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SYNTHESIS OF 6H-PYRIDO[4,3-b]CARBAZOLES

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Abstract: A few 6H-pyrido[4,3-b]carbazoles were prepared for cytotoxicity testing in cultures of human lung cancer cells. Methyl 6-methoxyindoleacetate 13, prepared by reduction of methyl 4-(2-nitro-5-methoxyphenyl)-3-oxobutyrate 11, was condensed with 3-acetylpyridine to give the vinyl indole 14 which was quarternized with p-nitrobenzyl bromide. Cyclization of this salt with the aid of sodium methoxide and ethyl nicotinate methiodide gave the 6H-pyrido[4,3-b]carbazole 16. Brief treatment with tributyl phosphine in boiling DMF gave the ester 17 which, after reduction with $LiAlH_4$ followed by treatment with methyl isocyanate, gave 5-hydroxymethyl-9-methoxy-11-methyl-6H-pyrido[4,3,-b]carbazole N-methylcarbamate 4.

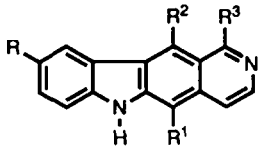
9-Methoxyolivacine 19 was oxidized to the aldehyde 22 with SeO_2. Reduction to the carbinol 24 proceeded smoothly with $NaCNBH_3$ in acid medium. Treatment with methyl isocyanate gave the carbamate 6 and the acetate 7 was prepared by acetylation of the carbinol 24.

In a previous paper[1] we reported the synthesis and antitumor activity of 5-hydroxymethyl-11-methyl-6H-pyrido[4,3-b]carbazole N-methylcarbamate, 1, and suggested a molecular mechanism to account for the antitumor activity of ellipticine 2 which differed from the one proposed by Auclair and Paoletti.[2] Since 9-methoxyellipticine, 3, is active in a variety of experimental tumor systems,[3] we decided to prepare and test the 9-methoxy derivative 4.[4]

In our suggested mechanism we postulated that the methyl group at C-5 in ellipticine is the site of metabolic activation but there is no compelling evidence to rule out activation at the alternate C-11 methyl group of 2. Since a successful synthesis of 5 has proven to be elusive thus far we decided to prepare the olivacine analogue, 6.[5] In this paper we report the synthesis of the 6H-pyrido[4,3-b]carbazoles, 4, 6 and 7.

The synthesis of 4 was carried out using the same method described for the preparation of 1 with a few significant modifications (Scheme 1).

Commercially available 3-methyl-4-nitroanisole 8 was treated with ethyl oxalate and NaH to give the pyruvate ester which, on oxidation with H_2O_2 in NaOH solution, gave after acidification, the acid 9.[6] Treatment with $SOCl_2$ gave 10 which was condensed with the anion prepared from methyl acetoacetate and NaH gave 11 Ammonolysis furnished the ester 12 which was then reduced with Pd/C and ammonium formate to give 13. Condensation of the ester 13 with 3-acetylpyridine in the presence of H_2SO_4 gave the vinylindole 14, quaternization of which with p-nitrobenzyl bromide gave the quaternary salt 15. Cyclization and aromatization of 15 to 16 was carried out in the presence of $NaOCH_3$ followed by treatment with ethyl nicotinate methiodide. The methiodide salt was found to give more consistent yields of 17 then treatment with ethyl nicotinate methobromide.



1 R = H, R^1 = $CH_2OOCNHCH_3$, R^2 = CH_3, R^3 = H

2 R = R^3 = H, R^1 = R^2 = CH_3

3 R = OCH_3, R^1 = R^2 = CH_3, R^3 = H

4 R = OCH_3, R^1 = $CH_2OOCNHCH_3$, R^2 = CH_3, R^3 = H

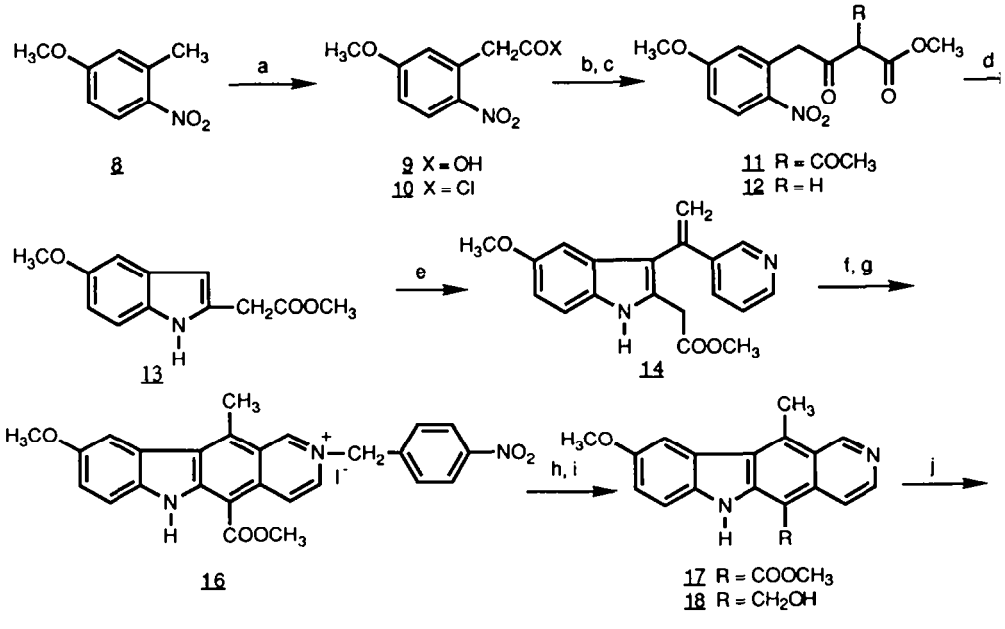
5 R = R^3 = H, R^1 = CH_3, R^2 = $CH_2OOCNHCH_3$

6 R = OCH_3, R^1 = CH_3, R^2 = H, R^3 = $CH_2OOCNHCH_3$

7 R = OCH_3, R^1 = CH_3, R^2 = H, R^3 = CH_2OOCCH_3

Dequaternization using nitrosodimethylaniline and sodium methoxide, which was successful in the synth 1, gave 17 in poor yield, owing to the difficulty in separating the desired ester from the nitrone formed in the re Heating 16 with triphenylphosphine in DMF[7] did not give a clean reaction product owing in part to the forma triphenylphosphine oxide which was difficult to remove. It is known that triphenylphosphine reduces nitro groups t triphenylphosphine oxide.[8] The most successful procedure consisted of heating 16 in boiling DMF with four equival tributylphosphine for a short period of time. Excess reagent and solvent were easily removed by distillation and t product tributylphosphine oxide was separated by chromatography. Reduction of 17 furnished the alcohol 18.

Scheme I

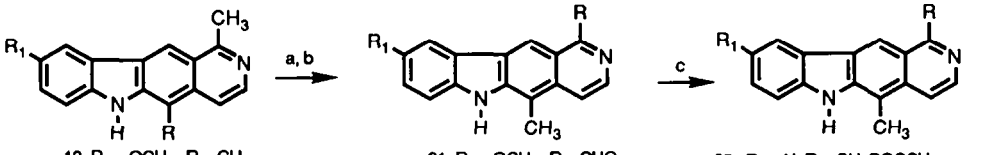


a: (i) $(COOCH_3)_2$, NaH (ii) H_2O_2, NaOH; b: (i) $SOCl_2$ (ii) $CH_3COCH_2COOCH_3$, NaH ; c: NH_4OH, MeOH; d: Pd/C, decalin; e: 3-acetylpyridine, H_2SO_4; f: p-nitrobenzyl bromide; g: $NaOCH_3$, MeOH, ethyl nicotinate methiodide; h: n-Bu_3P, DMF; i: $LiAlH_4$; j: CH_3NCO, DMAP.

When the carbinol 18 was stirred with CH_3NCO and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2, the cloudy suspension clarified while being stirred overnight. The carbamate 4 was obtained, but the NMR spectrum indicated that the material was a mixture of isomers formed in the ratio of 2:1. When a DMSO solution of this mixture was gradually heated to 65°C, one of the isomers was converted to the other and upon cooling reversion to the original mixture did not occur. Attempts to separate the isomers has been unsuccessful thus far. When the reaction was carried out in $CHCl_3$ the isomer ratio was 20:1.[9]

Because attempts to prepare olivacine 20 by a modification of Moody's short synthesis of ellipticine[10] failed,[11] we resorted to the synthesis of 9-methoxyolivacine described by Besselievere and Husson.[12-14] The conversion of 19 and 20 to the carbamate 6 and the acetate 7 and 25 is shown in scheme II.

Scheme II



19 $R_1 = OCH_3$, $R = CH_3$
20 $R_1 = H$, $R = CH_3$

21 $R_1 = OCH_3$, $R = CHO$
22 $R_1 = H$, $R = CHO$
23 $R_1 = OCH_3$, $R = CH_2OH$
24 $R_1 = H$, $R = CH_2OH$

25 $R_1 = H$, $R = CH_2OOCCH_3$
6 $R_1 = OCH_3$, $R = CH_2OOCNHCH_3$
7 $R_1 = OCH_3$, $R = CH_2OOCCH_3$

a: SeO_2, b: $NaCNBH_3$; c: CH_3NCO or acetic anhydride.

Oxidation of 19 and 20 with SeO_2 gave the aldehydes 21 and 22 as deep red crystalline solids.[15] Reduction with either $NaBH_4$ or $LiAlH_4$ was unsuccessful but $NaCNBH_3$ in acid solution gave the desired carbinols 23 and 24. Treatment of 24 with CH_3NCO in CH_2Cl_2 in the presence of DMAP gave the carbamate 6 as a single isomer. The acetates 25 and 7 were obtained by acetylation of the respective carbinols 23 and 24.

Compounds 4, 6, 7 and 25 were tested for cytotoxicity against four human lung cancer cell lines in tissue culture at the Albany Medical College by Dr. J. R. Ruckdeschel and Mr. R. Portuese. The results will be reported elsewhere. Suffice it to say that the carbamates 4 and 6 appear to be more cytotoxic than either ellipticine or adriamycin which were used as standards.

EXPERIMENTAL

All reactions were carried out in an atmosphere of dry nitrogen and in flame-dried glassware. Tetrahydrofuran and dioxane were distilled over sodium-benzophenone before use. CH_3NCO and CF_3COOH were distilled before use and all other starting materials were used as received from the supplier. Infrared spectra were recorded on a Perkin-Elmer Model 298 spectrometer. Proton NMR spectra were run on a Varian XL-200 (200 MHz) spectrometer using $(CH_3)_4Si$ as the internal standard and are reported in parts per million. Mass spectra were obtained on a Hewlett-Packard Model 5987A GC/MS spectrometer using isobutane as the CI gas. Melting points were taken on a Mel-temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Despite careful drying some 6H-pyrido[4,3-b]carbazoles retained H_2O tenaciously. Proton signals attributed to H_2O were observed in the NMR spectra.

5-Methoxy-2-nitrophenylacetic acid, 9: Ten grams (0.06M) of 3-methyl-4-nitroanisole 8 was added to a y suspension obtained by mixing 9.1 mL (0.067M) of diethyl oxalate and 3.9g (0.07M) of CH_3ONa in 50 mL of dry ether. mixture was stirred under reflux for 10 h and the thick orange suspension was treated with H_2O. The resulting solutio treated alternately with 30-32% H_2O_2 and 10 N NaOH. The resulting suspension was filtered to remove unreacted 3-m 4-nitroanisole (20%) and the filtrate was cooled to 5°C before being acidified with conc. HCl. The white solid that sepa was collected on a filter, washed thoroughly with H_2O and dried. Wt. 9.2g (72%), m.p. 174-176°C (lit value:[6] 174-176°C (KBr) λ 3140-2740, 2660, 1715, 1620, 1580, 1510, 1410, 1340, 1320, 1290, 1260, 1200, 1175, 1090, 1040, 955, 830, 760, 710, 630 cm^{-1}; NMR (DMSO-d_6) δ 8.13 (1H, d, J=8.8, H_3), 7.10-7.04 (2H, m, H_4, H_6), 3.97 (2H, s, CH_2), 3.86 s, OCH_3); MS m/e 212 (M+1).

Methyl (5-Methoxy-2-nitrobenzoyl)-acetoacetate,11: A suspension of 10.0g (0.047M) of the acid 9, 3.6 r $SOCl_2$, 0.5 mL of dry DMF in 125 mL of dry toluene was stirred at room temperature overnight and then warmed at 50°C a clear solution resulted. A solution of 10.7 mL (0.1 M) of methyl acetoacetate in 50 mL of THF was added dropwise o period of 40 min. to a stirred cold (0-5°C) suspension of 2.4g (0.1 M) of NaH in THF. The resulting solution was added t cooled solution of the acid chloride, 10, and the resulting mixture was allowed to stir overnight. Water was added an organic layer was separated. The aqueous layer was extracted with ether (3 x 100 mL) and the combined organic layers washed with H_2O and dried over Na_2SO_4. The filtered organic layer was concentrated to dryness and the residue dissolved in 25 mL of Et_2O-CH_3OH (1:1). On cooling at -20°C overnight the crystals that separated were collected and c Wt. 12.6g (82%), suitable for use in the next step. The analytical sample melted at 78-79°C after crystallization from CH IR (KBr) λ 2960, 2850, 1710, 1620-1390, 1350-1250, 1190, 1090, 1035, 950, 910, 890, 840, 760, 730, 630 cm^{-1}; ($CDCl_3$) δ 8.19 (1H, d, J=9.0, H_3); 6.90 (1H, dd, J=2.8, 9.0, H_4), 6.77 (1H, d, J=2.6, H_6), 4.50 (2H, s, CH_2), 3.99 (3 OCH_3), 3.84 (3H, s, $COOCH_3$), 2.40 (3H, s, $COCH_3$); MS m/e 310 (M+1).

Anal. Calcd. for $C_{14}H_{15}NO_7$: C, 54.37; H, 4.85; N, 4.53. Found: C, 54.45; H, 4.90; N, 4.58.

Methyl-4-(5-Methoxy-2-nitrophenyl)-3-oxobutyrate,12: Ten mililiters of NH_4OH was added to a suspension of (0.41 M) of the keto-ester 11 in 100 mL of CH_3OH. The resulting mixture was stirred at room temperature until the rea was complete (30-45 min) as monitored by TLC. The white solid was collected, wt. 6.5g. Concentration of the filtrate ga additional 1.65g of 12 for a combined yield of 8.15g (75%) suitable for use in the next step. After crystallization from CH the analytical sample melted at 85-87°C. IR (KBr) λ 3470, 3130, 2980, 2850, 710, 1590, 1500, 1440, 1400, 1200, 1010, 865, 850, 760, 750, 700, 630, 620 cm^{-1}; NMR ($CDCl_3$) δ 8.19 (1H, d, J=9.2, H_3), 6.89 (1H, dd, J=2.8, 9.2, H_4), (1H, d, J=2.8, H_6), 4.20 (2H, s, $ArCH_2$), 3.87 (3H, s, OCH_3), 3.77 (3H, s, $COOCH_3$), 3.66 (2H, s, CH_2); MS m/e 268 (M+1

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.87; N, 5.24. Found: C, 53.97; H, 4.90, N, 5.22.

Methyl-5-Methoxyindole-2-acetate, 13: To a suspension of 6.0g (0.024 M) of 13 in 180 mL of dry CH_3OH there added 650 mg of 10% Pd/C followed by 17.5g (0.278 M) of ammonium formate. After stirring at room temperature f min. the reaction mixture was filtered (Celite) and the filtrate was evaporated to dryness to leave a residue which was tritu with H_2O, filtered and dried. Wt. 4.82g (90%). After crystallization from CH_3OH the analytical sample melted at 96-98°C (KBr) λ 3370, 3020, 2970, 2840, 1720, 1595, 1485, 1445, 1395, 1330, 1205, 1120, 1035, 1010, 980, 950, 845, 770, 735, 695, 625 cm^{-1}; NMR ($CDCl_3$) δ 8.53 (1H, s, NH), 7.23 (1H, d, J=4.0, H_5), 7.01 (1H, d, J=2.4, H_4), 6.81 (1H, dd, J 8.8, H_6), 6.27 (1H, d, J=1.0, H_3), 3.82 (3H, s, OCH_3), 3.82 (2H, s, CH_2), 3.74 (3H, s, $COOCH_3$); MS m/e 220 (M+1).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: 65.81; N, 6.02; N, 6.39.

1-[2-(Carbomethoxymethyl)-3-(5-methoxyindole)]-1-(3-pyridyl)-ethene,14: To a solution of 11.41g (0.051 M) c ester 13 and 18.7 mL (0.17 M) of 3-acetylpyridine in 310 mL of CH_3OH, there was added dropwise with stirring 26.7 r

conc. H_2SO_4. The mixture was refluxed for 6.5 h, cooled and poured into ice-water. The solution was brought to pH 8.5-9.0 by addition of NH_4OH and the solid that separated was collected, washed with H_2O and dried. After crystallization from CH_3OH there was obtained 11.03g (67%) of the desired vinyl indole 14, m.p. 163-164°C. IR (KBr) λ 3210-2810, 1730, 1610, 1590, 1470-1440, 1295, 1250, 1205, 1170, 1115, 1065, 1030, 1015, 915, 845, 815, 730, 715, 675, 645 cm^{-1}; NMR ($CDCl_3$) δ 8.82 (1H, s, NH), 8.70 (1H, d, J=2.0), 8.53 (1H, d, J=4.6), 7.62-7.18 (1H, m,), 6.82 (1H, dd, J=2.3, 8.8), 6.57 (1H, s), 5.82 (1H, s, =CH), 5.42 (1H, s, =CH), 3.72 (2H, s, CH_2), 3.71 (3H, s, OCH_3), 3.66 (3H, s, $COOCH_3$); MS m/e 323 (M+1).

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.67; H, 5.69; N, 8.65.

The corresponding p-nitrobenzyl pyridinium bromide 15 was prepared by allowing 3.95g (0.012 M) of the above vinyl indole to react with 8.1 g (0.037 M) of 4-nitrobenzyl bromide in 100 mL of dry acetone overnight and then filtering the quaternary salt 15. After washing with fresh acetone and drying the salt melted at 190-193°C (dec.). Wt. 6.05g (92%). IR (KBr) λ 3340, 3010, 2960, 1740, 1630, 1575, 1485, 1350, 1295, 1210, 1160, 1070, 945, 810, 710 cm^{-1}; NMR (DMSO-d_6) δ 11.43 (1H, s, NH), 9.23 (1H, d, J=5.8), 9.14 (1H, s), 8.56 (1H, d, J=8.0), 8.23-8.17 (2H, m), 7.72 (1H, d, J=8.6), 7.33 (1H, d, J=9.0), 6.73 (1H, dd, J=2.0, 8.8, H_6), 6.15 (1H, s, =CH), 6.03 (1H, s, =CH), 5.69 (2H, s, CH_2N^+), 3.83 (2H, s, CH_2COOCH_3), 3.63 (3H, s, OCH_3), 3.44 (3H, s, $COOCH_3$).

Anal. Calcd. for $C_{26}H_{24}BrN_3O_5$: C, 58.00; H, 4.49; N, 7.81. Found: C, 58.09; H, 4.53; N, 7.78.

2-(4-Nitrobenzyl)-5-carbomethoxy-9-methoxy-11-methyl-6H-pyrido[4,3-b]carbazolium Iodide,16: To a solution of 8.00g (0.015 M) of the salt 15 in 800 mL of dry CH_3OH there was added 16.0g (0.055 M) of ethyl nicotinate methiodide. A solution of CH_3ONa prepared by dissolving 860 mg (0.037 M) of Na in 90 mL of CH_3OH was added and the resulting dark red solution was allowed to stir at room temperature for 3 h during which time an orange solid separated. The mixture was left overnight, filtered and the solid was washed with CH_3OH to leave 8.2g (95%) of 16, m.p. 268-270°C (dec.). It was used directly in the next step. IR (KBr) λ 3440, 2960, 1680, 1625, 1600, 1480, 1345, 1200, 1070, 1030, 865, 810, 740 cm^{-1}.

5-Carbomethoxy-9-methoxy-11-methyl-6H-pyrido[4,3-b]carbazole,17: A mixture of 3.5g (6mM) of 16, and 5.05 mL (0.184 M) of tributylphosphine in 50 mL of dry DMF was refluxed for 15 min and cooled to room temperature. The volatiles were removed by distillation in vacuo and the residue was washed with hexane (2 x 50 mL). The residual dark oil was chromatographed on a silica gel column using CH_2Cl_2: CH_3OH (98:2) as the eluant. The solid that was obtained was crystallized from ethyl acetate to give 1.01g (52%) of 17, m.p. 178-180°C; IR (KBr) λ 3400, 2960, 1675, 1605, 1480, 1445, 1325, 1300, 1215, 1070, 1040, 875, 840, 790, 700 cm^{-1}; NMR ($CDCl_3$) δ 10.34 (1H, s, NH), 9.60 (1H, brs, H_1), 8.81 (1H, d, J=6.3, H_3), 8.58 (1H, brs, H_4), 7.71 (1H, d, J=2.3, H_{10}), 7.35 (1H, d, J=8.6, H_7), 7.14 (1H, dd, J=2.4, 8.7, H_8), 4.11 (3H, s, OCH_3), 3.95 (3H, s, $COOCH_3$), 3.16 (3H, s, C-11, CH_3).; MS m/e 321 (M+1).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$: C, 71.23; H, 5.04; N, 8.75. Found: C, 71.11; H, 5.12; N, 8.68.

5-Hydroxymethyl-9-methoxy-11-methyl-6H-pyrido[4,3-b]carbazole,18: The ester 17 was added portionwise to a stirred suspension of 0.86g (0.023 M) of $LiAlH_4$ in 350 mL of THF and the reaction mixture was stirred at room temperature for 4 h before being quenched by the addition of 1.5 mL of H_2O. Then 200 mL of $CHCl_3$ was added and after stirring the suspension was filtered. The filtrate was evaporated to dryness to leave 1.22g of the carbinol 18. The solid that remained on the filter was washed thoroughly with warm $CHCl_3$. Evaporation of the dried $CHCl_3$ extracts gave an additional 0.46g of 18 making the total 1.68g (74%). Recrystallization from CH_3OH afforded the analytical sample, m.p. 209-211°C (dec.). IR (KBr) λ 3300-2840, 1605, 1485, 1410, 1300, 1260, 1220, 1150, 1040, 990, 820 cm^{-1}; NMR (DMSO-d_6) δ 11.28 (1H, s, NH), 9 69 (1H, s, H_1), 8.41 (1H, d, J=6.0, H_3), 8.05 (1H, d, J=6.0, H_4), 7.88 (1H, d, J=2.2, H_{10}), 7.51 (1H, d, J=8.7, H_7), 7.19 (1H, dd, J=2.4, 8.7, H_8), 5.22 (2H, s, CH_2OH), 3.91 (3H, s, OCH_3), 3.28 (3H, s, C_{11}-CH_3); MS m/e 293 (M+1).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.59. Found: C, 73.83; H, 5.57; N, 9.56.

5-Hydroxymethyl-9-methoxy-11-methyl-6H-pyrido[4,3-b]carbazole N-methylcarbamate,4: (a) To a suspensic 100 mg (0.342 mM) of 18 in 100 mL of dry $CHCl_3$ containing 50 mg of dissolved DMAP there was added 0.5 mL of CH_3I and the suspension was stirred overnight. The resulting clear solution was washed with a phosphate buffer, pH 6 to ren the DMAP. After washing with H_2O and drying over Na_2SO_4 the solution was evaporated to dryness. An NMR spectru the crude carbamate revealed very little of the isomer with a CH_2OH signal at 5.59 ppm. Chromatography on a silica column using $CHCl_3/CH_3OH$ (10:1) as the eluant gave 62 mg (53%) of the desired carbamate, 4, m.p. 210-215°C (dec.) (KBr) λ 3340-3300, 2960, 1695, 1610, 1530, 1480, 1220, 1155-1145, 1050, 995, 810 cm^{-1}: NMR (DMSO-d_6) δ 11.45 s, NH), 9.72 (1H, s, H_1), 8.44 (1H, d, J=6.1, H_3), 7.94 (1H, d, J=6.0, H_4), 7.88 (1H, d, J=2.3, H_{10}), 7.50 (1H, d, J=8.6, 7.21 (1H, dd, J=2.4, 8.7, H_8), 7.04 (1H, m, NH-CH_3), 5.74 (2H, s, CH_3), 3.91 (3H, s, OCH_3), 3.30 (3H, s, C-11, CH_3), (3H, d, J=4.7, $NHCH_3$).

Anal. Calcd. for $C_{20}H_{19}N_3O_3 \cdot H_2O$: C, 65.38; H, 5.76; N, 11.42. Found: C, 65.62; H, 5.48; N, 11.34.

(b). A similar run was carried out in 50 mL of dry CH_2Cl_2 using 50 mg of 18, 20 mg of DMAP and 0.25 mL of CH_3NCO. TL the resulting carbamate showed two spots with similar Rf values. All attempts to separate this mixture was unsuccessful. NMR spectrum showed two sets of peaks with the methylene proton signals being at δ 5.74 and 5.59 in a ratio of 2:1 variable temperature ^1H NMR study showed that as the temperature increased the upfield signal at 5.59 ppm gradu diminished until at 65°C the entire NMR spectrum showed that only one isomer was present. On cooling to 25°C the mis signals did not re-appear.[10]

Anal. Calcd. for $C_9H_{15}NO_2.0.1\ H_2O$: C, 63.15; H, 8.83; N, 8.19. Found: C, 63.02; H, 8.78; N, 8.22.

1-Formyl-5-methyl-9-methoxy-6H-pyrido[4,3,-b]carbazole,21: A suspension of 1.4g (5.0 mM) o methoxyolivacine 19 in 300 mL of dry dioxane was heated under reflux until a clear solution resulted. Then 620 mg (mM) of SeO_2 was added and refluxing was contined for 5 h. The hot reaction mixture was filtered through a bed of Ce The solid was washed with $CHCl_3$ and the combined filtrates were evaporated to dryness. The residue chromatographed on silica gel using CH_2Cl_2-CH_3OH (19:1) as the eluant. There was obtained 1.02g (69%) of a deep crystalline solid, m.p. 250-258°C (lit. value:[15] m.p. 270°C). IR (KBr) λ 3300, 2840, 1690, 1625, 1585, 1490, 1410, 1 1180, 1040, 880, 845, 815, 770, 670, 620 cm^{-1}; NMR (DMSO-d_6) δ 11.37 (1H, s, NH), 10.35 (1H, s, H_{11}), 9.83 (1H CHO), 8.69 (1H, d, J=6.0, H_3), 8.29 (1H, d, J=5.8, H_4), 7.85 (1H, d, J=2.0, H_{10}), 7.48 (1H, d, J=9.0, H_7), 7.19 (1H, dd, J= 8.8, H_8), 3.91 (3H, s, OCH_3), 3.34 (s, H_2O), 2.86 (3H, s, CH_3); MS m/e 291 (M+1).

1-Formyl-5-methyl-6H-pyrido[4,3,-b]carbazole,22: Oxidation of olivacine 20 was carried out in the same wa described for the oxidation of 19, in 46% yield, m.p. 288-290°C (dec.). IR (KBr) λ 3260-2630, 1695, 1615, 1590, 1 1255, 1215, 1155, 880, 745 cm^{-1}; NMR (DMSO-d_6) δ 11.57 (1H, s, NH), 10.36 (1H, s, H_{11}), 9.86 (1H, s, CHO), 8.72 (1H J=6.0, H_3), 8.33-8.30 (2H, m), 7.57 (1H, d, J=3.6), 7.31-7.25 (2H, m), 3.32 (s, H_2O), 2.89 (3H, s, CH_3); MS m/e 261 (M+1

Anal. Calcd. for $C_{17}H_{12}N_2O \cdot 0.6\ H_2O$: C, 75.27; H, 4.87, N, 10.33. Found: C, 75.20; H, 4.83; N, 10.95.

1-Hydroxymethyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole,23: A suspension of 0.5g (1.72 mM) aldehyde 21 in 100 mL of abs. C_2H_5OH containing 4 mL of CF_3COOH was stirred at room temperature until a clear solu resulted. Then 1.6g (25.5 mM) of $NaCNBH_3$ was added and stirring was continued for 30 min. The mixture concentrated to 50 mL and then 200 mL of $CHCl_3$ was added. The organic layer was washed with $NaHCO_3$ solut followed by H_2O and then brine. Concentration of the dried $CHCl_3$ left 0.48g (95%) of almost pure carbinol, 24, suitable use in the next step. An analytical sample was obtained after chromatography on silica gel using $CHCl_3$-CH_3OH as developing solvent, m.p. 198-201°C. IR (KBr) λ 3400-3080, 2920, 1620, 1480, 1395, 1285, 1200, 1030, 810, 765 c

NMR (DMSO-d_6) δ 11.18 (1H, s, NH), 8.97 (1H, s, H_{11}), 8.32 (1H, d, J=6.0, H_3), 7.92-7.86 (2H, m, H_4, H_2), 7.44 (1H, d, J=8.6, H_7), 7.13 (1H, dd, J=2.6, 8.6, H_8), 5.34 (1H, t, OH), 5.20 (2H, d, J=5.2, $C\underline{H_2}OH$), 3.89 (3H, s, OCH_3), 3.31 (s, H_2O), 2.80 (3H, s, CH_3); MS m/e 293 (M+1).

Anal. Calcd. for $C_{18}H_{16}N_2O_2 \cdot 0.25\ H_2O$: C, 72.84; H, 5.48; N, 9.44. Found: C, 72.81; H, 5.59; N, 9.09.

1-Hydroxymethyl-5-methyl-6H-pyrido[4,3-b]carbazole,24: Reduction of 22 was carried out as described above in 75% yield, m.p. 240-243°C (dec.). IR (KBr) λ 3340-3060, 1605, 1388, 1255, 1230, 1060, 870, 815, 750, 725 cm^{-1}; NMR (DMSO-d_6) δ 8.97 (1H, s, NH), 8.37-8.30 (3H, m), 7.91 (1H, d, J=6.4), 7.55-7.25 (3H, m), 5.22 (2H, s, $C\underline{H_2}OH$), 3.18 (s, H_2O), 2.89 (3H, s, CH_3); MS m/e 263 (M+1).

Anal. Calcd. for $C_{17}H_{14}N_2O \cdot 0.5\ H_2O$: C, 75.28; H, 5.53; N, 10.37. Found: C, 75.19; H, 5.62; N, 10.29.

1-(Hydroxymethyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole N-methylcarbamate,6: A suspension of 340 mg (1.16 mM) of 24, 260 mg of DMAP in 180 mL of CH_2Cl_2 was stirred at room temperature for 30 min. before 2.1 mL of CH_3NCO was added. The mixture was stirred for 18 h and then concentrated to about 10 mL. The clear solution was cooled in an ice-salt bath for 2 h and the yellow crystals which separated were washed with cold (-20°C) CH_2Cl_2. After drying there was obtained 215 mg (54%) of 6, m.p. 225-228°C (dec.). IR (KBr) λ 3320, 3220, 1690, 1605, 1490, 1415, 1280, 1210, 1150, 1040, 870, 800, 765 cm^{-1}; NMR (DMSO-d_6) δ 11.21 (1H, s, NH), 8.88 (1H, s, H_{11}), 8.33 (1H, d, J=6.0, H_3), 7.95-7.89 (2H, m, H_4, H_{10}), 7.45 (1H, d, J=8.8, H_7), 7.18-7.12 (2H, m, H_8, $N\underline{H}CH_3$), 5.74 (2H, s, CH_2), 3.89 (3H, s, OCH_3), 3.32 (s, H_2O), 2.81 (3H, s, C-5 CH_3), 2.61 (3H, d, J=4.4, $NHCH_3$); MS m/e 350 (M+1).

Anal. Calcd. for $C_{20}H_{19}N_3O_2 \cdot 0.67\ H_2O$: C, 66.49; H, 5.68; N, 11.63. Found: C, 66.57; H, 5.46; N, 11.33.

1-Acetoxymethyl-5-methyl-9-methoxy-6H-pyrido[4,3,-b]carbazole,7: A solution of 51 mg (0.175 mM) of the carbinol 24, 230 μl of pyridine and 230 μl of acetic anhydride in 20 mL of $CHCl_3$ was stirred at room temperature overnight. The solution was washed thoroughly with H_2O. After drying the solution was concentrated to dryness to leave a red oil which, after chromatography on silica gel (ethyl acetate/hexane, 2:1), gave 26 mg (44%) of the acetate 7, m.p. 240°C (dec.). IR (KBr) λ 3460-2800, 1735, 1600, 1490, 1415, 1225, 1180, 1035, 815, 775 cm^{-1}; NMR (DMSO-d_6) δ 8.42 (1H, s, H_{11}), 8.37 (1H, d, J=6.0, H_3), 8.19 (1H, s), 7.71 (1H, d, J=6.0, H_4), 7.54 (1H, s, NH), 7.30 (1H, d, J=8.8, H_7), 7.11 (1H, d, J=8.8, H_8), 5.80 (2H, s, CH_2), 3.91 (3H, s, OCH_3), 2.58 (3H, s, OCH_3), 2.16 (3H, s, $OCOCH_3$), 1.82 (s, H_2O); MS m/e 335 (M+1).

Anal. Calcd. for $C_{20}H_{18}N_2O_3 \cdot 0.5\ H_2O$: C, 69.07; H, 5.53; N, 8.17. Found: C, 70.22; H, 5.57; N, 8.17.

1-Acetoxymethyl-5-methyl-6H-pyrido[4,3,-b]carbazole,25: Acetylation of 23 gave 25 in 46% yield, m p. 228-230°C. IR (KBr) λ 3400-2800, 1730, 1600, 1470, 1415, 1375, 1235, 1030, 915, 870, 830, 745, 730 cm^{-1}; NMR ($CDCl_3$) δ 8.59 (1H, s), 8.41 (1H, d, J=6.2), 8.17 (1H, d, J=2.8), 8.13 (1H, d, J=4.4), 7.80-7.18 (2H, m), 5.82 (2H, s, CH_2), 2.71 (3H, s, CH_3), 2.14 (3H, s, $COCH_3$), 1.6 (s, H_2O); MS m/e 305 (M+1).

Anal. Calcd. for $C_{19}H_{16}N_2O_2 \cdot 0.4\ H_2O$: C, 73.26; H, 5.39; N, 8.99. Found: C, 73.13, H, 5.35; N, 8.82.

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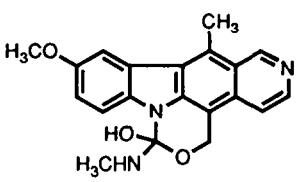

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The presence of the 9-methoxy group in 4 renders the indole nitrogen more nucleophilic thereby assisting in the attack on the carbamate carbonyl. An analogous thermolabile isomer was not observed in the synthesis of 1 presumably due to the absence of a 9-methoxy function.

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