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A COMMON AND GENERAL ACCESS TO BERBERINE AND BENZO [c] PHENANTHRIDINE ALKALOIDS

René Beugelmans and Michèle Bois-Choussy*

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France

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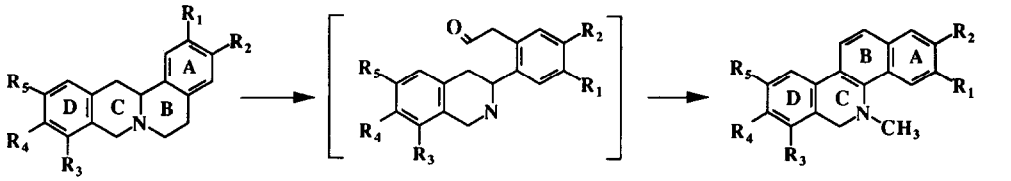
Abstract : The $S_{RN}1$ reactions between o-iodobenzamides and the enolate anion from 2-acetyl homoveratric acid lead to key tricyclic compounds which are easily converted to either berberine or benzo [c] phenanthridine ring systems providing thus a high-yielding and versatile access to both classes of alkaloids.

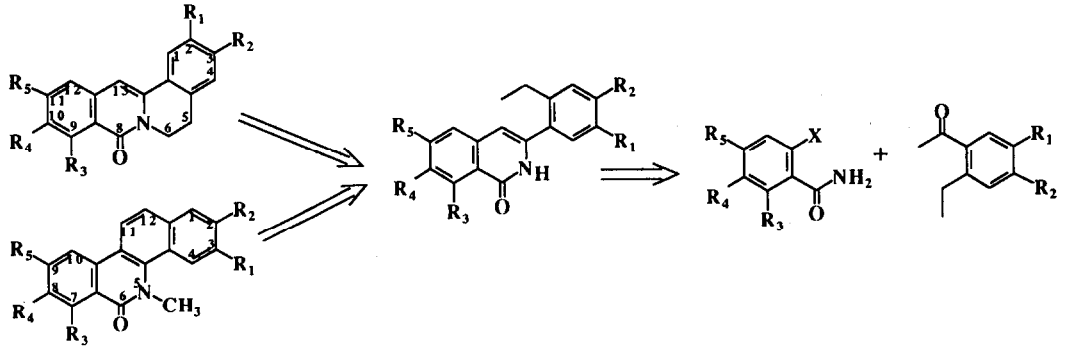
Benzo[c]phenanthridine alkaloids have been shown to be biosynthesised from the corresponding berberine alkaloids[1,2] presumably via a 3-[2-carbonylmethylaryl] isoquinoline intermediate[3] (Scheme I).



SCHEME I

Substituted 3-arylisoquinolines have been isolated as natural compounds[4a], while others have been obtained by multistep total syntheses[4b,c]. It was therefore conceivable to synthesize both classes of alkaloids if an efficient access to the common precursor could be achieved.

Retrosynthetic considerations indicate that coupling o-halobenzamide as a substrate with the enolate anion from an appropriately substituted acetophenone under $S_{RN}1$ conditions might provide a straighforward access to the key 3-arylisoquinolone[5,6] and hence to berberine or to benzo [c] phenanthridine alkaloids (Scheme II).



SCHEME II

We report here a general and direct $S_{RN}1$ access to properly substituted 3-arylisoquinolones from which berberine or benzo[c]phenanthridine derivatives are synthesised by ring closure of the two carbon chain either on position 2 or 4 of the isoquinolone ring.

RESULTS AND DISCUSSION

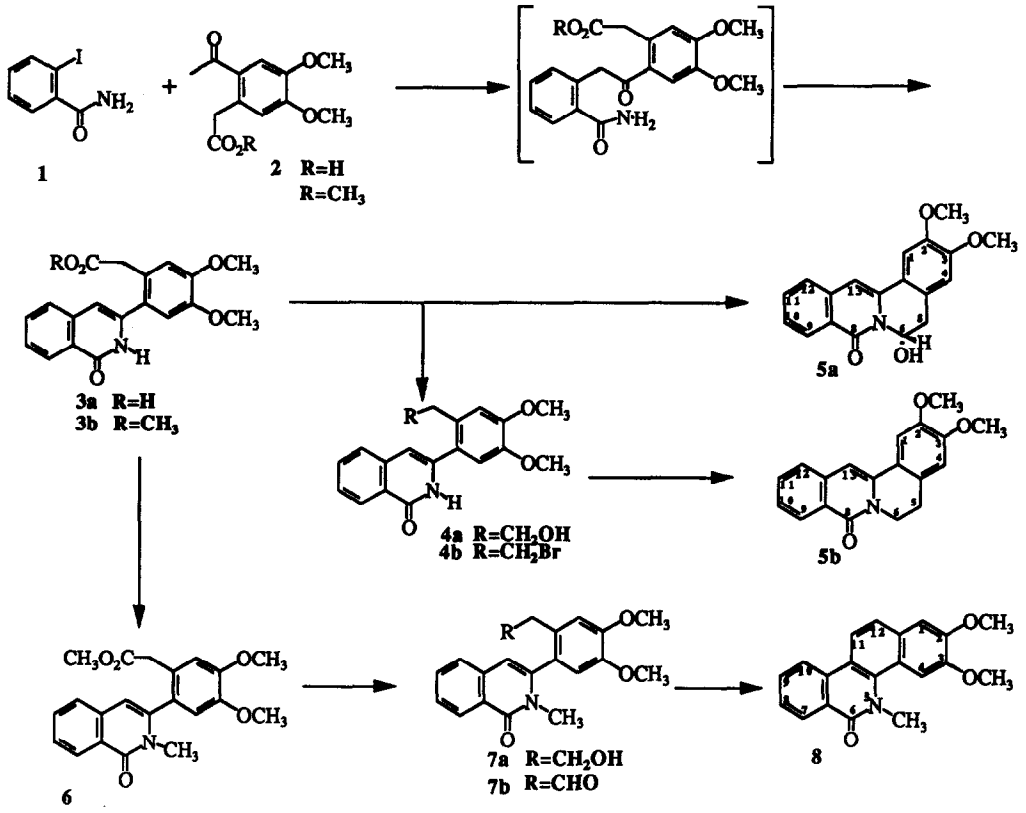
o-Acetyl homoveratric acid **2**, readily prepared[7] from commercially available homoveratric acid, has the substitution pattern of the acetophenone required to elaborate ring A of both groups of alkaloids. Since the enolate anion of **2** had not been used before as nucleophile for $S_{RN}1$ chemistry, we carried out preliminary investigations with o-iodobenzamide **1** in order to define the best experimental conditions. Test reactions with various solvents, various concentration of base and of nucleophile, and various irradiation conditions, were performed. The product was the isoquinolone **3a**, obtained in a one pot reaction as consequence of the spontaneous cyclisation of the primary $S_{RN}1$ product under the basic reaction conditions. It was determined that the quickest and most efficient reaction leading to **3a** took place in liquid ammonia at -33°C with 1,1 equivalent of **2** and a large excess of base (t-BuOK), this presumably was related to an increase of enolate anion concentration. The tricyclic acidic compound **3a** was converted to the methyl ester **3b**, more tractable for purification and further transformations; the overall yield of **3b** from **1** was 85%. An attempt to prepare **3b** directly by conducting the $S_{RN}1$ reaction on the methyl ester of **2** led to a less selective result and poor yield.

The reaction between **1** and the enolate derived form **2** took place *via* the four-step $S_{RN}1$ mechanism :

Initiation	ArX	$\xrightarrow{hv/e^-}$	$ArX^{\bullet -}$	Eq. 1
Propagation	$ArX^{\bullet -}$	$\longrightarrow$	$X^- + Ar^\bullet$	Eq. 2
	$Ar^\bullet + Nu^-$	$\longrightarrow$	$ArNu^{\bullet -}$	Eq. 3
	$ArNu^{\bullet -} + ArX$	$\longrightarrow$	$ArNu + ArX^{\bullet -}$	Eq. 4

We have indeed observed that no substitution product **3a** (ArNu) was formed in the dark since photostimulation is required to initiate the $S_{RN}1$ mechanism by generating the radical anion $ArX^{\bullet -}$ (Eq. 1) and that in the presence of an electron trapping substance (0.1 equivalent of p-dinitrobenzene), 80% of unchanged substrate **1** was recovered after two hours irradiation.

Access to the tetracyclic berberine skeleton : Smooth reduction of the ester **3b**, ($CaCl_2/NaBH_4$, THF, 20°C, 5 h) led directly to the 6-hydroxy-8-oxoberberine **5a** as the major product (80%) because the aldehyde, obtained by reduction of the CO_2CH_3 function, spontaneously reacted with the amide nitrogen ; the alcohol **4a** was also isolated. A fast $AlLiH_4$ reduction (THF/reflux, 5 min) gave **4a** as the only product. Further treatment of **4a** with PBr_3 gave **5b** in one pot since the bromide **4b** (not isolable) reacted as soon as it was formed with the amide nitrogen. Thus, 8-oxoprotoberberine **5b**[8] was obtained in two steps from **3b**.



SCHEME III

Access to the benzo[c]phenanthridine skeleton : Protection of the amide nitrogen function of **3a** is necessary in order to direct the electrophilic attack of the two carbon chain terminus on position 4 of ring **C**. Therefore N-Methyl isoquinolone ester **6** was prepared from **3b**, or, in a more direct fashion, from the crude product **3a** which thus underwent esterification and N-methylation in one pot (CH_3I, K_2CO_3, DMF). In both pathways, N-alkylation of the isoquinolone was highly selective leading to only minute amounts (8%) of O-alkylation product **17a**. Reduction of the methyl ester function led to the alcohol **7a**, the oxidation of which (Corey's reagent) triggered a spontaneous biomimetic ring closure by electrophilic attack of the aldehyde (**7b**) onto the enamine function[3c]. Thus, the tetracyclic compound **8** possessing the 6-oxo-benzo[c]phenanthridine ring system[9] was obtained in three steps from **3a**.

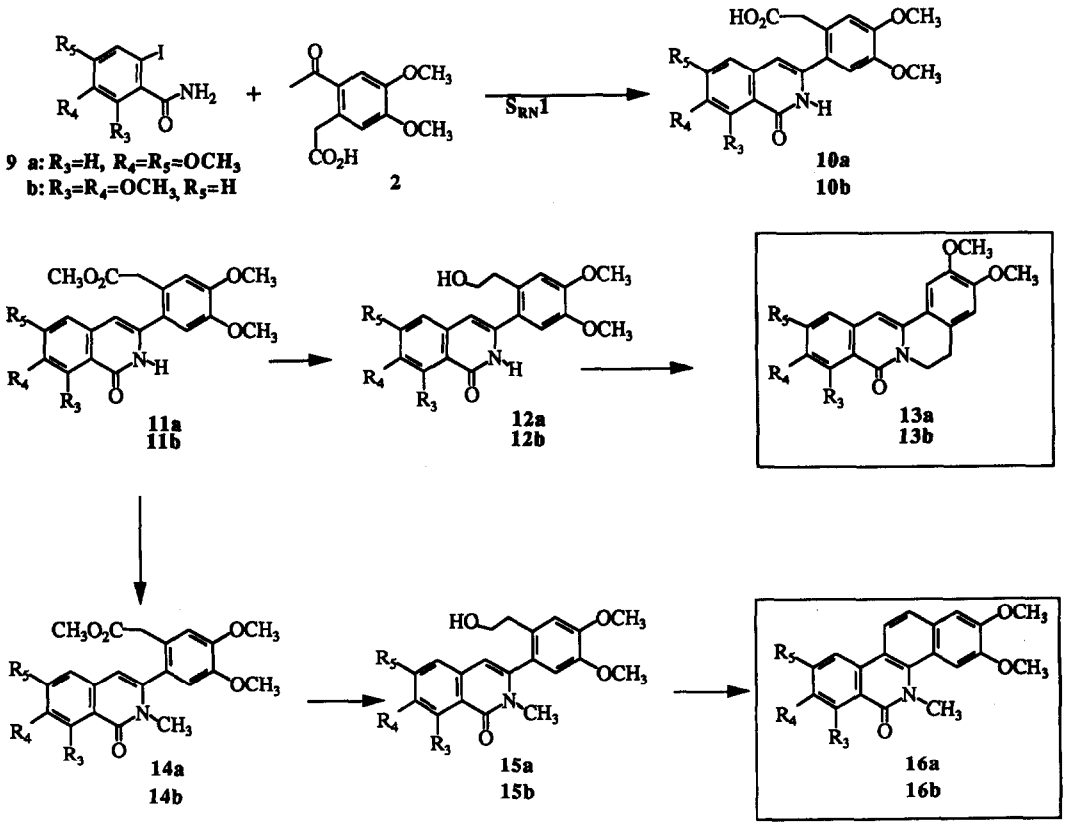
Access to alkaloids : Many alkaloids from natural origin carry oxygen substituents on ring **A** (positions 2, 3) and ring **D** (positions 9, 10, or 10, 11 of berberine ; positions 7, 8 or 8, 9 of benzo[c]phenanthridine) and both families of alkaloids can be obtained by extending the strategy depicted in Scheme III to properly substituted substrates. In the present study we have chosen as targets fully methoxylated alkaloids, and thus, two methoxylated substrates namely **9a** (R_3 = H, R_4, R_5 = OCH_3) and **9b** (R_3, R_4 = OCH_3 ; R_5 = H) were required. These were readily prepared from 3,4-dimethoxy and from 2,3-dimethoxy benzoic acid after ortho iodination, performed in high yield via a thallation reaction[10].

$S_{RN}1$ reactions between **9a** or **9b** and **2** (Scheme IV) gave the expected tricyclic compounds **10a** or **10b** in slightly lower yields than those obtained from reactions with the unsubstituted substrate **1**, because of reduction of the intermediate aryl radical Ar•. The transfer of a second electron to Ar• (Eq. 5) in competition with the attack by Nu^- (Eq. 3) is a well documented chain termination process[11] which consequently decreases the yield of ArNu .

Termination $Ar\bullet \xrightarrow{e^-} Ar^- \xrightarrow{H^+} ArH$ Eq. 5

Esters **11a** and **11b** have thus been obtained in yields of 72% from **9a** and 68% from **9b**.

Functional group transformations of **11a** or **11b** similar to those depicted for **3b** (Scheme IV) afforded 2,3,10,11-tetramethoxyoxoberberine **13a**[13,14], 2,3,9,10-tetramethoxyoxoberberine **13b**[8], O-methyl-oxyfagaronine **16a**[15] and 2,3,7,8-tetramethoxy-5-methyl-benzophenanthridone **16b** in yields close to those of **5b** and **8**.



SCHEME IV

CONCLUSION

Derivatives whose ring C is oxygenated are known to be easily converted to berberine or benzo[c]phenanthridine alkaloids by well established and efficient reduction procedures. Thus, xylopinine is reported to be obtained from **13a** in 80% yield[12] and likewise, benzo[c]phenanthridine alkaloids can be prepared in quantitative yields from their 6-oxygenated precursors[3c,16] such as **16a** or **16b**.

The convergent strategy based upon a key $S_{RN}1$ reaction for the one step assembly of all atoms of these target molecules provides thus a very short route to a great number of alkaloids from readily available starting materials.

EXPERIMENTAL SECTION

General : Melting points were recorded on a Reichert apparatus and were uncorrected. ^1H nuclear magnetic resonance spectra (^1H NMR) were obtained in $CDCl_3$ using a Bruker WP 200 SY (200 MHz) machine. Mass spectra were recorded on a AEI-MS.50 (IE) and a Kratos MS 80 (high resolution) apparatus. Purifications of products were performed by thin layer chromatography on silica gel. Products were crystallised from methanol/ethylether or dichloromethane/pentane.

Materials :

2-Iodobenzamide (**1**) : prepared from 2-iodobenzoic acid by treatment with cyanuric chloride and ammonia.[17]

2-Acetyl homoveratric acid (**2**)

To a solution of homoveratric acid (10 g, 51 mmol) in anhydrous methanol (60 ml) was added boron trifluoride etherate (9 ml) and the mixture was refluxed 1 h. Water was added and the ester was extracted with dichloromethane. After in vacuo removal of solvent, the oily ester was dissolved in acetic anhydride (25 ml) and perchloric acid (2 ml) was added to the cooled solution. The mixture was stirred two hours at room temperature.[7] After addition of ice the product was extracted by ethylacetate. After in vacuo removal of solvent, purifications was achieved by cristallisation in mixture CH_2Cl_2/ether/heptane affording white cristals of the methylester of **2** (11 g, 85%). M.p. 100-102°C. ^1H NMR δ 2.60 (s, 3H, $COCH_3$), 3.73 (s, 3H, CO_2CH_3), 3.90 (s, 2H, CH_2), 3.95 (s, 6H, 2 x OCH_3), 6.65 (s, 1H), 7.20 (s. 1H). MS. (E.I.) m/z 252 (M^+). Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.93 ; H, 6.34. Found : C, 61.99 ; H, 6.47.

The ester was heated in HCl 6N for 2 h at 60°C then extraction by ethylacetate gave the acid **2** as a white powder m.p. 168-170°C. ^1H NMR δ 2.60 (s, 3H, $COCH_3$), 3.85 (s 2H, CH_2), 3.95 (s, 6H, 2 x OCH_3), 6.85 (s, 1H), 7.35 (s, 1H).

3,4-Dimethoxy-6-iodobenzamide (**9a**)

3,4-dimethoxybenzoic acid was halogenated on the ortho position in 80% yield by the thallation-iodination procedure[10] and then converted to the amide. M.p. = 193-195°C. ^1H-NMR δ 3.90 (s, 6H, 2 x OCH_3), 6.13 (bs, 2H, $-NH_2$), 7.13 (s, 1H), 7.27 (s, 1H). MS m/z = 307 (M^+) 291.

2,3-Dimethoxy-6-iodobenzamide (**9b**)

2,3-dimethoxybenzoic acid was prepared according to a reported procedure[10] (yield 83%) and converted to the amide **9b**. M.p. 203-204°C. ^1H NMR δ 3.86 (s, 6H, 2 x OCH_3), 5.73 (b.s. 1H) and 5.86 (b.s. 1H) NH_2, 6.63 (d, J = 9 Hz, 1H), 7.43 (d, J = 9 Hz, 1H). MS. m/z 307 (M^+), 291.

Optimized procedure for $S_{RN}1$ access to (**3b**), (**11a**), (**11b**).

In a 100 ml two-necked Pyrex flask containing freshly sublimed t-BuOK (11 mmol), ammonia (50

ml) was condensed through a dry ice condenser cooled at -78°C. Under argon atmosphere, the ketone **2** (1,1 mmol) and the substrate : **1**, **9a**, or **9b** (1 mmol) were successively introduced. External irradiation of the ammonia solution (-33°C) was performed by a high pressure mercury lamp (Hanovia 400W) and the course of the reaction was monitored by analyzing aliquots (TLC). After consumption of the substrate (60 min), NH_4Cl was added and the solvent was evaporated in a well ventilated hood. Water (100 ml) was added to the residue and the alkaline solution was extracted with ethyl acetate (2 x 50 ml) to remove benzamide (when formed by competitive reduction). The aqueous phase, made acidic by 5% HCl was extracted by ethyl acetate (2 x 50 ml) and by sec-butanol (2 x 10 ml). The crude mixture of acidic products (**3a**, **10a** or **10b** along with **2** in excess) obtained after evaporating the combined organic phases was esterified (1 h reflux in anhydrous methanol (10 ml) containing boron trifluoride etherate (1 ml)) . After addition of water extraction with ethyl acetate afforded the corresponding esters which were purified by TLC. Yields are those of pure products refered to the starting iodoamide.

3-[2-(Methoxycarbonyl methyl) 4,5-dimethoxyphenyl]1(2H) isoquinolone (3b)

M.p. 181-182°C ; yield, 85% ; ^1H NMR δ 3.70 (s, 2H, $C\underline{H}_2$), 3.73 (s, 3H, $CO_2C\underline{H}_3$), 3.93 (s, 6H, 2 x $OC\underline{H}_3$), 6.60 (s, 1H, $\underline{H}_4$), 6.90 (s, 1H), 7.10 (s, 1H), 7.4-7.7 (m, 3H, arom.), 8.33 (d, J = 8 Hz, 1H, H_8), 11.2 (b. s, 1H, N$\underline{H}$). MS (E.I.), m/z 353 (M^+), 338 (M^+-CH_3), 321 (M^+-OCH_3), 293 (M^+-CO_2CH_3). Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98 ; H, 5.42. Found : C, 67.83 ; H, 5.29.

Reduction of 3b

Method A : To calcium borohydride, prepared by mixing in dry THF (20 ml) $NaBH_4$ (38 mg, 1 mmol) and anhyd. $CaCl_2$ (2.88 mg, 1 mmol) for 0.5 h, **3b** (176 mg, 0.5 mmol) dissolved in THF (10 ml) was added. After 5 h stirring at rt, separation by TLC afforded the hydroxyberberine **5a** (130 mg, 80%) along with **4a** (16 mg, 10%).

Method B : The ester **3b** (176 mg, 0.5 mmol) was refluxed in dry THF (40 ml) with $AlLiH_4$ (190 mg, 5 mmol) for 5 min. After addition of HCl 2N, and extraction by EtOAc, **4a** was obtained as the only product which was used without purification.

3[2 hydroxy ethyl 4,5-dimethoxyphenyl] 1(2H) isoquinolone (4a)

M.p. 210-213°C. ^1H NMR δ 2.86 (t, J = 5 Hz, 2H, $C\underline{H}_2$-CH_2OH), 3.86 (s, 3H, $OC\underline{H}_3$), 3.96 (s, 3H, $OC\underline{H}_3$), 4.10 (t, J = 5 Hz, 2H, $C\underline{H}_2OH$), 6.56 (s, 1H, H_4), 6.83 (s, 1H), 6.90 (s, 1H), 7.50 (t, J = 8 Hz, 1H), 7.66 (m, 2H), 8.36 (d, J = 8 Hz, 1H, H_8), 9.46 (b.s., 1H, N$\underline{H}$). MS (EI) m/z 325 (M^+). Exact mass calcd for $C_{19}H_{19}NO_4$: 325.1313. Found: 325.1299.

6-Hydroxy-8-oxoprotoberberine (5a)

M.p. 253-255°C. ^1H NMR δ 3.19 (m, J < 3 Hz, 2H, $C\underline{H}_2$), 3.95 (s, 3H, $OC\underline{H}_3$), 4.01 (s, 3H, $OC\underline{H}_3$), 6.75 (m, J < 3 Hz, 1H, CHOH), 6.80 (s, 1H ; $\underline{H}_4$), 6.94 (s, 1H ; $\underline{H}_1$), 7.27 (s, 1H ; $\underline{H}_{13}$), 7.45 (t, J = 8 Hz, 1H), 7.58 (d, J = 8 Hz, 1H, $\underline{H}_{12}$), 7.66 (t, J = 8 Hz, 1H), 8.39 (d, J = 8 Hz, 1H, $\underline{H}_9$). MS (EI) m/z 327 (M^+), 305 (M^+-OH_2). Exact mass calcd for $C_{19}H_{17}NO_4$: 323.1157. Found 323.1138.

8-Oxoprotoberberine (5b)

The isoquinolone alcohol **4a** (162 mg, 0.5 mmol) was added to a cooled (ice bath) solution of phosphorus tribromide (135 mg, 0.5 mmol) in pyridine (10 ml) and left overnight at rt. Water was added and the product extracted by ethylacetate. After removal of the solvent, the crude product was subjected to TLC to yield **5b**.[8,14] (76 mg, 50%). M.p. 188-189. ^1H NMR δ 2.93 (t, J = 6 Hz, 2H, CH_2-5), 3.96 (s, 3H, $OC\underline{H}_3$), 4.0 (s, 3H, $OC\underline{H}_3$), 4.40 (t, (J = 6 Hz, 2H N-$C\underline{H}_2$-6), 6.76 (s, 1H ; $\underline{H}_4$), 6.90 (s, 1H, $\underline{H}_1$), 7.30 (s, 1H, $\underline{H}_{13}$), 7.43 (m, 1H,), 7.60 (m, 2H), 8.43 (d, J = 8 Hz,1H, $\underline{H}_9$). MS (EI) m/z 307 (M^+), 292 (M^+-CH_3). Exact mass calcd for $C_{19}H_{17}NO_3$: 307.1208. Found: 307.1199.

N-methyl, 3-[2-(methoxy carbonyl methyl) 4,5-dimethoxyphenyl] 1(2H) isoquinolone (**6**).

The isoquinolone ester **3b** (353 mg, 1 mmol) (or the crude outcome of the $S_{RN}1$ reaction containing **3a**) was heated at 80°C for 1 h in DMF (10 ml) with ICH_3 (0.12 ml, 2 mmol) in the presence of K_2CO_3 (690 mg, 5 mmol). Work up and TLC yielded **6** as a viscous oil (323 ml, 88%). ^1H NMR δ 3.33 (s, 3H, N-CH_3), 3.56 (s, 3H, CO_2CH_3), 3.43 (d, J = 8 Hz, 1H) and 3.60 (d, J = 8 Hz, 1H, = $CH_2CO_2CH_3$), 3.90 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.43 (s, 1H, H_4), 6.76 (s, 1H), 6.90 (s, 1H), 7.50 (m, 2H), 7.63 (d, 1H), 8.46 (d, J = 8 Hz, 1H,H_8). MS (EI) m/z 367 (M^+), 352 (M^+-CH_3), 308 (M^+-CO_2CH_3). Exact mass calcd for $C_{21}H_{21}NO_5$: 367.1420. Found: 367.1421.

N-methyl 3-[2-hydroxyethyl 4,5-dimethoxyphenyl] 1(2H) isoquinolone (**7a**).

Reduction of the isoquinolone methyl ester **6** (183 mg, 0.5 mmol) by $LiAlH_4$ (190 mg, 5 mmol) in THF (40 ml) for 15 min at r.t. and classical work up gave **7a** as an oil (119 mg, 70 %). ^1H NMR δ 2.70 (m, 1H) and 2.80 (m, 1H, CH_2-CH_2OH), 3.30 (s, 3H, N-CH_3), 3.76 (m, 2H CH_2OH), 3.87 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.47 (s, 1H), 6.77 (s, 1H), 6.92 (s, 1H), 7.52 (m, 2H), 7.67 (t, J = 8 Hz, 1H), 8.47 (d, J = 8 Hz, 1H, H_8). MS (E.I.) m/z 339 (M^+), 321 (M^+-CH_3). Exact mass calcd for $C_{20}H_{21}NO_4$: 339.1470. Found: 339.1461.

2,3-Dimethoxy-5-methyl-6 oxo-benzo(c)phenanthridine (**8**)

The isoquinolone alcohol **7a** (119 mg, 0.35 mmol) dissolved in CH_2Cl_2, was stirred with pyridinium chlorochromate (1.5 eq) at r.t. for 2 h. Work up afforded **8**[9] (95 mg, 85). M.p. 190-192°C . ^1H NMR δ 4.06 (s, 9H, 2 x OCH_3 + N-CH_3), 7.22 (s, 1H, H_1), 7.60 (m, 3H, H_8, H_4, H_{12}) and 7.80 (t, J = 8 Hz, 1H, H_9), 8.13 (d, J = 9 Hz, 1H, H_{11}), 8.30 (d, J = 8 Hz, 1H, H_{10}), 8.54 (d, J = 8 Hz, 1H, H_7). MS (E.I.) m/z 319 (M^+), 304 (M^+-CH_3). Exact mass calcd for $C_{20}H_{17}NO_3$: 319.1208. Found: 319.1201.

3-[2-(Methoxycarbonyl methyl)-4,5-dimethoxy phenyl] 6,7-dimethoxy-1 (2H)-isoquinolone (**11a**)

$S_{RN}1$ coupling of **9a** (307 mg, 1 mmol) with **2** (262 mg, 1.1 mmol) followed by esterification of the crude **10a** gave the ester **11a** (297 mg, 72%). M.p. 207-209°C. ^1H NMR δ 3.65 (s, 2H, CH_2), 3.77 (s, 3H, CO_2CH_3), 3.92 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 6.48 (s, 1H, H_4), 6.83 (s, 1H), 6.95 (s, 1H), 6.96 (s, 1H), 7.78 (s, 1H, H_8), 9.87 (b.s. 1H, NH). MS (EI) m/z 413 (M^+), 398 (M^+-CH_3), 382 (M^+-OCH_3), 354 (M^+-CO_2CH_3). Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.94 ; H, 5.57. Found : C, 63.67 ; H, 5.54.

3-[2-(Methoxy carbonyl methyl-4,5 dimethoxyphenyl]-7,8-dimethoxy-1 (2H)-isoquinolone (**11b**)

$S_{RN}1$ coupling of **9b** (307 mg, 1 mmol) with **2** (262 mg, 1.1 mmol) followed by esterification of the crude **10b** gave the ester **11b** (280 mg, 68%). M.p. 196-200°C. ^1H NMR δ, 3.67 (s, 2H, CH_2), 3.76 (s, 3H, CO_2CH_3), 3.93 (s, 3H, OCH_3), 3.97 (s, 6H, 2 x OCH_3), 4.0 (s, 3H, OCH_3), 6.43 (s, 1H, H_4), 6.83 (s, 1H), 6.95 (s, 1H), 7.30 (d, J = 8 Hz, 1H), 7.39 (d, J = 8 Hz, 1H), 10.0 (b.s. 1H, NH). MS (E.I.) m/z 413 (M^+), 398 (M^+-CH_3), 382 (M^+-OCH_3), 354 (M^+-CO_2CH_3). Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.94 ; H, 5.57. Found : C, 63.75 ; H, 5.57.

3-[2-(Hydroxyethyl)-4,5-dimethoxyphenyl]6,7-dimethoxy 1(2H) isoquinolone (**12a**)

The isoquinolone ester **11a** (206 mg, 0.5 mmol) reduced according to method B gave **12a** (164 mg, 85%). M.p. 130-133°C. ^1H NMR δ 2.85 (m, 2H, CH_2-CH_2-OH), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.03 (s, 6H, 2 x OCH_3), 4.12 (m, 2H, CH_2OH), 6.6 (s, 1H, H_4), 6.83 (s, 1H) ; 6.92 (s, 1H), 6.98 (s, 1H, H_5), 7.75 (s, 1H, H_8), 12.09 (b.s., 1H, NH). MS (E.I.) m/z 385 (M^+), 367 (M^+-OH_2), 354 (M^+-CH_2OH). Exact mass calcd for $C_{21}H_{23}NO_6$: 385.1526. Found: 385.1505.

3-[2-Hydroxyethyl)-4,5-dimethoxyphenyl]-7,8-dimethoxy-1(2H)-isoquinolone (**12b**)

The isoquinolone ester **11b** (206 mg, 0.5 mmol) reduced according to method B gave **12b** (165 mg,

$OC\underline{H}_3$), 3.96 (s, 6H, 2 x $OC\underline{H}_3$), 4.10 (m, 2H, $C\underline{H}_2OH$), 6.5 (s, 1H, $\underline{H}_4$), 6.8 (s, 1H), 6.9 (s, 1H), 7.33 (d, J = 8 Hz, 1H) , 7.40 (d, J = 8 Hz, 1H). MS (EI) m/z 385 (M^+), 367 (M^+-H_2O), 354 (M^+-CH_2OH). Exact mass calcd for $C_{21}H_{23}NO_6$: 385.1526. Found: 385.1535.

2,3,10,11-Tetramethoxy-8-oxo-berberine (13a)

The isoquinolone alcohol **12a** (165 mg, 0.4 mol) treated with PBr_3/Pyr like **4a** gave **13a**[8,13,14] (80 mg, 51%). M.p. 198-199°C. lit. 196.5-198°C. ^1H NMR δ 2.87 (m, 2H, N-CH_2-$C\underline{H}_2$), 3.92 (s, 3H, $OC\underline{H}_3$), 3.97 (s, 3H, $OC\underline{H}_3$), 4.0 (s, 6H, 2 x $OC\underline{H}_3$), 4.33 (m, 2H, N-$C\underline{H}_2$), 6.76 (s-1H) and 6.86 (s-1H) H_1 and H_4, 6.95 (s, 1H, $\underline{H}_{12}$), 7.26 (s, 1H, $\underline{H}_{13}$), 7.83 (s, 1H, $\underline{H}_9$). MS (E.I.) m/z 367 (M^+), 352 (M^+-CH_3). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.68 ; H, 5.72. Found C, 68.27 ; H, 5.38.

2,3,9,10 Tetramethoxy-8-oxo-berberine (13b)

The isoquinolone alcohol **12b** (165 mg, 0.42 mol) treated with PBr_3 like **4a** gave **13b**[8] (75 mg, 46%). M.p. 186-188°C ; ^1H NMR δ 2.93 (m, 2H, N-$CH_2C\underline{H}_2$), 3.93 (s, 3H, $OC\underline{H}_3$), 3.95 (s, 3H, $OC\underline{H}_3$), 3.98 (s, 3H, $OC\underline{H}_3$), 4.02 (s, 3H, $OC\underline{H}_3$), 4.32 (m, 2H, N-$C\underline{H}_2$), 6.75 (s, 1H) and 6.77 (s, 1H) H_1 and H_4 ; 7.23 (s, 1H, $\underline{H}_{13}$), 7.32 (s, 2H, collapsed AB quartet $\underline{H}_{11}$ and $\underline{H}_{12}$). MS (EI) m/z 367 (M^+), 352 (M^+-CH_3). Anal. Calcd for $C_{21}H_{21}NO_5$ C, 68.88 ; H, 5.72. Found C, 68.37 ; H, 5.56.

N-methyl-3[2-(methoxycarbonylmethyl)-4,5-dimethoxyphenyl] 6,7 dimethoxy 1(2H) isoquinolone (14a)
3[2-(methoxycarbonyl methyl)-4,5-dimethoxyphenyl]1,6,7-trimethoxy isoquinoline (17a)

The isoquinolone ester **11b** treated like **3b** with CH_3I/K_2CO_3 in DMF gave **14a** (363 mg, 85%) and the O-methylated product **17a** (34 mg, 8%).

14a : oil ; ^1H NMR δ 3.30 (s, 3H, N-$C\underline{H}_3$), 3.43 (d, J = 16 Hz, 1H) and 3.56 (d, J = 16 Hz, 1H) : $C\underline{H}_2$-CO_2CH_3, 3.60 (s, 3H, $CO_2C\underline{H}_3$), 3.90 (s, 3H, $OC\underline{H}_3$), 3.96 (s, 3H, $OC\underline{H}_3$),4.0 (s, 3H, $OC\underline{H}_3$), 4.03 (s, 3H, $OC\underline{H}_3$), 6.32 (s, 1H, $\underline{H}_4$), 6.72 (s, 1H), 6.80 (s, 1H), 6.87 (s, 1H), 7.80 (s, 1H, $\underline{H}_8$). MS (E.I.) m/z 427 (M^+), 412 (M^+-CH_3), 396 (M^+-OCH_3), 3.68 (M^+-CO_2CH_3). Exact mass calcd for $C_{23}H_{25}NO_7$: 427.1631. Found: 427.1604.

17a : Oil ; ^1H NMR δ 3.60 (s, 3H, CO_2-$C\underline{H}_3$), 3.76 (m, 2H, $C\underline{H}_2$), 3.93 (s, 6H, 2 x $OC\underline{H}_3$), 4.03 (s, 6H, 2 x $OC\underline{H}_3$), 4.13 (s, 3H, $OC\underline{H}_3$), 6.86 (s, 1H, $\underline{H}_4$), 7.03 (s, 1H), 7.10 (s, 1H), 7.26 (s, 1H), 7.50 (s, 1H), M.S. (E.I.) m/z 427 (M^+), 412 (M^+-CH_3).

N-methyl-3-[2-methoxycarbonyl methyl)-4,5-dimethoxyphenyl] 7,8-dimethoxy 1(2H) isoquinolone (14b)
3[2-(methoxycarbonylmethyl)-4,5-dimethoxyphenyl] 1,7,8-trimethoxyisoquinoline (17b)

The isoquinolone ester **11b** (413 mg, 1 mol) treated like **11a** gave **14b** (367 mg, 86) and the O-methylated compound **17b** (34 mg, 8%).

14b : oil ; ^1H NMR δ 3.3 (s, 3H, N-$C\underline{H}_3$), 3.43 (d, J = 16 Hz, 1H) and 3.56 (d, J = 16 Hz, 1H) : $C\underline{H}_2$, 3.6 (s, 3H, $CO_2C\underline{H}_3$), 3.9 (s, 3H, $OC\underline{H}_3$), 4.0 (s, 6H, 2 x $OC\underline{H}_3$), 4.07 (s, 3H, $OC\underline{H}_3$), 6.30 (s, 1H, $\underline{H}_4$), 6.72 (s, 1H), 6.9 (s, 1H), 7.20 (d, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H). MS (E.I.) m/z 427 (M^+), 412 (M^+-CH_3), 396 (M^+-OCH_3), 368 (M^+-CO_2CH_3). Exact mass calcd for $C_{23}H_{25}NO_7$: 427.1631. Found: 427.1642

17b : M.p. 120-122°C. ^1H NMR δ 3.56 (s, 3H, $CO_2C\underline{H}_3$), 3.92 (s, 3H, $OC\underline{H}_3$), 3.93 (s, 3H, $OC\underline{H}_3$), 3.95 (s, 5H, $C\underline{H}_2$ + $OC\underline{H}_3$), 4.0 (s, 3H, $OC\underline{H}_3$), 4.16 (s, 3H, $OC\underline{H}_3$), 6.9 (s, 1H, $\underline{H}_4$), 7.13 (s, 1H), 7.33 (s, 1H), 7.46 (d, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H
), MS (E.I.) m/z 427 (M^+), 412 (M^+-CH_3). Exact mass calcd for $C_{23}H_{25}NO_7$: 427.1630. Found: 427.1648.

N-methyl-3-(2-hydroxyethyl)-4,5-(dimethoxyphenyl] 6,7 dimethoxy 1(2H) isoquinolone (15a)

The isoquinolone ester **14a** (241 mg, 0.5 mol) reduced according to method used for **6** gave **15a** (140 mg, 70%). M.p. 150°C., ^1H NMR δ 2.70 (m, 1H,) and 2.80 (m, 1H) : $C\underline{H}_2CH_2OH$, 3.30 (s, 3H, N-$C\underline{H}_3$), 3.76 (m, 2H, $C\underline{H}_2OH$), 3.87 (s, 3H, $OC\underline{H}_3$), 3.95 (s, 3H, $OC\underline{H}_3$), 3.98 (s, 3H, $OC\underline{H}_3$), 4.0 (s,

3H, $OC\underline{H}_3$), 6.33 (s, 1H), 6.70 (s, 1H), 6.76 (s, 1H), 6.83 (s, 1H), 7.67 (s, 1H), MS (E.I.) m/z 399 (M^+), 384 (M^+-CH_3). Exact mass calcd for $C_{22}H_{25}NO_6$: 399.1681 Found: 399.1683.

N-methyl-3-[2-(hydroxyethyl)-4,5-dimethoxyphenyl] 7,8-dimethoxy 1(2H) isoquinolone (15b)

Reduction of isoquinolone ester **14b** (214 mg, 0.5 mmol) by same method as above gave **15b** (140 mg, 70%) as an oil ^1H NMR δ 2.60 (m, 1H) and 2.76 (m, 1H) $C\underline{H}_2CH_2OH$, 3.26 (s, 3H, N-$C\underline{H}_3$), 3.76 (m, 2H, $CH_2O\underline{H}$), 3.86 (s, 3H, $OC\underline{H}_3$), 3.96 (s, 6H, 2 x $OC\underline{H}_3$), 4.03 (s, 3H, $OC\underline{H}_3$), 6.33 (s, 1H), 6.73 (s, 1H), 6.86 (s, 1H), 7.2 (d, J = 8 Hz, 1H) and 7.33 (d, J = 8 Hz, 1H). MS (E.I.) m/z 399 (M^+), 384 (M^+-CH_3). Exact mass calcd for $C_{22}H_{25}NO_6$: 399.1681. Found: 399.1670.

2,3,8,9-Tetramethoxy-5-methyl 6-oxo-benzo[c]phenanthridine (16a)

The isoquinolone alcohol **15a** (140 mg, 0.35 mmol) treated like **7a** by $ClCrO_3$-Pyr gave **16a** (110 mg, 82%). M.p. 245-247°C. ^1H NMR δ 4.06 (s, 3H, $OC\underline{H}_3$), 4.08 (s, 6H, 2 x $OC\underline{H}_3$), 4.09 (s, 3H, $OC\underline{H}_3$), 4.13 (s, 3H, N-$C\underline{H}_3$), 7.22 (s, 1H, $\underline{H}_1$), 7.61 (s, 1H) and 7.62 (s, 1H) $\underline{H}_4$ and $\underline{H}_{10}$, 7.63 (d, J = 9 Hz, 1H, $\underline{H}_{12}$), 7.95 (s, 1H, $\underline{H}_7$), 8.04 (d, J = 9 Hz, 1H, $\underline{H}_{11}$). MS (E.I.) m/z 379 (M^+), 364 (M^+-CH_3). Exact mass calcd for $C_{22}H_{21}NO_5$: 379.1420. Found: 379.1419.

2,3,7,8-Tetramethoxy-5-methyl 6-oxo-benzo(c)phenanthridine (16b)

The isoquinolone alcohol **15b** (140 mg, 0.35 mol) treated like **7a** gave **16b** (115 mg, 86%). M.p. 125-128°C. ^1H N.M.R. δ 3.96 (s, 3H, $OC\underline{H}_3$), 4.0 (s, 3H, $OC\underline{H}_3$), 4.03 (s, 6H, 2 x $OC\underline{H}_3$), 4.08 (s, 3H, N-$C\underline{H}_3$), 7.16 (s, 1H, $\underline{H}_1$), 7.40 (d, J = 8 Hz, 1H, $\underline{H}_9$), 7.50 (s, 1H, $\underline{H}_4$), 7.58 (d, J = 9 Hz, 1H, $\underline{H}_{12}$), 8.03 (d, J = 8 Hz, $\underline{H}_{10}$ + d J = 9 Hz, $\underline{H}_{11}$). MS (E.I.) m/z 379 (M^+), 364 (M^+-CH_3). Exact mass calcd for $C_{22}H_{21}NO_5$: 379.1420. Found: 379.1405.

REFERENCES AND NOTES

1. Takao, N., Kamigauchi, M., and Okada, M., *Helv. Chim. Acta*, **1983**, *66*, 473 and ref. therein.
2. Yagi, A., Nonaka, G., Nakayama, S., and Nishioka, I., *Phytochem.*, **1977**, *16*, 1197.
3. Among a number of benzo(c)phenanthridine alkaloids of various substitution pattern and various oxidation levels which were obtained from corresponding berberines : a) 6-Oxychelerythrine : Onda, M., and Yamaguchi, H., *Chem. Pharm. Bull.*, **1979**, *27*, 2076. b) Corynoline analog : Onda, M., Yamaguchi, H., and Harigaya, Y., *Chem. Pharm. Bull.*, **1980**, *28*, 866. c) Chelerythrine and dihydrochelerythrine : Hanaoka, M., Motonishi, T., and Mukai, C., *J. Chem. Soc., Chem. Comm.*, **1984**,, 718. d) Fagaronine and Nitidine : Hanaoka, M., Yamagishi, H., Marutani, M., and Mukai, C., *Tetrahedron Lett*, **1984**, *25*, 5169. e) Sanguilutine and dihydro sanguilutine : Hanaoka M., Kobayashi, N., Shimada, Ken Ichi and Mukai, C., *J. Chem. Soc., Perkin I*, **1987**, 677.
4. Corydalic acid methyl ester has been obtained by a biomimetic synthesis from corysamine which belongs to the berberine family : a) Hanaoka, M., Yoshida, S., and Mukai, C., *J. Chem. Soc., Chem. Comm.*, **1984**, 1703 and by multi step total synthesis by two groups. b) Cushman, M., and Wong, W.C., *J. Org. Chem.*, **1984**, *49*, 1278. c) Clark, R.D., and Jahangir, *J. Org. Chem.*, **1989**, *54*, 1174.
5. Beugelmans, R., and Bois-Choussy, M., *Synthesis*, **1981**, 729.
6. Beugelmans, R., Ginsburg, H., and Bois-Choussy, M., *J. Chem. Soc., Perkin I*, **1982**, 1149
7. Kamal, A., Akram Sandhu, M., *Tetrahedron Letters*, **1963**, *10*, 611
8. Ninomiya, I., Naito, T., and Takasugi, H., *J. Chem. Soc., Perkin I*, **1975**, 1720.
9. Ninomiya, I., Yamamoto, O., and Naito, T., *J. Chem. Soc., Perkin I*, 1983, 2165.
10. Dyke, S.F., and Tiley, E.P., *Tetrahedron*, **1975**, *31*, 561.

11. Rossi, R.A., de Rossi, R.H., Aromatic Substitution by the $S_{RN}1$ Mechanism, chap. 9, p. 239, A.C.S. Monograph, American Chemical Society, Washington, D.C., 1983.
12. Kametani, T., Sugai, T., Shoji, Y., Honda, T., Satoh, F., and Fukumoto, K., *J. Chem. Soc., Perkin I*, **1977**, 1151.
13. Haimova, M.A., Ognyanov, V.I., and Mollov, N.M., *Synthesis*, **1980**, 845.
14. Lenz, G.R., *J. Org. Chem.*, **1974**, *39*, 2839.
15. Ishii, H., Chen, I.S., and Ishikawa, T., *J. Chem. Soc., Perkin I*, **1987**, 671.
16. For a recent review : Simanek, V., in the Alkaloids, Vol. 26, Chap. 4, p. 185, A. Brossi Ed. Academic Press, 1985.
17. Venkataraman, K., and Wagle, D.R., *Tetrahedron Lett*, **1979**, *20*, 3037.