Synthesis of *ortho*-Substituted Aminopyridines. Metalation of Pivaloylamino Derivatives

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The three isomeric pivaloylaminopyridines were lithiated in more than 80% yields. Aminopyridine derivatives were treated by 2.5-3 equivalents of the complex BuLi-TMEDA at −10° in diethyl ether. Reaction of the lithiated species with various electrophiles afforded a number of *ortho*-substituted pivaloylaminopyridines in good yields. Secondary pyridine alcohols were oxidized to the corresponding aminopyridyl ketones. Pyridopyrimidines, benzonaphthyridines as well as an analogue of the natural antitumor alkaloid ellipticine has been synthesized showing the versatility of the method.

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Our interest in the synthesis of polysubstituted pyridines as synthetic tools led us some years ago to look for powerful functionalization methods. Great progress has been made with the development of the directed (*ortho*) lithiation of pyridines [1] [2] [3]. It is actually the only convenient way to introduce electrophiles onto the pyridine ring, since classical substitutions are not easy and often not regioselective. During the last fifteen years some reports have demonstrated that pyridine activated by halogens [4], hydroxy derivatives [5], carboxylic acid derivatives [6] and sulfonic acid derivatives [7] as well as the unsubstituted pyridine ring itself [8], can be lithiated. Aminopyridines are important starting materials in these series and their metalation appears as an attractive challenge for us. We showed in 1982 that 3-pivaloylaminopyridine undergoes lithiation at the C-4 position [9]. It was the first lithiation of a ring-unsubstituted aminopyridine, which had been previously claimed to be unfeasible [10]. The *N*-pivaloylamino moiety proved to be a good *ortho*-directing substituent toward metalation as in the aromatic series [11] and various 4-substituted 3-pivaloylaminopyridines could be obtained. These preliminary results were followed by those of Türner [12], who reported some results on the lithiation of 2-, 3- and 4-aminopyridines.

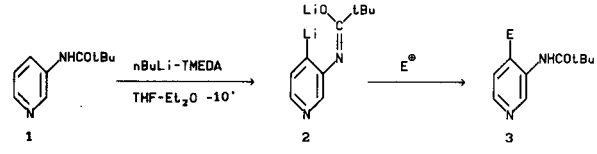
As our first study of 3-pivaloylaminopyridine lithiation proved to be promising, the work was pursued and extended to 4- and 2-aminopyridines. We wish to report here the results in this area. Moreover lithiation proved to be a very convenient and selective pathway to polyfunctional pyridines and some applications will be given.

1) Metalation of 3-Pivaloylaminopyridine **1**.

In a previous paper we reported a convenient method of functionalization of the 3-pivaloylaminopyridine **1** by metalation affording 4-substituted 3-pivaloylaminopyridine **3** in good yields [9].

This work was followed by a paper of Türner [12] who described the lithiation of the three isomeric pivaloylaminopyridines using the same *ortho*-directing group and metalating reagent, *i.e.* respectively the pivaloylamino moiety and *n*-butyllithium. Lithiation yields of 3-pivaloylaminopyridine were found lower than in the case of the 2-and 4-derivatives. The author isolated an addition product when dimethyl disulfide was used as the electrophile and correlated the decreasing yields with the ability of the 3-isomer to undergo addition.

Scheme 1



In order to improve the yields of metalation and because of our own results we continued our work. The results reported in Table 1 were obtained when the reaction was carried out in diethyl ether at −10° in the presence of 2.5 or 3 equivalents of *n*-butyllithium complexed by 2.5 or 3 equivalents of tetramethylethylendiamine (TMEDA). Lithiated pyridines **2** were reacted with various electrophiles leading to the corresponding 4-substituted 3-pivaloylaminopyridine **3**.

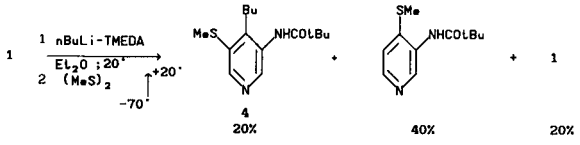
Table 1

Compound No.	Electrophile	E	Yield [%]
3a	D_2O,MeOD [a]	D	80
3b	C_6H_5-CHO [a]	C_6H_5-CHOH	75
3c	2-MeO-C_6H_4-CHO [a]	2-MeO-C_6H_4-CHOH	50
3d	2,4-Cl_2-C_6H_3-CHO [a]	2,4-Cl_2-C_6H_3-CHOH	60
3e	2-thienaldehyde [a]	2-thienyl-CHOH	65
3f	CH_3-CHO [b]	CH_3-CHOH	75
3g	CO_2 [c]	CO_2H	85
3h	$(C_6H_5)_2CO$ [a]	$(C_6H_5)_2COH$	85

[a] Electrophile 2.5 equivalents, 1 hour −10°. [b] Electrophile 7.5 equivalents, 15 hours −70°. [c] A solution of the lithiated compound **2** was poured onto a large excess of crushed dry ice.

When the reaction mixture was quenched with deuteriomethanol and deuterium chloride, the deuterio compound **3** (E = D) was synthesized in 80% yield. It proves that the intermediate dilithio species was formed at least in this ratio. The observed yields using aldehydes as electrophiles were in good agreement with this result. It should be noted that under the same experimental conditions an addition product has been observed using dimethyl disulfide. However the addition-product ratio is slightly lower (20%) than that observed by Türner (28%) [12] but more 3-pivaloylaminopyridine remain unchanged.

Scheme 2



If the structural features claimed by Türner are of major importance for lithiation chemoselectivity, experimental factors (metalating agent, solvent, electrophile ...) appear to be essential. The use of *n*-butyllithium/TMEDA chelate instead of *n*-butyllithium and diethyl ether instead of tetrahydrofuran prevent in most cases the addition reaction from proceeding to far.

Metalation of 2-substituted 3-pivaloylaminopyridines **5** occurred at carbon-4 providing trisubstituted pyridines **6** (Table 2). It will be noticed that 2-chloro-3-pivaloylaminopyridine (**5c**) (R = Cl) afforded the 2-butyl derivative **6c** (R' = Bu) but in low yield (20%).

Scheme 3

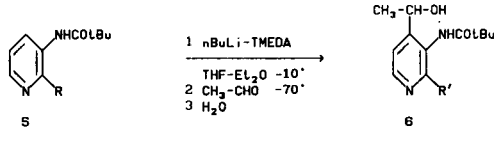


Table 2

Metalation of 2-Substituted 3-Pivaloylaminopyridines

3-Pivaloylamino pyridine	R	Product	R'	Yield [%]
5a	OMe	**6a**	OMe	32
5b	NHCOtBu	**6b**	NHCOtBu	50
5c	Cl	**6c**	Bu	20

2) Metalation of 2- and 4-(Pivaloylamino)pyridines.

As with 3-(pivaloylamino)pyridine **1**, the 2 and 4 isomers **7** and **10** can be very conveniently *ortho*-lithiated under similar conditions (−10°, diethyl ether, BuLi-TMEDA chelate 2.5 equivalents). Lithiated pyridines **8** and **11** reacted easily with various electrophiles leading to the corresponding 2,3- and 3,4-disubstituted pyridines in good to excellent yield (Tables 3-4).

a) 3-Substituted 2-(Pivaloylamino)pyridines.

Scheme 4

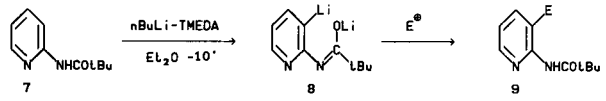
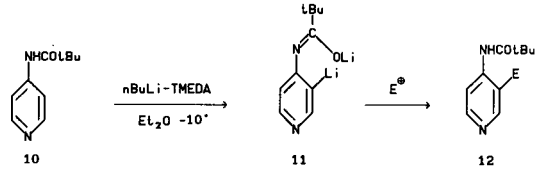


Table 3

Products	Electrophile	E	Yield [%]
9a	D_2O	D	85
9b	C_6H_5-CHO	C_6H_5-CHOH	70
9c	C_6H_5-CO-C_6H_5	$(C_6H_5)_2$COH	90
9d	CO_2	CO_2H	80

b) 3-Substituted 4-(Pivaloylamino)pyridines.

Scheme 5

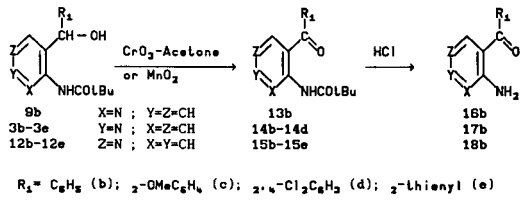


2-(Pivaloylamino)pyridine **7** and 4-(Pivaloylamino)pyridine **10** were regioselectively lithiated at carbon-3 and the reaction was completely chemoselective. This was shown by the crude reaction mixture analysis (tlc and ^1H nmr) after efficient steam-distillation of light impurities (TMEDA, benzaldehyde ...). Yields of purified *ortho*-disubstituted pyridines are very good and sometimes almost quantitative. The synthetic advantage of directed lithiation beside other functionalization methods is proved by the rapid synthesis of 2- and 4-(pivaloylamino)nicotinic acids **9d** and **12g**. These *ortho*-aminonicotinic acids were readily prepared in two steps with overall yields higher than 80% starting from easily accessible 2- and 4-aminopyridines. These *ortho* bifunctionnal synthons have been previously prepared using a multistep sequence starting from the expensive pyridine-2,3- and -3,4-dicarboxylic acids with low overall yields [13].

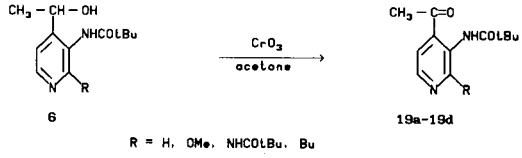
3) Synthesis of *ortho*-Aminoaroylpyridines.

Secondary *ortho*-(pivaloylaminopyridyl)methanols and ethanols previously prepared from 2-,3- and 4-(pivaloylamino)pyridines **1**, **7** and **10** as well as 2-substituted 3-(pivaloylamino)pyridines **6** were readily oxidized to the corresponding ketones in high yields using manganese dioxide in refluxing toluene [14] or chromic anhydride in acetone [15]. Warming of the resulting *ortho*-(pivaloylaminopyridyl) ketones in 3*N* hydrochloric acid afforded some *ortho*-(aminopyridyl) aryl ketone.

Scheme 6



Scheme 7



Ortho-Aminobenzoylpyridines **13, 14** and **15** are useful synthons which were previously prepared from the corresponding *ortho*-pyridinedicarboxylic acids in lower yields. For example (4-amino-3-pyridyl) phenyl ketone was synthesized by us in four steps starting from 4-aminopyridine with an overall yield of 65%. The same derivative was obtained from pyridine-3,4-dicarboxylic acid *via* an eight step sequence with a low overall yield [16].

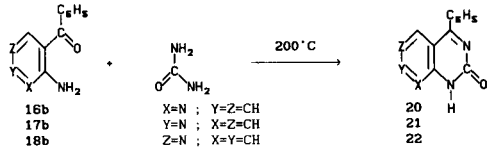
4) Synthesis of Fused Polyheterocycles from *ortho*-aminopyridyl Ketones.

The bifunctional reactivity of the previous *ortho*-aminopyridyl ketones was briefly examined. As expected, condensations with other bifunctional reagents bearing either nucleophilic and electrophilic centers led to the corresponding fused heterocycles.

a) Pyridopyrimidines.

Ortho-Aminobenzoylpyridines **16b, 17b** and **18b** react with hot molten urea to give the corresponding pyridopyrimidinones **20, 21** and **22** in high yield.

Scheme 8



b) Tetrahydrobenzonaphthyridines and Analogues.

Condensation between cyclohexanone and *ortho*-aminopyridyl ketones afforded the corresponding naphthyridines **23, 24** and **25** in high yields. Modified Friedlander conditions using an acidic catalysis (sulfuric acid/acetic acid) gave the best results. Condensations could be more expeditiously performed on the pivaloylamino derivatives by adding small amounts of water to the reaction mixture.

Scheme 9

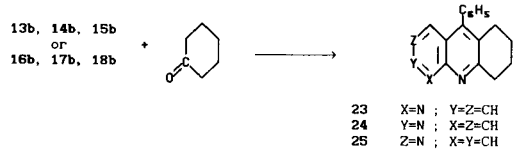
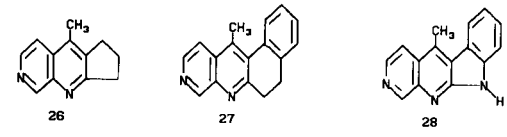


Table 4

Products	Electrophile	E	Yield [%]
12a	D_2O	D	90
12b	C_6H_5-CHO	C_6H_5-CHOH	70
12c	2-MeO-C_6H_4-CHO	2-MeO-C_6H_4-CHOH	60
12d	2,4-Cl_2-C_6H_3-CHO	2,4-Cl_2-C_6H_3-CHOH	65
12e	2-thienaldehyde	2-thienyl-CHOH	60
12f	$(C_6H_5)_2CO$	$(C_6H_5)_2COH$	85
12g	CO_2	CO_2H	95

In the same way, (3-amino-4-pyridyl) methyl ketone was condensed with cyclopentanone, β-tetralone and 2-indolinone to give respectively compounds **26, 27** and **28.**

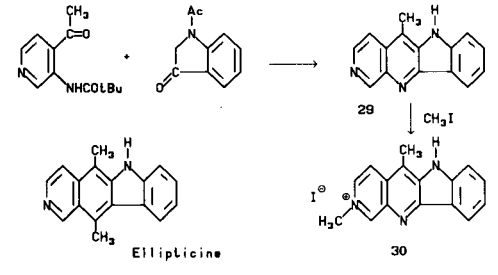
Scheme 10



c) Azaellipticines.

Finally (3-pivaloylamino-4-pyridyl) methyl ketone **19a** was condensed with *N*-acetyl-3-indolinone. This route to pyrido[4,3-*b*]carbazole analogues has been previously checked by us with *ortho*-aminoformylpyridine [17] using Friedlander basic catalysis. In the case of an *ortho*-aminoketone, condensation is best performed on the pivaloylamino derivative under acidic catalysis. A completely deoxygenated atmosphere was require in order to avoid side oxidation of 3-indolinone to indigo. 5-Methyl-6*H*-indolo[3,2-*b*][1,7]naphthyridine **29** was isolated in 21% yield as an insoluble solid. This azaellipticine was well characterized as the corresponding 2-methylellipticinium iodide salt **30** obtained by reaction of **29** with methyl iodide.

Scheme 11



Conclusion.

Metalation of aminopyridine derivatives afforded a very convenient route to various *ortho*-substituted pyridines. This method appears to be very interesting not only for the 2 and 4 isomers but also for 3-aminopyridine. In this case the use of ethyl ether as the solvent and butyllithium complexed with TMEDA as the reagent, allowed good lithiation yields. *ortho*-Aminopyridyl ketones were easily prepared by oxidation of the corresponding alcohols. The former compound appeared to be a useful synthetic tool for the construction of different fused rings such as pyridopyrimidines, benzonaphthyridines and an analogue of the natural product ellipticine.

EXPERIMENTAL

Melting points were determinated on a Kofler apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Varian A60 or T60 instrument at 60 MHz and a Brucker WP80 instrument at 80 MHz in deuteriochloroform or in DMSO-d_6 using tetramethylsilane or hexamethyldisiloxane respectivley as internal standards. The ^{13}C nmr spectra were recorded on a Brucker WH90. The following abreviations were used: s (singlet), d (doublet), m (multiplet). Coupling constants measured for the pyridine ring are: J (H2-H3) = J (H5-H6) = 4-5 Hz; J (H3-H4) = J (H3-H5) = 8-10 Hz; J (H2-H4) = J (H4-H6) = 1-2 Hz.

General Procedure for the Synthesis of (Pivaloylamino)pyridines.

To an ice cooled solution of 94 g (1 mole) of aminopyridine and 101 g (1 mole) of triethylamine in a mixture of 400 ml of tetrahydrofurane and 150 ml of ether was added dropwise a solution of 120.5 g (mole) of pivaloyl chloride. The resulting mixture was stirred for variable times, hydrolyzed with 200 ml of water and extracted with chloroform. The extract was dried (magnesium sulfate) and evaporated to dryness. Recrystallisation from toluene gave white crystals.

2-Methoxy-3-pivaloylaminopyridine (**5a**).

The starting material was 2-methoxy-3-aminopyridine obtained from 2-chloro-3-aminopyridine as starting material in the usual manner. Compound **5a** was prepared by the general procedure described above. The reaction mixture was stirred for 20 hours. Compound **5a** was obtained as an oil in 95% yield; ^{1}H nmr (deuteriochloroform): 1.30 (s, 9H, *t*-Bu), 4.03 (s, 3H, OCH_3), 6.85 (dd, 1H, 5-H), 7.85 (dd, 1H, 6-H), 8.66 (dd, 1H, 4-H), 8.0 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.22; H, 7.85; N, 13.30.

2,3-Dipivaloylaminopyridine (**5b**).

Compound **5b** was prepared by the general procedure starting from commercial 2,3-diaminopyridine. The reaction time was of 20 hours. 2,3-Dipivaloylaminopyridines was obtained in 50% yield as a solid, mp 136°; ^{1}H nmr (deuteriochloroform): 1.27 and 1.33 (2s, 2·9H, *t*-Bu), 7.14 (dd, 1H, 5-H), 8.03 (dd, 1H, 6-H), 8.20 (dd, 1H, 4-H), 9.08 and 9.75 (2s, 2·1H, NH).

Anal. Calcd. for $C_{15}H_{23}N_3O_2$: C, 64.96; H, 8.36; N, 15.15. Found: C, 64.75; H, 8.60; N, 15.10.

2-Chloro-3-pivaloylaminopyridine (**5c**).

The starting material was 2-chloro-3-aminopyridine. Compound **5c** was obtained as an oil in 90% yield; ^{1}H nmr (deuteriochloroform): 1.30 (s, 9H, *t*-Bu), 7.20 (dd, 1H, 5-H), 8.02 (dd, 1H, 6-H), 8.68 (dd, 1H, 4-H), 8.0 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_{13}ClN_2O$: C, 56.44; H, 6.16; N, 13.16. Found: C, 56.30; H, 6.20; N, 13.23.

General Procedure for the Metalation of Pivaloylaminopyridines.

To a solution of pivaloylaminopyridine (25 mmoles) and 6.3 g of TMEDA (62.5 mmoles) in 150 ml of anhydrous ether cooled to −70° was added dropwise 39 ml of butyllithium (1.6 *M* in hexane) (62.5 mmoles). The mixture was stirred for 15 minutes and heated to −10°. After 2 hours of stirring a precipitate appears and the suspension was cooled again to −70° before introduction of the electrophile.

Electrophile: Deuterium Oxide-Deuteriomethanol.

A mixture of deuteriomethanol-deuterium oxide 1/1 (6 ml) was added dropwise to a suspension of the lithio derivative prepared as described above at −70°. The reaction mixture was heated at room temperature and stirred one hour before hydrolysis with 50 ml of water. The aqueous layer was extracted three time with chloroform and then the combined layers were dried and evaporated to dryness to leave an oil.

Electrophile: Carbon Dioxide.

A suspension of 25 mmoles of the lithio pivaloylaminopyridine in diethyl ether prepared as described above was added to a suspension of a large excess of dry ice in 100 ml of diethyl ether. After one hour the reaction mixture was hydrolyzed with 50 ml of 0.5*N* hydrochloric acid.

Electrophile: Aromatic Aldehydes.

To a suspension of the lithio derivative prepared as described above, cooled to −70° was added a solution of an aldehyde in anhydrous THF. The obtained mixture was stirred for 2 hours at 0° and hydrolyzed with a large excess of water at the same temperature. An oil was obtained after decantation, extraction with chloroform and drying. The crude product was steam-distillated to eliminate excess TMEDA and aldehyde. Purification of the substituted pyridine was performed by recrystallization from diethyl ether or by flash chromatography on silcia gel with chloroform and a small amount of ethanol.

Electrophile: Benzophenone.

Twenty-five mmoles of the lithiated species prepared as described above was added to a solution of 11.4 g (62.5 mmoles) in 100 ml of anhydrous diethyl ether. The reaction mixture was hydrolyzed after 1 hour of stirring with 50 ml of water. The precipitate was filtered, dried and purified if necessary.

4-Deuterio-3-pivaloylaminopyridine (**3a**).

The deuterium incorporation determinated from the ^{1}H nmr spectrum was determined to be 80%. The 4-deuterio-3-pivaloylaminopyridine (**3a**) was purified by steam-distillation and recrystallization from hexane; ^{1}H nmr (DMSO-d_6): 1.20 (s, 9H, *t*-Bu), 7.25 (d, 1H, 5-H), 8.20 (d, 1H, 6-H), 8.80 (s, 1H, 2-H), 9.30 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_{13}DN_2O$: C, 67.02; H, 7.31; N, 15.63. Found: C, 67.10; H, 7.39; N, 15.59.

3-Pivaloylaminopyridine-4-carboxylic Acid (**3g**).

This compound was obtained as a colourless solid in 85% yield, mp 286° (lit [12], yield = 46%, mp 295°); ^{1}H nmr (DMSO-d_6): 90 Mz, 1.19 (s, 9H, *t*-Bu), 7.76 (d, 1H, 5-H), 8.33 (d, 1H, 6-H), 10.87 (s, 1H, 2-H), 11.12 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.20; H, 6.41; N, 12.47.

Phenyl(3-pivaloylamino-4-pyridyl)methanol (**3b**).

This compound was obtained as a solid in 75% yield, mp 210° (lit [12] yield = 53%, mp 199-204°); ^{1}H nmr (DMSO-d_6): 1.05 (s, 9H, *t*-Bu), 5.90 (d, 1H, H(CH-O), 6.70 (d, 1H, OH), 7.20 (m, 5H, phenyl protons), 8.25 (d, 1H, 6-H), 8.85 (s, 1H, 2-H), 9.30 (s, 1H, NH) (J H-OH = 4 Hz).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.90; H, 7.03; N, 9.72.

(2-Methoxyphenyl)(3-pivaloylamino-4-pyridyl)methanol (**3c**).

This compound was obtained as a solid in 50% yield, mp 176°; ^{1}H nmr (DMSO-d_6): 1.10 (s, 9H, *t*-Bu), 3.60 (s, 3H, OCH_3), 5.75 (d, 1H, H(CH-O)), 6.57 (d, 1H, OH), 6.70 (d, 2H, 3'- and 6'-H), 7.05 (d, 2H, 4'- and 5'-H), 7.20 (d, 1H, 5-H), 8.15 (d, 1H, 6-H), 8.80 (s, 1H, 1-H), 9.25 (s, 1H, NH), (J 3'-4'

= J 6'-5' = 9 Hz; J H-OH = 2 Hz).

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.60; H, 6.90; N, 9.00.

(2,4-Dichlorophenyl)(3-pivaloylamino-4-pyridyl)methanol (**3d**).

This compound was obtained as a solid in 60% yield, mp 220°; ^{1}H nmr (DMSO-d_6): 1.05 (s, 9H, *t*-Bu), 6.05 (m, 1H, H(CH-O)), 6.4 (m, 1H, OH), 7-7.4 (m, 3H, 5-H and phenyl protons), 8.3 (d, 1H, 6-H), 8.5 (s, 1H, 2-H), 9.1 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{18}Cl_2N_2O_2$: C, 57.80; H, 5.15; N, 7.93. Found: C, 57.42; H, 5.05; N, 7.95.

(3-Pivaloylamino-4-pyridyl)(2-thienyl)methanol (**3e**).

This compound was obtained as a solid in 65% yield, mp 154°; ^{1}H nmr (DMSO-d_6): 1.10 (s, 9H, *t*-Bu), 6.10 (s, 1H, H(CH-O)), 6.70 (m, 1H, 3'-H), 6.85 (dd, 1H, 4'-H), 7.40 (m, 1H, 5-H), 8.00 (m, 1H, 5'-H), 8.25 (d, 1H, 6-H), 8.85 (s, 1H, 2-H), 9.30 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 59.94; H, 6.17; N, 9.18.

Electrophile: Dimethyl Disulfide.

A solution of *n*-butyllithium, 1.6*M* (16 ml, 33.6 mmoles) was added to a mixture of 3-pivaloylaminopyridine (11.2 mmoles) and 3.9 g of TMEDA (33.6 mmoles) in anhydrous ether at −70°. The reaction mixture was slowly heated to 20° and stirred for 1 hour at this temperature. A standard workup afforded 1.95 g of a crude product which was purified by liquid chromatography. The ^{1}H nmr spectrum analysis of the raw crude product led to the following results:

3-Pivaloylaminopyridine (**1**).

This unreacted starting amounted to 20% (lit [12] trace).

4-Butyl-5-methylthio-3-pivaloylaminopyridine (**4**).

Compound **4** (20%) had (lit [12] 28%); ^{1}H nmr (deuteriochloroform): 0.93 (t, 3H, CH_3), 1.36 (s, 9H, *t*-Bu), 1.40 (m, 4H, CH_2-CH_2), 2.46 (s, 3H, SCH_3), 2.60 (m, 2H, $ArCH_2$), 8.16 (s, 1H, 6-H), 8.50 (s, 1H, 2-H).

4-Methylthio-3-pivaloylaminopyridine.

This compound (40%) had (lit [12] 42%); ^{1}H nmr (deuteriochloroform): 1.36 (s, 9H, *t*-Bu), 2.50 (s, 3H, CH_3), 7.15 (d, 1H, 5-H), 7.53 (s, 1H, NH), 8.28 (d, 1H, 6-H), 9.05 (s, 1H, 2-H).

General Procedure for the Preparation of 1-(3-Pivaloylamino-4-pyridyl)-ethanols.

A solution of *n*-butyllithium (1.6*M*) in hexane (21 ml, 33.6 mmoles) was added to a solution of 2 g of 3-pivaloylaminopyridine (11.2 mmoles) and of 3.9 g of TMEDA (33.6 mmoles) in diethyl ether at −70°. The suspension was stirred for 2 hours at room temperature. Then 3.5 g of redistillated acetaldehyde (79.5 mmoles) was added at −70° and the mixture was stirred overnight at this temperature. A standard workup and purification of the crude material by liquid chromatography afforded the alcohols.

1-(3-Pivaloylamino-4-pyridyl)ethanol (**3f**).

This compound was obtained as a solid in 75% yield, mp 92°; ^{1}H nmr (deuteriochloroform): 1.30 (s, 9H, *t*-Bu), 1.53 (d, 3H, CH_3), 4.95 (q, 1H, H(CH-O)), 7.00 (d, 1H, 5-H), 8.10 (d, 1H, 6-H), 9.33 (s, 1H, 2-H), 9.80 (s, 1H, NH), (J CH-CH_3 = 6 Hz).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.92; H, 8.10; N, 12.55.

1-(2-Methoxy-3-pivaloylamino-4-pyridyl)ethanol (**6a**).

This compound was obtained in 32% yield as a solid (the yield determinated by nmr analysis of the crude product wa about 60%), mp 115-116°; ^{1}H nmr (deuteriochloroform): 1.30 (s, 9H, *t*-Bu), 1.43 (d, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.80 (q, 1H, H(CH-O)), 7.10 (d, 1H, 5-H), 8.06 (d, 1H, 6-H); (J CH-CH_3 = 7 Hz).

Anal. Calcd. $C_{13}H_{20}N_2O_3$: C, 61.90; H, 7.94; N, 11.11. Found: C, 61.90; H, 8.15; N, 11.00.

1-(2,3-Dipivaloyamino-4-pyridyl)ethanol (**6b**).

This compound was obtained as a solid in 50% yield after purification (about 80% before purification), mp 220° subl; ^{1}H nmr (deuteriochloroform): 1.33 (s, 18H, *t*-Bu), 1.46 (d, 3H, CH_3), 4.83 (q, 1H, H(CH-O)), 7.33 (d, 1H, 5-H), 8.23 (d, 1H, 6-H), 8.90 and 9.03 (2·s, 2·1H, NH); (J CH-CH_3 = 7 Hz).

Anal. Calcd. for $C_{17}H_{27}N_3O_3$: C, 63.16; H, 8.59; N, 13.02. Found: C, 63.51; H, 8.40; N, 13.10.

1-(2-Butyl-3-pivaloylamino-4-pyridyl)ethanol (**6c**).

The starting material was 2-chloro-3-pivaloylaminopyridine **5c** and the alcohol was obtained in 20% yield as a solid, mp 153-154°; ^{1}H nmr (deuteriochloroform): 1.00 (t, 3H, CH_3), 1.30 (s, 9H, *t*-Bu), 1.43 (d, 3H, CH_3), 1.50 (m, 4H, $(CH_2)_2$), 2.60 (t, 2H, Ar-CH_2), 4.8 (q, 1H, H(CH-O)), 7.23 (d, 1H, 5-H), 8.40 (d, 1H, 6-H), 7.76 (s, 1H, NH), (J CH-CH_3 = 6 Hz).

Anal. Calcd. for $C_{16}H_{26}N_2O_2$: C, 69.06; H, 9.35; N, 10.07. Found: C, 68.68; H, 9.60; N, 10.10.

3-Deuterio-2-pivaloylaminopyridine (**9a**).

This compound was obtained as a solid in 85% yield; ^{1}H nmr (DMSO-d_6): 1.37 (s, 3H, *t*-Bu), 7.00 (dd, 1H, 5-H), 7.67 (dd, 1H, 4-H), 8.23 (dd, 1H, 6-H), 8.33 (m, 1H, NH).

Anal. Calcd. for $C_{10}H_{13}DN_2O$: C, 67.02; H, 7.31; N, 15.63. Found: C, 66.95; H, 7.30; N, 15.65.

2-Pivaloylaminopyridine-3-carboxylic Acid (**9d**).

This compound was obtained as a solid in 80% yield, mp 300°; ^{1}H nmr (deuteriotrifluoroacetic acid): 1.57 (s, 3H, *t*-Bu), 8.33 (dd, 1H, 5-H), 9.10 (dd, 1H, 6-H), 9.30 (dd, 1H, 4-H).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.32; H, 6.30; N, 12.43.

Diphenyl(2-pivaloylamino-3-pyridyl)methanol (**9c**).

This compound was obtained as a solid in 90% yield, mp 183°; ^{1}H nmr (DMSO-d_6): 0.78 (s, 3H, *t*-Bu), 6.87 (dd, 1H, 5-H), 7.20 (m, 11H, phenyl protons and 4-H), 7.60 (s, 1H, OH), 8.20 (dd, 1H, 6-H), 9.6 (s, 1H, NH).

Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.67; H, 6.67; N, 7.78. Found: C, 76.63; H, 6.71; N, 7.59.

Phenyl(2-pivaloylamino-3-pyridyl)methanol (**9b**).

This compound was obtained as a solid in 70% yield, mp 115° (lit [12] yield = 63%, mp 114-117°); ^{1}H nmr (DMSO-d_6): 1.19 (s, 9H, *t*-Bu), 4.95 (m, 1H, OH), 5.83 (s, 1H, CH-O), 7.05 (dd, 1H, 5-H), 7.30 (s, 5H, phenyl protons), 7.50 (dd, 1H, 6-H), 8.65 (m, 1H, NH).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 72.03; H, 7.10; N, 9.75.

3-Deuterio-4-pivaloylaminopyridine (**12a**).

This compound was obtained as a solid in 90% yield; ^{1}H nmr (DMSO-d_6): 1.2 (s, 9H, *t*-Bu), 7.67 (d, 1H, 5-H), 8.37 (s, 1H, 2-H), 8.37 (d, 1H, 6-H), 9.50 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_{13}DN_2O$: C, 67.02; H, 7.31; N, 15.63. Found: C, 67.15; H, 7.41; N, 15.62.

4-Pivaloylaminopyridine-3-carboxylic Acid (**12g**).

This compound was obtained in 95% yield, mp 260° dec; ^{1}H nmr (deuteriotrifluoroacetic acid): 1.57 (s, 9H, *t*-Bu), 8.18 (d, 1H, 5-H), 9.05 (d, 1H, 6-H), 9.63 (s, 1H, 2-H).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.41; H, 6.28; N, 12.49.

Phenyl(4-pivaloylamino-3-pyridyl)methanol (**12b**).

This compound was obtained in 70% yield, mp 180°; ^{1}H nmr (DMSO-d_6): 1.05 (s, 9H, *t*-Bu), 5.97 (s, 1H, CH-O), 7.27 (s, 5H, phenyl protons), 8.10 (d, 1H, 5-H), 8.35 (d, 1H, 6-H), 8.40 (s, 1H, 2-H).

Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.84; H, 7.05; N, 9.80.

(2-Methoxyphenyl)(4-pivaloylamino-3-pyridyl)methanol (**12c**).

This compound was obtained in 60% yield, mp 178°; ^{1}H nmr (deuteriochloroform): 1.15 (s, 9H, *t*-Bu), 3.83 (s, 3H, CH_3), 4.57 (m, 1H, O-H), 6.1 (s, 1H, CH-O), 6.83 to 7.3 (m, 4H, phenyl protons), 8.0 (s, 1H, 5-H), 8.27 (s, 2H, 2- and 6-H), 9.7 (m, 1H, NH).

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 9.91. Found: C, 68.59; H, 6.98; N, 8.85.

(2,4-Dichlorophenyl)(4-pivaloyamino-3-pyridyl)methanol (**12d**).

This compound was obtained in 65% yield, mp 212-213°; ^{1}H nmr (deuteriochloroform): 1.1 (s, 9H, *t*-Bu), 6.10 (s, 1H, CH-O), 7.50 (s, 2H, 5'- and 6'-H), 7.6 (s, 1H, 3'-H), 8.0 (s, 1H, 2-H), 8.05 (d, 1H, 5-H), 8.33 (d, 1H, 6-H), 9.6 (m, 1H, NH).

Anal. Calcd. for $C_{17}H_{18}Cl_2N_2O_2$: C, 57.80; H, 5.14; N, 7.93. Found: C, 57.62; H, 5.15; N, 7.91.

(4-Pivaloylamino-3-pyridyl)(2-thienyl)methanol (**12e**).

This compound was obtained in 60% yield, mp 164°; ^{1}H nmr (deuteriochloroform): 1.03 (s, 9H, *t*-Bu), 5.97 (s, 1H, CH-O), 6.07 (s, 1H, OH), 6.57 (dd, 1H, 3'-H), 6.83 (dd, 1H, 4'-H), 7.2 (dd, 1H, 5'-H), 7.88 (s, 1H, 2-H), 8.17 (d, 1H, 5-H), 8.33 (d, 1H, 6-H), 9.63 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.40; H, 6.25; N, 9.67.

Diphenyl(4-pivalylamino-3-pyridyl)methanol (**12f**).

This compound was obtained in 85% yield, mp 260°; ^{1}H nmr (DMSO-d_6): 0.83 (s, 9H, *t*-Bu), 7.25 (m, 10H, phenyl protons), 7.8 (m, 1H, O-H), 8.2 (d, 1H, 5-H), 8.37 (d, 1H, 6-H), 9.8 (s, 1H, 2-H).

Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.67; H, 6.67; N, 7.78. Found: C, 76.63; H, 6.67; N, 7.63.

General Procedures for Oxidation of Pivaloylaminopyridine Alcohols.

With Chromium Trioxide in Acetone (Method A).

To a solution of 0.01 mole of the alcohol in anhydrous acetone cooled to −40° was added 2 g of chromium trioxide (0.02 mole). The reaction mixture was stirred for 3 hours at 5-10°. Isopropyl alcohol was then added and the *p*H adjusted to 8 with a solution of sodium bicarbonate. After filtration and decantation the aqueous layer was extracted with chloroform. The organic layer was washed with water, dried and evaporated. The crude ketone was purified by recrystallisation or by flash chromatography.

With Manganese Dioxide in THF (Method B).

A suspension of 1.74 g (0.2 mole) of freshly prepared manganese dioxide in a solution of 0.01 mole of the alcohol in anhydrous THF was stirred for 48 hours. The suspension was filtrated and the solid washed three times with 20 ml of THF. Evaporation of the solvent afforded the crude ketone which was purified as described above.

With Manganese Dioxide in Toluene (Method C).

A suspension of 1.74 g (0.2 mole) of freshly prepared manganese dioxide in 250 ml of toluene was refluxed for 1 hour in a vessel equipped with a Dean-Stark tube. The alcohol (0.01 mole) was added and the mixture refluxed for 3 additional hours. The suspension was cooled, and the solid extracted with chloroform. Evaporation of the organic layers afforded the ketones which were purified as previously described.

Phenyl (2-Pivaloylamino-3-pyridyl) Ketone (**13b**).

This compound was obtained using method C as a solid, mp 137°, in 98% yield; ^{1}H nmr (DMSO-d_6): 0.83 (s, 9H, *t*-Bu), 7.30 (dd, 1H, 5-H), 7.50 (m, 5H, phenyl protons), 7.83 (dd, 1H, 4-H), 8.52 (dd, 1H, 6-H), 9.97 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.27; H, 6.49; N, 9.86.

Phenyl (3-Pivaloylamino-4-pyridyl) Ketone (**14b**).

This compound was obtained using method C in 99% yield as a solid, mp 105°; ^{1}H nmr (DMSO-d_6): 0.85 (s, 9H, *t*-Bu), 7.30 (d, 1H, 5-H), 7.50 (s, 5H, phenyl protons), 8.45 (d, 1H, 6-H), 8.55 (s, 1H, 2-H), 9.55 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.28; H, 6.41; N, 9.83.

(2-Methoxyphenyl) (3-Pivaloylamino-4-pyridyl) Ketone (**14c**).

Compound **4b** was obtained using method C in 95% yield as a solid, mp 123°; ^{1}H nmr (DMSO-d_6): 0.95 (s, 9H, *t*-Bu), 3.75 (s, 3H, CH_3), 6.95 (d, 2H, 4'- and 5'-H), 7.30 (d, 1H, 5-H), 7.55 (d, 2H, 3'- and 6'-H), 8.40 (d, 1H, 6-H), 8.60 (s, 1H, 2-H), 9.50 (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.65; H, 7.12; N, 8.87.

(2,4-Dichlorophenyl) (3-Pivaloylamino-4-pyridyl) Ketone (**14d**).

This compound was obtained using method C in 95% yield as a solid, mp 107°; ^{1}H nmr (DMSO-d_6): 1.40 (s, 9H, *t*-Bu), 7.15 (d, 1H, 5-H), 7.35 (s, 2H, 3'- and 5'-H), 7.5 (s, 1H, 6'-H), 8.35 (d, 1H, 6-H), 10.05 (s, 1H, 2-H), 11.00 (m, 1H, NH).

Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O_2$: C, 58.13; H, 4.59; N, 7.98. Found: C, 57.93; H, 4.65; N, 7.84.

Phenyl (4-Pivaloylamino-3-pyridyl) Ketone (**15b**).

Compound **15b** was obtained using method C in 90% yield as a solid, mp 104°; ^{1}H nmr (DMSO-d_6): 1.1 (s, 9H, *t*-Bu), 7.5 (m, 5H, phenyl protons), 8.0 (d, 1H, 5-H), 8.5 (s, 1H, 2-H), 8.7 (d, 1H, 6-H).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 71.91; H, 6.39; N, 9.85.

(2-Methoxyphenyl)(4-Pivaloylamino-3-pyridyl) Ketone (**15c**).

Compound **15c** was obtained using method C in 99% yield as a solid, mp 118°; ^{1}H nmr (DMSO-d_6): 1.37 (s, 9H, *t*-Bu), 3.73 (s, 3H, CH_3), 7.05 (t, 2H, 2'- and 3'-H), 8.33 (q, 1H, 4'-H), 8.53 (q, 1H, 5'-H), 9.5 (d, 1H, 5-H), 9.58 (s, 1H, 2-H), 9.67 (d, 1H, 6-H).

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.28; H, 6.50; N, 8.98.

(2,4-Dichlorophenyl)(4-Pivaloylamino-3-pyridyl) Ketone (**15d**).

Compound **15d** was obtained using method C in 99% yield as a solid, mp 137°; ^{1}H nmr (DMSO-d_6): 1.2 (s, 9H, *t*-Bu), 7.30 (s, 1H, NH), 7.6 (s, 2H, 6'- and 5'-H), 7.8 (s, 1H, 3'-H), 8.35 (d, 1H, 5-H), 8.40 (s, 1H, 2-H), 8.65 (d, 1H, 6-H).

Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O_2$: C, 58.13; H, 4.59; N, 7.98. Found: C, 58.03; H, 4.80; N, 7.92.

(4-Pivaloylamino-3-pyridyl) (2-Thienyl) Ketone (**15e**).

Compound **15e** was obtained using method C in 95% yield as a solid, mp 101-102°; ^{1}H nmr (DMSO-d_6): 1.37 (s, 9H, *t*-Bu), 7.2 (dd, 1H, 4'-H), 7.28 (d, 1H, 5'-H), 7.78 (d, 1H, 3'-H), 8.58 (s, 2H, 2- and 5-H), 8.98 (s, 1H, 6-H), 11.02 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{16}N_2OS$: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.38; H, 5.58; N, 9.62.

Methyl (3-Pivaloylamino-4-pyridyl) Ketone (**19a**).

Compound **19a** was obtained using method A and method B in 80% yield as a solid, mp 131°; ^{1}H nmr (deuteriochloroform): 1.37 (s, 9H, *t*-Bu), 2.70 (s, 3H, CH_3), 7.66 (d, 1H, 6-H), 10.06 (s, 1H, 2-H).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.45; H, 7.32; N, 12.72. Found: C, 65.1; H, 7.2; N, 12.9.

Methyl (2-Methoxy-3-pivaloylamino-4-pyridyl) Ketone (**19b**).

This compound was obtained as an oil in 80% yield using method B ^{1}H nmr (deuteriochloroform): 1.33 (s, 9H, *t*-Bu), 2.56 (s, 3H, OCH_3), 7.00 (d, 1H, 5-H), 8.03 (d, 1H, 6-H).

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.38; H, 7.15; N, 11.25.

(2,3-Dipivaloylamino-4-pyridyl) Methyl Ketone (**19c**).

Compound **19c** was obtained using method B in 50% yield as a solid, mp 132°; ^{1}H nmr (deuteriochloroform): 1.26 (s, 9H, *t*-Bu), 1.33 (s, 9H, *t*-Bu), 2.53 (s, 3H, CH_3), 7.30 (d, 1H, 5-H), 8.30 (d, 1H, 6-H), 8.83 and 9.63 (2s, 21H, NH).

Anal. Calcd. for $C_{17}H_{25}N_3O_3$: C, 63.95; H, 7.84; N, 13.16. Found: C, 63.75; H, 7.92; N, 13.05.

(2-Butyl-3-pivaloylamino-4-pyridyl) Methyl Ketone (**19d**).

Compound **19d** was obtained using method B in 50% yield as a solid, mp 92-94°; ^{1}H nmr (deuteriochloroform): 0.93 (t, 3H, CH_3), 1.33 (s, 9H, *t*-Bu), 1.40 (m, 4H, CH_2-CH_2), 2.60 (s, 3H, CH_3), 2.76 (t, 2H, Ar-CH_2), 7.3 (d, 1H, 5-H), 8.49 (d, 1H, 6-H).

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.57; H, 8.70; N, 10.14. Found: C, 69.16; H, 8.90; N, 9.97.

General Procedure for Amide Hydrolysis.

A solution of 0.018 mole of the pivaloylaminopyridine derivative in 100 ml of 3*N* hydrochloric acid was heated for 24 hours at 90° on a water-bath. A mixture of diluted ammonia and ice was then added to precipitate the amine. The reaction mixture was extracted three times with chloroform. Evaporation of chloroform and recrystallisation afforded the aminopyridine.

2-Amino-3-benzoylpyridine (**16b**).

This compound was obtained in 75% yield as a solid, mp 147°; ^{1}H nmr (deuteriochloroform): 6.55 (dd, 1H, 5-H), 7.15 (s, 2H, NH_2), 7.5 (m, 5H, phenyl protons), 7.7 (dd, 1H, 4-H), 8.2 (dd, 1H, 6-H).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.40; H, 5.13; N, 14.16.

3-Amino-4-benzoylpyridine (**17b**).

This compound was obtained in 75% yield as a solid, mp 128°; ^{1}H nmr (deuteriochloroform): 6.8 (s, 2H, NH_2), 7.05 (d, 1H, 5-H), 7.50 (s, 5H, phenyl protons), 7.65 (d, 1H, 6-H), 8.30 (s, 1H, 2-H).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.49; H, 5.10; N, 14.17.

4-Amino-3-benzoylpyridine (**18b**).

Compound **18b** was obtained in 90% yield as a solid, mp 162°; ^{1}H nmr (dueteriochloroform): 6.57 (d, 1H, 5-H), 6.72 (m, 2H, NH_2), 7.50 (m, 5H, phenyl protons), 8.12 (d, 1H, 6-H), 8.5 (s, 1H, 2-H).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.53; H, 5.20; N, 13.95.

General Procedure for the Synthesis of Pyridopyrimidines.

A mixture of 0.01 mole of aminopyridyl phenyl ketone and of 3 g of urea was heated at 200° during 2 hours. After cooling the resulting mixture was poured in 50 ml of water. After several days the pyridopyrimidine crystallized. The solid was crystallized from ethyl alcohol.

4-Phenyl-1,2-dihydropyrido[2,3-*d*]-2-pyrimidinone (**20**).

This compound was obtained in 98% yield as a solid, mp >260°; ^{1}H nmr (DMSO-d_6): 80 MHz, 7.20 (dd, 1H, 5-H), 7.55 (s, 5H, phenyl protons), 8.00 (dd, 1H, 6-H), 8.42 (s, 1H, NH), 8.68 (dd, 1H, 7-H).

Anal. Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.81; H, 4.11; N, 18.75.

4-Phenyl-1,2-dihydropyrido[3,4-*d*]-2-pyrimidinone (**21**).

Compound **21** was obtained in 98% yield as a solid, mp >260°; ^{1}H nmr (DMSO-d_6): 80 MHz 7.39 (d, 1H, 5-H), 7.47 (s, 5H, phenyl protons), 8.24 (d, 1H, 6-H), 8.40 (s, 1H, NH), 8.63 (s, 1H, 8-H).

Anal. Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.90; H, 4.21; N, 18.70.

4-Phenyl-1,2-dihydropyrido[4,3-*d*]-2-pyrimidinone (**22**).

This compound was obtained in 99% yield as a solid, mp 276°; ^{1}H nmr (DMSO-d_6): 7.23 (d, 1H, 8-H), 7.63 (s, 5H, phenyl protons), 8.57 (d, 1H, 7-H), 8.73 (s, 1H, 5-H), 12.0 (s, 1H, NH).

Anal. Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.91; H, 3.86; N, 18.49.

General Procedure for the Application of the Friedlander Reaction to Aminopyridyl Ketones.

A solution of 0.01 mole of the *ortho*-aminopyridyl ketone or of *ortho*-pivaloylaminopyridyl ketone in 25 ml of a mixture of acetic acid and of sulfuric acid (10/1) and 0.01 mole of the proper ketone was refluxed for 12 hours. Addition of 5 ml of water allowed an increased of the yield in the case of the amide. The reaction mixture was poured on 50 ml of concentrated ammonia and ice (25 g). The mixture was extracted with chloroform and the crude product obtained after evaporation was purified by crystallization from diethyl ether or by chromatography.

10-Phenyl-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridine (**23**).

Cyclohexanone and amine **16b** or amide **13b** were used as starting materials. Compound **23** was obtained as a solid in 70% yield, mp 161°; ^{1}H nmr (deuteriochloroform): 1.85 (m, 4H, $(CH_2)_7$ and $(CH_2)_8$), 2.60 (t, 2H, $(CH_2)_9$), 3.25 (t, 2H, $(CH_2)_6$), 7.10 to 8.80 (m, 7H, 1-, 2-H and phenyl protons) 8.90 (dd, 1H, 3-H); ms: M+260-261.

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.05; H, 6.19; N, 10.76. Found: C, 83.10; H, 6.17; N, 10.75.

10-Phenyl-6,7,8,9-tetrahydrobenzo[*b*][1,7]naphthyridine (**24**).

Cyclohexanone and amine **17b** or amide **14a** were used as starting materials. Compound **24** was obtained in 99% yield as a solid, mp 175°; ^{1}H nmr (DMSO-d_6): 1.80 (m, 4H, $(CH_2)_7$ and $(CH_2)_8$), 2.55 (m, 2H, $(CH_2)_9$), 3.15 (m, 2H, $(CH_2)_6$), 7.05 (d, 1H, 1-H), 7.20 (m, 5H, phenyl protons), 8.30 (d, 1H, 2-H), 9.20 (s, 1H, 4-H) (J H1-H2 = 6 Hz).

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.05; H, 6.19; N, 10.76. Found: C, 82.94; H, 6.18; N, 10.74.

10-Phenyl-6,7,8,9-tetrahydrobenzo[*b*][1,6]naphthyridine (**25**).

Cyclohexanone and amine **18b** or amide **15b** were used as starting materials. Compound **25** was obtained in 90% yield as a solid, mp 160°; ^{1}H nmr (deuteriochloroform): 1.95 (m, 4H, $(CH_2)_7$ and $(CH_2)_8$), 2.65 (t, 2H, $(CH_2)_9$), 3.20 (t, 2H, $(CH_2)_6$, 7.35 (m, 5H, phenyl protons), 7.75 (d, 1H, 4-H), 8.60 (d, 1H, 3-H), 8.75 (s, 1H, 1-H) (J H3-H4 = 3 Hz).

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.05; H, 6.16; N, 10.76. Found: C, 82.95; H, 6.39; N, 10.50.

5-Methyl-7,8-dihydro-6*H*-cyclopenta[*b*][1,7]naphthyridine (**26**).

This compound was obtained as a solid in 30% yield, mp 72°; ^{1}H nmr (deuteriochloroform): 2.2 (m, 2H, CH_2), 2.57 (s, 3H, CH_3), 3.13 (m, 4H, 2·CH_2), 7.67 (d, 1H, 4-H), 8.53 (d, 1H, 3-H), 9.37 (s, 1H, 1-H).

Anal. Calcd. for $C_{12}H_{12}N_2 \cdot H_2O$: C, 65.45; H, 7.27; N, 12.7. Found: C, 65.60; H, 7.10; N, 13.1.

5-Methyl-10,11-dihydronaphtho[3,2-*a*][1,7]naphthyridine (**27**).

Compound **27** was obtained as a solid in 25% yield, mp 173°; ^{1}H nmr (DMSO-d_6): 2.8 (s, 3H, CH_3), 2.9 (m, 4H, CH_2-CH_2)), 7.3 (m, 3H, 7-, and 8-and 9-H), 7.51 (m, 1H, 6-H), 7.85 (d, 1H, 4-H), 8.45 (d, 1H, 3-H), 9.11 (s, 1H, 1-H).

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.93; H, 5.69; N, 11.38. Found: C, 82.80; H, 5.65; N, 11.23.

5-Methyl-6*H*-indolo[2,3-*b*][1,7]naphthyridine (**28**).

Condensation of 2.4 g of oxindole (0.018 mole) with 2 g of methyl (3-pivaloylaminopyridyl) ketone **19a** (0.0091 mole) using the same procedure described above, afforded **28** in 22% yield, mp >260°; ^{1}H nmr (DMSO-d_6): 3.05 (s, 3H, CH_3), 7.30 (m, 3H, 7-, 8- and 9-H), 8.03 (d, 1H, 4-H), 8.26 (d, 1H, 6-H), 8.40 (d, 1H, 3-H), 9.11 (s, 1H, 1-H). We did not succeed in purifying compound **28**. This compound was however well characterized by its derivative.

2,5-Dimethyl-6*H*-indolo[2,3-*b*][1,7]naphthyridinium Iodide.

The compound was obtained by reaction of **28** with an excess of methyl iodide as a solid in 70% yield, mp >260°; ^{1}H nmr (DMSO-d_6): 3.12 (s, 3H, CH_3), 4.48 (s, 3H, CH_3), 7.41 (m, 3H, 7-, 8- and 9-H), 8.26 (d, 1H, 4-H), 8.62 (m, 2H, 3- and 6-H), 9.71 (s, 1H, 1-H).

Anal. Calcd. for $C_{16}H_{14}IN_3$: C, 51.22; H, 3.76; N, 11.20. Found: C, 51.09; H, 3.80; N, 11.09.

5-Methyl-6*H*-indolo[3,2-*b*][1,7]naphthyridine (**29**).

(11-Azaellipticine).

N-Acetyl-3-indolinone (3.26 g, 0.0186 mole) and pyridyl methyl ketone **19a** (2 g, 0.0091 mole) were reacted following the procedure described above, to give the 11-azaellipticine **30** in 21% yield, mp >260°; ^{1}H nmr (DMSO-d_6): 2.85 (s, 3H, CH_3), 7.5 (m, 3H, 7-H, 8-H and 9-H), 8.33 (d, 1H, 10-H), 8.45 (d, 1H, 3-H), 9.43 (s, 1H, 1-H) (J H3-H4) = 6 Hz; J H9-H10 = 8 Hz). We did not succeed in purifying compound **30**, which was however well characterized by its derivative **31**.

2,5-Dimethyl-6*H*-indolo[3,2-*b*][1,7]naphthyridinium Iodide (**30**).

Compound **29** reacted with an excess of methyl iodide to give **30** in 70% yield, mp >260°; ^{1}H nmr (DMSO-d_6): 2.8 (s, 3H, CH_3), 4.55 (s, 3H, CH_3), 7.43 (m, 3H, 7-, 8- and 9-H), 8.10 (d, 1H, 4-H), 8.45 (m, 2H, 3- and 10-H), 9.80 (s, 1H, 1-H).

Anal. Calcd. for $C_{16}H_{14}IN_3$: C, 51.22; H, 3.76; N, 11.20. Found: C, 50.95; H, 3.80; N, 10.79.

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