HETEROCYCLES, Vol. 63, No. 8, 2004, pp. 1855 - 1873
Received, 31st May, 2004, Accepted, 8th July, 2004, Published online, 9th July, 2004

ALLYLIC DEHYDRATION, RETRO-PINACOL, PINACOL-LIKE AND ENAMIDE REACTIONS: SYNTHESIS OF NEW ISOQUINOLINES

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Abstract - Depending upon the conditions, heating of 1,10a-dihydro-2*H*,5*H*-pyrrolo-[1,2-*b*]isoquinoline-3,10-diones in polyphosphoric or hydrochloric acid gives rise to hydride transfer and oxidative processes. Mono or dienyl lactams, or mixtures of dimers and acids or hydroxyacids of the isoquinoline series were thus formed. Procedures leading specifically to each of these products have been found.

INTRODUCTION

The 2-pyrrolidinone ring system is common to many molecules with great value in medicinal chemistry.[1] 2-Pyrrolidinone-5-carboxylic acid (pyroglutamic acid) (Scheme 1), which has been called "the forgotten amino acid",[2] is a biologically important member of the "chiral pool".[3] Cyclization of *N*-arylmethylpyroglutamic acids leads to ketones (**1**).[4] The benzo[*f*]indolizine skeleton[5] of compounds (**1**) can be manipulated, leading to naphtoindolizidine[4d, 6] or phenanthroindolizidine[4b, 7] alkaloids, which have attracted much attention because they exhibit interesting biological properties.[8] 1,10a-Dihydro-2*H*,5*H*-pyrrolo[1,2-*b*]isoquinoline-3,10-diones (**1**)**,** or their oximes are subject to a variety

of skeletal rearrangements in Beckmann,[9a] Schmidt[4g,h, 9b] or Semmler-Wolff[4c, 9c] conditions. (Chart 1). We have previously described that treatment of **1a** (R = H) in neat PPA led to a new dehydration.[10a] Dienyl lactam (**2a**) was the sole product isolated from this heating with an anhydrous acid (Scheme 1). Because of the potential biological properties of pyrrolidinones, we have extended this preparation to other ketones (**1**) and studied their reactivity with hot hydrochloric acid. This leads to unexpected reactions such as allylic dehydrations, retro-pinacol, pinacol-like rearrangements and enamide reactions, which yield a variety of new isoquinolines. An interesting dimer formation was also observed. The understanding of the mechanism of formation of these dimers allowed us to specifically obtain good yields of each isoquinoline reported.

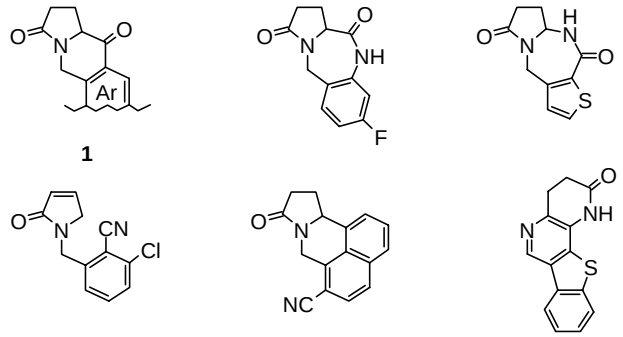
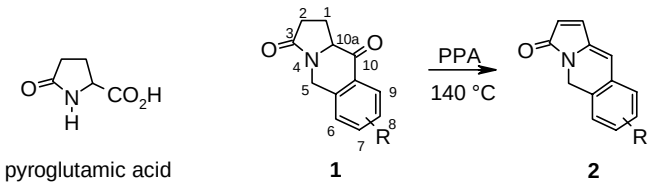


Chart 1. Some Compounds Issued from Beckmann, Schmidt or Semmler-Wolff Rearrangements of Ketones (1), or of Their Oximes



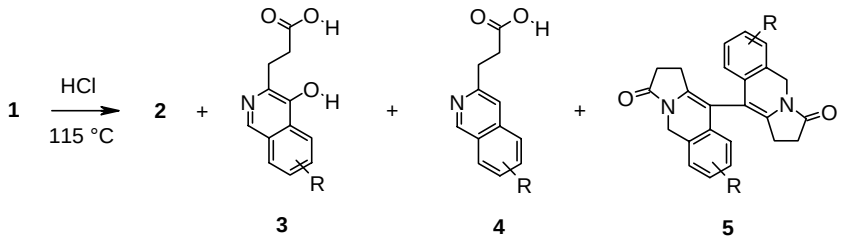
pyroglutamic acid **1** **2**

Scheme 1

RESULTS AND DISCUSSION

Generalization of the formation of the dienyl lactams (**2**) from pyrrolo[1,2-*b*]isoquinoline-3,10-diones (**1**) was first checked, and treatment of substituted ketones **1** in hot PPA was performed (Table 1). Excepted for ketone (**1g**) (R = OMe) (Table 1, Entry 7), whatever the substitution was, lactams (**2**) were obtained in moderate to good yields. The low stability of *N*-methoxybenzyl lactams towards acids[11] probably explains the low yield of compound (**2g**). Treatment of ketones (**1**) in refluxing concentrated aqueous HCl was then examined, and four main products (**2**-**5**) were obtained (Scheme 2). Whereas lactams (**2**) and isoquinolines (**3**) and (**4**) were easily identified from the results of previous works[10a,b] the characterization of compounds (**5**) was more difficult. Indeed its symmetry led to a strong simplification of the NMR spectra that showed only half a molecule. X-Ray analysis of product (**5b**) (R = 8-Cl) provided the exact

structure of these dimers. This X-Ray spectrum reveals complex π-π "stacked" interactions[12] between the aromatic rings of three neighbouring molecules that might be of interest to materials chemists (Figure 1). The same pattern of products was obtained with other ketones (**1**) (Table 2).



Scheme 2

Table 1. Reactions of Lactams (1) with Polyphosphoric Acid[a]

Entry	R	Product	Yield (%)[b]
1	H	**2a**	70
2	8-Cl	**2b**	71
3	8-Me	**2c**	66
4	6-Cl	**2d**	87
5	6-Me	**2e**	55
6	8-Br	**2f**	96
7[c]	8-OMe	**2g**	24
8	6,8-Cl_2	**2h**	90
9	5-Ph	**2i**	81

[a] Lactam (**1**) (11 mmol), PPA (50g), 140 °C, 1-4 h. [b] Refers to isolated yield.

[c] The reaction was conducted at 120 °C for 2 h.

Table 2. Representative Reactions of Lactams (1) with Concentrated Hydrochloric Acid[a]

Entry	R	Product	Yield (%)[b]	Product	Yield (%)[b]	Product	Yield (%)[b]	Product	Yield (%)[b]
1	H	**2a**	0.5	**3a**	21	**4a**	26	**5a**	44
2	8-Cl	**2b**	3	**3b**	31	**4b**	19	**5b**	25
3	8-Br	**2f**	2	**3f**	14	**4f**	9	**5f**	69

[a] Lactam (**1**) (8.5 mmol), HCl 37% (40 mL), 115 °C, 36 h. [b] Refers to isolated yield of crude product.

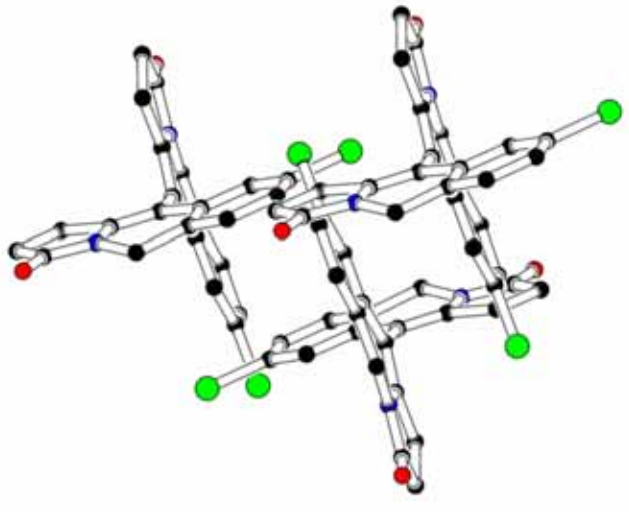
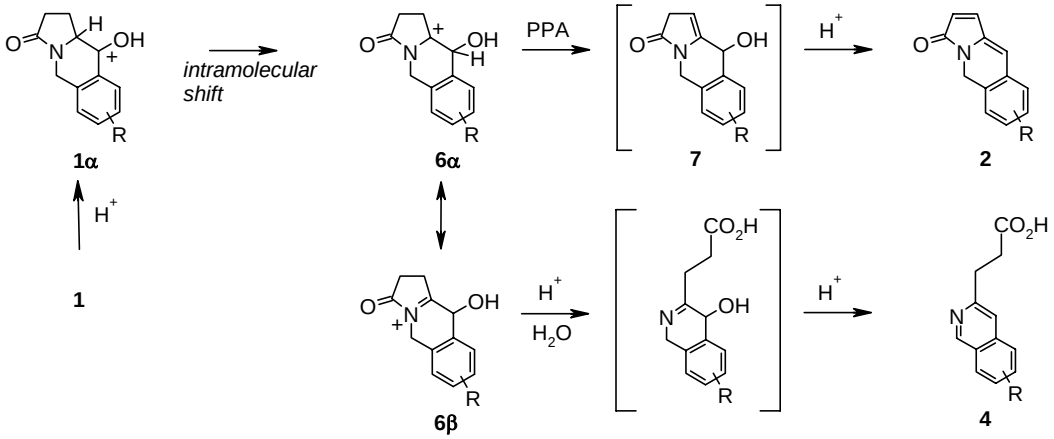


Figure 1. **Crystal structure of 5b showing the formation of π–π "stacked" interactions between the aromatic rings of two neighboring molecules in a unit cell comporting three dimer molecules[12] (Cl: green; O: red; N, blue; C, black; hydrogen atoms are omitted for clarity)**

It was difficult to perform a good separation between acids (**3**) and (**4**), and the related yields were poorly reproducible. Two syntheses, in principle identical, can lead to 50% differences in the relative yields, depending of the size of the flask, the type of condenser, the stirring speed or the exact temperature. Thus more work was performed in order to understand the formation of isoquinolines (**3**) and (**4**) and of dimers (**5**), and to find conditions leading to better reproducibility, yields and separation of acids (**3** and (**4**).

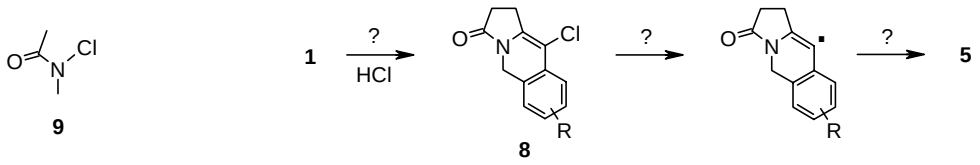


Scheme 3

Two parallel mechanisms can account for the formation of **2**[10a] and **4** (Scheme 3): Protonation of ketones (**1**) leading to **1α** was followed by a retro-pinacol reaction. This *intramolecular* hydride shift[13a] yields the *N*-acyliminium salts (**6α**, **6β**) which in anhydrous conditions (such as in PPA) evolve to enamides (**7**).[13b]

Then an allylic dehydration gives lactams (**2**). Hydrolysis of the N-acyliminium salts (**6α**, **6β**) occurs in concentrated HCl, leading to hydroxyimines which dehydrate to **4** (Scheme 3).

A more intriguing fact was the coupling of ketones (**1**) leading to products (**5**) coming from a pinacol-like reaction**.** In literature[14a] only two examples of compounds of the type $(RCO\text{-}N\text{-}CH{=}CH)_2$ are described.[14b] The first one is the natural bis lactam ilicifoline, a Berberine dimer alkaloid,[14c] and the other one is a bis[oxyberberine] formed during the pyridinium chlorochromate oxidation of oxyberberine.[14d] The mechanism leading to this product cannot be extended to reactions of ketones (**1**) in strongly acidic conditions. We ruled out a photochemical pinacol reaction[15] because the same results were obtained in the dark. In the same way, metal promoted pinacol[16] or McMurry[17] reactions were not possible because the HCl utilized was of analytical grade, free of metal traces.



Scheme 4

Table 3. Investigation of a Radical Pathway for the Reactions of Lactam (1b) with Concentrated Hydrochloric Acid[a]

Entry	Catalyst (%)	**2b** Yield (%)[b]	**3b** Yield (%)[b]	**4b** Yield (%)[b]	**5b** Yield (%)[b]
1	HQ (20)	1	24	33	15
2	NBS (10)	0.5	28	34	20
3	$FeCl_2$ (10)	0.5	18	17	17

[a] Lactam (**1b**) (8.5 mmol), HCl 37% (80 mL), 115 °C, 30 h. [b] Refers to isolated yield of crude product.

Other possibilities for dimerization of radicals were then considered. It is known that pyrrolidinones easily form radicals in the position α to the nitrogen,[18] and it can be envisioned that traces of Cl_2 in the HCl[19] lead to the formation of radicals in the 10a position of molecules (**1**)**.** However such a radical (or the cation-radical[20] formed after protonation of the ketone group[10a]) is expected to lead to dimers from the 10a and not from the 10 position.[21] Another possibility for a radical reaction requires an addition–elimination[22] of HCl to the ketone group of compounds (**1**), giving the vinyl chlorides (**8**)[23] Such chlorides are vinylogs of chloramides (**9**) (Scheme 4) which give radicals (or cation-radicals) either thermally[24] or in the presence of a strong acid[25] or of ferrous ions.[25] Thus, conditions were designed to interfere with a radical pathway. For instance 5-10% of $FeCl_2$, NBS, AIBN or hydroquinone was added to

the reaction media, but the reproducibility and the yields did not change noticeably (Table 3) and the corresponding mechanism was ruled out.

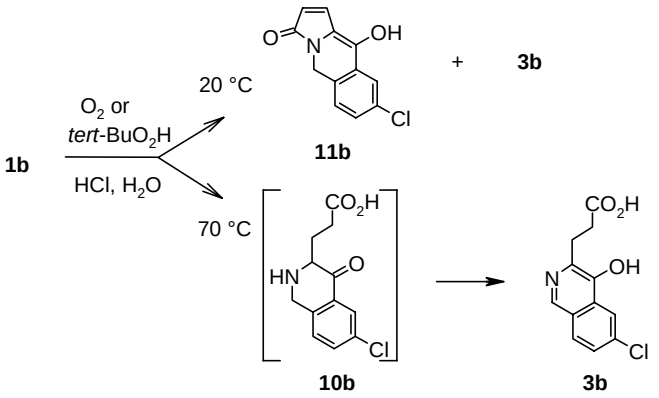
Table 4. Reactions of Lactams (1) in Oxidative Conditions

Entry	Reagent[a]	Acid (mL)	Catalyst	t/h	T (°C)	**3** Yield (%)[b]	**11** Yield (%)[b]	Recovered **1** Yield (%)[c]
1	**1b**	37% HCl (100)	Oxygen[d]	18	20	24	41	35
2	**1b**	48% HBr (100)	Oxygen[d]	36	20	24	21	55
3	**1b**	37% HCl (50)	*t*-BuO_2H[e]	10	70	45	0	36[f]
4	**1b**	37% HCl (100)[g]	air	168	20	30	0	70
5	**1a**[h]	37% HCl (600) / H_2O (400)	air	5	55	70[i]	0	ND

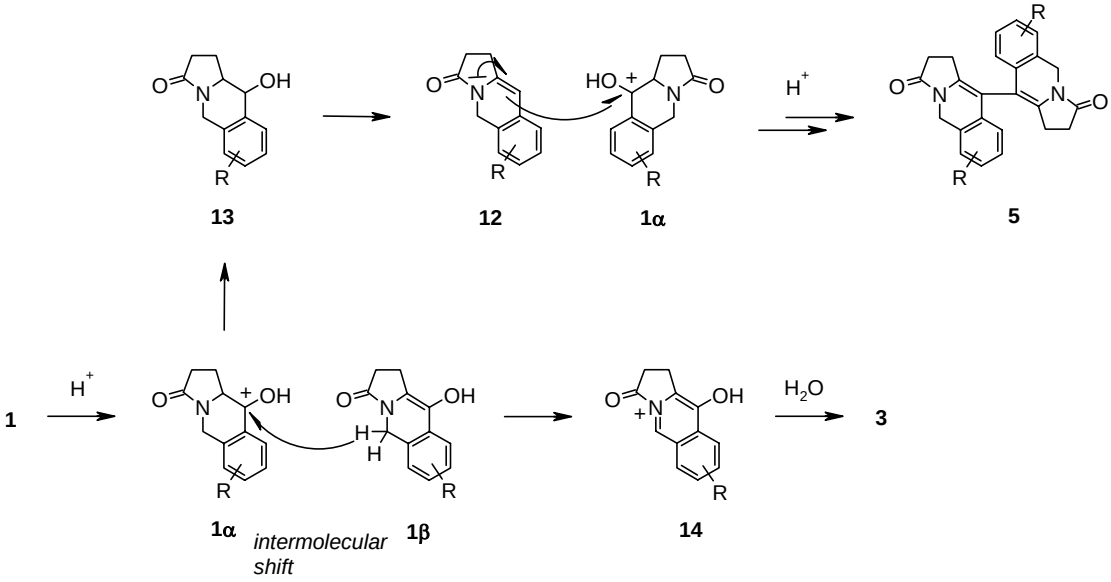
[a] Lactam (**1b**) (8.5 mmol) or lactam (**1a**) (200 mmol). [b] Refers to isolated yield of crude product. [c] Yield obtained by NMR spectrometry. [d] Oxygen was slowly bubbled inside the solution. [e] *tert*-BuO_2H (0.68 mmol) in water (3 mL) was added in 10 fractions. [f] Amino ketone (**10b**) was also observed by NMR spectrometry. [g] The reaction was performed in a closed round bottomed flask. [h] The reaction was realized in a large 3 L beaker, opened to the air, with a strong magnetic stirring. [i] Lactam (**2a**) (0-5%) was also obtained.

Another possible pathway implies oxidation from atmospheric oxygen which could explain the notable influence of the flask, condenser and stirring. During the course of reactions performed at 110 °C with 37% aqueous HCl (Table 2), variable amounts of compounds (**10**) were observed as intermediates, and it is known that this type of amino ketone readily undergoes oxidation to provide the fully aromatic products.[26] Model reactions with ketone (**1b**) were then realized at lower temperature, in hydrochloric or hydrobromic acid, with addition of *tert*-butyl hydroperoxide or while bubbling oxygen (Scheme 5) (Table 4). These reactions confirm that an oxidation process can lead to hydroxyisoquinolines (**3**). Interestingly

under these mild conditions no dimer (**5b**) or isoquinoline (**4b**) was formed while another oxidized product (**11b**) was also obtained. The solubility of enol (**11b**) is very low, thus this compound can easily be separated from the isoquinoline (**3b**) by filtration of the reaction mixture, while CH_2Cl_2/water partition leads to nearly pure acid (**3b**). The likely mechanism at 70 °C is an opening of the lactam ring yielding aminoketones (**10**) whose oxidation gives isoquinolines (**3**)**.** At 20 °C, ring opening leading to **10** then to **3** is slower, and oxidation of the lactam rings gives **11**. Application of these observations led to the design of an improved synthesis of hydroxyisoquinoline (**3a**): a strong magnetic stirring of ketone (**1a**) in dilute HCl, at 55 °C in a large beaker open to the air, gives a 70% reproducible yield of pure hydroxy acid (**3a**). Under these conditions only a very low amount (less than 5%) of dimer (**5a**) was also formed (Table 4, Entry 5).



Scheme 5



Scheme 6

During a part of this study hydrochloric was replaced by hydrobromic acid. The most interesting result from these reactions of **1a** and **1c** was that in some experiments, 5% of alkene (**12a**) (R = H)[4a] or 12% of **12c** (R = 8-Me) were isolated. Formation of enamides (**12**) can be explained by an *intermolecular* hydride

shift between the enol form of unprotonated ketones (**1**) and its protonated form **1α** (Scheme 6), which is a route rather similar to the *intramolecular* hydride shift leading to compounds (**2**)[10a] (Scheme 3). This yields alcohols (**13**) then alkenes (**12**). It is known that enamides react with electrophiles.[27] In the present reaction, condensation of enamide (**12**) with protonated ketone (**1α**) led to the pinacol-like derivatives (**5**). The driving force for the intermolecular hydride shift reaction can be the formation of aromatized isoquinolinium salts (**14**) which later hydrolyze to hydroxy acids (**3**).

Table 5. HOMO and LUMO Energies Calculated by DFT (B3LYP, 6-31G*)[28]

Molecule (R = H)	LUMO kcal/mole	HOMO kcal/mole
1	-41.1	-146.5
1α	-171.5	-241.0
1β	-18.2	-117.7
12	-17.1	-120.5
13	-8.0	-146.8
14	-153.4	-238.8
6 α or β	-157.2	-236.0

The geometries of these molecules were refined by using *ab initio* DFT calculations[28] (B3LYP, 6-31 G* basis set) and the energies of the molecular orbitals were calculated. Results were visualized with the help of SPARTAN software.[28] Values of the HOMO and LUMO energies are reported in Table 5. Protonated ketone (**1α**) (R=H) and *N*-acyliminium salts (**6α**, **6β**) (R=H) (Scheme 3) have very similar orbital energies and can be considered in equilibrium. It must be noted that all the geometry optimizations converged to the geometry **6β** rather than that of **6α** These acyliminium salts (**6α**, **6β**) can indeed be good starting materials for the two reaction pathways leading to compounds (**2**) and (**4**) (Scheme 3). Although ketone (**1**) (R=H) and its enol form (**1β**) have comparable HOMO and LUMO energies, their shape differ markedly, **1** being strongly bent while **1β** is almost flat and possesses nearly the same geometry as that of **14**. HOMO energies of **12** (R=H) and enol (**1β**) are higher than the LUMO of intermediate cation (**1α**).[29] Application of frontier orbital theory[30] allows us to consider that hydride transfer from **1β** leading to **13** and **14** (Scheme 6) is a very favorable process. Similarly, according to the same criterions, the reaction of **12** with cation (**1α**) shoulds proceed easily. In Figure 2, HOMO's of **1β** and **12** and the LUMO of the cation (**1α**) have been represented. It can easily be seen that there is a good match between the shapes of the HOMO and that of the LUMO at the positions where reactions are supposed to occur. It is interesting

to notice that the two different molecules (**1β**) and (**12**)**,** in addition to have almost the same orbital energies, also have very similar shapes of their HOMO's.

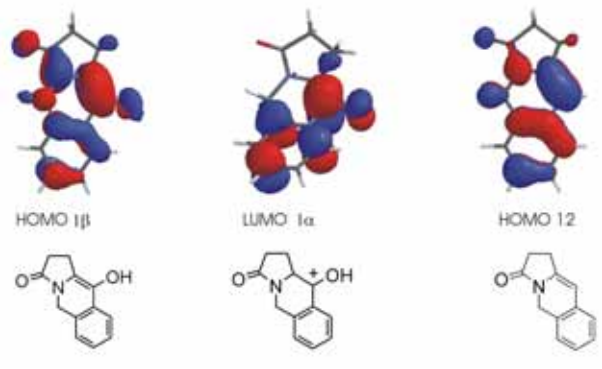
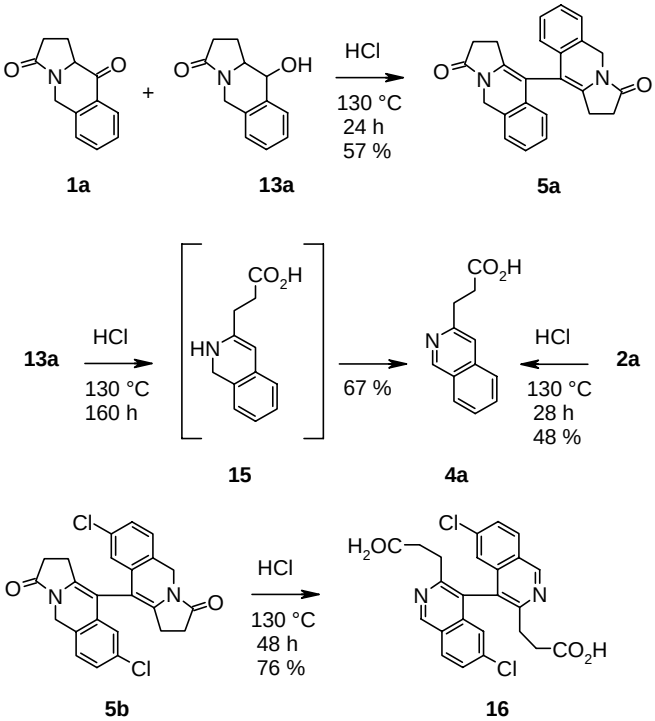


Figure 2. HOMO of 12 (R=H) and enol (1β) (R=H) and LUMO of cation (1α) (R=H) by DFT B3LYP/6-311+G.[28]

This hypothesis of alcohols (**13**) being key intermediates in the formation of dimers (**5**) was then experimentally confirmed. Heating of a mixture of 1 g of **1a** with an equimolar amount of **13a**[4a] at 130 °C for 24 h in concentrated HCl yielded 1.05 g (57%) of isolated dimer (**5a**). This yield strongly exceeded (cf. Table 2) the amount (0.4g, 22%) of **5a** which could be obtained if only ketone (**1a**) had yielded the dimer (**5a**), without intervention of enamide (**12a**) (other products observed by NMR spectrum were **1a**, **2a**, **3a**, **4a** and **15a** (Scheme 7).



Scheme 7

Observation of lactam ring hydrolysis of **1** (Scheme 5) opened the question of the stability of compounds (**2, 5** and **12)** formed in these reactions (Schemes 2 and 6). Thus **13a**[4a] (as a precursor of **12a**) was heated in HCl leading rapidly to an amino acid (**15**). This was followed by an oxidation of the dihydroisoquinoline (**15**) which occurred slowly, leading to 67% of aromatized isoquinoline (**4a**) as the only compound isolated. This formation of acids (**4**) starting from alcohols (**13**) was very clean and proved to be the best known way to obtain these compounds. The same reaction was also performed with the diene (**2a**) also leading to the same acid (**4a**), but the reaction medium was less clean than starting from **13a**. In the same way, heating **5b** in HCl led to the formation of isoquinoline (**16**), the exact duration of these oxidations being strongly dependent of the size of the opening of the air condenser (Scheme 7).

CONCLUSION

The heating of 1,10a-dihydro-2*H*,5*H*-pyrrolo[1,2-*b*]isoquinoline-3,10-diones in acidic media leads to allylic dehydration, retro-pinacol, pinacol-like and enamide reactions, giving many different isoquinolines. The understanding of these hydride transfers and oxidative processes allows the specific and easy synthesis of dimers (**5**), condensed isoquinolines (**2**, **11**) and of acids (**3**, **4** and **16**) in medium to good yields. Moreover this work can contribute to the understanding of the formation of alkaloids dimers like ilicifoline or bis[oxyberberine].

EXPERIMENTAL

All solvents and reagents were purchased from commercial sources and used as received. Temperature reactions are given in Tables and refer to bath temperature. Melting points were carried out with an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded in the ATR mode on a “Tensor 27” Bruker spectrometer, and the ^{1}H and ^{13}C NMR spectra on a Varian ‘Gemini 2000’ at 200 MHz or 50 MHz using tetramethylsilane as an internal reference. Elemental analyses were performed by the «Service Central de Microanalyses» (CNRS, Vernaison, France).

*Pyrrolo[1,2-b]isoquinolin-3(5H)-one (**2a**):* Using the procedure as described for the synthesis of **2h**, 70 % of lactam (**2a**) was obtained after heating at 140 °C for 1 h, mp 164-165 °C (CH_2Cl_2, acticarbon); IR 1665 1650, 1570, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 4.97 (s, 2H), 6.23 (s, 1H), 6.32 (d, *J* = 5.5 Hz, 1H), 7.15 (d, *J* = 5.5 Hz, 1H), 7.19-7.32 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 42.4, 110.4, 124.3, 126.7, 127.7, 128.1, 128.6, 129.7, 130.5, 133.1, 137.4, 169.2. Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95. Found: C, 78.44; H, 4.55.

*8-Chloropyrrolo[1,2-b]isoquinolin-3(5H)-one (**2b**):* Using the procedure as described for the synthesis of **2h**, 71 % of lactam (**2b**) was obtained after heating at 140 °C for 90 min, mp 197-199 °C (CH_2Cl_2, acticarbon); IR 1660, 1645, 1595, 1535 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 4.93 (s, 2H), 6.15 (s, 1H), 6.35 (d, *J* = 5.6 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 7.17 (d, *J* = 5.6 Hz, 1 H), 7.23 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 42.2, 108.8, 125.0, 127.6, 128.0, 128.4, 128.7, 131.6, 133.3, 133.4, 138.4, 169.4. Anal. Calcd for $C_{12}H_8NOCl$: C, 66.22; H, 3.70. Found: C, 66.15; H, 3.84.

*8-Methylpyrrolo[1,2-b]isoquinolin-3(5H)-one (**2c**):* Using the procedure as described for the synthesis of **2h**, 66 % of lactam (**2c**) was obtained after heating at 140 °C for 90 min, mp 174-176 °C (CH_2Cl_2, acticarbon); IR 1670, 1645, 1590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.35 (s, 3H), 4.93 (s, 2H), 6.20 (s, 1H), 6.31 (d, *J* = 5.8 Hz, 1H), 7.05-7.12 (m, 3H), 7.14 (d, *J* = 5.8 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 20.8, 42.3, 110.7, 124.2, 126.6, 127.6, 128.7, 129.5, 129.6, 133.1, 137.4, 137.5, 169.3. Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 78.92; H, 5.68.

*6-Chloropyrrolo[1,2-b]isoquinolin-3(5H)-one (**2d**):* Using the procedure as described for the synthesis of **2h**, 87 % of lactam (**2d**) was obtained after heating at 140 °C for 90 min, mp 187-190 °C (CH_2Cl_2, acticarbon); IR 1665, 1650, 1630, 1535 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 4.97 (s, 2H), 6.18 (s, 1H), 6.37 (d, *J* = 5.7 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.16 (d, *J* = 5.7 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1 H), 7.31 (dd, *J* = 7.6, 1.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 41.4, 109.2, 125.0, 126.3, 128.4, 128.7, 129.2, 131.8, 133.0, 133.1, 137.8, 168.9. Anal. Calcd for $C_{12}H_8NOCl$: C, 66.22; H, 3.70. Found: C, 66.29; H, 3.87.

*6-Methylpyrrolo[1,2-b]isoquinolin-3(5H)-one (**2e**):* Using the procedure as described for the synthesis of **2h**, 55 % of lactam (**2e**) was obtained after heating at 140 °C for 3 h, mp 183-184 °C (AcOEt, acticarbon); IR 1670, 1650, 1590 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.30 (s, 3H), 4.88 (s, 2H), 6.21 (s, 1H), 6.37 (d, *J* = 5.6 Hz, 1H), 7.06-7.30 (m, 3H), 7.18 (d, *J* = 5.6 Hz, 1H). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 78.80; H, 5.61.

*8-Bromopyrrolo[1,2-b]isoquinolin-3(5H)-one (**2f**):* Using the procedure as described for the synthesis of **2h**, 96 % of lactam (**2f**) was obtained after heating at 140 °C for 90 min, mp > 220 °C (CH_2Cl_2, acticarbon); IR 1660, 1645, 1630, 1530 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 4.89 (s, 2H), 6.13 (s, 1H), 6.34 (dd, *J* = 5.8, 0.6 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.16 (d, *J* = 5.8 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.1 Hz, 1 H), 7.38 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 42.2, 108.7, 121.3, 125.1, 128.2, 129.2, 130.5, 131.2, 131.9, 133.3, 138.4, 169.1. Anal. Calcd for $C_{12}H_8NOBr$: C, 54.99; H, 3.08. Found: C, 55.10; H, 3.12.

*8-Methoxypyrrolo[1,2-b]isoquinolin-3(5H)-one (**2g**):* Using the procedure as described for the synthesis of **2h**, 24 % of lactam (**2g**) was obtained after heating at 120 °C for 2 hs, mp 125-129 °C (AcOEt, acticarbon); IR 1670, 1645, 1580, 1460 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.83(s, 3H), 4.9 (s, 2H), 6.18 (s, 1H), 6.32 (d, *J* = 5.6 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 8.3, 2.5 Hz, 1 H), 7.15 (d, *J* = 5.7 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20. Found: C, 72.99; H, 5.34.

*6,8-Dichloropyrrolo[1,2-b]isoquinolin-3(5H)-one (**2h**):* Finely powdered ketone (**1h**) (1g, 4.0 mmol) was quickly added to hot (140 °C) stirred PPA (40 g). The mixture was vigorously stirred for 5 h. The hot mixture was poured over crushed ice (150 mL). The yellow solid obtained was washed with water to afford 90% of lactam (**2h**), mp 160-162 °C (AcOEt, acticarbon); IR 1675, 1650, 1585 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 4.91 (s, 2H), 6.09 (s, 1H), 6.39 (d, *J* = 5.7 Hz, 1H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.16 (d, *J* = 5.7 Hz, 1H), 7.30 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 41.2, 107.8, 125.7, 126.0, 126.8, 128.5, 133.12, 133.14, 133.5, 133.9, 138.8, 168.9. Anal. Calcd for $C_{12}H_7NO\ Cl_2$: C, 57.17; H, 2.80. Found: C, 56.93; H, 2.98.

*5-Phenylpyrrolo[1,2-b]isoquinolin-3 5H)-one (**2i**):* Using the procedure as described for the synthesis of **2h**, 81 % of lactam (**2f**) was obtained after heating at 140 °C for 2 h, mp 100-102 °C (AcOEt, acticarbon); IR 1660, 1645, 1585 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 6.21 (d, *J* = 5.6 Hz, 1H), 6.31 (s, 1H), 6.36 (s, 1H), 7.18 (d, *J* = 5.6 Hz, 1H), 7.15-7.30 (m, 9H). Anal. Calcd for $C_{18}H_{13}NO$: C, 83.37; H, 5.05. Found: C, 83.19; H, 4.99.

*3-(4-Hydroxy-3-isoquinolinyl)propanoic acid (**3a**)*: In a large, opened to air 3 L beaker were added 37% HCl (600 mL), water (400 mL) and ketone (**1a**) (40g, 200 mmol). The mixture was heated (55 °C) and vigorously stirred for 5 h. The resulting yellow solid obtained was washed with water to afford 0-5% of dimer (**5a**). The solution was evaporated and the residue was washed with a small amount of water then with CH_2Cl_2 to remove some traces of compounds (**1a** and **2a**), leading to 70% of acid (**3a**), mp 179-181 °C (H_2O, acticarbon); IR 1670, 1575 cm^{-1}; ^{1}H NMR (200 MHz, D_2O/NaOD) δ = 2.50 (t, *J* = 8.6 Hz, 2H), 3.12 (t, *J* = 8.6 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.61 (td, *J* = 5.7, 0.7 Hz, 1H), 7.91 (d, *J* = 7.4 Hz, 1H), 8.20 (dd, *J* = 8.2, 0.7 Hz, 1H), 8.31 (s, 1H); ^{13}C NMR (50 MHz, D_2O/NaOD) δ = 31.9, 40.0, 125.2, 128.9, 129.6, 130.5, 131.9, 134.2, 137.2, 141.9, 158.9, 186.3. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10. Found: C, 66.32; H, 5.16.

*3-(6-Chloro-4-hydroxy-3-isoquinolinyl)propanoic acid (**3b**) and 8-Chloro-10-hydroxypyrrolo[1,2-b]-isoquinolin-3(5H)-one (**11b**).* Oxygen was slowly bubbled for 18 h in a stirred solution of 2 g (8.5 mmol) of ketone (**1b**) in 100 mL of 37% HCl (100 mL). The solid was filtered, washed with a small amount of

HCl, with water then with acetone, giving 41% compound (**11b**), mp 166 °C (decomp) (D_2O); IR 1695, 1630, 1590, 1560 cm^{-1}; ^1H NMR (200 MHz, D_2O/NaOD) δ = 4.59 (s, 2H), 5.68 (d, *J* = 4.9 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.35 (d, *J* = 4.9 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (50 MHz, D_2O/NaOD) δ = 44.5, 107.5, 120.9, 126.1, 126.7, 130.2, 132.5, 135.1, 135.3, 135.7, 163.5, 166.9. Anal. Calcd for $C_{12}H_8NO_2Cl$: C, 61.69; H, 3.45. Found: C, 61.23; H, 3.72.
The solution was evaporated and the residue was washed with water. Washing with acetone removed 35% of ketone (**1b**). The resulting solid was acid (**3b**) 24%, mp 178-180 °C (H_2O, acticarbon); IR 1700, 1650, 1610, 1575, 1555 cm^{-1}; ^1H NMR (200 MHz, D_2O/NaOD) δ = 2.47 (t, *J* = 8.8 Hz, 2H), 3.09 (t, *J* = 8.8 Hz, 2H), 7.38 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 8.13 (d, *J* = 2.2 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR (50 MHz, D_2O/NaOD) δ = 31.9, 39.9, 124.0, 129.1, 130.0, 131.5, 134.6, 135.7, 136.8, 142.8, 158.0, 186.2. Anal. Calcd for $C_{12}H_{10}NO_3Cl$: C, 57.27; H, 4.01. Found: C, 57.53; H, 4.52.

*3-(4-Hydroxy-6-methyl-3-isoquinolinyl)propanoic acid (**3c**):* This compound was isolated in variable yield from the heating of ketone (**1c**) in 37 % HCl, mp 128-130 (D_2O, acticarbon); IR 1695, 1650, 1620, 1590, 1560, 1490 cm^{-1}; ^1H NMR (200 MHz, D_2O/NaOD) δ = 2.51 (t, *J* = 8.8 Hz, 2H), 2.52 (s, 3H), 3.12 (t, *J* = 8.8 Hz, 2H), 7.36 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1 H), 8.24 (s, 1H); ^{13}C NMR (50 MHz, D_2O/NaOD) δ = 23.96, 31.8, 40.0, 123.8, 129.9, 130.2, 131.0, 134.4, 137.1, 140.9, 141.8, 158.2, 186.2. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67. Found: C, 67.90; H, 5.39.

*3-(4-Hydroxy-8-methyl-3-isoquinolinyl)propanoic acid (**3e**):* This compound was isolated in variable yield from the heating of ketone (**1e**) in 37 % HCl, mp 177-178 °C (D_2O, acticarbon); IR 1700, 1670, 1620, 1590, 1550 cm^{-1}; ^1H NMR (200 MHz, D_2O/NaOD) δ = 2.50 (t, *J* = 8.8 Hz, 2H), 2.65 (s, 3H), 3.12 (t, *J* = 8.8 Hz, 2H), 7.32 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.48 (dd, *J* = 8.6, 6.8 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1 H), 8.44 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR (50 MHz, D_2O/NaOD) δ = 20.7, 31.9, 39.9, 123.5, 129.4, 130.1, 130.9, 133.9, 134.4, 137.7, 142.3, 159.3, 186.2. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67. Found: C, 67.28; H, 5.44.

*3-(3-Isoquinolinyl)propanoic acid (**4a**). and 3-(1,2-Dihydro-3-isoquinolinyl)propanoic acid (**15**):* Alcohol (**13a**) (1g, 5 mmol) in 37% HCl (50 mL) was refluxed for 24 h, leading to a solution of pure acid (**15**), ^1H NMR (200 MHz, D_2O/NaOD) δ = 2.44 (t, *J* = 7.6 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 4.54 (s, 2H), 4.83 (s, 1H) 7.28 (br s, 4H). The reflux was continued for 160 h; the solution was then evaporated leading to **4a** hydrochloride. Ethanol (5 mL) then propylene oxide (1.25 mL) was added to the residue. After 12 h the solution was cooled at – 40 °C for 24 h. The solid obtained was washed with a small amount of CH_2Cl_2, leading 67% of acid (**4a**), mp 181-182 °C (acetone, acticarbon); IR 1715, 1630, 1595 cm^{-1}; ^1H NMR (200

MHz, D_2O/NaOD) δ = 2.60 (t, *J* = 7.2 Hz, 2H), 3.06 (t, *J* = 7.2 Hz, 2H), 7.46 (s, 1H), 7.57 (t, *J* = 6 Hz, 1H), 7.63-7.78 (m, 2H), 7.91 (d, *J* = 8.3 Hz, 1H), 8.72 (s, 1H); ^{13}C NMR (50 MHz, D_2O/NaOD) δ = 36.1, 40.2, 121.2, 128.8, 129.3, 129.7, 130.3, 133.9, 139.1, 154.2, 155.6, 184.9. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51. Found: C, 71.74; H, 5.30.

*3-(6-Chloro-3-isoquinolinyl)propanoic acid (**4b**):* This compound was isolated in variable yield from the heating of ketone (**1b**) in 37 % HCl, mp 167-168 °C (D_2O, acticarbon); IR 1710, 1630, 1590, 1570 cm^{-1}; ^{1}H NMR (200 MHz, D_2O/NaOD) δ = 2.58 (t, *J* = 7.9 Hz, 2H), 3.03 (t, *J* = 7.9 Hz, 2H), 7.17 (s, 1H), 7.31 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.44 (s, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 8.72 (s, 1H); ^{13}C NMR (50 MHz, D_2O/NaOD) δ = 36.0, 39.9, 119.7, 126.8, 127.0, 129.8, 131.6, 138.8, 139.0, 153.4, 155.4, 184.4. Anal. Calcd for $C_{12}H_{10}NO_2Cl$: C, 61.16; H, 4.28. Found: C, 61.34; H, 3.97.

*3-(6-Methyl-3-isoquinolinyl)propanoic acid (**4c**):* This compound was isolated in variable yield from the heating of ketone (**1c**) in 37 % HCl, mp 182-184 °C (D_2O, acticarbon); IR 1725, 1655, 1570, cm^{-1}; ^{1}H NMR (200 MHz, D_2O/NaOD) δ = 2.49 (s, 3H), 2.62 (t, *J* = 8.0 Hz, 2H), 3.10 (t, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.9 Hz, 1H), 7.48 (s, 1H), 7.57 (s, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 8.97 (s, 1H). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.63; H, 6.41.

*3-(6-Bromo-3-isoquinolinyl)propanoic acid (**4f**):* This compound was isolated in variable yield from the heating of ketone (**1f**) in 37 % HCl, mp 191-192 °C (D_2O, acticarbon); IR 1710, 1635, 1590, cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.3-3.3 (m, 4H), 7.25-7.80, m, 4H), 8.12 (s, 1H). Anal. Calcd for $C_{12}H_{10}NO_2Br$: C, 51.46; H, 3.60. Found: C, 51.11; H, 3.54.

*1,1',5,5'-Tetrahydro-10,10'-bipyrrolo[1,2-b]isoquinoline-3,3'(2H,2'H)-dione (**5a**):* A stirred mixture of ketone (**1a**) (1 g, 5 mmol) and alcohol (**13a**) (1.010 g, 5 mmol) in 37% HCl (20 mL) was heated at 130 °C for 24 h. The solid was washed with 10% HCl, then with CH_2Cl_2, leading to 57% of dimer (**5a**), mp 198-203 °C (DMF).; IR 1675, 1575, 1470 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.40-2.70 (m, 8H), 4.94 (d, *J* = 16.9 Hz, 2H), 5.09 (d, *J* = 16.9 Hz, 2H), 6.89 (dd, *J* = 6.3, 1.4 Hz, 2H), 7-7.14 (m, 6H); ^{13}C NMR (50 MHz, acetone-d_6/DMSO-d_6) δ = 23.0, 28.8, 44.0, 103.8, 123.0, 126.7, 127.2, 128.0, 128.5, 133.2, 142.1, 175.7. Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47. Found: C, 78.12; H, 5.49.

*8,8'-Dichloro-1,1',5,5'-tetrahydro-10,10'-bipyrrolo[1,2-b]isoquinoline-3,3'(2H,2'H)-dione (**5b**):* This compound was isolated from the heating of ketone (**1b**) in 37 % HCl, mp > 230 °C (DMF); IR 1715, 1655, 1630, 1595, 1490 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.59 (br s, 8H), 4.92 (d, *J* = 16.9 Hz, 2H),

5.04 (d, *J* = 16.9 Hz, 2H), 6.80 (d, *J* = 1.9 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 7.11 (dd, *J* = 8.2, 1.9 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 22.5, 28.3, 43.3, 102.4, 121.9, 125.0, 126.4, 127.7, 133.3, 134.0, 141.8, 175.0. Anal. Calcd for $C_{24}H_{18}N_2O_2Cl_2$: C, 65.91; H, 4.15. Found: C, 66.19; H, 4.38.

6,6'-Dichloro-1,1',5,5'-tetrahydro-10,10'-bipyrrolo[1,2-b]isoquinoline-3,3'(2H,2'H)-dione ***(5d)****:* This compound was isolated in variable yield from the heating of ketone (**1d**) in 37 % HCl, mp >230 °C (DMF); IR 1715, 1650, 1590 cm^{-1}; ^{1}H NMR 200 MHz, ($CDCl_3$) δ = 2.60 (s, 8H), 4.95 (d, *J* = 18.0 Hz, 2H), 5.13 (d, *J* = 18.0 Hz, 2H), 6.75 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 2H), 7.14 (dd, *J* = 7.6, 1.2 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 22.4, 28.3, 42.4, 102.8, 120.6, 124.9, 127.0, 128.9, 132.7, 133.5, 140.9, 174.9. Anal. Calcd for $C_{24}H_{18}N_2O_2Cl_2$: C, 65.91; H, 4.15. Found: C, 66.23; H, 4.03.

8,8'-Dibromo-1,1',5,5'-tetrahydro-10,10'-bipyrrolo[1,2-b]isoquinoline-3,3'(2H,2'H)-dione ***(5f)****:* This compound was isolated in variable yield from the heating of ketone (**1f**) in 37 % HCl, mp > 230 °C (DMF). IR 1700, 1650, 1605 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.59 (s, 8H), 4.89 (d, *J* = 16.6 Hz, 2H), 5.03 (d, *J* = 16.6 Hz, 2H), 6.94 (d, *J* = 2.1 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 2H), 7.25 (dd, *J* = 7.8, 2.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 22.6, 28.4, 43.5, 102.3, 122.2, 128.1, 130.2, 131.5, 133.7, 137.4, 141.9, 175.0. Anal. Calcd for $C_{24}H_{18}N_2O_2\ Br_2$: C, 54.78; H, 3.45. Found: C, 54.61; H, 3.40.

3-(4-Oxo-1,2,3,4-tetrahydro-3-isoquinolinyl)propanoic acid ***(10a)****:* This compound was observed by NMR spectrum during the heating of ketone (**1a**) in 37% HCl, ^{1}H NMR (200 MHz, D_2O/NaOD) δ = 1.87-2.02 (m, 1 H), 2.08-2.25 (m, 1H), 2.25-2.41 (m, 2H), 3.55-3.75 (m, 1H), 4.15 (s, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1 H), 7.97 (d, *J* = 7.9 Hz, 1H).

3-(6-Chloro-4-oxo-1,2,3,4-tetrahydro-3-isoquinolinyl)propanoic acid ***(10b)****:* This compound was observed during the heating of ketone (**1b**) in 37 % HCl, ^{1}H NMR (200 MHz, D_2O/NaOD) δ = 1.78-2.12 (m, 1 H), 2.12-2.42 (m, 1H), 2.42-2.58 (m, 2H), 3.65-3.75 (m, 1H), 3.92 (d, *J* = 15.5 Hz, 1H), 4.01 (d, *J* = 15.5 Hz, 1H), 7.26 (d, *J* = 8 Hz, 1H), 7.49 (d, *J* = 8 Hz, 1H), 8.02 (s, 1H).

1,5-Dihydropyrrolo[1,2-b]isoquinolin-3(2H)-one ***(12a)****:* This compound was isolated in variable yield from the heating of ketone (**1a**) in 48% HBr, mp 128-129 °C (acetone); IR 1700, 1660, 1600, 1490 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ = 2.54 (t, *J* = 7.4 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 4.83 (s, 2H), 5.56 (t, *J* = 1.6 Hz, 1H), 6.93 (dd, *J* = 6.1, 1.6 Hz, 1H), 7.02-7.18 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 22.8, 28.6, 43.4, 99.5, 124.5, 125.91, 125.96, 125.98, 127.62, 131.4, 140.3, 175.0. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 77.91; H, 5.92.

*8-Methyl-1,5-dihydropyrrolo[1,2-b]isoquinolin-3(2H)-one (**12c**):* This compound was isolated in variable yield from the heating of ketone (**1c**) in 48 % HBr, mp 140-141 °C (acetone); IR 1705, 1660, 1640, 1610, 1505 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ = 2.21 (s, 3H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 4.72 (s, 2H), 5.46 (t, *J* = 1.7 Hz, 1H), 6.77 (s, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 20.9, 22.9, 28.8, 43.3, 99.6, 123.1, 125.3, 125.9, 126.6, 131.3, 137.3, 140.4, 175.0. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58. Found: C, 78.72; H, 6.21.

*3-[3'-(2-Carboxyethyl)-6,6'-dichloro-4,4'-bisisoquinolin-3yl]propanoic acid (**16**):* A stirred mixture of dimer (**5b**) (1.9 g, 4.3 mmol) and 37% HCl (150 mL) was heated at 130 °C for 48 h. The solution was evaporated, the solid obtained was recrystallized from water (acticarbon) leading to 76% of dimer (**16**), mp 136-142 °C (H_2O, acticarbon); IR 1715, 1610, 1570, 1485 cm^{-1}; ^1H NMR (200 MHz, D_2O/NaOD) δ = 2.11-2.45 (m, 4H), 2.45-2.72 (m, 4 H), 6.95 (d, *J* = 1.8 Hz, 2H), 7.45 (dd, *J* = 8.9, 1.8 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H), 9.32 (s, 2H). ^{13}C NMR (50 MHz, D_2O/NaOD) δ = 34.2, 39.3, 125.2, 126.7, 127.8, 131.1, 133.5, 139.2, 140.3, 155.4, 155.7, 184.0. Anal. Calcd for $C_{24}H_{18}N_2O_4\ Cl_2$: C, 61.42; H, 3.87. Found: C, 61.04; H, 4.11.

ACKNOWLEDGEMENTS

We thank Johnson and Johnson Pharmaceutical Research and Development, and the Norbert Segard Foundation for financial support.

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