An efficient synthesis of (±) 4-hydroxy-9-methoxy-5,11-dimethyl-6H-1,2,3,4-tetrahydro-benzo[b]carbazole†

Mohamed Larbi Bengaouer & Abbes Boukhari*
Laboratory of Organic Synthesis, Modeling and Optimization of Chemical Processes, Department of Chemistry Badji Mokhtar-Annaba University, B.O. 12, 23000, Annaba, Algeria
E-mail: boukhari.abbas@univ-annaba.org

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In this study, new tetracyclic compounds similar to benzo[b]carbazole have been synthesized. Their structures have been characterized by IR, 1H and 13C NMR, mass spectral and CHN analysis, and correspond to 4-hydroxy-9-methoxy-5,11-dimethyl-6H-1,2,3,4-tetrahydro-benzo[b]carbazole and 9-methoxy-5,11-dimethyl-6H-1,2,3,4-tetrahydro-benzo[b]carbazole. The condensation of 6-methoxy-1,4-dimethyl-9H-carbazole with ethyl 4-chloro-4-oxo-butanoate gives ethyl 4-(6-methoxy-1,4-dimethyl-9H-carbazol-3-yl)-4-oxobutanoate when using tin tetrachloride as catalyst. After reduction of the carbonyl function, the ethyl 4-(6-methoxy-1,4-dimethyl-9H-carbazol-3-yl)butanoate has been obtained. After the saponification reaction, intramolecular cyclisation of the acid form in presence of trifluoroacetic anhydride is followed by reduction of the ketone group by sodium borohydride which leads to the formation of the hydroxylated compound. Therefore, 9-methoxy-5,11-dimethyl-6H-1,2,3,4-tetrahydro-benzo[b]carbazole is obtained in the intramolecular cyclization reaction of 1,4-dimethyl-6-methoxy-3-(4-oxobutyl)-9H-carbazole.

Keywords: 6-Methoxy-1,4-dimethyl-9H-carbazole, trifluoroacetic anhydride, intramolecular cyclisation, Lemieux-Johnson oxidation, tin tetrachloride

Results and Discussion

It was therefore decided to synthesize a derivative of ellipticine whose D pyridine ring (I), (Figure 1), was replaced by a hydroxylated saturated hydrocarbon ring, the 4-hydroxy-9-methoxy-5,11-dimethyl-6H-1,2,3,4-tetrahydro-benzo[b]carbazole 8, by using the intramolecular cyclisation reaction, in presence of the trifluoroacetic anhydride, (CF₃CO)₂O (Ref 10), on the compound 6-methoxy-1,4-dimethyl-carbazole 2 (taken as the starting product), unlike C (Asche et al.¹¹, and F.O. McCarthy et al.¹²), where the D ring is phenyl. Thereafter, the hydroxyl ion could be used to graft a sugar or an amino sugar in order to obtain more stable molecules, soluble in water and bio-available. Among the products obtained that interest us the most, is the substitution product that took place on the carbon position 3 of the carbazole. It should be noted that a mixture of three products has been obtained (series of products 4a₁ and 4b₁). The derivatives, 4a₁ and 4b₁, have been obtained with good yield, and others products (4a₂, 4a₃ and 4b₂, 4b₃), in traces. Standard electrophilic substitution reactions on the readily available 1,4-dimethyl-9H-carbazole are generally non-selective, that will occur either at position 3, 6 or 9, while methods for the selective substitution at a given position are lacking.¹³

Heterocyclic derivates form a very important class of organic compounds because of their wide application in medicine, agriculture, and technology.¹ Pyrido[4,3-b]carbazole and a large numbers of its derivatives and analogues are well known for their potent antitumor activities and anti-mitotic properties. Many of its derivatives which have different DNA binding affinities show antitumor and cytotoxic effects and exhibit promising results in the treatment of breast-cancer metastases and brain tumors which have reached significant synthetic interest.⁶,⁷ Other pyrido[4,3-b]carbazole alkaloids like ellipticine (Figure 1) are also of significant synthetic interest due to their potential biological applications. Unfortunately, they present a major drawback namely their toxicity (renal and cardiovascular disorders). To remedy their toxicity some of these molecules have been subject to many structural changes in the hope of achieving equally active compounds, accompanied by lesser side effects. According to the literature, one of the strategies developed is to replace the pyridine heterocycle by other rings such as pyrrole, thiophene or pyrimidine but never by a saturated ring.

† Dedicated to the memory of Professor François Tillequin
Indeed, Letois et al.\textsuperscript{14} have confirmed in their study that attempts of mononitration of the 6-methoxy-1,4-dimethyl-9\textit{H}-carbazole always led to the formation of a dinitro derivative, on the carbon in position 3 and 8, even with only one equivalent of nitric acid. The reaction is then followed by the reduction of 4\textit{a} by the method of Clemmensen\textsuperscript{15} (Scheme I), which gave the compound 5\textit{a}. According to the technique of Lemieux-Johnson\textsuperscript{16}, the following step is an oxidation of the terminal double bond by OsO\textsubscript{4}, which would lead to an aldehyde function at the chain end. The product is the compound 6\textit{a}, which is then subjected to the action of SnCl\textsubscript{4} to give the product 7 (Scheme II) after intramolecular cyclisation reaction. Saponification of compound 5\textit{b} led to acid 6\textit{b}. The intramolecular cyclisation reaction with trifluoroacetic anhydride leads to the compound 9. Treatment of
ketone 9 with sodium borohydride in methanol at RT gave the hydroxyl derivative 8 (Scheme III).

Rings A and B (Figure 1) were provided from the starting compound which was the 5-methoxy-indole 1 by employing the method of Cranwell and Saxton\(^7\) with hexane-2,5-dione to produce the 6-methoxy-1,4-dimethyl-9H-carbazole 2. Therefore, the ring C has been formed when we obtained the product of this reaction yielding 65% as indicated in Scheme IV.

Then we brought our personal touch and replaced the pyridinic ring D by cyclohexane to form compound 8. Access to this compound was carried out via a Friedel-Crafts acylation reaction on 6-methoxy-1,4-dimethylcarbazole 2 with 1-chloro-4-pentenoic acid 3a (Scheme V).
Each acylium ion formed in presence of SnCl$_4$ occupies, by the reaction of electrophilic substitution, positions 3, 7 and 8 (Figure 2) of the carbazole 2, which provides us with compound 4a$_1$ (Table I). The products were isolated by column chromatography (CH$_2$Cl$_2$-cyclohexane: 76/24) and their structure has been determined by inspection of their spectral data and is shown in Table II.

The same reaction was carried out with aluminum chloride as Lewis acid and resulted in a product whose mass spectrum (DCI/NH$_3$) had a molecular ion M$^+$ at m/z 202.1 in $^{13}$C NMR spectrum. The $^1$H NMR spectra have confirmed signal at δ 9.74, which thus marks the presence of the proton of aldehyde. It was found that the peak at δ 9.74, which belongs to the aldehyde CHO group, was lost during the intramolecular cyclisation reaction in anhydrous dichloromethane at low temperature (−78°C) in presence of SnCl$_4$ (Scheme II). Neither the $^1$H NMR spectrum nor the IR detected the presence of compound 8.

While studying the literature, all cases of cyclisation reactions from an aldehyde in presence of Lewis acid, we obtained the formation of an alcohol through following mechanism (Scheme III).

Following this failure, we decided to carry out the intramolecular cyclisation reaction by replacing the 1-chloro-4-pentenoic acid 3a by ethyl 4-chloro-4-oxobutanoate 3b (Scheme V).
The same procedure was applied to compound 4b to obtain ethyl 3-(1,4-dimethyl-6-methoxy-9H-carbazol-3-yl)-4-oxobutanoate 5b (Scheme I) which was subjected to saponification to give the carboxylic acid derivative 6b. The use of the trifluoroacetic anhydride upon the compound 6b allowed arriving at compound 8, having an alcohol function in 4-position (Scheme VII).

Indeed, the 5b ester was dissolved in a mixture of ethanol-water (1/1) and 4 equivalents of KOH was then added. The result was remarkable because the acid was obtained quantitatively. The mass spectrum (DIC/NH₃) had a molecular ion [M]+ at m/z 312 corresponding to the molecular formula C₁₉H₂₁NO₃. The IR showed the characteristic bands of a carboxylic acid compound with a broad band at 3600 cm⁻¹ corresponding to the −OH stretching vibration and a band at 1725 cm⁻¹ of the carbonyl function. The use of a standard method applied for the cyclisation of aryl alkanoic acids by activation of carbonyl in order to create an intermediate mixed anhydride by the action of (CF₃CO)₂O upon carboxylic acid, which allowed easy access to the corresponding ketone 9 by reaction of the acid 5b with (CF₃CO)₂O in dichloromethane, with a yield of 98%. Finally, the reduction of 9 resulted in the alcohol 8 by action of NaBH₄ in methanol (100%). The mass spectrum (DIC/NH₃) has a molecular ion [M]+ at m/z 295 corresponding to the molecular formula C₁₉H₂₃NO₂ and another ion with m/z 278 corresponding to M⁺ −OH. The ¹H NMR showed, a particular signal at δ 5.15 which is a proton corresponding to the −CHOH group in this molecule (Scheme VII). In the ¹³C NMR spectrum, the characteristic peak (Ar-CHOH) appeared at δ 65.0.

Experimental Section
Melting points were measured on a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4250 instrument. ¹H NMR spectra were recorded on a Bruker HX 270 (200 MHz) and ¹³C NMR on a Bruker AC 300 instrument (75 MHz) using CDCl₃ as solvent. Chemical shifts were measured in δ (ppm) taking TMS as internal standard and coupling constants were in Hertz. Deuterated chloroform signal for carbon spectra (triplet, δ 77.26). Mass spectra were measured on a Nermag R-10-1OC (EI) or AEI MS-902 (high...
resolution) instrument. Merck silica gel 60H was used to conduct short-column chromatography. TLC plates were developed in various dichloromethane-hexanes, ethyl acetate-hexane solvent systems. Visualization of spots was effected with iodine vapors. The acid chloride 3a was prepared by reacting SOCl₂ with a pentanoic acid solution in anhydrous CH₂Cl₂ and heating to reflux. Commercially available ethyl 4-chloro-4-oxo-butanoate 3b was used.

Procedure for the preparation of product 4a

The 6-methoxy-1,4-dimethyl-9H-carbazole 2 (2.7 g, 12 mmol) was dissolved in anhydrous dichloromethane (10-15 mL). The 2 eq. of 1-chloro-4-pentenoic acid (1.4 g, 12 mmol) was then added with stirring at RT under an argon atmosphere for 5 min. This was then followed by a drop-wise addition of 2 eq. of tin tetrachloride (2.8 mL, 24 mmol). After 5 min stirring, the reaction was then stopped by adding 1 mL of triethylamine (0.73 g, 6.24 mmol) and the solvent was evaporated under reduced pressure. The residue obtained was diluted in dichloromethane and washed with 1N sodium hydroxide solution. The organic layers were dried over anhyd. Na₂SO₄, filtered and the solvent evaporated. The residue was purified by silica gel column chromatography.

1-(6-Methoxy-1,4-dimethyl-9H-carbazol-7-yl)pent-4-en-1-one, 4a₂: ¹H NMR (270 MHz, CDCl₃): δ 2.52 (2H, m, H-12), 2.53 (3H, s, CH₃), 2.87 (3H, s, CH₃), 3.21 (2H, t, H-11), 4.03(3H, s, O-CH₃), 5.00 (1H, dd, ³J = 10, ⁴J = 2, H-14b), 5.10 (1H, dd, ³J = 17, ⁴J = 2, H-14a), 5.95 (1H, m, H-13), 6.92 (1H, d, ³J = 7, H-3), 7.15 (1H, d, ³J = 7, H-2), 7.60 (1H, d, ³J = 2, H-5), 7.95 (1H, d, ³J = 2, H-5).

1-(6-Methoxy-1,4-dimethyl-9H-carbazol-8-yl)pent-4-en-1-one, 4a₃: ¹H NMR (270 MHz, CDCl₃): δ 2.60 (2H, m, H-12), 2.53 (3H, s, CH₃), 3.30 (2H, t, H-11), 4.00 (3H, s, O-CH₃), 5.00 (1H, dd, ³J = 10, ⁴J = 2, H-14b), 5.10 (1H, dd, ³J = 17, ⁴J = 2, H-14a), 6.00 (1H, m, H-13), 6.90 (1H, d, ³J = 7, H-3), 7.15 (1H, d, ³J = 7, H-2), 7.60 (1H, d, ³J = 2, H-5), 8.15 (bs, NH); CI-MS: m/z (Irel,%): 308[M+H]⁺ (100), 292(4), 226(2). Anal. Calcd for C₂₀H₂₁NO₂: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.24; H, 6.78; N, 4.61%.

Scheme VII — Reaction for obtaining compound 8 via the ethyl 3-chloro-4-oxobutanoate 3b
Preparation of product 4b

6-Methoxy-1,4-dimethyl-9H-carbazole 2 (2 g, 8.89 mmol) was dissolved in anhydrous dichloromethane (10-15 mL). 3 eq. of ethyl 4-chloro-4-oxo-butanoate were added dropwise to the reaction mixture at RT under an argon atmosphere for 5 min. This was followed by a drop-wise addition of tin tetrachloride (10-15 mL). 3 eq. of ethyl 4-chloro-4-oxo-butanoate, 4b

Ethyl 4-(6-methoxy-1,4-dimethyl-9H-carbazol-3-yl)-4-oxobutanoate, 4b: CH₂Cl₂-hexanes: 74/26. Yield 2.029 g (43%). IR (KBr): 3360 (N-H), 3980 (C-H), 1740 (C=O), 1670 (C=O), 1580 (C=C), 1406 (C-C), 1330 (Ar-C), 1347 (Ar-C), 1410 (Ar-C), 1536 (Ar-C), 1670 (C=O); 1H NMR (270 MHz, CDCl₃): δ 1.30 (3H, t, CH₃), 2.53 (3H, s, CH₃), 2.80 (2H, t, H-12), 3.00 (3H, s, CH₃), 3.32 (2H, t, H-11), 3.95 (3H, s, O-CH₂), 4.20 (2H, q. CH₂CH₂), 7.10 (1H, dd, δJ = 9, δJ = 2, H-7), 7.42 (1H, d, δJ = 9, H-8), 7.58 (1H, s, H-2), 7.79 (1H, s, H-5), 8.09 (bs, NH); 13C NMR (75 MHz, CDCl₃): δ 14.1 (Aliphat.CH₂), 16.4 (Ar-CH₂), 17.4 (Ar-CH₂), 28.9 (Aliphat.CH₂), 36.3 (Aliphat.CH₂), 55.9 (O-CH₂), 60.6 (O-CH₂), 106.7 (Ar-CH), 111.2 (Ar-C), 113.8 (Ar-CH), 116.3 (Ar-CH), 122.1 (Ar-C), 124.9 (Ar-C), 126.7 (Ar-CH₂), 128.9 (Ar-C), 133.0 (Ar-C), 134.7 (Ar-C), 141.0 (Ar-C), 153.6 (Ar-C), 173.5 (O-C=O), 201.9 (C=O); CI-MS: m/z (Irel,%): 354[M+H]⁺ (5), 308(3), 280(100), 252(21). Anal. Calcd for C₁₇H₂₂NO₂: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.42; H, 6.59; N, 3.99%.

6-Methoxy-1,4-dimethyl-3- pent-4- enyl-9H-carbazole 5a and ethyl 4-(6-methoxy-1,4-dimethyl-9H-carbazol-3-yl)butanoate, 5b

Preparation of the catalyst zinc amalgam

12 g wool of zinc were mixed with 1.2 g (4.43 mmol) mercury chloride (HgCl₂). To this, 15 mL of water and 0.6 mL of 1N hydrochloric acid were added. The mixture was stirred for 5 min and decanted.

Reduction of 4a,4b to obtain 5a,5b

A mixture of this amalgam of zinc was added to 1 g (3.24 mmol) 4a or 1 g (2.83 mmol) 4b in 40 mL (0.68 mol) of acetic acid and 5 mL (55 mmol) of concentrated hydrochloric acid. The reaction mixture was heated for about 1 h, then poured into 400 mL water and extracted with dichloromethane (3x30 mL). The combined organic layers were dried over anhyd. Na₂SO₄.

Crude weight of 5a: Yield 0.93 g (97%). 1H NMR (270 MHz, CDCl₃): δ 1.73 (2H, m, H-11), 2.17 (2H, m, H-12), 2.49 (3H, s, CH₃), 2.78 (2H, t, H-10), 2.80 (3H, s, CH₃), 3.95 (3H, s, O-CH₂), 4.99 (1H, dd, δJ = 10 Hz, δJ = 2 Hz, H-14b), 5.07 (1H, dd, δJ = 17, δJ = 2, H-14a), 5.87 (1H, m, H-13), 7.04 (1H, dd, δJ = 9, δJ = 2, H-7), 7.25 (1H, s, H-2), 7.36 (1H, d, δJ = 9, H-8), 7.75 (1H, d, δJ = 2, H-5), 7.75 (bs, NH); CI-MS: m/z (Irel,%): 293 [M+H]⁺ (57), 252 (9), 238 (100), 223 (15), 195 (21), 174 (50), 167 (6), 147 (40), 133 (12), 117 (4), 104 (8). Anal. Calcd for C₁₀H₁₄N₂O: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.90%; H, 7.95; N, 4.67%.

Crude weight of 5b: Yield 0.95 g (95%). 1H NMR (270 MHz, CDCl₃): δ 1.28 (3H, t, CH₂CH₃), 1.95 (2H, m, H-11), 2.40 (2H, t, H-10), 2.55 (3H, s, CH₃), 2.98 (3H, s, CH₃), 2.82 (2H, t, H-12), 3.95 (3H, s, O-CH₂), 4.15 (2H, q, CH₂CH₂), 7.02 (1H, s, H-2), 7.08 (1H, d, δJ = 9, δJ = 2, H-7), 7.36 (1H, d, δJ = 9, H-8), 7.75 (1H, d, δJ = 2, H-5), 7.80 (bs, NH); Anal. Calcd for C₁₆H₂₂NO₂: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.21; H, 7.49; N, 4.15%.

9-Methoxy-5,11-dimethyl-6-carbazol-3- yl)butanal, 6a: To 0.65 g (2.20 mmol) of 5a was dissolved in a water / diethyl ether mixture (1/1), then cooled to 0°C, it was added 0.06 g (0.23 mmol) of osmium tetroxide (OsO₄) in 2.5% solution in 2-methyl-2-propanol. Sodium metaperiodate (NaIO₄, 1.39 g, 6.5 mmol) was then gradually added. The reaction mixture was allowed to stir overnight. The aqueous phase was isolated and extracted with ether (3x30 mL). The combined organic phase was washed with pure water, then brine and finally dried over anhyd. Na₂SO₄, the solvent evaporated and the residue purified by flash chromatography to obtain compound 6a (Hexane/ethyl acetate: 90/10). Yield 0.514 g (79%). 1H NMR (270 MHz, CDCl₃): δ 2.51 (3H, s, CH₃), 2.53 (2H, m, H-11), 2.81 (3H, s, CH₃), 2.83 (2H, m, H-10), 3.91 (2H, t, H-12), 3.92 (3H, s, O-CH₂), 7.02 (1H, dd, δJ = 9, δJ = 2, H-7), 7.37 (1H, d, δJ = 9, H-8), 7.72 (1H, d, δJ = 2 Hz, H-5), 7.77 (bs, NH), 9.74 (s, 1H, CHO); CI-MS: m/z (Irel,%): 293 [M+H]⁺ (100), 278(11), 238(4). Anal. Calcd for C₁₀H₁₄NO: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.28; H, 7.19; N, 4.81%.

9-Methoxy-5,11-dimethyl-6H-1,2,3,4-tetrahydrobenzo[b]carbazole, 7

Tin tetrachloride (SnCl₄, 0.09 mL, 0.34 mmol) was added drop-wise at RT under an argon atmosphere to a solution of aldehyde 6a (0.1 g, 0.34 mmol) diluted in anhydrous dichloromethane (10 mL). The mixture was stirred for 5 min. The reaction was then stopped by the addition of a few drops of triethylamine. After evaporation of solvent, the residue obtained was diluted in dichloromethane and washed with 1N
sodium hydroxide solution. Organic phases were
dried over anhyd Na₂SO₄ and the solvent evaporated.
The pure compound 7 was obtained after purification
by flash chromatography by hexane/ethyl acetate
94/6. Yield 0.06 g (64%). ¹H NMR (270 MHz, CDCl₃): δ 9.0 (4H, m, 2CH₂), 2.30 (3H, s, CH₃), 2.75 (3H, s,
CH₃), 2.80 (4H, m, 2CH₂), 3.93 (3H, s, O-CH₃), 7.02
(1H, dd, 3J = 9, 4J = 2, H-7), 7.33 (1H, d, 3J = 9,
H-8), 7.68 (bs, NH), 7.73 (d, 1H, 4J = 2 Hz, H-5);
EI-MS: m/z (Irel, %) 279 [M⁺] (100), 265 (51), 249 (9),
237 (15), 205 (5), 140 (75), 125 (25), 109 (62), 96
(58), 84 (44), 70 (29); CI-MS: m/z (Irel, %) 280
[M+H]+'(13), 256 (100), 240 (9). Anal. Calcld for
C₁₉H₂₃NO: C, 81.68; H, 7.49; N, 4.97%.

4-(6-Methoxy-1,4-dimethyl-9H-carbazol-3-yl)butanoic
acid, 6b

0.1 g of ester 5b (0.28 mmol) was dissolved in a
mixture of 4 mL water / ethanol (1/3). Then 0.17 g of
potassium hydroxide (3 mmol) was added. The
mixture was stirred at RT overnight. Thereafter, water
and alcohol were removed; the residue was dissolved
in water and then extracted with ether. The ether
phase was discarded. The aqueous phase was
neutralized with a molar solution of sulfuric acid and
extracted with ether, dried over anhyd. Na₂SO₄ and
the solvent evaporated to give 0.09 g of 6b. Yield
0.09 g (99%). ¹H NMR (270 MHz, CDCl₃): δ 1.95
(2H, m, H- 11), 2.43 (2H, m, H-10), 2.48 (3H, s,
CH₃), 2.80 (3H, s, CH₃), 2.82 (2H, m, H- 12), 6.98
(1H, s, H-2), 7.00 (1H, dd, 3J = 9, 4J = 2, H-7), 7.36
(1H, d, 3J = 9, H-8), 7.70 (1H, d, 4J = 2, H-5), 7.09
(bs, NH, D₂O exchangeable); ¹³C NMR (75 MHz,
CDCl₃): δ 15.7 (ArCH₂), 19.5 (ArCH₂), 25.3 (Aliphat.CH₂,CH₂),
29.6 (Aliphat.CH₂), 35.6 (Aliphat.CH₂), 55.9 (O-CH₃),
102.0 (Ar-CH), 106.1 (Ar-C), 109.8 (Ar-CH), 112.1
(Ar-CH), 117.5 (Ar-C), 119.5 (Ar-CH), 124.0 (Ar-C);
126.9 (Ar-C), 132.4 (Ar-C), 133.7 (Ar-C), 134.5 (Ar-CH),
155.6 (Ar-C), 173.4 (COOH). Anal. Calcld for
C₁₉H₂₃NO₃: C, 73.29; H, 6.80; N, 4.50. Found: C,
73.32; H, 6.87; N, 4.48%.

1,2,3,4-Tetrahydro-5,11-dimethyl-9-methoxy-6H-benzo[b]-carbazol-4-one, 9

Acid 6b (0.256 g, 0.82 mmol) was dissolved in
10 mL of anhydrous dichloromethane and treated with
1 mL of trifluoroacetic anhydride (CF₃CO)₂O, at RT.
After 5 min, the reaction mixture was concentrated
under reduced pressure to provide a crude residue
which was taken up in a mixture of dichloromethane
and a saturated solution of NaHCO₃. The aqueous solution
was separated and extracted twice with 10 mL of
dichloromethane. The combined organic solutions
were stirred for 5 min with 15 mL of a 10% sodium
hydroxide solution. The aqueous phase was
adjusted by two times 10 mL of dichloromethane. The
combined organic solution was dried over anhyd. Na₂SO₄,
filtered and then distilled under reduced pressure to afford 9.
Yield 0.254 g (99%). IR (KBr): 3345 (N-H), 2960 (C-H),
2920 (C-H out of plane), 1920 (C=O), 1685 (C=O),
1590 (C=C), 1500 (C=C), 1310 (C-O), 1240 (C-H out of plane);
¹H NMR (270 MHz, CDCl₃): δ 2.18 (2H, m, H-2), 2.72
(2H, t, H-1), 2.83 (6H, s, 2CH₃), 3.11 (2H, t, H-3), 3.94
(3H, s, O-CH₃), 7.11 (1H, dd, 3J = 9, 4J = 2, H-8), 7.38
(1H, d, Ar, 3J = 9, H-7), 7.79 (1H, s, 6H-10), 8.05 (bs,
NH, D₂O exchangeable); ¹³C NMR (75 MHz,
CDCl₃): δ 15.8 (ArCH₂), 16.3 (ArCH₂), 23.1 (CH₂), 27.4 (CH₂),
41.0 (CH₂), 56.3 (O-CH₃), 107.4 (Ar-CH), 111.4 (Ar-CH),
115.5 (Ar-C), 125.0 (Ar-C), 127.9 (Ar-C), 133.5 (Ar-C),
136.3 (Ar-C), 153.8 (Ar-C), 197.0 (Ar-C=O). Anal.
Calcld for C₁₉H₁₉NO₃: C, 77.79; H, 6.53; N, 4.77. Found:
C, 77.76; H, 6.56; N, 4.71%.

4-Hydroxy-9-methoxy-5,11-dimethyl-6H-1,2,3,4-
tetrahydro-benzo[b]carbazole, 8

To a solution of ketone 9 (0.087 g, 0.29 mmol) in
40 mL of methanol, sodium borohydride (0.044 g,
1.16 mmol) was added. After 15 min of stirring at RT,
the solution was concentrated under reduced pressure.
The residue was taken up in 10 mL of dichloromethane
and washed with 10 mL of water. The combined
organic phase was dried over anhyd. Na₂SO₄ and
concentrated after filtration to give the corresponding
alcohol 8. Yield 0.073 g (84%). IR (KBr): 3350 (N-H
and O-H), 2980 (C-H), 2920 (C-H), 1650 (C=O),
1580 (C=C), 1470 (C=C), 1320 (C-O), 1120 (C-O),
990 (C-H out of plane); ¹H NMR (270 MHz, CDCl₃):
δ 2.20 (2H, m, H-2), 2.62 (3H, s, CH₃), 2.71 (2H, t,
H-1), 2.72 (3H, s, CH₃), 3.07 (2H, m, H-3), 3.94 (3H, s,
O-CH₃), 5.15 (1H, t, CH-OMH), 7.05 (1H, dd, 3J = 9 Hz,
4J = 2, H-8), 7.35 (1H, d, 3J = 9, H-7), 7.74 (1H, d,
4J = 2, H-10), 7.79 (bs, NH, D₂O exchangeable); ¹³C NMR
(spectrum (75 MHz, CDCl₃): δ 15.9 (ArCH₂), 17.6 (ArCH₂), 24.1 (CH₂),
29.7 (CH₂), 32.4 (CH₂), 56.1 (O-CH₃), 65.8 (Ar-CHOH),
106.6 (Ar-C), 110.7 (Ar-CH), 112.5 (Ar-CH), 1129 (Ar-C),
125.3 (Ar-C), 128.5 (Ar-C), 134.9 (Ar-C), 153.4 (Ar-C); CI-MS:
m/z (frel, %) 296[M+H]+'(5), 295(23), 278 [M– OH]+(100).

Found: C, 77.31; H, 7.27; N, 4.48%.

Conclusion

In summary, we have developed new derivatives of
benzo[b]carbazole, namely 4-hydroxy-9-methoxy-5,11-

dimethyl-6H-1,2,3,4-tetrahydro-benzo[b]carbazole 8 and 9-methoxy-5,11-dimethyl-6H-1,2,3,4-tetrahydro-benzo[b]carbazole. The contribution of the method of Cranwell and Saxton for obtaining compound 2 has been of great benefit. Indeed, formation of the compound 8 bypasses the saponification step of the ethyl 3-(6-methoxy-1,4-dimethyl-9H-carbazol-3-yl)butanoate 5b, made from the 6-methoxy-1,4-dimethyl-9H-carbazole 2, then by a saponification reaction for the obtaining the 6b derivative acid. Furthermore, the following synthesis has allowed us to build the saturated cycle using the Friedel-Crafts reaction in trifluoroacetic anhydride. The yields obtained in the different reactions are quite significant. If the product would prove to be effective in the treatment of cancer, hydroxyl function will subject in the future for grafting sugars or amino sugars, which would increase the solubility and bioavailability of the molecule.

References
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