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Synthesis of *Vinca* Alkaloids and Related Compounds, XIII[1]

Syntheses Starting from 2-(Ethoxycarbonyl)tryptamine

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The Pictet-Spengler reaction of 2-(ethoxycarbonyl)tryptamine (**1**) with aldehyde esters **2** and **3** leads to unexpected products (**4a** and **9a/10a**, resp.). The structures of the new compounds were elucidated by spectroscopic and chemical means.

Synthese von *Vinca*-Alkaloiden und verwandten Verbindungen, XIII[1]

Synthesen ausgehend von 2-(Ethoxycarbonyl)tryptamin

Die Pictet-Spengler-Reaktion von 2-(Ethoxycarbonyl)tryptamin (**1**) mit den Aldehydestern **2** und **3** ergab unerwartete Produkte (**4a** bzw. **9a/10a**). Die Konstitution der neuen Verbindungen wurde durch spektroskopische und chemische Methoden aufgeklärt.

Earlier we developed a simple method for the preparation of 2-(ethoxycarbonyl)tryptamine (**1**)[2]. Tryptamine obtained by hydrolysis and decarboxylation of this compound can be readily used for the synthesis of *Vinca* alkaloids[3]. For the sake of comparison it seemed to be of interest to investigate the reaction of **1** with both the aldehyde diester **2**, used, e. g., in *Kuehne*'s vincamine synthesis[4], and the related monoester **3**.

For the preparation of the aldehyde esters first the reaction of various enamines of n-butyraldehyde with acrylic ester was investigated. It is well known that, depending on the reaction conditions, the respective pyrrolidine enamine can react with either one[5] or two[4] mol equivalents of acrylic ester. The instability of the pyrrolidine enamine prompted us to study also the behaviour of other enamines. It was found that the much more stable morpholine enamine reacts even with an excess of acrylic ester exclusively with one mol equivalent of the partner, and yields after hydrolysis the aldehyde **3**, thus providing a convenient route for the preparation of the monoester aldehyde.

The Pictet-Spengler type reaction of tryptamines substituted in position C-2, as e. g. of 2,3-dihydro-2-oxotryptamine[6] often results in "spiro" coupling at position C-3.

However, compound **1** behaved differently with aldehydes. On boiling the hydrochloride of **1** in glacial acetic acid with monoester **3**, the enamide **4a** was isolated in about 55% yield. The Schiff's base formed in the first step does not attack the indole ring, probably because of steric hindrance caused by the C-2 ester group.

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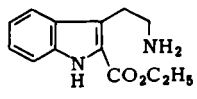
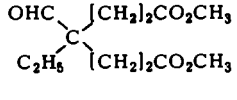
In complete agreement with structure **4a**, ^1H and ^{13}C NMR data attest the presence of the unchanged 2-(ethoxycarbonyl)indole moiety. The increased ^1H chemical shift for the side chain methylene protons adjacent to the nitrogen (3.76 ppm) indicates *N*-acylation and the carbon-13 resonance at 167.5 ppm is readily assignable to the C-2′ amide carbonyl group. The partial structure $-CH=C(Et)-$ within the six-membered lactam ring is evidenced by the ^1H multiplet at 5.56 ppm exhibiting only allylic couplings, by the ethyl group resonances, and the olefinic carbon signals.



1



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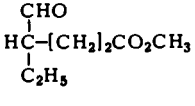

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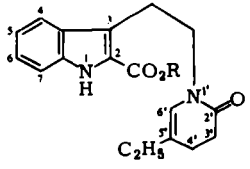
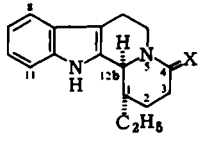
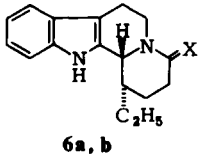


4	R
a	C_2H_5
b	H

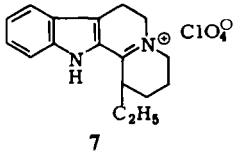


5a, b

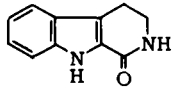
5,6	X
a	O
b	H_2



6a, b



7



8

The ester **4a** can be hydrolyzed in 90% yield to give the acid **4b**, which, on boiling with glacial acetic acid, undergoes decarboxylation accompanied by ring closure. Thus, the 1:2 mixture of the stereoisomeric lactams **5a** and **6a** has been obtained in 60% yield. The lactams can be separated by fractionated crystallization. The same products were obtained in a ratio of 1:1 in a yield of 88% by heating the aldehyde **3** in acetic acid with tryptamine.

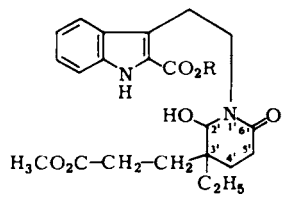
Structural assignment of **5a** and **6a** was accomplished by NMR spectroscopy. Supporting evidence for the ring closure is provided by the ^1H multiplets at 4.66 and 4.96 ppm, respectively, attributable to the angular proton 12b-H. The relatively large chemical shifts are consistent with methine groups being adjacent to an amide nitrogen. Of further corroborative value is the significant downfield shift of the signal due to the equatorial C-6 methylene protons (5.20 and 5.31 ppm in **5a** and **6a**, respectively) as

compared with that of their axial partner (approx. 3.3 ppm), a finding consistent with the former protons assuming – by virtue of the ring closure – a position coplanar with the amide carbonyl group.

According to well-known stereochemical relationships[7], the chemical shift values of the ethyl side chain methylene carbons [25.19 (**5a**) and 17.49 ppm (**6a**)] suggest that the ethyl group assumes equatorial orientation with respect to ring D in **5a** and axial orientation in **6a** which settles the relative configuration of 12b-H and C-1 side chain as *cis* in **5a** and *trans* in **6a**.

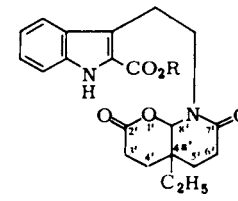
By reacting the mixture of the lactams **5a** and **6a** with phosphorus pentasulfide, then with Raney-Ni, they were converted into products **5b** and **6b**. These were oxidized with sodium dichromate to give the already known[3] iminium salt **7**, easy to utilize in later steps of the vincamine synthesis.

The tryptamine ester **1** was then reacted with the diester aldehyde **2**. Schiff base formation with the sterically more crowded aldehyde proceeded at a slower rate as compared to **3**, and thus, competitive isocarbostyril[8] formation (**8**) substantially increases (45%). By acidification of the alkali-soluble fraction a mixture of two substances (**9a** and **10a**) was obtained, which was treated without separation with diazomethane to yield the methyl esters **9b** (36%) and **10b** (5%). The structures of **9b** and **10b** were supported by their NMR spectra and by chemical conversion.

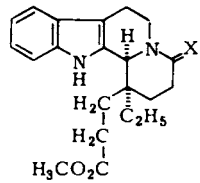


9a, b

9, 10	R
a	H
b	CH_3

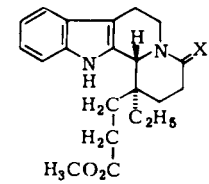


10a, b



11a, b

11,12	X
a	O
b	H_2



12a, b

Spectral comparison reveals that carbon atoms of the tryptamine moiety show practically the same chemical shifts in **9b** and **10b** as in **4a**. The only exception is due to the difference in the alkoxycarbonyl side chains at C-2. According to NMR data, the $\Delta^{5',6'}$ double bond of **4a** has disappeared in **9b** and **10b**. **9b** features an additional methoxycarbonyl group which, according to chemical shift values (carbonyl carbon at 173.71, OMe protons at 3.68 ppm), is attached to an alkyl group. Spectral analysis showed the latter to consist of a CH_2CH_2 sequence attached to C-3' (quaternary carbon

at 37.95 ppm). The presence of the 2'-OH group in **9b** follows from the occurrence in the ^1H NMR spectrum of an "isolated" proton signal at 4.46 ppm exhibiting 5 Hz splitting with the (exchangeable with D_2O) OH proton. The absence of 2'-H (OH) and of methoxycarbonyl signals in the spectra of **10b**, along with overall spectral similarities to **9b**, suggest the formation of a lactone ring. A more detailed spectral comparison lends support to this conclusion. Thus chemical shift of 8a'-H in **10b** increases by 0.54 ppm with respect to its value in **9b** (2'-H) which is accompanied by a 8.7 ppm increase in the chemical shift of C-8a' *vs.* that of C-2' in **9b**, whereas carbon C-4a' becomes more shielded (by 4.1 ppm) in **10b**. Also, in accord with expectation, the lactone carbonyl carbon resonance appears at higher fields (170.22 ppm) than its methoxycarbonyl counterpart.

If the original mixture of **9a** and **10a** was heated in acetic acid and finally the free carboxyl group was esterified in the system methanol/sulfuric acid, 1:1 mixture of the two esters (**11a** and **12a**), described already by *Kuehne*[4], was obtained in fair yield. The *cis*-ester **11a** was an intermediate of vincamine synthesis. The two products were converted in the known way[4] to the esters **11b** and **12b**, respectively.

In view of the fact that our conclusions regarding the stereo-structure of **11a** and **12a** were just the opposite of that of *Kuehne*[4], X-ray diffraction was invoked as a final proof (*A. Kálmán* et al.). The investigation of **11b** unambigously proved that the melting points assigned to the stereo-structures given by *Kuehne* were confounded.

The following conclusions can be drawn from the above experiments:

a) tryptamines with an ester group in position C-2 are less inclined to form C-3 "spiro" compounds under the conditions of the Pictet-Spengler reaction;

b) though compounds of type **1** can be converted into intermediates useful for the synthesis of vincamine, their previous conversion into tryptamine gives a higher yield.

Experimental Part

IR spectra: Spectromom 2000. – ^1H NMR spectra: Perkin-Elmer R12 (60 MHz). The ^1H and ^{13}C NMR spectra were obtained at 100.1 and 25.16 MHz, respectively, in Fourier transform mode, using a Varian XL-100-15 NMR spectrometer. The chemical shift values are reported with respect to internal TMS. Assignment of carbon-13 NMR spectra is based on standard FT NMR procedures. – MS: JEOL-JMS-01-SG-2 (70 eV). – Melting points and boiling points were uncorrected.

Methyl 4-formylhexanoate (**3**)

a) To a solution of 1-morpholino-1-butene[9] (28.20 g, 200 mmol) in 150 ml of dry acetonitrile a solution of methyl acrylate (21.50 g, 250 mmol) in 50 ml of dry acetonitril was added dropwise at 0°C. The mixture was refluxed for 36 h. Next, a mixture of 12 ml glacial acetic acid and 80 ml water was added, and the mixture was refluxed for further 8 h. After cooling, the solution was diluted with water and extracted with ether. The organic phase was washed free of acid and dried over magnesium sulfate. The solvent was distilled off in vacuo and the residue was fractionated in vacuo. Yield 20.00 g (63.2%), b. p. 96 – 98°C/10 Torr (Lit.[5] 95 – 98°C/10 Torr), $n_D^{25} = 1.4320$. – IR (film): 1730 cm^{-1} (ester and aldehyde C=O). – ^1H NMR (60 MHz, $CDCl_3$): δ = 0.93 (3H, t, CH_3), 3.63 (3H, s, CH_3O), 9.66 (1H, s, aldehyde H).

b) To a solution of methyl acrylate (76.25 g, 885 mmol) in 300 ml absol. methanol 1-morpholino-1-butene[9] (51.00 g, 360 mmol) was added dropwise at 0 °C under argon atmosphere. The solution was kept standing for 4 h at room temperature, then refluxed for 40 h. Next, 22 ml of glacial acetic acid and 100 ml of water were added and refluxing was continued for further 10 h. After partial evaporation of the methanol, the residue was worked up as described in point a). Yield 33.0 g (58%), b. p. 100 – 104 °C/15 Torr, n_D^{25} = 1.4330.

Ethyl 3-[2-(5-ethyl-1,2,3,4-tetrahydro-2-oxo-1-pyridinyl)ethyl]-2-indolecarboxylate (**4a**)

A solution of **1** · HCl (10.00 g, 31.7 mmol) and **3** (6.00 g, 37.9 mmol) in 100 ml of glacial acetic acid was refluxed for 24 h. The solvent was evaporated in vacuo. The residue was dissolved in a mixture of 100 ml water and 80 ml dichloromethane, and the solution was alkalified with 40% sodium hydroxide solution to pH 8. The organic part was dried over magnesium sulfate, and the solvent was evaporated in vacuo. The residue was crystallized from methanol/water. Yield 5.90 g (55%), m. p. 120 – 121 °C. – IR (KBr): 3150 (NH), 1705 (ester C=O), 1640 cm^{-1} (amide C=O and C=CH). – ^{1}H NMR (100.1 MHz, $CDCl_3$): δ = 0.84 (3H, t, *J* = 7.3 Hz, 5'-ethyl CH_3), 1.44 (3H, t, *J* = 7 Hz, ester CH_3), 1.88 (2H, q, *J* = 7.3 Hz, 5'-ethyl CH_2), 2.06 (2H, t, *J* = 8 Hz, 3'-H_2), 2.44 (2H, m, *J* = 7, 9, and 1.8 Hz, 4'-H_2), 3.38 (2H, m, 3-CH_2), 3.76 (2H, m, NCH_2), 4.45 (2H, q, *J* = 7 Hz, ester OCH_2), 5.56 (1H, m, 6'-H), 7.0 – 7.8 (4H, m, aromatic H), 8.94 (1H, br, s, NH). – ^{13}C NMR ([D_6]DMSO): δ = 12.08 (5'-ethyl CH_3), 14.25 (ester CH_3), 23.66 (CH_2-4', -3'), 26.14 (5'-ethyl CH_2), 30.90 (C-3'), 46.27 (NCH_2), 60.24 (ester OCH_2), 112.49 (C-7), 119.50 (C-4), 119.70 (C-5'), 119.79 (C-3), 120.15 (C-5), 123.79 (C-2), 123.88 (C-6') 124.80 (C-6), 127.72 (C-3a), 136.50 (C-7a), 161.84 (ester CO), 167.49 (C-2'). – MS: *m/e* (%) = 340 (21.0), 295 (0.58), 267 (0.29), 251 (0.34), 243 (0.60), 215 (100), 202 (4.10), 186 (1.80), 169 (20.0), 138 (31.0), 115 (3.40), 84 (10.0), 41 (7.3).

$C_{20}H_{24}N_2O_3$ (340.4) Calcd. C 70.56 H 7.11 N 8.23 Found C 70.28 H 7.10 N 8.40

3-[2-(5-Ethyl-1,2,3,4-tetrahydro-2-oxo-1-pyridinyl)ethyl]-2-indolecarboxylic acid: (**4b**): The solution of **4a** (3.00 g, 8.81 mmol) in 2 N NaOH (50 ml) was refluxed for 6.5 h. The white precipitate separating on cooling was dissolved by adding 400 ml of water, and the solution was filtered. The filtrate was acidified with glacial acetic acid to pH 5. The white crystals which separated were filtered off, washed with cold water and dried. Yield 2.50 g (91%), m. p. 198 – 200 °C (foaming), m. p. 201 – 202 °C (from methanol). – IR (KBr): 3190 (NH), 1680, 1650 cm^{-1} (broad) (acid and amide C=O, C=CH).

$C_{18}H_{20}N_2O_3$ (312.4) Calcd. C 69.20 H 6.45 N 8.97 Found C 69.09 H 6.31 N 9.34

1α-Ethyl-2,3,6,7,12,12bα-hexahydroindolo[2,3-a]quinolizin-4(1H)-one (**5a**) *and 1α-ethyl-2,3,6,7,12,12bβ-hexahydroindolo[2,3-a]quinolizin-4(1H)-one* (**6a**)

a) **4b** (0.30 g, 0.96 mmol) was refluxed in 10 ml of glacial acetic acid for 24 h. After cooling, the reaction mixture was poured on 50 ml of water, and the solution was alkalified with 40% sodium hydroxide solution to pH 10, then extracted with dichloromethane. The organic phase was dried over magnesium sulfate, and the solvent was distilled off in vacuo. The residue was fractionally crystallized from ethyl acetate. Yield 0.050 g (19%) of **5a**, m. p. 213 – 215 °C. – IR (KBr): 3340 (NH), 1630 cm^{-1} (C=O). – ^{1}H NMR (100.1 MHz, [D_5]pyridine): δ = 0.90 (3H, t, *J* = 7.2 Hz, CH_3), 1.30 – 1.95 (4H, m, ethyl CH_2, 2-H_2), 2.10 – 3.35 (6H, m, 3-H_2, 1-H, 6-H_{ax}, 7-H_2), 4.66 (1H, m, 12b-H), 5.20 (1H, m, 6-H_{eq}), 7.1 – 7.6 (4H, m, aromatic H), 10.93 (1H, br, s, NH). – ^{13}C NMR ([D_5]pyridine): δ = 11.73 (CH_3), 21.31 (C-7), 22.52 (C-2), 25.19 (ethyl CH_2), 29.50 (C-3), 37.36 (C-1), 43.08 (C-6), 60.70 (C-12b), 109.90 (C-7a), 111.94 (C-11), 118.35 (C-8), 119.54 (C-9), 121.81 (C-10), 128.07 (C-7b), 135.58 (C-12a), 137.33 (C-11a). – MS: *m/e* (%) = 268

(57.8), 267 (9.3), 239 (16.2), 212 (18.8), 211 (12.7), 169 (100), 168 (19.3), 167 (14.0), 143 (13.2), 142 (11.1), 114 (19.4), 77 (7.8), 41 (18.4).

$C_{17}H_{20}N_2O$ (268.3) Calcd. C 76.08 H 7.51 N 10.44 Found C 76.15 H 7.68 N 10.44

When the mother liquor was concentrated to 1/3 of its volume, 0.10 g (39%) of **6a** separated. M. p. 240 – 242 °C. – IR (KBr): 3200 (NH), 1615 cm^{-1} C=O). – ^1H NMR (100.1 MHz, [D_5]pyridine): δ = 0.65 (3H, t, *J* = 7.2 Hz, CH_3), 1.10 (2H, m, ethyl CH_2), 4.96 (1H, dt, *J* = 3.5 and 1.7 Hz, 12b-H), 5.31 (1H, m, 6-H_{eq}), 7.1 – 7.6 (4H, m, aromatic H), 11.10 (1H, br, s, NH). – ^{13}C NMR ([D_5]pyridine): δ = 11.33 (CH_3), 17.49 (ethyl CH_2), 21.27 (C-7), 21.85 (C-2), 28.03 (C-3), 37.51 (C-1), 39.81 (C-6), 58.68 (C-12b), 110.00 (C-7a), 111.77 (C-11), 118.35 (C-8), 119.38 (C-9), 121.72 (C-10), 127.45 (C-7b), 133.15 (C-12a), 137.69 (C-11a), 169.87 (C-4). – MS: *m/e* (%) = 268 (77.9), 267 (13.0), 239 (23.4), 212 (21.4), 211 (17.8), 198 (7.0), 170 (24.0), 169 (100), 168 (69.0), 143 (10.8), 142 (8.2), 114 (12.8), 77 (4.2), 41 (8.0).

b) Tryptamine (9.60 g, 60.0 mol) and **3** (9.80 g, 62.0 mmol) were refluxed for 40 h in 100 ml of glacial acetic acid. Work-up as described in a) yielded 7.20 g (45%) of **5a**, m. p. 214 – 215 °C, and 7.00 g (43.5%) of **6a**, m. p. 240 – 242 °C.

1-Ethyl-1,2,3,4,7,12-hexahydro-6H-indolo[2,3-a]quinolizin-5-ium perchlorate (**7**): A mixture of **5a** and **6a** (1.10 g, 429 mmol) and phosphorus pentasulfide (0.95 g, 429 mmol) was stirred in 50 ml of tetrahydrofuran at room temperatur under argon atmosphere for 2 h. After filtration Raney-Ni catalyst (10 g) washed with tetrahydrofuran was added to the filtrate. The mixture was stirred under argon atmosphere for 3 h, allowed to stand overnight, then refluxed for 30 h. After filtering the solvent was evaporated in vacuo, and the residual oil was crystallized from methanol/water. Yield 0.70 g (92%) of **5b** and **6b**, m. p. 80 – 83 °C.

A mixture of **5b** and **6b** (0.80 g, 3.15 mmol) was dissolved in 15 ml of glacial acetic acid, and a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (1.20 g, 4.02 mmol) in 10 ml of glacial acetic acid was added. The mixture was kept standing for 2 days at room temperature. After diluting with 50 ml of water, magnesium perchlorate (1.60 g, 7.20 mmol) was added. A few hours later a yellow, crystalline salt separated. Yield 0.35 g (32%), m. p. 175 – 177 °C. After recrystallization from methanol, m. p. 177 – 178 °C. The salt obtained in this way agreed in every respect with the product prepared earlier[3].

2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-1-one (**8**): **1** · HCl (2.00 g, 6.35 mmol) was refluxed in 20 ml of glacial acetic acid for 72 h, and the solvent was then evaporated in vacuo. The residue was dissolved in dichloromethane and the solution was washed with 1 N HCl. The organic phase was washed with water and dried with magnesium sulfate. The solvent was evaporated and the solid residue crystallized from ethyl acetate. Yield 0.42 g (36%), m. p. 188 – 190 °C (Lit.[8] 183 – 185 °C). – IR (KBr): 3200 (indole NH), 1640 cm^{-1} (C=O). – ^1H NMR (60 MHz, $CDCl_3$): δ = 2.85 – 3.96 (4H, m, CH_2), 6.32 – 7.78 (5H, m, aromatic and indole H).

$C_{11}H_{10}N_2O$ (186.2) Calcd. C 70.94 H 5.41 N 15.04 Found C 70.92 H 5.60 N 15.07

Methyl 3-{2-[3-ethyl-2-hydroxy-3-(2-methoxycarbonylethyl)-6-oxo-1-piperidinyl]ethyl}-2-indolecarboxylate (**9b**) *and methyl 3-{2-[octahydro-2,7-dioxo-2H-pyrano[2,3-b]pyridine-8-yl]ethyl}-2-indolecarboxylate* (**10b**): The solution of **1** · HCl (4.00 g, 12.7 mmol) and **2** (4.40 g, 18.1 mmol) in 40 ml of glacial acetic acid was refluxed under argon atmosphere for 120 h. The residue was dissolved in 100 ml of water, the solution alkalified with 40% sodium hydroxide solution to pH 10 and extracted with ether. The ether phase was dried with magnesium sulfate, and the solvent was distilled off in vacuo. The residue was crystallized from ethyl acetate. Yield 1.00 g (47%) **8**, m. p. 189 – 190 °C.

The alkaline aqueous solution was clarified by heating with active carbon, then acidified under ice cooling with conc. hydrochlorid acid to pH 2. The white powderlike precipitate was filtered off, washed with water, and dried. Weight: 2.45 g (**9a** and **10a**). The raw acid mixture was suspended in 100 ml of dioxane. On adding ethereal diazomethane solution, the solid phase completely dissolved. The solid residue obtained by the evaporation was purified by fractional crystallization from ethyl acetate. Yield 2.00 g (36.5%) **9b**, m. p. 177 – 178 °C. – IR (KBr): 3200 (NH and OH), 1727 (aromatic ester C = O), 1702 (aliphatic ester C = O), 1612 cm^{-1} (amid C = O). – ^1H NMR (100.1 MHz, $CDCl_3$): δ = 0.76 (3 H, t, *J* = 7 Hz, ethyl CH_3), 3.67 (1 H, d, *J* = 5 Hz, exchangeable with D_2O, OH), 3.68 (3 H, s, $CH_2CO_2CH_3$), 3.97 (3 H, s, 2-CO_2CH_3), 4.46 (1 H, dd, *J* = 5 and 1.2 Hz, 2'-H), 7.1 – 7.9 (4 H, m, aromatic H), 8.79 (1 H, br, s, NH). – ^{13}C NMR ([D_6]DMSO + $CDCl_3$, 4:1): δ = 6.97 (ethyl CH_3), 21.95 (ethyl CH_2), 23.04 (C-4'), 23.76 (3-CH_2), 27.55 (3'-CH_2), 28.16* ($CH_2CO_2CH_3$), 28.65* (C-5') (* assignments may be reversed), 37.95 (C-3'), 46.22 (NCH_2), 51.30 ($CH_2CO_2CH_3$), 51.55 (2-CO_2CH_3), 84.86 (C-2'), 112.52 (C-7), 119.61 (C-4), 120.31 (C-3), 120.42 (C-5), 123.28 (C-2), 125.02 (C-6), 127.55 (C-3a), 136.49 (C-7a), 162.23 (2-CO), 169.01 (C-6'), 173.71 ($CH_2CO_2CH_3$). – MS: *m/e* (%) = 430 (0.5), 412 (0.2), 398 (3.0), 367 (0.5), 326 (0.8), 210 (1.2), 201 (100), 188 (4.5), 168 (22), 156 (8.4), 138 (4.0).

$C_{23}H_{30}N_2O_6$ (430.5) Calcd. C 64.16 H 7.02 N 6.50 Found C 63.96 H 6.87 N 6.73

On concentration of the mother liquor to 1/3 of its volume, 0.25 g (4.9%) **10b** precipitates. M. p. 175 – 177 °C. – IR (KBr): 3210 (NH), 1745 (lactone C = O), 1693 (ester C = O), 1628 cm^{-1} (amide C = O). – ^1H NMR (100.1 MHz, $CDCl_3$): δ = 0.78 (3 H, t, *J* = 7 Hz, ethyl CH_3), 3.96 (3 H, s, CO_2CH_3), 5.00 (1 H, d, *J* = 1.6 Hz, 8a'-H), 7.1 – 7.9 (4 H, m, aromatic H), 8.83 (1 H, br, s, NH). – ^{13}C NMR ($CDCl_3$ + [D_6]DMSO, 4:1): δ = 6.86 (ethyl CH_3), 23.17 (ethyl CH_2), 23.75 (3-CH_2), 26.32* (C-5'), 26.79* (C-4'), 27.71* (C-3'), 28.32* (C-6') (* assignments may be reversed), 33.85 (C-4a'), 47.59 (NCH_2), 51.36 (OCH_3), 93.60 (C-8a'), 112.52 (C-7), 119.68 (C-4), 120.07 (C-3), 120.30 (C-5), 123.48 (C-2), 124.98 (C-6), 127.75 (C-3a), 136.60 (C-7a), 162.29 (ester CO), 169.39 (C-7'), 170.22 (C-2'). – MS: *m/e* (%) = 398 (2.8), 367 (0.4), 326 (0.5), 210 (1.0), 201 (100), 188 (4.8), 169 (25), 156 (9.1), 138 (4.4).

$C_{22}H_{26}N_2O_5$ (398.4) Calcd. C 66.31 H 6.57 N 7.03 Found C 66.07 H 6.43 N 7.03

Methyl 1α-ethyl-1,2,3,4,6,7,12,12bα-octahydro-4-oxoindolo[2,3-a]quinolizine-1-propanoate (**11a**) *and methyl 1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydro-4-oxoindolo[2,3-a]quinolizine-1-propanoate* (**12a**): 0.50 g of raw acid mixture of **9a** + **10a** was refluxed in glacial acetic acid for 20 h. Next, glacial acetic acid was evaporated, the residue was dissolved in a mixture of 20 ml absol. methanol and 0.05 ml conc. sulfuric acid, and refluxed for 2 h. After cooling, 1 ml of pyridine was added to the reaction mixture, which was then poured on water and extracted with dichloromethane. The organic phase was washed with water and dried with magnesium sulfate. Evaporation of the solvent in vacuo yields an oily residue, 0.45 g. This was separated by preparative thin-layer chromatography on 20 × 20 cm Kieselgel 60 $PF_{254+366}$ adsorbent of 1.5 mm layer thickness with benzene/methanol (14:1.5). The pure substances were eluted from the adsorbent with dichloromethane/methanol (10:1). The solvent was evaporated in vacuo and the residue was crystallized from ethyl acetate. Substance with lower R_f value (**11a**): yield 0.20 g, m. p. 195 – 196 °C. – IR (KBr): 3300 (NH), 1722 (ester C = O), 1610 cm^{-1} (amide C = O). – ^1H NMR (100.1 MHz, [D_5]pyridine): δ = 0.97 (3 H, t, *J* = 7.5 Hz, ethyl CH_3), 3.42 (3 H, s, CO_2CH_3), 4.85 (1 H, br, s, 12b-H), 5.26 (1 H, m, 6-H_{eq}), 7.05 – 7.65 (4 H, m, aromatic H), 10.39 (1 H, br, s, NH). – ^{13}C NMR ([D_5]pyridine): δ = 8.43 (ethyl CH_3), 21.48 (C-7), 27.92 (1-CH_2, C-2), 28.39 (ethyl CH_2), 29.60 (CH_2CO_2R, C-3), 39.41 (C-1), 41.03 (C-6), 51.32 (OCH_3), 60.56 (C-12b), 111.97 (C-11), 112.64 (C-7a), 118.40 (C-8), 119.58 (C-9), 122.02 (C-10), 127.19 (C-7b), 131.86 (C-12a), 137.87 (C-11a), 170.12 (C-4), 173.84 (ester CO). – MS: *m/e* (%) = 354 (40.3), 323 (3.8), 281

(2.8), 212 (36.1), 211 (13.6), 171 (34.1), 169 (100), 168 (55.8), 143 (8.5), 142 (6.9), 115 (8.0), 55 (8.2), 41 (11.8), 18 (13.4).

$C_{21}H_{26}N_2O_3$ (354.4) Calcd. C 71.15 H 7.39 N 7.90 **11a**: Found C 70.94 H 7.33 N 8.12
12a: Found C 71.13 H 7.38 N 8.25

Substance of higher R_f value (**12a**): yield 0.20 g, m. p. 202 – 203 °C. – IR (KBr): 3250 (NH), 1731 (ester C=O), 1620 cm^{-1} (amide C=O). – ^1H NMR (100.1 MHz, [D_5]pyridine): δ = 0.59 (3H, t, J = 7.5 Hz, ethyl CH_3), 3.60 (3H, s, CO_2CH_3), 4.85 (1H, t, $J \approx$ 1.2 Hz, 12b-H), 5.27 (1H, m, 6-H_{eq}), 7.1 – 7.7 (4H, m, aromatic H), 10.47 (1H, br, s, NH). – ^{13}C NMR ([D_5]pyridine): δ = 7.45 (ethyl CH_3), 21.56 (C-7), 25.14 (ethyl CH_2), 27.57 (C-2), 28.77 (1-CH_2), 29.61 (C-3), 31.50 (CH_2CO_2R), 39.51 (C-1), 41.14 (C-6), 51.62 (OCH_3), 61.00 (C-12b), 111.89 (C-11), 112.90 (C-7a), 118.35 (C-8), 119.68 (C-9), 122.06 (C-10), 127.34 (C-7b), 132.10 (C-12a), 137.78 (C-11a), 170.05 (C-4), 174.44 (ester CO). – MS: *m/e* (%) = 354 (34.7), 212 (26.9), 211 (10.9), 170 (35.5), 169 (100), 168 (59.5), 143 (9.3), 142 (6.9), 115 (8.9), 55 (13.2), 43 (68.3), 41 (17.8), 18 (39.2).

Methyl 1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine-1-propanoate (**11b**): **11a** (1.00 g, 2.93 mmol) was converted into **11b** by the method described by *Kuehne*[4]. Yield 0.45 g (45%), m. p. 144 – 145 °C (Lit.[4] 149 – 150 °C). – IR (KBr): 3348 (NH), 2860 – 2703 (Bohlmann bands), 1718 cm^{-1} (ester C=O). – ^1H NMR (100.1 MHz, $CDCl_3$ + [D_6]DMSO, 4:1): δ = 1.09 (3H, t, J = 7.4 Hz, ethyl CH_3), 3.30 (1H, br. s, 12b-H), 3.50 (3H, s, CO_2CH_3), 6.9 – 7.5 (4H, m, aromatic H), 9.08 (1H, br, s, NH). – ^{13}C NMR ($CDCl_3$): δ = 7.92 (ethyl CH_3), 21.93* (C-7), 22.02* (C-3) (* assignments may be reversed), 28.59 (C-2), 28.69 (1-CH_2), 30.77 (ethyl CH_2), 32.55 (CH_2CO_2R), 39.38 (C-1), 51.29 (OCH_3), 54.09 (C-6), 56.76 (C-4), 66.47 (C-12b), 110.73 (C-11), 111.87 (C-7a), 117.82 (C-8), 119.24 (C-9), 121.37 (C-10), 126.96 (C-7b), 133.34 (C-12a), 136.17 (C-11a), 174.61 (ester CO). – MS: *m/e* (%) = 340 (63.7), 339 (61.4), 325 (9.6), 309 (6.9), 268 (21.2), 267 (100), 198 (6.9), 197 (22.2), 185 (12.4), 184 (6.5), 171 (6.9), 170 (30.1), 169 (20.8), 156 (6.8), 55 (6.2).

Methyl 1α-ethyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-a]quinolizine-1-propanoate (**12b**) was obtained from **12a** (1.00 g, 2.93 mmol) by the method described by *Kuehne*[4]. Yield 0.40 g (40%), m. p. 151 – 152 °C (Lit.[4] 144 – 145 °C). – IR (KBr): 3310 (NH), 2908 – 2712 (Bohlmann bands), 1716 cm^{-1} (ester C=O). – ^1H NMR (100.1 MHz, $CDCl_3$): δ = 0.67 (3H, t, J = 7.5 Hz, ethyl CH_3), 3.33 (1H, t, $J \approx$ 1.5 Hz, 12b-H), 3.80 (3H, s, CO_2CH_3), 6.95 – 7.55 (4H, m, aromatic H), 8.80 (1H, br, s, NH). – ^{13}C NMR ($CDCl_3$): δ = 7.21 (ethyl CH_3), 22.15* (C-7), 22.19* (C-3) (* assignments may be reversed), 25.41 (ester CH_2), 28.26 (C-2), 32.20 (1-CH_2), 33.10 (CH_2CO_2R), 39.57 (C-1), 52.07 (OCH_3), 54.10 (C-6), 56.95 (C-4), 66.46 (C-12b), 110.92 (C-11), 111.84 (C-7a), 117.71 (C-8), 119.11 (C-9), 121.29 (C-10), 126.83 (C-7b), 133.11 (C-12a), 136.47 (C-11a), 175.69 (ester CO).

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