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A Formal New Access to the Benzo[c]phenanthridine Alkaloids, Synthesis of Nitidine and O-Methyl Fagaronine Analogues.

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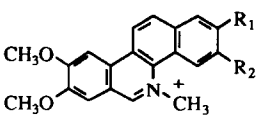
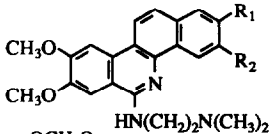
Abstract: Previously unreported 2-aryl-1-naphthylamines were obtained in good yields from 2-aryl-1-tetraloneoximes by using the Semmler-Wolf reaction but omitting the acetic anhydride usually present in the reaction mixture. From these amines, through the thermal cyclization of their corresponding ethyl carbamates, a new access to the benzo[c]phenanthridin-6(5H)-ones was found. Preparation of water-soluble Nitidine and O-Methyl Fagaronine analogues bearing an alkylamino side chain on the C-6 position was achieved from these compounds.

Naturally occurring benzo[c]phenanthridinium alkaloids such as Nitidine (**1a**) and Fagaronine (**1c**) display many biological effects,[1] including antitumor properties.[2, 3] In 1976 a pre clinical NCI investigation revealed that Nitidine displayed a narrow antitumor spectrum, an acute toxicity and an instability.[4, 5] Fagaronine was also reported to inhibit various reverse transcriptases[6] and more recently, these compounds were shown to inhibit HIV 1 and 2 reverse transcriptases.[7] Because of a strong interest in their biological activities, synthesis of the benzo[c]phenanthridine ring system and of the alkaloids of this family has been an important area of heterocyclic chemistry. It has been reviewed repeatedly[8-12], and new syntheses[13-26] and improvements[27-30] of known methods have been published since then.

In the course of our research on synthesis and biological studies of new antitumor compounds, we decided to replace the iminium pharmacophore of these alkaloids by a dimethylaminoethylamino side chain on the C-6 position, thus generating the analogues **2a-c**. These compounds presented the same substituent pattern as the alkaloids Nitidine and Fagaronine, with a ionizable dibasic side-chain which was designed in order to maintain (or to increase) their water solubility.

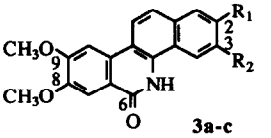


1a Nitidine
1c Fagaronine



a: $R_1 + R_2 = OCH_2O$
b: $R_1 = R_2 = OCH_3$
c: $R_1 = OH$, $R_2 = OCH_3$

2a-c

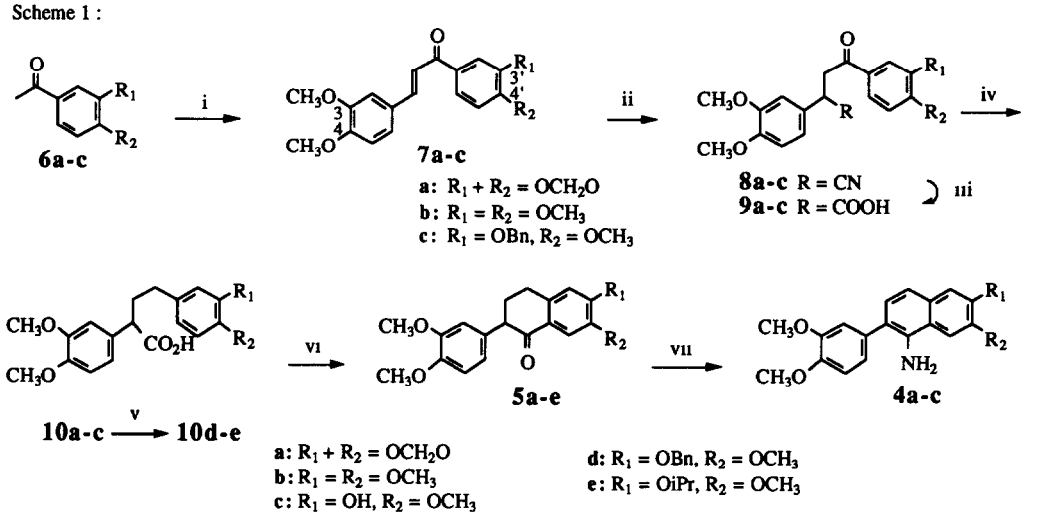


3a-c

In this paper, we describe the synthesis of the analogues **2a-b** which have been prepared through a new access to the benzo[c]phenanthridin ring system.

Two methods were already available to obtain the required key intermediates benzo[c]phenanthridin-6(5H)-ones **3** : either the photocyclization of the corresponding o-bromobenzoylnaphthylamides[31] or the condensation of naphthylisocyanates with arynes[22]. However both methods can hardly be scaled up, and since we recently found a new way to prepare various 1-naphthylamines from 1-tetralones[32] we decided to look for an access to the unknown 2-aryl-1-naphthylamines **4** from 2-aryl-1-tetralones **5**.
Thus we undertook the preparation of the 2-aryl-1-tetralones **5a-c** using the well-known[33] and improved[12,34-39] Robinson's method (**6** → **7** → **8** → **9** → **10** → **5**) with a minor modification in the course of the preparation of the Fagaronine analogue **2c**, where we introduced the use of a benzylic ether instead of an isopropylic one[39] in order to obtain more easily crystallizable intermediate compounds. This group was of course hydrogenolyzed at step (iv) but the hydroxy acid **10c** obtained was easily reprotected either with the same group to give **10d** or with the isopropyl one to give **10e**.

Scheme 1 :



i : 3,4-MeOC$_6$H$_3$CHO, NaOH 10%, EtOH. ii : KCN, AcOH, EtO(CH$_2$)$_2$OH, 120°C. iii : NaOH 20%, EtOH, reflux. iv : $PdCl_2$, H_2. v : RBr, K_2CO_3, DMF reflux then NaOH 20% EtOH, reflux. vi : $POCl_3$, K_2CO_3, Acetonitrile, 0°C to 25°C. vii : see scheme 2.

This little modification led us to observe that :

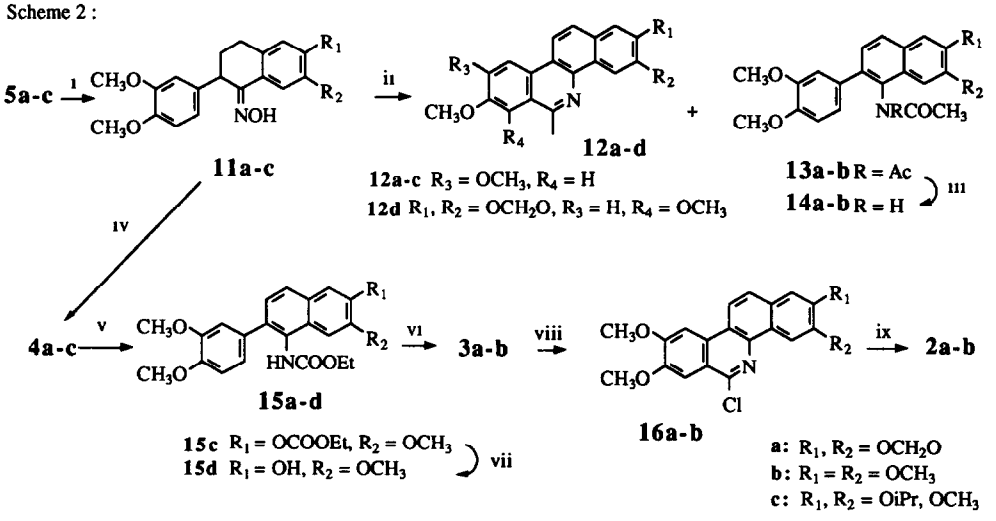
a) Starting from the 3-hydroxy-4-methoxybenzaldehyde the phenolic acid **10c** was obtained with a 43 % overall yield. Because of a lower yield of the cyclization of the benzylated acid **10d** into tetralone **5d**, (30% instead of 70-80% for the other cases), we resorted to an isopropyl protecting group for this cyclization step. With this method, we obtained the isopropylated compound **5e** in an overall yield of 33 % instead of the reported[39] 28% .

b) In our hands, contrary to an earlier report[39], cyclization of the isopropylated acid **10e** into **5e** never gave any amount of phenolic tetralone **5c**. On the other hand, starting from the phenolic acid **10c**, under the very efficient cyclization conditions used[40], the compound **5c** was easily obtained in a 69% yield.

Unfortunately, trials to obtain the 2-aryl-1-naphthylamines **4** from 2-aryl-1-tetralones **5** according to our previously published method,[32] never gave rise to any sizeable amount of amine. Thus we resorted to a careful study of the Semmler-Wolff reaction. On the eve of this century, Semmler[41] and Wolff[42] reported that, upon heating of cyclohexenoneoxime or 1-tetraloneoxime in a hydrogen chloride-saturated mixture of acetic acid and acetic anhydride, aniline derivatives or a mixture of naphthylamines derivatives were obtained. The scope, the reaction conditions and the proposed mechanisms of this reaction have been reviewed[43] and the different works published since then essentially deal with new conditions to achieve it[44, 45].

Preparation of 2-aryl-1-tetraloneoximes **11a-c** was easily performed and, as already reported for **11a**[3, 46, 47], the cyclized 6-methylbenzo[c]phenanthridines **12a-c** were obtained with the classical Semmler-Wolff reaction conditions. Moreover, unreported reaction products such as isomeric compound **12d** and N,N-diacetylated amino derivatives **13a-b** were obtained in variable amounts. Because of this, we studied the reaction parameters and found out that the amounts of hydrogen chloride dissolved into the reaction mixture (determined by weighting) was critical for the respective yields of the cyclized and diacetylated compounds. Table 1 illustrates this previously unreported effect in one instance.

Scheme 2 :



i : NH_2OH, HCl, pyridine, 100°C ; ii : Ac_2O, AcOH / HCl, 100°C ; iii : KOH / tBuOH reflux ; iv : HCl, ACOH, 100°C ; v : ClCOOEt, pyridine , 25°C, vi : diphenyl oxide, nBu_3N(Cat), 259°C ; vii : KOH / EtOH ; viii : $C_6H_5POCl_2$, 160°C ; ix : $NH_2(CH_2)_2NMe_2$, 120°C.

Table 1 : Semmler Wolf transformation of **11a** : Yields of compounds **12a**, **12d** and **13a**

% HCl (w/w) in the $AcOH/Ac_2O$ mixture	[HCl] = 20 %	[HCl] = 10 %
yield of **12a**	60 %	16 %
yield of **12d**	0.7 %	0.2 %
yield of **13a**	1 %	31 %

Surprisingly, attempts to hydrolyse the diacetylated amines **13a-b** under various basic conditions (LiOH, NaOH, KOH) never gave the free amines **4a-b** but rather the monoacetylated compounds **14a-b**. A strong steric hindrance seems to be the only reason which could explain the quite incredible stability of **14a-b** toward hydrolysis.

In order to avoid the occurrence of these diacetylated derivatives and the corresponding cyclized ones, we simply omitted the acetic anhydride responsible for this.[3] To our relief, the previously unreported 2-aryl-1-naphthylamines **4a-b** were then obtained in good yields. Probably because the traces of water present in the reaction mixture are no longer eliminated by reacting with the acetic anhydride, isopropyl ether of compound **11c** is cleaved under these new conditions. Thus the reaction of oxime **11c** yielded the phenolic amine **4c** only.

To obtain the benzo[c]phenanthridin-6(5H)-one **3** from amines **4**, we investigated the thermal cyclization of urethanes **15**. Such a ring closure has been used in another instances[48] and is probably proceeding via a pericyclic mechanism[49-52]. Thus, upon treatment of amines **4** with ethyl chloroformate, the urethanes **15a-c** were easily obtained, as hard foams. Then, thermal cyclization of the first two compounds gave the benzo [c]phenanthridin-6(5H)-ones **3a-b** in 80-85 % yield from amines **4**. Unfortunately, when this cyclization technique was applied to the product **15c** arising from the carbamoylation of the phenolic naphthylamine **4c**, decomposition was the sole result. The same phenomenon occurred with the phenolic urethane **15d** or with the product of its acetylation.

Chlorination of compounds **3a-b** was best achieved with phenylphosphonic dichloride. Then the 6-chlorinated derivative **16a-b** easily underwent substitution in boiling 2-dimethylamino ethylamine to give the 6-aminosubstituted benzo[c]phenanthridines **2a-b**.

In conclusion, the outcome of the classical Semmler-Wolff reaction of 2-aryl-1-tetraloneoximes is mainly dependent on the amount of hydrogen chloride dissolved in the acetic acid / acetic anhydride mixture. A two-fold decrease of hydrochloric acid concentration caused the near disappearance of any cyclized compound **12** and a substantial increase in the yield of diacetylated product **13**. Experiments without acetic anhydride enabled us to point out that it has little role in the course of the Semmler-Wolff reaction, aside from causing the occurrence of acetylated compounds and corresponding derivatives.

Starting from the amines **4a-c**, in order to achieve the preparation of the proposed analogues **2a-c**, we developed the thermal cyclization of the urethanes **15a-b** which led to the key intermediate benzo[c]phenanthrin-6(5H)-ones **3a-b** in good yield.

In spite of the thermal treatment of the less stable urethanes **15c** or **15d** which failed to give the corresponding cyclized Fagaronine precursors, this method formally provides a new and very simple access to the other benzo[c]phenanthrine alkaloids.

EXPERIMENTAL

General Procedures. Melting points are uncorrected, ^1H NMR spectra were recorded on a Bruker AC-200 MHz spectrometer in, unless stated otherwise, $CDCl_3$. Chemical shifts (δ) are reported in part per million relative to Me_4Si as internal standard and all the coupling constants (J) are given in Hz. Signals identification was often done with the help of NOE effect. Elemental analyses were performed by the Service Central de Microanalyses (CNRS ICSN, Gif-sur-Yvette, France) on the isolated products. Pure commercially available solvents were used, without further treatment.

Various intermediate compounds were obtained according to well known and already published methods. Compounds **7a**[35], **7b**[33], **8a**[34], **8b**[33], **9a**[34], **9b**[33], **10b**[33], **10e**[39], **5a**[34], **5b**[33], **5c**[39], **5e**[34] had their NMR spectra and other physical data (mp, elemental analysis) corresponding to the published ones. Thus these are not described. For all other compounds prepared according to well reported methods, the yields, NMR and analytical data are reported here for the first time. The adopted numbering system corresponds to the one used in references 36-40.

3-Benzyloxy-4-methoxyacetophenone (6c). The method used is closely related to the already published one[39]. Benzyl chloride (90.7 mL, 0.7 mol) and anhydrous potassium carbonate (136 g, 0.98 mol) were added to a mixture of isovanillin (100 g, 0.65 mol) and dimethyl formamide, (DMF, 260 mL). The mixture was stirred for two days at room temperature, DMF was removed *in vacuo* and the oil obtained was poured into a large excess of water. The precipitate was filtered off and recrystallized from cyclohexane to afford 3-Benzyloxy-4-methoxybenzaldehyde (147.5 g, 92.5 %, mp = 63°C). **3-Benzyloxy-4-methoxybenzaldehyde** (147.1 g, 0.61 mol) in dry diethyl ether (3.3 l) was added dropwise in 2 h, below 5°C, to 1.5 mol of methyl magnesium iodide prepared in diethyl ether in the usual way. The solution was stirred for a further 2h period at room temperature and the resulting mixture was filtered and the precipitate was washed with dry diethyl ether. It was then suspended in water, decomposed by addition of 20% aqueous ammonium chloride and extracted with diethyl ether. After usual work-up[39], the organic layer was evaporated and the residue was recrystallized from cyclohexane to afford **1-(3-Benzyloxy-4-methoxyphenyl)ethanol** (116 g, 73%, mp = 62°C). Jones reagent (from 0.8 mol of potassium chromate) was added dropwise to a solution of **1-(3-Benzyloxy-4-methoxyphenyl)ethanol** (99 g, 0.38 mol) in acetone (1.5 l) below 10°C. Stirring was maintained for 45 mn and then methanol (100 mL) was added to the solution. The acetone was removed in vacuo, the residue suspended in water, filtered, washed with water and recrystallized from cyclohexane over norit to afford the acetophenone **6c** (86.7 g, 88 %, mp = 78°C). δ 2.52 (s, 3 H, CH_3), 3.94 (s, 3 H, OCH_3), 5.19 (s, 2 H, $CH_2C_6H_5$), 6.86-7.57 (m, 8 H, Ar).

General procedures for preparations of chalcones **7**, 4-oxobutyronitriles **8**, 4-oxobutyric acids **9** and 2,4-diaryl butyric acids **10** were identical to those described in references 33, 34, 35, 39. The numbering sytem adopted is similar to the one used in ref. 39.

3'-Benzyloxy-3,4,4'-trimethoxy-chalcone (7c) : 92 %, mp = 154 °C (from n-butanol), δ 3.84 (s, 3 H, OCH_3), 5.12 (s, 2 H, $CH_2C_6H_5$), 6.89-6.94 (m, 2 H, H-3, H-5), 7.17 (ddd, 1 H, J = 1.0, 2.6, 8.2, H-4'), 7.35 (d, 1 H, J = 15.7, Ha), 7.33 (m, 10 H, H-2', H-5', H-6', H-2, H-6, C_6H_5), 7.76 (d, 1 H, J = 15.7, Hb). Anal. Calcd. for $C_{25}H_{24}O_5$: C, 74.2; H, 6.0. Found: C, 74.4; H, 5.9.

4-(3'-Benzyloxy-4'-methoxy)phenyl-2-(3,4-dimethoxyphenyl)-4-oxobutyronitrile (8c) : 85 %, mp = 140 °C (from ethanol), δ 3.37 (dd, 1 H, J = 6.3, 17.6, H-3), 3.59 (dd, 1 H, J = 17.6, 7.7, H-3), 3.85, 3.87, 3.92 (s, 9 H, OCH_3), 4.47 (dd, 1 H, J = 6.3, 7.7, H-2), 5.15 (s, 2 H, $CH_2C_6H_5$), 6.82 (d, 1 H, J = 8.4, H-5), 6.86 (m, 1 H, H-5'), 6.88 (d, 1 H, J = 2.1, H-2), 6.93 (dd, 1 H, J = 2.1, 8.4, H-6), 7.23-7.53 (m, 7 H, H-2', H-6', C_6H_5). Anal. Calcd. for $C_{26}H_{25}NO_5$: C, 72.4; H, 5.8; N, 3.3. Found: C, 72.4; H, 5.9; N, 3.3.

2-(3,4-Dimethoxyphenyl)-4-(3'-benzyloxy-4'-methoxy)phenyl-4-oxobutyric acid (9c) : 94 % mp = 188 °C (from ethanol), δ (DMSO d6) 3.24 3.24-3.37 (m, 2 H, CH_2-3), 3.76, 3.79, 3.89, (3s, 9 H, OCH_3), 4.04 (m, 1 H, H-2), 6.88-7.00 (m, 3 H, H-2, H-5, H-5'), 7.12 (dd, 1 H, J = 8.4, 2.0, H-6), 7.36-7.51 (m, 5 H, C_6H_5), 7.62 (d, 1 H, J = 2.2, H-2'), 7.74 (dd, 1 H, J = 8.4, 2.2, H-6'), 12.29 (s, 1 H, COOH). Anal. Calcd. for $C_{26}H_{26}O_7$: C, 69.3; H, 5.8. Found: C, 69.5; H, 5.7.

2-(3,4-Dimethoxyphenyl)-4-(3',4'-methylenedioxyphenyl) butyric acid (10a) : Oily compound[34] used directly after drying. A sample crystallized on standing after two months. mp = 80 °C, δ 1.98 (m, 1 H, H-3), 2.30 (m, 1 H, H-3), 2.47 (m, 2 H, CH_2-4), 3.46 (m, 1 H, H-2), 3.85 , 3.86 (2s, 6 H, OCH_3), 5.90 (s, 2 H, OCH_2O), 6.56 (dd, 1 H, J = 1.5, 7.8, H-5), 6.62 (d, 1 H, J = 1.5, H-2), 6.70 (d, 1 H, J = 7.8, H-6), 6.78-6.87 (m, 3 H, H-2', H-5', H-6').

2-(3,4-Dimethoxyphenyl)-4-(3'-hydroxy-4'-methoxy)phenyl butyric acid (10c) : 95 %, mp = 105 °C (from ethanol-water), δ 2.0-2.40 (m, 2 H, CH_2-3), 2.45-2.60 (m, 2 H, CH_2-4), 3.50 (m, 1 H, H-2), 3.87, 3.88 (2s, 9 H, OCH_3), 6.63-6.84 (m, 6 H, Ar, Ar'), 7.26 (s, 1 H, OH). Anal. Calcd. for $C_{19}H_{22}O_6$: C, 65.9; H, 6.4. Found: C, 65.5; H, 6.3.

2-(3,4-Dimethoxyphenyl)-4-(3'-benzyloxy-4'-methoxy)phenyl butyric acid (10d) : Compound (**10c**) (34.8 g, 0.1 mol), benzylchloride (37.5 mL 0.4 mol) and K_2CO_3 (82.9 g, 0.6 mol) were mixed in DMF (200 mL). The mixture was heated at 100 °C overnight and, after a filtration, concentrated to dryness. The residue left was diluted in 75 % ethanol (400 mL) KOH (35 g) was added and this mixture was boiled for 6 hours. Ethanol was removed in vacuo, the residue was diluted in water, the suspension obtained was acidified with concentrated HCl and left to crystallize. Recrystallization of the air-dried solid from cyclohexane yielded **10d** (42 g, 96 %, mp = 118 °C) δ 2.03 (m, 1 H, H-3), 2.32 (m, 1 H, H-3), 2.50 (m, 2 H, CH_2-4), 3.46 (m, 1 H, H-2), 3.86 (s, 9 H, OCH_3), 5.12 (s, 2 H, $CH_2C_6H_5$), 6.72-6.82 (m, 6 H, Ar, Ar'), 7.27-7.50 (m, 5H, C_6H_5). Anal. Calcd. for $C_{26}H_{28}O_6$: C, 71.5; H, 6.5. Found: C, 71.8; H, 6.6.

2-(3,4-Dimethoxyphenyl)-4-(3'-isopropyloxy-4'-methoxy)phenyl butyric acid (10e) : Compound **10c** (33 g, 0.095 mol), 2-bromopropane (33 mL 0.35 mol) and K_2CO_3 (69 g, 0.57 mol) were mixed in DMF (200 mL). The mixture was boiled overnight and, after a filtration, was evaporated to dryness. The residue was diluted in 75 % ethanol (400 mL) KOH (35 g) was added and this mixture was boiled for 6 h. Ethanol was evaporated under reduced pressure, the residue was diluted in water, the suspension obtained was acidified with concentrated HCl and left to crystallize. The collected and air dried solid was recrystallized from heptane to yield **10e** (26.9 g, 73 %, mp = 103 °C. Lit[39] : 104 °C).

General procedure for the synthesis of 2-aryl-1-tetralones 5a-e : Except for the purification procedure, the method used is closely related to the already published one[40]. Phosphorous oxychloride (38.2 g, 0.41 mol) was added dropwise to an ice-cooled solution of the required acid **10a-e** (0.082 mol) in acetonitrile (400 mL) in the presence of K_2CO_3 (25 g, 0.18 mol). The suspension was stirred 1 h at the same temperature and the ice bath was removed. After a further hour under stirring, the temperature was then raised to a gentle refux. At the disappearance of acids **10a-e** (4-8 h, T.L.C. monitoring), the deeply pink suspension was poured onto ice-water and extracted with methylene chloride. Aside from the case of the preparation of **5c** in the course of which a simple washing of the organic layer with water was performed, the organic layer obtained was washed with 20 % aqueous NaOH and dried over magnesium sulfate *without washing to neutrality* before

evaporation to dryness. This procedure enabled us to remove a hightly coloured substance upon recrystallization over Norit.

2-(3,4-Dimethoxyphenyl)-6-benzyloxy-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (5d) : 30 %, mp = 140 °C (from methanol) δ 2.39 (m, 2 H, CH_2-3), 2.94 (m, 2 H, CH_2-4), 3.69 (m, 1 H, H-2), 3.84, 3.86, 3.93 (3s, 9 H, OCH_3), 5.22 (s, 2 H, $CH_2C_6H_5$), 6.73-6.80 (m, 4H, H-5, H-2', H-5', H-6'), 7.41 (m, 5 H, C_6H_5), 7.61 (s, 1 H, H-8). Anal. Calcd. for $C_{26}H_{26}O_5$: C, 74.6; H, 6.3. Found: C, 74.9; H, 6.3.

2-(3,4-Dimethoxyphenyl)-6-isopropyloxy-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (5e) : 77 % (from **10c**), mp = 123 °C (from heptane), lit[39] : 122 °C.

General procedure for the preparation of oximes 11a-c : The method used is identical to the already published one[46] :

2-(3,4-Dimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalene-1(2H)-oneoxime (11a) : 90 %, mp = 135 °C (from ethanol-water) lit[46] : 171 °C δ 1.26-2.23 (m, 2 H, CH_2-3), 2.43-2.70 (m, 2 H, CH_2-4), 3.80-3.81 (2s, 6 H, OCH_3), 4.69 (m, 1 H, H-2), 5.94 (s, 2 H, OCH_2O), 6.55 (s, 1 H, H-5), 6.62 (dd, 1 H, J = 2.0, 8.1, H-6'), 6.72 (d, 1 H, J = 2.0, H-2'), 6.72 (d, 1 H, J = 8.1, H-5'), 7.48 (s, 1 H, H-8). Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.9; H, 5.6; N, 4.1; O, 23.4. Found: C, 66.4; H, 5.7; N, 4.1; O, 23.8.

2-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydronaphthalen-1(2H)-one oxime (11b) : 91 %, mp = 208 °C (from ethanol) δ 2.10 (m, 2 H, CH_2-3), 2.56 (m, 2 H, CH_2-4), 3.79, 3.80, 3.87, 3.88 (4s, 12 H, OCH_3), 4.71 (m, 1 H, H-2), 6.56 (s, 1 H, H-5), 6.62 (dd, 1 H, J = 1.8, 8.2, H-6'), 6.72 (d, 1 H, J = 8.2, H-5'), 6.73 (d, 1 H, J = 1.8, H-2'), 7.52 (s, 1 H, H-8). Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.2; H, 6.5; N, 3.9; O, 22.4. Found: C, 67.6; H, 6.4; N, 3.9; O, 22.3.

2-(3,4-Dimethoxyphenyl)-6-isopropyloxy-7-methoxy-3,4-dihydronaphthalen-1(2H)-oneoxime (11c) : mp = 50 °C (hard foam) δ 1.33 (d, 6 H, J = 6.0, CH_3-*i*-Pr), 2.00 (m, 2 H, CH_2-3), 2.50 (m, 2 H, CH_2-4), 3.74, 3.76, 3.79 (3s, 9 H, OCH_3), 4.50 (sept, 1 H, J = 6.0, H-*i*-Pr), 4.65 (m, 1 H, H-2), 6.53 (s, 1 H, H-5), 6.59 (dd, 1 H, J = 1.8, 8.4, H-6'), 6.67 (d, 1 H, J = 8.4, H-5'), 6.68 (d, 1 H, J = 1.8, H-2'), 7.46 (s, 1 H, H-8).

General procedure for the synthesis of 6-methylbenzo[c]phenanthridines 12a-d and N-diacetyl derivatives 13a-b : In a thick glassed 250 mL flask stoppered with a teflon cap, oxime **11a-c** (8.8 mmol) and 45 mL of a 50-125 acetic acid-anhydride acetic mixture containing a measured weight of dissolved hydrogen chloride (20 % when saturation is attained at 0°C) were heated at 100 °C with an oil bath for 5 h. The mixture was cautiously poured onto water (300 mL) and basified with concentrated ammonia. The suspension was extracted with methylene chloride, the organic layer was dried (K_2CO_3) before evaporation of the solvent. Most of the compounds **12a** or **12b** were obtained by direct recrystallization of the residue. The mother liquors were then chromatographed over silica gel, eluting with heptane-ethyl acetate (1/1,v/v) thus yielding some more compounds **12** along with the diacetylated amines **13**. Yields obtained for compounds **12b** and **13b** are very close to the one given in the text for compounds **12a** and **13a** in table 1. Direct purification of **12c** was not possible and a partial hydrolysis of the corresponding diacetylamine as for the preparation of compound **14a-b** was necessary prior a chromatography.

8,9-Dimethoxy-6-methyl-2,3-methylenedioxybenzo[c]phenanthridine (12a) : mp = 233 °C (from pyridine-methanol) lit[53] : 233 °C δ (DMSO d6) 3.15 (s, 3 H, CH_3), 4.02, 4.11 (2s, 6 H, OCH_3), 6.23 (s, 2 H, OCH_2O), 7.54 (s, 1 H, H-1), 7.67 (s, 1 H, H-7), 7.97 (d, 1 H, J = 9.4, H-12), 8.20 (s, 1 H, H-10), 8.65 (s, 1 H, H-4), 8.65 (d, 1 H, J = 9.4, H-11). Anal. Calcd. for $C_{21}H_{17}NO_4$: C, 72.6; H, 4.9; N, 4.0; O, 18.4. Found: C, 72.5; H, 5.1; N, 4.0; O, 18.0.

2,3,8,9-Tetramethoxy-6-methylbenzo[c]phenanthridine (12b) : mp > 260°C (from toluene) δ 3.10 (s, 3 H, CH_3), 4.06, 4.07, 4.14, 4.20 (4s, 12 H, OCH_3), 7.26 (s, 1 H, H-1), 7.46 (s, 1 H, H-7), 7.79 (d, 1 H, J = 9.0, H-12), 7.89 (s, 1 H, H-10), 8.25 (d, 1 H, J = 9.0, H-11), 8.79 (s, 1 H, H-4). Anal. Calcd. for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85; O, 17.61. Found: C, 72.8; H, 5.8; N, 3.9; O, 17.6.

3,8,9-Trimethoxy-2-isopropyloxy-6-methylbenzo[c]phenanthridine (12c) : mp = 211 °C (washed in hot methanol) δ 1.49 (d, 6 H, J = 6.0, CH_3-*i*-Pr), 3.07 (s, 3 H, CH_3), 4.04, 4.11, 4.17 (3s, 9 H, OCH_3), 4.77 (sept, 1 H, J = 6.0, H-*i*-Pr) 7.28 (s, 1 H, H-1), 7.40 (s, 1 H, H-7), 7.74 (d, 1 H, J = 9.0, H-12), 7.84 (s, 1 H, H-10), 8.19 (d, 1 H, J = 9.0, H-11), 8.78 (s, 1 H, H-4). Anal. Calcd. for $C_{24}H_{25}NO_4$: C, 73.6; H, 6.4; N, 3.6; O, 16.4. Found: C, 73.4; H, 6.3; N, 3.4; O, 16.3.

7,8-Dimethoxy-6-methyl-2,3-methylenedioxybenzo[c]phenanthridine (12d) : mp = 196 °C (from heptane) δ 3.33 (s, 3 H, CH_3), 4.02, 4.04 (2s, 6 H, OCH_3), 6.11 (s, 2 H, OCH_2O), 7.22 (s, 1 H, H-1), 7.56 (d, 1 H, J = 9.1, H-12), 7.76 (d, 1 H, J = 8.8, H-9), 8.27 (d, 1 H, J = 8.8, H-10), 8.38 (d, 1 H, J = 9.1, H-11), 8.80 (s, 1 H, H-4). Anal. Calcd. for $C_{21}H_{17}NO_4$: C, 72.6; H, 4.9; N, 4.0; O, 18.4. Found: C, 72.2; H, 4.9; N, 4.1; O, 18.3.

N,N-Diacetyl-1-amino-2-(3,4-dimethoxyphenyl)-6,7-methylenedioxy naphthalene (13a) : mp = 168 °C (washed in pentane) δ 2.15 (s, 6 H, $(COCH_3)_2$), 3.82, 3.91 (2s, 6 H, OCH_3), 6.07 (s, 2 H, OCH_2O), 6.82 (d, 1 H, J = 2.3, H-2'), 6.83 (dd, 1 H, J = 2.3, 8.6, H-6'), 6.90 (s, 1 H, H-5), 6.91 (d, 1 H, J = 8.6, H-5'), 7.18 (s, 1 H, H-8), 7.35 (d, 1 H, J = 8.4, H-3), 7.75 (d, 1 H, J = 8.4, H-4). Anal. Calcd. for $C_{23}H_{21}NO_6$: C, 67.8; H, 5.2; N, 3.4; O, 23.6. Found: C, 67.6; H, 5.3; N, 3.3; O, 23.5.

1-(N,N-Diacetyl)amino-6,7-dimethoxy-2-(3,4-dimethoxyphenyl)naphthalene (13b) : mp = 173 °C (from heptane) δ 2.16 (s, 6 H, $(COCH_3)_2$), 3.83, 3.91, 3.94, 4.01 (4s, 12 H, OCH_3), 6.81 (s, 1 H, H-5), 6.84 (dd, 1 H, J = 1.9, 8.7, H-6'), 6.85 (d, 1 H, J = 1.9, H-2'), 6.91 (d, 1 H, J = 8.7, H-5'), 7.19 (s, 1 H, H-8), 7.37 (d, 1 H, J = 8.3, H-3), 7.79 (d, 1 H, J = 8.3, H-4). Anal. Calcd. for $C_{24}H_{25}NO_6$: C, 68.1; H, 6.0; N, 3.3; O, 22.7. Found: C, 68.1; H, 5.9; N, 3.7; O, 22.3.

General procedure for the synthesis of naphthylamines 4a-c : In a thick glassed 250 mL flask stoppered with a teflon cap, oximes **11a-c** (8.8 mmol) and 45 mL acetic acid containing a mesured weight of dissolved hydrogen chloride (10 % when saturation is attained at 0°C) were heated with an oil bath at 100 °C for 5 h. The mixture was cautiously poured onto water (100 mL) and basified with concentrated ammonia. The suspension was extracted with methylene chloride, the organic layer was dried (K_2CO_3) and evaporated. The residue obtained was chromatographed over silica gel eluting with heptane-ethyl acetate 1/1, v/v.

1-Amino-6,7-methylenedioxy-2-(3,4-dimethoxyphenyl)naphthalene (4a) : 60 %, mp = 214 °C (from toluene-heptane) δ 3.90, 3.93 (2s, 6 H, OCH_3), 6.03 (s, 2 H, OCH_2O), 6.96 (d, 1 H, J = 8.5, H-5'), 7.00 (s, 1 H, H-5), 7.02 (dd, 1 H, J = 1.9, 8.5, H-6'), 7.10 (s, 1 H, H-8), 7.15 (d, 1 H, J = 8.4, H-3), 7.24 (d, 1 H, J = 8.4, H-4), 7.25 (d, 1 H, J = 1.9, H-2'). Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.6; H, 5.3; N, 4.3; O, 19.8. Found: C, 70.7; H, 5.2; N, 4.2; O, 20.1.

1-Amino-6,7-dimethoxy-2-(3,4-dimethoxyphenyl)naphthalene (4b) : 53 %, mp = 134 °C (from toluene-heptane) δ 3.89, 3.91, 4.00 (3s, 12 H, OCH_3), 6.95 (d, 1 H, J = 8.8, H-5'), 7.01 (s, 1 H, H-5), 7.03 (dd, 1 H, J = 1.9, 8.8, H-6'), 7.11 (s, 1 H, H-8), 7.15 (d, 1 H, J = 1.9, H-2'), 7.17 (d, 1 H, J = 8.2, H-3), 7.28 (d, 1 H, J = 8.2, H-4). Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.8; H, 6.2; N, 4.1; O, 18.9. Found: C, 70.7; H, 6.2; N, 4.0; O, 19.3.

2-(3,4-Dimethoxyphenyl)-6-hydroxy-7-methoxy-1-aminonaphthalene (4c) : 22 % (from **5e** through **11c**), mp = 200 °C (from toluene-heptane) δ (DMSO d6) 3.83, 3.84, 3.95 (3s, 9 H, OCH3), 5.17 (s, 2 H, NH_2), 6.94-7.03 (m, 4 H, H-3, H-4, H-6', H-2'), 7.05 (s, 1 H, H-5), 7.10 (d, 1 H, J = 8.2, H-5'), 7.48 (s, 1 H, H-8), 9.36 (s, 1 H, OH). Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.1; H, 5.9; N, 4.3; O, 19.7. Found: C, 69.9; H, 6.0; N, 4.2; O, 19.8.

Procedure for the synthesis of the acetamides 14a-b : The mixtures of compound **13a-b** (1 mmol), potassium hydroxide pellets (3 g, 10-15 % water) and *ter*-butanol (60 mL) were heated at reflux for 2 h. The mixture was poured onto water and the insoluble compound was extracted with methylene chloride. The organic layer was washed with water, dried (K_2CO_3) before evaporation to dryness. The residue obtained was recrystallized by dissolving in boiling toluene and then heptane was added until saturation, upon which recrystallisation occured on cooling.

N-Acetyl-1-amino-2-(3,4-dimethoxyphenyl)-6,7-methylenedioxynaphthalene (14a) : 67 %, mp = 215 lit[3] : 210 °C δ (DMSO d6) 2.04 (s, 3 H, $COCH_3$), 3.80, 3.83 (2s, 6 H, OCH_3), 6.19 (s, 2 H, CH_2), 6.98 (dd, 1 H, J = 1.8, 8.3, H-6'), 7.07 (d, 1 H, J = 8.3, H-5'), 7.08 (dd, 1 H, J = 1.8, H-2'), 7.23 (s, 1 H, H-8), 7.39 (d, 1 H, J = 8.6, H-3), 7.41 (s, 1 H, H-5), 7.78 (d, 1 H, J = 8.6, H-4), 9.58 (s, 1 H, NH). Anal. Calcd. for $C_{21}H_{19}NO_5$: C, 69.0; H, 5.2; N, 3.8; O, 21.9. Found: C, 68.6; H, 5.1; N, 3.4; O, 21.8.

Preparation of compound 14a from the amine 4a : Amine **4a** (0.3 g, 0.93 mmol) and acetic anhydride (0.1 g, 0.97 mmol) in pyridine (10 mL) were boiled for 1 h. After ususal workup, the monoacetylated compound **14a** (0.24g, 70 %, from toluene-heptane) was obtained. Melting point, NMR spectra and Rf of this sample were identical with the ones of the compound obtained above.

N-Acetyl-1-amino-6,7-dimethoxy-2-(3,4-dimethoxyphenyl)naphthalene (14b) : 61 %, mp = 115 °C, m/z = 381 δ (DMSO d6) 2.0 (s, 3 H, $COCH_3$), 3.75, 3.78, 3.84, 3.89 (4s, 12 H, OCH_3), 6.93 (dd, 1 H, J = 1.9, 8.2, H-6'), 7.02 (d, 1 H, J = 8.2, H-5'), 7.03 (dd, 1 H, J = 1.9, H-2'), 7.13 (s, 1 H, H-8), 7.33 (d, 1 H, J = 8.5, H-3), 7.36 (s, 1 H, H-5), 7.75 (d, 1 H, J = 8.5, H-4), 9.53 (s, 1 H, NH). Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.3; H, 6.1; N, 3.7. Found: C, 68.9; H, 6.2; N, 3.3.

Procedure for the synthesis of urethanes 15a-c : A solution of the required amine **4a-c** (3 mmol) and ethyl chloroformate (0.59 mL, 6 mmol) in pyridine (20 mL) was stirred 3 h. The mixture was evaporated to dryness, the residue taken up in 10 % hydrochloric acid and the resulting suspension was extracted with methylene chloride. The organic layer was washed with 10 % hydrochloric acid, dried over K_2CO_3 and evaporated to dryness. The hard foam obtained couldn't be properly crystallized and NMR spectra were showing traces of pyridine. Here are reported the NMR and mass spectra of these partially characterized compounds :

N-1-[2-(3,4-Dimethoxyphenyl)-6,7-methylenedioxynaphthyl]ethylcarbamate (15a) : δ 1.20 (m, 3 H, CH_3), 3.83, 3.89 (2s, 6 H, OCH_3), 4.12 (m, 2 H, CH_2), 6.01 (s, 2 H, OCH_2O), 6.90-6.92 (m, 3 H, H-2', H-5', H-6'), 7.09 (s, 1 H, H-5), 7.23 (s, 1 H, H-8), 7.28 (d, 1 H, J = 7.8, H-3), 7.60 (d, 1 H, J = 7.8, H-4).

N-1-[2-(3,4-Dimethoxyphenyl)-6,7-dimethoxynaphthyl]ethylcarbamate (15b) : δ 1.28 (m, 3 H, CH_3), 3.86, 3.91, 3.97, 3.99 (4s, 12 H, OCH_3), 4.12 (q, 2 H, J = 7.2, CH_2), 6.93 (s, 3 H, H-2', H-5', H-6'), 7.13 (s, 1 H, H-5), 7.23 (s, 1 H, H-8), 7.31 (d, 1 H, J = 8.4, H-3), 7.66 (d, 1 H, J = 8.4, H-4).

N-1-[2-(3,4-Dimethoxyphenyl)-6-ethoxycarbonyloxy-7-methoxynaphthyl] ethylcarbamate (15c) : m/z (C.I.) = MH^+ = 470. δ 1.21 (m, 3 H, $NCO_2CH_2\underline{CH_3}$), 1.39 (t, 3 H, J = 7.1, $OCO_2CH_2\underline{CH_3}$), 3.86, 3.91, 3.94 (3s, 9 H, OCH3), 4.13 (m, 2 H, $NCO_2\underline{CH_2}CH_3$), 4.34 (q, 2 H, J = 7.1, $OCO_2\underline{CH_2}CH_3$), 6.94 (s, 3 H, H-2', H-5', H-6'), 7.33 (s, 1 H, H-5), 7.35 (d, 1 H, J = 8.5, H-3), 7.60 (s, 1 H, H-8), 7.70 (d, 1 H, J = 8.5, H-4).

N-1-[2-(3,4-Dimethoxyphenyl)-6-hydroxy-7-methoxynaphthyl] ethylcarbamate (15d) : Urethane **15c** (0.5 g) and potassium hydroxide pellets (2 g) dissolved in ethanol (100 mL) were stirred at room temperature overnight. The resulting solution was poured onto water and acidified with concentrated hydrochloric acid. The precipitate was extracted with methylene chloride, the organic layer was washed with water, dried over $MgSO_4$ and evaporated to dryness. The hard foam obtained (0.43 g) again could not be properly crystallized Here is reported the NMR and mass spectra of compound **15d** : m/z (C.I.) = MH^+ =

398. δ 1.21 (m, 3 H, CH_3), 3.86, 3.91, 3.99 (3s, 9 H, OCH_3), 4.10 (m, 2 H, CH_2), 6.16 (s br, 1 H, OH), 6.93 (s, 3 H, H-2', H-5', H-6'), 7.23 (s, 1 H, H-8), 7.25 (s, 1 H, H-5), 7.30 (d, 1 H, J = 8.5, H-3), 7.63 (d, 1 H, J = 8.5, H-4).

Procedure for the synthesis of benzo[c]phenanthridin-6(5H)-ones 3a-b : The solution of urethanes **15a-b** (0.01 mol) in diphenylether (60 mL) in which was added 10 drops of tributylamine was heated to boiling temperature for 4 h. After cooling, the resulting suspension was diluted in an excess of heptane and the precipitate was filtered, washed with methylenechloride and with boiling methanol. After drying, analytically pure benzo[c] phenanthridin-6(5H)-ones were obtained.

2,3-Methylenedioxy-8,9-dimethoxybenzo[c]phenanthridin-6(5H)-one (3a) : 86 % (from **4a**), mp > 260 °C lit[31] : > 340 °C. δ (CF_3COOD) 4.09, 4.20 (2s, 6 H, OCH_3), 6.04 (s, 2 H, OCH_2O), 7.14 (s, 1 H, H-10), 7.36 (s, 1 H, H-1), 7.68-7.81 (m, 3 H, H-4, H-7, H-12), 8.03 (d, 1 H, J = 8.8, H-11). Anal. Calcd. for $C_{20}H_{15}NO_5$: C, 68.7; H, 4.3; N, 4.0; O, 22.9. Found: C, 68.6; H, 4.5; N, 4.0; O, 22.8.

2,3,8,9-Tetramethoxybenzo[c]phenanthridin-6(5H)-one (3b) : 81 % (from **4b**), mp > 260 °C. δ (CF_3COOD) 3.89, 3.95, 4.08 (3s, 12 H, OCH_3), 7.03 (s, 1 H, H-10), 7.19 (m, 1 H, H-12), 7.40-7.51 (m, 3 H, H-4, H-1, H-7), 7.79 (m, 1 H, H-11). Anal. Calcd. for $C_{21}H_{19}NO_5$: C, 69.0; H, 5.2; N, 3.8; O, 21.9. Found: C, 68.6; H, 5.3; N, 3.8; O, 22.2.

Procedure for the synthesis of 6-chlorobenzo[c]phenanthridines 16a-b: Benzo[c]phenanthridin-6(5H)-one **3a-b** (1.4 mmol) in phenylphosphonic dichloride (20 mL) was heated in an oil bath at 160 °C for 6 h. The mixture was poured onto an excess of crushed ice, the suspension was basified with concentrated ammonia and stirred for 2 h. The precipitate was filtered, washed with water and chromatographed over alumina (7 % water) eluting with a mixture of ethyl acetate and heptane 1,1 v/v. The residue obtained after evaporation of the pure compound containing fractions was recrystallized in a mixture of ethyl acetate an heptane. Note: These chlorinated derivatives are rather difficult to obtain as pure crystalline compounds. However, when ommiting the purification procedures and using the crude product, no difficuties were encountered in the course of the purification of the substitution products.

6-Chloro-2,3-methylenedioxy-8,9-dimethoxybenzo[c]phenanthridine (16a) : Yield : 57 % ; mp > 260 °C lit[22] > 300 °C. δ 4.09, 4.14 (2s, 6 H, OCH_3), 6.11 (s, 2 H, OCH_2O), 7.20 (s, 1 H, H-1), 7.71 (s, 1 H, H-7), 7.78 (d, 1 H, J = 8.9, H-12), 7.82 (s, 1 H, H-10), 8.17 (d, 1 H, J = 8.9, H-11), 8.56 (s, 1 H, H-4). Anal. Calcd. for $C_{20}H_{14}NClO_4$: C, 65.3; H, 3.8; N, 3.8; Cl, 9.6; O, 17.4. Found: C, 64.8; H, 4.1; N, 3.8; Cl, 9.5; O, 17.0.

6-Chloro-2,3,8,9-tetramethoxybenzo[c]phenanthridine (16b) : Yield : 53 %, mp > 260 °C. δ 4.09, 4.04, 4.08, 4.16 (4s, 12 H, OCH_3), 7.20 (s, 1 H, H-1), 7.69 (s, 1 H, H-7), 7.79 (d, 1 H, J = 8.8, H-12), 7.81 (s, 1 H, H-10), 8.15 (d, 1 H, J = 8.8, H-11), 8.59 (s, 1 H, H-4). Anal. Calcd. for $C_{21}H_{18}NClO_4$: C, 65.7; H, 4.7; N, 3.7; Cl, 9.2; O, 16.7. Found: C, 65.6; H, 4.8; N, 3.6; Cl, 9.4; O, 16.7.

Procedure for the synthesis of 6-amino substituted benzo[c]phenanthridines 2a-b : 6-chlorobenzo[c]phenanthridines (**16a-b**) (7 mmol) in 2-(N,N-dimethylamino) ethylamine (20 mL 0.22 mol) was boiled for a 7 h period. The solution was then evaporated to dryness in vacuo and the residue was dissolved in methylene chloride. This organic layer was washed with 10 % sodium hydroxide, and water and then dried over K_2CO_3. After evaporation to dryness, the residue was recrystallized in a mixture of toluene and heptane, to yield the free bases (**2a-b**), partially hydrated.

6-{[2'-(Dimethylamino)ethyl]amino}-2,3-methylenedioxy-8,9-dimethoxy benzo[c]phenanthridine (2a) : Yield : 52 %, mp = 157 °C. δ (DMSO d6) 2.29 (s, 6 H, $N(CH_3)_2$), 2.68 (m, 2 H, CH_2-2'), 3.82 (m, 2 H, CH_2-1'), 3.94, 4.02 (2s, 6 H, OCH_3), 6.14 (s, 2 H, OCH_2O), 7.34 (s, 1 H, H-1), 7.53 (m, 2 H, NH, H-12), 7.72 (s, 1 H, H-7), 7.97 (s, 1 H, H-10), 8.33, (d, 1 H, J = 9 1, H-11),

8.39 (s, 1 H, H-4). Anal. Calcd. for $C_{24}H_{25}N_3O_4$, H_2O: C, 65.9; H, 6.2; N, 9.6; O, 18.3. Found: C, 66.0; H, 6.1; N, 9.5; O, 17.9.

6-{[2'-(Dimethylamino)ethyl]amino}-2,3,8,9-tetramethoxy benzo[c]phenanthridine (2b) : Yield : 33 %, mp = 186 °C. δ (DMSO d6) 2.29 (s, 6 H, $N(CH_3)_2$), 2.69 (m, 2 H, CH_2-2'), 3.91 (m, 2 H, CH_2-1'), 3.91, 3.94, 4.02 (3s, 12 H, OCH_3), 7.36 (s, 1 H, H-1), 7.55 (m, 2 H, NH, H-12), 7.72 (s, 1 H, H-7), 7.97 (s, 1 H, H-10), 8.32, (d, 1 H, J = 9.1, H-11), 8.48 (s, 1 H, H-4). Anal. Calcd. for $C_{25}H_{29}N_3O_4$, 3/4 H_2O: C, 66.9; H, 6.9; N, 9.4; O, 16.9. Found: C, 66.8; H, 6.7; N, 9.7; O, 16.5.

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REFERENCES AND NOTES

1 Simeon, S.; Rios, J.L.; Villar, A. *Pharmazie* **1989**, *44 (9)*, 593-597.
2 Stermitz, F.R.; Gillespie, J.P.; Amoros, L.G.; Romero, R.; Stermitz, T.A.; Larson, K.A.; Earl, S.; Oyz, J.E. *J. Med. Chem.* **1975**, *18*, 708-713.
3 Zee Cheng, R.K.Y.; Cheng, C.C. *J. Med. Chem.* **1975**, *18*, 66-71.
4 Hamlin, R.L.; Pipers, F.S.; Mguyen, K.; Milhalko, P.; Folk, R.M. U.S. NTIS, PB-261267, 72pp. From: Gov. Rep. Announce. Index (U.S.) 1977, 77(6), 94. *Chem. Abstr.* **1976**, *87*, 145670.
5 Sufness, M.; Douros, J. in Methods in Cancer Research Vol. 16; De Vita Jr., V.T.; Busch, H., Eds.; Academic Press: New York, 1979; 474.
6 Sethi, V.S. *Ann. N.Y. Acad. Sci.* **1977**, *284*, 508-516.
7 Tan, G.T.; Miller, J.F.; Kinghorn, A.D.; Hughes, S.H.; Pezzuto, J.M. *Biochem. Biophys. Res. Comm.* **1992**, *185(1)*, 370-378.
8 Rodd's chemistry of carbon compounds, 2° edition; Elsevier: Amsterdam 1978; Coffey, S., Ed.; Vol IV part H, p 173-197.
9 Hearn, M.J.; Swanson, S.L. *J. Heterocycl. Chem.* **1981**, *18*, 207-222.
10 Phillips, S.D.; Castle, R.N. *J. Heterocycl. Chem.* **1981**, *18*, 223-232.
11 Ninomiya, I.; Naito, T. *Recent. Dev. Nat. Carbon. Compd.* **1984**, *10*, 9-90.
12 Ishii, H.; Chen, I-S.; Ichikawa, Y-I.; Kawanabe, E.; Ichikawa, M.; Ichikawa, T.; Kuretani, K.; Inomata, M.; Hoshi, A. *Chem. Pharm. Bull.* **1985**, *33(10)*, 4139-4151.
13 Carty, A.; Elliot, I.W.; Lenior, G.M. *Can. J. Chem.* **1984**, *62*, 2435-2439.
14 Beugelmans, R.; Chastanet, J.; Ginsburg, H.; Quintero-Cortes, L.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 4933-4938.
15 Novikov, V.P.; Kolesnikov, V.T. *Zh. Org. Khim.* **1986**, *22(8)*, 1732; *Chem. Abstr.* **1987**, *107*, 6903.
16 Blasko, G.; Cordell, G.A. *J. Heterocycl. Chem.* **1989**, *26*, 1601-1603.
17 Maslennikova, L.V.; Sladkov, V.I.; Suvorov, N.N. *Zhur. Org. Khim.* **1990**, *26(2)*, 441-445; *Chem. Abst.* **1990**, *113*, 23 664.
18 Takano, S.; Suzuki, M.; Kijima, A. Ogasawara, K. *Tetrahedron. Lett* **1990**, *31(16)*, 2315-2318.
19 Rozkov, U.S.; Sladov, V.I.; Turdybekov, K.; Lindeman, S.V.; Kolesnikov, A.Y.; Stuchkov, Y.T.; Suvorov, N.N. *Zh. Org Khim.* **1989**, *25(6)*, 1292; *Chem. Abstr.* **1990**, *112*, 76913.
20 Olugbade, T.A.; Waigh, R.D.; Mackay, S.P. *J. Chem. Soc. Perkin. Trans. I* **1990**, 2657-2660.
21 Duval, O.; Mavoungou Gomes, L. *Tetrahedron* **1990**, *46(4)*, 1253-1256.
22 Rigby, J.H.; Holsworth, D.D. *Tetrahedron Lett.* **1991**, *32(41)*, 5757-5760.
23 Pérez D.; Guitán, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 5911-5917.

24 Martín, G.; Guitán, E.; Castedo, L.; Saa, J.M. *J. Org. Chem.* **1992**, *57*, 5907-5911.
25 Suzuki, M.; Nakanishi, T.; Kogawa, O.; Ishikawa, K. Kobayashi, F.; Ekimoto, H. European patent EP 487930 (1992); *Chem. Abstr.*, **1992**, *117*, 191706.
26 Beugelmans, R.; Bois-Choussy, M. *Tetrahedron* **1992**, *48(38)*, 8285-8294.
27 Hanakoa, M.; Yamagishi, H.; Marutani, M.; Mukai, C. *Chem. Pharm. Bull.* **1987**, *35(6)*, 2348-2354.
28 Kessar, S.V.; Gupta, Y.P.; Balakrishnan, P.; Sawal, K.K.; Mohammad, T.; Dutt, M. *J. Org. Chem.* **1988**, *53*, 1708-1713.
29 Pyrko, A.N. *Khim. Geterotsikl. Soedin.* **1990**, *12*, 1693; *Chem. Abstr.* **1991**, *114*, 206991.
30 Sazonova, N.M.; Levina, I.I.; Bezrukov, I.A.; Ershova, Y.A.; Sladkov, V.I., Safonova, T.S.; Suvorov, N.N. *Khim. Farm. Zh.* **1991**, *25(7)*, 31-34; *Chem. Abst.* **1991**, *115*, 183 640.
31 Kessar, S.V.; Singh, M.; Balakrishnan, P. *Tetrahedron Lett.* **1974**, 2269-2270.
32 Janin, Y.L.; Bisagni, E. Synthesis **1993**, *1*, 57-59.
33 Richardson, T.; Robinson, R. Seijo, E. *J. Chem. Soc.* **1937**, 835-841.
34 Arthur, H.R. Ng, Y.L. *J. Chem. Soc.* **1959**, 4010-4012.
35 Zee Cheng, R.K.Y.; Cheng, C.C. *J. Heterocycl. Chem.* **1973**, *10*, 85-88.
36 Ishii, H.; Ishikawa, T.; Deushi, T.; Harada, K-I.; Watanabe, T.; Ueda, E.; Sakamoto, M.; Kawanabe, E.; Takahashi, T.; Ichikawa, Y-I.; Takizawa, K.; Masuda, T.; Chen, I-S. *Chem. Pharm. Bull.* **1983**, *31(9)*, 3024-3038.
37 Ishii, H.; Kawanabe, E.; Harada, K-I.; Deushi, T.; Ueda, E.; Watanabe, T.; Ichikawa, Y-I.; Sakamoto, M.; Ishida, T.; Takahashi, T.; Nakajima, K.; Ichikawa, T. *Chem. Pharm. Bull.* **1983**, *31(9)*, 3039-3055.
38 Ishii, H.; Deushi, T.; Sakamoto, M.; Nakajima, K.; Ishida, T.; Harada, K-I.; Takahashi, T.; Kawanabe, E.; Masuda, T.; Ichikawa, T. *Chem Pharm. Bull.* **1983**, *31(9)*, 30563073.
39 Ishii, H.; Chen, I-S.; Ichikawa, T. *J. Chem. Soc. Perkin. Trans. I* **1987**, 671-676.
40 Ishii, H.; Chen, I-S.; Ueki, S.; Masuda, T.; Morita, K.; Ichikawa, T. *J Chem. Soc. Perkin. Trans. I* **1987**, 2415-2420.
41 Semmler, W.; *Chem. Ber.* **1892**, *25*, 3352-3356.
42 Wolff, L.; Gabler, M.; Heyl, F. *Justus Liebigs Ann. Chem.* **1902**, *322*, 351-391.
43 Conley, R.T.; Ghosh, S. in *Mechanisms of Molecular migration Vol 4*; Thyagarajan, B.S., Ed.; Wiley-Interscience: New York, 1971; p 251-307.
44 Mannering, G.C.; Keene, *R.T. Chem Ind. (London)* **1973**, *17 nov.* 1069.
45 Tamura, Y.; Yoshimoto, Y.; Sakai, K.;.Kita, Y. *Synthesis* **1980**, 483-484, and references therein.
46 Gopinath, K.W.; Govindachari, T.R.; Parthasarathy, P.C.; Viswanathan, N. *J. Chem. Soc.* **1959**, 4012-4014.
47 Gopinath, K.W.; Govindachari, T.R.; Viswanathan, N. *Tetrahedron* **1961**, *14*, 322-325.
48 Eiden, F.; Nagar, B.S. *Arch. Pharm. (Weinheim, Ger.)* **1964**, *297*, 488-492.
49 Eloy, F.; Deryckere, A. *J. Heterocycl. Chem.* **1970**, *7*, 1191-1193.
50 MacMillan, J.H.; Washburne, S.S. *J. Org. Chem.* **1973**, *38(17)*, 2982-2984.
51 Overman, L.E.; Tsuboi, S. *J. Am Chem. Soc.* **1977**, *99(8)*, 2813-2815.
52 For a reference investigating the thermal transformation of urethane into isocyanate see Bordzilovskii, V.Ya.; Sadikov, B.M.; Sutulo, A.G. Zh. Prikl. Khim. (Petrograd) **1992**, *65*, 175; *ChemInform.* **1992**, *23 (52)*, 71.
53 Gopinath, K.W.; Govindachari, T.R.; Viswanathan, N. *Curr. Sci.* **1959**, *28(6)*, 241-242.