Acta Chemica Scandinavica, 1998: 52: 784–789
Printed in UK – all rights reserved

ACTA
CHEMICA SCANDINAVICA
ISSN 0904-213X

Stereochemistry of Dimerisation of Indole-3-acetic Acid and its Propyl Ester

Tine M. Fatum, Uffe Anthoni, Carsten Christophersen* and Per Halfdan Nielsen

Department of Chemistry, The H. C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

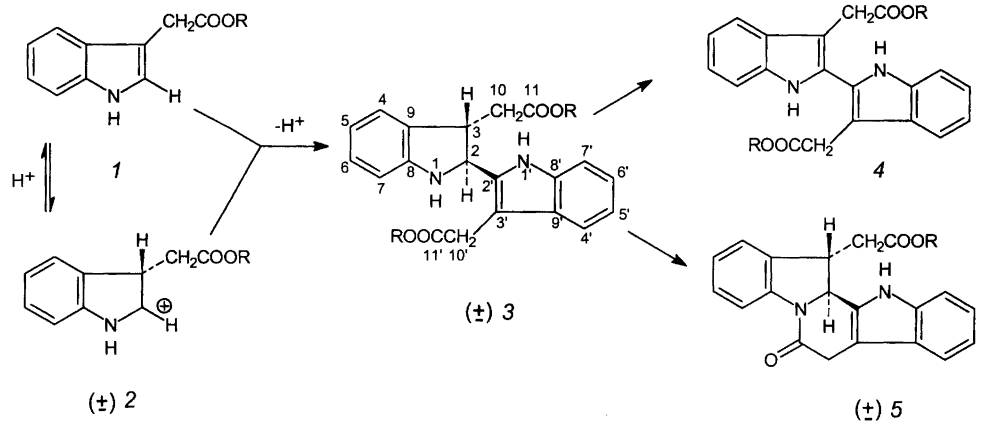
Fatum, T. M., Anthoni, U., Christophersen, C. and Nielsen, P. H., 1998. Stereochemistry of Dimerisation of Indole-3-acetic Acid and its Propyl Ester. – Acta Chem. Scand. 52: 784–789. © Acta Chemica Scandinavica 1998.

The mechanism, stereochemistry and products of the dimerisation of indole-3-acetic acid **1a** and its propyl ester **1b** in TFA and H_3PO_4 have been investigated. The major products in both acids were 2-(indolin-2-yl)indole dimers, **3a/b**, which were readily converted into the corresponding pentacyclic lactams **5a/b** with the pyrido[1,2-*a*:3,4-*b*']biindole skeleton. Ccompound **5a** was studied by X-ray crystallography and shown to be the 2,3-*trans*-isomer. The reaction proceeds via electrophilic attack of the protonated species **2** on free **1** with steric approach control to form the *trans*-stereoisomeric **3** and/or **5**.

Dimerisation of indole-3-acetic acid methyl ester (**1**, R = Me) in trifluoroacetic acid (TFA) proceeds according to Scheme 1.[1] The initially formed dimer (**3**, R = Me) on being heated above the melting point is converted into the corresponding lactam (**5**, R = Me). The parent indole-3-acetic acid (**1a**) in TFA at room temperature has been reported to form the dimer (**3a**) in 75% yield[1] but it is not clear whether it is stable or is transformed spontaneously into the pentacyclic lactam (**5a**).[1,2] Moreover, neither the experimental procedure nor the structure of the products has been adequately described and the mechanism and stereochemistry of the dimerisation are unknown. As part of a continuing study of the acid-catalysed dimerisation and cyclisation of indole derivatives the dimerisation of **1a** and the propyl ester (**1b**) in TFA and phosphoric acid has been investigated.

Results and discussion

Dimerisation of **1a** *and* **1b**. Dimerisation of **1a** in TFA, according to direct ^{1}H NMR analysis of the reaction mixture, was complete after 4 h. Concentration of the reaction mixture furnished almost pure **3a** as the trifluoracetate with three similar acid dissociation constants $pK_a = 3.8$, 5.2, and 6.3. Addition of ammonia to pH 4.5 followed by recrystallisation furnished the hemihydrate of **3a**, which slowly decomposed at room temperature. Boiling of a solution of **3a** in ethanol or acetonitrile led



(±) 2 (±) 3 4 (±) 5

Scheme 1. **a**; R = H; **b**; R = $^{12}CH_2{}^{13}CH_2{}^{14}CH_3$.

* To whom correspondence should be addressed.

to lactamisation to **5a** in fair yield (68%). The relative stereochemistry of **5a** was determined to be *trans* by X-ray analysis (see later).

In order to investigate the influence of solvent on the reaction **1a** was dissolved in H_3PO_4 and the solution was neutralised and extracted into EtOAc. The main product **3a** was obtained in a yield of 53% while 26% **1a** remained unreacted. During the purification procedure a new compound **4a** was isolated. The structure of **4a** revealed itself as the symmetrical 2,2′-biindole from a molecular ion at *m/z* 348 and the close resemblance of ^1H and ^{13}C NMR spectra to those reported for the corresponding diethyl ester.[3] These results show that **3a** in phosphoric acid does not cyclise immediately to **5a** but is sufficiently stable to undergo oxidation to **4a**.

The dimerisation of **1b** in TFA and H_3PO_4 was investigated analogously. The ^1H NMR spectrum of **1b** in TFA revealed the presence of a dimer, **3b**. Evaporation and purification of the products by column chromatography provided **3b**, **5b** and a trimer in the ratio 77 : 21 : 2. The spectral properties (^1H and ^{13}C NMR, MS, IR) of **3b** and **5b** are in good agreement with the data given for the corresponding methyl esters and indicate these to be propyl ester analogues of **3a** and **5a**, respectively. The mass spectrum of the trimer showed a molecular ion at *m/z* 589 corresponding to a molecular formula $C_{36}H_{35}N_3O_5$ indicating a trimeric structure with one propyl ester group converted into a lactam. This was verified by the ^{13}C NMR spectrum, which displayed three different carbonyl resonances, two at δ 171 and one at δ 161, suggesting the presence of two ester and one amide group.

The propyl ester **1b** in H_3PO_4, gave **1b**, **3b** and a new compound in the approximate ratio 3 : 4 : 5. The molecular ion at *m/z* 392 of the new compound accords with **3b** having had one ester group hydrolysed by the phosphoric acid. The ^1H NMR spectrum displayed signals of only one propyl group, but showed no sign of cyclisation (H2 at δ 5.06 and H4–H7 at 6.7–7.8 ppm). The ^{13}C NMR spectrum displayed only one ester carbonyl resonance at 171 ppm. Since H2 and H3 have a *trans* relationship the mechanism can be described as electrophilic attack of the protonated species **2** on the free acid **1** with a sterically controlled approach.

Stereochemistry. The stereochemistry of **5a** was established by single-crystal X-ray diffraction data. The molecular conformation and the atom labelling are illustrated in Fig. 1. The bond lengths and angles given in Table 2 are all in agreement with expected values.[4] An intramolecular NH···O hydrogen bond [2.800(1) Å] connects the indole NH (H1) and acid carbonyl O13. Molecules related by translation symmetry along the *b*-axis are connected by intermolecular hydrogen bonds O12–H12···O112 $[x, -1+y, z]$ with a distance of 2.639(1) Å. The molecule contains two planar entities, the indole and the indoline ring systems, with an interplanar angle of 29°. The six-membered lactam ring

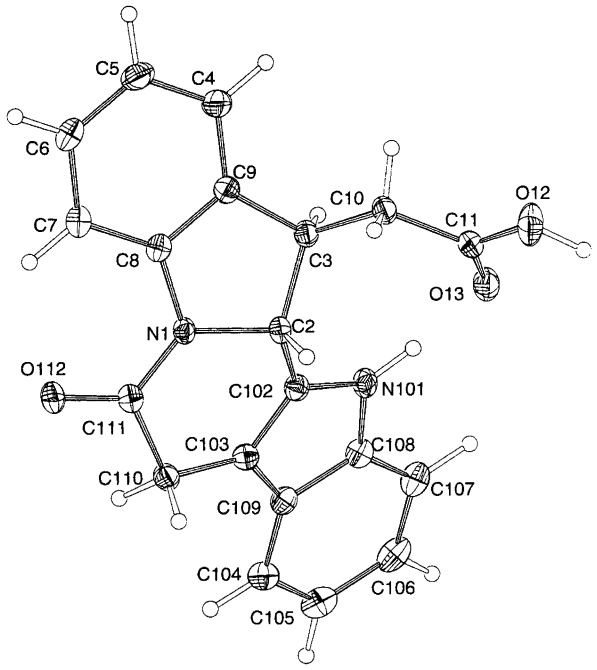


Fig. 1.

adopts a boat conformation with C111 deviating only by 0.266(2) Å from the plane of the indoline ring which brings O112 close to H7 [O112–H7 2.327(15) Å]. The two chiral centers C2 and C3 have the same absolute configuration, i.e., with H2 and H3 in a *trans* configuration with the torsion angle H2–C2–C3–H3 of 142.3(13)°. *trans*-Stereochemistry has also been reported for the major products from the dimerisation of tryptophan derivatives in TFA.[5]

Since the H2–C2–C3–H3 torsion angle in indolines is typically of the order of 0–35° for *cis* compounds and 106–155° for *trans* compounds,[6] the coupling constant between H2 and H3 in 2,3-disubstituted indolines following the Karplus equation is within 6–11 Hz for both isomers. Consequently this coupling constant does not distinguish between *cis* and *trans* isomers.

However, Thomas[7] noted that protonation of the indoline-*N* is often followed by an increase in the coupling constant between H2 and H3 in the *cis*-configuration and a decrease in the *trans*-configuration. This result was subsequently utilised to determine the stereochemistry of 2,2′-dimers of tryptophan derivatives.[5] This principle was applied to the dimers **3a** and **3b** which both have a free indoline NH. According to our results **3a** and **3b** are both *trans* dimers. Provided Thomas' results are correct, the coupling constant between H2 and H3 must decrease on protonation in both cases. However, it decreases from 10.8 to 10.4 Hz for **3a** but increases from 8.6 to 10.4 Hz for **3b**. These conflicting results imply that the method is not generally applicable as assumed.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker 250 AM or a Varian XL-400 spectrometer with the

solvent as an internal standard. ^{1}H NMR spectra are presented in the order: δ, signal integral, multiplicity, assignment, and coupling constant in Hz. Infrared spectra were recorded with a Perkin Elmer 1760X FT-IR spectrophotometer. Mass spectra were obtained on a JEOL JMS-HX110A spectrometer using the direct inlet system. Column chromatography was carried out on Lobar Si-60 or RP-18 (Merck). TFA (99%) was from Aldrich and **1a** from Fluka. **1b** was prepared from **1a** and 1-propanol[8]: ^{1}H NMR ($CDCl_3$): δ 0.91 (t, J=7.5, H14), 1.64 (m, J=7.1, H13), 3.77 (s, H10), 4.06 (t, J=6.7), 7.09–7.62 (H2, H4–H7), 8.10 (br s, H1). ^{13}C NMR: δ 9.9 (C14), 21.6 (C13), 31.0 (C10), 66.0 (C12), 108.1–135.7 (C2–C9), 171.8 (C11).

trans-*2,3-Dihydro-2,2'-biindole-3,3'-diacetic acid monohydrochloride* (**3a**·HCl). **1a** was dissolved in TFA, left for 20 h and taken to dryness *in vacuo*. The crude **3a**·TFA was dissolved in EtOAc and the hydrochloride precipitated with gaseous HCl. Pale red solid, m.p. 174–182 °C. Anal. $C_{20}H_{19}ClN_2O_4$: C, H, N. FAB–MS (NBA): m/z 351 $[M+H]^+$. IR (KBr, cm^{-1}): 3407s, 3227s, 3062s, 1713s, 1567 m, 1490 m, 1463 m, 1412 m, 1389 m, 1320 m, 1219 m, 747 m. The hydrochloride is almost insoluble in water and (^{1}H and ^{13}C NMR) decomposes partially to **5a** on dissolution in EtOH or DMSO.

trans-*2,3-Dihydro-2,2'-biindole-3,3'-diacetic acid bistrifluoroacetate* (**3a**·2TFA). **1a** was dissolved in TFA and taken to dryness *in vacuo* finally leaving **3a**·2TFA contaminated with a small amount of **5a**. Attempted purification by dissolution in EtOAc and precipitation with Et_2O resulted in partial decomposition. Almost colourless solid, hygroscopic and unstable. M.p. 64–65 °C and decomposes with evolution of gas at 122–123 °C. FAB–MS (NBA): m/z 351 $[M+H]^+$. ^{1}H NMR (DMSO-d_6): δ 11.9 (s, 5 H, OH), 11.19 (s, 1 H, NH-1'), 6.9–7.6 (8 H, aromatic protons), 5.09 (d, 1 H, H2, J=10.4), 3.96 (m, 1 H, H3), 3.78 (s, 2 H, H10'), 2.72 (dq, 2 H, H10, J=4.2+8.0, 16). ^{13}C NMR (DMSO-d_6): δ 30.0 (C10'), 36.9 (C10), 45.2 (C3), 60.3 (C2), 108–146 (aromatic C), 158.3 (q, CF_3), 167.5 (CO), 170.5 (CO), 173.6 (q, CO, TFA).

trans-*2,3-Dihydro-2,2'-biindole-3,3'-diacetic acid* (**3a**·½H_2O). **1a** (0.600 g, 3.42 mmol) was dissolved in TFA (15 ml) and stirred at RT for 20 h to give the trifluoroacetate of **3a**. Titration of an aqueous solution with 0.1 M NaOH established the acidity constants of protonated **3a** to be approximately pK_a=3.8, 5.2, and 6.3 corresponding to one NH_2^+ and two COOH groups. Addition of aqueous ammonia to pH 4.5 gave a colourless precipitate, m.p. 105–110 °C (decomp.). After filtration and freeze–drying, spectral (MS, NMR, IR) and elemental analysis (C, H, N) corresponded to the composition **3a**·2CF_3COONH_4·H_2O. Even prolonged freeze–drying failed to remove the co-precipitated ammonium trifluoroacetate as TFA and ammonia indicating strong hydrogen bonds to the COOH groups in the crystalline state.

However, recrystallisation from water–EtOH (1:1) left pure **3a** as a colourless hemihydrate, m.p. 125–130 °C (decomp.) after sintering at 80 °C. The compound slowly decomposed at room temperature with a concomitant strong smell of skatole. Anal. $C_{20}H_{19}N_2O_{4\frac{1}{2}}$: C, H, N. FAB–MS (NBA): m/z 351 $[M+H]^+$. ^{1}H NMR (DMSO-d_6): δ 2.55 (dd, 1 H, H10, J=9.1+16.2), 2.66 (dd, 1 H, H10, J=4.0+16.2), 3.3 (brs, 2 H, OH), 3.68 (s, 2 H, H10'), 3.80 (ddd, 1 H, H3, J=4.0+9.1+10.8), 4.82 (d, 1 H, H2, J=10.8), 6.0 (brs, 1 H, H1), 6.57–7.42 (8 H, aromatic protons), 11.08 (s, 1 H, H1'). ^{13}C NMR (DMSO-d_6): δ 30.8 (C10'), 37.9 (C10), 45.5 (C3), 61.4 (C2), 105–152 (aromatic C), 165.0 (CO). IR (KBr, cm^{-1}) 2000–3600vs, br, centered at 3286, submaximum at 2500 (hydrogen bonded νOH), 1708vs (ν_{as}COO), 1406s (δOH), 1243s (νCO). The bands corresponding to vibrations of the COOH group were identified by comparison with the Raman spectrum, where these bands were much weaker. The presence of the strong OH stretching vibration and the absence of carboxylate stretching indicates strong hydrogen bonding in **3a** but without proton transfer to a zwitterion structure.

Table 1. Crystal data and structure refinement for **5a**.

Empirical formula	$C_{20}H_{16}N_2O_3$
Formula weight/g mol^{-1}	332.35
Radiation	1.541 84 Å
T/K	122(2)
Crystal system	Monoclinic
Space group	$P2_1/c$
a/Å	11.200(3)
b/Å	10.0306(12)
c/Å	15.005(3)
β/°	111.72(2)
V/Å^3	1566.0(6)
Z	4
F(000)	696
Crystal size/mm	0.20×0.25 ×0.35
D_x/g cm^3	1.410
Absorption coefficient/mm^{-1}	0.783
Refl. used in determination of cell parameters	22
τ range/°	39.5–44.0
τ range for data collection/°	4.25–74.91
Range of h	−13 to 13
Range of k	−12 to 12
Range of l	−18 to 18
R_{int}	0.025
Measured reflections (incl. standard refl.)	8839
Independent reflections (total and refined)	3226
Observed reflections [$I>2\sigma(I)$]	2976
Calc. $w=1/[\sigma^2(F_o^2)+(0.0609P)^2+0.5159P]$ where $P=(F_o^2+2F_c^2)/3$	291
R for $F>4\sigma(F)$	0.0369
$wR2$ for all F^2 data	1.044
Extinction coefficient	0.0040(4)
Max. shift/esd	−0.063
Max. and min. Δ/e Å^{-3}	0.0310 and −0.22

Table 2. Bond lengths (Å) and angles (°) and selected torsion angles (°) for **5a**.

Bond lengths			
N1–C111	1.357(2)	C11–O12	1.329(2)
N1–C8	1.421(2)	N101–C102	1.375(2)
N1–C2	1.5021(14)	N101–C108	1.385(2)
C2–C102	1.495(2)	C102–C103	1.360(2)
C2–C3	1.554(2)	C103–C109	1.432(2)
C3–C9	1.517(2)	C103–C110	1.489(2)
C3–C10	1.531(2)	C104–C105	1.384(2)
C4–C9	1.389(2)	C104–C109	1.406(2)
C4–C5	1.399(2)	C105–C106	1.406(2)
C5–C6	1.382(2)	C106–C107	1.386(2)
C6–C7	1.395(2)	C107–C108	1.398(2)
C7–C8	1.396(2)	C108–C109	1.416(2)
C8–C9	1.391(2)	C110–C111	1.512(2)
C10–C11	1.504(2)	C111–O112	1.238(2)
C11–O13	1.209(2)		
Angles			
C111–N1–C8	125.62(10)	O12–C11–C10	110.38(10)
C111–N1–C2	125.23(9)	C102–N101–C108	107.84(10)
C8–N1–C2	109.05(9)	C103–C102–N101	110.63(11)
C102–C2–N1	107.60(9)	C103–C102–C2	122.42(10)
C102–C2–C3	120.07(10)	N101–C102–C2	126.84(10)
N1–C2–C3	105.16(9)	C102–C103–C109	107.12(10)
C9–C3–C10	108.70(9)	C102–C103–C110	121.78(11)
C9–C3–C2	102.28(9)	C109–C103–C110	131.11(11)
C10–C3–C2	113.90(9)	C105–C104–C109	118.58(12)
C9–C4–C5	118.91(12)	C104–C105–C106	120.97(12)
C6–C5–C4	120.26(12)	C107–C106–C105	121.86(12)
C5–C6–C7	121.60(11)	C106–C107–C108	117.07(12)
C6–C7–C8	117.56(11)	N101–C108–C107	129.86(12)
C9–C8–C7	121.39(11)	N101–C108–C109	108.07(10)
C9–C8–N1	109.53(10)	C107–C108–C109	122.06(11)
C7–C8–N1	129.06(11)	C104–C109–C108	119.45(11)
C4–C9–C8	120.27(11)	C104–C109–C103	134.21(12)
C4–C9–C3	128.06(11)	C108–C109–C103	106.31(10)
C8–C9–C3	111.67(10)	O112–C111–N1	121.74(11)
C11–C10–C3	117.54(10)	O112–C111–C110	119.90(11)
O13–C11–O12	123.04(11)	N1–C111–C110	118.35(10)
O13–C11–C10	126.58(11)		
Torsion angles			
H2–C2–C3–H3	142.3(13)	C3–C10–C11–O13	5.4(2)
N1–C2–C3–C10	130.80(10)	C9–C3–C10–C11	−178.00(10)
C103–C110–C111–O112	158.55(11)	C2–N1–C111–C110	−7.2(2)
C8–N1–C111–O112	−11.0(2)	C2–C102–C103–C110	4.3(2)
C111–N1–C8–C7	12.7(2)	C3–C2–C102–C103	−150.07(11)

Dimerisation of **1a** *in phosphoric acid.* **1a** (593 mg, 3.39 mmol) was suspended in 85% H_3PO_4 (50 ml). Even after 20 h at RT some undissolved solid still remained in the brown solution and the reaction mixture contained more than 50% of **1a**. The solution was poured into a stirred mixture of CH_2Cl_2 (100 ml) and 50% aqueous K_2CO_3 (150 ml) with ice-cooling, after which a brown viscous oil dropped out of solution. Separation of 100 mg of this oil on an RP-18 column eluted with acetonitrile–H_2O mixtures yielded **1a** (53%), **3a** (26%), **4a** (8%) and some minor constituents (13%).

2,2′-Biindole-3,3′-diacetic acid (**4a**). MS *m/z* (% rel. int.): 348 (M^+, 38), 347 (40), 304 (42), 257 (100), 128 (60). IR (KBr, cm^{-1}): 3386s, 3261s, 3057s, 2924s, 1702s, 1451s, 1341s, 1187s, 1024s, 1000s, 746s. ^1H NMR (DMSO-d_6) 3.79 (s, 4 H, H10 and H10′), 7.11–7.61 (8 H, aromatic protons), 11.34 (s, 2 H, H1 and H1′), 12.3 (br s, 2 H, H12 and H12′). ^{13}C NMR: δ 30.6 (H10 and H10′), 107.8 (C3 and C3′), 111.3–128.0 (aromatic carbons), 136.4 (C2 and C2′), 173.4 (C11 and C11′).

Pentacyclic lactam **5a**. When **3a** or the trifluoroacetate was heated for some time in ethanol, **5a** precipitated as a pale red solid, m.p. 251 °C (decomp.). Anal. $C_{20}H_{16}N_2O_3$: C, H, N. MS *m/z* (% rel. int.), 332 (M^+, 20), 272 ($M^+ - CH_3COOH$, 100), 243 ($C_3H_6O_2$, 30). IR (KBr, cm^{-1}): 3313ms, 3062ms, 1718s, 1621s, 1589s,

Table 3. Atomic coordinates and equivalent isotropic displacement parameters for **5a**. *U*(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	*y*	*z*	*U*(eq)
N1	0.16409(9)	0.00534(9)	0.05070(7)	0.0166(2)
C2	0.19817(11)	−0.13665(11)	0.03878(8)	0.0163(2)
C3	0.23558(11)	−0.20026(12)	0.13991(8)	0.0173(2)
C4	0.17873(13)	−0.10926(13)	0.28253(9)	0.0242(3)
C5	0.12945(13)	−0.00235(14)	0.31807(9)	0.0267(3)
C6	0.09007(12)	0.11270(13)	0.26444(9)	0.0232(3)
C7	0.09715(11)	0.12575(12)	0.17397(9)	0.0200(3)
C8	0.14551(11)	0.01788(12)	0.13899(8)	0.0170(2)
C9	0.18677(11)	−0.09787(12)	0.19269(8)	0.0182(2)
C10	0.16913(12)	−0.33351(12)	0.14014(9)	0.0195(3)
C11	0.20706(12)	−0.45089(12)	0.09411(8)	0.0203(3)
O12	0.13363(10)	−0.55556(9)	0.09258(8)	0.0328(3)
O13	0.29161(9)	−0.45371(9)	0.06221(7)	0.0260(2)
N101	0.38325(10)	−0.23016(10)	−0.00446(7)	0.0195(2)
C102	0.29274(11)	−0.13453(12)	−0.01012(8)	0.0173(2)
C103	0.29362(11)	−0.03675(12)	−0.07265(8)	0.0181(2)
C104	0.43340(12)	−0.01370(13)	−0.17800(9)	0.0221(3)
C105	0.52549(12)	−0.08056(14)	−0.20187(9)	0.0255(3)
C106	0.57588(12)	−0.20301(14)	−0.15868(10)	0.0258(3)
C107	0.53605(12)	−0.26197(13)	−0.09084(9)	0.0240(3)
C108	0.44241(11)	−0.19470(12)	−0.06732(8)	0.0195(3)
C109	0.38947(11)	−0.07185(12)	−0.11049(8)	0.0188(2)
C110	0.20584(12)	0.08026(12)	−0.09150(9)	0.0195(3)
C111	0.15944(11)	0.10656(12)	−0.01046(8)	0.0175(2)
O112	0.11909(8)	0.21855(8)	−0.00105(6)	0.0214(2)

1484s, 1461 m, 1408s, 738ms. ^{1}H NMR (DMSO-d_6): δ 12.6 (br s, 1 H, OH), 11.1 (s, 1 H, NH), 8.20–7.12 (8 H, aromatic protons), 5.58 (ddd, 1 H, H2, J=2.5, 4.3, 11.0), 3.90 (ddd, 1 H, H3, J=3.5, 8.5, 11.0), 3.83 (dd, 1 H, H10′, J=4.3, 19.6), 3.78 (dd, 1 H, H10′, J=2.5, 19.6), 3.41 (dd, 1 H, H10, J=3.6, 16.4), 3.06 (dd, 1 H, H10, J=8.5, 16.4). ^{13}C NMR (DMSO-d_6): δ 31.2 (C10′), 36.4 (C10), 41.5 (C3), 62.1 (C2), 105.6 (C3′), 125.3 (C2′), 112 × 142 (aromatic C), 167.1 (C11′), 173.3 (C11).

Dimerisation of **1b** *in TFA.* **1b** (550 mg, 2.53 mmol) was dissolved in TFA (10 ml) and kept at RT for 24 h. Evaporation of the solvent yielded 600 mg of a brown viscous oil. 519 mg of this oil were purified by column chromatography on Si-60 (CH_2Cl_2–EtOH 15:1) giving four fractions with UV absorption. The most polar fraction (I) consisted of pure **3b**. Yield 167 mg (30%). Fraction II (229 mg) was further purified on Si-60 (CH_2Cl_2–EtOAc 10:1) giving **3b** (101 mg, 18%) and **5b** (61 mg, 13%). Fraction III consisted predominantly of a trimer (6 mg, 1%): MS *m/z* (% rel. int.): 589 (70, M^+), 529 (50, $M^+ - C_3H_8O$), 488 (100, $M^+ - C_5H_9O_2$), 443 (50), 383 (65), 269 (30).

Dimerisation of **1b** *in phosphoric acid.* **1b** (536 mg, 2.47 mmol) was suspended in 85% H_3PO_4 (30 ml). After 20 h at RT, the clear brown solution was diluted with water (300 ml) and CH_2Cl_2 (100 ml) and neutralised by addition of solid Na_2CO_3 little by little with ice cooling and rigorous stirring. The aqueous phase was separated and extracted with CH_2Cl_2 (70 ml) and the combined organic phases were dried ($MgSO_4$). Evaporation of the solvent yielded 355 mg of brown oil. This oil was purified by column chromatography on a Si-60 column eluted with CH_2Cl_2–EtOH 15:1 giving **3b** (116 mg, 21%), **5b** (3 mg, <1%) and unreacted starting material (42 mg, 8%). Subsequent elution with EtOH yielded a monopropyl ester of **3a** (34 mg).

trans-*2,3-Dihydro-2,2′-biindole-3,3′-diacetic acid dipropyl ester* (**3b**). MS *m/z* (% rel. int.): 434 (M^+, 40), 332 ($M^+ - C_5H_{10}O_2$, 100), 245 (50). IR (KBr, cm^{-1}): 3364ms, 2969ms, 1719s, 1610ms, 1485s, 1465s, 1314s, 1245s, 1167s, 742s. ^{1}H NMR ($CDCl_3$): δ 8.63 (s, 1 H, H1′), 7.7–6.6 (8 H, aromatic H), 4.94 (d, 1 H, H2, J= 8.6), 4.20 (br s, 1 H, H1), 4.04 (t, 2 H, H12′, J=6.8), 3.98 (m, 2 H, H12), 3.79 (m, 1 H, H3), 3.78 (d, 2 H, H10′, J=14.5), 2.79 (dd, 2 H, H10, J=6.8, ca. 17), 1.65 (m, 2 H, H13′), 1.58 (m, 2 H, H13, J=7.1), 0.94 (t, 3 H, H14′, J=7.4), 0.90 (t, 3 H, H14, J=7.4). The propyl groups were assigned taking advantage of the fact that the H12- and H10-protons displayed long-range coupling. ^{13}C NMR ($CDCl_3$): δ 10.1 (C14/C14′), 21.6/21.7 (C13/C13′), 29.9 (C10′), 37.1 (C10), 45.9 (C3), 61.1 (C2), 66.1/66.3 (C12/C12′), 105.7 (C3′), 109–150 (aromatic C), 127.9 (C2′), 172.0/172.1 (C11/C11′).

trans-*2,3-Dihydro-2,2′-biindole-3,3′-diacetic acid monopropyl ester.* The position of the ester group was not determined. MS (*m/z*, % rel. int.): 392 (10, M^+), 290 (40), 272 (100), 245 (45). ^{1}H NMR (DMSO-d_6): δ 0.86 (t, J=7.3, 2 H), 1.55 (m, J=7.3, 2 H), 2.78 (dd, J=

16.1, 8.2, 1 H), 2.84 (dd, J=16.1, 5.1, 1 H), 3.70 (d, J=16.1, 1 H), 3.74 (d, J=16.1, 1 H), 3.79, (m, 1 H), 3.95 (m, 2 H), 4.82 (d, J=10.4, 1 H), 6.6–7.6 (8 H, aromatic protons), 11.10 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ 10.2, 21.4, 36.5, 45.8, 60.6, 65.5, 108.7, 111.1–151.1 (13 C), 171.8.

Pentacyclic lactam **5b**. Recrystallisation from petrol ether–EtOH yielded dark needles, m.p. 197–200 °C. Anal. $C_{23}H_{22}N_2O_3$: C, H, N. MS m/z (% rel. int.): 374 (M^+, 20), 272 ($M^+ - C_5H_{10}O_2$, 100). IR (KBr, cm^{-1}), 3413ms, 2968 m, 1729s, 1636s, 1598s, 1481s, 1461ms, 1403s, 757ms. ^{1}H NMR ($CDCl_3$): δ 10.0 (s, 1 H, H1′), 7.1–8.4 (8 H, aromatic protons), 5.26 (ddd, 1 H, H2, J= 2.0, 4.6, 9.2), 4.23 (m, 2 H, H12), 4.15 (m, 1 H, H3), 3.90 (dd, 1 H, H10′, J=20.0, 2.0), 3.79 (dd, 1 H, H10′, J=20.0, 4.6), 3.32 (dd, 1 H, H10, J=17.7, 2.8), 2.88 (dd, 1 H, H10, J=17.7, 9.7), 1.74 (m, 2 H, H13, J=7.0), 1.00 (t, 3 H, H14, J=7.5). ^{13}C NMR ($CDCl_3$): δ 10.2 (C14), 21.8 (C13), 31.8 (C10′), 40.0 (C10), 41.5 (C3), 65.3 (C2), 67.4 (C12), 106.5 (C3′), 112–142 (aromatic C), 125.6 (C2′), 168.1 (C11′), 174.0 (C11).

Crystal structure determination of **5a**. The experimental details in the crystallographic study of **5a** are presented in Table 1 and the results in Tables 2 and 3. Diffraction data were collected on an Enraf–Nonius CAD-1 diffractometer at 122(2) K using the ω/2θ scan technique with graphite monochromated Cu Kα radiation. Data reduction was performed using the DREADD program package[9] including corrections for Lorentz and polarisation effects. The structure was solved by direct methods using SHELXS86 and least-squares refined on F^2 using SHELXL93.[10,11]

Acknowledgements. We thank Flemming Hansen for assistance in the experimental crystallographic work. The Danish Natural Science Research Council supported this research by financing the X-ray diffractometer.

References

1. Bergman, J., Koch, E. and Pelcman, B. *Tetrahedron Lett. 36* (1995) 3945.
2. Bergman, J. *Chem. Scr. 27* (1987) 539.
3. Bergman, J., Koch, E. and Pelcman, B. *Tetrahedron 51* (1995) 5631.
4. Chandrasekhar, K. and Raghunathan, S. *Acta Crystallogr., Sect. B 38* (1982) 2534.
5. Hashizume, K. and Shimonishi, Y. *Bull. Chem. Soc. Jpn. 54* (1981) 3806.
6. Based upon 102 hits from a search of the Cambridge Structural Database.
7. Thomas, W. A. In: Money, E. F., Ed., *Annual Review of NMR Spectroscopy I*, Academic Press, London 1968, pp. 72–74.
8. Cutler, H. G. *Plant Cell Physiol. 9* (1968) 593.
9. Blessing, R. H. *Crystallogr. Rev. 1* (1987) 467.
10. Sheldrick, G. M. *Acta Crystallogr., Sect. A 46* (1990) 467.
11. Sheldrick, G. M. SHELXL93. *Program for the Refinement of Crystal Ctructures.* University of Göttingen, Germany 1993.

Received October 9, 1997.