SYNTHESIS OF 4,5-DISUBSTITUTED-2-PIPERIDINONES FROM 4-PIPERIDINONES.

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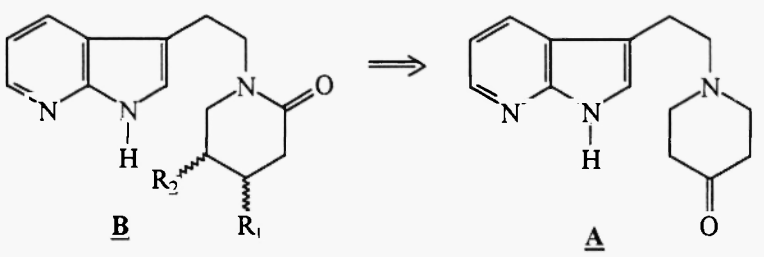
Abstract- A general method for the synthesis of 4,5-disubstituted-2-piperidinones as suitables synthons for the elaboration of analogs of corynantheidine and dihydrocorynantheine alkaloïds is described from 4-piperidinones as starting material.

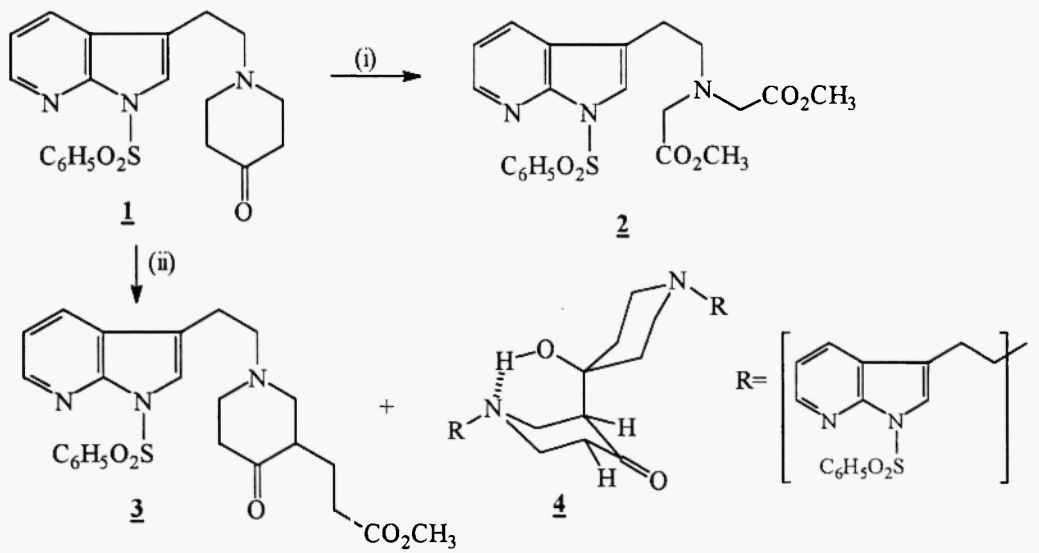
During a course of a recent project concerning the synthesis of 11-azaindoloquinolizidines disubstituted on the 2 and 3 positions, we required several 4,5-disubstituted-2-piperidinone (**B**) as suitables synthons. Several methods exist for the synthesis of indolo or benzoquinolizidines from a 3,4-disubstituted piperidine, by cyclization through a lead tetracetate oxydation (Fujji procedure) (1) or through a modified Polonovski reaction (2). However, such methods were uneffectives in the 7-azaindolic serie (3), no more than the use of an O-lactim ether obtained from a 4,5-disubstitued-2-oxopiperidine (4). In this context, we had to find a general strategy for the obtention of 11-azaindoloquinolizidines. Our approach consists in the transformation of 1-(azatryptophyl)-4-piperidinone (**A**) into 4,5-disubstituted-2-piperidinone (**B**) which can be further submitted to Bischler-Napieralsky cyclizations (5). In this paper, we describe the synthesis and the stereochemistry of such lactams obtained by a modified "Fujii procedure".

Scheme 1



In this context, our first consideration, was to find a general method of alkylation of 4-piperidinone **1** (6). Treatment of this last with LiHMDS at -78°C in THF followed by addition of ethyl iodide did not give any results; change of the base (LDA) or the use of a sylilated enol ether were no more effective. From these observations, we investigated over electrophilic species. Using methyl bromoacetate led exclusively to compound **2** through a retro-Michael type reaction. Structure of **2** was easily determined by ^{1}H-nmr with two singlet at δ 3.58 (4H) and 3.67 (6H) attributed to the methoxycarbonyl groups. Using methyl bromopropionate, the result was quite different, and we obtained the desired alkylated derivative **3** as the minor product (5%), admixed with 1-[2-(1-phenylsulfonylpyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-3-[1-[2-(1-phenylsulfonyl-pyrrolo[2,3-*b*] pyridin-3-yl)ethyl-4-hydroxypiperidin-4-yl]-4-piperidone **4**, resulting of an aldol condensation, as the major product (scheme 2).

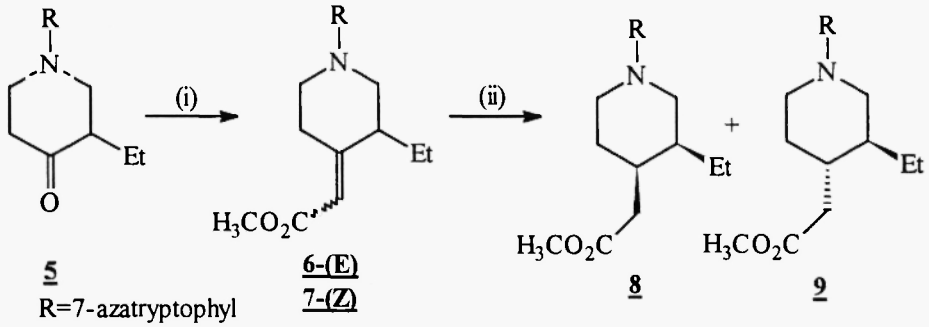
Scheme 2



(i) a) LiHMDS/THF/-78°C, b) $BrCH_2CO_2CH_3$ (ii) a) LiHMDS/THF/-78°C, b) $BrCH_2CH_2CO_2CH_3$

Structural determination of **4** was realized by mass spectrometry which indicated a $M^{+\cdot}$ peak at m/z = 767 and by nmr studies (2D COSY ^{1}H-^{1}H and ^{1}H-^{13}C) (7). The conformation of the piperidinone ring having the 3-substituant on an axial position is stabilized by the N-H interaction (8) and well confirmed by the observation of the 2D-COSY 1H-1H spectra which showed a "W" long range coupling between H-3_{eq} and H-5_{eq} (9). Finally our required 1-(7-aza tryptophyl-2-yl)-3-ethyl-4-piperidinone **5** was obtained by condensation of 3-ethyl-4-piperidinone (10) with 7-aza-(2-bromoethyl)indole (11) according to our published method (6). Treatment of **5** with methyl diethylphosphonoacetate and potassium tertiobutylate in dimethylformamide led to the diastereoisomeric mixture of methyl 1-[2-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-3-ethylpiperidine -$\Delta^{4,\alpha}$ -acetates **(E)-6/(Z)-7** in a 3.5/1 ratio (12) (scheme 3).

Scheme 3

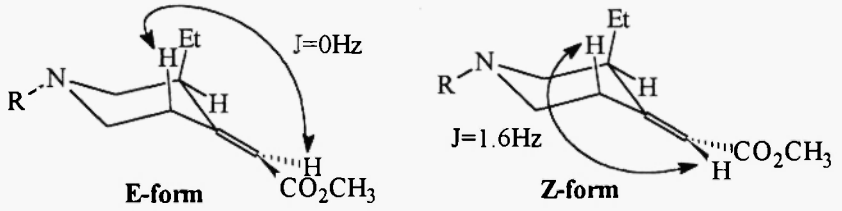


5 R=7-azatryptophyl **6-(E)** **7-(Z)** **8** **9**

(i) $(EtO)_2POCH_2CO_2CH_3$/tBuOK/DMF (10°C) (ii) H_2/Pd-C 10%/MeOH

Determination of the structure of the two isomers was made evident by ^1H and ^{13}C-nmr .^{13}C-nmr spectrum showed for **6** the following caracteristic signals at δ 163.0 (C-4), δ 112.7 (=CH), δ 167.0 CO_2CH_3 and for **7**: δ 163.5 (C-4), 114.2 (=CH), 166.8 (CO_2CH_3). ^1H-nmr spectrum showed the vinylic proton of **6** at δ 5.28 as a singlet, while the vinylic proton of **7** at δ 5.68 as a doublet with $J_{(Hvin.-H3ax)}$ =1.6 Hz. This coupling is only observable when the homoallylic proton is perpandicular to the double bond plan (13). Concerning the Z-isomer **7**, the vinylic proton is coupled only to one proton ($H\text{-}3_{ax}$), while in the E-form **6**, no coupling is observed with H-5. Only an axial position for the ethyl group can explain these observations (scheme 4).

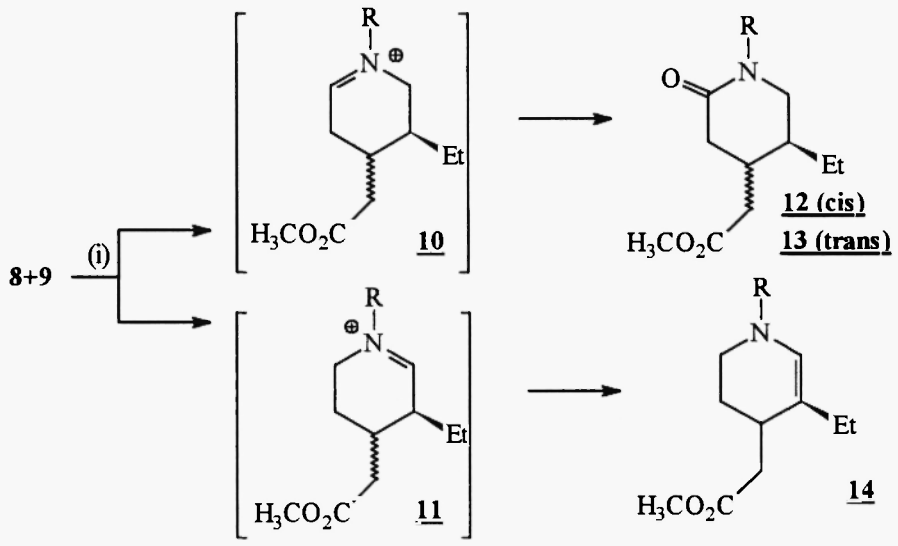
Scheme 4



Subsequent hydrogenation of the diastereoisomers **6** and **7** on a palladium support (Pd-C 10%, CH_3OH) at atmospheric pressure led to the two diastereoisomeric methyl 1-[2-(1H-pyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-3-ethyl-4-piperidine acetate ***cis*-(±)-(8)** and ***trans*-(±) -(9)** in a 1.5/1 ratio (14). Determination of their structures was made by ^1H and ^{13}C-nmr, which showed the disparition of the insaturations, and by the apparition of two tertiary carbons at δ 37.4 and 38.4 for the C-4. Complete ^{13}C attributions of the diastereoisomers were in good agreement with those obtained by Bonjoch and coll. concerning the N-benzyl derivatives (10). Oxydation step was then investigated on compound **8,9** . As treatment of the mixture, following the classical "Fujii" procedure failed to give the expected azaindoloquinolizidines, we investigated several modifications of this procedure. Best result was obtained using five equivalent of mercuric acetate ($HgOAc_2$/EDTA/H_2O/C_2H_5OH). In these conditions, regioisomeric intermediary imminium salts **10,11** formed and evolved to the formation of the two

lactams **12,13** for **10** (45% yield), while the reaction evolved to the elimination product **14** in the case of **11** (scheme 5).

Scheme 5



R=7-azatryptophyl (i) $Hg(OAc)_2$,EDTA/EtOH/H_2O

Characterization of the two lactams was made by ^{13}C-nmr (15) and by comparison with the values of litterature concerning the trans-N-benzyl and N-indolyl-5-ethyl-2-oxopiperidineacetate described by Fujii and Coll. (16).

In conclusion, we have reported an efficient synthesis of diastereoisomeric lactams **12** and **13** using an adapted "Fujii procedure". Studies are now in progress for the stereoselective functionnalisation of the 3-position of the piperidinic ring.

References and notes

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(7) compound 4: 60 %; mp: 145-147 °C; ms (FAB^+): 767 (61 %), 495 (24 %), 285 (41 %), 145 (100 %); ^{1}H-nmr ($CDCl_3$, 400 MHz) δ: 1.50 (m, 2H, H-3'$_{eq}$ and H-5'$_{eq}$), 2.18-1.19 (m, 2H, H-3'$_{ax}$ and H-5'$_{ax}$), 2.25 (m, 1H, H-3$_{eq}$), 2.44 (m, 1H, H-5), 2.61 (m, 2H, H-5 and H-6), 2.77 (m, 1H, H-2), 2.83 (m, 2H, Ar-CH_2CH_2), 2.88 (m, 2H, Ar-CH_2), 2.95 (m, 2H, H-6'), 3.04 (m, 1H, H-6), 3.07 (m, 2H, Ar-CH_2CH_2), 3.10 (m, 1H, H-2), 3.17 (m, 2H, H-2'), 3.25 (m, 2H, Ar-CH_2), 7.14 (m, 2H, H-5"),7.48 (m, 8H, H-2$_{ar}$ et H-3,4,5$_{phe}$), 7.80 (d, J = 8.7 Hz, 2H, H-4$_{ar}$), 8.13 (m, 4H, H-2,6$_{ar}$), 8.35 (d, J = 5.2 Hz, 2H, H-6$_{ar}$); ^{13}C-nmr ($CDCl_3$, 100 MHz) δ: 23.4 and 20.5 (2C, Ar-CH_2CH_2). 33.5 and 33.2 (C-3' and C-5'), 41.5 (C-5), 48.2 and 47.9 (C-2' and C-6'), 52.4 (C-6), 54.4 (C-2), 56.2 and 56.0 (2C, Ar-CH_2CH_2), 56.7 (C-3), 68.1 (C-4'), 116.5 and 114.5 (2C, C-3$_{ar}$), 119.0 and 118.8 (2C, C-5$_{ar}$), 122.7 and 122.4 (2C, C-3a$_{ar}$), 123.7 (2C, C-2$_{ar}$), 127.9 (4C, C-2,6$_{ar}$), 128.6 (2C, C-4$_{ar}$), 129.0 (4C, C-3,5$_{ar}$), 134.1 and 134.0 (2C, C-4$_{ar}$), 138.4 and 138.3 (2C, C-1$_{ar}$), 145.3 and 145.0 (2C, C-6$_{ar}$), 147.5 and 147.4 (2C, C-7a$_{ar}$), 208.5 (C-4).

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(12) compound 6; 69 %;mp : 105-107 °C; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 0.91 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.20-2.10 (m, 2H, CH_2CH_3), 2.18 (m, 1H, H-3), 2.40-2.80 (m, 5H, H-5, H-6 et H-2$_{ax}$), 2.80-3.50 (m, 5H, H-1', H-2' et H-2$_{eq}$), 3.73 (s, 3H, OCH_3), 5.67 (s, 1H, $CHCO_2CH_3$), 7.07 (m, 1H, H-5"), 7.24 (s, 1H, H-2"), 8.06 (dd, J = 7.8 and 1.4 Hz, 1H, H-4"), 8.32 (dd, J = 4.7 Hz and 1.4 Hz, 1H, H-6"),12.01 (s, 1H, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 11.8 (CH_2CH_3), 23.1 (C-2'), 24.0 (CH_2CH_3), 27.6 (C-5), 46.7 (C-3), 50.8 (OCH_3), 54.8 (C-6), 58.6 (C-2), 59.2 (C-1'), 112.4 (C-3"),112.7 ($CHCO_2Me$), 114.8 (C-5"),120.2 (C-3a"),122.5 (C-2"), 127.1 (C-4"), 142.0 (C-6"),149.0 (C-7a"), 163.0 (C-4), 167.0 (CO). Compound 7; 19 %; mp: 106-108 °C; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 0.93 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.5-1.96 (m, 2H, CH_2CH_3), 1.96-2.25 (m, 3H, H-5 et H-3), 2.45-2.78 (m, 3H, H-6 et H-2$_{ax}$), 2.78-3.30 (m, 5H, H-1', H-2' et H-2$_{eq}$), 3.69 (s, 3H, OCH_3), 5.68 (d, $J_{Hvinyl-H-5ax}$ = 1.6 Hz, 1H, =$CHCO_2Me$), 7.07 (m, 1H, H-5"), 7.23 (s, 1H, H-2"),7.94 (d, J = 7.8 Hz, 1H, H-4"),8.32 (d, J = 4.8 Hz, 1H, H-6"),11.40 (s, 1H, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 11.8 (CH_2CH_3). 23.1 (C-2'), 25.4 (CH_2CH_3), 33.6 (C-5), 39.0 (C-3), 50.8 (OCH_3), 55.4 (C-6), 57.3 (C-2), 58.8 (C-1'), 112.7 (C-3"),

114.2 ($\underline{C}HCO_2Me$), 115.1 (C-5"), 120.3 (C-3a"), 122.5 (C-2"), 127.3 (C-4"), 142.2 (C-6"), 149.0 (C-7a"), 163.5 (C-4), 166.8 (CO).

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(14) Only an analytical sample of the major isomer ***cis* (±)-8** could be obtained in a satisfactory degree of purity; mayor isomer ***cis* (±)-8**: ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 11.8 ($CH_2\underline{C}H_3$), 20.6 ($\underline{C}H_2CH_3$), 23.0 (C-2'), 28.6 (C-5), 34.1 (C-4), 39.9 (C-3), 51.4 ($O\underline{C}H_3$), 53.4 (C-6), 55.1 (C-2), 59.5 (C-1'), 112.5 (C-3"),114.7 (C-5"),120.2 (C-3a"),122.4 (C-2"),127.1 (C-4"),141.9 (C-6"),149.0 (C-7a"),173.7 (CO); minor isomer ***trans* (±)-(9)**: ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 11.0 ($CH_2\underline{C}H_3$), 23.2 ($\underline{C}H_2CH_3$), 23.8 (C-2'), 31.8 (C-5), 37.3 (C-4), 38.4 ($\underline{C}H_2CO_2Me$), 41.8 (C-3), 51.6 ($O\underline{C}H_3$), 53.7 (C-6), 58.7 (C-2), 59.6 (C-1'), 112.4(C-3"),115.3 (C-5"),120.2 (C-3a"),122.1 (C-2"),127.4 (C-4"),142.8 (C-6"),148.9 (C-7a"), 173.9 (CO).

(15) compound **12**: ^{1}H-nmr ($CDCl_3$, 360 MHz) δ: 0.8 (m, J = 7.3 Hz, 3H, $C\underline{H}_3$), 1.1- 3.2 (m, 10H, 2 H-3, H-4, H-5, 2 H-6, $C\underline{H}_2CO_2CH_3$, $CH_2\underline{C}H_3$), 3.52-3.70 (m, 2 H-1', 2 H-2', $OC\underline{H}_3$), 7.05 (dd, J = 5.2 and 4.7 Hz, H-5"), 7.16 (s, H-2"),7.98 (dd, J 4.7 and 1.3 Hz H-4"), 8.28 (dd, H-6"), 9.90 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 11.8 ($CH_2\underline{C}H_3$). 20.8 ($\underline{C}H_2CH_3$), 23.1 (C-2'), 32.0 (C-4), 33.9 (C-3), 36.6 ($\underline{C}H_2CO_2Me$), 38.0 (C-5), 48.2 (C-6*), 50.4 (C-1'*), 51.8 ($O\underline{C}H_3$), 111.5 (C-3"),115.4 (C-5"),120.2 (C-3a"),122.6 (C-2"),127.4 (C-4"),142.8 (C-6"),148.9 (C-7a"),168.6 (C-2), 172.7 (CO); ^{1}H-nmr ($CDCl_3$, 360 MHz), compound **13** δ: 0.76 (m, J = 7.4 Hz, 3H, $C\underline{H}_3$), 1.1- 3.5 (m, 10H, 2 H-3, H-4, H-5, 2 H-6, $C\underline{H}_2CO_2CH_3$, $CH_2\underline{C}H_3$), 3.45-3.75 (m, 2 H-1', 2 H-2', $OC\underline{H}_3$), 7.03 (dd, J = 5.2 and 4.7 Hz, H-5"), 7.16 (s, H-2"), 8.00 (dd, J 4.7 and 1.3 Hz H-4"), 8.28 (dd, H-6"), 10.10 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 10.9 ($CH_2\underline{C}H_3$), 23.2 (C-2'*), 23.3 ($CH_2\underline{C}H_3$*), 33.8 (C-4), 38.1 ($\underline{C}H_2CO_2Me$), 38.9 (C-5), 43.0 (C-3), 50.4 (C-1'), 51.7 ($O\underline{C}H_3$), 53.4 (C-6), 111.5 (C-3"),115.4 (C-5"),120.2 (C-3a"),122.6 (C-2"),127.4 (C-4"),142.8 (C-6"),148.9 (C-7a"),168.8 (C-2), 172.5 (CO)

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