, 57.21; H, 7.62.

Dimethyl (4-Formyl-4-pentylheptanedioate) (**13c**).

This compound was obtained as a colorless oil, yield 46%, bp 140-150°/27 Pa; ir (film, cm^{-1}): 2700, 1730.

Anal. Calcd. for $C_{15}H_{26}O_5$ (286.38): C, 62.91; H, 9.15. Found: C, 62.84; H, 9.37.

Condensation of **1** and **13**.

Homotryptamine **1** (17.4 g, 0.1 mole) and **13** (0.2 mole) were heated under reflux in acetic acid (50 ml) for 24 hours. The cooled mixture was diluted with water (200 ml), extracted with dichloromethane (4 x 50 ml), the extract was washed with water (100 ml), neutralized with a saturated solution of sodium hydrogen carbonate, and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue crystallized from ethyl acetate to give **14**. The mother liquor was concentrated and chromatographed (column: Φ 56 x 500 mm, adsorbent: Reanal Kieselgel G, overpressure: 0.2 MPa, eluent: ethyl acetate-acetone 6:4). Products were eluted in the order **16**, **15**, and **14**. Compound **3a** was obtained as a by-product in the reactions of **13a** and **13b** in 4% and 13% yields, respectively. On the other hand, we could not isolate **15c**, **16a**, and **16c**.

Hexahydro-1,8-bis[3-(1*H*-indol-3-yl)propyl]-4a-methyl-1*H*,3*H*-1,8-naphthyridine-2,7-dione (**14a**).

This compound was obtained as colorless prisms, the combined yield was 28%, mp 214°; ir (potassium bromide, cm^{-1}): 3300, 1627; ^{1}H-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 1.05 (s, 3H, Me), 1.2-3.4 (m, 18H), 3.66 (m, 2H, 3-H_{eq}, 6-H_{eq}), 4.41 (s, 1H, 8a-H), 6.94 (d, J = 2 Hz, 2H, indole 2 protons), 7.0-7.9 (m, 8H, indole 4-7 protons), 10.26 (bs, 2H, indole NH protons).

Anal. Calcd. for $C_{31}H_{36}N_4O_2$ (496.66): C, 74.97; H, 7.31; N, 11.28. Found: C, 74.71; H, 7.37; N, 11.18.

4a-Ethylhexahydro-1,8-bis[3-(1*H*-indol-3-yl)propyl]-1*H*,3*H*-1,8-naphthyridine-2,7-dione (**14b**).

This compound was obtained as colorless prisms, the combined yield was 18%, mp 214°; ir (potassium bromide, cm^{-1}): 3300, 1631; ^{1}H-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 0.81 (t, J = 7 Hz, 3H, Me), 1.38 (q, J = 7 Hz, 2H, ethyl CH_2), 1.4-3.1 (m, 18H), 3.66 (m, 2H, 3-H_{eq}, 6-H_{eq}), 4.32 (s, 1H, 8a-H), 6.95 (d, J = 2 Hz, indole 2 protons), 6.80-7.80 (m, 8H, indole 4-7 protons), 9.66 (bs, 2H, indole NH protons); ^{13}C-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 7.4 (Me), 22.4 (2C, propyl 3), 27.2 (2C, 4, 5[a]), 27.9 (2C, propyl 2[a]), 29.2 (2C, 3, 6), 31.9 (ethyl CH_2), 36.4 (4a), 46.0 (2C, propyl 1), 78.2 (8a), 111.4 (2C, indole 7), 118.4 (2C, indole 4), 118.5 (2C, indole 6[b]), 121.2 (2C, indole 5[b]), 121.8 (2C, indole 2[b]), 127.2 (2C, indole 3a), 136.4 (2C, indole 7a), 170.9 (2C, 2, 7); ms: [70 eV, 230°, m/z (%)] 510 (46) (M), 492 (0.95), 481 (1.8), 393 (4.8), 380 (4.5), 354 (6.4), 338 (1.3), 295 (2.0), 282 (5.7), 281 (8.0), 263 (1.5), 235 (2.8), 228 (5.3), 226 (14), 185 (8.8), 171 (8.2), 165 (7.2), 157 (100), 156 (67), 144 (20), 143 (12), 131 (20), 130 (55).

Anal. Calcd. for $C_{32}H_{38}N_4O_2$ (510.69): C, 75.26; H, 7.50; N, 10.97. Found: C, 75.43; H, 7.76; N, 10.69.

Hexahydro-1,8-bis[3-(1*H*-indol-3-yl)propyl]-4a-pentyl-1*H*,3*H*-1,8-naphthyridine-2,7-dione (**14c**).

This compound was obtained as colorless prisms, the combined yield was 24%, mp 162°/193°; ir (potassium bromide, cm^{-1}): 3300, 1628; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.85 (t, J = 6 Hz, 3H, Me), 1.0-3.0 (m, 26H), 3.66 (m, 2H, 3-H_{eq}, 6-H_{eq}), 4.22 (s, 1H, 8a-H), 6.87 (d, J = 3 Hz, 2H, indole 2 protons), 7.0-7.7 (m, 8H, indole 4-7 protons), 7.98 (bs, 2H, indole NH protons).

Anal. Calcd. for $C_{35}H_{44}N_4O_2$ (552.77): C, 76.05; H, 8.02; N, 10.14. Found: C, 75.88; H, 8.03; N, 9.86.

Methyl {1-Methyl-1,2,3,4,6,7,8,13b-octahydro-4-oxo-13*H*-pyrido[1',2':1,2]azepino[3,4-*b*]indole-1-propionate (1,13b l) (**15a**).

This compound was obtained as a white crystalline powder, yield 0.1%, mp 220°; ir (potassium bromide, cm^{-1}): 3400, 3313 (NH), 1717 (COO), 1635 (CON); ^{1}H-nmr (deuteriochloroform, δ, ppm): 1.21 (s, 3H, 1-Me), 1.4-3.0 (m, 13 H), 3.62 (s, 3H, OMe), 4.33 (m, 1H, 6-H_{eq}), 4.57 (s, 1H, 13b-H), 7.1-7.7 (m, 4H, 9-12 protons), 7.68 (bs, 1H, indole NH).

Anal. Calcd. for $C_{21}H_{26}N_2O_3$ (354.45): C, 71.16; H, 7.39; N, 7.90. Found: C, 70.91; H, 7.44; N, 8.18.

Methyl {1-Ethyl-1,2,3,4,6,7,8,13b-octahydro-4-oxo-13*H*-pyrido[1',2':1,2]azepino[3,4-*b*]indole-1-propionate} (1,13b l) (**15b**).

This compound was obtained as a white crystalline powder, yield 6.5%, mp 210°; ir (potassium bromide, cm^{-1}): 3416, 3395 (NH), 1727 (COO), 1613 (CON); ^{1}H-nmr (deuteriochloroform, δ, ppm): 1.06 (t, J = 7.4 Hz, 3H, ethyl CH_3), 1.4-3.0 (m, 15H), 3.62 (s, 3H, OMe), 4.34 (m, 1H, 6-H_{eq}), 4.69 (s, 1H, 13b-H), 7.0-7.7 (m, 4H, 9-12 protons), 8.10 (bs, 1H, indole NH); ^{13}C-nmr (deuteriochloroform, δ, ppm): 8.0 (ethyl CH_3), 18.3 (8), 25.5 (7[a]), 26.9 (ethyl CH_2[a]) 27.2 (2[a]), 28.2 (propionate α[b]), 28.4 (3[b]), 28.4 (propionate β[b]), 39.6 (1), 45.3 (6), 51.8 (OMe), 66.6 (13b), 110.8 (12), 113.7 (8a), 118.0 (9), 119.4 (10), 121.9 (11), 127.6 (8b), 130.4 (13a), 135.7 (12a), 169.9 (4), 174.0 (COO); ms: [70 eV, 160°, m/z (%)] 368 (76) (M), 367 (2.6), 366 (2.8), 353 (0.6), 339 (2.6), 338 (3.3), 337 (9.6), 336 (7.8), 308 (3), 307

(4), 295 (11), 281 (2.6), 280 (2.6), 279 (3), 272 (2.7), 265 (4.6), 226 (85), 198 (6.7), 185 (46), 184 (85), 183 (100), 170 (5.8), 169 (12), 168 (21), 167 (42), 157 (19), 156 (38), 143 (6), 130 (15).

Anal. Calcd. for $C_{22}H_{28}N_2O_3$ (368.48): C, 71.71; H, 7.66; N, 7.60. Found: C, 71.56; H, 7.40; N, 7.73.

Methyl {1-Ethyl-1,2,3,4,6,7,8,13b-octahydro-4-oxo-13*H*-pyrido[1',2':1,2]azepino[3,4-*b*]indole-1-propionate} (1,13b u) (**16b**).

This compound was obtained as an amorphous substance, yield 7%; ir (film, cm^{-1}): 3400, 1731, 1615; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.71 (t, J = 7 Hz, 3H, ethyl CH_3), 0.8-3.2 (m, 15H), 3.79 (s, 3H, OMe), 4.24 (m, 1H, 6-H_{eq}), 4.69 (s, 1H, 13b-H), 7.0-7.65 (m, 9-12 protons), 9.37 (b, 1H, indole NH); ^{13}C-nmr (deuteriochloroform, δ, ppm): 7.1 (ethyl CH_3), 18.1 (8), 23.4 (ethyl CH_2[a]), 25.5 (7[a]), 26.1 (2[a]), 28.0 (propionate α[b]), 28.3 (propionate β[b]), 29.6 (3[b]), 39.7 (1), 44.9 (6), 52.4 (OMe), 66.1 (13b), 110.9 (12), 112.7 (8a), 117.8 (9), 119.2 (10), 121.6 (11), 127.5 (8b), 130.3 (13a), 135.5 (12a), 169.9 (4), 176.0 (COO).

Anal. Calcd. for $C_{22}H_{28}N_2O_3$ (368.48): C, 71.71; H, 7.66; N, 7.60. Found: C, 72.04; H, 7.91; N, 7.37.

Pictet-Spengler Condensation of **1** and **12**.

Homotryptamine **1** (17.4 g, 0.1 mole) and a formyl-ester **12** (0.1 mole) were heated under reflux in acetic acid (100 ml) for 24 hours, then the mixture was cooled, diluted with water (400 ml), and extracted with dichloromethane (4 x 100 ml). The extract was washed with water (100 ml), neutralized with a saturated solution of sodium hydrogen carbonate, and dried over sodium sulfate. The solvent was removed at reduced pressure, and a first crop of **17** was crystallized from ethyl acetate. The mother liquor was chromatographed (column: Φ 50 x 500 mm, adsorbent: Reanal Kieselgel G, overpressure: 0.2 MPa, eluent: ethyl acetate-acetone 6:4) to give a second crop of **17** and isomer **18** except the case of **18b** which we could not isolate.

1-Ethyl-1,2,3,4,6,7,8,13b-octahydro-13*H*-pyrido[1',2':1,2]-azepino[3,4-*b*]indol-4-one (1,13b l) (**17b**).

This compound was obtained as a white crystalline powder, the combined yield was 39%, mp 181°; ir (potassium bromide, cm^{-1}): 3413, 3205, 3179, 1613; ^{1}H-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 1.05 (t, J = 7.3 Hz, 3H, CH_3), 1.4-3.1 (m, 12H), 4.53 (ddd, J_1 = 13.0 Hz, J_2 = 7.0 Hz, J_3 = 4.0 Hz, 1H, 6-H_{eq}), 4.59 (d, J = 3 Hz, 1H, 13b-H), 6.85-7.55 (m, 4H, 9-12 protons), 10.27 (bs, 1H, indole NH); ^{13}C-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 11.6 (CH_3), 19.3 (8), 21.6 (2), 23.5 (ethyl CH_2), 26.6 (7), 28.3 (3), 38.0 (1), 46.5 (6), 63.4 (13b), 110.9 (12), 112.2 (8a), 117.4 (9), 118.5 (10), 120.9 (11), 127.8 (8b), 135.0 (13a), 135.5 (12a), 169.5 (4); ms: [70 eV, 160°, m/z (%)] 283 (22), 282 (100) (M), 281 (8), 267 (1), 265 (1), 253 (7), 239 (1.7), 226 (32), 210 (3.7), 198 (7), 185 (23), 184 (85), 183 (80), 169 (17), 168 (20), 167 (28), 157 (23), 156 (32), 155 (10), 154 (10), 143 (6), 141 (6.5), 130 (17).

Anal. Calcd. for $C_{18}H_{22}N_2O$ (282.39): C, 76.56; H, 7.85; N, 9.92. Found: C, 76.40; H, 8.14; N, 9.68.

1,2,3,4,6,7,8,13b-Octahydro-1-pentyl-13*H*-pyrido[1',2',1,2]-azepino[3,4-*b*]indol-4-one (1,13b l) (**17c**).

This compound was obtained as a white crystalline powder, the combined yield was 51%, mp 180°; ir (potassium bromide, cm^{-1}): 3253, 1604; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.92 (t, J = 6 Hz, 3H, Me), 1.0-3.0 (m, 18H), 4.57 (d, J = 3 Hz, 1H, 13b-H), 4.64 (m, 1H, 6-H_{eq}), 7.0-7.6 (m, 4H, 7-12 protons), 8.26 (bs, 1H, indole NH).

Anal. Calcd. for $C_{21}H_{28}N_2O$ (324.47): C, 77.73; H, 8.70; N, 8.63. Found: C, 77.56; H, 8.96; N, 8.65.

1-Methyl-1,2,3,4,6,7,8,13b-octahydro-13*H*-pyrido[1',2':1,2]-azepino[3,4-*b*]indole-4-one (1,13b u) (**18a**).

This compound was obtained as a white crystalline powder, yield 3.3%, mp 231°; ir (potassium bromide, cm^{-1}): 3231, 1605; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.93 (d, J = 7 Hz, 3H, Me), 1.5-3.1 (m, 10H), 4.40 (m, 1H, 6-H_{eq}), 4.90 (d, J = 5 Hz, 1H, 13b-H), 7.0-7.65 (m, 4H, 9-12 protons), 8.11 (bs, 1H, indole NH); ^{13}C-nmr (deuteriochloroform, δ, ppm): 12.8 (Me), 17.9 (8), 25.8 (7), 28.1 (2[a]), 28.2 (3[a]), 32.8 (1), 44.7 (6), 54.1 (13b), 110.7 (8a), 111.2 (12), 117.8 (9), 119.1 (10), 121.4 (11), 127.8 (8b), 132.5 (13a), 135.7 (12a), 170.4 (4).

Anal. Calcd. for $C_{17}H_{20}N_2O$ (268.36): C, 76.09; H, 7.51; N, 10.44. Found: C, 75.96; H, 7.39; N, 10.45.

1,2,3,4,6,7,8,13b-Octahydro-1-pentyl-13*H*-pyrido[1',2':1,2]-azepino[3,4-*b*]indol-4-one (1,13b u) (**18c**).

This compound was obtained as a white crystalline powder, yield 3%, mp 173°; ir (potassium bromide, cm^{-1}): 3236, 3207, 1628; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.80 (t, J = 6 Hz, 3H, Me), 0.9-3.1 (m, 18H), 4.41 (m, 1H, 6-H_{eq}), 4.93 (d, J = 4.5 Hz, 1H, 13b-H), 7.0-7.7 (m, 4H, 7-12 protons), 8.26 (bs, 1H, indole NH).

Anal. Calcd. for $C_{21}H_{28}N_2O$ (324.47): C, 77.73; H, 8.70; N, 8.63. Found: C, 77.51; H, 8.99; N, 8.55.

Reduction of Lactams **17** and **18**.

Lithium aluminium hydride (3.67 g) was suspended in dry tetrahydrofuran (130 ml), a lactam **17** or **18** (0.05 mole) was added in small portions and the resulting mixture was boiled under argon for 4 hours. The reaction was quenched carefully with a solution of sodium hydroxide (40 m/m %, 250 ml) using an ice-water bath. The organic layer was separated and the alkaline phase was extracted with tetrahydrofuran (2 x 50 ml). The combined organic phase was dried over sodium sulfate, tetrahydrofuran was removed *in vacuo*, and the residue was chromatographed (column: Φ 40 x 300 mm, adsorbent: Reanal Kieselgel G, overpressure 0.2 MPa, eluent: ethyl acetate-acetone 6:4). The products were crystallized from methanol as a base or from methanol-ethyl acetate as the hydrochloride salt.

1-Ethyl-1,2,3,4,6,7,8,13b-octahydro-13*H*-pyrido[1',2':1,2]-azepino[3,4-*b*]indole (1,13b l) (**19b**).

This compound was obtained as a white crystalline powder, yield 64%, mp 116°; ir (potassium bromide, cm^{-1}): 3400; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.90 (t, J = 7 Hz, 3H, Me), 1.10-2.20 (m, 9H, 1-H, 2-H_2, 3-H_2, 7-H_2, ethyl CH_2), 2.40-3.20 (m, 6H, 4-H_2, 6-H_2, 8-H_2), 3.84 (d, J = 4.5 Hz, 1H, 13b-H), 6.90-7.65 (m, 4H, 9-12 protons), 7.80 (b, 1H, indole NH).

Anal. Calcd. for $C_{18}H_{24}N_2$ (268.41): C, 80.55; H, 9.01; N, 10.44. Found: C, 80.75; H, 8.86; N, 10.31.

1,2,3,4,6,7,8,13b-Octahydro-1-pentyl-13*H*-pyrido[1',2':1,2]-azepino[3,4-*b*]indole (1,13b l) (**19c**).

This compound was obtained as a white crystalline powder, yield 58%, mp 100°; ir (potassium bromide, cm^{-1}): 3400; ^{1}H-nmr (deuteriochloroform, δ, ppm): 0.86 (t, J = 6 Hz, 3H, Me), 1.2-2.3

(m, 15H), 2.4-3.6 (m, 6H, 4-H_2, 6-H_2, 8-H_2), 3.85 (d, J = 5 Hz, 1H, 13b-H), 6.90-7.65 (m, 4H, 9-12 protons), 7.81 (b, 1H, indole NH).

Anal. Calcd. for $C_{21}H_{30}N_2$ (310.42): C, 81.24; H, 9.74; N, 9.02. Found: C, 80.92; H, 9.97; N, 9.04.

1-Methyl-1,2,3,4,6,7,8,13b-octahydro-13*H*-pyrido[1',2':1,2]-azepino[3,4-*b*]indole (1,13b u) (**20a**).

This compound was isolated as the hydrochloride salt in the form of colorless prisms, yield 56%, mp (salt) 247°; ir (salt, potassium bromide, cm^{-1}): 3400, 3200 (NH), 2500-2800 (NH); (base, 10% solution in chloroform, cm^{-1}): 3453 (NH), 2773, 2744, 2700, 2683, 2667 (Bohlmann bands); ^{1}H-nmr (base, deuteriochloroform, δ, ppm): 0.89 (d, J = 7 Hz, 3H, Me), 1.15-3.35 (m, 13H), 3.54 (d, J = 3 Hz, 1H, 13b-H), 6.9-7.6 (m, 4H, 9-12 protons), 7.65 (b, 1H, indole NH).

Anal. Calcd. for $C_{17}H_{22}N_2$•HCl (290.84): C, 70.21; H, 7.97; Cl, 12.19; N, 9.63. Found: C, 69.99; H, 8.14; Cl, 12.38; N, 9.66.

1-Ethyl-1,2,3,4,6,7,8,13b-octahydro-13*H*-pyrido[1',2':1,2]-azepino[3,4-*b*]indole-4,8-dione (1,13b l) (**21b**).

From the oxidation of **17b**, 37% of **21b** and 41% of **17b** were isolated, therefore the corrected yield was 63%, mp 281°; ir (potassium bromide, cm^{-1}): 3453, 3236, 1627, 1607; ^{1}H-nmr (deuteriochloroform + DMSO-d_6, δ, ppm): 1.09 (t, J = 7 Hz, 3H, CH_3), 1.4-3.5 (m, 10H), 4.34 (m, 1H, 6-H_{eq}), 4.90 (bs, 1H, 13b-H), 7.0-7.5 (m, 3H, 10-12 protons), 8.32 (m, 1H, 9-H), 11.37 (bs, 1H, indole NH); ms: [70 eV, 180°, m/z (%)] 297 (19.4), 296 (100) (M), 268 (8.2), 267 (8.9), 240 (10.0), 239 (10.6), 212 (5.9), 199 (20.0), 198 (84.6), 197 (9.3), 171 (13.1), 170 (34.7), 169 (12.9), 144 (5.5), 143 (15.3), 55 (5.0).

Anal. Calcd. for $C_{18}H_{20}N_2O_2$ (296.37): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.69; H, 6.96; N, 9.58.

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