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Syntheses of Large-Ring Bis-Indolic Dilactams

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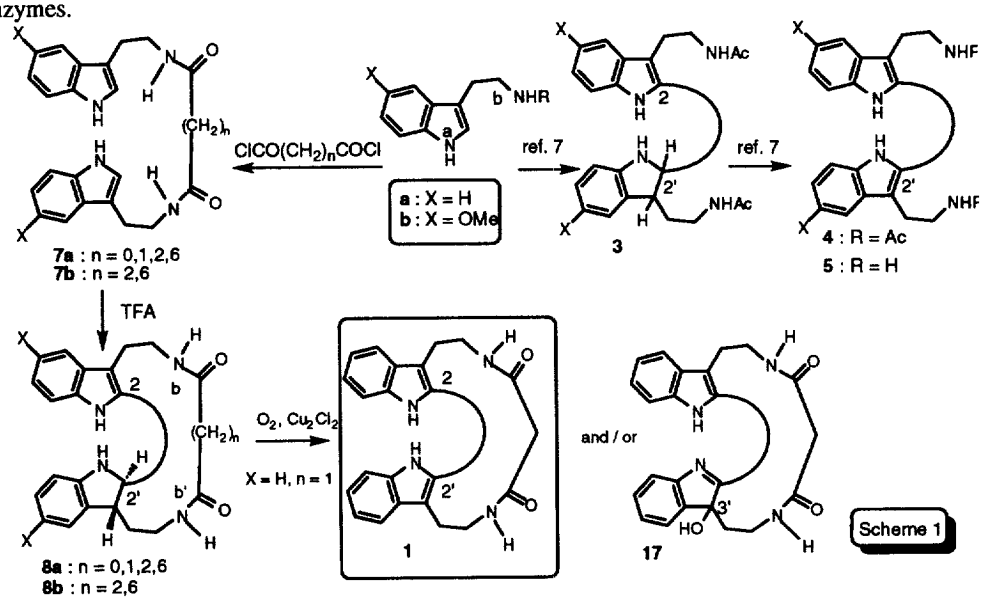
Abstract : Fifteen macrocycles ranging from 11 to 26 atoms, containing two tryptamine units connected by an acyl chain between the N(b) and N(b') atoms and a (poly)methylene linker (or a bond) between C(2) or C(6'), were prepared by two different procedures.

Large-size ring formation still constitutes to be a challenge for organic chemists, even though specific methodologies have been designed by Lehn.[3] Besides purely physical interests in ionic[4] or molecular[5] recognition, macrocycles can have interesting biological properties, as it has been known for a long time for cyclopeptides and macrolide antibiotics.[6] It is not easy to explain why a cyclic large molecule is biologically more efficient than a linear or even a branched one, but it is an obvious fact that cyclic peptides have a far better bioavaibility and metabolic stability than their linear counterparts. This can be the consequence of the occurence of highly lipophilic conformations, in which polar (cleavable) groups are protected from action of enzymes.



In this paper we describe the preparation of two kinds of macrocycles **1** and **2**, containing two tryptamine molecules connected by an acyl chain between the N(b) and N(b') atoms. In the first series (**1**), carbons 2 and 2' are linked by a single bond; while in the second series (**2**), these carbons are spaced by a polymethylene

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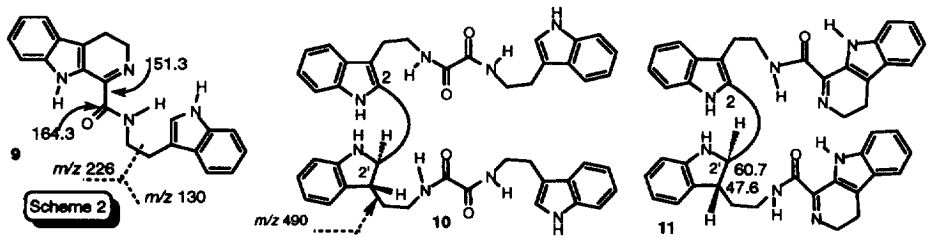
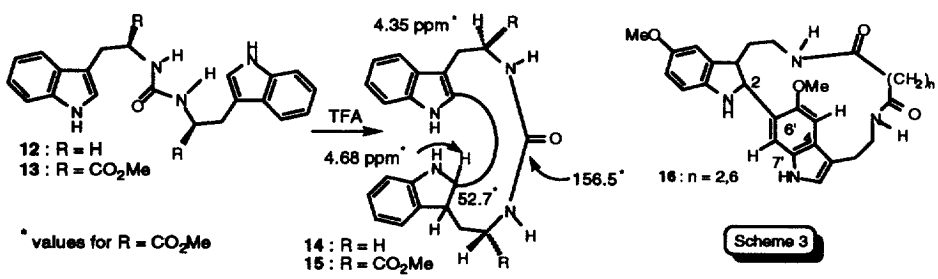
chain. This work was initiated by our findings[7] on the melatoninergic activity of our 2,2'-melatonin dimer **4b**, which was synthesized (Scheme 1) in two steps from melatonin itself: acidic dimerization to **3b** and oxidation of the latter to **4b**. Since it is known that melatonin receptors can accept an acyl group larger than acetyl,[8] we intended to prepare cyclic diamides **8**, whose conformation (and especially the dihedral angle between the indolic systems) could be influenced by the lenght of the diamide chain.

We first tried to hydrolize (aqueous HCl or NaOH) **4a** and **4b** into "bis-tryptamines" **5a** and **5b** but the yields were lower than 20%. Therefore, we changed the sequence, and we tried to perform the lactamization before the ring closure, applying our former "dimerization-oxidation" reaction to diamide **7**.[9]

When X=H and n=1,2 or 6, acidic treatment (TFA, r.t., ~24 h, tlc monitoring) afforded macrodilactam **8a** as a sole isomer.[10] The depicted stereochemistry is thought to be identical as in the acyclic series.[11] The reaction can be performed on a 10 mmol scale, with yields varying from 41% (n=1) to 28% (n=6). Dilactam **7a** (n=0) gives a mixture of four derivatives in TFA at r.t.: the expected cyclic diamide **8a** (n=0), a β-carboline **9**, together with the products of their acidic dimerization **10** and **11** (Scheme 2). The ratio between these derivatives varies with the reaction time. In pure TFA **8a** (n=0) can be isolated in 19% yield after 4 h as a mixture of two rotamers (it is known that α-ketoamides have a high torsional barrier),[12] along with 5% of β-carboline **9**. After 10 days, **7a** nearly disappeared, and we obtained **10** (7%) and **11** (7%) together with 4% of remaining **8a** (n=0). After 3 weeks, the major product was **11** (13%), followed by **10** (11%). Finally, the highest yield of **10** (13%) could be reached after 18 h in a mixture of TFA:CH_2Cl_2 1:10 v/v.



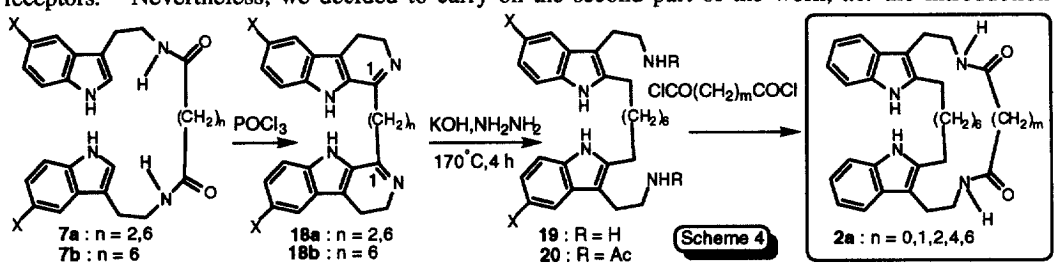
The formation of a β-carboline like **9** was never observed with **7**, when n≠0: it can be the result of steric effects appearing during the cyclization of **7a** (n=0) into **8a** (n=0). This kind of Bischler-Napieralsky-like ring closure was already observed by Biswas et al.[13] in trifluoroacetic acid anhydride. It can be noted that the 1-acyl-β-carboline system is encountered in several important classes of natural products like eudistomines[14] and oxopropalines.[15] Structural assignement[16] of **9**, **10** and **11** is based on the characteristic UV absorption of the 1-carboxamido-2,3-dihydro-β-carboline system (221, 247, 291, 332 nm) for **13**, superimposed to that of the indole-indoline one for **15** (224, 246, 285, 294, 333 nm), as well as on ^{13}C NMR data and MS fragmentation.



We could also observe that the ureas **12** and **13** (prepared by the action of triphosgene on tryptamine and methyl L-tryptophanate, respectively) cyclized into **14** (32%) and **15** (25%) in TFA (48 h, r.t.). ^{1}H and ^{13}C NMR spectra of **15** clearly proved the complete stereoselectivity of the ring closure (Scheme 3).

When X=OCH_3, acidic cyclization of **7b** (n=2,6) follows two ways, as in the acyclic series. Beside the expected 2,2'-cyclization to **8b** (n=2,6), obtained in a yield of 17 and 12%, respectively, was observed a 2,6'-cyclization giving rise to 17-and 21-membered ring products **16** (Scheme 3), whose structure was extensively studied by ^{1}H and ^{13}C COSY experiments.[17] To our knowledge, these latter derivatives are the first bis-indolic "ansa" compounds ever described.

The oxidation of indole-indoline **8** into bis-indole **1** proved to be far more troublesome than in the acyclic series.[7] It was studied in detail on compound **8a** (n=1). After a range of unsuccessful attempts, it was found that dioxygen could afford **1a** (n=1) in 38% yield in a 10:1 acetic acid-water mixture, at r.t. for 3 days in the presence of 0.1 equiv of Cu_2Cl_2, if the reaction, work-up, and chromatographic separation were performed in darkness. Otherwise the only product was the 3'-hydroxyindolenine **17** (Scheme 1) obtained as a sole isomer in 55% yield (this structure is given on the basis of similar observations in the acyclic series).[18] Unfortunately, according to the biological tests, none of these compounds showed promising affinities for melatonin receptors.[19] Nevertheless, we decided to carry on the second part of the work, *i.e.* the introduction of a



polymethylene linker between carbons 2 and 2'. It has been shown in the literature that 2-substituted tryptamines can be prepared from 1-substituted-3,4-dihydro-β-carbolines by reductive cleavage of the C1-N2 azometine bond.[20] Since bis-3,4-dihydro-β-carbolines are theorically obtainable from diamides **7**, we tried to follow the sequence **7** → **18** → **19** → **2** (Scheme 4). $POCl_3$ in boiling toluene (24 h) converted **7a** (n=2,6) and **7b** (n=6) into **18a** (n=2, 56%, n=6, 29%) and **18b** (n=6, 56%). [21] Reductive cleavage of the β-carboline rings of **18a** (n = 6) and **18b** (n=6) along the Harley-Mason procedure (Huang Minlong modification of the Wolff-Kishner reaction) gave the corresponding bis-tryptamines **19a** (n=6) and **19b** (n=6) in very good yields.[22] Acetylation of the latter two (AcCl, Et_3N) gave the respective diamides **20a** and **20b**. Interestingly, the ^{1}H NMR signals of **20a** in DMSO are not doubled, which excludes the presence of rotamers.

Unfortunately, the lactamization of **19** by acid dichlorides has been far less successful. The "best" results were gained by using stoechiometric amounts of the acylating reagent. Yields varied from 29% (**2a**: n=6, m=2) to 94% (**2a**: n=6, m=0). It could be noted that high-dilution conditions after Lehn[3] nearly triplicated the yield of **2a**: for n=m=6 it increased from 13% to 36%. Five compounds of type **2a** have been synthesized, whose ring size varies from 20 to 26 carbon atoms. At 293 °K in d_6-DMSO ^{1}H NMR spectra of all the derivatives **2a** showed the symmetry of the molecule. Albeit in most cases compounds **2a** possessed sharp melting points, and ^{1}H or ^{13}C NMR spectra lacked parasite peaks, combustion analyses are not satisfactory, perhaps due to inorganic pollution (chelation). Otherwise, HREIMS, as well as UV, IR, and NMR data left no doubt on the structures.[23]

Cytotoxicity of **2a** was measured on experimental leukemia cells L 1210: compound **2a** (n=6, m=4) exhibits an IC_{50} of 17.4 µM/L. Other biological data will be reported in due course.

We are currently working on the chemical modification of the links between the indole 2-positions.

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9. Diamides **7a** (n=0, 1, 2, 6) and **7b** (n=1, 2, 6) were prepared from tryptamine or 5-methoxytryptamine and the corresponding diacid dichloride (1 equiv), in CH_2Cl_2, in the presence of Et_3N (1 equiv) at r.t. (26%-92%, not optimized).
10. Unless mentioned, all compounds gave satisfactory analyses. UV, IR, ^1H NMR, HREIMS and, in most cases, ^{13}C NMR were performed. Typical data for **8**: **8a** (n=2). mp=198-200 °C. UV: 223, 284, 292 nm. IR (KBr): 3302, 3057, 2936, 1634, 1545 cm^{-1}. HREIMS: calc. 402.2056, found 402.2072. ^1H NMR (d_6-DMSO): 3.38 (m, 1H, 3'-H), 4.85 (dd, 1H, J=4.5 and 13.5 Hz, 2'-H). ^{13}C NMR: 30.9 (CO-$\underline{CH_2}$), 35.9 ($\underline{CH_2}$-N), 46.9 (C-3'), 59.9 (C-2')[COSY].
11. In these cyclizations only one isomer was observed. The value of the coupling constant between 2'-H and 3'-H varies from 4.5 Hz (**8a**, **n=1**) to 9 Hz (**8a**, n=6), therefore it does not allow to conclude on the relationship between them. A conformational study by molecular dynamics (Insight II) of these compounds revealed that the length of the diamide chain does not influence notably the relative orientation of the aromatic systems: the dihedral angle between C2'-H and C3'-H would be about 140° for a *trans* relationship, and around 20° for a *cis* one. The observed coupling constants are consistent with a *trans* system.
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16. HREIMS data: **8a** (n=0): $C_{22}H_{22}N_4O_2$, calc. 374.17505, found 374.17498; **9**: $C_{22}H_{20}N_4O$, calc. 356.1742, found 356.1690. HRFABMS (glycerol) data: **10**: $C_{44}H_{44}N_8O_4$, calc. 748.3456, found 748.3471; **11**: $C_{44}H_{41}N_8O_2$ $[M+H]^+$, calc. 713.3101, found 713.3229.
17. **16** (n=2) UV: 225, 280, 300 nm. IR (KBr): 3298, 2944, 1640, 1560, 1551, 1491 cm^{-1}. MS: base peak m/z 160. HREIMS $C_{26}H_{30}N_4O_4$, calc. 462.2259, found 462.2263. ^1H NMR (d_6-DMSO): 2.90 (m, 1H, H-3), 4.96 (d, J=11 Hz, 1H, H-2), 7.20 (d, J=1 Hz, H-4'), 7.63 (s, 1H, H-7'). ^{13}C NMR: 50,3 (C-3), 63.3 (C-2), 127.0 (C-6').
18. **1a** (n=1) UV: 229, 315 nm. ^1H NMR (CD_3OD): 3.06 (m, 4H, Ar-CH_2), 3.35 (m, 4H, CH_2-N), 3.75 (s, 2H, $COCH_2CO$). ^{13}C NMR: 110.0 (C-3), 128.5 (C-2), 136.6 (C-6a). **17** UV: 244 (sh), 253 (sh), 369 nm. HREIMS $C_{23}H_{22}N_4O_3$, calc. 402.1692, found 402.1716. ^{13}C NMR (CD_3OD): 86.9 (C-3').
19. Melatoninergic activity was evaluated by displacement of 2-^{125}I-melatonin of his receptors in homogenate of *pars tuberalis* of sheep brain.
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21. **18a** (n=6) UV: 225 (sh), 242 (sh), 319, 351 (sh). HREIMS $C_{28}H_{30}N_4$, calc. 422.2470, found 422.2461. ^{13}C NMR ($CDCl_3$): 162.6 (C-1).
22. **19a** (n=6)(85%), mp 55-56 °C. HREIMS $C_{28}H_{38}N_4$, calc. 430.3096, found 430.3084. **19b** (n=6)(99%), ^{13}C NMR ($CDCl_3$): 153.7 (C-5). EIMS m/z 174, base peak.

23. **2a**

				HREIMS		^{13}C NMR ($CDCl_3$ or d_6DMSO, 353°K*)		
n	yield	mp °C	formula	calc.	found	C=O	indole C-2	indole C-7a
0	94	74-75	$C_{30}H_{36}N_4O_2$	484.2838	484.2831	159.7	135.5	136.7
1	33	123-125	$C_{31}H_{38}N_4O_2$	498.2995	498.2915	167.5	135.3	136.9
2	29	196-197	$C_{32}H_{40}N_4O_2$	512.3151	512.3152	172.5	135.3	136.6
4	36	129-131	$C_{34}H_{44}N_4O_2$	540.3461	540.3464	171.5*	135.4*	136.6*
6	36	236	$C_{36}H_{48}N_4O_2$	568.3792	568.3777	171.7*	135.4*	136.6*