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Synthesis of Tricyclic Phenylpyrrole Lactams, New Models of Antitubulin Agents

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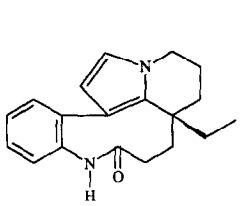
Abstract: *The tricyclic lactams **3** and **4** having a phenylpyrrole framework have been prepared from the arylpyrroles **5** and **16** respectively. These structural analogs of rhazinilam **1** present, like the latter, an interesting antitubulin and cytotoxic activity.*

Rhazinilam **1**[1], an indole secoalkaloid related to the aspidospermane group, has been isolated from different Apocynaceae species, but its biological activity was not known up to date.

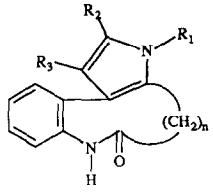
In the tubulin-microtubular system this compound was proven to be a new antitubulin agent showing both a taxol-type activity on the disassembly of microtubules and a vinblastine-type activity on their assembly.[2a,2b]

Within the scope of our research program, we aimed at the elucidation of the structural requirement for tubulin binding. We prepared a series of analogs of rhazinilam **1**, the tricyclic lactams **2** in which the spatial relationship between the aromatic subunits depends on the size of the lactam ring. In particular the dihedral angle between the phenyl and the pyrrole ring of these analogs can range from 0° (n = 0) to 90° (n = 3).

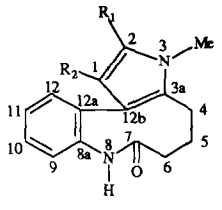
We describe here the synthesis of compounds **3** and **4** which are found to inhibit the *in vitro* depolymerization of purified bovine brain tubulin.



1 (-)



2 (n=0 ⟶ n=4)
R_1=H ou Me R_2,R_3=H ou alkyl



3 R_1= n-Bu R_2=Me
4 R_1=R_2=H

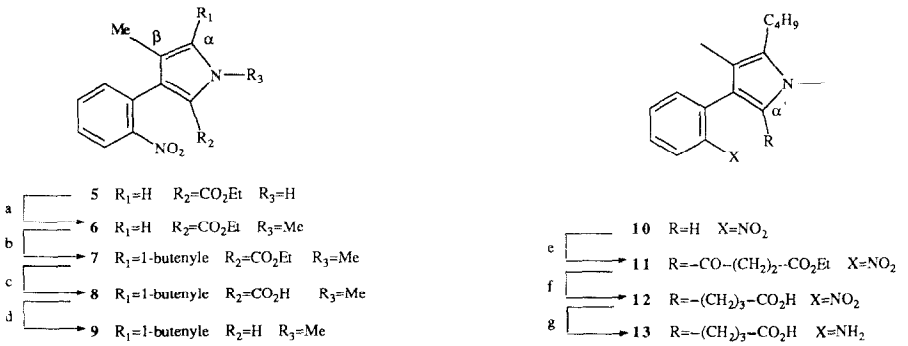
Synthesis of lactam 3 carrying a hydrophobic chain on the pyrrole ring :

The starting phenylpyrrole **5** is obtained according to Barton and Zard[5] from (2-nitrophenyl)-1-nitro-2-propene.[6] The reaction series described in scheme 1 leads to the α'-unsubstituted phenylpyrrole **10.**

The formation of the 9-membered lactam ring requires the setting of a suitably functionalized 4-carbon chain that is branched on position α' by Friedel-Crafts acylation.

The treatment of phenylpyrrole **10** with β-carbomethoxypropionic acid chloride leads to the ketopyrrole **11** that gives directly the acid **12** on reaction with $NaBH_4$, probably by reduction of an azafulvenium type intermediate[8] (Scheme 1).

After reduction of the nitro group, one obtains the amino acid **13** that cyclises specifically into the lactam **3** (yield : 59%) in presence of CMC under high dilution conditions.[10]



(Synthesis of **5**) : CN-CH_2-CO_2Et 1.2 eq ; DBU 1.5 eq ; THF/t-BuOH : 2/1 ; 3 h at 50°C ; yield : 98%. (a) NaH ; p-TosMe ; THF ; 50°C ; yield : 90%. (b) CH_3-CH_2-CH_2-CHO 6 eq ; THF ; HCl conc., $MgSO_4$ anh ; yield : 80%. (c) NaOH conc./MeOH : 1/2 ; yield : 90%. (d) Quinoline ; Cu_2O ; 170°C ; yield : 90%. (**9** → **10**) Pd/C at 10% ; AcOEt ; H_2 3 Atm ; yield : 90%. (e) Cl-CO-CH_2-CH_2-CO_2Et 2.3 eq ; $ZnCl_2$ anh 1.5 eq ; CH_2Cl_2 anh ; reflux 2 h; yield : 55%. (f) $NaBH_4$ 1 eq ; EtOH at 95%. (g) PtO_2 ; EtOH ; H_2 3 Atm ; yield : 90%.

Scheme 1

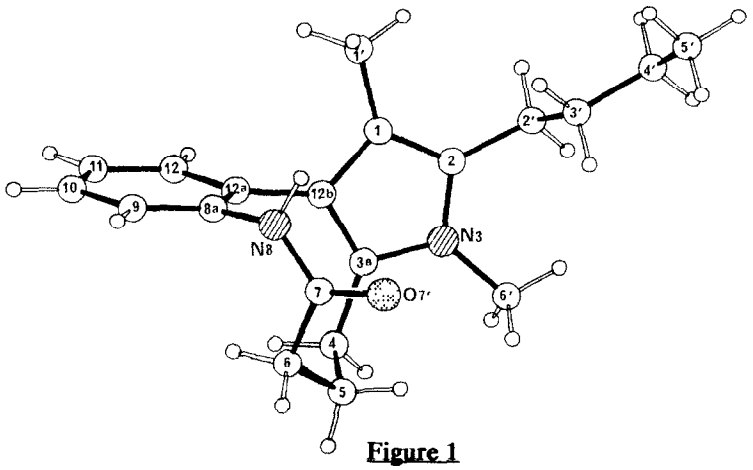


Figure 1
(perspective view of lactam **3**)

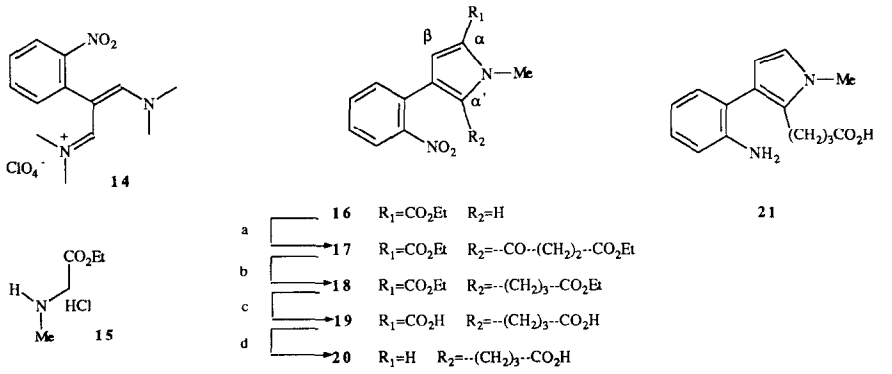
Figure 1 shows the structure of lactam **3** obtained by X-ray analysis.[11] It establishes the conformation of the 9-membered lactam ring. Indeed the dihedral angle between the aromatic rings are close to those measured for rhazinilam **1** ; the value of the dihedral angle is 85° for **3** whereas one measures 90° for rhazinilam **1**.[4] This tricyclic compound with a phenylpyrrole subunit possesses the structural profile of rhazinilam **1** and thus constitutes a first simplified model of this alkaloid.

Synthesis of the α,β unsubstituted lactam 4 :

The starting compound for the synthesis of lactam **4** is the phenylpyrrole **16** which is prepared from o-nitrophenyl acetic acid *via* the vinamidinium salt **14** and the sarcosine hydrochloride **15** according to Gupton and coll.[12]

The reduction of the ketone function of the desactivated ketopyrrole **17** is accomplished only in acidic medium in presence of $NaBH_4$[13] yielding phenylpyrrole **18.**

The decarboxylation of the α-pyrrole acidic function of compound **19** is carried out only in the absence of solvent by using the method described by Elguero and coll.[14] for 3-methylpyrrole. After reduction of the nitro group, the amino acid **21** is obtained and cyclised under the same conditions as before to yield the unsubstituted α,β lactam **4**[15] (yield : 63%) (Scheme 2).



(Synthesis of **14**) 1/o-NO_2-C_6H_4-CH_2-CO_2H 1 eq ; $POCl_3$ 3 eq ; DMF 15 eq. 2/$NaClO_4$ 1.1 eq/H_2O.3/recrystallisation MeOH. Total yield : 53%. (**14** —> **16**) : **14** 1eq ; **15** 1.5 eq ; NaH (60% in mineral oil) 2.5 eq ; EtOH anh ; yield : 60%. (a) Cl-CO-CH_2-CH_2-CO_2Et 2.3 eq ; $ZnCl_2$ anh 1.5 eq : CH_2Cl_2 anh ; reflux 2 h ; yield : 55%. (b) $NaBH_4$ 3.2 eq ; CF_3CO_2H ; 0°C; yield: 88%. (c) NaOH/MeOH : 1/9 ; reflux ; yield : 90%. (d) 1/Cu powder ; 150°C ; 5 mm of Hg 2/retake with AcOEt ; yield : 70%. (**20** —> **21**) PtO_2 ; EtOH ; H_2 1 Atm ; yield : 90%.

Scheme 2

The lactams **3** and **4** (new compounds of series **2**) have the capacity to interact with tubulin in a rhazinilam-type fashion. This observed activity, although it remains inferior to that of rhazinilam **1** (~ 1/200), confirms the importance of the dihedral angle values since the 7 and 8 membered lactams of type **2** (respectively n = 1 and n = 2 with R_1 = R_3 = Me and R_2 = butyl) are inactive *vis-à-vis* tubulin.[3]

The final results of the structure-activity correlation will be presented shortly.

Acknowledgements

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9. Spectral data of **3** : IR ($CHCl_3$) : 3377, 1660. UV (EtOH) λ_{max} (ϵ) : 202 (15700) ; 228 ep (4650); 285 (4000). SM(IE) : 310 ($M^{+\cdot}$), 257, 225. NMR^{1}H 400 MHz ($CDCl_3$) : 0.94 (t, J = 7.5, 3H, $\underline{CH_3}$-CH_2-) ; 1.37 (sext, J = 7.5, 2H, CH_3-$\underline{CH_2}$-) ; 1.46 (quint, J = 7.5, 2H, CH_3-CH_2-$\underline{CH_2}$-) ; 1.64 (s, 3H, C_1-Me) ; 1.79 (multiplet, 1H) ; 1.86 (q*, J = 12, 1H) ; 2.01 (td, J = 12, J = 1.5, 1H) ; 2.15 (multiplet, 2H) ; 2.52 (t, J = 7.5, 2H, C_2-$\underline{CH_2}$) ; 2.71 (ddd, J = 15, J = 3, J = 3, 1H) ; 3.45 (s, 3H, N-Me) ; 6.43 (s*, 1H, N-H) ; 7.28 (m, 1H) and 7.38 (m, 4H) (arom. H). NMR^{13}C ($CDCl_3$): 9.74 ($\underline{C}H_3$-C_1) ; 13.99 ($\underline{C}H_3$-CH_2-) ; 22.50 (CH_3-$\underline{C}H_2$-) ; 24.61 (CH_3-CH_2-$\underline{C}H_2$-) ; 25.73 (-$\underline{C}H_2$-C_2) ; 26.27 (C_4) ; 29.78 (N-$\underline{C}H_3$) ; 32.44 (C_5) ; 33.42 (C_6) ; 112.07 (C_1) ; 118.85 (C_{12b}); 127.36 (C_2) ; 128.15 (C_{11} and C_{12}) ; 129.11 (C_{3a}) ; 131.76 (C_9 and C_{10}) ; 138.54 (C_{8a} or C_{12a}); 138.57 (C_{12a} or C_{8a}) ; 176.93 (C_7).
10. CMC = tosylate of 1-cyclohexyl-3-(2-morpholino-4-ethyl)carbodiimide :
    reaction conditions : a methylene chloride solution of amino acid (10^{-3} M) is added during a 30 h period by means of a syringe pusher to a methylene chloride solution of CMC (10^{-3} M) at room temperature.
11. Crystallographic data of **3** : $C_{20}H_{26}N_2O$, M = 310.44, Monoclinic, $P2_1/n$, a = 9.873(3), b = 9.068(3), c = 20.167(8) Å, β = 95.66(2)°, V = 1796.8 Å^3, d_c = 1.148 gcm^{-3}, Z = 4 ; λ (CuKα)= 1.5418 Å, diffractometer Nonius CAD4, μ = 4.8 cm^{-1} (negligible absorption). Optimized structure by least squares, complete matrix. Hydrogen atoms, placed at theoretical position (d = 1.00 Å). R = 0.067, R_w = 0.108 ($R_w = [\Sigma_w(F_o - \mid F_c \mid)^2/\Sigma_w F_o^2]^{1/2}$) for 2420 observed reflexions. ($I \geq 3\sigma(I)$). The list of atomic coordinates, interatomic distances and valence angles was deposited as complementary doumentation at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, United Kingdom.
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15. Spectral data of **4** : IR ($CHCl_3$) :3379, 1662. UV (EtOH) λ_{max} (ϵ) : 223 (8149), 261 (1853). SM(IC) : 241 (MH^+), 199, 182. NMR^{1}H 400 MHz ($CDCl_3$) : 1.72 (m, 2H, CH_2) ; 1.91 (m, 2H, CH_2) ; 2.13 (m, 2H, CH_2) ; 3.57 (s, 3H, N-Me) ; 5.86 (d, J = 3, 1H, C_1-H) ; 6.54 (s*, 1H, NH); 6.58 (d, J = 3, 1H, C_2-H) ; 7.29 (m, 1H) and 7.39 (m, 3H) (H aromatic). NMR^{13}C ($CDCl_3$) : 25.31 (C_4); 26.33 (C_5) ; 33.61 (N-CH_3 and C_6) ; 107.43 (C_1) ; 119.64 (C_{12b}) ; 121.41 (C_2) ; 128.08 (C_{11} and C_{12}) ; 128.41 (C_{10}) ; 129.75 (C_{3a}) ; 131.37 (C_9) ; 138.24 (C_{8a} and C_{12a}) ; 176.92 (C_7).