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SYNTHESIS OF SUBSTITUTED INDOLIZINO[8,7-*b*]INDOLES FROM HARMINE AND THEIR BIOLOGICAL ACTIVITY

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The reaction of harmine with phenacyl bromides or ethyl bromoacetate gives quaternized harmine derivatives. The cyclization of the phenacylharminium salts yields the corresponding 2-aryl-11H-indolizino[8,7-b]indoles. Vilsmaier-Haack formylation of 11H-indolizino[8,7-b]indoles leads to the corresponding 3,10-bisformyl derivatives. The acylation proceeds selectively at C(3) to give 3-acetyl-2-aryl-11H-indolizino[8,7-b]indole.

Keywords: harmine, phenacyl bromides, antimicrobial, cytotoxic, and anticholinesterase activities, acetylation, cyclization, formylation.

Plant metabolites containing the 11H-indolizino[8,7-*b*]indole unit such as the alkaloids harmicidine [1] and trichotomine [2] have valuable pharmacological properties. The tetrahydro-11H-indolizino[8,7-*b*]indole fragment is a structural element of plant cytotoxic indole-containing subincanadine alkaloids [3, 4]. We attempted to construct this heterocyclic unit by synthetic transformations of the available plant alkaloid, harmine (**1**). Some reactions of this compound have been described in our previous work [5, 6].

We have shown that the reaction of harmine **1** with phenacyl bromides **2a-c** in ethanol leads to the formation of harminium salts **3a-c**. Similarly, the action of ethyl bromoacetate on harmine **1** leads to quaternized salt **4** (Scheme 1). We should point out that the preparation of 9H-β-carbolinium salts holds interest in light of the high antimicrobial (including antimalarial) activity of various quaternized β-carboline derivatives [7-9].

Phenacylharminium salts **3a-c** undergo facile cyclization upon treatment with KOH to give 11H-indolizino[8,7-*b*]indole derivatives **5a-c** in 77-85% yield. Thus, this method reproduces a reported approach to the synthesis of indolizines [10].

The methods described for constructing the indolizino[8,7-*b*]indole unit are based on the Pictet-Spengler [11, 12] and Bischler-Napieralski reactions [13, 14] of tryptamine or tryptophan derivatives, the reaction of 3,4-dihydro-β-carboline with 2-acetoxyacrylates [15, 16], and the 1,3-dipolar cycloaddition of derivatives of β-carboline azomethine ylids [17]. Our method for obtaining this heterocyclic unit features a high yield of

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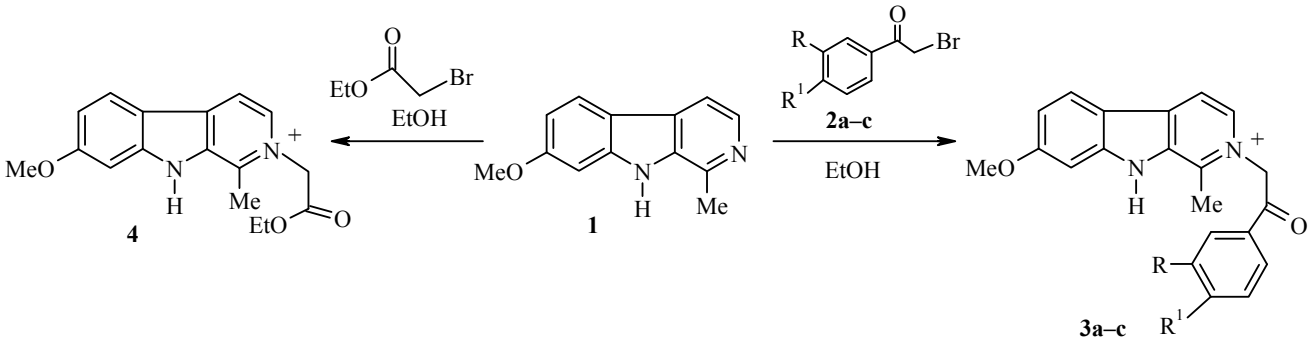
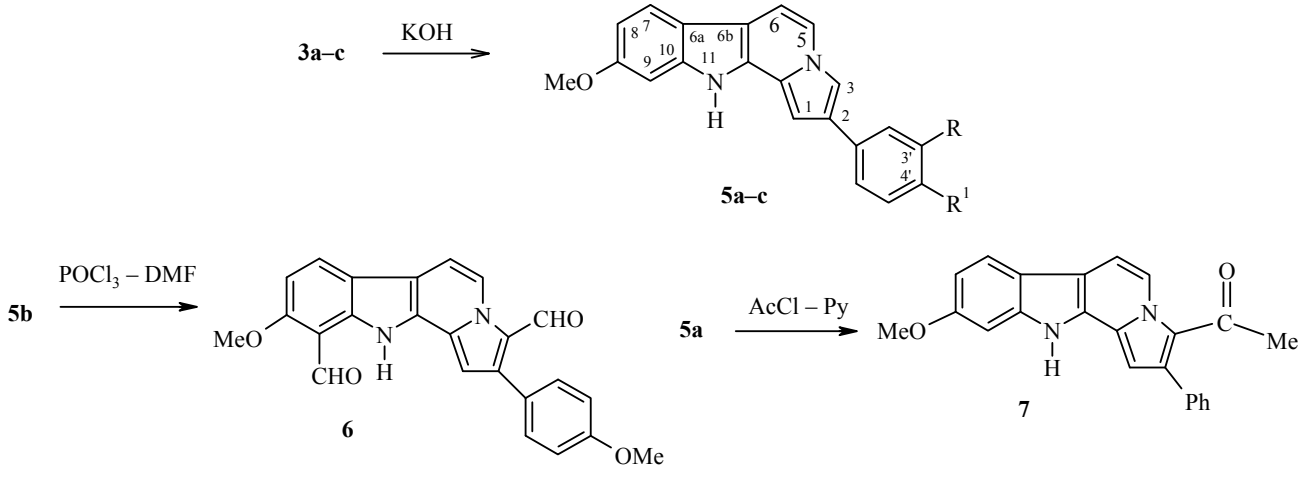
Scheme 1



2, **3 a** R = R^1 = H; **b** R = H, R^1 = OMe; **c** R = R^1 = Cl

tetracyclic derivatives of 11H-indolizino[8,7-*b*]indole. These results have led us to study the reactivity of products **5a-c**. The Vilsmaier-Haack formylation of compound **5b** led to 9-methoxy-2-(4-methoxyphenyl)-11H-indolizino[8,7-*b*]indole-3,10-dicarbaldehyde (**6**). Harmine **1** is characteristically inert under these conditions. Thus, the reaction reveals the effect of the indolizine fragment in the structure of compound **5b**. The acetylation of compound **5a** under conditions employed for N–O-acylation with MeCOCl/pyridine proceeds readily and selectively at C-3 of the indolizinoindole to give 3-acetyl-9-methoxy-2-phenyl-11H-indolizino[8,7-*b*]indole (**7**) (Scheme 2). The structure of the compounds synthesized was established from the spectral data. The signals for H-1 at δ 6.96-7.01 ppm and H-3 at δ 7.99-8.12 ppm, which appear as broadened doublets, are a distinguishing feature of the ^{1}H NMR spectra of 11H-indolizino[8,7-*b*]indoles **5a-c**. The introduction of a substituent at C-3 of the indolizinoindoles (compounds **6** and **7**) leads to disappearance of the signal for H-3 proton and a characteristic downfield shift for proton H-5. The compounds synthesized have characteristic UV spectra typical for quaternized amines (**3a-c** and **4**) or conjugated indolizinoindole systems (**5a-c**, **6**, and **7**).

Scheme 2



5 a R = R^1 = H; **b** R = H, R^1 = OMe; **c** R = R^1 = Cl

Biological screening of products **3a-c**, **4**, and **5a-c** included determination of the antimicrobial activity relative to Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) as well as yeast fungi *Candida albicans* by the agar diffusion test. The reference substances were gentamycin for bacteria and nystatin for *Candida albicans*. We found that N(2)-phenacylharminium bromide (**3a**) and N(2)-(3,4-dichlorophenacyl)harminium bromide (**3b**) have marked

antimicrobial activity relative to the Gram-positive species *Bacillus subtilis*. Bromide **3b** and indole derivatives **5a-c** display moderate activity relative to the Gram-positive species *Staphylococcus aureus*. Bromide **4** has moderate antibacterial activity relative to the test species *Bacillus subtilis*. Moderate antimicrobial activity toward yeast fungi *Candida albicans* was found for compounds **3a**,**b, 5a**,**b**.

Cytotoxic properties have been reported for harmine and its derivatives [18]. The cytotoxicity of compounds **3a-c**, **4**, and **5a-c** was studied relative to the survival of larvae of brine shrimp *Artemia salina* (Leach). The experiments were carried out for two-day-old larvae under conditions of *in vitro* cultivation. The reference compound was 13-dimethylamino-1,10β-epoxy-5,7α,11β(H)-guai-3,4-en-6,12-olide (the active substance of preparation Arglabin), which has antitumor activity [19]. We found that bromide **3a** has cytotoxic activity relative to larvae of brine shrimp *Artemia salina* (Leach).

Harmine has tranquillizing and anesthetizing action and has been used for the treatment of Parkinson's disease. This property has been attributed to its capacity to inhibit acetylcholinesterase. 2-Methylnorharmane [20] and quaternized harmine derivatives display anticholinesterase activity [21]. We have found that 2-phenacylharminium bromide (**3a**) and its cyclization product **5a** display higher anticholinesterase activity (0.308 and 0.251 μA, respectively) relative to the model inhibitor, prozerin (0.115 μA). This result indicates that the compounds synthesized may be considered as reversibly-competitive inhibitors of acetylcholinesterase.

EXPERIMENTAL

The IR spectra were taken on an Avatar 360 esp Fourier spectrometer for KBr pellets. The UV spectra were taken on an HP 8453 UV-vis spectrometer in ethanol (c 10^{-4} mol/liter). The ^{1}H and ^{13}C NMR spectra were taken on a Bruker AV-300 spectrometer at 300 and 75 MHz, respectively, for compounds **3a-c** and **4** and on a Bruker AV-600 spectrometer at 600 and 150 MHz, respectively, for compounds **5a-c**, **6**, and **7** in DMSO-d_6 (compounds **3a-c**, **5a-c**, and **7**), CD_3OD (compound **4**), and $CDCl_3$ (compound **6**). Different types of proton-proton and carbon-proton shift correlations (COSY, COXH, COLOC) were used to assign the signals in the NMR spectra of compounds **3a-c**, **5**, and **6**. A DFS Thermo Scientific high-resolution mass spectrometer was used to take the mass spectra and determine the molecular masses and elemental composition. The ionizing voltage was 70 eV and the injector temperature was 270-300°C. The melting points were found using a Koefler block.

The reaction course was followed by thin-layer chromatography on Silufol UV-254 plates. The reaction products were isolated by recrystallization or chromatography on a silica gel column.

Preparation of N-Aroylmethyl Harmine Salts 3a-c (General Method). A mixture of harmine **1** (0.6 g, 0.28 mmol) and corresponding aroylmethyl bromide **2a-c** (0.30 mmol) in ethanol (15 ml) was heated at reflux for 30 min until the solid was completely dissolved. The reaction mixture was evaporated to half volume. Then, ethyl acetate (5 ml) was added to the residue. After cooling, the precipitate formed was filtered off to give salts **3a-c** as yellow crystals.

2-Phenacylharminium Bromide (3a) was obtained in 86% yield; mp 280°C (dec.). IR spectrum, ν, cm^{-1}: 3057, 3014, 2951, 1691, 1633, 1595, 1565, 1530, 1469, 1434, 1340, 1296, 1228, 1164, 1134, 1079, 1026, 990, 925, 811, 796, 761, 685, 632. UV spectrum, λ_{max}, nm (log ε): 202 (5.30), 204 (5.31), 254 (5.53), 291 (5.67), 295 (5.68), 336 (5.81), 490 (4.87). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.95 (3H, s, CH_3); 3.38 (2H, br. s, CH_2); 4.01 (3H, s, CH_3O); 7.12 (1H, dd, J = 8.8, J = 2.1, H-6); 7.30 (1H, d, J = 2.1, H-8); 7.68 (2H, m, C_6H_5); 7.75 (1H, m, C_6H_5); 8.18 (1H, d, J = 8.8, H-5); 8.21 (2H, m, 2H, C_6H_5); 8.32 (1H, d, J = 5.6, H-4); 8.42 (1H, d, J = 5.6, H-3); 12.65 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 15.22 (q, CH_3); 55.79 (q, CH_3O); 62.68 (t, CH_2); 94.09 (d, C-8); 125.08 (d, C-5); 113.38 (d, C-4); 114.06 (d, C-6); 114.45 (s, C-4b); 124.49 (d, C-4'); 128.51 (d, C-3',5'); 129.12 (d, C-2',6'); 131.43 (s, C-9a); 133.52 (s, C-4a); 134.86 (s, C-1); 137.51 (d, C-3); 139.41 (s, C-1'); 147.96 (s, C-8a); 162.97 (s, C-7); 191.52 (s, C=O). Found, %: C 61.72; H 3.98; Br 19.91; N 7.14. $C_{21}H_{19}BrN_2O_2$. Calculated, %: C 61.33; H 4.66; Br 19.43; N 6.81.

2-(4-Methoxyphenacyl)harminium Bromide (3b) was obtained in 91% yield; mp 316-318°C (dec.). IR spectrum, ν, cm^{-1}: 3404, 3082, 2972, 1664, 1601, 1515, 1437, 1355, 1213, 1167, 1128, 1009, 991, 933, 828, 799, 736, 704, 676, 612. UV spectrum, λ_{max}, nm (log ε): 203 (5.31), 223 (5.38), 254 (5.54), 269 (5.59), 335 (5.81), 493 (4.69). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.98 (3H, s, CH_3); 3.38 (2H, br. s, CH_2); 3.98 (3H, s, CH_3O); 4.01 (3H, s, CH_3O); 7.15 (1H, dd, *J* = 8.5, *J* = 2.1, H-6); 7.30 (1H, d, *J* = 2.1, H-8); 7.32 (2H, d, *J* = 8.0, C_6H_5); 7.88 (2H, d, *J* = 8.0, C_6H_5); 8.21 (1H, d, *J* = 8.5, H-5); 8.30 (1H, d, *J* = 5.6, H-4); 8.40 (1H, d, *J* = 5.6, H-3); 12.65 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 15.68 (q, CH_3); 56.60 (q, CH_3O); 58.22 (q, CH_3O); 63.12 (t, CH_2); 94.60 (d, C-8); 114.18 (d, C-4); 114.88 (s, C-4b); 115.89 (d, C-3',5'); 115.46 (d, C-6); 125.63 (d, C-5); 129.12 (d, C-2',6'); 131.12 (s, C-9a); 132.18 (s, C-4a); 134.86 (s, C-1); 135.12 (s, C-1'); 138.62 (d, C-3); 148.06 (s, C-8a); 155.62 (s, C-4'); 164.48 (s, C-7); 190.48 (s, C=O). Found, %: C 60.39; H 4.50; Br 18.54; N 6.25. $C_{22}H_{21}BrN_2O_3$. Calculated, %: C 59.87; H 4.80; Br 18.11; N 6.35.

2-(3,4-Dichlorophenacyl)harminium Bromide (3c) was obtained in 84% yield; mp 310-312°C (dec.). IR spectrum, ν, cm^{-1}: 3053, 3009, 1680, 1633, 1583, 1565, 1466, 1392, 1339, 1295, 1264, 1211, 1133, 1079, 1030, 972, 934, 832, 820, 778, 675, 634, 610. UV spectrum, λ_{max}, nm (log ε): 201 (5.30), 257 (5.54), 338 (5.82), 414 (6.02), 422 (6.04), 427 (6.05), 490 (4.28).^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.95 (3H, s, CH_3); 3.38 (2H, br. s, CH_2); 4.01 (3H, s, CH_3O); 7.16 (1H, dd, *J* = 8.8, *J* = 2.1, H-6); 7.32 (1H, d, *J* = 2.1, H-8); 7.68 (1H, d, *J* = 8.6, H-5'); 7.95 (1H, dd, *J* = 8.6, *J* = 2.0, H-6'); 8.20 (1H, d, *J* = 8.8, H-5); 8.25 (1H, d, *J* = 2.0, H-2'); 8.33 (1H, d, *J* = 5.6, H-4); 8.45 (1H, d, *J* = 5.6, H-3); 12.70 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 15.60 (q, CH_3); 49.66 (t, CH_2); 56.29 (q, CH_3O); 94.91 (d, C-8); 114.12 (d, C-4); 114.31 (s, C-4b); 114.93 (d, C-6); 125.09 (d, C-5); 129.09 (d, C-6'); 131.18 (d, C-5'); 132.07 (d, C-2'); 132.66 (s, C-9a); 133.37 (s, C-4'); 134.57 (s, C-4a); 135.37 (s, C-1'); 135.56 (d, C-1); 138.66 (s, C-3'); 140.31 (d, C-3); 147.05 (s, C-8a); 164.34 (s, C-7); 190.67 (s, C=O). Found, %: C 52.27; H 3.57; Br 17.04; Cl 15.02; N 5.51. $C_{21}H_{17}BrCl_2N_2O_2$. Calculated, %: C 52.53; H 3.57; Br 16.64; Cl 14.77; N 5.83.

2-(Ethoxycarbonylmethyl)harminium Bromide (4) was obtained in 80% yield by the reaction of harmine **1** with ethyl bromoacetate according to the method described above, mp 298-300°C (dec.). IR spectrum, ν, cm^{-1}: 2996, 2904, 2785, 1731, 1680, 1634, 1582, 1566, 1515, 1453, 1377, 1294, 1261, 1209, 1164, 1132, 1023, 949, 869, 804, 736, 695, 675, 637. UV spectrum, λ_{max}, nm (log ε): 204 (5.31), 253 (5.53), 324 (5.78), 337 (5.82), 426 (6.06), 493 (6.20). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37 (3H, t, *J* = 7.0, CH_3); 2.96 (3H, s, CH_3); 3.95 (3H, s, CH_3O); 4.37 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 5.66 (2H, br. s, CH_2); 6.91 (1H, dd, *J* = 8.0, *J* = 2.1, H-6); 7.02 (1H, d, *J* = 2.1, H-8); 7.97 (1H, m, H-5); 8.12 (1H, d, *J* = 6.0, H-4); 8.35 (1H, d, *J* = 6.0, H-3); 12.65 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 14.37 (q, CH_2CH_3); 15.83 (q, CH_3 at C-1); 55.36 (q, CH_3O); 57.92 (t, CH_2); 63.90 (t, CH_2CH_3); 94.87 (d, C-8); 114.53 (s, C-4b); 114.67 (d, C-4); 114.93 (d, C-6); 124.74 (d, C-5); 133.57 (s, C-4a); 135.66 (d, C-3); 135.80 (s, C-9a); 139.74 (s, C-8a); 147.75 (s, C-1); 165.14 (s, C-7); 167.62 (s, C=O). Found, %: C 53.48; H 4.88; Br 20.74; N 7.62. $C_{17}H_{19}BrN_2O_3$. Calculated, %: C 53.82; H 5.01; Br 21.11; N 7.39.

Preparation of substituted 11H-indolizino[8,7-*b*]indoles 5a-c (General Method). A 50% aqueous solution of KOH (3 eq.) was added to a hot saturated solution of quaternary salt **3a-c** in ethanol. The reaction mixture was maintained for 5-10 min at 65-70°C until no further precipitate formed. After cooling, the crystals were filtered off and washed with aqueous methanol and ether to give indolizinoindoles **5a-c**.

9-Methoxy-2-phenyl-11H-indolizino[8,7-*b*]indole (5a) was obtained in 85% yield; mp 223-225°C. IR spectrum, ν, cm^{-1}: 3080, 2969, 1622, 1581, 1537, 1497, 1438, 1400, 1326, 1309, 1239, 1220, 1158, 1026, 817, 780, 760, 730, 693, 503. UV spectrum, λ_{max}, nm (log ε): 209 (5.34), 221 (5.39), 223 (5.40), 241 (5.48), 273 (5.60), 338 (5.82), 345 (5.97). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.81 (3H, s, OCH_3); 6.78 (1H, dd, *J* = 8.3, *J* = 2.2, H-8); 6.99 (1H, br. d, *J* = 1.5, H-1); 7.05 (1H, d, *J* = 2.2, H-10); 7.17 (1H, d, *J* = 7.0, H-6); 7.21 (1H, m, H-4'); 7.39 (2H, m, H-3', H-5'); 7.70 (2H, d, *J* = 8.2, H-2', H-6'); 7.77 (1H, d, *J* = 8.3, H-7); 7.96 (1H, dd, *J* = 7.0, *J* = 1.1, H-5); 7.99 (1H, dd, *J* = 1.5, *J* = 1.1, H-3); 11.89 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.63 (q, OCH_3); 93.36 (d, C-1); 95.40 (d, C-10); 105.06 (d, C-6); 109.26 (d, C-8); 109.50 (s, C-11a); 111.48 (d, C-3); 117.86 (s, C-6b); 119.26 (d, C-5); 119.84 (d, C-7); 124.93 (s, C-11b); 125.66 (d, C-2',6'); 124.65 (d, C-4');

127.25 (s, C-2); 128.96 (s, C-6a); 129.17 (d, C-3', C-5'); 135.34 (s, C-1'); 139.30 (s, C-10a); 157.20 (s, C-9). Mass spectrum, *m/z* (I_{rel}, %): 314 (3), 313 (22), 312 $[M]^+$ (100), 298 (17), 297 (72), 268 (14), 156 (15). Found: *m/z* 312.1255 $[M]^+$. $C_{21}H_{16}N_2O$. Calculated: M 312.1257.

9-Methoxy-2-(4-methoxyphenyl)-11H-indolizino[8,7-*b*]indole (5b) was obtained in 80% yield; mp 245-248°C. IR spectrum, ν, cm^{-1}: 3392, 3117, 3009, 2961, 2926, 2835, 1646, 1620, 1578, 1547, 1433, 1377, 1339, 1282, 1325, 1159, 1096, 949, 837, 749, 736, 648, 631. UV spectrum, λ_{max}, nm (log ε): 222 (5.29), 276 (5.62), 297 (5.69), 333 (5.80), 338 (5.82), 344 (5.84). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.76 (3H, s, OCH_3 at C-9); 3.89 (3H, s, OCH_3 at C-4'); 6.63 (1H, dd, *J* = 8.5, *J* = 2.2, H-8); 6.96 (1H, br. d, *J* = 1.5, H-1); 7.05 (1H, d, *J* = 2.2, H-10); 7.12 (2H, m, *J* = 8.2, H-3',5'); 7.22 (1H, d, *J* = 7.0, H-6); 7.62 (2H, m, *J* = 8.2, H-2',6'); 7.70 (1H, d, *J* = 8.5, H-7); 7.91 (1H, dd, *J* = 7.0, *J* = 1.1, H-5); 8.03 (1H, br. d, *J* = 1.5, H-3); 11.86 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.46 (q, OCH_3); 56.22 (q, OCH_3); 94.08 (d, C-1); 96.03 (d, C-10); 105.12 (d, C-6); 110.42 (d, C-8); 110.43 (s, C-11a); 111.81 (d, C-3); 114.46 (d, C-3',5'); 118.66 (s, C-6b); 119.58 (d, C-5); 120.41 (d, C-7); 125.13 (s, C-11b); 124.65 (s, C-1'); 127.18 (s, C-2); 129.45 (s, C-6a); 126.18 (d, C-2',6'); 140.15 (s, C-10a); 158.06 (s, C-9); 160.26 (s, C-4'). Mass spectrum, *m/z* (I_{rel}, %): 344 (4), 343 (25), 342 $[M]^+$ (100), 328 (13), 327 (50), 284 (13), 171 (14). Found: *m/z* 342.1365 $[M]^+$. $C_{22}H_{18}N_2O_2$. Calculated: M 342.1363.

2-(3,4-Dichlorophenyl)-9-methoxy-11H-indolizino[8,7-*b*]indole (5c) was obtained in 77% yield; mp 231-233°C. IR spectrum, ν, cm^{-1}: 3647, 3385, 3124, 2962, 2833, 1191, 1555, 1498, 1466, 1327, 1220, 1078, 1025, 941, 872, 826, 787, 748, 699, 676. UV spectrum, λ_{max}, nm (log ε): 201 (5.30), 243 (5.49), 270 (5.59), 288 (5.66), 336 (5.81), 344 (5.84). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (3H, s, OCH_3); 6.78 (1H, dd, *J* = 8.5, *J* = 2.4, H-8); 7.01 (1H, br. d, *J* = 1.6, H-1); 7.05 (1H, d, *J* = 2.4, H-10); 7.22 (1H, d, *J* = 7.1, H-6); 7.61 (1H, d, *J* = 8.4, H-5'); 7.70 (1H, dd, *J* = 8.4, *J* = 2.2, H-6'); 7.78 (1H, d, *J* = 8.5, H-7); 7.91 (1H, d, *J* = 2.2, H-2'); 7.96 (1H, dd, *J* = 6.8, *J* = 0.9, H-5); 8.12 (1H, br. d, *J* = 1.6, H-3); 11.88 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.44 (q, OCH_3); 93.35 (d, C-1); 95.20 (d, C-10); 105.44 (d, C-6); 109.17 (d, C-8); 109.27 (s, C-11a); 112.16 (d, C-3); 117.57 (s, C-6b); 119.01 (d, C-5); 119.70 (d, C-7); 124.43 (s, C-11b); 125.04 (s, C-1'); 125.55 (d, C-6'); 126.88 (d, C-5'); 128.28 (s, C-2); 128.64 (s, C-6a); 131.04 (d, C-2'); 131.66 (s, C-3'); 136.19 (s, C-4'); 139.13 (s, C-10a); 157.00 (s, C-9). Mass spectrum, *m/z* (I_{rel}, %): 382 (64), 381 (25), 380 $[M]^+$ (100), 367 (54), 366 (18), 365 (85), 337 (19). Found: *m/z* 380.0475 $[M]^+$. $C_{21}H_{14}Cl_2N_2O$. Calculated: M 380.0478.

9-Methoxy-2-(4-methoxyphenyl)-11H-indolizino[8,7-*b*]indole-3,10-dicarbaldehyde (6). $POCl_3$ (0.3 ml) was added to DMF (5 ml) at 0°C. The solution was left for 30 min and then compound **5b** (0.3 g, 0.88 mmol) was added. The reaction mixture was left for 18 h at room temperature with periodic stirring. 10% Aqueous sodium acetate (15 ml) was added and the mixture was stirred for an additional 1 h. The reaction mixture was extracted with chloroform. The extract was washed with water and evaporated. The residue was subjected to chromatography on an alumina column using methylene chloride as the eluent. The fraction containing the product was recrystallized from ethyl acetate to give 0.21 g (65%) dialdehyde **6**; mp 242-244°C. UV spectrum, λ_{max}, nm (log ε): 222 (4.42), 234 (4.39), 248 (4.43), 341 (4.31), 386 (4.49), 396 (4.72). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.90 (6H, s, CH_3O at C-9 and CH_3O at C-4'); 6.86 (1H, d, *J* = 8.2, H-8); 6.95 (1H, s, H-1); 7.03 (2H, d, *J* = 8.4, H-3',5'); 7.50 (2H, d, *J* = 8.4, H-2',6'); 7.63 (1H, d, *J* = 7.0, H-6); 7.85 (1H, d, *J* = 8.2, H-7); 9.52 (1H, d, *J* = 7.0, H-5); 9.62 (1H, s, CHO at C-3); 9.66 (1H, s, CHO at C-10); 11.49 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.35 (q, OCH_3); 55.47 (q, OCH_3); 94.47 (d, C-1); 109.60 (d, C-6); 111.23 (d, C-8); 113.65 (s, C-10); 113.98 (d, C-3',5'); 115.54 (s, C-11a); 120.50 (s, C-6b); 120.63 (d, C-5); 121.35 (d, C-7); 121.63 (s, C-1'); 122.95 (s, C-3); 128.07 (s, C-6a); 128.19 (s, C-2); 132.56 (d, C-2',6'); 140.01 (s, C-10a); 146.38 (s, C-11b); 160.26 (s, C-4'); 160.40 (s, C-9); 179.22 (d, CHO at C-3); 185.57 (CHO at C-10). Mass spectrum, *m/z* (I_{rel}, %): 400 (5), 399 (26), 398 $[M]^+$ (100), 383 (21), 355 (15), 353 (11), 199 (10). Found: *m/z* 398.1264 $[M]^+$. $C_{24}H_{18}N_2O_4$. Calculated: M 398.1268.

3-Acetyl-9-methoxy-2-phenyl-11H-indolizino[8,7-*b*]indole (7). Acetyl chloride **(**0.2 ml) was added with stirring to a suspension of indolizine **5a** (0.2 g) in a mixture of chloroform (5 ml) and pyridine (0.5 ml). The solid dissolved to give a yellow-green solution. After 30 min, the reaction mixture was diluted by the addition of

chloroform (10 ml). The solution was washed with three 3-ml water portions and evaporated. The residue was crystallized from 1:1 ethyl acetate–methanol to give 0.15 g (72%) yellow crystalline acetate **7**, mp 233°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.96 (3H, s, CH_3); 3.85 (3H, s, CH_3O); 6.82 (1H, s, H-1); 6.87 (1H, dd, *J* = 8.2, *J* = 2.0, H-8); 7.09 (1H, d, *J* = 2.0, H-10); 7.41 (2H, m, H-2', H-6'); 7.48 (3H, m, H-3', H-4', H-5'); 7.65 (1H, d, *J* = 5.6, H-5); 7.96 (1H, d, *J* = 8.2, H-7); 9.68 (1H, d, *J* = 5.6, H-5); 12.15 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 29.97 (q, CH_3); 55.55 (q, OCH_3); 95.14 (d, C-10); 101.69 (d, C-1); 107.49 (d, C-6); 109.96 (d, C-8); 114.87 (s, C-11a); 116.50 (s, C-6b); 120.49 (d, C-5); 121.14 (d, C-7); 121.43 (s, C-3); 127.33 (s, C-1'); 127.65 (s, C-6a); 127.76 (d, C-4'); 128.48 (d, C-3', C-5'); 130.05 (d, C-2', C-6'); 137.38 (s, C-11b); 138.46 (s, C-2); 140.63 (s, C-10a); 158.57 (s, C-9); 186.88 (s, C=O). Found, %: C 77.57; H 5.05; N 7.85. $C_{23}H_{18}N_2O_2$. Calculated, %: C 77.95; H 5.12; N 7.90.

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