Synthesis and Study of N-Substituted 1,2-Dihydropyridines[1]

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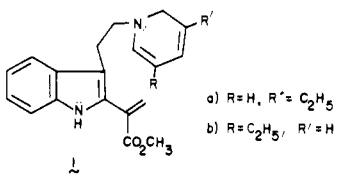
Abstract: A synthetic methodology to the reactive 1,2-dihydropyridine ring system has been developed. This method involves the use of 2-azabicyclo[2.2.0]hex-5-ene (**2**) as a synthetic equivalent for 1,2-dihydropyridine (**3**). In contrast to 1,2-dihydropyridine **3**, 2-azabicyclo[2.2.0]hex-5-ene (**2**) is stable and its N-substituted derivatives can be readily prepared. The ring opening of the N-substituted 2-azabicyclo[2.2.0]hex-5-enes to the dihydropyridines can be accomplished by heating either in the gas phase or an inert solvent. The scope and applications of this synthetic method are discussed.

The 1,2-dihydropyridines are potentially valuable intermediates for the preparation of complex heterocycles.[2] However, simple 1,2-dihydropyridines without electron-withdrawing groups on the ring are relatively rare.[3] This fact is undoubtedly due to the reactivity of this heterocycle toward oxidation, dimerization, and polymerization. There has been recent interest in 1,2-dihydropyridines because of their possible role in biosynthesis.[4] For example, dihydropyridines (**1a,b**)



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have been proposed as key intermediates in the biosynthesis of the indole alkaloids.[4] Although these compounds have never been isolated or synthesized, their postulation provides a remarkably simple hypothesis for understanding the known biosynthetic relationships among major families of indole alkaloids. Furthermore, these biosynthetic studies suggest[5] that dihydropyridines such as the dehydrosecodines **1a,b** and related compounds may provide efficient routes to the important indole alkaloids.[6]

The most common synthetic route to these N-substituted 1,2-dihydropyridines has been the reduction of pyridinium ions with hydride reducing agents.[7] This technique, although successful in a few simple cases, has difficulties such as overreduction to the tetrahydropyridine. Because of the reactivity of 1,2-dihydropyridines, it is unlikely that they would survive many steps in a synthetic sequence that would be necessary to prepare complex compounds such as the dehydrosecodines. For this reason, we have developed a less reactive synthetic equivalent for the potentially valuable 1,2-dihydropyridines.

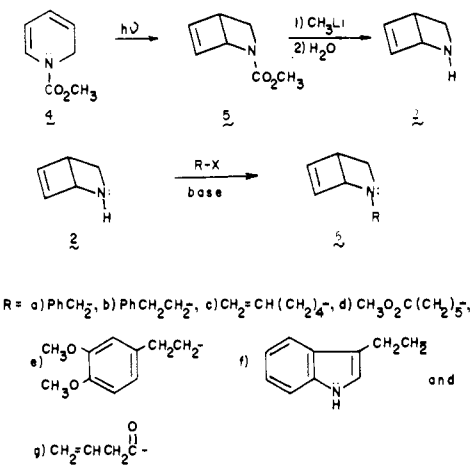
We have investigated 2-azabicyclo[2.2.0]hex-5-ene (**2**)[8] as a suitable synthetic equivalent of 1,2-dihydropyridine **3**. Although **3** and **2** are valence isomers, the latter does not contain

2 **3**

the reactive dienamine function and is not a pyridine derivative. It is considerably more stable to both polymerization and oxidation and undergoes N-alkylation without difficulty. Because of the ring strain present in the 2-azabicyclo[2.2.0]hex-5-ene ring system, it is labile with respect to thermal ring opening to the isomeric 1,2-dihydropyridine. These properties make **2** and its derivatives valuable masked 1,2-dihydropyridines.

The amine **2** was most conveniently prepared by the hydrolysis of the carbamate derivative[9] using methyllithium. The carbamate **5** could be prepared routinely on a multigram scale (ca. 40 g) by irradiation of the dihydropyridine **4** in acetone. The stability of the dihydropyridine to these conditions is due to the electron-withdrawing ability of the *N*-acyl group.

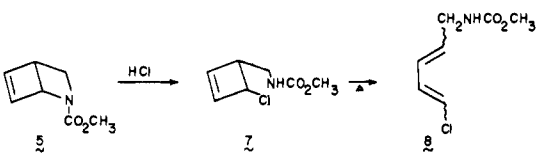
Alkylation and acylation of amine **2** occur without difficulty, and a number of derivatives have been prepared using this method.



4 **5** **2**

2 **6**

The alkyl derivatives are tertiary amines and purification techniques take advantage of their basicity. For example, a standard procedure is to separate the basic product of alkylation from the neutral alkylating agent by extraction with 5% HCl. These azetidines are stable to this process.[10] This behavior is in contrast to the acyl derivatives, which rapidly react with HCl to give ring-opened products. For example, treatment of **5** with HCl in benzene gave the ring-opened cyclobutene **7**. This cyclobutene is thermally labile and readily undergoes ring opening to the butadiene **8**.



5 **7** **8**

Nitrogen substituted acyl-1,2-dihydropyridines can be useful compounds for synthesis. Because of the presence of the electron-withdrawing group on nitrogen they are stable. However, the acyl group can be either removed by hydrolysis or reduced to an alkyl substituent if desired. Also, the *N*-acyl-1,2-dihydropyridines, in contrast to the *N*-alkyl-1,2-dihydropyridines, behave as dienes rather than enamines in cycloaddition reactions.[11]

The amine **2** also reacts as a typical secondary amine with electron-deficient double bonds to give conjugate addition (**6h** and **6i**). These compounds give dihydropyridines that would

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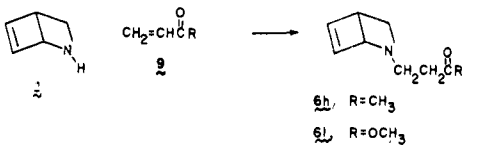
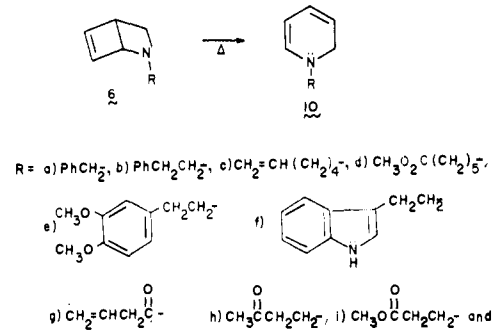
Table I. Kinetic Data for the Thermal Ring Opening of 2-Azabicyclo[2.2.0]hex-5-enes to the 1,2-Dihydropyridines

compd	E_A	A
6a	30.6	1.96×10^{13}
5	32.0	6.47×10^{12}



be very difficult to obtain using previously known methods.

The 1,2-dihydropyridines **10** can be prepared by heating the 2-azabicyclo[2.2.0]hex-5-enes either in solution or in the gas phase. The rate of this thermal ring opening in the gas phase is sensitive to the substitution on nitrogen. The *N*-methyl derivative (**6i**) has a half-life of 0.77 h at 125 °C in contrast to



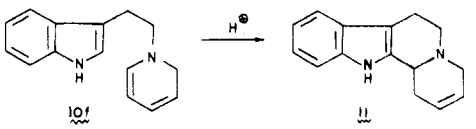
the *N*-carbomethoxy derivative (**5**), which has a half-life of 1.13 h at 157 °C. Similar observations were also made in benzene solution on the *N*-benzyl- and *N*-carbomethoxy-2-azabicyclo[2.2.0]hex-5-enes (**6a** and **5**). The kinetic data for these compounds are reported in Table I.

These observations are consistent with the lone pair of electrons on nitrogen being stabilized by interacting with the LUMO of the developing diene. Since the lone pair of electrons of *N*-alkylamines lies closer in energy to the LUMO of the diene this stabilizing interaction will be greater with *N*-alkylamines than *N*-acylamines.

The commonly used method for inducing the ring opening on a preparative scale is flash thermolysis.[13] A 5–10% benzene solution of the substrate is frozen in dry ice-acetone. This mixture is then evaporated through an evacuated hot tube and the product is collected at −196 °C.

Several attempts to prepare the parent 1,2-dihydropyridine by the thermal ring opening of 2-azabicyclo[2.2.0]hex-5-ene have not been successful. Although the product produced in these thermal reactions has ^{1}H NMR spectral features typical of a 1,2-dihydropyridine, it is very unstable and could not be characterized completely.

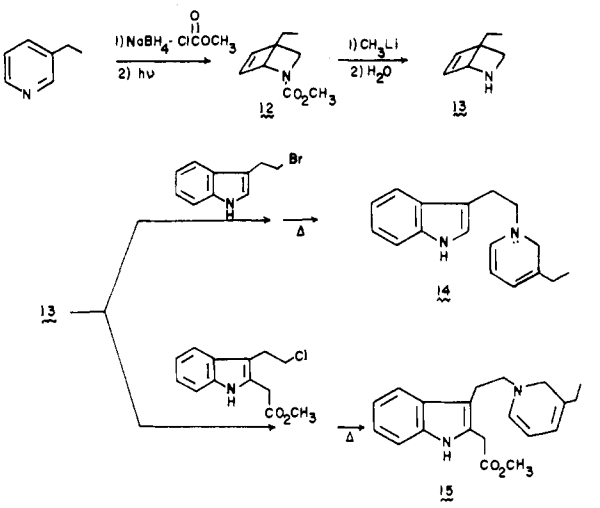
The extensive studies of Wenkert[14] indicate that dihydropyridines such as **10f** could be valuable intermediates in alkaloid total synthesis. Treatment of **10f** with HCl in methanol does indeed produce the indoloquinolizidine **11** as suggested by Wenkert's earlier studies.



The transformation illustrated above has previously employed 1,2,3,4-tetrahydropyridines and 1,4-dihydropyridines.[16] The availability of 1,2-dihydropyridines will now allow their utility to be explored in this methodology. There are two advantages of 1,2-dihydropyridines over 1,2,3,4-tetrahydropyridines. The dihydropyridines are more stable than the analogous tetrahydropyridines[17] and after cyclization the additional double bond in the ring can be used for further structural elaboration.

For natural product total synthesis the 3- or 5-ethyl-1,2-dihydropyridine derivatives are useful. Since the reduction of pyridinium ions occurs regiospecifically, the carbamate **12** is readily available. Application of the above described methodology can provide a synthesis of N-substituted 5-ethyl-1,2-dihydropyridines.

We have successfully prepared dihydropyridines **14** and **15**



from 3-ethylpyridine. The significance of these results is that they demonstrate that our method can be applied to relatively complex molecules and that these compounds may be useful intermediates in alkaloid synthesis. For example, Scott and Yeh[4c] have proposed a tautomer of the achiral dihydropyridine **15** as an intermediate in the in vitro antipodal interconversion of the *Strychnos* alkaloids. This would suggest that **15** could be an intermediate in a biomimetic synthesis of these *Strychnos* alkaloids. This possibility is presently being explored.

In summary, we have developed a synthetic methodology to the N-substituted 1,2-dihydropyridines using a masked 1,2-dihydropyridine. This technique has been applied to a number of 1,2-dihydropyridines that were previously unknown or inaccessible. The availability of 1,2-dihydropyridines will allow for their exploration as intermediates for the total synthesis of complex heterocycles. Also, our approach should be applicable to the elusive dehydrosecodines, whose preparation would be of both synthetic and biosynthetic interest.

Experimental Section

The proton magnetic resonance spectra (^{1}H NMR) were recorded using a Varian EM-360 or HFT-80 spectrometer. Apparent coupling constants are reported and the multiplicities are indicated using s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. The carbon-13 magnetic resonance spectra (^{13}C NMR) were recorded using a Varian CFT-20 spectrometer. Chemical shifts for both the ^{13}C and ^{1}H NMR spectra are reported as δ values in parts per million from tetramethylsilane as an internal standard. The high-resolution mass spectra were recorded with an AEI-MS30, and the low-resolution mass spectra were recorded with a Hewlett-Packard 5983. Both spectrometers were operated at an ionization voltage of 70 eV. The preparative scale gas-liquid chromatography was carried out on a Hewlett-Packard 5830A instrument equipped with a thermal conductivity detector. The infrared spectra were recorded with a Perkin-Elmer 727 or 567 spectrometer. The relative intensities are indicated by s = strong, m = medium, and w = weak. Microanalyses were performed by Gailbraith Laboratories, Knoxville, Tenn.

N-Carbomethoxy-2-azabicyclo[2.2.0]hex-5-ene (5). A 4% acetone solution (1300 mL) of the *N*-carbomethoxy-1,2-dihydropyridine[9] was

irradiated, using a Southern New England Ultraviolet Co. Rayonet RPR-208 photochemical reactor equipped with lamps with a maximum output at 3500 Å, until gas–liquid chromatography (5 ft × ⅛ in. SE-30 column at 135 °C) indicated the absence of the 1,2-dihydropyridine **4**. Removal of the solvent followed by chromatography on basic Al_2O_3 eluting with ether–pentane (1:4) gave the crude 2-azabicyclo[2.2.0]hex-5-ene. This was further purified by bulb-to-bulb distillation giving ca. 16.0 g (50%) of pure **5**. The physical properties of **5** are the same as previously reported.[9]

2-Azabicyclo[2.2.0]hex-5-ene (2). A 100-mL three-necked flask was equipped with a magnetic stirring bar, and rubber septa were attached to two of the necks. The third neck was connected to a mercury bubbler so that the system could be alternately evacuated and flushed with dry nitrogen. The flask was charged with a slight positive pressure of nitrogen. Dry tetrahydrofuran (20 mL) and 51 mmol of methyllithium–LiBr complex (25 mL of 2.06 M from Alfa Inorganics) was added using a syringe through one of the septa. The flask was cooled in an ice–acetone cold bath and 2.00 g of *N*-carbomethoxy-2-azabicyclo[2.2.0]hex-5-ene (**5**) was added slowly. The reaction mixture was allowed to stir for 15 min and 15 mL of water followed by 15 mL of saturated NaCl was added. The organic layer was separated and the aqueous layer extracted with ether. The organic fractions were combined and dried with anhydrous sodium carbonate. The amine **2** was concentrated by the removal of the solvent using an efficient distillation apparatus (we have used an 8-in. Nester-Faust spinning band column) and then purified by bulb-to-bulb distillation. The amine at this point is contaminated with solvent but is suitable for carrying out alkylations and acylations.

The amine **2** can be further purified by preparative gas chromatography (8 ft × ¼ in., 15% SE-30, column temperature 70 °C); ^{1}H NMR (HFT-80, benzene-d_6) δ 1.55 (s, 1 H, NH); 2.73 (d, broad, 1 H, J = 8.0 Hz), 3.00–3.28 (m, 1 H), 3.51 (t, broad, 1 H, J = 8.0 Hz), 4.28 (s, broad, 1 H), 6.10 (t, 1 H, J = 3.0 Hz), and 6.30 (t, 1 H, J = 3.0 Hz); ^{13}C NMR (CFT-20, $CDCl_3$) δ 16.3, 43.1, 46.2, 140.50, and 143.0; IR (PE 727, film) 3260 (N–H), 1655 (C=C), 1415 (m), 1295 (s), 1150 (s), 825 (s), 740 (s), and 680 cm^{-1} (s).

The physical properties of **2** are consistent with those previously reported.[8]

Reaction of *N*-Carbomethoxy-2-azabicyclo[2.2.0]hex-5-ene with HCl. To a three-neck round-bottom flask equipped with a magnetic stirrer was added 500 mg of *N*-carbomethoxy-2-azabicyclo[2.2.0]-hex-5-ene followed by 20 mL of dry benzene. The system was cooled (ice–H_2O) for 10 min. Hydrogen chloride gas was slowly bubbled in for 5 min. The reaction mixture was allowed to warm to room temperature and stirred for an additional 10 min. The solvent was removed and the residue chromatographed (silica gel, 95% $CHCl_3$–5% CH_3OH): ^{1}H NMR (EM-360, benzene-d_6) δ 2.73–3.67 (m, 6 H), 4.50–5.67 (m, 1 H), 5.00–5.57 (br, NH), 5.67–5.93 (m, 2 H); IR (film) 3350 (s), 1530 (s), 1268 (s), 772 (s) cm^{-1}; MS (70 eV) *m/e* (rel intensity) 177.0 (3.6) and 175.0 (11.1). The cyclobutene **7** (100 mg) was dissolved in 300 μL of benzene and passed through the hot tube as described for the thermal ring opening of cyclobutenes **6a–j** to the 1,2-dihydropridines **10a–j** except that the temperature of the hot tube was higher (ca. 375 °C). The product was recrystallized from pentane, which yielded 70 mg of white needles: mp 53.5–54.0 °C; ^{1}H NMR (benzene-d_6, HFT-80) δ 3.40 (s, 3 H), 3.40–3.60 (br, 2 H), 4.30–4.80 (br, NH, 1 H), 5.00–5.34 (m, 3 H), 6.40–6.70 (m, 1 H); IR (KBr), 3345 (s, N–H), 1691 (s, C=O), and 1541 cm^{-1} (s); MS (70 eV) *m/e* (rel intensity) 80.1 (100), 108.0 (91), 140 (80), 65.1 (62), 175 (11), and 177 (3.6).

Anal. ($C_7H_{10}ClNO_2$) C, H.

General Procedure for the Alkylation of 2-Azabicyclo[2.2.0]hex-5-ene. The bicyclic amine–tetrahydrofuran distillate (5–10 mL), obtained from the workup of carbamate hydrolysis, was added to a round-bottom flask containing a stirring bar, 0.5 equiv of diisopropylamine, and 0.5 equiv of the appropriate alkylating agent. Best results were obtained when these reactions were carried out under an inert atmosphere. The mixture was stirred at room temperature until the bicyclic amine was consumed (24 h). At the completion of the reaction, the organic phase was extracted with 5% HCl. The acidic fractions were combined, neutralized with a saturated Na_2CO_3 solution, then extracted with ether. The ether extracts were combined and dried (Na_2CO_3) and the solvent was removed in vacuo. The N-substituted 2-azabicyclic[2.2.0]hex-5-ene obtained was reasonably pure at this point but can be further purified by passing through a basic alumina column with ether or an ether–pentane eluent followed by bulb-to-bulb distillation. The yields reported are overall from the carbamate.

Further attempts at purification by techniques such as fractional distillation or gas–liquid chromatography usually result in slow decomposition of the bicyclic amines **6**. Analysis by proton magnetic resonance (^{1}H NMR) indicates that the bicyclic amines **6** are greater than 95% pure at this stage. Common impurities are usually residual traces of solvent. A typical ^{1}H NMR spectrum of a bicyclic amine is shown in Figure 1 with the adsorptions assigned (note: H_4 is obscured by the aliphatic hydrogens of the tryptophyl substituent).

***N*-Benzyl-2-azabicyclo[2.2.0]hex-5-ene (6a):** yield 49%; ^{1}H NMR (acetone-d_6, HFT-80) δ 2.40–2.60 (m, 1 H), 2.95–3.23 (m, 1 H), 3.35–3.80 (m, 3 H), 4.25–4.40 (m, 1 H), 6.23 (t, 1 H, J = 2.5 Hz), and 7.50 (t, 1 H, J = 2.5 Hz); ^{13}C NMR (acetone-d_6, CFT-20) δ 36.5, 52.4, 56.0, 64.9, 124.6, 126.1, 126.3, 135.0, 137.1, and 141.8; IR (film) 1492 (m), 1470 (m), 1335 (m), 745 (s), and 695 cm^{-1} (s).

This compound was characterized by conversion to the known tetrahydropyridine via **10c** by $NaBH_4$ reduction.

***N*-(2-Phenylethyl)-2-azabicyclo[2.2.0]hex-5-ene (6b):** yield 25%; ^{1}H NMR (benzene-d_6, HFT-80) δ 2.23–3.01 (m, 6 H), 3.59 (d of d, 1 H, J = 8, 7 Hz), 4.33–4.50 (m, 1 H), 6.03 (t, 1 H, J = 3 Hz), and 6.31 (t, 1 H, J = 3 Hz); IR (film) 2925 (s), 1450 (m), 745 (s), and 695 cm^{-1} (s); high-resolution mass spectrum *m/e* 185.1250 ($C_{13}H_{15}N$ requires 185.1204).

***N*-(5-Hexenyl)-2-azabicyclo[2.2.0]hex-5-ene (6c):** yield 35%; ^{1}H NMR (benzene-d_6, HFT-80) δ 1.23–2.58 (m, 9 H), 2.85–3.08 (m, 1 H), 3.63 (d of d, 1 H, J = 8, 7 Hz), 4.38–4.53 (m, 1 H), 4.78–6.03 (m, 3 H), 6.10 (t, 1 H, J = 3.0 Hz), and 6.32 (t, 1 H, J = 3.0 Hz); IR (film) 2940 (s), 1640 (m), 990 (m), 910 (m), and 750 cm^{-1} (m); high-resolution mass spectrum *m/e* 163.1348 ($C_{11}H_{17}N$ requires 163.1361).

Methyl 6-(2-Azabicyclo[2.2.0]hex-5-en-1-yl)hexanoate (6d): yield 35%; ^{1}H NMR ($CDCl_3$, HFT-80) δ 1.15–2.65 (m, 11 H), 3.1–3.3 (m, 1 H), 3.65 (s, 3 H), 3.68 (t, 1 H, J = 8 Hz), 6.23 (t, 1 H, J = 3 Hz), and 6.56 (t, 1 H, J = 3 Hz); IR (film) 2930 (s), 1730 (s, C=O), 1440 (s), 1360 (s), and 750 cm^{-1} (s); high-resolution mass spectrum *m/e* 209.1411 ($C_{12}H_{19}NO_2$ requires 209.1415).

***N*-(3,4-Dimethoxyphenyl-β-ethyl)-2-azabicyclo[2.2.0]hex-5-ene (6e):** yield 40%; ^{1}H NMR (benzene-d_6, HFT-80) δ 2.36–3.08 (m, 6 H), 3.45 (s, 3 H), 3.50 (s, 3 H), 3.59–3.76 (m, 1 H), 4.45–4.53 (m, 1 H), 6.08–6.15 (m, 1 H), 6.32–6.39 (m, 1 H), and 6.65–6.70 (d, 3 H); IR (film) 2945 (s), 2850 (m), 1505 (s), 1465 (m), 1028 (s), and 750 cm^{-1} (s); high-resolution mass spectrum *m/e* 245.1420 ($C_{15}H_{19}NO_2$ requires 245.1415).

3-[β-(2-Azabicyclo[2.2.0]hex-5-en-2-yl)ethyl]indole (6f): yield 26%; mp 95–96 °C dec, recrystallized from pentane–ether; ^{1}H NMR (benzene-d_6, HFT-80) δ 2.34–2.56 (m, 1 H), 2.69–3.08 (m, 5 H), 3.61 (d of d, 1 H, J = 8, 7 Hz), 4.39–4.54 (m, 1 H), 6.11 (t, 1 H, J = 3 Hz), 6.28 (t, 1 H, J = 3 Hz), 6.65 (d, 1 H, J = 2.5 Hz), 7.06–7.36 (m, 3 H), and 7.53–7.81 (m, 1 H); IR (film) 3400 (m), 2925 (s), 1450 (m), 735 cm^{-1} (s); high-resolution mass spectrum *m/e* 252.1596 ($C_{17}H_{20}N_2$ requires 252.1626).

***N*-But-3-enoyl-2-azabicyclo[2.2.0]hex-5-ene (6g):** yield 34%; mp 60–60.5 °C; ^{1}H NMR (HFT-80, $CDCl_3$) δ 1.83 (d of d, 2 H, J = 6.5, 1.0 Hz), 3.32–4.24 (m, 3 H), 4.87–5.05 (m, 1 H), 5.63–7.08 (m, 5 H); IR (KBr) 1658 (s), 1605 (s), 1450 (s), 1425 (s), and 755 cm^{-1} (s).

Anal. ($C_9H_{11}NO$) C, H.

***N*-(3-Oxobutyl)-2-azabicyclo[2.2.0]hex-5-ene (6h):** yield 33%; ^{1}H NMR (benzene-d_6, HFT-80) δ 1.77 (s, 3 H), 2.00–3.00 (m, 6 H), 3.43–3.86 (m, 1 H), 4.27–4.37 (m, 1 H), 6.02–6.10 (m, 1 H), and 6.27–6.35 (m, 1 H); IR (film) 2935 (s), 2835 (s), 1700 (s, C=O), 1600 (w, C=C), 1356 (s), 1261 (s), and 751 cm^{-1} (s); high-resolution mass spectrum *m/e* 151.1018 ($C_{19}H_{13}NO$ requires 151.0997).

Methyl β-(2-Azabicyclo[2.2.0]hex-5-en-2-yl)propanoate (6i): yield 35%; ^{1}H NMR (benzene-d_6, HFT-80) δ 2.00–3.00 (m, 6 H), 3.33 (s, 3 H), 3.43–3.62 (m, 1 H), 4.30–4.40 (m, 1 H), 5.98–6.04 (m, 1 H), and 6.23–6.30 (m, 1 H); IR (film) 1736 (s, C=O), 1436 (s), 1165 (s), and 750 cm^{-1} (s); high-resolution mass spectrum *m/e* 167.0935 ($C_9H_{13}NO_2$ requires 167.0946).

General Procedures for the Preparation of 1,2-Dihydropyridines from 2-Azabicyclo[2.2.0]hex-5-enes. We have observed that the most general and convenient method for carrying out the conversion of the N-substituted 2-azabicyclo[2.2.0]hex-5-enes to the 1,2-dihydropyridines is by using a flash thermolysis technique. The apparatus we used is shown in Figure 2. The inner 1.0-cm tube was wrapped with Nichrome resistance wire to give a total resistance of 26 Ω. When the

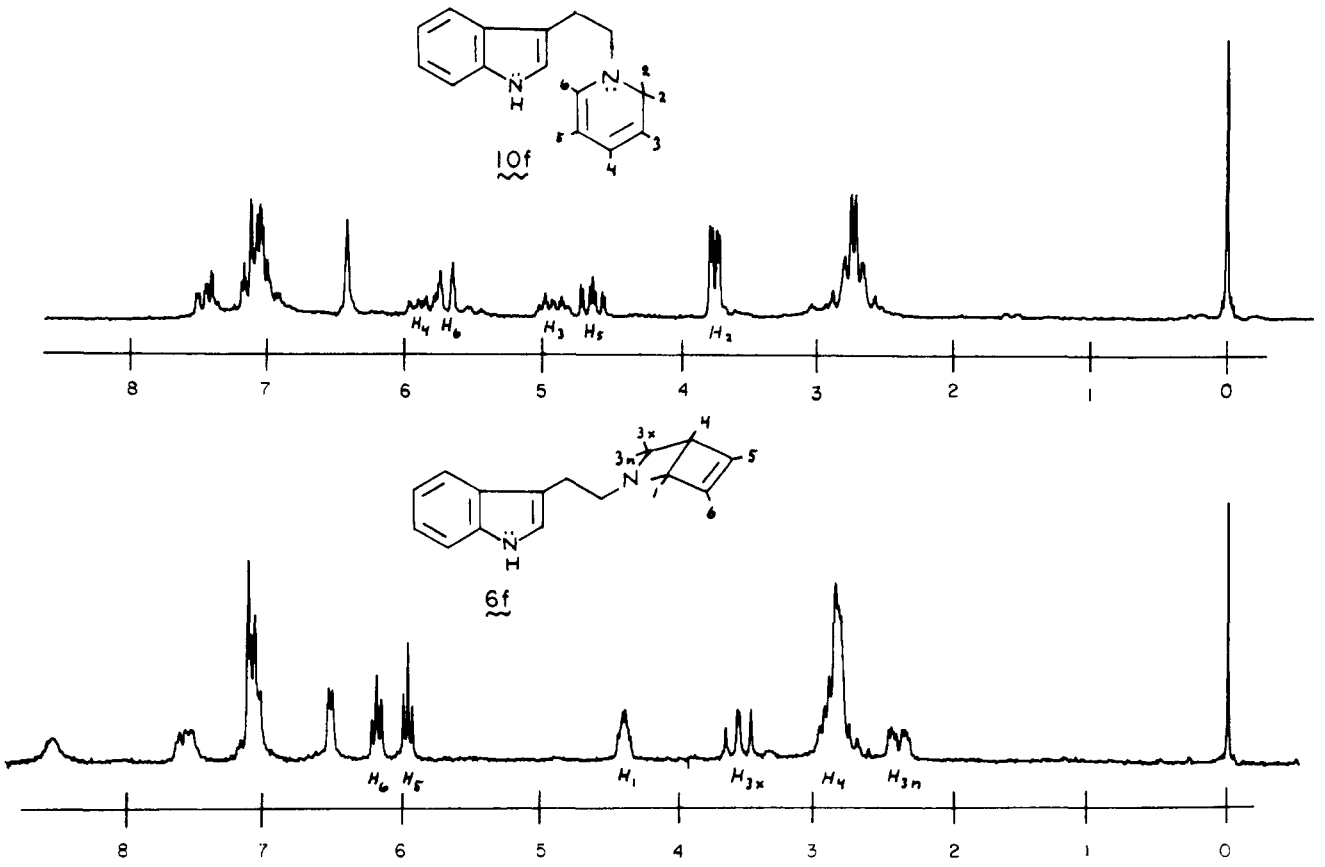


Figure 1.

tube was evacuated to 10^{-3}-10^{-4} Torr it was determined that 43 V was adequate to achieve the necessary temperature (ca. 340 °C) to induce ring opening of the N-substituted 2-azabicyclo[2.2.0]hex-5-enes. The inner tube was packed with short (2-4 mm) pieces of 3-mm glass tubing.

An essential design feature is that the 1.0-mm tube is only connected at one end to the rest of the apparatus. This allows wrapping the inner tube through the ₹ 24/40 joint with resistance wire. The reaction product is directed to the cold receiver flask. There are no large temperature gradients in the 1.0-cm reaction tube until the sample reaches the receiver flask. The above design feature allows for simultaneous evacuation of the inside and outside of the reaction tube when vacuum is applied to the apparatus.

The following procedure was used for passing relative volatile compounds through the hot tube. The sample was placed in a 50-mL ₹ 19/22 flask and attached to the apparatus. The sample was rapidly cooled in dry ice-acetone. The apparatus was evacuated and flushed with N_2. The sample was degassed. The receiver flask was cooled with liquid nitrogen. The apparatus was evacuated to ca. 10^{-4} Torr and the cooling bath was removed to allow evaporation of the sample through the hot tube. Slight warming of the sample may be necessary for evaporation. For nonvolatile compounds, the following modifications were necessary. A 10% solution of the reactant in benzene was prepared (for convenience the solvent was frequently benzene-d_6 in order that the product could be directly analyzed by NMR spectroscopy). This was placed in the 50-mL ₹ 19/22 flask and the sample was frozen in a dry ice bath. The sample was degassed and frozen again. The receiver was cooled in a liquid nitrogen bath. Heat was applied with the aid of a heat gun. This is a critical step. It is important to evaporate the sample as fast as possible.

The benzene plays two roles in this procedure. It remains frozen throughout the evaporation, keeping reactant cool in the condensed phase. Only the reactant on the surface of the benzene is carried through the hot tube. The benzene is also a carrier gas in this experiment.

Using this technique we have been able to prepare high molecular weight dihydropyridines such as **14** and **15** from thermally labile precursors. It is a very effective method for vaporizing high molecular weight compounds.

Sealed-Tube Thermolysis. The 2-azabicyclo[2.2.0]hex-5-ene (50-200 mg) was added to a Pyrex reaction vessel (this consisted of a 4.5 × 22 cm tube sealed at one end with an open 10 mm × 15 cm Pyrex tube attached to the other end). The sample was added to the tube and cooled in dry ice-acetone. The tube was evacuated and flushed several times with dry nitrogen. The tube was then evacuated to ca. 0.1 Torr and the 10-mm diameter tube sealed leaving a ca. 5-cm length attached to the reaction tube. The reaction tube was then placed in an oven for 1 h at 150 °C. The 10-mm diameter glass tip of the reaction tube was immersed in a dry ice-acetone bath, causing condensation of the product in this tip. Sometimes slight warming of the bulb was required for complete condensation of the product in the glass tip. Removal of this glass tip gave the product in essentially quantitative conversion.

Solution-Phase Thermolysis. A ca. 14% solution of the azabicyclo[2.2.0]hexene **6** was dissolved in benzene-d_6. The solution was frozen, flushed with N_2, and sealed. Heating the tube at 150 °C for 1-1.5 h produced the 1,2-dihydropyridines. This method was not as clean as the gas-phase techniques. Although no other products could be detected, the solution darkened considerably.

General Comments on 1,2-Dihydropyridines. The 1,2-dihydropyridines without electron-withdrawing groups on the ring are very reactive. In contact with the atmosphere they rapidly undergo oxidation and polymerization. Dimerization has also been observed in contact with a glass surface. They should be stored cold under an inert atmosphere and over potassium hydroxide pellets.

The 1,2-dihydropyridines produced in the gas phase are generally pure. The purity and structures of these compounds are best determined by NMR spectroscopy. The NMR spectrum for **10f** is shown in Figure 1. This is typical for 1,2-dihydropyridines produced by this scheme. The chemical shifts and multiplicities of the ring protons shown in Figure 1 are virtually identical for all other N-substituted 1,2-dihydropyridines without stabilizing electron-withdrawing groups on the ring. The common impurity produced by this method is the isomeric 2,3-dihydropyridine.[18] The presence of this compound is detected by the appearance of one or two methyl doublets at ca. δ 1.6. Since it is a thermal rearrangement product of the 1,2-dihydropyridines its formation usually can be suppressed by lowering the temperature of the hot reaction tube.

If further characterization for the 1,2-dihydropyridines is desired, they can be reduced to the more stable 1,2,5,6-tetrahydropyridines with sodium borohydride.[19] An independent synthesis of the 1,2,5,6-tetrahydropyridines can usually be accomplished by the alkylation of the commercially available 1,2,5,6-tetrahydropyridine or by reduction of the pyridinium salts with sodium borohydride.[19]

***N*-Methyl-2-azabicyclo[2.2.0]hex-5-ene (6j)** was prepared by $LiAlH_4$ reduction of the carbamate **5**. A 100-mL three-necked round-bottom flask equipped with rubber septum and magnetic stirrer and under an N_2 atmosphere was charged with 0.5 g of $LiAlH_4$ and 25 mL of dry ether. The reactants were cooled to 0 °C and 1.0 g of *N*-carbomethoxy-2-azabicyclo[2.2.0]hex-5-ene was slowly added. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The excess $LiAlH_4$ was decomposed by carefully adding 0.5 mL of H_2O and 1 mL of 10% NaOH followed by 0.5 mL of H_2O. The inorganic salt was filtered off and the organic layer dried over Na_2CO_3 and concentrated on a steam bath. The last trace of solvent was removed by a slow stream of N_2 to give 0.613 g of (80%) of the product: ^1H NMR ($CDCl_3$, EM-360) δ 2.28 (s, 3 H), 2.50 (d of d, 1 H, J = 7.5 Hz), 3.06-3.30 (m, 1 H), 3.68 (d of d, 1 H, J = 7.0, 6.5 Hz), 4.30-4.50 (m, 1 H), 6.30 (t, 1 H, J = 2.5 Hz), and 6.00 (t, 1 H, J = 2.5 Hz); IR (film) 2940 (s), 2850 (s), 1640 (s), 1460 (s), 1377 (m), 1300 (m), 1125 (m), 730 (w), 745 (s) cm^{-1}; MS (70 eV) *m/e* (rel intensity) M^+ 95 (36), 94 (100), 93 (11), 82 (17), 56 (21), 54 (22), 52 (30); high-resolution MS *m/e* 95.0728 (required for C_6H_9N, 95.0735).

Kinetic Studies on the Thermal Ring Opening of the 2-Azabicyclo[2.2.0]hex-5-enes to the 1,2-Dihydropyridines. Gas-Phase Reactions. To a 150-mL reaction vessel that had previously been purged with N_2 was added 25 μL of the 2-azabicyclo[2.2.0]hex-5-ene (**5** or **6j**). The sample was frozen in dry ice-acetone and the reaction vessel was evacuated and flushed several times with N_2. The reaction vessel was evacuated to ca. 0.01 Torr and was immersed in a fluidized bath that had been preheated to the desired temperature (125 °C for **5** and 157 °C for **6j**). The reaction was quenched by immersing one end of the reaction vessel in dry ice-acetone (−80 °C). This caused condensation of the sample, which was analyzed by gas chromatography (5 ft × ⅛ in. OV-1 on Chromosorb Q at 80 °C). Analysis by ^1H NMR spectroscopy gave the same result and indicated that sample decomposition had not occurred during the GLC analysis. Three runs were made for each compound giving first-order rate constants of 2.67×10^{-4} s^{-1} for **5** at 125 °C and 1.75×10^{-4} s^{-1} for **6j** at 157 °C.

Solution-Phase Reactions. All kinetic studies were performed in 99% benzene-d_6. A typical run involved the introduction of 75 μL of bicyclic material followed by 400 μL of benzene-d_6 into a glass 5-mm NMR tube. The solution was degassed by freeze-thaw cycles. The tube was sealed under high vacuum and heated by submersion in a constant-temperature oil bath. The constituents were analyzed by ^1H NMR by comparing the integration of the vinyl hydrogens at δ 6.00-6.30 in the bicyclic compound to that of the methylene hydrogens at δ 4.50 in the corresponding 1,2-dihydropyridine. The signal obtained for benzene-d_6 served as an internal standard.

***N*-Benzyl-1,2-dihydropyridine (10a)**: ^1H NMR (benzene-d_6, HFT-80) δ 3.58 (s, 2 H), 3.63 (d of d, 2 H, J = 4, 2 Hz), 4.60-5.05 (m, 2 H), 5.73-5.48 (m, 2 H), and 7.08 (s, broad, 5 H).

This dihydropyridine was reduced to the known 1,2,5,6-tetrahydropyridine with sodium borohydride in methanol.[20] The physical properties of this tetrahydropyridine were identical with those of the *N*-benzyl-1,2,5,6-tetrahydropyridine prepared from the reaction of benzyl chloride with 1,2,5,6-tetrahydropyridine.

***N*-(2-Phenylethyl)-1,2-hydropyridine (10b)**: ^1H NMR (benzene-d_6, HFT-80) δ 2.23-2.80 (m, 4 H), 3.71 (d of d, 2 H, J = 4, 2 Hz), 4.58-5.06 (m, 2 H), 5.65 (d of t, 1 H, J = 7, 0.5 Hz), 5.78-6.00 (m, 1 H) and 5.55-7.25 (m, 5 H).

***N*-(5-Hexenyl)-1,2-dihydropyridine (10c)**: ^1H NMR (benzene-d_6, HFT-80) δ 1.00-2.50 (m, 8 H), 3.68 (d of d, 2 H, J = 4, 2 Hz), and 4.60-6.05 (m, 7 H); IR (film) 2945 (s), 1640 (s), 1750 (s), and 910 cm^{-1} (s).

Methyl 6-(1,2-Dihydropyridin-1-yl)hexanoate (10d): ^1H NMR (benzene-d_6, EM-360) δ 0.87-2.67 (m, 10 H), 3.40 (s, 3 H), 3.73 (d of d, 2 H, J = 4, 1.0 Hz), 4.57-5.17 (m, 2 H), and 5.63-6.50 (m, 2 H); IR (film) 2940 (s), 1735 (s, C=O), 1665 (m), 1635 (m), 1435 (m), and 690 cm^{-1} (m).

***N*-(3,4-Dimethoxyphenyl-β-ethyl)-1,2-dihydropyridine (10e)**: ^1H NMR (benzene-d_6, HFT-80) δ 2.32-2.85 (m, 4 H), 3.43 (s, 3 H), 3.50 (s, 3 H), 3.80 (d of d, 2 H, J = 4, 2 Hz), 4.65-5.09 (m, 2 H), 6.54-6.06 (m, 2 H), and 6.59 (s, 3 H); IR (film) 3045 (s), 2950 (s), 2860 (s), 1631 (m), 1587 (m), 1509 (s), 1261 (s), 1231 (s), and 1026 cm^{-1} (s).

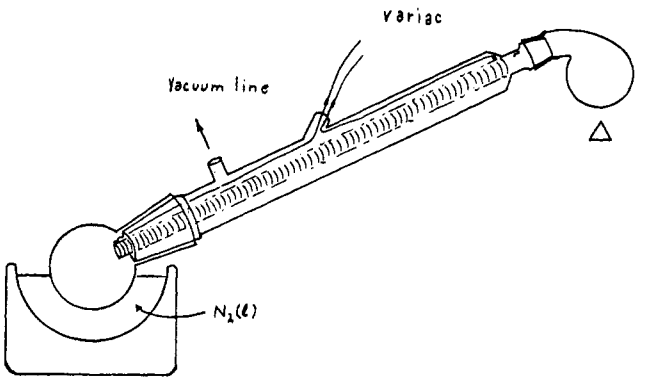


Figure 2.

3-[β-(1,2-Dihydropyridin-1-yl)ethyl]indole (10f): ^1H NMR (benzene-d_6, HFT-80) δ 2.50-3.18 (m, 4 H), 3.80 (d of d, J = 4, 2 Hz), 4.60-4.80 (m, 1 H), 4.84-5.11 (m, 1 H), 5.55-6.06 (m, 2 H), 6.5 (s, 1 H), and 6.90-7.75 (4 H); IR (CH_2Cl_2) 3440 (NH), 1631 (s), and 1566 cm^{-1} (s). This compound was converted into the known tetrahydrocarboline **11**.[7c]

Tetrahydrocarboline (11). Dry methanol (10 mL) (distilled over Mg) was placed in a round-bottom flask and cooled in an ice-water bath. Dry HCl gas was bubbled in for 3 min, followed by 15 mL more of dry methanol. To this reaction mixture 3-[β-*N*-(1,2-dihydropyridinyl)ethyl]indole (**10f**, 165 mg) was added. The solution was stirred for 10 min at room temperature. It was then carefully neutralized with 15% NaOH. The methanol was removed in vacuo and a saturated NaCl solution was added. The mixture was extracted with methylene chloride. The methylene chloride extracts were combined and dried $(MgSO)_4$. Removal of the methylene chloride afforded 160 mg of **11**. This product can be obtained in high purity by passing through an alumina column with ether. Recrystallization from ethanol gave pure **13**: mp 145-145.5 °C (lit. 144-144.5 °C); ^1H NMR ($CDCl_3$, HFT-80) δ 2.20-3.64 (m, 9 H), 5.74-5.80 (m, 2 H), 6.98-7.50 (m, 4 H), 7.63-7.75 (br s, 1 H).

***N*-But-3-enoyl-1,2-dihydropyridine (10g)**: ^1H NMR (HFT-80, benzene-d_6, HFT-80) δ 1.89 (d of d, 2 H, J = 7.0, 2.0 Hz), 4.41 (d of d, 2 H, J = 3.5, 2.0 Hz), 5.08-7.25 (m, 7 H).

***N*-(3-Oxobutyl)-1,2-dihydropyridine (10h)**: ^1H NMR (benzene-d_6, HFT-80) δ 1.95-2.11 (m, 2 H), 2.66-2.84 (m, 2 H), 3.26 (s, 3 H), 3.55-3.64 (m, 2 H), 4.60-4.97 (m, 2 H), and 5.70-5.90 (m, 2 H); IR (film) 1738 (s), 1632 (s), 1570 (s), 1438 cm^{-1} (s).

***N*-Carbomethoxy-5-ethyl-1,2-dihydropyridine**: yield 72%; ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7.0 Hz), 1.95 (q, 2 H, J = 7.0 Hz), 3.25 (s, 3 H), 4.25-4.50 (m, 1 H), 5.15 (d of d, 1 H, J = 8, 7 Hz), 5.5-5.7 (m, 1 H), and 6.56-6.75 (m, 1 H); IR (film) 2960 (s), 1705 (s), 1440 (s), and 725 cm^{-1} (s).

***N*-Carbomethoxy-2-aza-4-ethylbicyclo[2.2.0]hex-5-ene (12)**: ^1H NMR ($CDCl_3$, EM-360) δ 0.82-1.07 (t, 3 H, J = 7 Hz), 1.57-1.90 (q, 2 H, J = 7 Hz), 3.46-3.83 (m, 6 H), 4.57-4.62 (br d, 1 H), 6.50-6.65 (m, 2 H); IR (film) 2950 (s), 1700 (s), 1360 (s), 1185 (m), and 755 cm^{-1} (m).

4-Ethyl-2-azabicyclo[2.2.0]hex-5-ene (13). This compound was prepared as previously described for **2**: ^1H NMR (HFT-80, benzene-d_6) δ 0.75 (t, 3 H, J = 8 Hz), 1.50 (q, 2 H, J = 8 Hz), 2.9 (d of d, 1 H, J = 8, 7 Hz), 3.35 (d, 1 H, J = 8 Hz), 4.10 (m, 1 H), 6.07 (d, 1 H, J = 2 Hz), 6.35 (t, 1 H, J = 2 Hz); IR (film) 3315 (m, N-H), 2950 (s), 2925 (s), 2850 (m), 1625 (w), 1455 (m), 1320 (m), 1260 (w), 1090 (w), 980 (m), 800 (s), 740 (s) cm^{-1}; MS (70 eV) *m/e* (rel intensity) M^+ 109 (42), 108 (100), 93 (71), 80 (64), 67 (57); high-resolution MS *m/e* 109.0855 (required for $C_7H_{11}N$, 109.0891).

3-[β-(4-Ethyl-2-azabicyclo[2.2.0]hex-5-en-1-yl)ethyl]indole: mp 118.5-119.5 °C; ^1H NMR (HFT-80, $CDCl_3$) δ 0.74-0.92 (t, 3 H, J = 7 Hz), 1.55-1.65 (q, 3 H, J = 7 Hz), 2.83-2.91 (m, 5 H), 3.43-3.53 (d, 1 H, J = 8.1 Hz), 4.24-4.30 (m, 1 H), 6.19-6.22 (d, 1 H, J = 2.7 Hz), 6.55-6.62 (t, 1 H, J = 2.7 Hz), 6.85-6.88 (d, 1 H, J = 2.2 Hz), 7.06-7.23 (m, 3 H), 7.45-7.58 (m, 1 H), and 8.80 (s, br, 1 H); IR ($CHCl_3$) 3478 (s, N-H), 1456 (s), and 1086 cm^{-1} (s); high-resolution mass spectrum *m/e* 252.1596 (required for $C_{17}H_{20}N_2$, 252.1626).

3-β-(5-Ethyl-1,2-dihydropyridin-1-yl)ethyl]indole (14). This 1,2-dihydropyridine was prepared as previously described for **10f** except that $CHCl_3$ was necessary to dissolve the material prior to pyrolysis: ^1H NMR ($CDCl_3$, HFT-80) δ 0.95–1.13 (t, 3 H, J = 7 Hz), 1.87–2.15 (q, 2 H, J = 7 Hz), 3.78 (s, 3 H), 4.0–4.25 (m, 2 H), 5.04–5.24 (m, 1 H), 5.50–5.64 (m, 1 H), 6.50–6.75 (m, 1 H); IR (film) 3510 (s) and 1472 cm^{-1}.

Methyl 3-[β-(4-Ethyl-2-azabicyclo[2.2.0]hex-5-en-1-yl)ethyl]-indol-2-ylacetate. A solution of 0.25 g (3 mmol) of **13** (purified by GLC, 8 ft × ¼ in. 15% SE-30 at 50 °C), 0.5 g (1.9 mmol) of methyl 3-(β-chloroethyl)indol-2-ylacetate,[21] 0.25 mL of diisopropylamine, and 2.5 mL of ethyl acetate was placed in a glass tube. The reaction mixture was cooled to −78 °C and degassed. The tube was sealed and heated in an oil bath for 6.5 h. The product was worked up as previously described in the general procedure giving 55% yield of the 2-azabicyclo[2.2.0]hex-5-ene: ^1H NMR (HFT-80, benzene-d_6) δ 0.75 (t, 3 H, J = 8 Hz), 2.5 (d of d, 1 H, J = 8, 7 Hz), 2.7–2.8 (m, 4 H), 3.25 (s, 3 H), 3.45 (d, 1 H, J = 8 Hz), 3.5 (s, 2 H), 4.20–4.30 (m, 1 H), 6.0 (d, 1 H, J = 2 Hz), 6.2 (t, 1 H, J = 2 Hz), 7.0–7.25 (m, 3 H), 7.50–7.65 (m, 1 H), 7.9–8.1 (s, broad, NH); IR (film) 3380 (m, N–H), 2925 (s), 1735 (s, C=O), 1460 (m), 1000 (m), 718 (s) cm^{-1}; MS (70 eV) *m/e* (rel intensity) M^+ 324 (1.7), 219 (30), 156 (49), 135 (86), 122 (100), 107 (57); high-resolution mass spectrum *m/e* 324.1814 (required for $C_{20}H_{24}N_2O_2$, 324.1823).

Methyl 3-[β-(5-Ethyl-1,2-dihydropyridin-1-yl)ethyl]indol-2-ylacetate (15). The bicyclic amine (20 mg) was dissolved in 450 μL of benzene-d_6 and subjected to flash thermolysis at 10^{-4} Torr pressure: ^1H NMR (HFT-80, benzene-d_6) δ 0.95 (t, 3 H, J = 8 Hz), 1.80 (q, 2 H, J = 8 Hz), 2.6–2.9 (m, 4 H), 3.25 (s, 3 H), 3.5 (s, 2 H), 3.80 (m, 2 H), 4.70 (t, 1 H, J = 8 Hz), 5.5–7.2 (m, 2 H), 7.0–7.72 (m, 4 H), 8.35–8.5 (s, 1 H, broad, NH); IR (film) 3380 (m, N–H), 2960 (s), 2525 (s), 1735 (s, C=O), 1660 (w), 1610 (m), 1585 (m), 1460 (s), 1130 (w), 1165 (m), 740 (s) cm^{-1}.

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