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Synthesis of Analogue to Camptothecine

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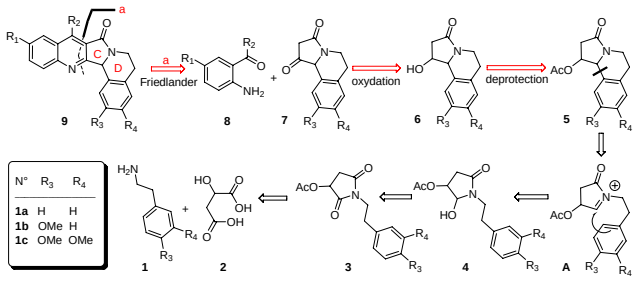
***Abstract*—**Camptothecin (CPT) is a cytotoxic quinoline alkaloid, which inhibits the DNA enzyme topoisomerase I (topo I). It was discovered in 1966 by M. E. Wall and M. C. Wani in systematic screening of natural products for anticancer drugs. It was isolated from the bark and stem of Camptotheca acuminata (Camptotheca, Happy tree), a tree native in China. CPT showed remarkable anticancer activity in preliminary clinical trials but also low solubility and (high) adverse drug reaction. Because of these disadvantages synthetic and medicinal chemists have developed numerous syntheses of Camptothecine [1][2][3] and various derivatives to increase the benefits of the chemical, with good results. In our method CPT analogues has be six steps starting from available material DL Malic acid.

***Keywords*—**Camptothecine, synthesis, analogue.

I. Introduction

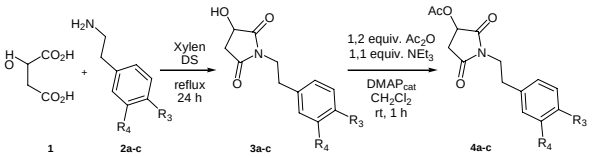
ANALOGUE to Camptothecine had been synthesized in six steps starting from available material (phenylethylamine **1**, and DL malic acid **2**). The condensation of phenylethylamine and DL malic acid gave imidoacetate **3**, the reduction of one of the two ketones is made in low temperature followed by π-cyclisation, deprotection and oxidation to obtained ketone tricycle[1] **7**. In the last step we reacted with aminobenzaldehyde or aminobenzoketones by Friedlander reaction as a key to obtained our final product.



Synthesis of Camptothecine.

II. Results and Discussion

From the point of view, the reactions between the DL-malic acid **1** and the substituted phenylethylamine or not **2a-c**, is carried out in a stage in toluene or xylene with backward flow under the azeotropic conditions. The experimental protocol employed underlines the unquestionable advantage in the case of use of xylene instead of toluene, thus showing the thermal character of the reaction and the results obtained are gathered in the following table1 (Scheme1). The outputs of this reaction is in conformation with those obtained in the literature in the case of chiral alcohols-imides and no influence is exerted, a priori, by the nature of the substituents R_3 and R_4 present in the structure of amine 3 of departure



Scheme 1. Synthesis of imide alcohols **3a-c** and corresponding imide-acetates **4a-c**

TABLE I SYNTHESE OF IMIDE-ACETATES **4 a-c**

Product N°	Groupe R_3	Groupe R_4	Imide-Alcohol **3** (%)	Imide-acetates **4** (%)
a	H	H	71	88
b	OMe	H	61	79
c	OMe	OMe	67	83

Alcohols **3a-c** thus obtained are protected by a grouping acetate. This protection is carried out under the traditional conditions with 1.2 equivalents of acetic anhydride in presence of a catalytic quantity of 4-dimethylaminopyridine (DMAP) and 1.1 equivalents of triethylamine in the anhydrous dichloromethane. After one hour of agitation ambient temperature has, awaited protected alcohols **4**a-c are obtained in good conditions, after the purification output ranges 79-88% (Table 1).

I. Synthesis of 5-acetyloxy-N-phenylethylsuccinamidals 5a-c

In our case, the most effective method is that of Park, 4 which consists in using 1, 16 equivalents of borohydrure of sodium in a mixture of methanol/dichloromethane in a report/ratio 1/1 (V/V) with -30 °C. Under these conditions, the reduction is complete in half hour and we exclusively isolated the hydroxy lactams 5a-c with outputs ranges from 56 to 68%.

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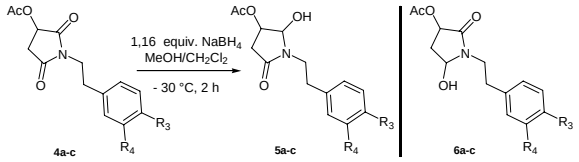


Scheme 2. Reduction of imides acetates- 4 a-c to hydroxy lactames corresponds 5 a-c.

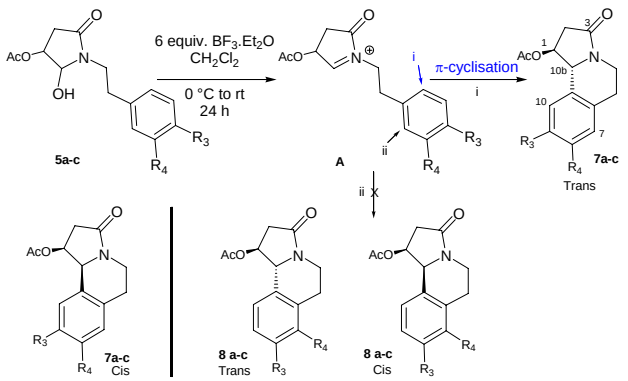
TABLE II OBTENTION DES HYDROXY LACTAMES **5 a-c**

Hydroxy lactame **5**	Groupe R_3	Groupe R_4	yield (%)
5a	H	H	68
5b	OMe	H	56
5c	OMe	OMe	60

It is significant to announce that during this reaction, we never observed the formation of neither of the hydroxy lactams of type 63 nor alcohol-amides, open which can be formed by double reduction of 58 and/or 63.

II.2.2. Access to the acetyloxypyrrolidinoisoquinoleines 7a-c

The key stage of our strategy, the construction of the tricyclic system **7** precursor of corresponding ketones 7 a-c, rests on a process of cyclization π-cation of Friedel-Crafts type. Formally, the 7a-c will rise from the intramolecular nucleophilic attack of the core benzene on N-acyliminium an ion formed intermediate in acid medium. The models 5a-c fulfills the necessary requirements to undergo a cyclization implying of such process. We thus treated them by a broad excess of BF3.EtO in the dichloromethane with 0°C. An increase of temperature for 24 H period followed by neutral hydrolysis of acid A provides the discounted products of cyclization 57a-c with suitable outputs ranging from 51 to 60% (Table 3).



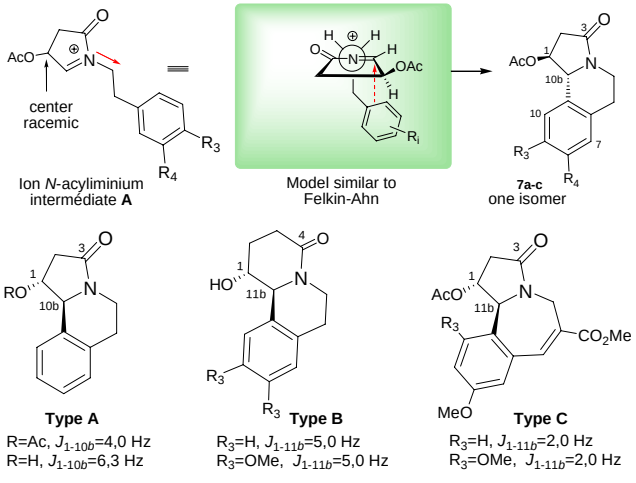
Scheme 3. Processus de cyclisation des hydroxy lactames 8a-c.

TABLE III LACTAMES CYCLICES **7a-c**

cyclic Lactame **7**	Groupe R_3	Groupe R_4	Yield (%)	Couplage H_1-H_{10b}
7a	H	H	60	3,78
7b	OMe	H	51	3,91
7c	OMe	OMe	57	3,83

The formation of these compounds would result from the trapping of intermediate N-acyliminium ion of type A by the aromatic nucleus by the least encumbered position.The regiospecificity of this reaction is confirmed by the absence in the reaction medium of the possible regioisomeres of 8a-c type. This is corroborated by their spectra NMR of the proton which shows two singulet aromatic in conformity with the structure of cyclic lactams 7a-c roposed instead of a doublet of doublet characteristic of the product of cyclization 8 a-c. Spectra NMR of C^{13} as those of program DEPT-135 of these compounds also show the presence of an additional quaternary carbon in comparison with those of their hydroxy congeneric lactams. This quaternary carbon is direct consequence of the reaction of cyclization which led exclusively to the only one diastereoisomer. Analysis NMR of the proton of these products showed in a nonambiguous way, the trans relation between the protons H1 and angular H10b in all the cases. The constant of coupling measured for these protons varies from 3,78 to 3,91 Hz (Table 3).

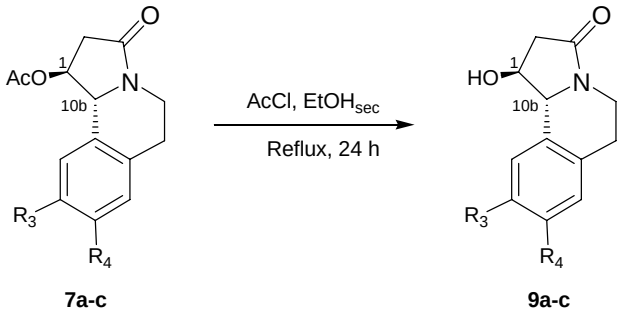
The diastereospecificity of this reaction can be explained by considering a model close to that proposed by Felkin-Ahn that we also adopted during preceding work in series of the maleimide and of succinimide. Indeed, this conformation supports the approach of nucleophilic, here it acts as a benzene aromatic system, side opposed to the acetate group carried by the core pyrrolidone leads to a single stereoisomeres 7a-c.



Scheme 4. Possible Intermediate for cyclisation of hydroxy lactames.

The stereochemistry of our compounds is identical to that observed in the literature for similar structures obtained besides by cyclization of the π-cation type of hydroxy lactams chiral. The constants of couplings between the two angular protons C_1-C_{10b} (compounds of the type A) or C_1-C_{11b} (compounds of types B and C) vary according to the nature of the nitrogenized core as that of the core to which it is amalgamated (Scheme 21).Those vary between 2 Hz (core pyrroloazepine) with 6,3 Hz (indolizidine).[4]

The hydrolysis of the function acetate of the acetyloxypyrrolidinoisoquinoleines 7a-c out of corresponding alcohol is ensured by the action of an acetyl chloride solution in anhydrous ethanol as solvent at a temperature active of ambient with that of the reflux.45 After 24 hours of reaction, awaited deproteges alcohols, the 1-hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]-isoquinolein-3-ones (9a-c), are isolated with 53% yielded. These results obtained are detailed in the table 4 which is as follows.



Scheme 5. Deprotection des acetates tricyclics **56a-c**.

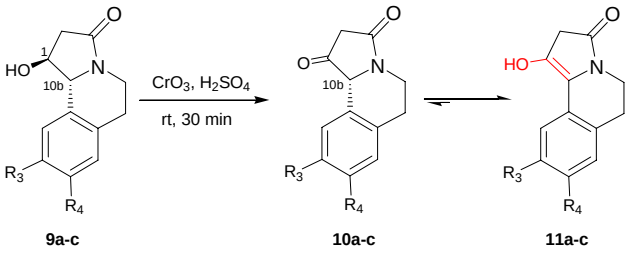
TABLE IV OBTENTION DES LACTAMES CYCLIQUES **57a-c**

Alcool cyclique **9**	Groupe R_3	Groupe R_4	Yield (%)	Couplage H_1-H_{10b}
9a	H	H	53	6,26
9b	OMe	H	49	7,04
9c	OMe	OMe	44	6,24

3.1. Oxidation of the hydroxypyrrolidinoisoquinoleines 5a-c

The hydroxypyrrolidinoisoquinoleines 5a-c are angular systems having two protons with properties acid and thus easily oxydizable. The choice of the agent of oxidation of this type of substrate for a process of a specific oxidation is completely crucial. In addition, it is largely well established that the oxidation of Jones makes it possible to transform a function alcohol into functional ketones. The effectiveness of this reaction, employing the chromic acid (the reagent of Jones), strongly depends on the freshness of this agent of oxidation as well as reactivity of the functional alcohol in comparison to other sites of the substrate.

From this point of view, preceding tricyclic alcohols 9a-c are treated by the reagent of Jones (prepared starting from 26,8 g of CrO_3 in 23 mL of concentrated H_2SO_4 and 100 distilled water mL) in acetone between 0 and -5°C. After 30 min of reaction, thin layer chromatography of the reaction crude shows the complete consumption of the reagents. After the traditional treatment of the crudes of reactants, desired ketones are obtained, but the corresponding enolic forms 11a-c only, certain forms are stabilized by the conjugation with the aromatic nucleus. The output of the insulated products are gathered in table 5 below.



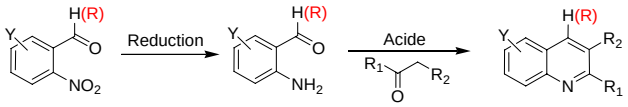
Scheme 6. Transformation of tricyclics alcools **9a-c** to correspondants enols **11a-c**.

TABLE V RESULTAT DE L'OXYDATION DES ALCOOLS TRICYCLICS 11a-c

Cyclic alcool **11**	Groupe R_3	Groupe R_4	Yield (%)	δ (OH) en ppm
11a	H	H	75	7,20 large
11b	OMe	H	64	1,91
11c	OMe	OMe	61	4,10 large

3.2. Application of the reaction of Friedländer to the enols 6a-c

The reaction of Friedländer is indisputably the most known method, to prepare quinolines as well as the similar aza-heterocycles. Although discovered almost 120 years ago, the reaction of Friedländer is still regarded as one of the most effective methods to prepare the aza-aromatic quinolines and compounds bicyclic connected. In its original form, this synthesis is usually made by the intermediary of a process in two stages, in the which reduction of a arylic o-nitroaldehyde (or vinyl 2-nitroaldehydes for the preparation of similar pyridines) is followed by the condensation with a functional carbonyl enolisable in presence of Brønsted acid or Lewis base like catalyst, used in stoichiometric or catalytic quantity (Scheme 7).



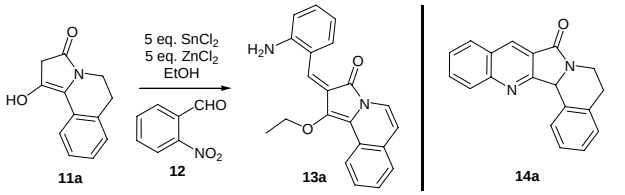
Scheme 7. Reaction de Friedländer.

The longetivity of the reaction of Friedländer is due mainly to its compatibility with a broad range of functional groups usable. With regard to aromatic o-aminoaldehydes, a range of functional groups is tolerated on aromatic rings. In the same way, for the carbonyl compounds, the literature is filled of symmetrical examples of ketones or not, even carrying

ketones in the said position has an additional substituent activation.

However one of the factors complicating this reaction is the relative instability of the intermediate aromatic *o*-amino aldehydes, which can easily undergo reactions of car-condensation. Modifications of these types of substrates are made such as those developed by Borsche (the *o*-nitrobenzaldehyde, for example, is converted into imine corresponding before the reduction of the nitro group). These processes are useful because they reduce the problems related to the instability of aryles o-aminoaldehydes but increase, alas, the number of synthetic operations which must be carried out. In order to circumvent these difficulties, the methods employ basic catalysts at the beginning of aromatic *o*-aminoaldehydes are under development. Simultaneously with those, direct procedures in ' a pot' starting from aromatic o-nitroaldehydes also emerged very recently.

As shows it the scheme 8 precedent, the compounds of the 6a-c type seem to be ideal candidates for the reaction of Friedländer for obtaining isoquinoleinopyrrolo-quinolines of the 14a-c type that we had fixed ourselves initially like objective. In order to test the feasibility of this reaction, we chose the enol 11a like model and the direct method mentioned above and described by Miller [7] like a procedure of choice to fill this objective.



Schema 8. Reaction of Friedländer 11a.

In accordance with the protocol optimized and employee by this author, to o-nitrobenzaldehyde (12) treated by 5 equivalents of $SnCl_2$ in EtOH with backward flow during one hour, we added 1 equivalent of the tricyclic enol 11a followed by 5 equivalents of $ZnCl_2$. The mixture is then heated to 70 °C under an atmosphere of argon during 4 hours, and after the usual treatment, the reactional crude is purified by chromatography on a column of silica to lead to a product which is identified as the cyclic amine-ether 13a with an output 50%. Other attempts with *o*-aminobenzaldehyde (prepared by reduction of 12 according to a procedure already described in the literature), did not lead to the required product 49a nor with other definite products. In all these cases the product isolated from unchanged departure 11a with poor yield accompanied by a significant decomposition of the matter premiere.

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