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SYNTHESIS OF *N*-(2-AMINOETHYL)- AND *N*-(3-AMINOPROPYL)CYTISINE

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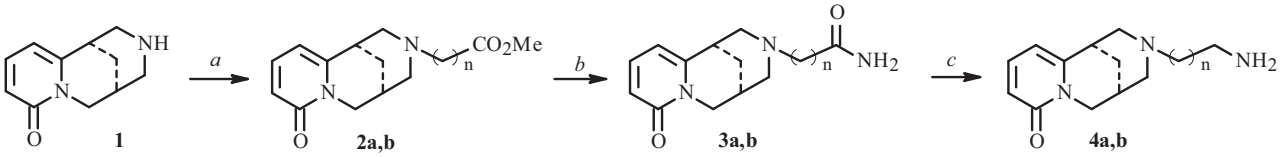
*2-(*N*-cytisinyl)acetamide or 3-(*N*-cytisinyl)propanamide were prepared by treatment of the methyl esters of* N*-cytisinylacetic or 3-(*N*-cytisinyl)propanoic acids with aqueous NH_4OH.* N*-(2-Aminoethyl)- or* N*-(3-aminopropyl)cytisine was synthesized by reduction of the amide with (i-Bu)$_2$AlH.*

Keywords: cytisine, 2-(*N*-cytisinyl)acetamide, 3-(*N*-cytisinyl)propanamide, *N*-(2-aminoethyl)- and *N*-(3-aminopropyl)cytisine.

(–)-Cytisine and its derivatives are attractive to researchers owing to their broad spectrum of biological activity (spasmolytic [1], cholinergic [2], analgesic [3]) due to their high affinity for nicotine–acetylcholine neuroreceptors (nAChRs) [4]. We found earlier that *N*-(2-hydroxyethyl)cytisine derivatives exhibited high antiarrhythmic activity [5, 6]. Compounds containing polymethylenamine fragments are known to possess high biological activity and are used to create antituberculosis, immunodepressive, and antiproliferative drugs [7, 8].

In continuation of research on and for the preparation of new biologically active (–)-cytisine derivatives containing 1,2-ethylene- or 1,3-propylenediamine groups, we synthesized *N*-(aminoalkyl)cytisines [9–11].

The starting compounds were methyl esters of *N*-cytisinylacetic (**2a**) [12] and 3-(*N*-cytisinyl)propanoic (**2b**) [13] acids. The methyl ester of *N*-cytisinylacetic acid (**2a**) was synthesized in 82% yield by the reaction of cytisine (**1**) and the methyl ester of bromoacetic acid in refluxing anhydrous acetone in 2 h in the presence of K_2CO_3. A Michael reaction of **1** and methylacrylate in MeOH at 20°C produced in 48 h **2b** in 95% yield.

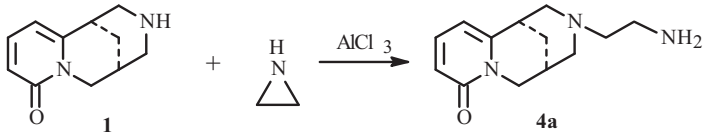


2a,3a,4a: n = 1; **2b,3b,4b:** n = 2

a. $BrCH_2COOMe$ (for **2a**), CH_2=CH-COOMe (for **2b**); *b.* NH_4OH, NH_4Cl; *c.* (*i*-Bu)$_2$AlH, CH_2Cl_2

Treatment of **2a** or **2b** with aqueous NH_4OH in the presence of NH_4Cl at 20–22°C produced in 4 h amides **3a** and **3b** in 80% yields. Reduction of **3a** or **3b** by a 12-fold molar excess of (*i*-Bu)$_2$AlH in refluxing CH_2Cl_2 gave in 2 h *N*-(2-aminoethyl)cytisine (**4a**) or *N*-(3-aminopropyl)cytisine (**4b**) in 15 and 98% yields, respectively. The low yield of **4a** compared with **4b** was probably related to polymerization of the reaction mixture as a result of a side reaction forming an aldehyde because of the high electrophilicity of the carbonyl in **3a**.

The reduction of **3b** was used as an example to show that the yield of desired diamine **4b** decreased to 90% if a 10:1 (*i*-Bu)$_2$AlH:amide mole ratio was used. The yield of **4b** was <40% if $LiAlH_4$ was used as the reductant. The pyridone ring of the amides (**3**) was not reduced in any of the experiments.



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Diamine **4a** was synthesized in one step by reacting **1** and aziridine in refluxing anhydrous benzene in the presence of $AlCl_3$. The yield of **4a** in this instance was 30%.

The structures of the synthesized compounds were established using PMR and ^{13}C NMR spectroscopy and homo- and heteronuclear two-dimensional HH-COSY and CH-CORR spectra.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded with Me_4Si internal standard on a Bruker AM-300 spectrometer (300.13 and 75.45 MHz, respectively). IR spectra were recorded on a Shimadzu IR Prestige-21 instrument. Mass spectra were measured in an MX-1300 spectrometer with input tank temperature 100°C and ionizing potential 12 and 70 eV or in a Shimadzu LC-MS-2010EV GC-MS with atmospheric pressure chemical ionization (APCI). Optical rotation angles were measured on a Perkin–Elmer 341 polarimeter (λ 589 nm) at 20°C. Melting points were determined on a Boetius microstage. TLC was carried out on Silufol (Merck) chromatographic plates using $CHCl_3$:MeOH (9:1) with detection by I_2.

We used pharmacopoeic (–)-cytisine that was isolated from *Thermopsis lanceolata*. Aziridine was prepared by the usual method [14]. Methyl esters of bromoacetic and acrylic acids were purchased (Aldrich). (*i*-Bu)$_2$AlH was a commercial 73% solution from Redkino pilot plant.

Elemental analyses of all compounds corresponded to those calculated.

Methyl Ester of *N*-Cytisinylacetic Acid (2a). A mixture of **1** (2.0 g, 10.52 mmol) and freshly calcined K_2CO_3 (2.5 g) in anhydrous acetone (50 mL) was stirred vigorously, refluxed, treated dropwise with methyl bromoacetate (1.61 g, 10.52 mmol) in acetone (10 mL), stirred under reflux for 30 min, cooled, and filtered to remove the precipitate, which was washed with $CHCl_3$ (30 mL). The filtrate was evaporated at reduced pressure. The residue was chromatographed over SiO_2 ($CHCl_3$:MeOH, 9:1) to afford **2a** (2.25 g, 82%) as yellow crystals, mp 95–96°C, $[\alpha]_D^{20}$ –168.7 ± 0.1° (*c* 0.305, $CHCl_3$), R_f 0.71. Mass spectrum (APCI, *m*/*z*, I_{rel}, %): 263 (83) $[M + H]^+$, 256 (17), 207 (13). IR spectrum (ν, cm^{-1}): 3300–3090, 3018–2760, 1730, 1650, 1570, 1545, 794.

PMR spectrum (C_6D_6, δ, ppm, J/Hz): 1.07 (1H, ddt, ^2J = 12.6, $^3J_{8anti\text{-}7}$ = 3.2, $^3J_{8anti\text{-}9}$ = 3.2, $^4J_{8anti\text{-}10endo}$ = 1.1, H_{anti}-8), 1.13 (1H, dtt, ^2J = 12.6, $^3J_{8syn\text{-}7}$ = 3.2, $^3J_{8syn\text{-}9}$ = 3.2, $^4J_{8syn\text{-}11endo}$ = 1.5, $^4J_{8syn\text{-}13endo}$ = 1.5, H_{syn}-8), 1.58 (1H, m, H-9), 2.20 (1H, m, H-7), 2.37 (1H, ddt, ^2J = 10.9, $^3J_{11endo\text{-}9}$ = 2.9, $^4J_{11endo\text{-}13endo}$ = 1.5, $^4J_{11endo\text{-}8syn}$ = 1.5, H_{endo}-11), 2.39 (1H, ddd, ^2J = 10.9, $^3J_{11exo\text{-}9}$ = 2.6, $^4J_{11exo\text{-}10exo}$ = 1.1, H_{exo}-11), 2.43 (1H, ddt, ^2J = 10.5, $^3J_{13endo\text{-}7}$ = 3.4, $^4J_{13endo\text{-}11endo}$ = 1.5, $^4J_{13endo\text{-}8syn}$ = 1.5, H_{endo}-13), 2.53 (1H, dd, ^2J = 10.5, $^3J_{13exo\text{-}9}$ = 2.4, H_{exo}-13), 2.74 (1H, d, ^2J = 16.7, H_A-14), 2.76 (1H, d, ^2J = 16.7, H_B-14), 3.20 (3H, s, OMe), 3.73 (1H, dd, ^2J = 15.0, $^3J_{10exo\text{-}9}$ = 6.6, H_{exo}-10), 4.08 (1H, d, ^2J = 15.5, H_{endo}-10), 5.40 (1H, dd, $^3J_{5\text{-}4}$ = 6.7, $^4J_{5\text{-}3}$ = 1.4, H-5), 6.53 (1H, dd, $^3J_{3\text{-}4}$ = 9.0, $^4J_{3\text{-}5}$ = 1.4, H-3), 6.80 (1H, dd, $^3J_{4\text{-}3}$ = 9.0, $^3J_{4\text{-}5}$ = 6.7, H-4).

^{13}C NMR spectrum (C_6D_6, δ, ppm): 25.24 (C-8), 28.10 (C-9), 35.59 (C-7), 49.85 (C-10), 50.65 (OMe), 58.25 (C-14), 58.51 (C-11), 59.12 (C-13), 103.20 (C-5), 117.04 (C-3), 138.07 (C-4), 151.61 (C-6), 163.08 (C-2), 170.21 (C-15).

Methyl Ester of 3-(*N*-Cytisinyl)propanoic Acid (2b). Cytisine (**1**, 1.00 g, 5.26 mmol) in MeOH (20 mL) was treated dropwise with methyl acrylate (0.54 g, 6.31 mmol) and stirred at room temperature (25°C) for 48 h. The solvent was removed at reduced pressure. The residue was recrystallized from C_6H_6 (2 mL) to afford **2b** (1.35 g, 95%) as colorless crystals, mp 89–90°C (C_6H_6), $[\alpha]_D^{20}$ –207.0 ± 0.5° (*c* 0.39, $CHCl_3$), R_f 0.75. Found: *m*/*z* 276.1461 $[M]^+$; calcd: MW 276.331. IR spectrum (ν, cm^{-1}): 1732, 1651, 1568, 1546, 798.

PMR spectrum (C_6D_6, δ, ppm, J/Hz): 0.99 (1H, ddt, ^2J = 12.6, $^3J_{8anti\text{-}7}$ = 3.1, $^3J_{8anti\text{-}9}$ = 3.1, $^4J_{8anti\text{-}10endo}$ = 1.1, H_{anti}-8), 1.10 (1H, dtt, ^2J = 12.6, $^3J_{8syn\text{-}7}$ = 3.2, $^3J_{8syn\text{-}9}$ = 3.2, $^4J_{8syn\text{-}11endo}$ = 1.7, $^4J_{8syn\text{-}13endo}$ = 1.6, H_{syn}-8), 1.55 (1H, m, H-9), 1.64 (1H, br.d, ^2J = 10.4, H_{exo}-11), 1.75 (1H, dd, ^2J = 10.5, $^3J_{13exo\text{-}7}$ = 2.1, H_{exo}-13), 1.95 (2H, t, $^3J_{15\text{-}14}$ = 6.8, 2H-15), 2.15 (1H, m, H-7), 2.23 (2H, t, $^3J_{14\text{-}15}$ = 6.8, 2H-14), 2.37 (1H, ddt, ^2J = 10.4, $^3J_{11endo\text{-}9}$ = 3.4, $^4J_{11endo\text{-}8syn}$ = 1.7, $^4J_{11endo\text{-}13endo}$ = 1.6, H_{endo}-11), 2.42 (1H, ddt, ^2J = 10.5, $^3J_{13endo\text{-}7}$ = 3.6, $^4J_{13endo\text{-}11endo}$ = 1.6, $^4J_{13endo\text{-}8syn}$ = 1.6, H_{endo}-13), 3.37 (3H, s, OMe), 3.67 (1H, ddd, ^2J = 15.5, $^3J_{10exo\text{-}9}$ = 6.9, $^4J_{10exo\text{-}11exo}$ = 1.0, H_{exo}-10), 3.97 (1H, d, ^2J = 15.5, H_{endo}-10), 5.38 (1H, dd, $^3J_{5\text{-}4}$ = 6.8, $^4J_{5\text{-}3}$ = 1.4, H-5), 6.50 (1H, dd, $^3J_{3\text{-}4}$ = 9.1, $^4J_{3\text{-}5}$ = 1.4, H-3), 6.82 (1H, dd, $^3J_{4\text{-}3}$ = 9.1, $^3J_{4\text{-}5}$ = 6.8, H-4).

^{13}C NMR spectrum (C_6D_6, δ, ppm): 25.70 (C-8), 28.07 (C-9), 32.35 (C-15), 35.58 (C-7), 49.80 (C-10), 51.13 (OMe), 53.30 (C-14), 59.48 (C-11), 60.48 (C-13), 103.09 (C-5), 116.84 (C-3), 138.10 (C-4), 151.58 (C-6), 162.99 (C-2), 171.98 (C-16).

General Method for Preparing Amides 3a and 3b. Ester **2a** or **2b** (1.0 g) dissolved in NH_4OH (20 mL, 28%, ρ 0.90 g/cm^3) was stirred, treated with NH_4Cl (0.20 g, 3.74 mmol), and held at room temperature for 4 h. The solvent was removed at reduced pressure. The residue was treated with MeOH (20 mL) and filtered to remove the inorganic precipitate. The filtrate was evaporated at reduced pressure. The residue was chromatographed over SiO_2 ($CHCl_3$:MeOH, 9:1) with one drop of Et_3N added to the eluent.

2-(*N*-Cytisinyl)acetamide (3a). Compound **2a** (1.00 g, 3.82 mmol) afforded **3a** (0.75 g, 80%) as colorless crystals, mp 173–174°C, $[\alpha]_D^{20}$ –204 ± 1° (*c* 0.09, $CHCl_3$), R_f 0.35. Mass spectrum (APCI, *m*/*z*, I_{rel}, %): 248 (100) $[M + H]^+$, 191 (23), 246 (100) $[M – H]^–$. IR spectrum (ν, cm$^{–1}$): 3427, 3300, 2922, 2852, 2816, 1681, 1649, 1566, 1544, 1458, 1379, 1145, 806.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.83 (1H, ddt, ^2J = 12.9, $^3J_{8anti-7}$ = 3.3, $^3J_{8anti-9}$ = 3.3, $^4J_{8anti-10endo}$ = 1.1, H_{anti}-8), 1.97 (1H, dtt, ^2J = 12.9, $^3J_{8syn-7}$ = 3.4, $^3J_{8syn-9}$ = 3.4, $^4J_{8syn-11endo}$ = 1.7, $^4J_{8syn-13endo}$ = 1.7, H_{syn}-8), 2.50 (1H, m, H-9), 2.53 (1H, dd, ^2J = 10.7, $^3J_{13exo-9}$ = 2.0, H_{exo}-13), 2.60 (1H, br.d, ^2J = 11.1, H_{exo}-11), 2.89 (1H, d, ^2J = 16.5, H_A-14), 2.90 (1H, ddt, ^2J = 10.7, $^3J_{13endo-7}$ = 3.6, $^4J_{13endo-11endo}$ = 1.7, $^4J_{13endo-8syn}$ = 1.7, H_{endo}-13), 2.98 (1H, d, ^2J = 16.5, H_B-14), 2.99 (1H, br.d, ^2J = 11.1, H_{endo}-11), 3.04 (1H, m, H-7), 3.90 (1H, ddd, ^2J = 15.5, $^3J_{10exo-9}$ = 6.4, $^4J_{10exo-11exo}$ = 1.4, H_{exo}-10), 4.18 (1H, d, ^2J = 15.5, H_{endo}-10), 5.19 (1H, br.s, H_A-N), 6.03 (1H, dd, $^3J_{5-4}$ = 6.8, $^4J_{5-3}$ = 1.5, H-5), 6.07 (1H, br.s, H_B-N), 6.46 (1H, dd, $^3J_{3-4}$ = 9.1, $^4J_{3-5}$ = 1.5, H-3), 7.31 (1H, dd, $^3J_{4-3}$ = 9.1, $^3J_{4-5}$ = 6.8, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.38 (C-8), 28.02 (C-9), 35.35 (C-7), 49.90 (C-10), 61.14 (C-14), 60.51 (C-11), 60.91 (C-13), 104.84 (C-5), 117.00 (C-3), 138.84 (C-4), 150.54 (C-6), 163.33 (C-2), 172.55 (C-15).

3-(*N*-Cytisinyl)propanamide (3b). Compound **2b** (1.0 g, 3.62 mmol) afforded **3b** (0.76 g, 80%) as colorless crystals, mp 192–193°C, $[\alpha]_D^{20}$ –212 ± 1° (*c* 0.17, $CHCl_3$), R_f 0.45. Mass spectrum (APCI, *m*/*z*, I_{rel}, %): 262 (100) $[M + H]^+$, 191 (62), 296 (100) $[M + 2H_2O – H]^–$. IR spectrum (ν, cm$^{–1}$): 3317, 3138, 1693, 1641, 1548, 1144, 800.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.85 (1H, ddt, ^2J = 12.8, $^3J_{8anti-7}$ = 3.2, $^3J_{8anti-9}$ = 3.2, $^4J_{8anti-10endo}$ = 1.2, H_{anti}-8), 1.98 (1H, dtt, ^2J = 12.8, $^3J_{8syn-7}$ = 3.2, $^3J_{8syn-9}$ = 3.2, $^4J_{8syn-11endo}$ = 1.6, $^4J_{8syn-13endo}$ = 1.6, H_{syn}-8), 2.26 (2H, t, ^2J = 6.3, 2H-15), 2.36 (1H, br.d, ^2J = 10.4, H_{exo}-13), 2.39 (1H, br.d, ^2J = 11.1, H_{exo}-11), 2.50 (1H, m, H-9), 2.51 (1H, dt, ^2J = 12.4, $^3J_{14A-15}$ = 6.2, H_A-14), 2.60 (1H, dt, ^2J = 12.4, $^3J_{14B-15}$ = 6.2, H_B-14), 2.99 (1H, ddt, ^2J = 10.4, $^3J_{13endo-7}$ = 3.4, $^4J_{13endo-11endo}$ = 1.7, $^4J_{13endo-8syn}$ = 1.6, H_{endo}-13), 3.04 (1H, m, H-7), 3.06 (1H, m, H_{endo}-11), 3.87 (1H, dd, ^2J = 15.5, $^3J_{10exo-9}$ = 6.5, H_{exo}-10), 4.13 (1H, d, ^2J = 15.5, H_{endo}-10), 4.90 (1H, br.s, H_A-N), 6.02 (1H, dd, $^3J_{5-4}$ = 6.9, $^4J_{5-3}$ = 1.3, H-5), 6.42 (1H, dd, $^3J_{3-4}$ = 9.1, $^4J_{3-5}$ = 1.3, H-3), 6.96 (1H, br.s, H_B-N), 7.29 (1H, dd, $^3J_{4-3}$ = 9.1, $^3J_{4-5}$ = 6.9, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.80 (C-8), 27.82 (C-9), 32.08 (C-15), 35.22 (C-7), 49.92 (C-10), 53.40 (C-14), 59.79 (C-11), 60.16 (C-13), 104.94 (C-5), 116.75 (C-3), 139.05 (C-4), 150.63 (C-6), 163.28 (C-2), 174.29 (C-16).

General Method for Preparing Diamines 4a and 4b. A solution of **3a** (0.5 g, 2.02 mmol) or **3b** (0.53 g, 2.02 mmol) in anhydrous CH_2Cl_2 (75 mL) was cooled to 0°C, stirred vigorously under Ar, treated over 5 min with (*i*-Bu)$_2$AlH (4.85 mL, 73% solution, 24.25 mmol), refluxed for 4 h, cooled, and treated with anhydrous C_6H_6 (50 mL) and NaF (10.2 g, 0.243 mol). The suspension was stirred for 1 h at 0°C, treated slowly dropwise with H_2O (1.31 mL, 72.87 mmol), and stirred for another hour at room temperature. The inorganic precipitate was filtered off and washed with hot MeOH (3 × 30 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed at reduced pressure. The residue was chromatographed over SiO_2 ($CHCl_3$:MeOH, 7:3).

***N*-(2-Aminoethyl)cytisine (4a).** Amide **3a** (0.50 g) afforded **4a** (0.074 g, 15%) as an oil, $[\alpha]_D^{20}$ –74 ± 1° (*c* 0.115, $CHCl_3$), R_f 0.1 ($CHCl_3$:MeOH, 9:1). Mass spectrum (APCI, *m*/*z*, I_{rel}, %): 234 (100) $[M + H]^+$, 191 (87). IR spectrum (ν, cm$^{–1}$): 3400–3050, 2926, 2787, 1651, 1566, 1546, 1139.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.80 (1H, br.d, ^2J = 12.7, H_{anti}-8), 1.91 (1H, br.d, ^2J = 12.7, H_{syn}-8), 2.35 (1H, m, H_{exo}-11), 2.36 (1H, m, H_{exo}-13), 2.38 (2H, br.s, H_2N), 2.40 (2H, t, $^3J_{10endo-9}$ = 6.1, 2H-15), 2.46 (1H, m, H-9), 2.66 (1H, dt, ^2J = 12.5, $^3J_{14A-15}$ = 6.1, H_A-14), 2.73 (1H, dt, ^2J = 12.5, $^3J_{14B-15}$ = 6.1, H_B-14), 2.88 (1H, dd, ^2J = 10.6, $^3J_{13endo-7}$ = 3.6, H_{endo}-13), 2.98 (1H, m, H-7), 3.01 (1H, br.d, ^2J = 11.1, H_{endo}-11), 3.88 (1H, dd, ^2J = 15.5, $^3J_{10exo-9}$ = 6.7, H_{exo}-10), 4.08 (1H, d, ^2J = 15.5, H_{endo}-10), 6.02 (1H, dd, $^3J_{5-4}$ = 6.9, $^4J_{5-3}$ = 1.4, H-5), 6.42 (1H, dd, $^3J_{3-4}$ = 8.9, $^4J_{3-5}$ = 1.4, H-3), 7.30 (1H, dd, $^3J_{4-3}$ = 8.9, $^3J_{4-5}$ = 6.9, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 25.92 (C-8), 28.01 (C-9), 35.49 (C-7), 37.88 (C-14), 50.07 (C-10), 58.80 (C-15), 60.12 (C-11), 60.44 (C-13), 104.86 (C-5), 116.53 (C-3), 138.92 (C-4), 151.39 (C-6), 163.52 (C-2).

***N*-(3-Aminopropyl)cytisine (4b).** Amine **3b** (0.53 g) afforded **4b** (0.486 g, 97%) as an oil, $[\alpha]_D^{20}$ –117 ± 3° (*c* 0.025, $CHCl_3$). Mass spectrum (APCI, *m*/*z*, I_{rel}, %): 248 (100) $[M + H]^+$, 191 (28), 296 (100) $[M + MeOH + H_2O – H]^–$. IR spectrum (ν, cm$^{–1}$): 3367–3157, 2926, 1647, 1544.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.46 (2H, p, ^3J = 6.6, 2H-15), 1.77 (1H, br.d, ^2J = 12.7, H_{anti}-8), 1.87 (2H, br.s, H_2N), 1.90 (1H, br.d, ^2J = 12.7, H_{syn}-8), 2.25 (1H, m, H_{exo}-13), 2.27 (1H, m, H_{exo}-11), 2.28 (2H, m, H-14), 2.42 (1H, m, H-9), 2.51 (2H, t, $^3J_{16\text{-}15}$ = 6.6, 2H-16), 2.93 (1H, m, H_{endo}-13), 2.95 (1H, m, H-7), 2.96 (1H, m, H_{endo}-11), 3.86 (1H, br.d, ^2J = 15.4, $^3J_{10exo\text{-}9}$ = 6.6, H_{exo}-10), 4.07 (1H, br.d, ^2J = 15.4, H_{endo}-10), 5.99 (1H, dd, $^3J_{5\text{-}4}$ = 6.8, $^4J_{5\text{-}3}$ = 1.4, H-5), 6.43 (1H, dd, $^3J_{3\text{-}4}$ = 9.0, $^4J_{3\text{-}5}$ = 1.4, H-3), 7.28 (1H, dd, $^3J_{4\text{-}5}$ = 6.8, $^3J_{4\text{-}3}$ = 9.0, H-4).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 26.07 (C-8), 28.12 (C-9), 29.69 (C-15), 35.57 (C-7), 40.31 (C-16), 50.07 (C-10), 55.76 (C-14), 60.49 (C-11), 60.53 (C-13), 104.53 (C-5), 116.55 (C-3), 138.65 (C-4), 151.51 (C-6), 163.57 (C-2).

Synthesis of Diamine 4a from Cytisine and Aziridine. A refluxing solution of **1** (1.0 g, 5.23 mmol) in anhydrous C_6H_6 (10 mL) was stirred vigorously, treated with $AlCl_3$ (0.53 g, 3.95 mmol), stirred for another 30 min, treated dropwise with a solution of aziridine (0.11 g, 2.63 mmol) in anhydrous C_6H_6 (3 mL), refluxed for another 40 min, diluted with C_6H_6 (30 mL), cooled to 0°C, treated dropwise with stirring with KOH solution (40 mL, 40%), and held at room temperature for 40 min. The organic layer was separated. The aqueous layer was washed with $CHCl_3$ (3 × 30 mL). The combined organic extract was dried over Na_2SO_4. The solvent was removed at reduced pressure. The residue was chromatographed over SiO_2 ($CHCl_3$:MeOH, 7:3) to afford **4a** (0.18 g, 30%) as an oil.

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