HETEROCYCLES, Vol.55, No.3, pp. 545 - 555, Received, 7th, December, 2000

A SINGLET OXYGEN MEDIATED NEW ACCESS TO HYDROXYINDOLENINE-CATHARANTHINE DERIVATIVES BY TWO SEQUENTIAL OXIDATIONS

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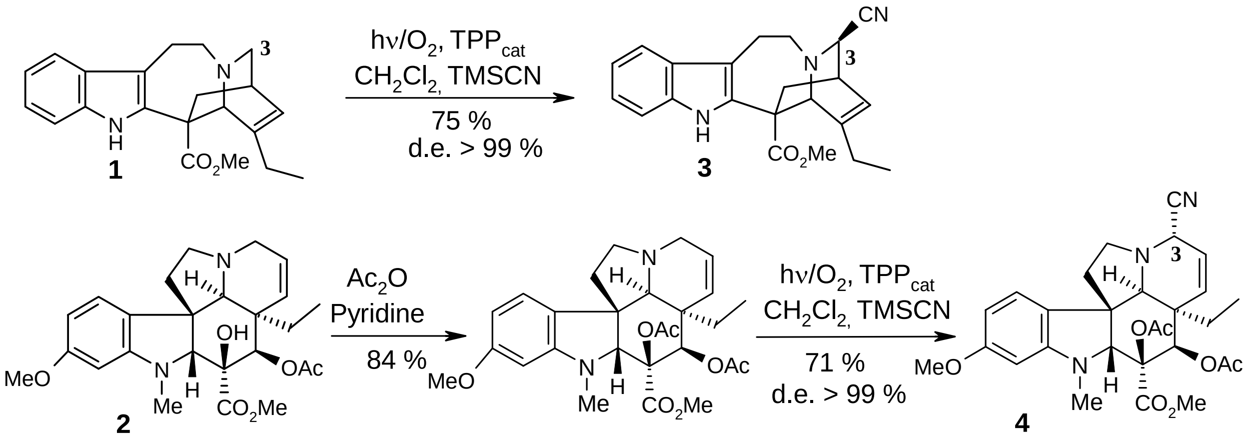
Abstract - Formation of hydroxyindolenine derivatives by photoinduced oxidation by singlet oxygen of intermediate 3β-cyanocatharanthine (**3**) allows us to synthesize under mild conditions new alkaloids derivatives, 3β-cyano-7β-hydroxyindolenine-catharanthine (**5**), 3β-cyano-7β-hydroxyindolinecatharanthine (**6**) and 7β-hydroxy-indolenine-catharanthine (**7**), bearing protected indole moities.

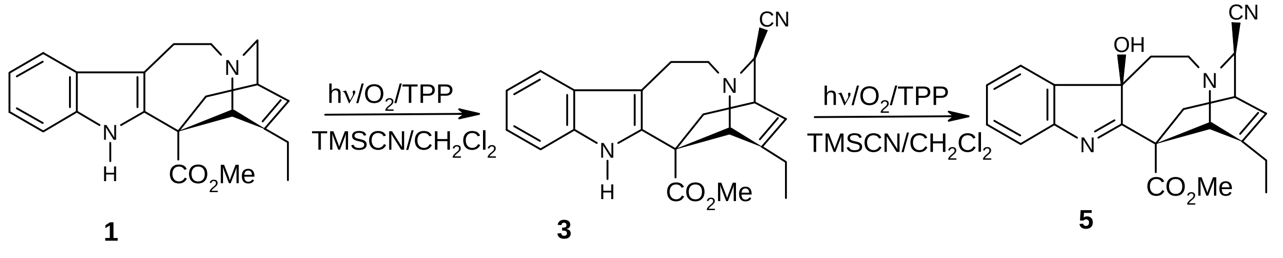
Vinca alkaloids are important anticancer agents known to diminish microtubule dynamics and assembly, resulting in the arrest of cell division at metaphase. They are used clinically for a variety of hematologic and solid tumors.[1] In our search concerning oxidation of some alkaloid tertiary amines by single electron transfer we were interested in the development of photochemical approaches, which could lead to new derivatives of catharanthine (**1**). The coupling of new functionnalized catharanthine derivatives with vindoline (**2**) moiety would lead to new bisindole alkaloids.

In a previous paper,[2] we described the photocyanation of catharanthine (**1**) and vindoline (**2**) leading respectively to the 3β-cyanocatharanthine (**3**) and 3β-cyano-16-acetylvindoline **(4**). High selectivities were observed and we obtained new derivatives of those alkaloids with high yields. The selectivity and mechanism of these oxidations were discussed (Scheme 1). We describe here a new reactivity observed during the photooxidation by visible light of catharanthine (**1**), leading to the formation of new hydroxyindolenine derivatives. It is noteworthy that we never observed such species with other indole alkaloids in these conditions.[3]



Scheme 1

The photocyanation of catharanthine (**1**) gives stereoselectively the 3β-cyanocatharanthine (**3**), as previously reported, and we obtain by further oxidation the formation of the corresponding hydroxyindolenine, the 3β-cyano-7β-hydroxyindolenine-catharanthine (**5**) (Scheme 2). The typical procedure used to realize the photocyanation of catharanthine (**1**) proceeds by the irradiation with visible light (λ>495 nm), in the presence of catalytic amount of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) as photosensitizer and trimethylsilyl cyanide (TMSCN), under oxygen bubbling. Thus, photocyanation of catharanthine (**1**) leads quantitatively to 3β-cyanocatharanthine (**3**) after 35 min.[2] A similar reaction sequence applied to this cyano compound leads quantitatively to the 3β-cyano-7β-hydoxyindolenine catharanthine (**5**) (74% yield after crystallisation) after 75 min. Noteworthy is the fact that the 3β-cyano-7β-hydroxyindolenine catharanthine (**5**) can be obtained directly from catharanthine (**1**) without isolation of the 3β-cyanocatharanthine (**3**) in 72% global yield after recrystallization.



Scheme 2

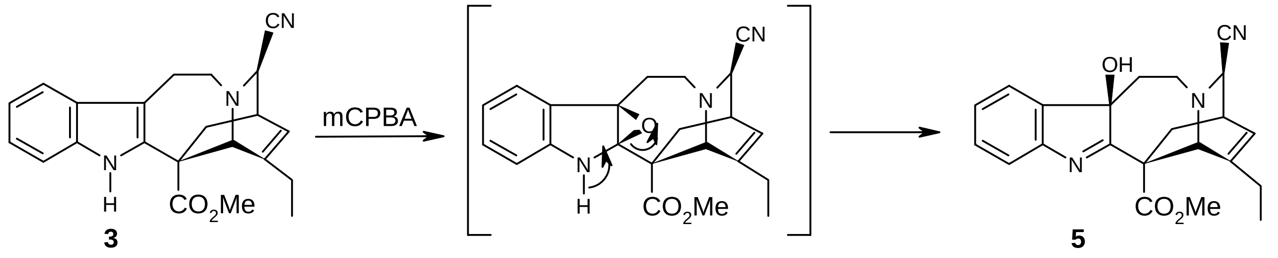
The structure of compound (**5**) has been unambiguously ascertained by complete spectroscopic determinations. Infrared spectroscopic data reveals the presence of the characteristic cyano and indolenine absorption peaks at 2220 cm^{-1} and 1555 cm^{-1} respectively. The presence of an hydroxy-substituted indolenine ring was proved from the observation of fragments at m/z 132 and a 16 mass units increase of the molecular weight in the MS spectrum. A complete ^{1}H NMR investigation with nOe connectivities permits us to assign all the chemical shifts and the absolute configuration :

-The chemical shifts at δ 187.7 for C_2 and δ 87.1 for C_7 are characteristic of the indolenine ring as well as the diseappearance of the N_a-H proton.

-Moreover, we find out a significative nOe connection between the H-3α proton and the H-6α proton indicating that the stereochemistry of the carbon atom C_3 is similar to that of 3β-cyano catharanthine (**3**).

-A significative nOe connection between the proton of the hydroxy function and the H-21 proton is characteristic of a β position of the hydroxyl group.

In order to confirm this structure by chemical ways, oxidation of the cyanated (**3**) by 3-chloroperoxybenzoic acid was performed in CH_2Cl_2 at room temperature. The peracid reacts preferentially with the C_2-C_7 indole double bond rather than oxidation of the nitrogen atom N_b desactivated by the presence of the cyano group substituted on the carbon next to the nitrogen atom. The reaction provided the expected product (**5**) but with a lower yield (30 %) than under our photooxidation conditions (Scheme 3). Such a result points out the selectivity and the mild conditions of our photooxidation method compared to chemical way

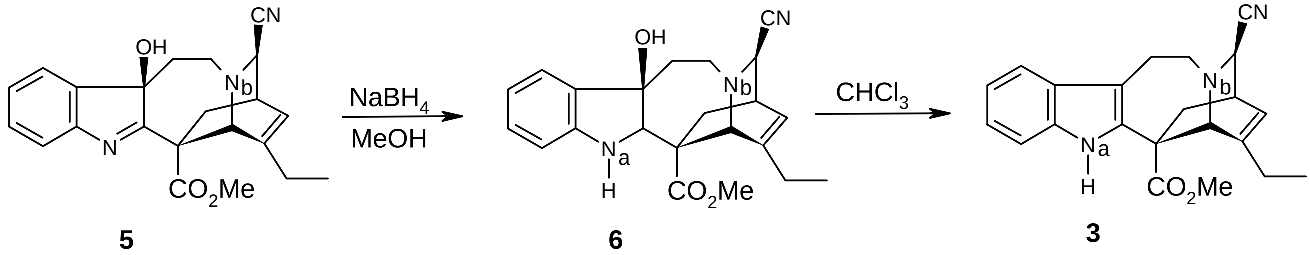


Scheme 3

This 3β-cyano-7β-hydroxyindolenine catharanthine (**5**) is of particularly value as it could lead by coupling with vindoline (**2**) in Polonovski-Potier conditions to new derivatives of highly functionalized anhydrovinblastine.

Moreover, we investigate the selective reduction of the hydroxyindolenine moiety in order to synthetize potential new anhydrovinblastine derivatives.

The addition of an excess of $NaBH_4$ to methanol solution of the 3β-cyano-7β-hydroxyindolenine catharanthine (**5**) provides the new cyano compound 3β-cyano-7β-hydroxyindoline catharanthine (**6**) (Scheme 4). Such a result is noteworthy because it is well-known that sodium borohydride reduces easily the α-amino nitrile function. But in this case, as previously observed during the oxidation of vindoline moiety,[2] the possibility of hydrogen bond between the hydrogen of the hydroxy group on the C-2 carbon atom and the nitrogen N_b lone pair prevents the iminium cation intermediate formation during the reduction. So, the reduction reaction takes place selectively on the indolenine moiety.



Scheme 4

To conclusively assign the structure of the 3β-cyano-7β-hydroxyindoline catharanthine (**6**), MS spectrum, ^{1}H and ^{13}C NMR and IR spectrum were investigated.

-The characteristic cyano and indoline absorption peaks at 2220 cm^{-1} and 1610 cm^{-1} respectively are present.

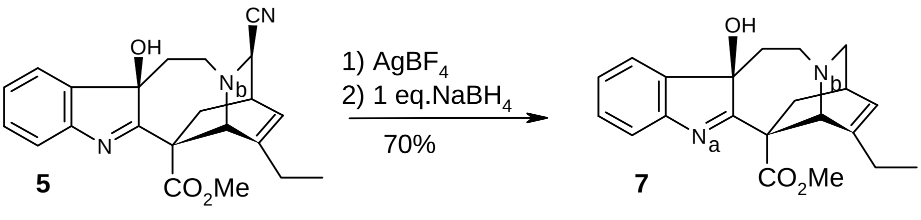
-A 2 mass units increase of the molecular weight detected by MS compared to the corresponding indolenine **5** confirms the reduction of the imine.

-The chemical shift at δ 87.2 for C_7 is characteristic of the indoline ring. The signal at δ 187.7 for the quaternary C_2 in the indolenine (**5**) is shifted significantly upfield to δ 75.1 by reduction of (**5**).

-The presence of the N_a-H proton at δ 3.61 ppm proves the reduction.

The 3β-cyano-7β-hydroxyindoline catharanthine (**6**) has been left in $CDCl_3$ in a NMR tube and leads quantitatively in three days to the 3β-cyanocatharanthine (**3**) by rearomatisation of the indole ring (Scheme 4). Interestingly, overoxidation by our mild photochemical conditions indole compound constitutes a protection of the indole ring *via* an hydroxy-substituted indolenine ring, which permits to avoid the protection of the indole nitrogen atom usually transformed in carbamate (Boc-protected compounds) or *N*-silyl group.[4]

The α-amino nitrile function of the 3β-cyano-7β-hydroxyindolenine catharanthine (**5**) was reduced by generating the iminium cation intermediate in presence of $AgBF_4$ before addition of the reductive agent. To avoid the simultaneous reduction of the indolenine moiety, just one equivalent of $NaBH_4$ is used to only reduce the iminium cation. Thus, the 7β-hydroxyindolenine catharanthine (**7**) is obtained in 70% yield (Scheme 5).



Scheme 5

In a study concerning the fragmentation-coupling of catharanthine and vindoline by trifluoroacetic anhydride reported in the literature,[5] several products formed from the final fragmentation intermediate have been identified among which the 7-hydroxyindolenine catharanthine. The stereochemistry of the C_7 carbon atom was not assigned.

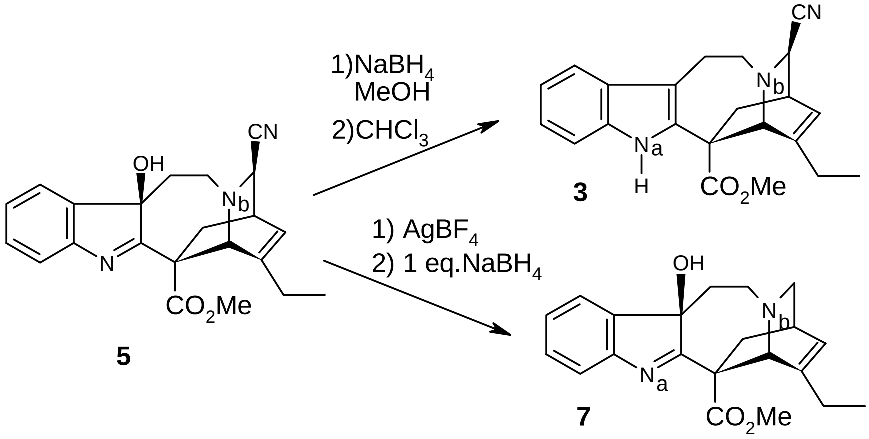
Complete spectroscopic determinations allow us to conclusively assign the structure of the 3β-cyano-7β-hydroxyindolenine catharanthine (**5**).

-IR data revealed the absence of the characteristic cyano absorption peak at 2220 cm^{-1} and the presence of the indolenine absorption peak at 1555cm^{-1} .

-A 25 mass units decrease of the molecular weight in the MS spectrum compared to the corresponding 3β-cyano-7β-hydroxyindolenine catharanthine (**4**) confirmed the reduction of the cyano group.

-Complete ^1H and ^{13}C NMR investigations permit us to assign all the chemical shifts and the absolute configuration. The diseappearance of the N_a-H proton and chemical shifts at δ 189.1 for C_2 and δ 87.5 for C_7 are in good agreement with reported values for other hydroxyindolenine rings.[5,6]

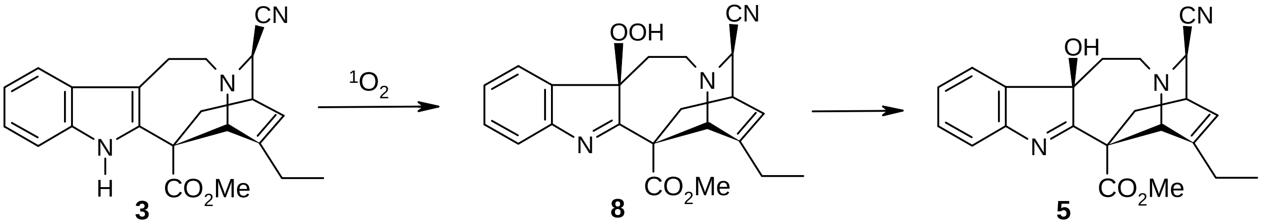
These results clearly show the duality of the reduction conditions leading selectively either to the cyano reduced compound, or to the indolenine moiety reduction (Scheme 6)



Scheme 6

We previously mentioned that such formation of hydroxyindolenine had never been observed from oxidation of other indole alkaloids in our photochemical conditions, in presence of TMSCN.

The *in situ* reduction of an hydroperoxyindolenine catharanthine intermediate (**8**) could explain the formation of the 3β-cyano-7β-hydroxyindolenine catharanthine (**5**) (Scheme 7).



Scheme 7

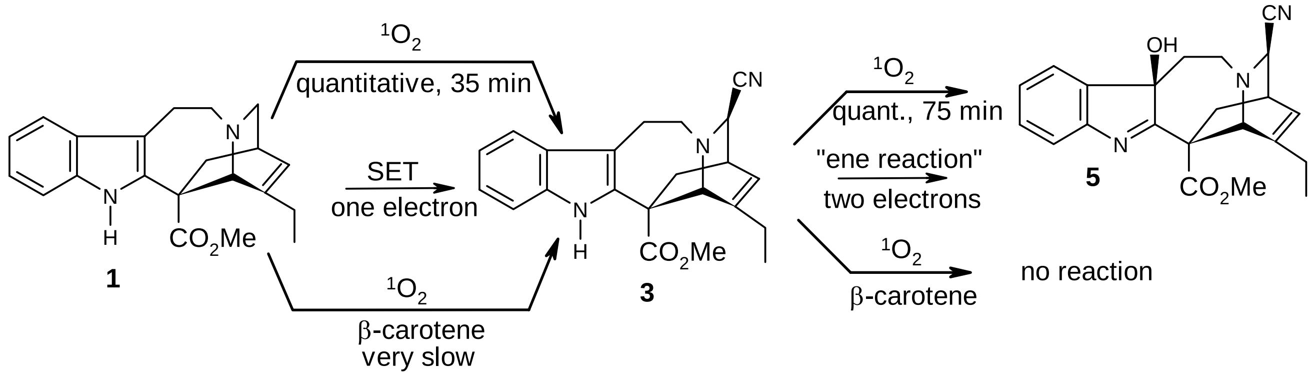
The presence of such an intermediate (**8**) has been described in the literature about the photooxidation of tryptamine derivatives, bearing a tertiary carbon atom C_2.[7] Typically, the formed hydroperoxide can close to the 1,2-dioxetane and then undergoes scission to carbonyl and amide fragments. 2,3-Disubstituted indoles are known to be susceptible to air oxidation to yield 3-hydroperoxyindolenines as primary products which rapidly proceed to give ring cleavage products.[7,8]

Singlet oxygen could be involved for the formation of the hydroperoxyindolenine (**8**) by ene-type addition on the indole moiety. TPP has been reported to be an efficient singlet oxygen producer.[9,10] It is understood that the regioselective addition of singlet oxygen, implicated in the enzymic and photogenic processes, may be ascribed to the nucleophilic character located at the C_7 position of the indole nucleus.[11] Therefore, the formation of compound (**5**) involving two successive oxidations is particularly interesting because two different mechanisms are involved.

The first mentionned oxidation of catharanthine (**1**) leading to the 3β-cyanocatharanthine (**3**) involves a single electron transfer photoinduced oxidation of the amine by the singlet oxygen generated by energy transfer between excited sensitizer and molecular oxygen (Scheme 8). A non-ambigous singlet oxygen oxidation by SET of some tertiary amines has been previously reported from such species.[12]

In order to confirm that the oxidizing species is singlet oxygen in our photochemical process, we made photooxidation of catharanthine (**1**) in presence of a well known singlet oxygen quencher as β-carotene ($k_q \approx 10^{10}$ M^{-1} s^{-1}).[10] The reaction was not totally inhibited but the rate was significantly slower. This result is in agreement with our hypothesis. In the case of single electron transfer reaction, the rate is controlled by diffusion ($\approx 10^{10-12}$ M^{-1} s^{-1}) so this reaction could not be totally quenched by a competitive reaction.

In contrast, the same quenching experiment performed to the oxidation of 3β-cyanocatharanthine (**3**) totally inhibites the formation of the 3β-cyano-7β-hydroxyindolenine catharanthine (**5**), even after few hours. The nitrogen atom in the 3β-cyanocatharanthine (**3**) is desactivated by the presence of the α-aminonitrile function, increasing its oxidation potential about 0.5V compare to the one of the catharanthine (**1**).[13] This gap prevent the nitrogen atom oxidation from singlet oxygen by single electron transfer. In this case, the 3β-cyanocatharanthine (**3**) is oxidized by the electrophilic classical reactivity of singlet oxygen (Scheme 8). A two electrons mechanism is now involved. The addition of singlet oxygen in an "ene" reaction way with electron-rich olefins like enamines had been assumed by theoretical calculations to be a nonconcerted process involving an ionic peroxide such as a zwitterion as the initial intermediate leading rapidly to the formation of the hydroperoxide. Typically, "ene" reactions proceed with a rate about 10^{4-6} M^{-1} s^{-1}. In this case, the inhibition reaction of singlet oxygen β-carotene, which is several decade faster, could efficiently and totally quench the oxidation process.



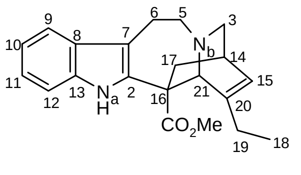
Scheme 8

In conclusion, our photosentized oxydation conditions allow us to prepare selectively with high yield many derivatives of catharanthine (**1**): 3β-cyanocatharanthine (**3**), 3β-cyano-7β-hydroxyindolenine catharanthine (**5**), 3β-cyano-7β-hydroxyindoline catharanthine (**6**) and 7β-hydroxyindolenine catharanthine (**7**). All those compounds involved in a Polonovski-Potier coupling reaction with vindoline moiety (**2**) could lead to new anhydrovinblastine derivatives. We managed to selectively reduced either the α-aminonitrile function or the indolenine group. We have pointed out the dual oxidation mechanism by singlet oxygen involving either a single electron transfer or a two electrons mechanism.

EXPERIMENTAL SECTION

All materials were obtained from commercial suppliers and used without further purification. IR spectra (cm^{-1} with polystyrene calibration, in $CHCl_3$) were recorded on a Perkin-Elmer 457 spectrophotometer . ^1H-NMR (200 MHz in $CDCl_3$, reference : TMS, δ_H=0.0 ppm) and ^{13}C-NMR (50.3 MHz in $CDCl_3$, reference : $CDCl_3$, δ_C=77.0 ppm) spectra were recorded on a Bruker AM200 spectrometer. Chemical shift data are reported in parts per million downfield from TMS, and coupling constant (J) are reported in hertz (Hz). GC-MS spectra (EI and CI) were performed on a HP G1019A (70 ev, *m/z*) spectrometer. Flash column and thin-layer chromatography were done by using Aluminum oxid 90 (Merck, act. II-III).

In the attribution of the NMR signals, the structures have the following numbering systems :



3β-Cyano-7β-hydroxyindolenine catharanthine (5). To a solution of 212 mg (0.59 mmol) of the 3β-cyanocatharanthine (**3**) in CH_2Cl_2 (13 mL) were added TMSCN (157 µL, 1.17 mmol, 2 éq.) and a catalytic amount of TPP (0.02 mmol). The mixture was irradiated under oxygen bubbling with a 1800W Xenon lamp through a UV cut-off glass filter ($\lambda \geq 495$ nm) at 20°C during 75 min. After reaction, monitored by TLC (Al_2O_3, CH_2Cl_2), 30 mL of 10 % Na_2CO_3 was added in the resulting reaction mixture. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting cyano product was filtered on aluminum oxide (hexane/AcOEt 8 : 2) and was recrystallized from MeOH to give 164 mg (74 %) of 3β-cyano-7β-hydroxyindolenine catharanthine (5), as a crystalline white solid. mp 198 °C. Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found : C, 69.85; H, 5.98; N, 11.02. IR (KBr)/cm^{-1} : 3350, 2950, 2230, 1730, 1555; ^1H NMR($CDCl_3$, 200 MHz) : δ 7.45 (m, 1H, H-9), 7.34 (m, 2H, H-12, H-11), 7.26 (m, 1H, H-10), 5.94 (m, 1H, H-15), 4.69 (d, 1H, $J_{21,15}$1.4, H-21), 3.81 (m, 1H, H_β-5), 3.64 (d, 1H, $J_{3\alpha,14}$1.7, H_α-3), 3.62 (s, 3H, OCH_3), 3.18 (m, 1H, H_α-5), 3.04 (m, 2H, H-14, H_α-17), 2.74 (d, 1H, $J_{OH,16\alpha}$1.7, OH), 2.16 (m, 3H, H_β-6, H-19), 1.99 (dd, 1H, $J_{17\beta,17\alpha}$14.4, $J_{17\beta,14}$3.0, H_β-17), 1.72 (m, 1H, H_α-6), 1.06 (t, 3H, $J_{18,19}$7.3, H-18); ^{13}C NMR ($CDCl_3$, 50.3 MHz,)187.74 (C-2), 170.79 ($COOCH_3$), 151.50 (C-13), 150.41 (C-20), 140.71 (C-8), 129.81 (C-11), 127.03 (C-10), 121.55 (C-12), 120.92 (C-9), 120.23 (C-15), 119.81 (CN), 87.18 (C-7), 58.01 (C-21), 56.80 (C-16), 52.91 ($COOCH_3$), 49.18 (C-3), 45.42 (C-5), 37.58 (C-17), 34.97 (C-14), 33.45 (C-6), 26.58 (C-19), 10.80 (C-18). MS (EI) m/z (relative intensity) 377 ($M^{+\cdot}$, 15), 336 (3), 318 (13), 277 (10), 232 (6), 217 (19), 186 (18), 160 (100), 157 (19), 146 (24), 132 (19), 130 (15), 107 (57), 77 (13), 59 (5).

Oxidation of 3β-cyanocatharanthine (3) with peracid. To a solution of 157 mg (0.43 mmol) of the 3β-cyanocatharanthine (**3**) in CH_2Cl_2 (15 mL) were added 132 mg (0.65 mmol) of 3-chloroperoxybenzoic acid in MeOH (5 mL). After stirring during 15 min, 30 mL of 10 % Na_2CO_3 was added at 0°C in the resulting reaction mixture. The product was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting product was purified by preparative layer chromatography on aluminum oxide (CH_2Cl_2 /MeOH 98 : 2). 48 mg (30%) of 3β-cyano-7β-hydroxyindolenine catharanthine (**5**) was obtained as an amorphous solid.

3β-Cyano-7β-hydroxyindoline catharanthine (6). 3β-Cyano-7β-hydroxyindolenine catharanthine (**5**) (150 mg, 0.40 mmol) was dissolved in MeOH (5mL) and excess of $NaBH_4$ (30 mg, 0.8 mmol)was addded at 0°C. The reaction was monitored by TLC (Al_2O_3, CH_2Cl_2). After stirring for 90 min, H_2O (1 mL) was added. The solvent was evaporated and the product was extracted with

CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting cyano product was purified by preparative layer chromatography on aluminum oxide ($CHCl_3$). 75.8 mg (50 %) of 3β-cyano-7β-hydroxyindoline catharanthine (**6**) was obtained as an amorphous solid. Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64.; N, 11.07. Found : C, 69.45; H, 6.78; N, 11.24. IR (cm^{-1}, neat): 3350, 2950, 2220, 1730, 1610; ^{1}H NMR($CDCl_3$, 200 MHz) : δ 7.14 (d, 1H, $J_{9,10}$7.6, H-9), 7.12 (dd, 1H, $J_{11,10}$7.6, $J_{11,12}$7.6, H-11), 6.76 (dd, 1H, $J_{11,10}$7.6, $J_{10,9}$7.6, H-10), 6.56 (d, 1H, $J_{12,11}$7.6, H-12), 5.85 (m, 1H, H-15), 4.14 (s, 1H, H-2), 4.03 (d, 1H, $J_{21,15}$1.4, H-21), 3.72 (m, 1H, H_{β}-5), 3.67 (s, 3H, OCH_3), 3.61 (d, 1H, $J_{3\alpha,14}$2.8, H_{α}-3), 3.61 (m, 1H, N_aH), 2.99 (m, 2H, H-14, H_{α}-5), 2.52 (dd, 1H, $J_{17\alpha,17\beta}$14.4, $J_{17\alpha,14}$4.7, H_{α}-17), 2.38 (s, 1H, OH), 2.22 (m, 3H, H_{β}-6, H-19), 1.85 (m, 1H, H_{α}-6), 1.63 (dd, 1H, $J_{17\beta,17\alpha}$14.4, $J_{17\alpha,14}$1.3, H_{β}-17), 1.08 (t, 3H, $J_{18,19}$7.3, H-18); ^{13}C NMR ($CDCl_3$, 50.3 MHz,) 174.82 ($COOCH_3$), 152.60 (C-13), 147.89 (C-20), 133.67 (C-8), 129.78 (C-11), 122.60 (C-10), 120.83 (C-15), 119.08 (C-9), 120.46 (CN), 109.53 (C-12), 83.22 (C-7), 75.15 (C-2), 59.31 (C-21), 58.41 (C-16), 52.86 ($COOCH_3$), 52.21 (C-3), 46.08 (C-5), 33.51 (C-17), 33.29 (C-14), 27.98 (C-6), 26.46 (C-19), 11.04 (C-18). MS (EI) m/z (relative intensity) 379 ($M^{+\cdot}$, 57), 361 (30), 350 (21), 336 (34), 332 (25), 320 (19), 306 (20), 291 (25), 276 (25), 273 (40), 244 (27), 232 (20), 214 (100), 192 (23), 180 (43), 169 (49), 157 (37).

7β-Hydroxyindolenine catharanthine (7). 3β-Cyano-7β-hydroxyindolenine catharanthine (**5**) (102 mg, 0.27 mmol) was dissolved in dry THF (4 mL) under argon atmosphere and a solution of $AgBF_4$ (104 mg, 0.54 mmol) in dry THF (2 mL) was addded. The reaction was monitored by TLC (Al_2O_3, CH_2Cl_2/MeOH 95.5 :0.5). The solvent was evaporated and the crude product was dissolved in MeOH (6 mL). Then, 12 mg (0.29 mmol) of $NaBH_4$ was added at 0°C. After stirring for 15 min, H_2O was added and the MeOH was evaporated under reduced pressure. The product was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting product was purified by preparative layer chromatography on aluminum oxide (CH_2Cl_2/MeOH 95.5 :0.5). 67 mg (70 %) of 7β-hydroxyindolenine catharanthine (**7**) was obtained as an amorphous solid. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found : C, 71.46; H, 6.76; N, 7.90. IR (cm^{-1}, neat): 3350, 2950, 1730, 1555; ^{1}H NMR($CDCl_3$, 200 MHz) : δ 7.45 (m, 1H, H-9), 7.34 (m, 2H, H-12, H-11), 7.26 (m, 1H, H-10), 5.92 (m, 1H, H-15), 4.58 (d, 1H, $J_{21,15}$1.5, H-21), 3.80 (m, 1H, H_{β}-5), 3.60 (s, 3H, OCH_3), 3.03 (m, 1H, H_{α}-5), 2.92 (ddd, 1H, $J_{17\alpha,17\beta}$13.1, $J_{17\alpha,14}$3.1, $J_{17\alpha,13\beta}$3.1, H_{α}-17), 2.90 (s, 1H, OH), 2.69 (m, 3H, H-14, H-3), 2.27 (m, 1H, H-19), 2.07 (m, 2H, H_{β}-6, H_{β}-17), 1.92 (m, 2H, H_{α}-6, H-19), 1.03 (t, 3H, $J_{18,19}$7.3, H-18); ^{13}C NMR ($CDCl_3$, 50.3 MHz,) 189.13 (C-2), 171.69 ($COOCH_3$), 151.68 (C-13), 148.37 (C-20), 141.34 (C-8), 129.49 (C-11), 126.68 (C-10), 123.14 (C-

12), 121.43 (C-9), 120.71 (C-15), 87.55 (C-7), 59.28 (C-21), 57.38 (C-16), 52.70 ($COOCH_3$), 46.97 (C-5), 46.58 (C-3), 39.41 (C-17), 33.03 (C-6), 31.01 (C-14), 26.39 (C-19), 10.59 (C-18). MS (EI) m/z (relative intensity) 352 ($M^{+\cdot}$, 5), 335 (2), 293 (2), 216 (2), 194 (3), 184 (5), 158 (5), 156 (5), 135 (100), 121 (6), 107 (42), 93 (4), 77 (4).

Oxidation of catharanthine (1) in presence of β-carotene. To a solution of 170 mg (0.506 mmol) of the catharanthine (**1**) in CH_2Cl_2 (60 mL) were added TMSCN (150 μL, 1.125 mmol) and a catalytic amount of TPP (0.02 mmol). 100 mg of β-carotene was added and the mixture was irradiated under oxygen bubbling with an Hanovia Q 81 (80 W) lamp through a UV cut-off glass filter ($\lambda \geq 495$ nm) at 20°C. The mixture was irradiated during 4 hours and then 30 mL of 10 % Na_2CO_3 was added in the resulting reaction mixture. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting product was filtered on aluminum oxide (hexane/AcOEt 8 : 2) and was recrystallized from MeOH to give 36 mg (20 %) of 3β-cyanocatharanthine (**3**).

ACKNOWLEDGEMENT

The authors are grateful to MENRT for a thesis grant to PR and they dedicace this paper to Professor J. Santamaria deceased in 1996.

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