Synthesis of Ellipticine and Olivacine by the Thermal Electrocyclic Reaction *via* Pyridine 3,4-Quinodimethane Intermediates

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A synthesis of the antitumor alkaloids ellipticine **1** and olivacine **2** is reported. The route involves a thermal electrocyclic reaction of conjugated hexatriene system **4** derived from 2-alkenylindole derivatives **5**. Heating of the 2-alkenylindole derivative **5b** at 450-460° gave ellipticine **1** (30%) and 11-demethylellipticine **14** (43%). In a similar manner, the thermolysis of the 2-alkenylindole **5c** afforded olivacine **2** (57%).

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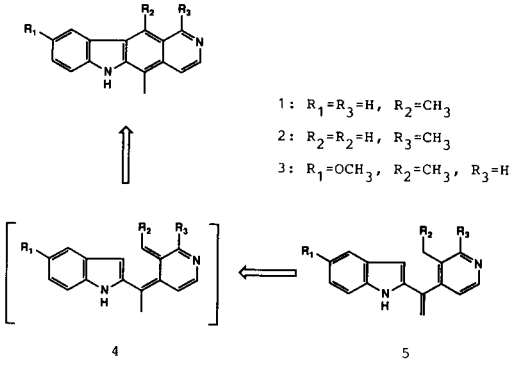
Members of the 6*H*-pyrido[4,3-*b*]carbazole alkaloids, ellipticine **1**, olivacine **2**, and 9-methoxyellipticine **3** have been isolated from many species since 1959 [1,2]. The discovery of their anticancer activity in several animals and human tumor systems has stimulated widespread interest in their synthesis [3]. A derivative of 9-hydroxyellipticine, *N*-methyl-9-hydroxyellipticinium acetate was commerciallized already for clinical use in the treatment of myeloblastic leukemia, advanced breast cancer, and other solid tumors [3], and then a water soluble derivative, 2-α-L-arabinosyl-9-hydroxyellipticinium bromide (SUN-4599) is now being evaluated in clinical trials [4]. As a result, many synthetic efforts to these alkaloids and their congenors have been developed including our synthetic routes *via* indole 2,3-quinodimethane and pyridine 3,4-quinodimethane intermediates [2,5,6,7]. We now describe here the synthesis of these alkaloids by the electrocyclic reaction of our latter case in detail.

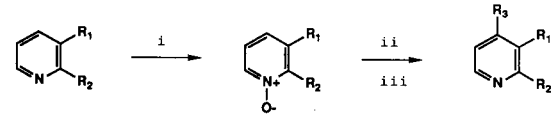
Scheme 1



The proposed synthesis is based on the strategy shown in Scheme 1, and involves an electrocyclic reaction of a conjugated hexatriene system **4** consisting with the 2 and 3-position of indole ring and the pyridine 3,4-quinodimethane structure formed *via* [1,5]-sigmatropy of an 2-alkenylindole derivative **5**.

Initially, the 4-acetylpyridine derivatives required for our purpose were 3-alkyl or 2,3-dialkyl-4-acetylpyridine **9a-c** whose synthesis is shown in Scheme 2. The alkylpyridines **6a-c** were converted to the *N*-oxidess **7a-c** by hydrogen peroxide in the usual manner [8]. Treatment of the *N*-oxides **7a-c** with dimethyl sulfate followed by cyanation with potassium cyanide gave the 4-cyanopyridines **8a-c** according to the method of Okamoto and Tani [9]. The addition of methyllithium to **8a-c** afforded the 4-acetylpyridines **9a-c** accompanied by the 2-acetylpyridines which were readily separated by column chromatography in each case.

Scheme 2



6a: R_1=CH_3, R_2=H
6b: R_1=C_2H_5, R_2=H
6c: R_1=R_2=CH_3

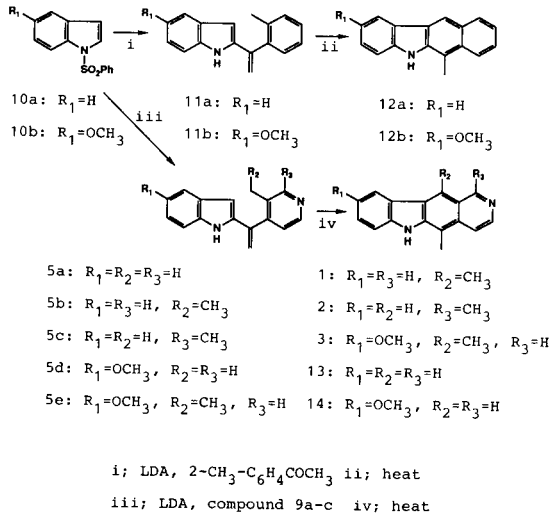
7a: R_1=CH_3, R_2=H
7b: R_1=C_2H_5, R_2=H
7c: R_1=R_2=CH_3

8a: R_1=CH_3, R_2=H, R_3=CN
8b: R_1=C_2H_5, R_2=H, R_3=CN
8c: R_1=R_2=CH_3, R_3=CN
9a: R_1=CH_3, R_2=H, R_3=$COCH_3$
9b: R_1=C_2H_5, R_2=H, R_3=$COCH_3$
9c: R_1=R_2=CH_3, R_3=$COCH_3$

i; 15% H_2O_2, CH_3COOH ii; $(CH_3)_2SO_4$, KCN iii; CH_3Li

As a model experiment, the possibility of 2-alkenylindoles **11a-d** to undergo an electrocyclic reaction to the benzo[*b*]carbazoles was examined. The 2-alkenylindoles **11a-b** were prepared by the following procedure. Condensation of *N*-benzenesulfonylindole **10a** treated with lithium diisopropylamide and 2-methylacetophenone afforded the 2-alkenylindole **11a** directly (33%). In a similar way, *N*-benzenesulfonyl-5-methoxyindole **10b** gave the 2-alkenyl-5-methoxyindole **11b** (35%). Thermal electrocyclic reaction of **11b** at 490-500° for 3 minutes gave the benzo[*b*]carbazole **12a** [6] (48%) along with the starting material **11a**. The methoxy analogue **11b** (480-500°, 3 minutes) also gave the benzo[*b*]carbazole **12b** (31%). It was found that this type of reaction proceeds at relatively high temperature.

Scheme 3



By analogy with this benzo[*b*]carbazole synthesis, condensation of 2-lithiated *N*-benzenesulfonylindole **10a** with 3-methyl-4-acetylpyridine **5a**, 3-ethyl-4-acetylpyridine **5b** and 2,3-dimethyl-4-acetylpyridine **5c** afforded the corresponding 2-alkenylindoles **5a** (35%), **5b** (21%) and **5c** (14%), respectively. In a similar fashion, condensation of 2-lithiated *N*-benzenesulfonyl-5-methoxyindole **10b** with 3-methyl-4-acetylpyridine **9a** and 3-ethyl-4-acetylpyridine **9b** gave the corresponding 2-alkenylindoles **5d** (32%) and **5e** (11%), respectively.

Thermal reaction of 2-alkenylindole **5a** at 490-500° for 3 minutes afforded 11-demethylellipticine **13** [6] in 57% yield along with a small amount of the starting material. Thermal reaction of **5b** resulted in the formation of ellipticine **1** (30%) [6] and 11-demethylellipticine **13** (43%) accompanied by the recovery of **5b** (12%) which were easily separated by preparative thin layer chromatography. The formation of **13** in the case of **5b** would be caused by the elimination of the methyl group as methane by a radical reaction on aromatization of the cyclization intermediate. In a similar way, 2-alkenylindole **5c** was heated at 470-480° for 3 minutes to give olivacine **2** [10] in 57% yield along with the recovery of **5c** (1.2%). Olivacine was identified by comparison of the nmr spectrum with an authentic spectrum. Finally, 2-alkenyl-5-methoxyindole **5d** was heated at 480-500° for 3 minutes to give 11-demethyl-9-methoxyellipticine **14** [11] in somewhat low yield (15%). Thermal reaction of 2-alkenyl-5-methoxyindole **5e** (460-470°, 3 minutes) gave only a small amount of 11-demethyl-9-methoxyellipticine **14** without any 9-methoxyellipticine **3**.

Although the synthesis of 9-methoxyellipticine **3** was unsuccessful, the synthesis of ellipticine **1** and olivacine **2** were completed by the initially proposed electrocyclic reaction using pyridine 3,4-quinodimethane intermediates **4**. As a result, it seems that this strategy is favorable to the synthesis of olivacine **2**.

EXPERIMENTAL

Melting points were determined by a Yanagimoto micro melting point apparatus and uncorrected. The ^{1}H nmr spectra were taken with JEOL PMX-60Si and JEOL FX-100 instruments with tetramethylsilane as an internal standard. The measurement solvent was used deuteriochloroform unless otherwise stated. The mass spectra were recorded on Hitachi M-80 and Shimadzu 6020 spectrometers. All reactions were carried out under a nitrogen atmosphere. Tetrahydrofuran (THF) dried and distilled from lithium aluminium hydrides before use. Silica gel (60-100 mesh, Merck Art 7734) and silica gel 60 PF_{254} (Merck Art 7747) were used for column and preparative thin layer chromatography. Commercially available 3-methylpyridine *N*-oxide **7a** (Tokyo Kasei Co. Ltd., p0419) was used as the starting material of 4-cyano-3-methylpyridine **8a**.

Preparation of Alkylpyridine *N*-Oxides **7**.

General Procedure.

A stirred solution of the alkylpyridines **6** (0.1 mole) and 15% aqueous hydrogen peroxide (15 ml) in acetic acid (100 ml) was heated at 100° for 3.5 hours. After cooling to room temperature, the mixture was neutralized with sodium carbonate and ethyl acetate (300 ml) was added. The mixture was filtered, the filtrate was washed with brine, dried over sodium carbonate and concentrated. The residue was distilled to give the *N*-oxides **7**.

3-Ethylpyridine *N*-Oxide (**7b**).

This compound was obtained as an oil (81%), bp 147-149°/1 torr; ^{1}H nmr: δ 1.27 (t, 3H, C*H*$_3$, J = 8 Hz), 2.63 (q, 2H, C*H*$_2$, J = 8 Hz); ms: (m/z) 123 (M^+).

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.50; H, 7.41; N, 11.20.

2,3-Dimethylpyridine *N*-Oxide (**7c**).

This compound was obtained as an oil (81.1%), bp 160-161°/1 torr; ^{1}H nmr: δ 2.33 (s, 3H, C*H*$_3$), 2.50 (s, 3H, C*H*$_3$); ms: (m/z) 123 (M^+).

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.45; H, 7.39; N, 11.30.

Preparation of 4-Cyanopyridine Derivatives **8**.

General Procedure.

The dimethyl sulfate (11.6 g, 92 mmoles) was added to the pyridine *N*-oxides **7** (84 mmoles) under cooling with ice and then the mixture was stirred at room temperature for 14 hours. After the addition of a 50% aqueous ethanolic solution (150 ml) of potassium cyanide (6.5 g, 100 mmoles) at 22-23° was completed, the stirring was continued at room temperature for 14 hours. Concentration of the mixture to half a volume followed by extraction with chloroform was carried out. The chloroform layer was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residual oil was purified by distillation (**8a** and **8b**) or silica gel column chromatography (100 g) using ethyl acetate/hexane (1:9 v/v) as the eluant in the case of **8c**.

4-Cyano-3-methylpyridine (**8a**).

This compound was obtained as an oil (72%), bp 85-86°/1 torr, mp 50-52° [lit value [12], 51-52.5°]; ^{1}H nmr: 2.52 (s, 3H, CH_3), 7.38 (d, 1H, C5-H, J = 6 Hz), 8.52 (d, 1H, C6-H, J = 6 Hz), 8.57 (s, 1H, C2-H); ms: (m/z) 118 (M^+).

4-Cyano-3-ethylpyridine (**8b**).

This compound was obtained as an oil (64%), bp 90-91°/1 torr; ^{1}H nmr: δ 1.35 (t, 3H, CH_3, J = 7 Hz), 2.89 (q, 2H, CH_2, J = 7 Hz), 7.44 (d, 1H, C5-H, J = 6 Hz), 8.57 (d, 1H, C6-H, J = 6 Hz), 8.65 (s, 1H, C2-H); ms: (m/z) 132 (M^+).

Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.81; H, 6.25; N, 21.12.

4-Cyano-2,3-dimethylpyridine (**8c**).

This compound was obtained as an oil (17%); ^{1}H nmr: δ 2.49 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.26 (d, 1H, C5-H, J = 6 Hz), 8.42 (d, 1H, C6-H, J = 6 Hz); ms: (m/z) 132 (M^+). This compound was used for the next reaction without further purification.

Preparation of 4-Acetylpyridine Derivatives **9**.

General Procedure.

A solution of methyllithium in ethyl ether [prepared from lithium (151 mmoles) and methyl iodide (74.6 mmoles) in anhydrous (100 ml)] was added to an ice cooled solution of 4-cyanopyridine derivatives **8** (38 mmoles) in anhydrous THF (100 ml) with stirring. The mixture was stirred at room temperature for 14 hours, then was poured into the aqueous ammonium chloride solution with ice. The mixture was extracted with benzene and then the benzene layer was washed with brine. After the benzene layer was dried over sodium sulfate and concentrated, the residue was purified by column chromatography (silica gel, 50 g) using ethyl acetate/hexane (5:95 v/v) as the eluant and distilled to give the 4-acetylpyridine derivatives **9**.

4-Acetyl-3-methylpyridine (**9a**).

This compound was obtained as an oil (71%), bp 93-95°/1 torr; ^{1}H nmr: δ 2.57 (s, 3H, COCH_3), 2.67 (s, 3H, CH_3), 7.70 (d, 1H, C5-H, J = 6 Hz), 8.48 (d, 1H, C6-H, J = 6 Hz), 8.48 (s, 1H, C2-H); ms: (m/z) 135 (M^+).

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.15; H, 6.80; N, 10.40.

4-Acetyl-3-ethylpyridine (**9b**).

This compound was obtained as an oil (61%), bp 123-124°/2 torr; ^{1}H nmr: δ 1.18 (t, 3H, CH_3, J = 8 Hz, CH_3), 2.57 (s, 3H, COCH_3), 2.81 (q, 2H, CH_2, J = 8 Hz), 7.36 (d, 1H, C5-H, J = 6 Hz), 8.54 (d, 1H, C6-H, J = 6 Hz), 8.55 (s, 1H, C2-H); ms: (m/z) 149 (M^+).

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.49; H, 7.50; N, 9.50.

4-Acetyl-2,3-dimethylpyridine (**9c**).

This compound was obtained as an oil (28%); ^{1}H nmr: δ 2.31 (s, 3H, COCH_3), 2.53 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 7.11 (d, 1H, C5-H, J = 6 Hz), 8.38 (d, 1H, C6-H); ms: (m/z) 149 (M^+).

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.51; H, 7.39; N, 9.35.

N-Benzenesulfonylindole (**10a**).

A solution of indole (22.4 g, 0.2 moles) in anhydrous THF (150 ml) was added to an ice-cooled solution of dimsyl sodium [prepared from 60% sodium hydride (8.8 g, 0.22 mole) and DMSO (100 ml) at 60° for 1 hour] with stirring. After the stirring was continued at room temperature for 1 hour, a solution of benzenesulfonyl chloride (35.3 g, 0.2 mole) in anhydrous THF (120 ml) was added dropwise to the solution with ice-cooling. After the completion of the addition, the mixture was stirred at room temperature for 2 hours. The mixture was poured into water and extracted with benzene. The solvent was washed with brine, dried over sodium sulfate and concentrated. The residue was distilled to give **10a** (23.8 g, 92%), bp 192°/3 torr, mp 78-79° [lit value [13], 78-79°].

N-Benzenesulfonyl-5-methoxyindole (**10b**).

A solution of 5-methoxyindole (5.5 g, 37.4 mmoles) in anhydrous THF (50 ml) was added dropwise to an ice-cooled solution of dimsyl sodium prepared from 60% sodium hydride (1.5 g, 37.5 mmoles) and DMSO (15 ml) with stirring. After the stirring was continued at room temperature for 1 hour, a solution of benzenesulfonyl chloride (6.7 g, 37.9 mmoles) in anhydrous THF (50 ml) was added dropwise to the reaction mixture with ice-cooling. After completion of the addition, the mixture was stirred at room temperature for 2 hours. The mixture was poured into water and extracted with benzene. The solvent was washed with brine, dried over sodium sulfate and concentrated. The residue was recrystallized from ethanol to give **10b** (7.7 g, 72%), mp 94-95°; ^{1}H nmr: δ 3.77 (s, 3H, OCH_3); ms: (m/z) 287 (M^+).

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.64; H, 4.56; N, 4.87. Found: C, 62.70; H, 4.55; N, 5.00.

Preparation of 2-Alkenylindole Derivatives **5** and **11**.

General Procedure.

A solution of *N*-benzenesulfonylindoles **10** (20 mmoles) in anhydrous THF (25 ml) was added to a stirred solution of LDA prepared from *n*-butyllithium (1.5 *M* hexane solution, 21 mmoles) and diisopropylamine (21 mmoles) in anhydrous THF (3 ml) with ice-cooling. After the stirring was continued for 1 hour, a solution of acetophenone or 4-acetylpyridines **9** (20 mmoles) in anhydrous THF (15 ml) was added dropwise to this mixture at −78°. The mixture was gradually warmed to room temperature and kept for 14 hours and then poured into aqueous ammonium chloride solution and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 70 g) using ethyl acetate/hexane (1-10:99-90 v/v) as the eluant to give the 2-alkenylindole derivatives **5** and **11**.

2-[1-(2-Tolyl)]ethenylindole (**11a**).

This compound was obtained in 33% yield as crystals, mp 66-68° (from pentane); ^{1}H nmr: δ 2.17 (s, 3H, CH_3), 5.17 (s, 1H, CH_2 x ½), 5.73 (s, 1H, CH_2 x ½); ms: (m/z) 233 (M^+).

Anal. Calcd. for $C_{17}H_{15}N$: C, 87.51; H, 6.48; N, 6.00. Found: C, 87.55; H, 6.43; N, 5.98.

2-[1-(2-Tolyl)]ethenyl-5-methoxyindole (**11b**).

This compound was obtained in 35% yield as crystals, mp 71-72° (from hexane); ^{1}H nmr: δ 2.16 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 5.07 (s, 1H, CH_2 x ½), 5.67 (s, 1H, CH_2 x ½); ms: (m/z) 263 (M^+).

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.84; H, 6.45; N, 5.31.

2-{1-[4-(3-Methyl)pyridyl]}ethenylindole (**5a**).

This compound was obtained in 35% yield as crystals, mp 149-151° (from ethyl ether); ^{1}H nmr: δ 2.18 (s, 3H, C*H*$_3$), 5.13 (s, 1H, C*H*$_2$ x ½), 5.81 (s, 1H, C*H*$_2$ x ½); ms: (m/z) 234 (M$^+$).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.21; H, 6.15; N, 12.02.

2-{1-[4-(3-Ethyl)pyridyl]}ethenylindole (**5b**).

This compound was obtained in 21% yield as crystals, mp 172-173° (from ethyl ether); ^{1}H nmr: δ 1.13 (t, 3H, C*H*$_3$, J = 7.5 Hz), 2.58 (q, 2H, C*H*$_2$, J = 7.5 Hz), 5.17 (s, 1H, C*H*$_2$ x ½), 5.81 (s, 1H, C*H*$_2$ x ½); ms: (m/z) 248 (M$^+$).

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28. Found: C, 81.98; H, 6.47; N, 11.11.

2-{1-[4-(3-Methyl)pyridyl]}ethenyl-5-methoxyindole (**5d**).

This compound was obtained in 14% yield as crystals, mp 178-179° (ethyl ether); ^{1}H nmr: δ 2.13 (s, 3H, C*H*$_3$), 2.53 (s, 3H, C*H*$_3$), 5.10 (s, 1H, C*H*$_2$ x ½), 5.79 (s, 1H, C*H*$_2$ x ½); ms: (m/z) 248 (M$^+$).

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28. Found: C, 82.19; H, 6.49; N, 11.25.

2-{1-[4-(3-Methyl)pyridyl]}ethenyl-5-methoxyindole (**5d**).

This compound was obtained in 32% yield as crystals (amorphous solid), mp 190-194°; ^{1}H nmr: δ 1.11 (t, 3H, C*H*$_3$, J = 8 Hz), 2.57 (q, 2H, C*H*$_2$, J = 8 Hz), 3.77 (s, 3H, OC*H*$_3$), 5.08 (s, 1H, C*H*$_2$ x ½), 5.80 (s, 1H, C*H*$_2$ x ½); ms (m/z) 278 (M$^+$).

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.70; H, 6.49; N, 10.29.

6-Methyl-5*H*-benzo[*b*]carbazole (**12a**).

2-Alkenylindole **11a** (100 mg) was heated at 490-500° (external) for 3 minutes and the reaction mixture was purified by preparative tlc on silica gel. Development with 5% ethyl acetate/hexane gave the starting material **11a** (46.8 mg, 47%) from the faster moving layer and the benzo[*b*]carbazole **12a** (47.0 mg, 48%) from the slower moving layer; mp 210-211° (lit value [6], 210-211°).

2-Methoxy-6-methyl-5*H*-benzo[*b*]carbazole (**12b**).

2-Alkenylindole **11b** (100 mg) was heated at 480-500° (external) for 3 minutes and the reaction mixture was purified by preparative tlc on silica gel. Development with 1% ethyl acetate/hexane gave the starting material **11b** (32.5 mg, 33%) from the faster moving layer and the benzo[*b*]carbazole **12b** (30.4 mg, 31%) from the slower moving layer, mp 227-229°; ^{1}H nmr: δ 2.80 (s, 3H, C*H*$_3$), 3.93 (s, 3H, OC*H*$_3$); ms: (m/z) 261 (M$^+$).

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.69; H, 5.80; N, 5.47.

5-Methyl-6*H*-pyrido[4,3-*b*]carbazole (**13**).

2-Alkenylindole **5a** (100 mg) was heated at 490-500° (external) for 3 minutes and the mixture was purified by preparative tlc on silica gel. Development with 5% methanol/chloroform gave the starting material **5a** (10 mg, 10%) from the faster moving layer and the pyridocarbazole **13** (56.7 mg, 57%) from the slower moving layer, mp 290-291° (lit value [6], 290-291°).

Ellipticine (**1**) and 5-methyl-6*H*-pyrido[4,3-*b*]carbazole (**13**).

2-Alkenylindole **5b** (200 mg) was heated at 450-460° (external) for 3 minutes and the mixture was purified by preparative tlc on silica gel. Development with 50% ethyl acetate/hexane gave **5b** (23.8 mg, 12%), the carbazole **13** (80.5 mg, 43%) and ellipticine **1** (59.8 mg, 30%), mp 309-312° (lit value [6], 309-312°), respectively.

Olivacine (**2**).

2-Alkenylindole **5c** (100 mg) was heated at 470-480° (external) for 3 minutes and the mixture was purified by preparative tlc on silica gel. Development with 20% hexane/ethyl acetate gave the starting material **5c** (1.2 mg, 1.2%) from the faster moving layer and olivacine **2** (57.0 mg, 57%) from the slower moving layer, mp >300° (lit value [10], >300°); ^{1}H nmr: δ 2.82 (s, 3H, C*H*$_3$), 3.04 (s, 3H, C*H*$_3$); ms: (m/z) 246 (M$^+$).

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 83.11; H, 5.89; N, 11.30.

9-Methoxy-5-methyl-6*H*-pyrido[4,3-*b*]carbazole (**14**).

2-Alkenylindole **5d** (100 mg) was heated at 480-500° (external) for 3 minutes and the mixture was purified by preparative tlc on silica gel. Development with 20% hexane/ethyl acetate gave the cabazole **14** (14.8 mg, 15%) as an amorphous solid, mp 243° (lit value [11], 243°); ^{1}H nmr: δ 2.72 (s, 3H, C*H*$_3$), 3.92 (s, 3H, OC*H*$_3$); ms: (m/z) 262 (M$^+$).

Compound **14** from **5e**.

2-Alkenylindole **5e** (100 mg) was heated at 460-470° (external) for 3 minutes and the mixture was purified by preparative tlc on silica gel. Development with 20% hexane/ethyl acetate gave the carbazole **14** (3.3 mg, 3.3%).

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