Synthesis and ^{13}C NMR Chemical Shifts of Some Pyrrolo |3,2-*g*| Quinolines and Pirido |2,3-*b*| Carbazoles

Gilberto A. Romeiro*

Instituto Militar de Engenharia, Rio de Janeiro, Brasil, Universidade Federal Fluminense, Instituto de Química, GQO, 24.020, Niterói, RJ, Brasil

Misbauhl A. Khan

Instituto Militar de Engenharia, Rio de Janeiro, Brasil
Islamia University, Chemistry Department, Bahawalpur, Pakistan

and

Vitor F. Ferreira

Universidade Federal Fluminense, Instituto de Química – GQO
24.020 Niterói, RJ, Brazil

Received: September 5, 1989; October 18, 1990; January 3, 1991

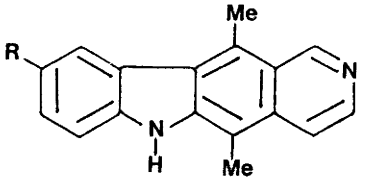
A síntese dos sistemas pirrolo |3,2-**g**| quinolina e pirido |2,3-**b**| carbazola é descrita, envolvendo a diazotação da 7-amino-2,4,8-trimetilquinolina (**6**) e redução à hidrazina correspondente (**6b**), seguida de uma ciclização do tipo "Fischer-Indole Synthesis" para produzir os derivados indólicos e carbazólicos. A desidrogenação da tetraidropiridocarbazola (**8a**) produz 2-piridocarbazola (**9**) com uma estrutura similar à elipticina. Adicionalmente, é descrita uma análise dos compostos obtidos neste trabalho por ressonância magnética nuclear de carbono-13.

A synthesis of pyrrolo |3,2-**g**| quinolines and pyrido |2,3-**b**| carbazoles system is described, involving the diazotation of 7-amino-2,4,8-trimethyl quinoline (**6**) and subsequent reduction to hydrazine **6b**, which leads, via Fisher-indole cyclization, to the title quinolines and carbazoles. Dehydrogenation of the tetrahydropyridocarbazole (**8a**) produced the pyridocarbazole (**9**) with ellipticine-like structure. ^{13}C NMR chemical assignment of the compounds obtained in this work is described.

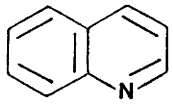
Key words: *ellipticine, Fisher-Indole Synthesis, pyrroloquinoline, pyridocarbazole.*

Introduction

Ellipticine (**1a**; 5, 11-dimethyl-6**H**-pirido | 4,3-**b** | carbazole) and 9-methoxyellipticine (**1b**) are alkaloids isolated from various plants of the Apocynaceae family[1-4]. These alkaloids and some related synthetic derivatives display pronounced anticancer activity in several animal and human tumor systems[5-8]. Many derivatives of ellipticine have been synthesized in an attempt to improve the antitumor properties[9-11] and 9-hydroxyellipticine (**1c**) is currently undergoing extensive clinical trials for the treatment of metastatic breast cancer, myeloblastic leukemia, and some solid tumors[12-15]. The anticancer activity of these compounds is related to their abillity to act as DNA double helix intercalators[16], but the mode of interaction is still unknown. Certainly, the steric constraints control this interaction. Therefore, it is important to synthesize new derivatives and compounds with similar structure that can increase their biological properties. Herein, we describe the synthesis of two new series of the title compounds, having a modified ellipticine structure and different pattern of substitution[17]



1a, R = H
1b, R = OMe
1c, R = OH



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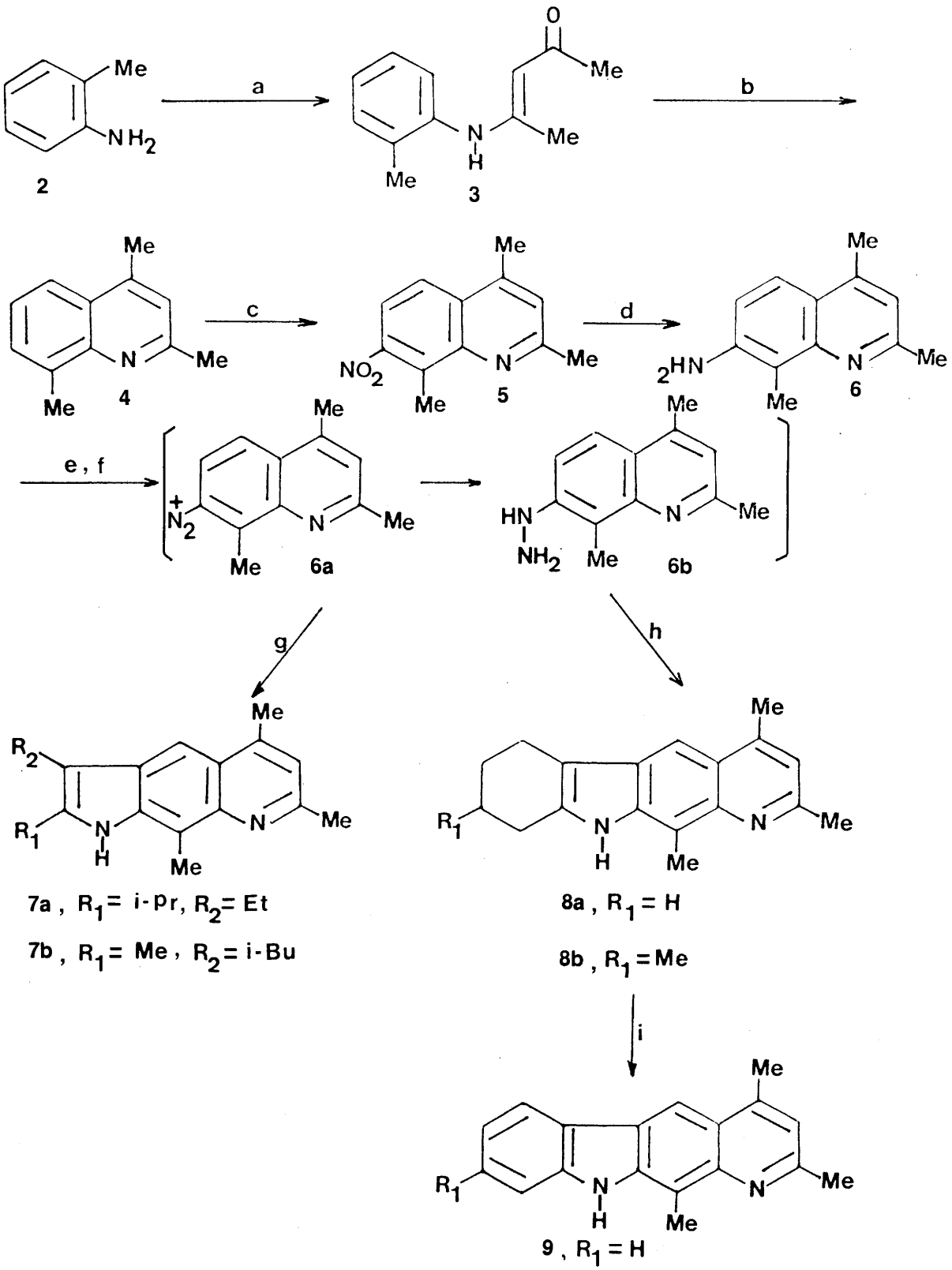
The preparation of pyrrolo |3,2-**g**| quinolines (**7a**, **7b**) and pyridotetrahydrocarbazoles (**8a**, **8b**) were based on the condensation between hydrazine intermediate (**6b**), generated *in situ*, and acyclic or cyclic ketones (Fisher-Indole cyclization)[18-19] to give (**7a**), (**7b**), (**8a**) and (**8b**) respectively. Compound (**8a**) was dehydrogenated to pro-

Scheme 1. *Synthetic approach to the Quinoline derivatives.*



a) Acetylacetone, reflux; b) H_2SO_4 conc., 100°C;
c) HNO_3/ H_2SO_4 conc., 0°C; d) NH_2NH_2/Pd/C, EtOH;
e) $NaNO_2$/HCl, 0°C; f) $SnCl_2/H_2O$; g)acyclic ketone/ AcOH, reflux; h) cyclic ketone/AcOH, reflux; i) Pd/C heating.

duce compound (**9**, Scheme 1), having ellipticine-like structure.

Results

In our synthetic strategy to carry out this synthesis, *o*-toluidine (**2**) was condensed with acetylacetone affording compound (**3**) which showed two new signals in ^{1}H NMR spectrum at 2.00 and 2.15 ppm related to the methyl groups. Acid promoted cyclization of (**3**) led directly to 2,4,8-trimethylquinoline (**4**) in 36% overall yield, which was then nitrated at low temperature to give (**5**) in 80% yield. Reduction of (**5**) with hydrazine, catalyzed by Pd supported on charcoal[20,21], gave (**6**), which showed an amino group, as indicated by its infrared absorption band at 3340 cm^{-1}. Analysis of its ^{1}H NMR spectrum showed two aromatics hydrogen doublet at 6.5 and 7.1 ppm indicative of the amino group being attached at the position 7 of the quinoline system. Diazotation of the later compound with sodium nitrite and hydrochloric acid followed by reduction with stanous chloride produced, *in situ*, the hydrazine intermediate (**6b**), which was converted into pyrrolo | 3,2-**g** | quinolines and pyrido | 2,3-**b** | carbazoles. The latter steps were acomplished by refluxing (**6b**) with acyclic and cyclic ketones in acetic acid during 3 hours to yield (**7a**), (**7b**), (**8a**) and (**8b**). Their IR spectra showed absortion band for N-H group~3400 cm^{-1}. Finally, heating the compound (**8**) in the presence of Pd/C afforded pyridocarbazole (**9**) in 3,2% overall yield from *o*-toluidine.

^{13}C NMR Analysis – The utility of model spectra combined with the ability to predict chemical shift for different classes of compounds has been recognized for some time as one of the valuable contribution of ^{13}C NMR analysis[22,23]. In the case of quinoline derivatives synthesized in this work, no systematic ^{13}C NMR correlation is found in the literature, except for pyrido |4,3-**b**| carbazoles (ellipticines)[24]. Since the quinolines moiety is found in several classes of natural products, it is of interest to have its structure completely assigned. The results of this study are presented in Table 1. Analysis of ^{13}C NMR spectra of (**4**), (**5**) and (**6**), and their comparison with the model quinoline (**10**) showed a deshielding effect at carbons 2,4 and 8 due to the introduction of the methyl groups. Introduction of nitro functionality at carbon 7 causes an expected deshielding effect of 18 ppm in this carbon and a shielding effect on the vicinal carbons 6 and 8. Introduction of the pyrrole ring, as in (**7a**), (**7b**), (**8a**) and (**8b**), affects mainly carbons 6 and 7 by deshielding carbon 6 and shielding carbon 7, with respect to the parent compound (**6**); C-5 is also affected. The numbering system utilized and the assignement of the side chain of compounds (**7a**) and (**7b**) are shown in Schem 2.

In summary, this work illustrates an efficient synthesis of pyrrolo |3,2-**g**| quinolines and pyrido |2,3-**b**| carbazoles starting from very accessible reagents, such as, acetylacetone and aromatic amines, using a experimental procedure very simple. The substances synthesized in this work have potential biological activity, and a complete analysis of the structures using. ^{13}C NMR spectroscopy were performed[24,25].

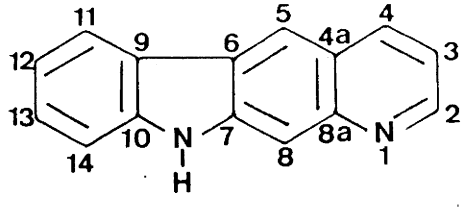
Experimental

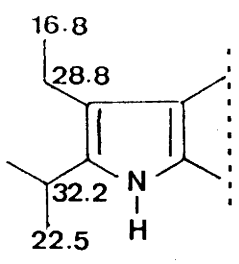
Melting points were observed on a Fischer-Jones apparatus and are not corrected. Infrared spectra were taken on Perkin – Elmer 180 spectrophotometer as KBr discs. ^{1}H NMR spectra were obtained with a Varian XL-100, EM-360 and CFT-20 spectrometers in $CDCl_3$ solutions and tetramethylsilane as internal satandard (δ=0 ppm) operating on continuous wave. ^{13}C NMR spectra were run on a Varian XL-100 and CFT-20 spectrometers with 8k memory operating in the Fourier transform mode. Spectra for 4000 and 5000 Hz were obtained from 4096 points (accuracy of ± 0.12 and ± 0.10 ppm, respectively). Regions of 0-50 ppm and 125-150 ppm were registered with sweep widths of 1000 and 500 Hz (accuracy of ± 0.025 and ± 0.0125 ppm), respectively. Multiplicities are indicated by s(singlet), d(doublet), t(triplet), q(quartet) and m(multiplet).

2,4,8-Trimethylquinoline (**4**). A solution *o*-toluidine (225 g, 2.1 mol) and acetylacetone (110 g, 1.1 mol) was refluxed under nitrogen for 2 hours. It was then poured into 1.0 l of water and extracted with benzene (3 x 500 ml). The combined organic extract was washed with brine, dried over sodium sulfate and evaporated to give a red oil (**3**), which showed the following ^{1}H NMR signals δ($CDCl_3$): 1.74 (s, 3H), 2.00 (s, 3H), 2.15 (s, 3H), 5.08 (s, 1H), 6.8-7.2 (m, 4H) and 11.30 ppm (s, 1H).

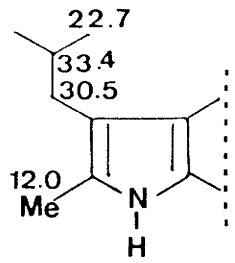
After cooling the oil (2-5°C), conc. sulfuric acid (200 ml) was added and the mixture heated at 100°C for 30 min. The reaction was poured into ice, basified with NaOH and the preciptate filtered, washed with water and dried under vacuum to yield 68.8g 36% of (**4**). mp (EtOH) 37°C (lit.[21], 39-40°C); IR (KBr) 2920, 1620, 1600, 1540, 1510, 1480, 1370, 1160, 1040, 860 and 760 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 2.48 (s, 3H, Me), 2.60 (s, 3H,

Scheme 2. *C*^{13} NMR chemical shifts assignments of the side chains of compounds **7a** and **7b** and numbering system utilized in this work.





7a



7b

Table 1. *^{13}C NMR Chemical shifts (δ) in ppm from TMS of the Quinoline compounds.*

	4	5	6	7a	7b	8a	8b	10[26]
C-2,s	157.2	158.8	156.7	156.4	153.4	153.5	153.2;	150.9,d
C-3,d	121.4	121.0	123.1	121.4	121.7	121.1	121.1;	121.5,d
C-4,s	143.8	142.7	143.6	139.6	139.8	139.5	139.7;	136.0,d
C-4a,s	129.9	141.8	118.4	123.7	124.6	122.9	123.0;	128.7,s
C-5,d	122.3	126.3	129.2	121.9	121.9	123.1	122.0;	128.3,d
C-6	124.8,d	118.2,d	111.1,d	115.5,s	115.3,s	115.0,s	115.5.s;	128.6,d
C-7	129.1,d	147.3,s	148.7,s	123.3,s	130.0,s	132.3,s	132.6,s;	129.7,d
C-8,s	137.0	127.0	127.2	127.6*	127.8*	127.5*	127.8*;	130.1,d
C-8a,s	146.9	146.6	142.6	145.0	145.1	145.0	145.2;	149.0,s
C-9,s	–	–	–	112.4	112.5	110.5	110.4	–
C-10,s	–	–	–	127.9*	127.7*	128.0*	128.0*	–
C-11,t	–	–	–	–	–	23.4*	20.9	–
C-12,t	–	–	–	–	–	20.8	29.7*	–
C-13	–	–	–	–	–	22.4,t*	31.6,d	–
C-14,t	–	–	–	–	–	28.4	31.7*	–
2-Me,q	25.4	25.1	24.9	24.8	25.0	25.0	25.0	–
4-Me,q	18.3*	19.0	18.4	19.9	19.4	19.2	19.3	–
8-Me,q	18.6*	19.9	24.2	22.5	22.6	23.6	24.4	–
13-Me,q	–	–	–	–	–	–	22.4	–

* Signals which can be exchanged.

Me), 2.73 (s, 3H, Me), 6.90 (s, 1H) and 7.1-7.7 ppm (m, 3H, aromatic hydrogens): m/e (relative intensity) 172 (M+1,20), 171 (M^+, 100), 170 (30), 156 (19), 128 (9), 85 (9) and 79 (7). Anal. calcd. for $C_{12}H_{13}N$: C, 84.2: H, 7.6: N, 8.2. Found C, 84.1: H, 7.4; N, 8.0.

7-Nitro-2,4,8-trimethylquinoline (**5**). To a stirred solution containing 1 g (4 mmol) of (**4**) in conc. sulfuric acid (20 ml) at 0°C was added dropwise a mixture of H_2SO_4: HNO_3 (1:1,10 ml) during 30 min. The mixture was poured into ice, neutralized with a solution of sodium hydroxide, filtered in a buchner and washed freely with cold water. Recrystallization from EtOH gave 0,74 g (85%) of (**5**): m.p.117-118°C; IR (KBr) 2950, 1600, 1570, 1550, 1370, 1130, 1030, 840 and 820 cm^{-1}; ^1H NMR δ ($CDCl_3$) 2.40 (s, 3H, Me), 2.60 (s, 3H, Me), 2.72 (s, 3H, Me), 7.04 (s, 1H), 7.30 (d, 1H, J=8 Hz) and 7.40 ppm (d, 1H, J=8 Hz; aromatic hydrogens): m/e (relative intensity) 217 (M+1,8), 216 (M^+,52), 209 (31), 186 (14), 171 (56), 170 (32), 155 (16), 128 (44), 77 (39): 39 (52) and 30 (100); anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.7: H, 5.5 ; N, 13.0. Found C, 66.5; H, 5.3; N, 12.8.

7-Amino-2,4,8-trimethylquinoline (**6**). To a solution containing 1 g (9,6 mmol) of (**5**) in 25 ml of anhydrous ethanol were added 2 ml of hydrazine and a catalytic amount of Pd/C (10%) and the mixture refluxed for one hour. The catalyst was removed by filtration, the solution poured into 50 ml of cold water and the solid filtered. Recrystallization from EtOH gave 0,68 g (80%) of (**6**): m.p. 129-130°C; IR (KBr) 3460, 3340, 1630, 1170, 960 and 850 cm^{-1}; ^1H NMR δ ($CDCl_3$) 2.58 (s, 6H, 2Me), 2.82 (s, 3H), 6.50 (d, 1H, J=8 Hz), 6.80 (s, 1H) and 7.10 ppm (d, 1H, J=8.0 Hz; aromatic hydrogens); m/e (relative intensity) 186 (M^+, 100) 185 (72), 171 (20); Anal. calcd for $C_{12}H_{14}N_2$: C, 77.4; H, 7.5; N, 15.1 Found C, 77.1; H, 7.2; N, 15.0.

General procedure for the preparation of (**7**a), (**7**b), (**8**a) and (**8**b). To a solution containing 2 g (10,75 mmol of (**6**) in 30 ml of conc. hydrochloric acid at 0°C was added dropwise a saturated solution of sodium nitrite (10 g/15 ml H_2O), the brownish solution (**6**a) was stirred for one hour and then added to 30 ml of a solution of stanous chloride in hydrochloric acid (12 g/10 ml). The mixture was stirred overnight (**6**), added to a solution of the appropriated ketone (10 mmol) in glacial acetic acid and then refluxed for 2-3 hours. The resulting mixture was filtered and the solution neutralized with sodium hydroxide to yield a solid, which was collected by filtration and dried under reduced pressure.

5, 7, 9-Trimethyl-3-ethyl-2s-propyl-1H-pyrrolo |3,2-g| quinoline (**7**). Obtained from 2-methylhexan-3-one in 40% yield and recrystallized from EtOH: m.p. 94-95°C; m/e (relative intensity) 281 (M^++1,13) 280 (M^++1, 60), 265 (27), 252 (21), 251 (100), 236 (23) and 118 (18); Anal. calcd. $C_{19}H_{24}N_2$: C, 81.4; H, 8.6; N, 10.0. Found C, 81.3; H, 8.5; N, 10.1.

2,5,7,9-Tetramethyl-3-isobutil-1H-pyrrolo | 3,2-g | quinoline (**7**b). Obtained from 5-methyl-hexan-2-one in 26% yield and recrystallized from EtOH: m.p. 80-81°C; IR (KBr) 3450, 2960, 2910, 1600, 1580, 1570, 1450, 1370, 1260, 1160, 860 and 840 cm^{-1}; ^1H NMR ($CDCl_3$) 0.94 (d, J= 6Hz, 3H), 1.95 (m, 1H), 2.30 (s, 3H), 2.45 (d, J= 6Hz, CH_2), 2.48 (s, 3H), 2.68 (s, 3H), 2.74 (3, 3H), 6.87 (s, 1H, aromatic), 7.62 (s, 1H, aromatic) and 8.20 ppm (br. 3, 1H, N-H); m/e (relative intensity) 280 (M^+, 59), 238 (51), 237 (100), 222 (10) and 119 (9).

2,4,11-Trimethyl-6,7,8,9-tetrahydro-10H-pyrido |2,3-b| carbazole (**8**a). Obtained from cyclohexanone in 40% yield and recrystallized from EtOH; m.p. 130-131°C; IR (KBr) 3400, 2960, 2840, 2910, 1600, 1570, 1360, 1340, 1030, 860 and 840 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.8-2.0 (m, 4H), 2.62 (s, 3H), 2.7 (s, 3H), 2.9 (s, 3H), 2.7-2.8 (m, 4H), 6.90 (s, 1H, aromatic), 7.50 (s, 1H) and 8.26 ppm (br. s, 1H, N-H), m/e (relative intensity) 264 (M^+, 13), 263 (48), 235 (43), 117 (16) and 30 (100); Anal. calcd for $C_{18}H_{20}N_2$: C, 81.8; H, 7.6; N, 10.6 Found C, 81.6; H, 7.5; N, 10.2.

2,4,8,11-Tetramethyl-6,7,8,9-tetrahydro-10H-pyrido | 2,3-b | carbazole (**8**b) Obtained from 3-methylcyclohexanone in 35% yield, recrystallized from EtOH: m.p. 187-188°C; IR (KBr) 3400, 2960, 2940, 1580, 1450, 1380, 1350, 1180, 1030 and 860 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.00 (d, 3H), 1.5-2.5 (m, 7H), 2.45 (s, 3H), 2.52 (s, 3H), 2.72 (s, 3H) 6.70 (s, 1H, aromatic hy-

drogen), 7.42 (s, 1H, aromatic hydrogen) and 8.00 ppm (s, 1H, NH); m/e (relative intensity) 278 (M^+, 98), 236 (100), 139 (10) and 118 (25); Anal. calcd for $C_{19}H_{22}N_2$: C, 82.0; H, 7.9; N, 10.1. Found C, 82.1; H, 7.7; N, 10,1.

*2,4,11-Trimethyl-10H-pyrido | 2,3-b | carbazole (***9**). A mixture containing 1 mmol of (**8a**), 100 mg of Pd/C and 5 ml of dowtherm oil was refluxed for 2 hours and extracted with a solution of hydrochloric acid (10%) (4 x 10 ml). The aqueous extract was neutralized with sodium hydroxide (1N) to yield a precipitate which was filtered, dried under vacuum, and recrystallized from EtOH to yield (**9**) in 30% yield; m.p. 180-181°C; IR (KBr) 3400 cm^{-1}; ^1H NMR δ ($CDCl_3$) 2.74 (s, Me), 2.88 (s, Me), 2.98 (s, Me), 7.1-8.3 (m, 6H aromatic hydrogen) and 8.74 (br. s, 1H, NH); m/e (relative intensity) 260 (M^+, 100), 246 (30); 217 (9), 149 (11), 130 (19), 87 (10), 57 (10) and 48 (52).

Acknowledgments

This work was supported by CNPq, FINEP and Instituto Militar de Engenharia. We are indebted to Professor Carlos Roque Duarte Correia for his valuable suggestions and analytical center of NPPN-UFRJ for the low resolution mass spectra.

References

1. S. Goodwin, A.F. Smith and E.C. Horning, *J. Am. Chem. Soc.* **81**, 1903 (1959).
2. J.W. Loder, *Aust. J. Chem.*, **19**, 1947 (1966) and references cited therein.
3. K.N. Kilminster, M. Sainsbury and B. Webb, *Phytochemistry* **11**, 389 (1972).
4. A. Ahlond, H. Fernandez, M.J.–Moore, C. Poupat, V. Sánchez, P. Potier, S.K. Kan and T.J. Sévenet, *J. Nat. Prod.* **44**, 193 (1981).
5. A. Auclair, *Arch. Biochem. Biophys.* **259**, 1, (1987).
6. M.Suffness and G.A. Cordell, *The Alkaloids*, A. Brossi, Ed. (Academic Press, New York, 1985), vol. XXV, p.l.
7. G.W. Gribble, G.L. Fletcher, D.M. Ketcha and K. Rajopadhye, *J. Org. Chem.* **54**, 3264-3269 (1989).
8. T. Honda, M. Kato, M. Inane, T. Shimamoto, K. Shima, T. Nakamshi, T. Tashide and T. Noguchi, *J. Med. Chem.* **31**, 1295 (1988).
9. G.W. Gribble and M.G. Saulnier, *Heterocycles* **23**, 1277 (1985).
10. L. Larue, C. Rivalles, G. Muzard, C. Paoletti, E. Bisagni and J. Paoletti, *J. Med. Chem.* **31**, 1951 (1988).
11. V.K. Kansal and P. Potier, *Tetrahedron* **42**, 2389 (1986).
12. P. Caille, J.M. Mondesir, J.P. Droz, P. Karbrat, A. Goodman, J.P. Ducret. C. Theodore, M. Spielman, J. Ronesse and J.L. Amiel, *Cancer Treat. Rep.* **69**, 901 (1985) and references cited therein.
13. J.B. Le Pecq, N. Dat-Xoung, C. Gosse and C. Paoletti *Proc. Natl. Acad. Sci.* **71**, 5078 (1974).
14. M. Sainsbury, *Chem. Brit.* 127 (1979); *Synthesis* 437 (1977).
15. D. Pelaprat, R. Oberlin, I. le Guen, B.P. Roques and J.B. Le Pecq, *J. Med. Chem.* **23**, 1330 and 1336 (1980).
16. E. Lescot, G. Mugard, J. Markovitz, J. Belleney, B.P. Roques and J.B. Le Pecq, *J. Med Chem.* **29**, 173 (1986).
17. To make ^{13}C NMR analysis (Table 1) homogeneous, the numbering system were changed to one described in Scheme 2.
18. E. Fischer and F. Jourdan, *Ber.* **16**, 2241-45 (1883); *J. Chem. Soc.* **46**, 52 (1884).
19. For recent reviews on Fischer Indole Synthesis, see: W.C. Sumpter and F.M. Miller, *Heterocyclic compounds with Indole and carbazole systems;* A. Weinsberg, Ed. (Interscience, New York, 1954) p. 9 and 77; H. Ishii, *Accts. Chem. Res.* **14**, 275 (1981); B. Robinson, *The Fischer Indole Synthesis* (Wiley, New York, 1982).
20. D.M. Bowen, R.W. Belfit Jr, and R.A. Walser, *J. Am. Chem. Soc.* **75**, 4307 (1953).
21. K. Marshall and R.H.F. Manske, *Can. J. Chem.* **30**, 711 (1952).
22. F.W. Wehrli and T. Wirthlin, *Interpretation of Carbon-13 NMR Spectra* (Heyden & Sons, London, 1976).
23. E. Breitmaier and W. Voelter, *^{13}C NMR Spectroscopy*, (Verlag Chemie, Basle, 1978).
24. Part of this work was presented at XXVII Congresso Brasileiro de Química, Rio de Janeiro (1987).
25. G.A. Romeiro, *PhD Dissertation;* Instituto Militar de Engenharia, Rio de Janeiro, 1985.
26. For earlier ^{13}C NMR Spectra of Quinolines and some of its derivatives, see: L.F. Johnson and W.C. Jankowski, *Carbon-13 NMR spectra* (Wiley Interscience, New York, 1972), spectra 330, 331, 335, 418 and 419; Pugmire *et al., J. Am. Chem. Soc.* **91**, 6381 (1969).