SYNTHESIS OF 5-OXOINDOLIZINE DERIVATIVES. II[1]: REACTION OF ETHYL PYRROLIDIN-2-YLIDENEACETATE (AN ENAMINE ESTER) WITH ACYCLIC α,β-UNSATURATED CARBONYL COMPOUNDS

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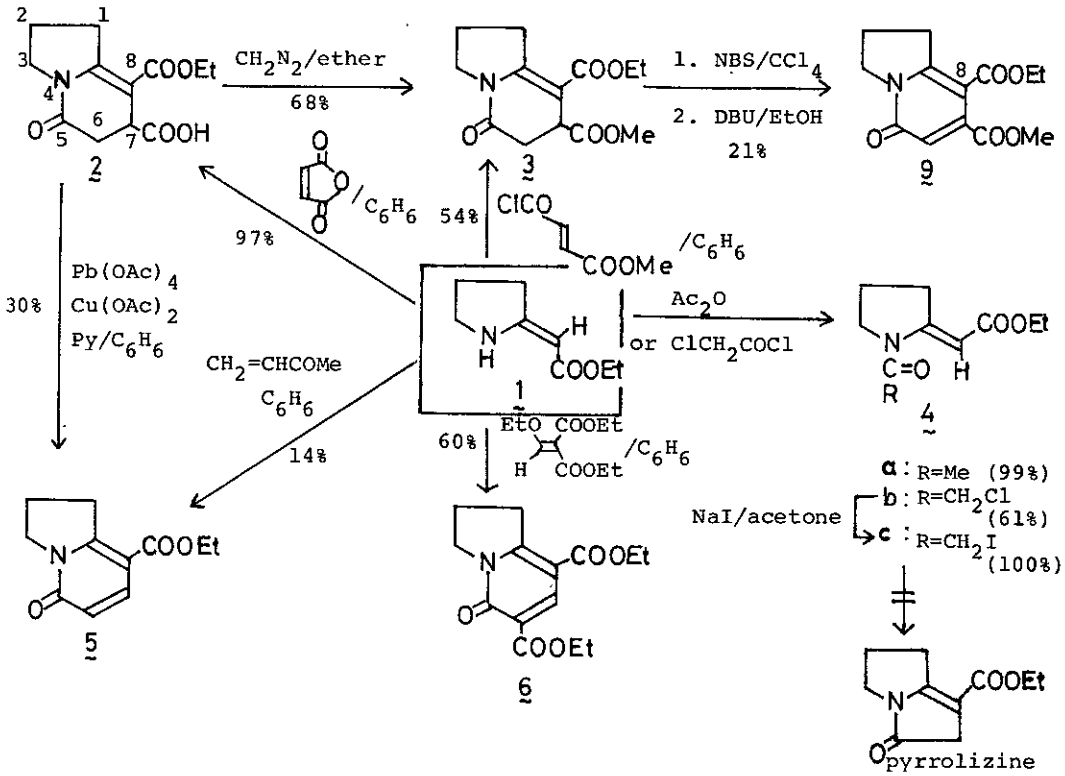
Abstract --- Synthesis of some 5-oxoindolizine derivatives using ethyl pyrrolidin-2-ylideneacetate (1) and acyclic α,β-unsaturated carbonyl compounds is described. The structures of Michael adducts, intermediates for 5-oxoindolizines, obtained by treatment of 1 with dimethyl acetylenedicarboxylate or methyl propiolate are discussed.

In the previous paper[1], we have reported that the reaction of an enamine ester (ethyl pyrrolidin-2-ylideneacetate, 1[2]) with maleic anhydrides (and maleimides) affords 5-oxoindolizine derivatives (e.g. 2) in good yields. In this communication, we wish to describe the further investigations on the reaction of 1 with acyclic α,β-unsaturated carbonyl compounds.

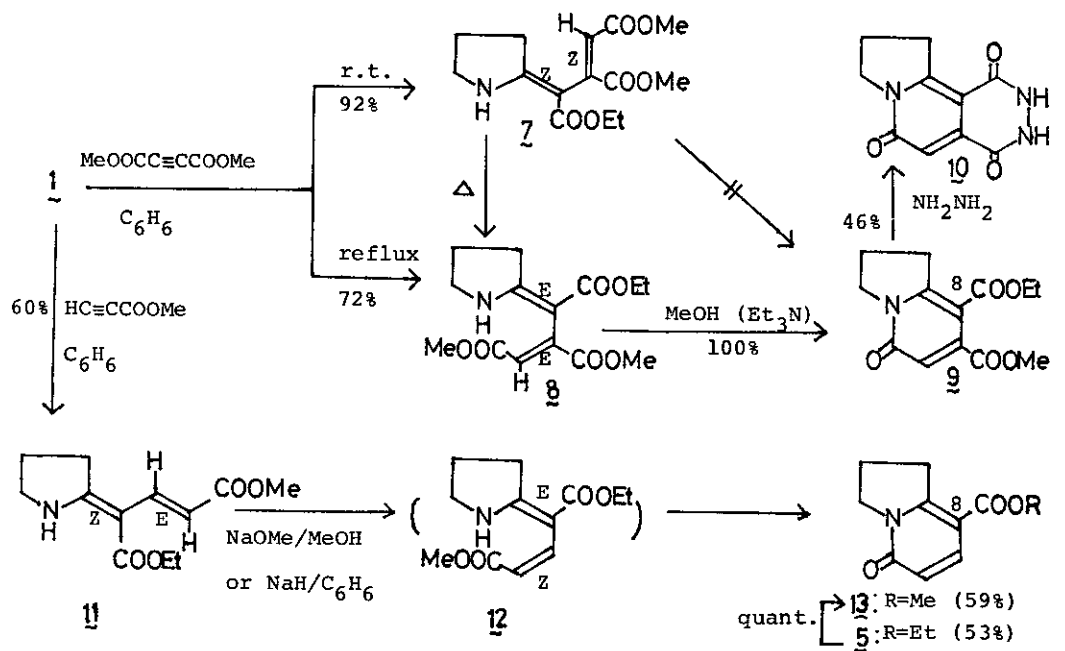
The reaction of 1 with methyl E-4-chloro-4-oxo-2-butenoate (fumaric acid mono methyl ester chloride) afforded hexahydroindolizine (3), which was identical with the compound prepared by the methylation of 2 with diazomethane (Scheme I). 1 was acylated with acetic anhydride or acyl chloride at the N-position (mostly) to give 4, however, these N-acyl enamines (4b and 4c) were shown to be too inert to cyclize to the pyrrolizine under several conditions. Considering from these results, the formation of 3 would be probably due to the intramolecular cyclization of ketene intermediate as presented by Hickmott and Sheppard[3]. The reaction of 1 with methyl vinyl ketone afforded indolizine (5) in low yield though the reaction mechanism is not clear. 5 was also obtained by treatment of 2 with lead tetraacetates. From diethyl ethoxymethylenemalonate, tetrahydroindolizine (6) was expectedly obtained, but in moderate yield.

Treatment of 1 with dimethyl acetylenedicarboxylate (DMAD) in benzene at room temperature afforded a Michael adduct (7) in excellent yield (Scheme II). This

Scheme I



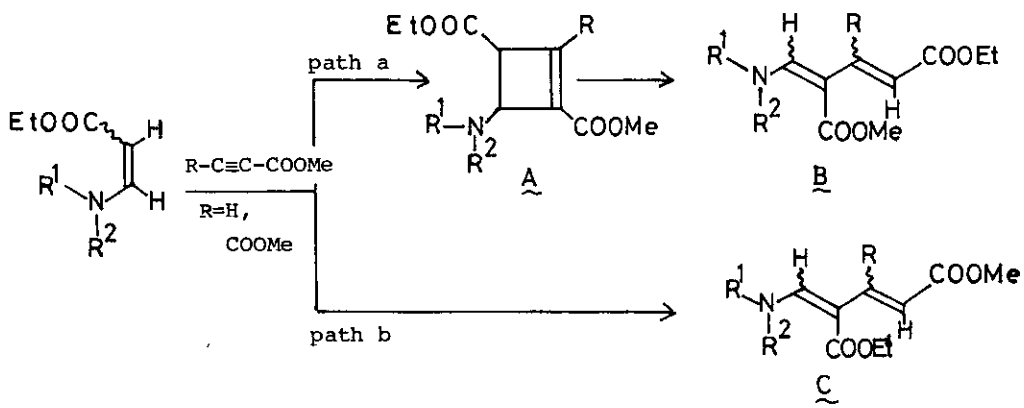
Scheme II



reaction at high temperature (refluxing in benzene) afforded 8 as a major product (72% isolated yield) with minor 7. A solution of pure 7 in benzene was refluxed for 10 hours to give an equilibrium mixture of 7 and 8 (ratio 1:5) containing no other isomer. On standing 8 in methanol at room temperature for a few hours, indolizine (9) was formed in high yield and this reaction was very accelerated by addition of triethylamine. But under the same condition 7 became turbid and colored to give no product. The relative position of two ester groups of 9 was confirmed by leading 9 to hydrazide (10). Further, 9 was alternatively prepared by the reaction of 3 with N-bromosuccinimide followed by treatment with 1,5-diazabicyclo-[5.4.0]undecene-5 (DBU). Similarly the reaction of 1 with methyl propiolate (MP) proceeded to give one Michael adduct (11); however long reaction times (1 week) and refluxing condition (in benzene) were necessary in this case. Although 11, like 7, did not cyclize to indolizine (5) by treatment with triethylamine, it was converted to 13 on treatment with sodium methoxide in boiling methanol. As 13 was easily prepared from 5 by the ester-exchange reaction in the presence of sodium methoxide, the reaction described above involves the overall process of trans-cis conversion (11 → 12), cyclization (12 → 5), and the exchange reaction of esters (5 → 13). Indeed treatment of 11 with sodium hydride in boiling benzene afforded 5.

Structural assignments of the Michael adducts (7, 8, and 11) are based on their reactivities, spectral data, and the structures of indolizines (9 and 5).

It is well-known that the reaction of enamines including enamine ketones and enamine esters with acetylenic esters[4] affords cyclobutene adducts (A), isolable in some cases, and/or dienamine esters (B and C). B is formed from cyclobutene



via bond rearrangement resulting in the insertion of two carbons into the enamine chain (path a)[5]. C is a single Michael adduct (Stork's product)[6]. In the reaction of 1 with DMAD and MP, path b is reasonable since the compound B can not be conducted to 9 or 5 having a carbethoxy group at the 8-position of indolizine ring. Our results are in accord with the argument reported by Raileanu et al.[6], who state about the reaction of primary and secondary enamine esters with acetylenic esters which does not proceed through the cyclobutene intermediates. The vinyl proton signals in the NMR spectra of 7 and 8 appear at δ5.77 and 6.70 ppm, respectively. Therefore the two carbomethoxy groups of 7 must be cis each other and the vinyl proton of 8 must be cis to the β-carbomethoxy group[5,6]. Similarly the vinyl protons of 11 must be trans each other judging from the signals at δ7.55 (d, J=16 Hz) and 6.1 (d, J=16 Hz) ppm. As it is known that in the reaction of Michael addenda with DMAD[6,7], preferable products are cis under conditions of kinetic control and trans isomers appear in equilibrium conditions, the formations of 7 at room temperature and 8 at high temperature seem to be rational. The simple cyclization of 8 to 9 under very mild conditions suggests that 8 lies in the E,E-configuration with a preferable cisoid conformation. Corroborative evidence was obtained from the UV spectra as follows: λ_{max}^{EtOH} nm (ε ; 7; 207 (10,000), 283 (14,000), 337 (9,100), 8; 205 (12,500), 282 (12,700), 373 (1,580), and 11; 290sh (15,400), 327 (33,900). The large extinction coefficient at 327 nm observed in 11 suggests that 11 is in the most planar and stable Z,E-configuration with a transoid conformation[5,6], which is preferably formed under thermodynamic conditions[8], while the small ones at 337 and 373 nm observed in 7 and 8, respectively, are characteristic for the cisoid diene conformations[9]. Further, the assumption for these cisoid conformations is supported by the consideration of molecular models, namely there are interactions between substituents in the transoid conformations for 7 and 8. As 8 is more stable than 7 in equilibrium conditions, however, 8 must be in the twist form, as supposed from its UV spectrum. Finally, the hydrogen bondings[10] between the amino and the carbethoxy groups in 7 and 11 support the propriety of their configurations.

In conclusion, it is clarified that this enamine ester (1) is useful and convenient for the synthesis of 5-oxoindolizine derivatives. Especially it is noteworthy that 8 formed from DMAD has led to 5-oxoindolizine (9) in exellent yield, since it is known that the dienamine esters formed from DMAD cyclize to α-pyrrolidones[5] or give no products[6].

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting apparatus and are not corrected. IR spectra were measured with a Hitachi 260-10 spectrometer and UV spectra were measured with a Hitachi 200-10 spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM 390 spectrometer using TMS as an internal standard and MS spectra were obtained on a Hitachi M-80 mass spectrometer.

General Procedure for the Syntheses of 3, 5, 6, 7, 8, and 11---A solution of ethyl pyrrolidin-2-ylideneacetate (1) (1 eq.) and the α,β-unsaturated compounds (1-1.5 eq.) in dry benzene was refluxed or allowed to stand at room temperature for 2-288 h. Evaporation of the solvent under reduced pressure gave an oily or crystalline residue, which was purified by column chromatography on silica gel using chloroform as eluent to give the compounds (3, 5, 6, 7, 8, and 11).

8-Ethoxycarbonyl-7-methoxycarbonyl-5-oxo-1,2,3,5,6,7-hexahydroindolizine (3)---By general procedure (methyl fumarate monochloride, 1.5 eq; reflux, 48 h): Yellow oil (yield, 54%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}; 1725, 1670, 1640, 1590 (C=O, C=C). ^{1}H-NMR ($CDCl_3$) δ ppm; 1.16 (t, 3H, J=7 Hz), 1.87 (quint, 2H, J=7.5 Hz), 2.70 (m, 2H), 3.17 (m, 2H), 3.57 (s, 3H), 3.63 (m, 2H), 4.11 (q, 2H, J=7 Hz). MS m/e; 267.1130 (M^+). $C_{13}H_{17}NO_5$ requires 267.1105. From 2: Treatment of 2 (500 mg, 1.98 mmol) with diazomethane in ether followed by chromatography on silica gel gave 3 as a yellow oil (358 mg, 68%).

Ethyl N-Acetylpyrrolidin-2-ylideneacetate (4a) and Ethyl N-Chloroacetylpyrrolidin-2-ylideneacetate (4b)---A solution of 1 (1 eq.) and acyl chloride (1 eq.) in dry benzene was refluxed for 1 h. After cooling, the benzene solution was washed with saturated sodium bicarbonate solution and water, dried over magnesium sulfate, and evaporated to give the compounds (4a and 4b). 4a: Colorless needles from isopropyl ether (yield, 99%). mp 107-110°C. IR ν_{max}^{KBr}cm^{-1}; 1690, 1610. ^{1}H-NMR ($CDCl_3$) δ ppm ; 1.25 (t, 3H, J=7.5 Hz), 1.95 (quint, 2H, J=7.5 Hz), 2.23 (s, 3H), 3.18 (t-d, 2H, J=7.5 Hz, 2 Hz), 3.73 (t, 2H, J=7.5 Hz), 4.12 (q, 2H, J=7.5 Hz), 6.8 (t, 1H, J=2 Hz). MS m/e; 197 (M^+). Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found : C, 61.11; H, 7.76; N, 7.14. 4b: Colorless needles from isopropyl ether (yield, 61%). mp 78-81°C. IR ν_{max}^{KBr}cm^{-1}; 1690, 1600. ^{1}H-NMR ($CDCl_3$) δ ppm; 1.21 (t, 3H, J=7.5 Hz), 1.97 (quint, 2H, J=7.5 Hz), 3.16 (t-d, 2H, J=7.5 Hz, 2 Hz), 3.8 (t, 2H, J=7.5 Hz), 4.1 (s, 2H), 4.1 (q, 2H, J=7.5 Hz), 6.87 (t, 1H, J=2 Hz). MS m/e; 231 (M^+). Anal. Calcd. for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.09; N, 6.05. Found : C, 51.62; H, 6.25; N, 5.99.

Ethyl N-Iodoacetylpyrrolidin-2-ylideneacetate (4c)---A mixture of 4b (46 mg, 0.2 m mol), sodium iodide (150 mg, 1 mmol), and acetone (20 ml) was refluxed for 5 h. After evaporation of the solvent under reduced pressure, the residue was extracted with benzene. The benzene extract was filtered and evaporated to give a yellow oil (66 mg, 100%) of 4c: ^{1}H-NMR ($CDCl_3$) δ ppm; 1.23 (t, 3H, J=7.5 Hz), 2.0 (quint, 2H, J=7.5 Hz), 3.17 (t-d, 2H, J=7.5 Hz, 2 Hz), 3.78 (t, 2H, J=7.5 Hz), 3.80 (s, 2H) 4.12 (q, 2H, J=7.5 Hz), 6.90 (t, 1H, J=2 Hz).

8-Ethoxycarbonyl-5-oxo-1,2,3,5-tetrahydroindolizine (5)---By general procedure (methyl vinyl ketone, 1.5 eq; reflux, 158 h): Colorless needles from hexane (yield, 13%). mp 100-103°C. IR ν_{max}^{KBr} cm^{-1}; 1690, 1660, 1650, 1590 (C=O, C=C). ^{1}H-NMR ($CDCl_3$) δ ppm; 1.33 (t, 3H, J=7 Hz), 2.20 (quint, 2H, J=7.5 Hz), 3.53 (t, 2H, J= 7.5 Hz), 4.16 (t, 2H, J=7.5 Hz), 4.28 (q, 2H, J=7 Hz), 6.35 (d, 1H, J=9 Hz), 7.88 (d, 1H, J=9 Hz). MS m/e; 207 (M^+). Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found : C, 63.63; H, 6.38; N, 6.77. From 2: A mixture of 2 (253 mg, 1 mmol), cupric acetate (50 mg), pyridine (0.3 ml), and benzene (8 ml) was stirred at room temperature until a homogeneous green solution of the mixture was got. After lead tetraacetate (1.3 g, 3 mmol) was added, the reaction mixture was stirred at room temperature for 2 h in the dark under argon and then refluxed for 1 h. After cooling, the mixture was filtered through a thin mat of alumina to remove inorganic materials. The alumina mat was washed with benzene (50 ml), hot methanol (50 ml), and ether (50 ml). The combined organic filtrates were washed with water, 5% hydrochloric acid, sodium bicarbonate solution, and water, then dried over magnesium sulfate, and evaporated to give colorless needles of 5 (yield, 30%). From 11: A suspension of 11 (35 mg, 0.146 mmol) and sodium hydride (50%, 8.5 mg, 0.175 mmol) in dry benzene (5 ml) was refluxed for 1 h. After removal of excess sodium hydride by fitration, the filtrate was evaporated to a solid, which was recrystallized from hexane to give pure 5 (yield, 54%).

6,8-Diethoxycarbonyl-5-oxo-1,2,3,5-tetrahydroindolizine (6)---By general procedure (ethoxymethylenemalonate, 1 eq; reflux, 288 h): Yellow needles from isopropyl ether (yield, 60%). mp 119-121°C. IR ν_{max}^{KBr} cm^{-1}; 1735, 1695, 1655. ^{1}H-NMR ($CDCl_3$) δ ppm; 1.38 (t, 6H, J=7.5 Hz), 2.23 (quint, 2H, J=7.5 Hz), 3.62 (t, 2H, J=7.5 Hz), 4.00-4.66 (m, 6H), 8.66 (s, 1H). MS m/e; 279 (M^+). Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found : C, 59.90; H, 6.18; N, 4.94.

Methyl Z,Z-4-Carbethoxy-3-carbomethoxy-4-(pyrrolidin-2-ylidene)-2-butenoate (7)---By general procedure (DMAD, 1 eq; room temperature, 24 h): Yellow needles from

acetone-hexane (yield, 92%). mp 91-93°C. IR $\nu_{max}^{KBr}cm^{-1}$; 3300 (NH), 1740, 1710, 1640 1585 (C=O, C=C). ^{1}H-NMR ($CDCl_3$) δ ppm; 1.21 (t, 3H, J=7 Hz), 2.02 (quint, 2H, J=7.5 Hz), 2.83 (t, 2H, J=7.5 Hz), 3.61 (t, 2H, J=7.5 Hz), 3.71 (s, 3H), 3.77 (s, 3H), 4.09 (q, 2H, J=7 Hz), 5.77 (s, 1H), 9.17 (br.s, 1H). MS m/e; 297 (M^+). Anal. Calcd. for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found : C, 56.33; H, 6.48; N, 4.66.

Methyl E,E-4-Carbethoxy-3-carbomethoxy-4-(pyrrolidin-2-ylidene)-2-butenoate (8)---By general procedure (DMAD, 1 eq; reflux, 2 h): Yellow needles from isopropyl ether (yield, 72%). mp 98-101°C. IR $\nu_{max}^{KBr}cm^{-1}$; 3360 (NH), 1715, 1655, 1615, 1585, (C=O, C=C). ^{1}H-NMR ($CDCl_3$) δ ppm; 1.17 (t, 3H, J=7 Hz), 1.98 (quint, 2H, J=7.5 Hz), 2.52 (m, 2H), 3.62 (t, 2H, J=7.5 Hz), 3.72 (s, 3H), 3.77 (s, 3H), 4.09 (br.q, 2H, J=7 Hz), 6.70 (s, 1H), 8.77 (br.s, 1H). MS m/e; 297 (M^+). Anal. Calcd. for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found : C, 56.41; H, 6.46; N, 4.81.

8-Ethoxycarbonyl-7-methoxycarbonyl-5-oxo-1,2,3,5-tetrahydroindolizine (9)---From 8: A solution of 8 (1 eq.) and triethylamine (1 eq.) in methanol was stirred at room temperature for 15 min. Evaporation of the solvent gave a yellow oil, which was chromatographed on silica gel using chloroform as eluent to afford 9. Colorless needles from isopropyl ether (yield, ~100%). mp 94.5-96°C. IR $\nu_{max}^{KBr}cm^{-1}$; 1735, 1695, 1670, 1585. ^{1}H-NMR ($CDCl_3$) δ ppm; 1.32 (t, 3H, J=7 Hz), 2.23 (quint, 2H, J= 7.5 Hz), 3.50 (t, 2H, J=7.5 Hz), 3.87 (s, 3H), 4.17 (t, 2H, J=7.5 Hz), 4.27 (q, 2H J=7 Hz), 6.43 (s, 1H). MS m/e; 265 (M^+). Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found : C, 58.70; H, 5.68; N, 5.26.

From 3: A solution of 3 (1.47 mmol), NBS (2.97 mmol), and benzoyl peroxide (4 mg) in carbon tetrachloride (10 ml) was refluxed for 48 h. After cooling, the precipitate (succinimide) formed was filtered off and washed with hot benzene. The combined filtrates were evaporated to give an oil, which was chromatographed on silica gel using chloroform as eluent to afford crude bromide (561 mg). The solution of this bromide (561 mg) and DBU (1.62 mmol) in ethanol (15 ml) was refluxed for 22 h. Evaporation of the solvent under reduced pressure gave an oil, which was submitted to a high resolution chromatography on silica gel using benzene-acetone (5:1) as eluent to give pure 9 in 21% yield.

5-Oxo-1,2,3,5-tetrahydroindolizine-7,8-dicarboxylic Acid N,N'-Hydrazide (10)---A solution of 9 (133 mg, 0.5 mmol) and hydrazine hydrate (250 mg, 5mmol) in ethanol (5 ml) was refluxed for 2 days. After cooling, the precipitate (116 mg) formed was separated by filtration. This solid was mixed with 5% hydrochloric acid, filtered, and washed with water to give white powder of 10 (49 mg, 46%).

mp >300°C. IR ν_{max}^{KBr}cm^{-1}; 3200 (NH), 1680, 1630 (C=O). ^{1}H-NMR (d_6-DMSO) δ ppm; 2.2 (quint, 2H, J=7.5 Hz), 3.62 (t, 2H, J=7.5 Hz), 4.10 (t, 2H, J=7.5 Hz), 6.43 (s, 1H) MS m/e; 219 (M^+).

Methyl E,Z-4-Carbethoxy-4-(pyrrolidin-2-ylidene)-2-butenoate (11)---By general procedure (MP, 1.5 eq; reflux, 4 days): Pale yellow needles from isopropyl ether (yield, 60%). mp 138-140°C. IR ν_{max}^{KBr}cm^{-1}; 3280 (NH), 1700, 1685, 1640, 1600, 1565 (C=O, C=C). ^{1}H-NMR ($CDCl_3$) δ ppm; 1.35 (t, 3H, J=7 Hz), 2.08 (quint, 2H, J=7.5 Hz), 2.98 (t, 2H, J=7.5 Hz), 3.67 (t, 2H, J=7.5 Hz), 3.70 (s, 3H), 4.20 (q, 2H, J=7 Hz), 6.10 (d, 1H, J=16 Hz), 7.55 (d, 1H, J=16 Hz), 9.47 (br.s, 1H). MS m/e; 239 (M^+). Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found : C, 60.48; H, 7.31; N, 5.85.

Methyl 5-Oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate (13)---From 5: A solution of 5 (0.3 mmol) and sodium methoxide (0.6 mmol) in methanol (5 ml) was refluxed for 3 h and then evaporated under reduced pressure to give an oil, which was extracted with chloroform (10 ml×3). The combined extracts were washed with 5% hydrochloric acid and water, dried over magnesium sulfate, and evaporated to give crystals of 13. Colorless needles from hexane (yield, ~100%). mp 148-150°C. IR ν_{max}^{KBr}cm^{-1}; 1720, 1640, 1590. ^{1}H-NMR ($CDCl_3$) δ ppm; 2.23 (quint, 2H, J=7.5 Hz), 3.57 (t, 2H, J=7.5 Hz), 3.83 (s, 3H), 4.18 (t, 2H, J=7.5 Hz), 6.42 (d, 1H, J=9 Hz), 7.91 (d, 1H, J=9 Hz). MS m/e; 193 (M^+). Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found : C, 62.25; H, 5.79; N, 7.30. From 11: Similarly, 13 was obtained from 11 in 59% yield by the method described above.

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