

TILIVALLINE, A NEW PYRROLO[2,1-*c*][1,4] BENZODIAZEPINE METABOLITE FROM *KLEBSIELLA*¹

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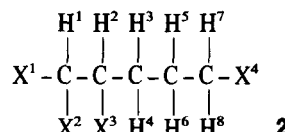
Abstract—From *Klebsiella pneumoniae* (+)(11S, 11aS) - 1,2,3,10,11,11a - hexahydro - 9 - hydroxy - 11 - (3' - indolyl) - 5H - pyrrolo[2,1-*c*][1,4]benzodiazepin - 5 - one (**1**) has been isolated for which the name tilivalline is suggested. Structure elucidation and synthesis are reported.

In the course of our investigations of the secondary metabolites of *Klebsiella pneumoniae* var. *oxytoca*² a new structural type, (+)(11S, 11aS) - 1,2,3,10,11,11a - hexahydro - 9 - hydroxy - 11 - (3' - indolyl) - 5H - pyrrolo[2,1-*c*][1,4] benzodiazepin - 5 - one (**1**) could be isolated for which the name tilivalline is suggested. Structure elucidation and synthesis will be reported here.

The elemental composition of **1** has been determined mass spectroscopically by exact mass measurement as C₂₀H₁₉N₃O₂. Characteristic features of the fragmentation pattern³ are ions at *m/z* 89, 90, 117 and 130 typical for indole derivatives CH-monosubstituted in the heterocyclic part.⁴ Treatment with D₂O indicates the presence of 3 exchangeable hydrogen atoms.

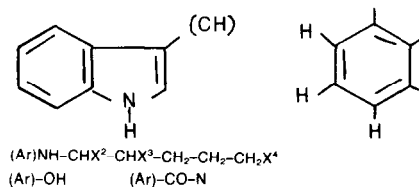
In the ¹H-NMR spectrum (Table 1) the following structural details can be recognized: (a) 2 broad signals at 9.1 and 10.5 ppm (1H each) which disappear upon addition of CD₃OD. The third exchangeable H (*v. MS* data) apparently gives a signal too broad to be recognized. (b) 8 protons in the aromatic region which—as demonstrated by Eu shift and partial decoupling experiments—comprise (i) a system of 3 vicinal H (7.5, br. d, 8 Hz; 6.6, t, 8 Hz; 7.0, br. d, 8 Hz) (ii) a system of 4 vicinal H (7.6, br. d, 8 Hz; 7.2, br. t, 8 Hz; 7.0, br. t, 8 Hz; 7.5, br. d, 8 Hz) apparently belonging to the indole benzene ring and (iii) a 1-H singlet (7.40 ppm) which suggests substitution of the indole ring at C-3 (3-methyl indole shows a signal at 7.00 ppm, 2-methyl indole at 6.14 ppm;⁵ for other alkyl indoles similar differences in the chemical shifts of the α- and β-protons have been observed).⁶ (c) 8 protons in the aliphatic region (which, as the ¹³C-NMR spectrum, *vide infra*, shows the presence of 5 sp³ carbon atoms only, have to be distributed between 3 CH₂ and 2 CH groups) belonging to the sequence 2 as shown by double resonance experiments. The 1H doublet (H¹) at 4.83 ppm couples only (9 Hz) with the 1H multiplet (H²) at 4.30 ppm. The chemical shift of H¹ suggests for X¹ and X² either two heteroatoms or one heteroatom and sp²-C carrying no H atom. Irradiation of the 4H multiplet centered at 1.80 ppm (2 CH₂) causes collapse of the H²-multiplet to a sharp doublet (9 Hz) and of the 2H multiplet (1 CH₂) at 3.73 ppm to a broad singlet. The chemical shift (1.80 ppm) indicates that the 2 CH₂-groups making up the multiplet carry only aliphatic C-substituents which have to belong to the sequence 2 since (see ¹³C-NMR data) no further sp³ C-atoms are available.

The position of the signals at 3.73 and 4.30 ppm is in agreement with X³ and X⁴ being heteroatoms.



The ¹³C-NMR spectrum contains signals for 2 CH₂ groups in the normal region (23.1 and 31.4 ppm), for CH₂X⁴ at 48.6 ppm, and for the 2 CH-groups at 61.1 and 62.2 ppm. Further on, 15 signals for sp² C-atoms are observed (112–168 ppm), one of them (168.0 ppm) typical for a CO-group. Eight signals correspond to the indole ring (lack of a resonance between 97 and 103 ppm is in agreement^{7,8} with substitution at C-3 as suggested by the ¹H-NMR spectrum), the remaining 6 can be attributed to a benzene ring. The carbonyl region of the IR spectrum shows a band at 1610 cm⁻¹ (aromatic lactam or H-bonded aromatic carboxylic acid).

Treatment of **1** with CH₂N₂ results in N-methylation of the indole-NH (**3**) (shift of the mass of M⁺ and those of the indole fragments, *vide supra*, by 14 u). Reaction with Ac₂O/pyridine at 20° yields a diacetate (**4**), at 60° a triacetate (**5**). In the IR spectrum of **4** two additional CO bands can be found at 1775 (phenolic OAc) and 1665 cm⁻¹ (amide). Partial saponification of **4** with HCl/dioxan yields **6** in agreement with the presence of one OAc-group. Since all exchangeable H (*vide supra*) can be acetylated the amide in **1** has to be tertiary. In the ¹H-NMR spectrum of **4** only the signal at 4.83 in **1** is shifted significantly to 6.33 ppm, hence X¹ in **2** has to be NH. The unusual position of the acetyl signals in **4** (0.92 and 1.72 ppm) shows the strong influence of an aromatic ring current. From the data obtained so far the following structural elements of **1** can be deduced (Scheme 1):

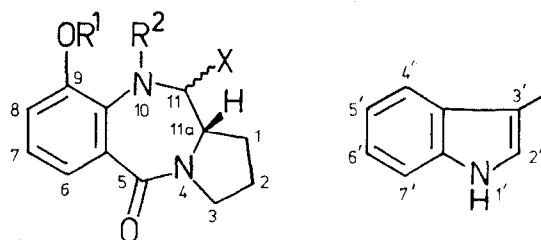


Scheme 1.

Table 1. ¹H-NMR data of 1,2,3,10,11,11a - hexahydro - 5H - pyrrolo[2,1-c][1,4]benzodiazepine derivatives

compound	C - atom						solvent
	3	2	1	11a	11 (←H)	11 (→H)	
<u>1</u>	3.88 m	1.66 m	1.66 m	4.43 m		4.92 d;9	pyridine-d ₅
	3.73 m	1.80 m	1.80 m	4.30 m		4.83 d;9	acetone-d ₆
<u>4</u> ⁺	3.67 m	2.05 m	2.05 m	4.00 m		6.33 d;12	CD ₂ Cl ₂
<u>8</u> ⁺⁺	3.90 m	1.63 m	1.63 m	4.40 m		4.90 d;9	pyridine-d ₅
<u>1</u> [']	3.41 + 3.79 m	0.87 + 1.28 m	1.92 m	4.32 m	5.30 d;3		pyridine-d ₅
<u>8</u> ^{'+++}	3.40 + 3.80 m	0.87 + 1.25 m	1.91 m	4.28 m	5.30 d;2		pyridine-d ₅
<u>15</u>	3.75 m	1.57 m	1.57 + 1.97 m	3.75 m	3.52 d;13.5; 1	3.13 dd;13.5;9	pyridine-d ₅

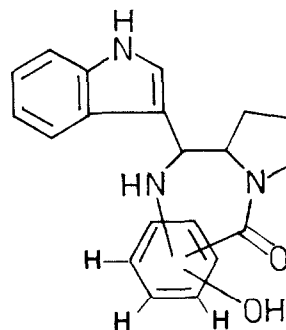
+ acetate: 0.92; s and 1.72; s. ++ OCH₃: 3.50.+++ OCH₃: 3.07



- 1: R¹ = R² = H, X = 3'-indolyl, C-11:
- 1': R¹ = R² = H, X = 3'-indolyl, C-11:
- 3: R¹ = R² = H, X = N-methyl-3'-indolyl, C-11: as in 1
- 4: R¹ = R² = Ac, X = 3'-indolyl, C-11: as in 1
- 5: R¹ = R² = Ac, X = N-acetyl-3'-indolyl, C-11: as in 1
- 6: R¹ = H, R² = Ac, X = 3'-indolyl, C-11: as in 1
- 8: R¹ = CH₃, R² = H, X = 3'-indolyl, C-11: as in 1
- 8': R¹ = CH₃, R² = H, X = 3'-indolyl, C-11: as in 1'
- 15: R¹ = R² = R³ = H, X = H

Since the indole moiety has to carry a CH-substituent only (*vide supra*) (Ar) has to be the benzene ring (NH is Ar- and not aliphatically substituted since in **4** only one ¹H-NMR signal has been shifted). As X³ and X⁴ are heteroatoms (*vide supra*) they have to be the N of the tertiary amide; hence for X² there remains the indole ring. The structural elements can, therefore, be combined as follows (7).

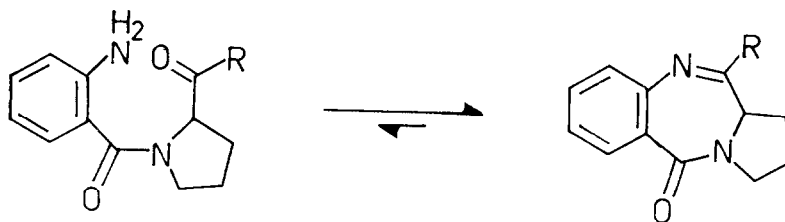
From the three possible combinations: NH, CO, OH; NH, OH, CO; and OH, NH, CO the first one can be excluded since by increment calculations the triplet of the central aromatic H would be expected at lowest field (in **1** it actually occurs at highest field, see above). From the other two the sequence OH, NH, CO is more likely since (a) a *m*-position of NH and CO would yield a highly strained *trans*-cyclo-octene system, and (b) 3-



hydroxy anthranilic acid could be isolated from the same culture medium.² Thus, structure **1** (so far no stereochemistry) can be suggested for a new metabolite.

Pyrrolo[2,1-c][1,4]benzodiazepines can be obtained synthetically by spontaneous cyclization^{9,10} of N - (2 - aminobenzoyl) - pyrrole - 2 - ketones (Scheme 2):

C-3 give a signal for the α -proton at ~ 8.2 ppm, while the β -proton in the corresponding 2-substituted indole gives a signal at ~ 7.2 ppm when DMSO- d_6 is used as solvent.



Scheme 2.

Starting the synthesis from L-proline would settle one of the two asymmetric centres (11a) of **1**. Introduction of the indole ring should be possible by treatment of the protected proline acid chloride with indole Grignard reagent which induces condensation at C-3 of the indole ring.¹¹⁻¹³

Protection of the amino and hydroxyl functions has to be done in a way that neither the acid-labile indole ring is attacked during the removal nor does the proline part suffer alkali-induced racemization. Introduction of the aromatic nitrogen as a NO_2 group which can be reduced prior to cyclization, and a benzyl (hydrogenolytic cleavage) or methyl ether (cleavage with $(\text{CH}_3)_3\text{SiI}$) for the aromatic OH have, therefore, been chosen.

The synthesis of **1/1'** and **8/8'** is summarized in Scheme 3. Benzyloxycarbonyl protected L-proline (**9**) was treated with $[(\text{CH}_3)_2\text{N}=\text{CHCl}]^+\text{Cl}^-$ to give the acid chloride **10** without affecting the centre of chirality.¹⁴ Since basic reaction conditions cannot be avoided during the Grignard reaction racemization of the ketone **11** occurred to a certain degree: synthetic **1** could be obtained with 77% optical purity only. Both, condensation (after hydrogenolytic removal of the benzyloxycarbonyl group) of **12** with the imidazole of 3-benzyloxy- or 3-methoxy-2-nitrobenzoic acid, resp., and the reduction of **13** and **14** (hydrogenolysis of the benzyl ether in the case of **14**, reduction of the nitro group with concomitant cyclization by condensation of the newly created amino group with the keto group, and hydrogenation of the resulting Schiff base were complicated by the low solubility of **12** and **13/14**, resp. (~ 1 mg/ml). Reduction of the Schiff bases yields two stereoisomers (**1/1'** and **8/8'**) the relative amount of which depends upon the phenol ether group: While roughly equal amounts of **8** and **8'** were obtained, in the case of the benzyl ether, however, the wrong (**11R**) isomer **1'** was formed predominantly (92%). While the benzyl group was removed readily during the hydrogenation step all attempts to cleave the methoxy group in **8/8'** with $(\text{CH}_3)_3\text{SiI}$ were unsuccessful. Synthetic and natural **1** proved to be identical with all respects (m.p., IR, UV, NMR, MS, chromatographic behavior).

The intermediates in the synthesis of **1** and **8** have been characterized by their mass (see Experimental) and NMR spectra (Table 2). The most important question whether the indole ring has actually been substituted in 3-position could be settled readily. The chemical shifts of the α - and β -protons, resp., in 3- and 2-acetyl indoles not only differ by about 1 ppm but they are also strongly influenced by the solvent.⁵ Indoles with an RCO-group at

By changing to the less polar CDCl_3 the α -proton is shifted by ~ 0.4 ppm to higher field, while the β -proton is hardly influenced (< 0.1 ppm). Now, the ketone **11** exhibits in CD_2Cl_2 a doublet (which collapses to a singlet upon addition of D_2O) at 7.92 ppm, in DMSO- d_6 , however, at 8.49 ppm ($\Delta = 0.57$ ppm) in accordance with the behavior expected for an α -proton. For the further interpretations of the NMR-spectra see Table 2. They are complicated since due to the restricted rotation of the amide group two conformers can be observed for **11**, **13** and **14**, which results in the duplication of several signals disappearing only at elevated temperatures.

The NMR spectra of the diastereomers **1/1'** and **8/8'** show characteristic differences (see Table 1), viz. a coupling constant for the protons at C-11 and C-11a of 2-3 Hz and of 9 Hz, resp. By considering Dreiding models it can be shown that independent of the conformation of the 7-membered ring the dieder angle of $\text{H}^{11} \cdots \text{C}-\text{C} \triangleleft \text{H}^{11a}$ in **15** is always significantly bigger ($\geq 140^\circ$) than that of $\text{H}^{11} \triangleright \text{C}-\text{C} \triangleleft \text{H}^{11a}$ ($\leq 90^\circ$). This is of importance in so far as in **1/1'** and **8/8'** the indolyl group should be oriented preferentially in an equatorial position and hence the diastereomers would most likely have different conformations. According to the Karplus-Conroy correlation the small coupling constant should correspond to the cisoid hydrogens ($\text{H}^{11} \triangleright \text{C}-\text{C} \triangleleft \text{H}^{11a}$, (**1', 8'**)) and the large one to the transoid (natural) orientation ($\text{H}^{11} \cdots \text{C}-\text{C} \triangleleft \text{H}^{11a}$) (**1, 8**). Since both natural and synthetic **1** are dextrarotatory they do possess the same absolute configuration; **1** is, therefore, (+) (**11S**, **11aS**) - 1,2,3,10,11,11a - hexahydro - 9 - hydroxy - 11 - (3' - indolyl) - 5H - pyrrolo[2,1-c][1,4]benzodiazepine - 5 - one.

From pyrrolo[2,1-c][1,4]benzodiazepine a series of potent antibiotics (anthramycin,^{15,16} sibiromycin,¹⁷⁻¹⁹ tomamycin,^{20,21} neothramycin²²) is derived which have been isolated from various lower fungi. They are all substituted in the pyrrolidine ring and carry at C-11 a carbonyl or a hydroxyl group or are (by elimination of the latter) Schiff bases. Thus, tilivalline is the first representative of a new class of pyrrolobenzodiazepine derivatives and the first compound containing the pyrrolobenzodiazepine ring system isolated from a bacterium.

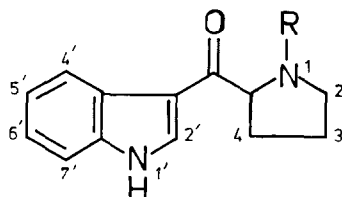
EXPERIMENTAL

¹H-NMR: Varian EM-390 (TMS, δ -values). ¹³C-NMR: Varian CFT-20 (CD_3COCD_3 as internal standard). Mass spectra: Varian MAT 731 (exact mass measurements), Varian CH7A (direct), Finnigan 3200 with data system 6100 (direct). IR: Perkin-Elmer 720. UV: Beckmann 25. Optical rotation: Perkin-Elmer Polarimeter 241. M.ps: Kofler (uncorrected). Column chromatography:

Table 2. ¹H-NMR data of 2-pyrroliidenyl-3'-indolyl ketones

Substance	Conditions	NH	H-2 ⁺	H-4'	H-5'-7'	H-2	H-3/H-4	H-5	OCH ₂ Ar OCH ₃	CH ₂ ArH	H-5''	H-4''' + 6'''
11	CD ₂ Cl ₂	9.70 m	7.92 d3	8.46 m	7.15-7.60 m	5.03-5.20 m	1.8 - 2.5 m	3.70 m	5.08 ^{\$} s 5.25 ^{\$\$} s	7.18 ^{\$} s 7.50 ^{\$\$} s		
	(CD ₃) ₂ SO	11.57 br.s	8.49 m	8.27 m	7.57 m	5.25 m	2.36 m	1.90 m	3.56 t	4.89 ^{\$} s	7.11 ^{\$} s	
	RT				7.27 m				5.10 ^{\$\$} s	7.42 ^{\$\$} s		
	(CD ₃) ₂ SO		8.27 m	8.23 m	7.50 1H m	5.17 dd8.1; 3.6	2.37 m	1.93 m	3.55 t6.6	5.00 s	7.20	
	100°				7.20 2H m							
12	(CD ₃) ₂ SO	++	8.46 s	8.26 m	7.55 1H m	4.50 t	2.25 m	1.73 m	2.85 m			
					7.25 2H m				3.04 m			
13	(CD ₃) ₂ SO	11.50 ^{\$}	8.35 ^{\$}	8.25	7.15-7.65 da	5.15 ^{\$} m	2.4 m	1.97 m	3.50 m	3.86 ^{\$} s	7.73 t7.5	7.15-7.65 m
		11.57 ^{\$\$}	8.62 ^{\$\$}			5.48 ^{\$\$} m				3.95 ^{\$\$} s		6.80 ^{\$} (=H-4''')
		d2				5.33 m(110°C)				3.90 s(110°C)		
14	(CD ₃) ₂ SO	11.47 ^{\$}	8.60 d2	8.27 m	7.18-7.62 m	5.20-5.58 m	2.4 m	1.93 m	3.67 m	5.25 ^{\$} s	7.47 t8	7.67 m
		11.53 ^{\$\$}								5.34 ^{\$\$} s		6.80 ^{\$} (=H-4''')
										5.3 br.s(80°)		

+ At lowest field due to the deshielding effect of the carbonyl group. ++ Both NH signals cannot be detected. \$\$\$ Signals marked by the same symbol (\$, \$\$) belong to the same conformer (\$ to \$\$ at 25° ~ 1:4)



11: R = COOCH₂C₆H₅

12: R = H

13: R = COC₆H₃(2-NO₂)(3-OCH₃)

14: R = COC₆H₃(2-NO₂)(3-OCH₂C₆H₅)

Silicagel 60, Merck, 0.04-0.06 mm. Tlc: Silicagel plates F 254/366, Woelm. Hplc: Polygosil 60-D10 and 60-D10 RP-8 (reversed phase), Macherey & Nagel.

Isolation of 1. 360l of the culture medium² of *Klebsiella pneumoniae* var. *oxytoca* were extracted with ethyl acetate and the concentrated organic phase was treated with 5% aqueous HCl. To the aqueous phase Na₂CO₃ was added till a pH of 8.5 was reached. The ethyl acetate extract of the alkaline solution was chromatographed (CHCl₃ with increasing—up to 50%—amounts of CH₃OH). The main fraction was redissolved in ethyl acetate and treated with an 0.6% aqueous solution of H₃BO₃ to remove 2,3-butanediol (the main metabolite of *Klebsiella*). The residue after evaporation of the organic phase was chromatographed again (CHCl₃/CH₃OH, 10:1) and finally purified by reversed phase hplc (CH₃OH/H₂O, 2:1). Yield: 48 mg 1 m.p. 168°. [α]_D²⁵ (CH₃OH) = +126.8°, [α]_D²⁵ = +131.3°. ¹H-NMR: see Table 1. ¹³C-

NMR: 168.0, 146.1, 137.9, 136.0, 126.4, 124.3, 123.3, 122.6, 121.1, 120.0, 120.0, 117.7, 117.2, 116.0, 112.6, 62.2, 61.1, 48.6, 31.4, 23.1, UV(CH₃OH): 219 (4.46), 239 (sh), 255 (sh), 278 (sh), 288 (sh), 232 (3.47). Mass spectrum: see Ref. 1. Mol. weight (mass spectroscopically) 333,1469 (Calc. for C₂₀H₁₉N₃O₂ 333.1477).

(11S, 11aS) - 1,2,3,10,11,11a - Hexahydro - 9 - hydroxy - 11 - [3' - (1' - methyl) - indolyl] - 5H - pyrrolo[2,1-c][1,4]benzodiazepin - 5 - one (3). To a CH₃OH solution of 1 an ether solution of CH₂N₂ was added till the yellow color remained. After 15 min the solvent was distilled off and the residue purified by tlc (CHCl₃/CH₃OH 8:1). Mol. weight (mass spectroscopically): 347.

(11S, 11aS) - 9 - Acetoxy - 10 - acetyl - 1,2,3,10,11,11a - hexahydro - 11 - (3' - indolyl) - 5H - pyrrolo[2,1-c][1,4]benzodiazepin - 5 - one (4) and (11S, 11aS) - 9 - Acetoxy - 1', 10 - diacetyl - 1,2,3,10,11,11a - hexahydro - 11 - (3' - indolyl) - 5H -

pyrrolo[2,1-c][1,4]benzodiazepin - 5 - one (5). 14 mg **1** were treated at room temp with 3 ml of a mixture of pyridine/Ac₂O (2:1) for 16 hr. After addition of H₂O the solvents were removed *in vacuo*. Column chromatography (CHCl₃/CH₃OH 12:1) yielded 2 mg **5** (mol. weight (mass spectroscopically) 459; MS *v.*¹) and 12 mg **4** (mol. weight (mass spectroscopically) 417; MS *v.*¹ NMR: *v.* Table 1, IR *v.* text). Reaction at 60° yields predominantly **5**.

(11S, 11aS) - 10 - Acetyl - 1,2,3,10,11,11a - Hexahydro - 9 - hydroxy - 11 - (3' - indolyl) - 5H - pyrrolo[2,1-c][1,4]benzodiazepin - 5 - one (6). 1 mg **4** was treated with 0.5 ml 18% HCl and 0.5 ml dioxane at 60° for 4 hr. Dilution with H₂O, extraction with CHCl₃ and purification by tlc (CHCl₃/CH₃OH 8:1) yielded **6**. Mol. weight (mass spectroscopically) 375 MS *v.*¹

(2S) - N - Benzyloxycarbonyl - 2 - pyrrolidinyl - 3' - indolyl - ketone (11). 6.35 g (0.05 mole) [CHCl=N(CH₃)₂]⁺Cl⁻ in 30 ml abs. CHCl₃ were reacted with a CHCl₃ soln of 12.5 g (0.05 mole) of (S) - N - benzyloxycarbonylprolin (**9**). After 15 min the solvent was removed and 100 ml abs. ether were added. This ether soln was added dropwise at 0° under vigorous stirring to a soln of indole Grignard (21.8 g = 0.2 mole C₂H₅Br, 4.8 g = 0.2 mole Mg, 11.7 g = 0.1 mole indole in 1 l ether). A precipitate was formed immediately. The stirring was continued for 1.5 hr. The reaction product was hydrolysed by addition of 250 ml conc. NH₄Cl soln, the precipitate was filtered off and recrystallized from C₂H₅OH. Yield 9.8 g (53%), m.p. 203°. [α]_D²⁵ (CH₃OH) = -102.7°, [α]_D²⁵ = -107.2°. UV (CH₃OH) 211 (4.44), 242 (4.12), 258 (sh), 299 (4.12). NMR: *s.* Table 2, MS: *m/z* 348 (7); M⁺, 204 (21); [M - indolylcarbonyl]⁺, 160(31); [204 - CO₂]⁺, 144 (31); [indolylcarbonyl]⁺ 91(100); C₇H₇⁺. IR: 1670, 1640 (sh) cm⁻¹ (CO).

(2S) - 2 - Pyrrolidinyl - 3' - indolyl - ketone (12). 8.5 g (24 mmole) **11** in 300 ml hot C₂H₅OH were added to a suspension of 0.1 g Pd-C (10%) in 50 ml C₂H₅OH prehydrogenated for 2 hr. Hydrogenation for 2 hr, removal of the catalyst, evaporation to dryness and recrystallization from C₂H₅OH yielded 5.0 g (95%) (**12**). m.p. 168°. [α]_D²⁵ = -82.6°, [α]_D²⁵ = -87.0°. UV (CH₃OH): 207 (4.41), 237 (4.12), 258 (3.96), 299 (4.10). NMR: *v.* Table 2, MS: *m/z* 214 (2); M⁺, 144 (14); [indolylcarbonyl]⁺, 70 (100); [M - indolylcarbonyl]⁺. IR: 1630 cm⁻¹ (CO).

(2S) - N - (3 - Benzyloxy - 2 - nitrobenzoyl) - 2 - pyrrolidinyl - 3' - indolyl - ketone (14). 1.09 g (4 mmole) 3 - benzyloxy - 2 - nitrobenzoic acid²⁴ in 25 ml abs. THF and 0.64 g (4 mmole) carbonyl-diimidazole were stirred for 1 hr. After addition of 0.86 g (4 mmole) **12** stirring was continued for 16 hr. The precipitate was filtered off and recrystallized from C₂H₅OH: 580 mg (31%) **14** m.p. 222°. [α]_D²⁵ = -214.8°, [α]_D²⁵ = -227.4°. UV (CH₃OH) 205 (4.73), 240 (4.26), 257 (4.09), 298 (4.18). NMR: *v.* Table 2, MS: *m/z* 469 (0.03); M⁺, 325 (2); [M - indolylcarbonyl]⁺, 256 (11); (C₇H₇O)(NO₂)C₆H₃CO⁺, 144 (55); [indolylcarbonyl]⁺, 91 (100); C₇H₇⁺. IR 1635 cm⁻¹ (CO).

(11S, 11aS) - and (11R, 11aS) - 1,2,3,10,11,11a - Hexahydro - 9 - hydroxy - 11 - (3' - indolyl) - 5H - pyrrolo[2,1-c][1,4]benzodiazepin - 5 - one (**1** + **1'**). 235 mg (0.5 mmole) **14** in 500 ml hot C₂H₅OH were added to a suspension of 50 mg Pd-C (10%) in 100 ml C₂H₅OH prehydrogenated for 2 hr. After hydrogenation for 4 hr the catalyst was filtered off and the solution evaporated to dryness. Yield: 163 mg (98%) of **1** + **1'**. Separation by hplc (hexane/isopropanol 3:1) and recrystallization from CH₃OH yielded 92% **1** and 8% **1'**. **1**: [α]_D²⁵ = +98.1°, [α]_D²⁵ = +101.3° (77% optical purity). In all other respects synthetic and natural **1** proved to be identical. **1'**: m.p. 252°. [α]_D²⁵ = +431.7°, [α]_D²⁵ = +455.6° (opt. purity should also be 77% only). UV (CH₃OH): 221 (4.45), 255 (sh), 278 (sh), 287 (3.55), 355 (3.31). NMR: *v.* Table 1, MS: *v.*¹ IR: 1620 cm⁻¹ (CO).

(2S) - N - (3 - Methoxy - 2 - nitrobenzoyl) - 2 - pyrrolidinyl - 3' - indolylketone (13). 3.94 g (20 mmole) 2 - Methoxy - 3 - nitrobenzoic acid²⁵ reacted as described for **14** yielded 2.59 g (33%) **13** m.p. 278°. [α]_D²⁵ = -255.5°, [α]_D²⁵ = -270.1°. UV: 207 (4.72), 238 (4.28), 255 (4.12), 297 (4.23). NMR: *v.* Table 2, MS: *m/z* 393 (0.5); M⁺, 249 (8); [M - indolylcarbonyl]⁺, 180 (100); (CH₃O)

(NO₂)C₆H₃CO⁺, 144 (100); [indolylcarbonyl]⁺. IR: 1665, 1610 cm⁻¹ (CO).

(11S, 11aS) - and (11R, 11aS) - 1,2,3,10,11,11a - Hexahydro - 11 - (3' - indolyl) - 9 - methoxy - 5H - pyrrolo[2,1-c][1,4]benzodiazepin - 5 - one (**8** + **8'**). 393 mg (1 mmole) **13** when reacted as described for **1** + **1'** yielded 333 mg (96%) **8** + **8'**. Separation by hplc (hexane/isopropanol 5:1) gave **8** and **8'** in a ratio of 48:52. **8**: m.p. 130°, [α]_D²⁵ = +64.1°, [α]_D²⁵ = +67.1° (optical purity probably as for synthetic **1**). UV (CH₃OH): 216 (4.51), 236 (sh), 255 (sh), 280 (sh), 288 (sh), 300 (sh). NMR: *v.* Table 1, MS: *v.*¹ mol. weight (mass spectroscopically) 347. IR: 1615 cm⁻¹ (CO).

8': m.p. 141, [α]_D²⁵ = +319.7°, [α]_D²⁵ = +337.5° (optical purity probably as for **1'**). UV (CH₃OH): 223 (4.61), 255 (sh), 280 (sh), 290 (sh), 334 (3.51). NMR: *v.* Table 1, MS: *v.*¹ mol. weight (mass spectroscopically) 347. IR: 1615 cm⁻¹ (CO).

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