Total Syntheses of (±)-*cis*- and *trans*-11-Methoxydeethyleburnamonine

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The total syntheses of 11-methoxydeethyleburnamonines (**4**) and (**13**) were carried out with use of 6-methoxytryptophyl bromide (**5**) as starting material. Compound **5** was converted in three steps to *trans*-ester **8**. Acid-catalysed epimerization of **8**, lithium aluminum hydride reduction of the ester group, tosylation and substitution with cyanide gave the *cis*-nitrile **12**. Acid-induced cyclization of **12** yielded mainly (±)-*trans*-11-methoxydeethyleburnamonine (**13**), whereas base-induced cyclization gave (±)-*cis*-11-methoxydeethyleburnamonine (**4**).

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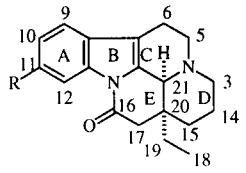
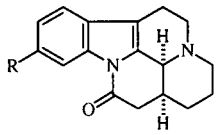
Introduction.

The indole alkaloid (–)-eburnamonine (**1**) [1] has long been of synthetic interest owing to its pharmacological properties [2]. Its 11-methoxy-substituted analog (–)-11-methoxyeburnamonine (**2**) has also been isolated from nature [3]. In contrast to **1**, however, little effort has been made to obtain it synthetically [4,5]. Our interest in an efficient synthesis of 11-methoxyeburnamonine derivatives was thus aroused, to enable pharmacological screening. In view of their close structural resemblance to the eburnamonine skeleton, the non-natural 20-deethyl derivatives of **1** and **2**, the 11-methoxydeethyleburnamonines **4** and **13** would also be expected to possess interesting pharmacological properties. The 20-deethyl derivatives have previously appeared only in a patent lacking synthetic details [6]. A detailed synthesis with full spectroscopic data of the title compounds **4** and **13** is reported below.

Figure 1



1 (R = H)
2 (R = OCH_3)



3 (R = H)
4 (R = OCH_3)

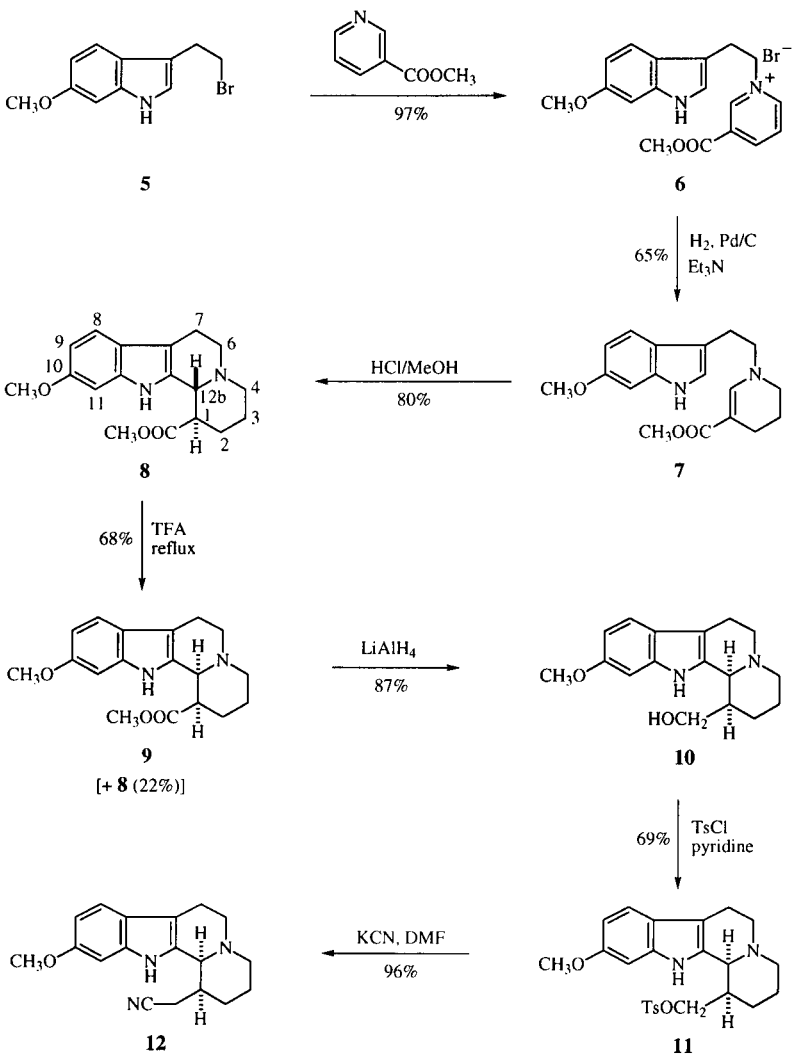
Results and Discussion.

Alkylation of methyl nicotinate with 6-methoxytryptophyl bromide [7] (**5**) gave the pyridinium salt **6**, which was hydrogenated over Pd/C catalyst to yield tetrahydropyridine **7** (Scheme 1). Pictet-Spengler cyclization of **7** in methanolic hydrogen chloride provided ester **8** (H-1 and H-12b *trans*). The overall yield of the three steps was 50%. Refluxing *trans*-ester **8** in trifluoroacetic acid for 2 hours yielded an equilibrium mixture of *trans*-ester **8** and its C-12b epimer, *cis*-ester **9** in 90% yield. The ratio of the isolated esters was 1:3 (**8**:**9**). Reduction of *cis*-ester **9** with lithium aluminum hydride in tetrahydrofuran at room temperature gave the *cis*-alcohol **10** (87%). Allowing **10** to react with tosyl chloride in pyridine at 4° overnight yielded the unstable *cis*-tosylate **11** (69%). Substitution of the *p*-toluenesulphonyloxy group in **11** with a cyano group was achieved using potassium cyanide in dimethylformamide to give the *cis*-nitrile **12** (96%).

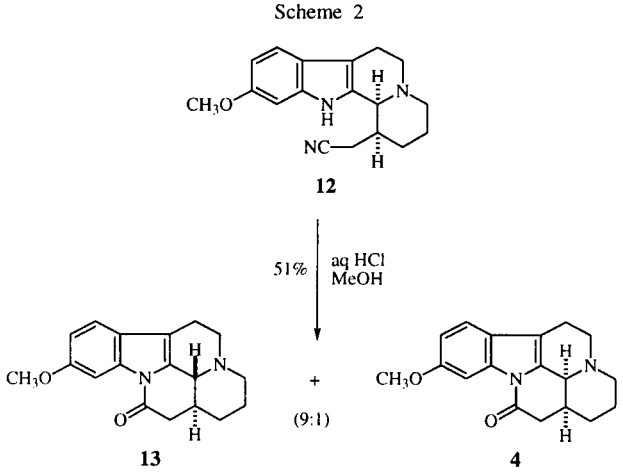
Cyclization of the *cis*-nitrile **12** using aqueous methanolic hydrochloric acid resulted in the formation of *trans*-11-methoxydeethyleburnamonine (**13**) (H-21 and C-20 ethyl *trans*) and a small amount of the *cis*-isomer **4** in a ratio of 9:1 (Scheme 2). This was different from the result where the same reaction conditions were used to effect the cyclization of the methoxy-lacking *cis*-nitrile [8]. In that case, epimerization did not occur and the sole product was *cis*-deethyleburnamonine (**3**). Evidently the presence of a methoxy group in the A ring caused a difference in the acid-induced cyclization behavior. MacPhillamy *et al.* have shown that a methoxy group in the aromatic ring considerably enhances the epimerization rate under acidic conditions [9]. The question then arises whether the epimerization occurs before or after cyclization. We have recently shown that *cis*-deethyleburnamonine (**3**) is not capable of epimerization due to the indole lone pair participation in the amide N-C-O system [10]. The same lone pair participation applies to compound **4**, with the difference that the methoxy group in the aromatic ring enhances the electron density in the aromatic ring. At least in theory, this could overcome the electron-withdrawing effect of the lactam moiety and enable epimerization. To test this possibility we refluxed *cis*-11-methoxydeethyleburnamonine (**4**) in trifluoroacetic acid overnight: no epimerization occurred. Hence, the epimerization must occur before cyclization, at the nitrile stage [11].

To obtain 11-*cis*-methoxydeethyleburnamonine (**4**) more selectively, we adopted our recently published basic cyclization approach [12]. The *cis*-nitrile **12** was cyclized with sodium methoxide in methanol to yield a mixture of *cis*-imine **14** (13%) and starting *cis*-nitrile **12** (73%) (Scheme 3). The *cis*-imine **14** was hydrolyzed in aqueous

Scheme 1



Scheme 2

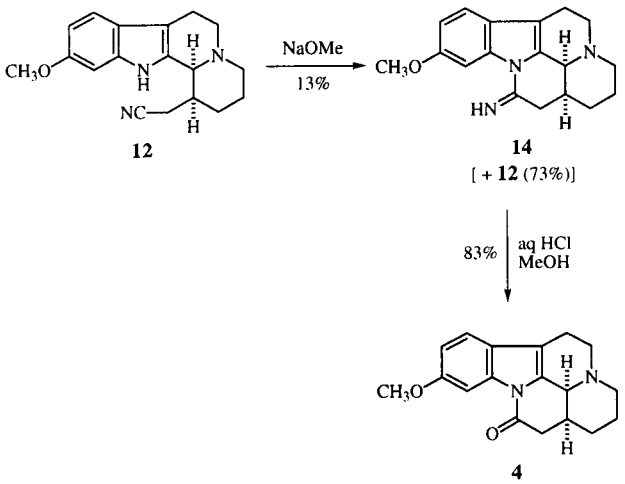


methanolic hydrogen chloride to afford *cis*-11-methoxydeethyleburnamonine (**4**) (yield 11% from **12**). If desired, the yield of the target molecule **4** can be further increased by recycling *cis*-nitrile **12**.

Conclusions.

Total syntheses of (±)-*cis*- and *trans*-11-methoxydeethyleburnamonine have been presented. Surprisingly, the acid treatment of *cis*-nitrile **12** resulted first in epimerization at C-12b, after which cyclization followed resulting mainly in compound **13**. The conclusion from this is that, if electron-donating substituents are present in the A-ring care must be taken when acidic conditions are applied. Base-induced cyclization provided the desired 11-methoxydeethyleburnamonine (**4**). The synthetic pathway described provides an efficient route to 11-methoxyeburnamonine derivatives, enabling their pharmacological testing.

Scheme 3



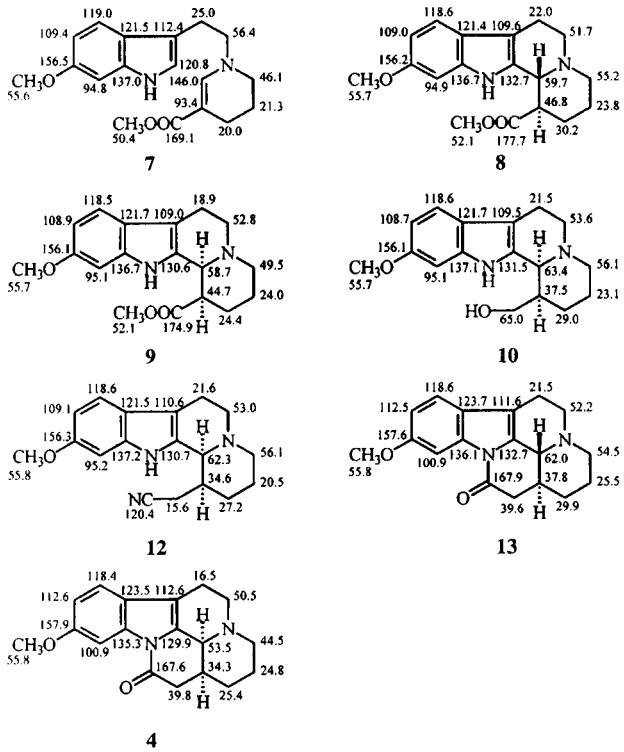
12

14

[+ 12 (73%)]

4

Chart



7 8 9 10 12 13 4

EXPERIMENTAL

Except where otherwise stated, all reactions were carried out under argon. Alkaline workup comprised addition of saturated aqueous sodium hydrogen carbonate, extraction with dichloromethane (3x), drying of the combined organic layers with anhydrous sodium sulphate, and evaporation of the solvent under vacuum. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 700 spectrophotometer. ^{1}H nmr and ^{13}C nmr spectra were recorded on a Varian Unity 400 spectrometer with tetramethylsilane as internal standard. Signal assignments are based on standard APT, DEPT, COSY, NOE, and HETCOR experiments. For the ^{13}C nmr data of compounds **4**, **7**, **8**, **9**, **10**, **12** and **13**, see Chart. EI and HR mass spectra were measured with a Jeol DX 303/DA 5000 mass spectrometer. Microanalyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer. Merck Kieselgel 60 (230-400 mesh) was used in column chromatography.

1-[2-[3-(6-Methoxyindolyl)]ethyl]-3-carbomethoxypyridinium Bromide (**6**).

6-Methoxytryptophyl bromide (**5**) and methyl nicotinate (244 mg, 1.78 mmoles) were dissolved in dry methanol (6 ml) and a small volume of dry diethyl ether. The solution was heated at 100° for 1 hour. The cooled crude product was triturated in a mortar with dry ether and finally dried *in vacuo* to give 650 mg (97%) of pyridinium salt **6**, mp 178-180° (methanol).

Methyl 1-[2-[3-(6-Methoxyindolyl)]ethyl]-1,4,5,6-tetrahydropyridine-3-carboxylate **7**.

Pyridinium salt **6** (833 mg, 2.1 mmoles) and triethylamine (0.5 ml) were dissolved in methanol (40 ml) followed by hydrogenation using Pd/C as catalyst (165 mg, 10%). After 16 hours the catalyst was removed by filtration. The solvent was evaporated and the residue purified by column chromatography (silica gel, dichloromethane/methanol, 99:1) to provide 438 mg (65%) of tetrahydropyridine **7**, mp 90-91° (dichloromethane/hexane); ir: ν 1660 (C=O), 1600 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.13 (br s, 1H, NH), 7.42 (d, J = 8.5 Hz, 1H, indole H-4), 7.35 (s, 1H, pyrid. H-2), 6.84 (m, 2H, indole H-2 and H-7), 6.80 (dd, 1H, J = 8.5, 2.0 Hz, indole H-5), 3.84 (s, 3H, arom. CH_3O), 3.65 (s, 3H, $COOCH_3$); ms: m/z 314 (12), 160 (18), 154 (100); hrms: Calcd. for $C_{18}H_{22}N_2O_3$: 314.1630. Found: 314.1636.

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.68; H, 7.14; N, 8.89.

Methyl 10-Methoxy-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-*a*]-quinolizine-1α-carboxylate (*trans*-Ester) (**8**).

Tetrahydropyridine **7** (674 mg, 2.14 mmoles) was dissolved in hydrogen chloride/methanol and the solution was stirred at room temperature for 18 hours. The solvent was evaporated and alkaline workup was performed. The crude product was purified by column chromatography (silica gel, dichloromethane:methanol, 99:1) to yield 539 mg (80%) of amorphous *trans*-ester **8**; ir: ν 2830-2750 (Wenkert-Bohlmann bands), 1710 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.04 (br s, 1H, NH), 7.32 (d, J = 8.5 Hz, 1H, H-8), 6.78 (d, J = 2.0 Hz, 1H, H-11), 6.73 (dd, J = 8.5, 2.0 Hz, 1H, H-9), 3.82 (s, 3H, arom. CH_3O), 3.80 (s, 3H, $COOCH_3$), 3.78 (d, J = 10.0 Hz, 1H, H-12b); ms: 314 (77), 313 (100), 253 (20), 227 (28), 200 (40), 199 (23); hrms: Calcd. for $C_{18}H_{22}N_2O_3$: 314.1630. Found: 314.1631.

Methyl 10-Methoxy-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]-quinolizine-1α-carboxylate (*cis*-Ester) (**9**).

trans-Ester **8** (476 mg, 1.51 mmoles) was dissolved in trifluoroacetic acid (12 ml) and the mixture was refluxed for 2 hours on an oil bath at 90°. After evaporation of the acid, alkaline workup was performed. Purification by column chromatography (silica gel, dichloromethane/methanol, 99:1-96:4) yielded 110 mg (22%) of starting *trans*-ester **8** and 324 mg (68%) of amorphous *cis*-ester **9**; ir: ν 2830-2750 (Wenkert-Bohlmann bands), 1720 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.29 (br s, 1H, NH), 7.33 (d, J = 8.5 Hz, 1H, H-8), 6.86 (d, J = 2.5 Hz, 1H, H-11), 6.76 (dd, J = 8.5, 2.5 Hz, 1H, H-9), 4.16 (br s, 1H, H-12b), 3.84 (s, 3H, arom. CH_3O), 3.66 (s, 3H, $COOCH_3$); ms: m/z 314 (76), 313 (100), 227 (49), 200 (80), 199 (50); hrms: Calcd. for $C_{18}H_{22}N_2O_3$: 314.1630. Found: 314.1642.

10-Methoxy-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1α-yl-methanol (*cis*-Alcohol) (**10**).

cis-Ester **9** (294 mg, 0.936 mmole) in dry tetrahydrofuran (25 ml) was added to a suspension of lithium aluminum hydride (179 mg, 4.72 mmoles) in tetrahydrofuran (25 ml). The mixture was stirred at room temperature for 1.5 hours. After alkaline treatment (aqueous sodium hydroxide) the mixture was filtered with suction through celite. The filter cake was washed with a mixture of methanol (10 ml) and dichloromethane (40 ml). Water (150 ml) was added to the filtrate and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 50 ml). Drying, evaporation of the solvent and purification of the residue by column chromatography (silica gel, dichloromethane/methanol, 94:6) yielded 233 mg (87%) of *cis*-alcohol **10**, mp 158.5-160° (dichloromethane), ir: ν 3600-3000 (broad, OH and NH), 2830-2750 (Wenkert-Bohlmann bands) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.98 (br s, 1H, NH), 7.32 (d, J = 9.0 Hz, 1H, H-8), 6.79 (d, J = 2.5 Hz, 1H, H-11), 6.75 (dd, J = 9.0, 2.5 Hz, 1H, H-9), 3.80 (s, 3H, arom. CH_3O), 3.83-3.55 (m, 2H, CH_2OH), 3.58 (br s, 1H, H-12b); ms: m/z 286 (100), 285 (97), 269 (38), 227 (28), 200 (47), 199 (35); hrms: Calcd. for $C_{17}H_{22}N_2O_2$: 286.1681. Found: 286.1688.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 70.70; H, 7.89; N, 9.44.

10-Methoxy-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizin-1α-yl-acetonitrile (*cis*-Nitrile) (**12**).

cis-Alcohol **10** (52 mg, 0.18 mmole) was dissolved in dry pyridine (1 ml) and *p*-toluenesulphonyl chloride (68 mg, 0.36 mmole) was added at 0°. The mixture was kept at 4° for 17 hours. Pyridine was evaporated at 0° *in vacuo*. The residue was treated with an excess of ice cold aqueous dilute sodium hydrogen carbonate and the solution was extracted with dichloromethane (3x). After drying and evaporation of the solvent the residual material was purified by column chromatography (silica gel, dichloromethane/methanol, 98:2) to give 55 mg (69%) of amorphous **11**; ^1H nmr (deuteriochloroform): δ 7.92 (br s, 1H, NH), 7.51 (d, J = 8.5 Hz, 2H, H-3' and H-5' of Ts), 7.29 (d, J = 9.0 Hz, 1H, H-8), 7.10 (d, J = 8.5 Hz, 2H, H-2' and H-6' of Ts), 6.86 (d, J = 2.0 Hz, 1H, H-11), 6.76 (dd, J = 9.0, 2.0 Hz, 1H, H-9), 4.20 (dd, J = 10.5, 9.0 Hz, 1H, CH_2OTs), 3.84 (s, 3H, CH_3O), 3.82 (dd, J = 10.5, 4.0 Hz, 1H, CH_2OTs), 3.38 (br s, 1H, H-12b), 2.34 (s, 3H, CH_3 of Ts). *cis*-Tosylate **11** (52 mg, 0.118 mmole) was then dissolved in *N,N*-dimethylformamide (2.0 ml) and potassium cyanide (40 mg, 0.61 mmole) was added. The mixture was stirred at 60° for 20 hours. The solvent was removed under reduced pressure and the residue dried further in high vacuum. After alkaline workup the residue was purified by column chromatography (silica gel, dichloromethane/methanol, 98.5:1.5) to yield 33.5 mg (96%) of solid **12**, mp 142-143° (dichloromethane/hexane); ir: ν 2830-2750 (Wenkert-Bohlmann bands), 2250 (CN) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.91 (br s, 1H, indole NH), 7.32 (d, J = 9.0 Hz, 1H, H-8), 6.84 (d, J = 2.5 Hz, 1H, H-11), 6.76 (dd, J = 9.0, 2.5 Hz, 1H, H-9), 3.83 (s, 3H, CH_3O), 3.44 (d, J = 2.0 Hz, 1H, H-12b); ms: m/z 295 (67), 294 (100), 227 (35), 200 (47), 199 (23); hrms: Calcd. for $C_{18}H_{21}N_3O$: 295.1685. Found: 295.1666.

Anal. Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 72.85; H, 7.26; N, 14.20.

trans-11-Methoxydeethyleburnamonine (**13**).

cis-Nitrile **12** (33 mg, 0.11 mmole) was dissolved in a 2:1 mixture of 32% aqueous hydrochloric acid and methanol (3 ml). The solution was refluxed for 16 hours. After alkaline workup, the crude product was purified by column chromatography (silica gel, dichloromethane/methanol, 96:4) to give 2 mg (5%) of **4** and 15 mg (46%) of amorphous **13**; ir: ν 1700 (C=O), 2830-2750 (Wenkert-Bohlmann bands) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.96 (d, J = 2.5 Hz, 1H, H-12), 7.27 (d, J = 9.0 Hz, 1H, H-9), 6.89 (dd, J = 9.0, 2.5 Hz, 1H, H-10), 3.87 (s, 3H, CH_3O); ms: m/z 296 (60), 295 (100); hrms: Calcd. for $C_{18}H_{20}N_2O_2$: 296.1525. Found: 296.1552.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.71; H, 6.73; N, 9.11.

cis-11-Methoxydeethyleburnamonine (**4**).

cis-Nitrile **12** (45 mg, 0.15 mmole) was dissolved in 0.08 *M* methanolic sodium methoxide (8.5 ml). The solution was refluxed for 4 hours, after which the methanol was evaporated. After alkaline workup, the crude product was purified by column chromatography (silica gel, dichloromethane/methanol, 94:6) to yield 33 mg (73%) of starting nitrile **12** and 6 mg (13%) of *cis*-imine **14**: ^1H nmr (deuteriochloroform): δ 8.28 (d, J = 2.5 Hz, 1H, H-12), 7.33 (d, J = 8.5 Hz, 1H, H-9), 6.89 (dd, J = 8.5, 2.5 Hz, 1H, H-10), 4.35 (m, 1H, H-21), 3.89 (s, 3H, CH_3O). The *cis*-imine (6 mg, 0.02 mmole) was dissolved in a 2:1 mixture of 32% aqueous hydrochloric acid and methanol (3 ml) and the resulting solution was refluxed for 0.5 hour. The reaction mixture was evaporated and alkaline workup was performed to give 5 mg (83%) of amorphous *cis*-11-methoxydeethyleburnamonine (**4**); ir: ν 1700 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.99 (d, J = 2.5 Hz, 1H, H-12), 7.31 (d, J = 9.0 Hz, 1H, H-9), 6.92 (dd, J = 9.0, 2.5 Hz, 1H, H-10), 4.36 (m, 1H, H-21), 3.89 (s, 3H, CH_3O); ms: m/z 296 (80), 295 (100), 252 (17), 239 (35); hrms: Calcd. for $C_{18}H_{20}N_2O_2$: 296.1525. Found: 296.1555.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.69; H, 6.64; N, 9.17.

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