Studies on Quinolizine Derivatives. XXIV.[1] Catalytic Hydrogenation of Cycl[3.3.3]azines

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The catalytic hydrogenation of the cycl[3.3.3]azine derivative (6) or 1-azacycl[3.3.3]azine derivative (15) with PtO_2 in tetrahydrofuran at atmospheric pressure gave the dihydrocyclazine derivative (10) or dodecahydro-1-azacycl[3.3.3]azine derivative (16), respectively. On the other hand, the catalytic hydrogenation of 6 or 19 in AcOH gave dodecahydrocyclazine (11) or dodecahydro-2-hydroxymethyl-1-azacyclazine (21), respectively. The catalytic hydrogenation of the hydrochloride 18 in MeOH gave methyl dodecahydro-5-methyl-1-azacycl[3.3.3]azine-2-carboxylate (20). Compounds 11, 20 and 21 should be useful as intermediates for the preparation of natural products, such as coccinelline and cernuine.

Keywords hydrocycl[3.3.3]azine; hydroazacycl[3.3.3]azine; cycl[3.3.3]azine; azacycl[3.3.3]azine; antiaromatic character; coccinelline; cernuine

Previously we reported the synthesis and antiaromatic character of unstable 2-methyl-1-azacycl[3.3.3] azine (**1**), which contains a nitrogen-bridged peripheral 12π electron system.[2] The azacycl[3.3.3]azine derivatives (**2**—**5**) were rather stable owing to the effect of their electron-attracting groups, but some characteristic reactivities were noted. The methylthio group on the azacyclazine ring in **2**, **3** and **4** was highly reactive with nucleophiles, such as amines or active methylene compounds.[1,3] Furthermore, the Diels-Alder reaction of azacyclazine (**5**) with a dienophile, methyl acetylenecarboxylate (MAC), gave the deaza compounds (**6**,**7**).[4] As part of our continuing studies on azacyclazines, we now wish to report that the catalytic reduction of cyclazines (**6**, **15**, **18**, **19**) with PtO_2 catalyst readily gave hydrogenated cyclazines (**10**, **11**, **16**, **20**, **21**). Compounds **11**, **20** and **21** should be useful as intermediates for the preparation of natural products, such as coccinelline[5] and cernuine.[6]

Farquhar *et al.*[7] reported that the catalytic reduction of diethyl cycl[3.3.3]azine-1,3-dicarboxylate (**8**) with PtO_2 catalyst in benzene gave the tetrahydrocyclazine (**9**). In the present paper, we describe the catalytic reduction of 1,4-dimethyl 3-ethyl 8-methylcycl[3.3.3]azine-1,3,4-tricarboxylate (**6**) with PtO_2 catalyst in tetrahydrofuran (THF) at atmospheric pressure to give the dihydrocyclazine (**10**), after absorption of 1 mol eq of hydrogen. The structure **10** was assigned to the dihydrocyclazine on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, in which the signals due to C_2-H, C_7-H, C_9-H were readily identifiable from their multiplicities and the methylene protons (C_5-H, C_6-H) gave a complex multiplet at higher field, δ (ppm): 2.7—3.1. On the other hand, when the reduction of **6** was carried out in AcOH, the dodecahydrocyclazine (**11**) was obtained in quantitative yield, after

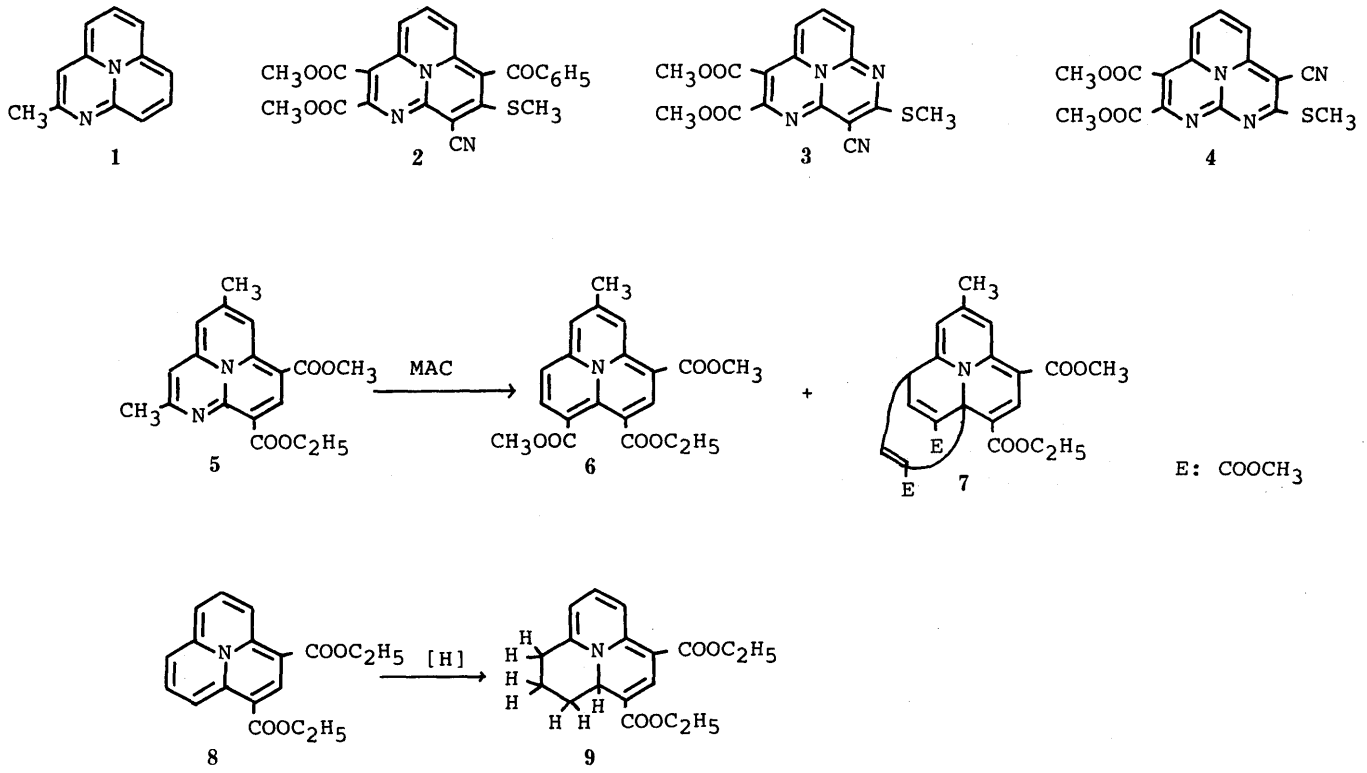


Chart 1

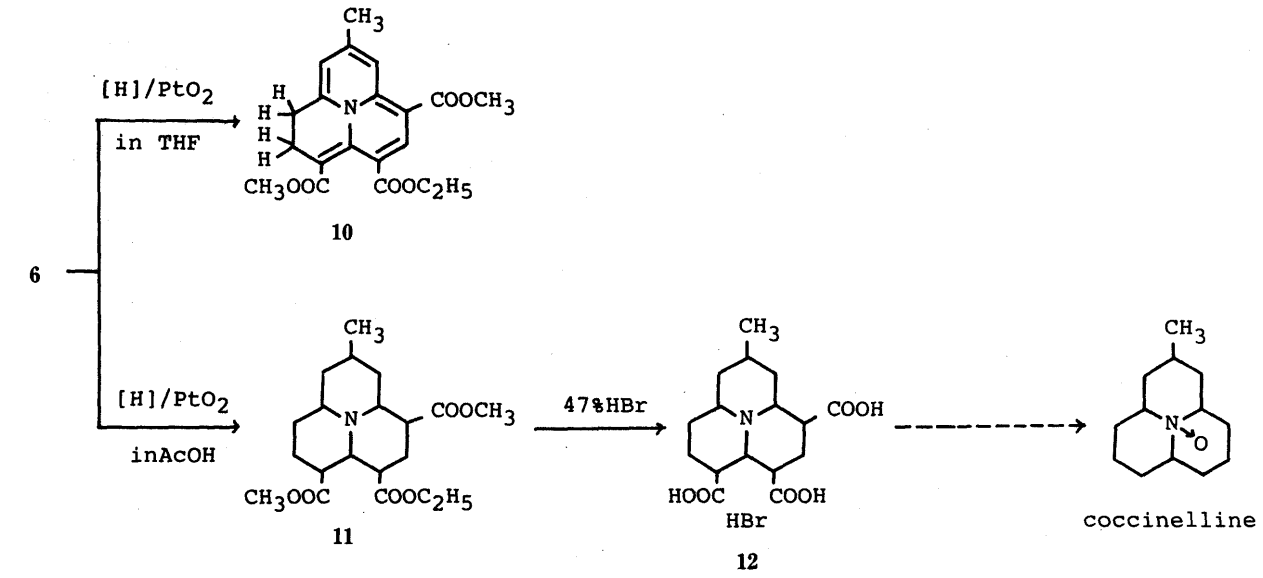
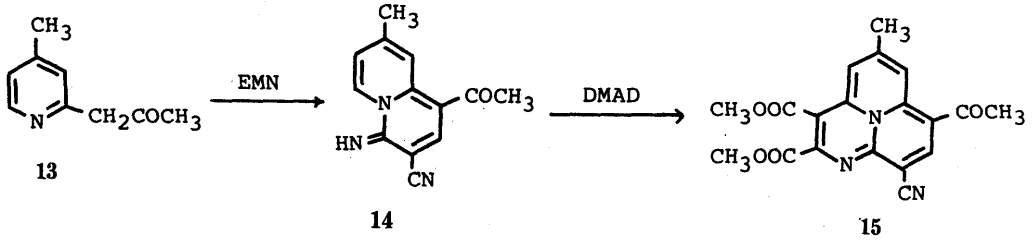


Chart 2



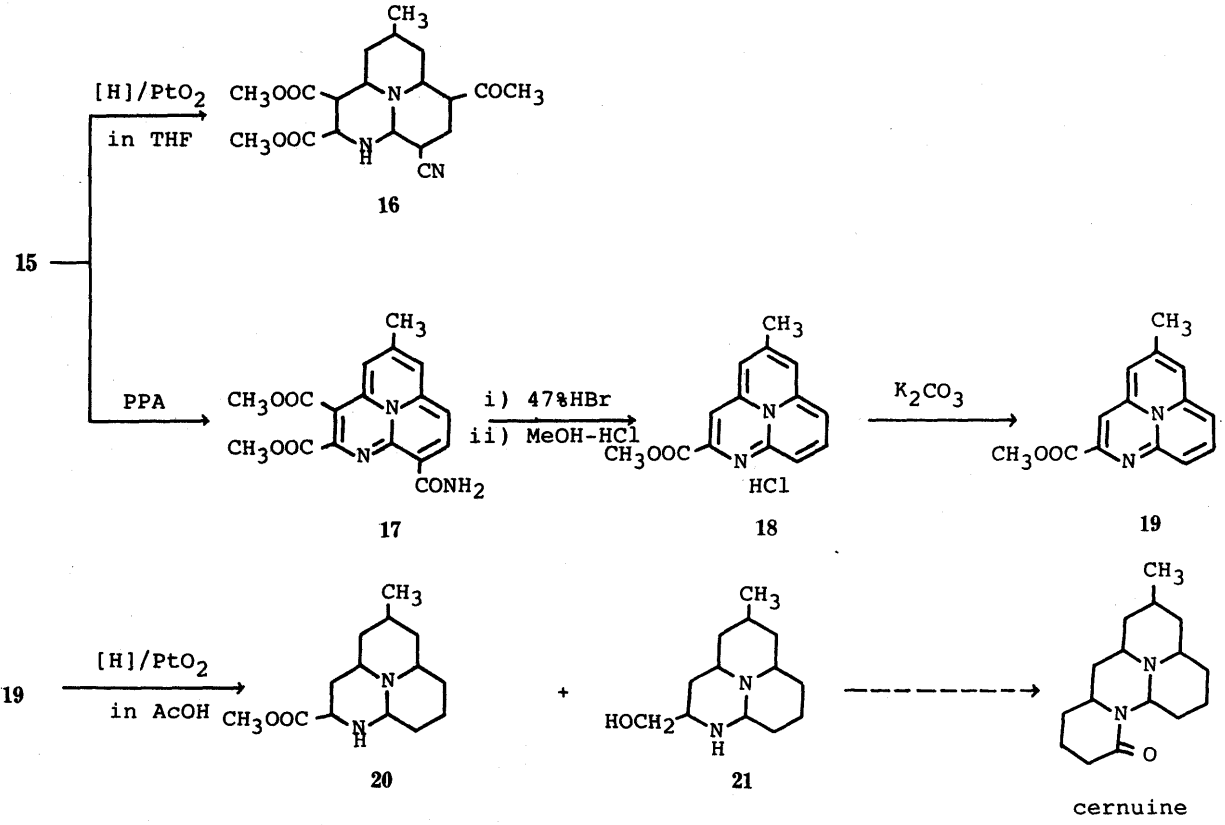


Chart 3

absorption of 6 mol eq of hydrogen. Then, a solution of **11** in 47% HBr was refluxed for 4 h to give 1,2,3,3a,4,5,6,6a,7,8,9,9a-dodecahydro-8-methylcycl-[3.3.3]azine-1,3,4-tricarboxylic acid hydrobromide (**12**), as hygroscopic crystals.

Next, we examined the catalytic reduction of the azacy-

clazine derivative (**15**), which was prepared by the reaction of 1-acetyl-3-cyano-4-imino-8-methyl-4*H*-quinolizine (**14**) with dimethyl acetylenedicarboxylate (DMAD), by the method described in the previous paper.[1] Thus, compound **15** was more readily reduced with PtO_2 catalyst in THF at atmospheric pressure to give the dodecahydroazacyclazine (**16**) than **6**. The ^{1}H-NMR ($CDCl_3$) spectrum of the reduced product **16** showed no vinyl protons and a sharp doublet at δ (ppm): 0.88 (3H, d, J=6 Hz, CH_3). In addition, the signals of two methoxycarbonyl groups (δ: 3.76) and one acetyl group (δ: 2.19) were observed. In order to obtain key intermediates (**20**, **21**) for the synthesis of the cernuine skeleton, we examined various conditions for removal of the methoxycarbonyl, acetyl, and cyano groups on **15**, and succeeded in the isolation of methyl 1-azacycl[3.3.3]azine-2-carboxylate (**19**) as an unstable compound. Thus, a mixture of **15** and polyphosphoric acid (PPA) was heated at 100 °C for 10 h to give the deacetylated compound, dimethyl 9-carbamoyl-5-methyl-1-azacycl[3.3.3]azine-2,3-dicarboxylate (**17**), in good yield. Then, a solution of **17** in 47% hydrobromic acid was refluxed for 4 h to give the hydrobromide, which was in turn converted to the hydrochloride (**18**) by esterification with MeOH–HCl. The free base, methyl 5-methyl-1-azacycl[3.3.3]azine-2-carboxylate (**19**), was obtained as unstable green crystals by treatment of **18** with potassium carbonate solution. The signals of all the ring protons of **19** appear at δ(ppm): 3.63—5.54, at comparatively high magnetic fields. Namely, compound **19** may have an antiaromatic character.[2]

The catalytic reduction of **19** with PtO_2 in THF gave an unidentified decomposition product, but the reduction of **19** in AcOH for 8 h absorbed *ca.* 6 mol eq of hydrogen to give the methoxycarbonyl compound (**20**) and the hydroxymethyl compound (**21**). Furthermore, the hydrogenation of **19** in AcOH for 24 h gave only **21** in good yield. On the other hand, the hydrogenation of the hydrochloride **18** in MeOH readily gave **20** in quantitative yield. Further work on the synthesis of coccinelline and cernuine is in progress.

Experimental

Melting points were determined with a Mitamura Mel-Temp and are uncorrected. Infrared (IR) spectra were recorded in KBr discs on a JASCO IRA-2 spectrometer. Ultraviolet (UV) spectra were recorded on a Hitachi EP-S2 spectrometer in 95% ethanol. ^{1}H-NMR spectra were obtained on a JNM-FX-90 (90 MHz) spectrometer with tetramethylsilane as an internal standard. Chemical shifts of ^{1}H-NMR signal are given in δ values (ppm). Abbreviations: s=singlet, br=broad, d=doublet, dd=doublet of doublets, t=triplet, and m=multiplet.

1,4-Dimethyl 3-Ethyl 5,6-Dihydro-8-methylcycl[3.3.3]azine-1,3,4-tricarboxylate (10) Compound **6** (0.001 mol)[4] was hydrogenated, at atmospheric pressure, in THF (50 ml) containing PtO_2 catalyst (50 mg). Hydrogen (1 mol eq) was absorbed during 8 h. The solution was then filtered and evaporated under reduced pressure and the residue was chromatographed on silica gel in benzene–$CHCl_3$ (1:1) to yield the dihydro compound **10** (76%), mp 210—212 °C. *Anal.* Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.59; H, 5.76; H, 3.85. UV λ_{max}^{EtOH} nm (log ε): 223 (4.25) sh, 254 (4.15), 299 (4.14), 338 (3.69) sh, 422 (4.19), 490 (3.82) sh. IR (KBr) cm^{-1}: 1700 (C=O), 1670 (C=O), 1650 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.34 (3H, s, $\underline{CH_3}$), 2.70—3.10 (4H, m, $\underline{CH_2CH_2}$), 3.67 (3H, s, $O\underline{CH_3}$), 3.81 (3H, s, $O\underline{CH_3}$), 4.23 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 6.52 (1H, s, C_7-H), 8.28 (1H, s, C_2-H), 8.70 (1H, s, C_9-H).

1,2,3,3a,4,5,6,6a,7,8,9,9a-Dodecahydro-8-methylcycl[3.3.3]azine-1,3,4-tricarboxylic Acid Hydrobromide (12) Compound **6** (0.001 mol) was hydrogenated, at atmospheric pressure, in AcOH (50 ml) containing PtO_2 catalyst (50 mg). Hydrogen (6 mol eq) was absorbed during 8 h. The solution was filtered and evaporated under reduced pressure and the residue was poured into ice-water (100 ml). The solution was made basic to litmus with K_2CO_3 and extracted with $CHCl_3$ (3×50 ml). The extract was washed with water (50 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give the oily dodecahydro compound (**11**) in quantitative yield. The ^{1}H-NMR spectrum of the crude product **11** was recorded. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, d, J=6 Hz, CH_3), 1.27 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 3.66 (6H, s, OCH_3), 4.15 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$). Without further purification, this oil was refluxed with 47% HBr (30 ml) for 4 h. The solution was evaporated under reduced pressure. The residue was recrystallized from MeOH–benzene to give **12** in 95% yield, mp 190 °C (dec.). *Anal.* Calcd for $C_{16}H_{24}BrNO_6$: C, 47.30; H, 5.95; N, 3.45. Found: C, 47.06; H, 3.67; N, 3.21. MS m/z: 325 (M^+ − HBr). IR (KBr) cm^{-1}: 1720 (br) (C=O). ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, d, J=5 Hz, CH_3).

Dimethyl 7-Acetyl-9-cyano-5-methyl-1-azacycl[3.3.3]azine-2,3-carboxylate (15) A solution of 1-(4-methyl-2-pyridinyl)-2-propanone (**13**) (0.01 mol), ethoxymethylenemalononitrile (EMN) (0.01 mol), and K_2CO_3 (2 g) in dimethylsulfoxide (DMSO) (20 ml) was stirred overnight at room temperature. The reaction mixture was poured into ice-water (300 ml). The solution was extracted with $CHCl_3$ (3×50 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was recrystallized from $CHCl_3$–MeOH to give 1-acetyl-3-cyano-4-imino-8-methyl-4*H*-quinolizine (**14**) (95%), mp 236—237 °C. *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.53; H, 5.03; N, 18.62. UV λ_{max}^{EtOH} nm (log ε): 226 (4.40), 246 (4.08) sh, 273 (3.90) sh, 283 (3.94), 302 (4.05), 356 (4.14) sh, 374 (4.25), 438 (4.10). IR (KBr) cm^{-1}: 2200 (CN), 1655 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s, $COCH_3$), 2.56 (3H, s, CH_3), 7.17 (1H, dd, J=2, 7 Hz, C_7-H), 7.70 (1H, br, NH), 8.04 (1H, s, C_2-H), 9.37 (1H, d, J=2 Hz, C_9-H), 9.61 (1H, d, J=7 Hz, C_6-H). A solution of **14** (0.01 mol) and DMAD (0.03 mol) in *N*,*N*-dimethylformamide (10 ml) was heated at 130 °C for 3 h. The reaction mixture was poured into ice-water (300 ml). The solution was extracted with $CHCl_3$ (3×50 ml). The extract was washed with H_2O (50 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was submitted to column chromatography on silica gel in benzene to yield **15** (37%), mp 232—233 °C (dec.). *Anal.* Calcd for $C_{19}H_{15}N_3O_5$: C, 62.46; H, 4.14; N, 11.50. Found: C, 62.22; H, 4.27; N, 11.32. IR (KBr) cm^{-1}: 2200 (CN), 1720 (C=O), 1655 (C=O), 1620 (C=O). UV λ_{max}^{EtOH} nm (log ε): 283 (4.43), 372 (4.13), 412 (3.98) sh, 437 (4.36), 462 (4.56). ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, CH_3), 2.20 (3H, s, $COCH_3$), 3.71 (3H, s, OCH_3). 3.78 (3H, s, OCH_3), 6.52 (1H, dd, J=0.5, 2 Hz, C_4-H), 7.08 (1H, s, C_8-H), 7.81 (1H, dd, J=0.5, 2Hz, C_6-H).

Dimethyl 7-Acetyl-9-cyano-1,2,3,3a,4,5,6,6a,7,8,9,9a-dodecahydro-5-methyl-1-azacycl[3.3.3]azine-2,3-carboxylate (16) Compound **15** (0.001 mol) was hydrogenated, at atmospheric pressure, in THF (50 ml) containing PtO_2 (50 mg). Hydrogen (6 mol eq) was absorbed during 12 h; the color of the solution changed from green to colorless. The solution was filtered and evaporated under reduced pressure. The residue was submitted to column chromatography on silica gel in benzene–$CHCl_3$ (2:1) to yield **16** (64%), mp 74—75 °C. *Anal.* Calcd for $C_{19}H_{17}N_3O_5$: C, 60.46; H, 7.21; N, 11.13. Found: C, 60.18; H, 7.46; N, 11.01. IR (KBr) cm^{-1}: 2180 (CN), 1740 (C=O), 1620 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, d, J=6 Hz, CH_3), 2.19 (3H, s, $COCH_3$), 3.76 (6H, s, OCH_3×2).

Dimethyl 9-Carbamoyl-5-methyl-1-azacycl[3.3.3]azine-2,3-dicarboxylate (17) A mixture of **15** (0.5 g) and an excess of PPA (10 g) was heated at 100 °C for 10 h. The reaction mixture was poured into ice-water (300 ml). The solution was made basic to litmus with K_2CO_3, and extracted with $CHCl_3$ (3×50 ml). The extract was washed with water (50 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give **17** as crude crystals (78%), which were recrystallized from $CHCl_3$–MeOH to give green needles, mp 269—271 °C (dec.). *Anal.* Calcd for $C_{17}H_{15}N_3O_5$: C, 59.82; H, 4.43; N, 12.31. Found: C, 59.68; H, 4.53; N, 12.25. IR (KBr) cm^{-1}: 1740 (C=O), 1700 (C=O), 1655 (C=O). UV λ_{max}^{EtOH} nm (log ε): 272 (4.43), 382 (4.14), 417 (4.34), 439 (4.49). ^{1}H-NMR ($CDCl_3$) δ: 1.77 (3H, s, CH_3), 3.59 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 5.29 (1H, d, J=9 Hz, C_7-H), 5.49 (1H, dd, J=1, 2 Hz, C_4-H or C_6-H), 6.29 (1H, dd, J=1, 2 Hz, C_4-H or C_6-H), 7.26 (1H, d, J=9 Hz, C_8-H), 5.36 (1H, br, NH), 8.71 (1H, br, NH).

Methyl 5-Methyl-1-azacycl[3.3.3]azine-2-carboxylate (19) A solution of **17** (0.5 g) in 47% HBr (20 ml) was refluxed for 3 h. The solution was evaporated under reduced pressure. A solution of the residue in MeOH–HCl (100 ml) was refluxed for 10 h. The solution was evaporated under reduced pressure to give the hydrochloride **18** (67%), mp 136 °C (dec.). A solution of **18** (0.5 g) in water (50 ml) was made basic to litmus with K_2CO_3 and extracted with $CHCl_3$ (3×30 ml). The extract was dried

(Na_2SO_4) and evaporated under reduced pressure to give **19** as unstable crude crystals (97%), which were carefully recrystallized from CH_2Cl_2–MeOH to give green needles, mp 168—170 °C. *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.87; H, 5.11; N, 11.64. IR (KBr) cm^{-1}: 1710 (C=O). UV λ_{max}^{EtOH} nm (log ε): 227 (4.21), 256 (4.09) sh, 280 (4.33) sh, 291 (4.35), 306 (4.17) sh, 388 (4.12) sh, 409 (4.18) sh, 434 (4.22). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s, CH_3), 3.59 (3H, s, OCH_3), 3.63 (1H, d, J=2 Hz, C_4-H or C_6-H), 4.09 (1H, dd, J=1, 8 Hz, C_7-H or C_9-H), 4.27 (1H, s, C_3-H), 4.32 (1H, dd, J=1, 9 Hz, C_7-H or C_9-H), 4.33 (1H, d, J=2 Hz, C_4-H or C_6-H), 5.54 (1H, dd, J=8, 9 Hz, C_8-H).

Hydrogenation of 18 and 19 a) Compound **19** (0.001 mol) was hydrogenated, at atmospheric pressure, in AcOH (50 ml) containing PtO_2 (50 mg). Hydrogen (*ca.* 6 mol eq) was absorbed during 8 h. The solution was then worked up as in the case of **11** to yield methyl 1,2,3,3a,4,5,6,6a,7,8,9,9a-dodecahydro-5-methyl-1-azacycl[3.3.3]azine-2-carboxylate (**20**) (62%) and 1,2,3,3a,4,5,6,6a,7,8,9,9a-dodecahydro-2-hydroxymethyl-5-methyl-1-azacycl[3.3.3]azine (**21**) (7%). b) Compound **19** (0.001 mol) was hydrogenated, at atmospheric pressure, in AcOH (50 ml) containing PtO_2 (50 mg) for 24 h. The solution was then worked up as in a) to yield **21** (98%), mp 141 °C. *Anal.* Calcd for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78; N, 12.49. Found: C, 69.53; H, 10.85; N, 12.33. MS m/z: 224 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, J=6 Hz, CH_3). c) Compound **18** (0.001 mol) was hydrogenated, at atmospheric pressure, in MeOH (100 ml) containing PtO_2 (50 mg) for 24 h. The solution was then worked up as in a) to yield the oily product **20** (98%). MS ($C_{14}H_{24}N_2O_2$) m/z: 252 (M^+). IR (KBr) cm^{-1}: 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, d, J=5 Hz, CH_3), 3.71 (3H, s, OCH_3).

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