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# RING EXPANSION OF SOME 4-AMINOAZETIDIN-2-ONES INTO 4-AMINO-5-IMINOPYRROLIDIN-2-ONES

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*Key Words*

*β-cyanoamides* *4-aminoazetidin-2-ones* *4-amino-5-iminopyrrolidin-2-ones* *iminium ions*

*Abstract:* Ring opening of 4-aminoazetidin-2-ones of three series ( 1-benzazepine, quinoline and linear analog ) using trimethylsilyl cyanide (TMSCN ) led stereospecifically to β-cyanoamides which could cyclize into 4-amino-5-iminopyrrolidin-2-ones in the presence of $AlCl_3$ These heterocycles were also prepared by one-pot reaction (TMSCN + $AlCl_3$ ) . A structural study of these compounds was performed, including X-ray

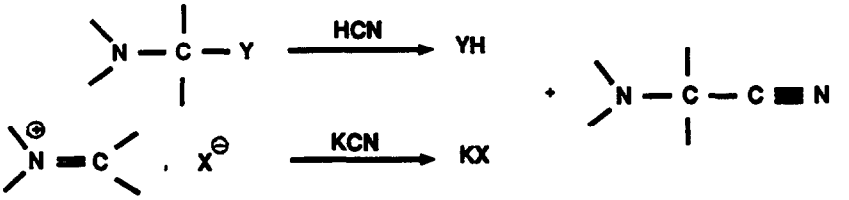
## INTRODUCTION

This work is a continuation of our investigations (1)(2) about the reactivity of some 4-aminoazetidin-2-ones (β-amino-β-lactams), which were prepared by addition of phenyl isocyanate to enamines.

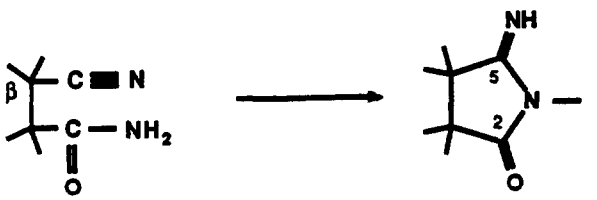
In this paper, we study the ring expansion of these heterocycles into 4-amino-5 -iminopyrrolidin-2 ones.

The strategy of this transformation in based upon the two following considerations :

- α-aminonitriles can be prepared from *gem*-difunctionnal amino-derivatives with HCN(3) or from iminium salts with KCN (4a),(5),(6),(7) .



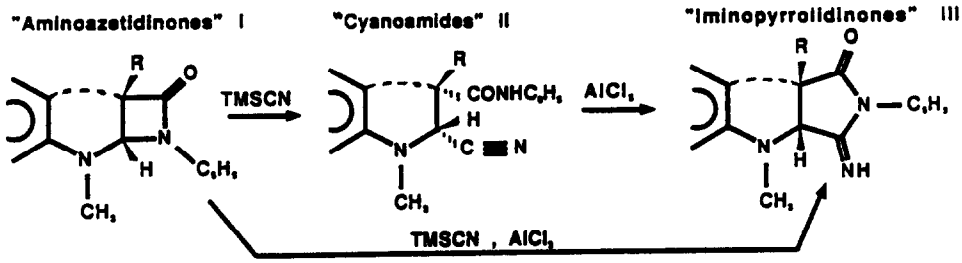

-β-cyanoamides can be converted into 5-iminopyrrolidin-2-ones, by intramolecular cyclization (8),(9),(10)



Starting from these results, the ring expansion of our 4-aminoazetidin-2-ones **I** into the 4-amino-5-iminopyrrolidin-2-ones **III** could be achieved by a two-step process (scheme 1):

- cleavage of the N-1—C-4 bond of the aminoazetidinones by incorporation of a cyano group leading stereospecifically to the β-cyanoamides **II**, in the presence of trimethylsilyl cyanide (TMSCN),
- intramolecular cyclization of **II**, induced by anhydrous $AlCl_3$ .

The use of a mixture of TMSCN and $AlCl_3$ allowed the one-pot synthesis of the iminopyrrolidinones **III**.




- Scheme 1 -

Our results concerning three series of β-amino-β-lactams, in which the amine moiety is either included in heterocycle (quinoline, 1-benzazepine) or not (linear analog) are described here.

## RESULTS

Azetidinones **1,2,3,4** were allowed to react in benzene at room temperature with TMSCN (11) and with or without $AlCl_3$. Two types of compounds were synthetized : the cyanoamides **10,20,30,40** and the iminopyrrolidinones **11,21,31,41.** Our results are shown in scheme 2.

The cyanoamides **10, 20a + 20b** and **40** were prepared using TMSCN without $AlCl_3$ with a 50% yield. However, a catalytic amount of $AlCl_3$ (1/350) was needed for the transformation of **3** into **30** which was always obtained along with about 30% of its cyclization derivative **31.**

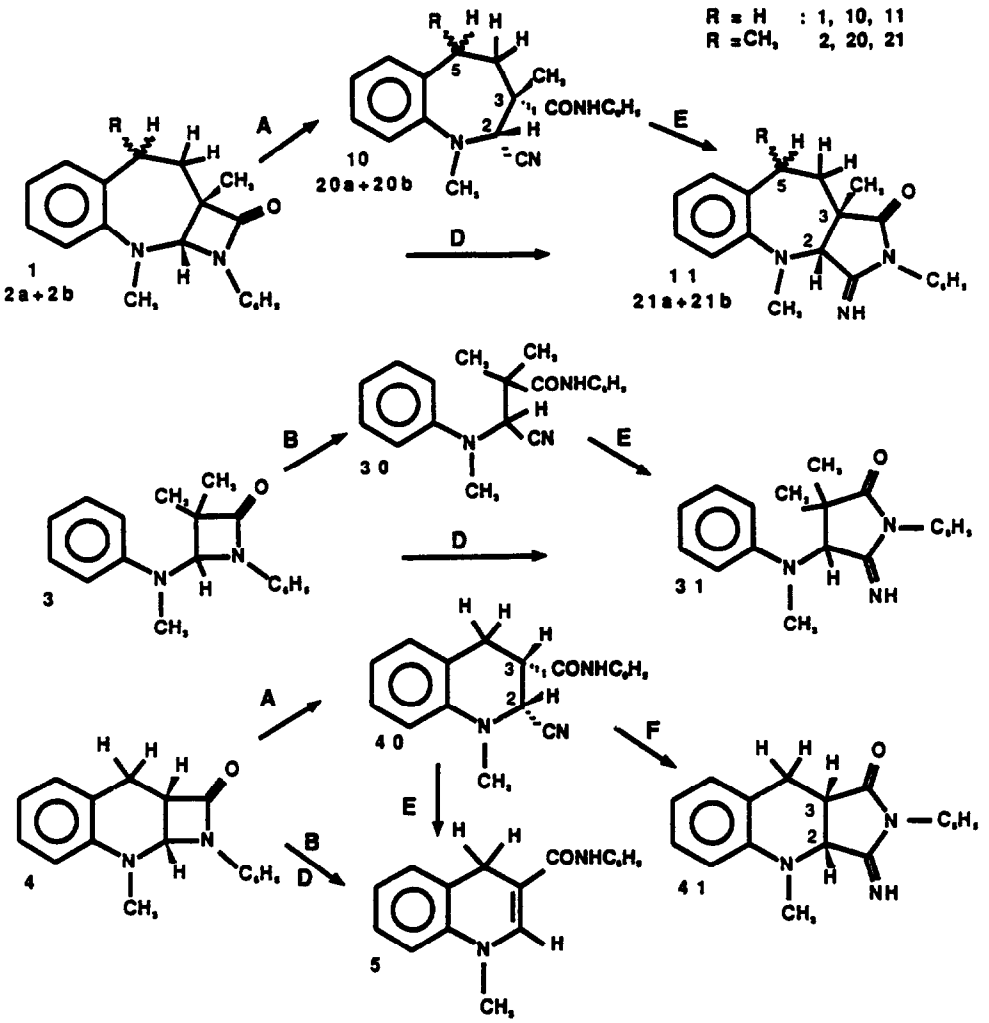
The synthesis of the iminopyrrolidinones **11,21,31** was achieved either from the cyanoamides **10,20,30** or from the azetidinones **1,2,3** (one-pot procedure). In both cases 1 eq. of $AlCl_3$ *per* 1 5 eq. of starting material was used. Yields ranged from 70% to 26% .

With the quinoline derivatives the H-3 substituent induced the previously reported (1),(12) rearrangement of **4** into **5** as well as HCN elimination from **40** which also led to **5** .The iminopyrrolidinone **41** was only avaible by treatment of **40** under alkaline conditions (10) but with a poor yield (10%-not optimized)

In agreement with our previous studies (1),(2) the synthesis of the cyanoamides was diastereospecific As in the starting aminoazetidinones the relationship between H-2 and $CH_3$-3 (or H-2 and H-3) was *cis* and was conserved during the intramolecular cyclization process into iminopyrrolidinones.

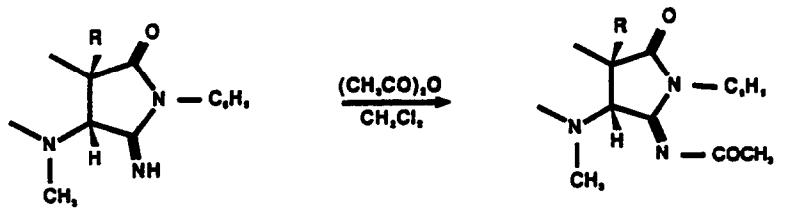
For structural elucidation essentially, N-acetylation of iminopyrrolidinones **11,21,31** leading to **12,22,32** was performed with an 80% yield using $(CH_3CO)_2O$ in $CH_2Cl_2$ at room temperature (scheme 3).

Compounds **20, 21** and **22** were obtained from the unseparated mixture **2a + 2b** in the two stereomeric forms **a** and **b**. In the **a** series $CH_3$-3 and $CH_3$-5 were *trans* whereas in the **b** series they were *cis*.




Reagents A: TMSCN/$C_6H_6$ B: TMSCN/$AlCl_3$ catalytic/$C_6H_6$ D: TMSCN/$AlCl_3$/$C_6H_6$
E: $AlCl_3$/$C_6H_6$ F: NaOH-EtOH 1,5 N

-Scheme 2-

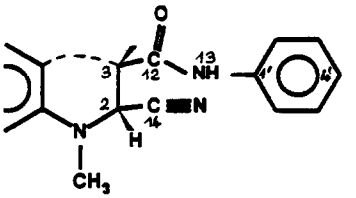



- Scheme 3 -

Some selected spectroscopic data of the cyanoamides and the iminopyrrolidinones studied are reported in Tables I and II.

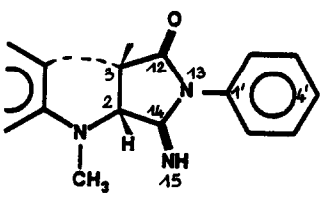
N-acetylated iminopyrrolidinones **12,22,32** showed similar data with additional signals assigned to the acetyl group: νC=O 1675-1700 $cm^{-1}$ ; δ$COCH_3$: 183 and 25 ppm .

TABLE I : β-CYANOAMIDES



| | IR | | $^1$H NMR | $^{13}$C NMR | | |
|---|---|---|---|---|---|---|
| | ν C=O | ν C≡N | δ H-2 | δ C-2 ($^1$J) | δ C-12 | δ C-14 |
| **10** | 1675 | 2250 | s.4.44 | 62.58 (142) | 171.60 | 114 94 |
| **20a** | 1662 | 2250 | s:4.36 | 61.46 (145) | 172.75 | 115.57 |
| **20b** | " | " | s:4.0 | 62.73 (147) | 171.63 | 116.14 |
| **30** | | | s:4.99 | 62.50 (142) | 172.46 | 116.14 |
| **40** | 1660 | | d.d:4.67 | 53.26 (151) | 168.48 | 117 33 |

TABLE II : IMINOPYRROLIDINONES



| | IR | | $^1$H NMR | $^{13}$C NMR | | |
|---|---|---|---|---|---|---|
| | ν C=O | ν C=N | δ H-2 | δ C-2 ($^1$J) | δ C-12 | δ C-14 |
| **11** | 1735 | 1650 | s:4.11 | 72.31(138) | 178 75 | 164 45 |
| **21a** | 1720 | 1640 | s:3.94 | 70.17(148) | 178.71 | 162.25 |
| **21b** | " | " | s:3.75 | 72.85(146) | 179 05 | 163.00 |
| **31** | 1730 | 1655 | s:4.81 | 67.41(139) | 180.40 | 164 41 |
| **41** | | | d:4.47 | | | |

The mass spectra of the iminopyrrolidinones showed a non classical fragmentation with loss of HCN + H (M- 28) with 1-benzazepine derivatives .$^2$H incorporation experiments are in progress to afford an explanation

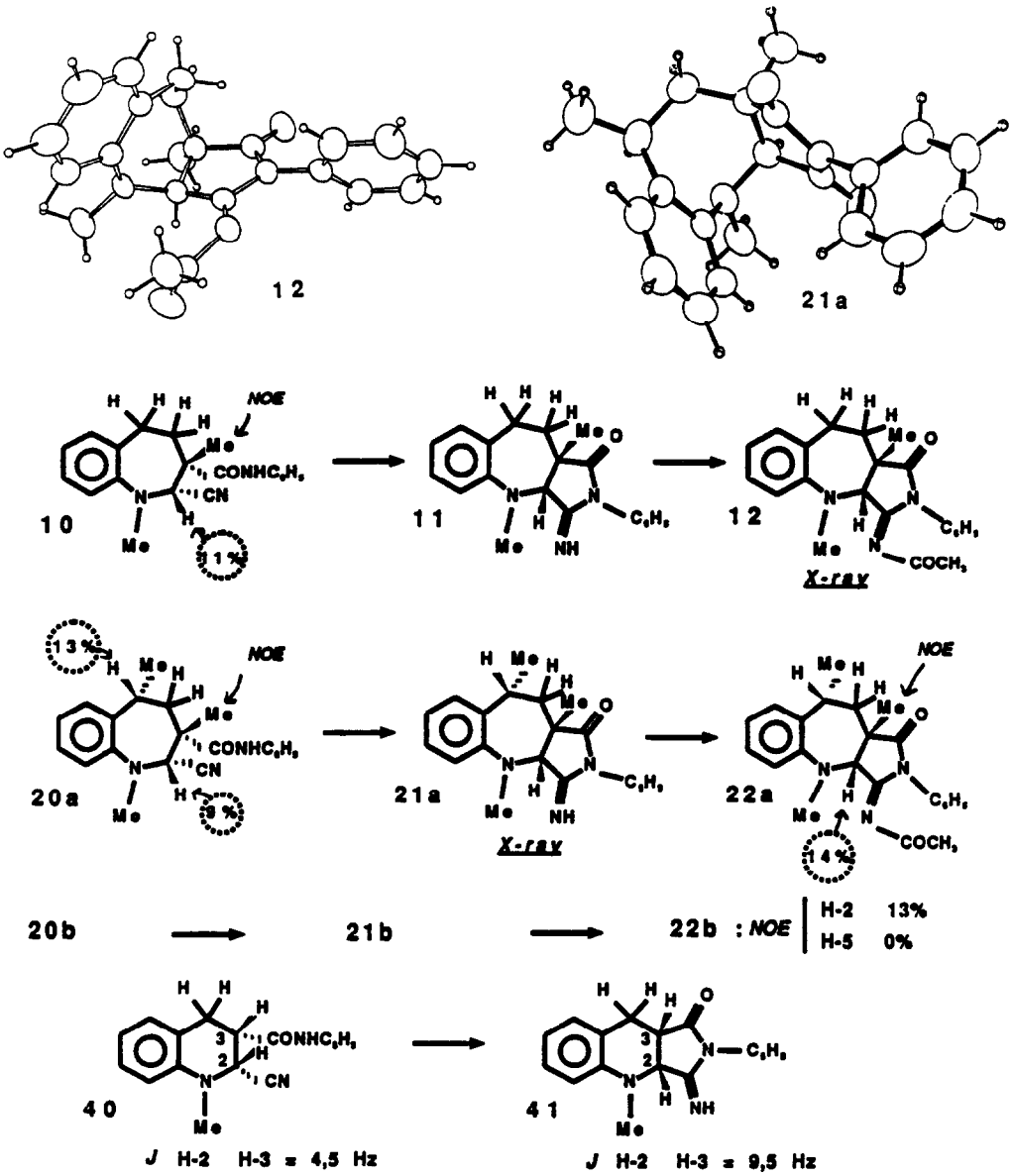
The quinoline and 1-benzazepine derivatives were stereospecifically prepared and their relative configurations established. We would like to emphasize that both the cyclization step into iminopyrrolidinones and the N-acetylation occurred with retention of the configurations.

Compounds **10,11,12,20,21,22** (1-benzazepine derivatives)

X-ray crystallographic study of **12** and **21a** and NOE experiments with **10, 20a, 22a, 22b** demonstrated clearly the spatial relationship between $CH_3$-3 and both H-2 and H-5 (scheme 4).

Compounds **40,41**( quinoline derivatives)

The high *J*H-2 H-3 value (9,5 Hz) indicated a *cis* relationship between these two eclipsed hydrogen atoms of **41** and those of **40**. The small *J*H-2 H-3 (4,5 Hz) value suggested a staggered conformation (13) for **40** .

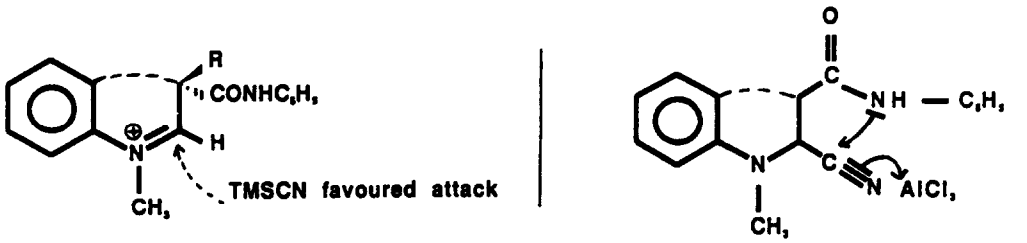



- Scheme 4 -

## DISCUSSION

The stereochemistry of this ring expansion reaction was entirely controlled during the first step.

As found in our previous works (1),(2) in which we described the reactivity of the aminoazetidinone using various YH reagents (such as $CH_3OH$, $CH_3SH$, HCl....) an iminium ion was postulated as an intermediate The TMSCN attack on this iminium ion occurred stereospecifically on the same face as the amido group and probably with its assistance (scheme 5).




- Scheme 5 -

In the second step, ring closure was carried out by intramolecular nucleophilic addition of the amide to the cyano group. Many reactions of this type, involving nitrogen (or oxygen) nucleophiles and leading to heterocycles of various ring sizes, have been reported (8),(9),(10),(14). In our experiments, the nucleophilicity of the amido-nitrogen atom allowed cyclization but the C≡N triple bond had to be activated (4b) by a Lewis acid ($AlCl_3$) The stereochemistry remained unchanged in this step. (scheme 5).

In the one-pot synthesis the same process most probably occurred too.

## CONCLUSION

This work is a new illustration of the synthetic potential of 4-aminoazetidin-2-ones ( β-amino-β-lactams). Indeed, iminium ions, bearing an amido group, can be generated from this class of compounds. We have previously reported examples of heterocyclisations involving this type of iminium ions (2). In this study, the use of TMSCN, which allowed the introduction of the cyano group, led to an efficient preparation of iminopyrrolidinones (15) .

## EXPERIMENTAL SECTION

### GENERAL

Melting points were determined on a Kofler apparatus and were not corrected. Elemental analyses were carried out at the Faculté de Pharmacie ( Université de Paris XI ) Purifications by column chromatography were done on 70-230 mesh silical gel (Merck) and eluent composition was given in volume TLC analyses were performed on pre-coated aluminium sheets of silical gel 60 F254 (layer thickness:0.22 mm)(Merck) and components were visualized with UV light and iodine. Indicated *Rf* values were determined using purification eluents All reactions were controlled by TLC. IR spectra were recorded on a Perkin-Elmer 377 instrument (KBr pellets) NMR spectra were recorded on a Brucker AM300 FT spectrometer at the Centre Regional de Mesures Physiques de l'Ouest (CRMPO) at 300 MHz ($^1$H) or 75 MHz ($^{13}$C). Chemical shifts were expressed in ppm downfield from TMS and coupling constants (*J*) in Hertz . $^1$HNMR · AB systems were presented in the following order : H-α (m:centered) the more deshielded, H-β (m:centered) the more shielded, *J*H-α H-β For NOE experiments the samples were prepared using $N_2$. $^{13}$C NMR · broad band and gated decoupling spectra were recorded. The assignments were made using chemical shifts and coupling constants ($^1J$ and long range coupling). Values with an asterisk* could be interverted. The conventional mass spectra were determined on a Varian MAT 311 double-focusing instrument at the CRMPO with a source temperature of 140°C, an ion accelerating potential of 3 kV, and ionizing electrons of 70 eV and 300 µA. Direct Insertion Probe was used MIKE spectra were recorded on the same spectrometer (2nd Field Free Region) . Atom numbers are shown in Tables I and II .

**Compound 10**

To a solution of **1** (1g; 3,4 mmol) in 20 ml of dry benzene, TMSCN (1g; 10 mmol) was added with a syringe under nitrogen. The reaction mixture was stirred at room temperature for 5 days and then cooled (ice bath) before the addition of 5 ml of water. Stirring continued for 1 h. After separation of the benzenic layer the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($K_2CO_3$) and concentrated. The precipitation of the pure 2R*3S* diastereomer of **10** was obtained by addition of ether. Yield · 60% Purification of **10** was also performed by column chromatography on silica gel using 95:5 $CH_2Cl_2$-ether as eluent

mp 168°C *Rf* 0,7 IR: νC=O· 1675, νC≡N: 2250, νNH: 3345, $^1$HNMR ($CDCl_3$), $CH_3$-1(s·3 04),H-2 (s 4 44), $CH_3$-3(s:1 62), H-4α(m:2.05), H-4β(m:1.98), *J*H-4α H-4β (12), H-5α (m:2.98), H-5β(m:2.76), *J*H-5α H-5β (14),H-13 and Ar (m:7.00-7.60).NOE($CD_2Cl_2$) H-2 : +11%. $^{13}$CNMR: ($CDCl_3$), $CH_3$-1(43 15),C-2(62.58), *J*C-2 H-2(142), C-3(49.10), $CH_3$-3(25.27), C-4(33.00), C-5(30.98), C-6(130.02), C-7(124.59), C-8(127.80), C-9 (119 52), C-10(147.29), C-11(135.17), C-12(171.60), C-14(114.94), C-1'(137 48), C-2'6'(120.53), C-3'5' (129 13), C-4'(124.85). MS . M$^+$: 319(36), 291(7), 199(14), 198(10), 188(13), 187(9), 173(24), 159(12), 158(100), 157(28), 144(10), 133(16), 132(37), 131(18), 130(13), 120(13), 119(20), 118(15), (117(14), 91(17), 77(11). $C_{20}H_{21}N_3O$ : calcd: 319.1684 ; found : 319.169. Anal : calcd : C:75.21, H:6.62, N:13.15 , found C.75 07, H 6.73, N:13.05.

**Compounds 20 a +20 b**

The above procedure was repeated to obtain a mixture of the diastereomers **20 a** (2R* 3S* 5S*) and **20 b** (2R* 3S* 5S*) in a 60:40 ratio. Yield : 50% . Chromatography solvent : 95:5 $CH_2Cl_2$ -ether. Recrystallization in toluene allowed the obtention of the **20 a** isomer 90% pure.

*Rf* 0.7, IR: νC=O : 1662, νNH:3345, νC≡N: 2250, $^1$HNMR:($CD_2Cl_2$) isomer **a** 90%), $CH_3$-1(s:3 02), H-2 (s.4.36), $CH_3$-3(s.1.66), H-4α(m:1.85), H-4β (m:1.81), *J*H-4α H-4β (13), H-5(m:3.20), $CH_3$-5(d·1.47), H-13 and Ar(m.7 00-7.60). NOE:H-2 : +9%,H-5 : +13%.($CD_2Cl_2$, mixture **a** + **b**, isomer **b**)$CH_3$-1(s:3.18), H-2(s ≈4), H-5 (m 3.34), $CH_3$-5(d:1.36), H-13 and Ar(m:7.00 -7.60). $^{13}$CNMR: ($CDCl_3$, isomer **a** 90%),$CH_3$-1(44 12), C-2 (61.46), *J*C-2 H-2 (145), C-3(49.38), C-4(38.89), C-5(29.19), $CH_3$-3 and $CH_3$-5 (21.53 ; 21.78), C-6(125 21*), C-7(124 42), C-8(127.27), C-9(119.28), C-10(148.45), C-11(138.96), C-12(172.75), C-14(115 57), C-1' (137.00), C-2'6'(121.02), C-3'5'(129.00), C-4'(125.13*). ($CDCl_3$, mixture **a** + **b**, isomer **b**) C-2(62.73), *J*C-2H-2 (147), C-12(171.63), C-14(116.14). MS: M$^+$ 333(50), 334(11), 305(10), 213(17), 212(12), 188(14), 187(32), 173(18), 172 (100), 171(19), 158(17), 157(56), 156(10), 147(31), 146(50), 145(21), 144(19), 132(47), 131(25), 130(10), 119(22), 91(17); $C_{21}H_{23}N_3O$:calcd:333.1841,found:333.184 . Anal: calcd: C:75.64, H 6.95, N·12 60 , found: C:75 50, H:6.98, N:12.64

**Compound 30**

The reaction was performed using the previous procedure with an extra addition of a catalytic amount of $AlCl_3$ (2mg, 0.01 mmol). After 7 days the reaction residue was chromatographed (80:20 $CH_2Cl_2$-ether) The faster eluded compound **30** (*Rf 0.9*) was always obtained along with about *30% of 31*, the slower eluded product (*Rf* 0.7). **30** was actually transformed into **31** on the silica gel .

$^1$HNMR :($CD_2Cl_2$, **30**:70% + **31**:30%),$CH_3$-1(*s*:2.98), H-2(*s*:4.99), 2$CH_3$3(*s*:1.52 and *s*:1.51), H-13(s:7 91), Ar(m:6.50-7 60). $^{13}$CNMR :($CD_2Cl_2$, **3O**:70% + **31**:30%), $CH_3$-1(37.91), C-2(62 50), *J*C-2 H-2(142), C-3 (48.52), 2$CH_3$-3(23.94 ; 23.55), C-12(172.46), C-14(116.14).

**Compound 40**

The same procedure was used. After purification by chromatography (95:5 $CH_2Cl_2$.ether) the 2R*3S* diastereomer of **40** precipitated slowly. Yield : 50%.

mp: 170°C *Rf*:0.5 IR: νC=O:1660, νNH: 3280, $^1$HNMR : (CDCl3) CH3-1(s:3.04), H-2(dd:4 67), H-3 (m:3 18), *J*H-2 H-3 (4.5), H-4α (m:3.39), H-4β (m:3.05), *J*H-4α H-4β (16.6), JH-4α H-3 (6), *J*H-4β H-3(5), *J*H-4β H-2(2), H-13(s:7.90), Ar(m.6.70-7.40). $^{13}$CNMR:($CDCl_3$) $CH_3$-1(37.92),C-2(53.26), *J*C-2 H-2(151),C-3 (44.61), C-4(28.08), C-5(128.83), C-6(120.28), C-7(128.53), C-8(113.52), C-9(143.10), C-10(120.55), C-12 (168 48), C-14(117.33), C-1'(137.17), C-2'6'(120.39), C-3'5'(129.05), C-4'(124.99) MS: M$^+$.291(3), 264(25) 173(15), 172(100), 144(24), 143(16). $C_{18}H_{17}N_3O$ . calcd: 291.1371 ; found: 291.137. Anal · calcd · C:74 20 H·5 88, N.14.42 ; found : C:74.14, H:5.90, N:14.47 .

**Compound 11**

- The preparation of **11** from **1** was performed using the general procedure described for **10** but $AlCl_3$ (300 mg , 2.2 mmol) was added under cooling and the reaction was faster (36h).

- 11 was also prepared from **10**, by stirring for 36h in 20 ml of dry benzene at room temperature with the same amount of $AlCl_3$.

Purification through a silica gel column chromatography using 80:20 $CH_2Cl_2$-ether as eluent afforded pure 2R* 3S* diastereomer of **11** which precipitated by addition of ether. Yield : 70%.
mp.127°C Rf : 0.8 IR : νC=O: 1735, νNH: 3225, νC=N: 1650 $^1$HNMR: ($CDCl_3$), $CH_3$-1(s:3 27), H-2 (s 4.11), $CH_3$-3 (s:1.49), H-4α (m:2.31), H-4β (m·2.09), *J*H-4α H-4β (14), H-5α (m:3.00), H-5β (m:2.87), *J*H-5α H-5β(16.6), H-15(s:6.97), Ar(m:6.80-7.50). $^{13}$CNMR : ($CDCl_3$), $CH_3$-1(44.10), C-2(72 31), *J*C-2 H-2 (138), C-3 ( 47.51), $CH_3$-3 (24.19), C-4(32.61), C-5(29.99), C-6(130.71), C-7(122.47), C-8(126.95), C-9 (119.90), C-10 (146.64), C-11(131.96), C-12(178.75), C-14(164.45), C-1′(132.49), C-2′6′(127.26), C-3′5′ (129.34), C-4′(128.49) MS : M$^+$: 319(3), 292(14), 291(89), 189(11), 188(100), 187(79), 173(34), 132(16) $C_{20}H_{21}N_3O$ · calcd: 319.1684, found: 319.170. 291 : [M-H-HCN]$^+$ $C_{19}H_{19}N_2O$. 188 : $C_{11}H_{12}N_2O$ 187 · $C_{11}H_{11}N_2O$. MIKE : 319→304, 291,188; 291→263,188; 188→173,160; 187→172,170,159,143 Anal calcd C 75 21, H:6.63, found : C:73.44, H:6.65.

**Compounds 21a + 21b**

The two previous procedures were used to obtain a mixture of diastereomers **21a** (2R* 3S* 5R*) and **21b** (2R* 3S* 5S*) in a 60:40 ratio which was not separated. Chromatography solvent 80:20 $CH_2Cl_2$-ether. Yield . 70%. The **21a** isomer (> 95% pure) was prepared from the purified one **20a** (recryst. : $C_2H_5OH$).
Rf : 0.8 IR: νC=O :1720, νNH : 3280, νC=N : 1640. $^1$HNMR: ($CDCl_3$) **21a** : $CH_3$-3(s:3.16), H-2 (s·3 94), $CH_3$-3(s:1.38) 2H-4(m:2.00), H-5(m:3.48),$CH_3$-5(d:1.38), H-15 and Ar(m:6.70-7.40). **21b** :$CH_3$-1 (s:3.15), H-2 (s.3.75), $CH_3$-3 (s:1.42), H-4α(m:2.27), H-4β (m:2.18), *J*H-4α H-4β (13.8), H-5(m:3.20), *J*H-4α H-5(8), *J*H-4β H-5(9.8), $CH_3$-5(d:1.24), H-15 and Ar (m:6.40-7.40 ). $^{13}$CNMR :($CDCl_3$) **21a** :$CH_3$-1(41.63), C-2 (70 17), *J*C-2 H-2(148), C-3(46.55), CH3-3(25.53*), C-4(39.02), C-5(30.00), CH3-5(20.00*), C-6(125.70), C-7 (124 66), C-8 (126.57), C-9(120.73), C-10(145.85), C-11(139.96), C-12(178.71), C-14(162.25), C-1′(131.89), C-2′6′(127.26), C-3′5′(129.56), C-4′(128.48). **21b** (mixture **21a** + **21b**) : $CH_3$-1(41.90), C-2 (72.85), *J*C-2 H-2 (146), C-3(47.23), $CH_3$-3(26.12*), C-4(37.77), C-5(36.78), $CH_3$-3(26.86*), C-10(145.63), C-11(138 71), C-12 (179.05), C-14(163.00). MS: M$^+$ :333(2), 318(2), 306(24), 305(99), 189(15), 188(100), 187(84), 173(47), 146(21), 132(23), 131(15); $C_{21}H_{23}N_3O$ : calcd:333.1841 ; found: 333.184. 305: [M-H-HCN]$^+$: $C_{20}H_{21}N_2O$; 188: $C_{11}H_{12}N_2O$; 187.$C_{11}H_{11}N_2O$; MIKE: 333 → 318,305; 318 → 301,291; 305 → 288,278,213,203, 291→276,264,335,187. Anal : calcd: C:75.65, H:6.95, N:12.60 ; found: C:75.52, H: 7.09, N:12.43

**Compound 31**

Following the two procedures already described. Chromatography solvent: 95:5 $CH_2Cl_2$-ether.Yield: 26%. mp: 115°C Rf: 0.4 IR: νC=O:1730; νNH 3300; νC=N:1655. $^1$HNMR: ($CDCl_3$) $CH_3$-1(s:2.91), H-2(s:4 81), 2$CH_3$-3(s:1 .55 , s:1.26), H-15 and Ar(m:6.70-7.60). $^{13}$CNMR:($CDCl_3$) $CH_3$-1(34.96), C-2(67.41), *J*C-2 H-2 (139), C-3(44.84), 2$CH_3$-3(27.14 and 19.35), C-12(180.40), C-14(164.41), C-1′(133.00),C-2′6′(127.28), C-4′ (128 67), C-1″(149.51), C-2″6″(112.72), C-4″(118.19), C-3′5′3″5″(129.44 and 129.50). MS: M$^+$:307(4), 202(50), 188(13), 187(100); $C_{19}H_{21}N_3O$: calcd: 307.1684; found : 307.168. 187: $C_{11}H_{11}N_2O$. MIKE:307→292, 279,202; 277→250,209. Anal: calcd: C:74.24, H:6.88, N:13.73; found : C:74.27, H:6.95, N:13.56.

**Compound 41**

Product **40** (500 mg ; 1.5 mmol) was stirred in 15 ml of ethanolic 1.5 NaOH during two days at room temperature. 20 ml of water was added and the solution was extracted with $CH_2Cl_2$. The organic layer was dried ($K_2CO_3$) and concentrated. The residue was purified by column chromatography on silica gel using 80·20 $CH_2Cl_2$-ether as eluent. By addition of ether, the pure 2R*3S* diastereomer of **41** precipitated. Yield: 10%.
mp 177°C Rf : 0.5 $^1$HNMR:($CDCl_3$), $CH_3$-1(s:3.24), H-2(d:4.47), H-3(m:3.52), *J*H-2 H-3(9.5),H-4α (m.3 06), H-4β (m:2.87), *J*H-4α H-4β (14), *J*H-4α H-3(3), *J*H-4β H-3(6.2), H-15 and Ar(m.6 60-7 50) MS. M$^+$ 291(30), 263(7), 173(100), 144(43); $C_{18}H_{17}N_3O$ . calcd: 291.1371; found: 291.137. 263 [M-CO]$^+$: $C_{17}H_{17}N_3$ 173: $C_{10}H_9N_2O$ .

**General procedure for acetylation (compounds 12, 22a + 22b, 32)**

Iminopyrrolidinones (500 mg ; 1.5mmol) and $(CH_3CO)_2O$ (500 mg ; 4.9 mmol) in 2 ml of $CH_2Cl_2$ were stirred for 5h at room temperature. Then the mixture was basified with 10 ml of 1N NaOH and extracted with $CH_2Cl_2$. The organic layer was dried ($K_2CO_3$) and concentrated. The residue was purified by column chromatography using 95:5 $CH_2Cl_2$-ether as solvent. Yield: 80%.

**Compound 12** . mp: 165°C Rf: 0.45 IR: νC=O:1675 and 1760, νC=N:1640. $^1$HNMR: ($CDCl_3$), $CH_3$-1 (s·3 19), H-2 (s:4.68), $CH_3$-3(s:1.38*), H-4α(m:2.38), H-4β(m:2.19), *J*H-4α H-4β(13.6), H-5α(m:3 10), H-5β(m2.85), *J*H-5 αH-5β(17), $CH_3$-15(s:1.51*), Ar(m:6.70-7.50). $^{13}$CNMR:($CDCl_3$),$CH_3$-1(44.12), C-2(70.71), *J*C-2 H-2 (133), C-3 (48.29), $CH_3$-3(23.11), C-4(34.81), C-5(30.01), C-6(131.31), C-7(120.34), C-8(127 02) , C-9 (118.01), C-10(146.06), C-11(127.02), C-12(178.72), C-14(158.85), C-15(183.17), $CH_3$-15(25.99), C-1′ (132 76), C-2′6′(127.13), C-3′5′(129.02), C-4′(128.66). MS:M$^+$ : 361(21), 318(27), 230(98), 231(14), 188(43), 187(100), 132(38); $C_{22}H_{23}N_3O_2$: calcd: 361.1790; found: 361.180.

**Compound 22a** : Rf: 0.6 IR:νC=O: 1678 and 1768, νC=N:1624. $^1$HNMR:($CDCl_3$), $CH_3$-1(s:2 99), H-2 (s 4 47), $CH_3$-3(s:1.37), 2H-4(d:2.10), *J*H-4 H-5 (9.95), H-5(m:3.51), $CH_3$-5(d:1.38), $CH_3$-15(s.2 07), Ar(m:6.75 and 7.13-7.31). NOE : H-2 : 14% .

**Compound 22b** : Rf: 0.5 $^1$HNMR: ($CDCl_3$), $CH_3$-1(s:3.11), H-2 (s:4.24), $CH_3$-3(s:1.46), H-4α(m:2.25), H-4β(m 2 18, *J*H-4α H-4β(13.5), *J*H-4α H-5(9.9), *J*H-4β H-5(7.3), H-5(m:3.15), $CH_3$-5(d:1.25), $CH_3$-15(s:1 81), Ar(m·6.60 and 7.03-7.31) . NOE: H-2 :13% ;H-5: 0% . MS (**22a + 22b**): M$^+$ :375(36), 376(8), 360(3), 347(7), 332(25), 318(9), 305(12), 231(14), 230(100), 201(16), 188(34), 187(100), 147(10), 146(53), 144(16), 132(23), 131(17). $C_{23}H_{23}N_3O_2$: calcd: 379.1947; found: 379.194 . 188: $C_{11}H_{12}N_2O$ ; 187: $C_{11}H_{11}N_2O$ .

**Compound 32** : Rf: 0.63 mp:122°C IR:νC=O: 1700 and 1755, νC=N:1650. $^1$HNMR: ($CDCl_3$), $CH_3$-1 (s.2.91), H-2 (s:5.13), 2$CH_3$-3(s:1.55 and s:1.24), $CH_3$-15(s:1.87), Ar(m:6.70-7.60). $^{13}$CNMR:($CDCl_3$), $CH_3$-1 (35.53), C-2 (63.22), *J*C-2H-2(146), C-3(44.00), 2$CH_3$-3(28.26 and 18.49), C-12(180.61), C-14(157 28), C-15 (183.67), $CH_3$-15(24 87), C-1′(132.76), C-2′6′(127.00), C-4′(128.84), C-1″(148.24), C-2″6″(112.77), C-4″ (118.77), C-3′5′3″5″(129.19 and 129.52). MS: M$^+$: 349(56), 306(16), 292(21), 244(81), 229(81), 188(21), 187(100); $C_{21}H_{23}N_3O_2$ : calcd: 349.1790, found: 349.179. 188 : $C_{11}H_{12}N_2O$; 187:$C_{11}H_{11}N_2O$. Anal. calcd C.72.18, H:6 63, N:12.02; found: C.72.23, H:6.75, N:11.95 .

## X-RAY ANALYSES

**21a** : $C_{21}H_{23}N_3O$ Mr = 333 4, monoclinic, $P2_1/c$, a = 10 185(7), b=12 660(5), c = 14 021(6) Å, β = 98 94(4)°, V = 1786(1) $Å^{-3}$, Z = 4, $D_x$ = 1 24 Mg m-3, λ(MoKα) = 0 71069Å, μ = 0 73 cm-1, F(000) = 712, T = 293 K, final R = 0 043 for 1737 observations

The sample (prism 0 20*0 26*0 28 mm) was studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation.The cell parameters were obtained by fitting a set of 25 high-theta reflections The data collection [ $2\theta_{max}$ = 50°, scan ω/2θ = 1, $t_{max}$ = 60 s, range HKL H 0,12 K 0,15 L -16,16 , intensity controls without appreciable decay (0 2%)]gave 3488 reflections, 1737 of which were independent ($R_{int}$ = 0 028 ) with I>3σ(I)

After Lorenz and polarization corrections the structure was solved with the Semi Invariants Method (SIR88) which reveals all the non-hydrogen atoms of the molecule After isotropic (R = 0 12) refinement, then anisotropic (0 088) refinement, the hydrogen atoms were located using a Fourier Difference ( between 0 46 and 0 27 $eÅ^{-3}$) The whole structure was refined by the full-matrix least-square techniques ( use of F magnitude , x , y, z, $\beta_{ij}$ for C, N and O atoms, x, y, z for H atoms , 296 variables and 1737 observations , $\omega = 1/\sigma(F_O)^2 = [\sigma^2(I) + (0\ 04F_O^2)^2]^{-1/2}$ ) with the resulting R = 0 044, $R_\omega$ = 0 044 and $S_\omega$= 0 87 (residual $\Delta\rho \leq 0\ 34\ eÅ^{-3}$ )

**12** : $C_{22}H_{23}O_2N_3$ Mr = 361 5, triclinic, P-1, a = 7 949(5), b=10 925(4), c = 11 248(4) Å, α = 85 57(4), β = 88 89(4), γ = 74 38(3)°, V = 938(1) $Å^{-3}$, Z = 2, $D_x$ = 1.28 Mg m-3, λ(MoKα) = 0 71069Å , μ = 0.78 cm-1, F(000) = 384, T = 293 K, final R = 0 047 for 1912 observations.

The sample (prism 0 25*0 30*0.35 mm) was studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection [$2\theta_{max}$ = 50°, scan ω/2θ = 1, $t_{max}$ = 60 s, range HKL H 0,6 K -13,13 L -13,13 , intensity controls without appreciable decay (0.9%)] gave 3554 reflections from which 1912 independent ($R_{int}$ = 0 021 ) with I>3σ(I)

After Lorenz and polarization corrections the structure was solved with Direct Method which reveals all the non-hydrogen atoms of the molecule After isotropic (R = 0 11) refinement, then anisotropic (0 09) refinement, the hydrogen atoms were located using a Fourier Difference ( between 0 47 and 0 22 $eÅ^{-3}$) The whole structure was refined by the full-matrix least-square techniques ( use of F magnitude ; x , y, z, $\beta_{ij}$ for C, O and N atoms, and x, y, z for H atoms , 314 variables and 1912 observations , $\omega = 1/\sigma(F_O)^2 = [\sigma^2(I) + (0\ 04F_O^2)^2]^{-1/2}$ ) with the resulting R = 0.047 , $R_\omega$ = 0 047 and $S_\omega$= 1 15 (residual $\Delta\rho \leq 0\ 17\ eÅ^{-3}$ ) Atomic scattering factors from International Tables for X-ray Crystallography (1974) (16) All the calculations were performed on a Digital MicroVAX 3100 computer with the MolEN package (17)

## NOMENCLATURE

**10** N-phenyl(2R*3S*)1,3-dimethyl-2-cyano-2,3,4,5-1*H*-1-benzazepine-3-carboxamide .
**20a** N-phenyl(2R*3S*5R*)1,3,5-trimethyl-2-cyano-2,3,4,5-1*H*-1-benzazepine-3-carboxamide .
**20b** (2R*3S*5S*) .

**30** N-phenyl-2,2-dimethyl-3-(N-methylanilino)-3-cyanopropanamide .

**40** N-phenyl(2R*3S*)1-methyl-2-cyano-1,2,3,4-tetrahydroquinoline-3-carboxamide

**11** (3aR*10aS*)3-imino-4,10a-dimethyl-2-phenyl-3,3a,4,9,10,10a-hexahydropyrrolo[3,4-b][1]benzazepin-1(2*H*)-one . **12** 3-acetylimino derivative .

**21a** (3aR*10aS*9R*)3-imino-4,9,10a-trimethyl-2-phenyl-3,3a,4,9,10,10a-hexahydropyrrolo[3,4-b][1] benzazepin-1(2*H*)-one . **21b** (3aR*10aS*9S*) . **22a** + **22b** 3-acetylimino derivatives.

**31** 5-imino-1-phenyl-3,3-dimethyl-4-(N-methylanilino)-1,3,4,5-tetrahydro-2*H*-pyrrol-2-one

**32** 5-acetylimino derivative

**41** (3aR*9aS*)3-imino-4-methyl-2-phenyl-2,3,3a,4,9,9a-hexahydro-1*H*-pyrrolo[3,4-b]quinolin-1-one

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