zine, 5860-49-1; 2-methyl-1-piperidinepropanol, 94-88-2; *cis*-hexahydro-6-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine, 114583-09-4; *trans*-hexahydro-6-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine, 114583-10-7; hexahydro-9a-methyl-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine, 110423-48-8; 2-methyl-1-piperidineethanol, 17719-74-3; *cis*-hexahydro-5-methyl-5*H*-oxazolo[3,2-*a*]pyridine, 114583-11-8; *trans*-hexahydro-5-methyl-5*H*-oxazolo[3,2-*a*]pyridine, 114583-12-9; hexahydro-8a-methyl-5*H*-oxazolo-[3,2-*a*]pyridine, 114583-13-0; 3-methyl-1,3-tetrahydrooxazine, 21635-18-7; *N*-methylpyrrolidine, 120-94-5; 1-pyrrolidineacetonitrile, 29134-29-0; 1-methyl-2-pyrrolidinecarbonitrile, 20297-37-4; *N*-methylpiperidine, 626-67-5; 1-piperidineacetonitrile, 3010-03-5; 1-methyl-2-piperidinecarbonitrile, 18747-95-0; tryptamine, 61-54-1.

A New Method for the Formation of Nitrogen-Containing Ring Systems via the Intramolecular Photocycloaddition of Vinylogous Amides. A Synthesis of Mesembrine†,[1]

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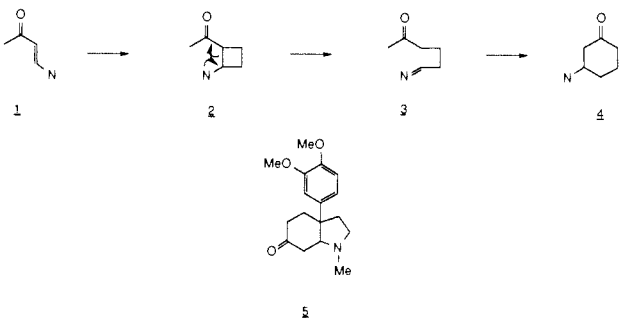
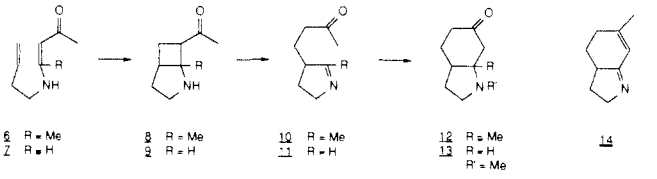
We report herein our preliminary results with the intramolecular photocycloaddition of vinylogous amides, which leads to a new and general method for the synthesis of nitrogen-containing ring systems. Several groups have reported on the intramolecular photocycloaddition of vinylogous amides and imides.[5-7] However, in none of the previously reported cases has the chemistry of the ketoimine **3**, which results from retro-Mannich fragmentation of the photoadduct **2**, been exploited (Scheme I). The intramolecular photocycloaddition of *suitably substituted* vinylogous amides begins a cascade of reactions that terminates in the formation of a new carbon–carbon bond via Mannich closure of the intermediate ketoimine, i.e., **3** → **4** (Scheme I). We report herein the application of this photoaddition–retro-Mannich–Mannich sequence to a synthesis of the alkaloid mesembrine, **5**.[8-10]

To establish the viability of the sequence outlined in Scheme I, the reaction of vinylogous amides **6** and **7** (Scheme II), resulting from the condensation of 3-butenylamine with acetyl acetone and sodio formyl acetone, respectively, was examined.[11] Irradiation of a 0.026 M solution of **6** in acetonitrile through Pyrex, using a medium-pressure mercury lamp, led to the formation not of **8** but instead to **10**,[12] the product of photoaddition and retro-Mannich fragmentation, consistent with results obtained by Schell

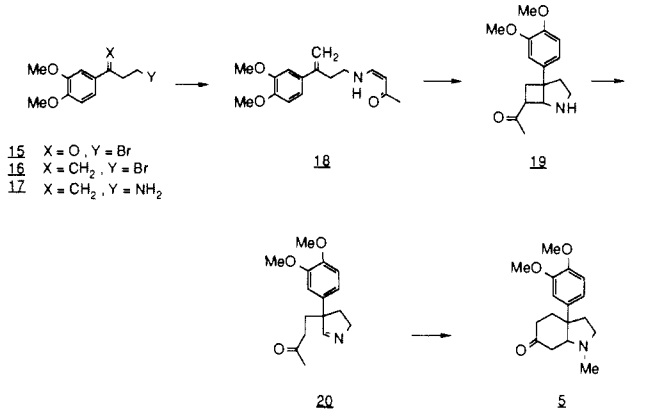
Scheme I



Scheme II



Scheme III



in a related system.[5] On treatment with base, or simply on standing at room temperature in chloroform solution, the ketoimine was converted to the unsaturated imine, **14**, via tautomerization of the imine to enamine, addition to the carbonyl group, and elimination of water. The conversion of **10** (or the corresponding iminium ketone, obtained on reaction of **10** with trimethyloxonium tetrafluoroborate in methylene chloride) to **12**, the desired Mannich product, could not be accomplished under either acidic or basic reaction conditions. However, irradiation of **7**, lacking the methyl group of **6** and therefore precluding the formation of products analogous to **14**, led to the formation of the ketoimine **11**. Reaction of **11** with 1 equiv of trimethyloxonium tetrafluoroborate in methylene chloride, followed by treatment of the derived iminium ketone with 15% aqueous hydrochloric acid, led to the formation of the photocycloaddition–retro-Mannich–Mannich product **13**, isolated as its DNP derivative in 50% overall yield.

The utility of ketoimines such as **3** in the synthesis of alkaloids has already been demonstrated,[8] and we describe herein the application of this methodology to an efficient synthesis of mesembrine, **5** (Scheme III). The requisite photosubstrate **18** was prepared as outlined below. Reaction of veratrole with 3-bromopropionyl chloride led to the formation of **15** in 82% yield, which on treatment with the Tebbe reagent[13] led to the formation of styryl bromide **16** in 93% yield. Treatment of **16** with ammonia led to the formation of amine **17** in 89% yield. Condensation with 4-chloro-3-buten-2-one[14] led to the formation of the photosubstrate **18** in 77% yield. Irradiation in the usual manner led, via **19**, to

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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(4) Fellow the the Medical Scientist Training Program, University of Chicago.

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the formation of the photocycloaddition–reto-Mannich product **20**, in 74% yield. Methylation with trimethyloxonium tetrafluoroborate followed by treatment with 4-dimethylaminopyridine in reluxing acetonitrile produced mesembrine, **5**, in 84%g yield, identical (^{1}H NMR, IR, MS) with an authentic sample.[15]

This efficient synthesis of the alkaloid mesembrine (seven steps, 33% overall yield) illustrates the utility of the vinylogous amide photocycloaddition–retro-Mannich–Mannich sequence. The application of this methodology to the construction of more complex alkaloids is currently in progress in our laboratory and will be reported in due course.

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Registry No. (±)-**5**, 6023-73-0; **6**, 114634-41-2; **7**, 114634-44-5; (±)-**10**, 114634-42-3; (±)-**11**, 114634-45-6; **13**, 67175-84-2; **13** (DNP derivative), 114634-46-7; (±)-**14**, 114634-43-4; **15**, 105174-63-8; **16**, 114634-47-8; **17**, 114634-48-9; **18**, 114634-49-0; (±)-**20**, 114634-50-3; $ClCO(CH_2)_2Br$, 15486-96-1; $ClCH{=}CHCOOCH_3$, 7119-27-9; veratrole, 91-16-7.

Supplementary Material Available: Spectral data for **15–20** (1 page). Ordering information is given on any current masthead page.

(15) We thank Professors Albert Meyers (Colorado State University) and Stephen Martin (University of Texas at Austin) for generously providing authentic samples of mesembrine.

On the Tautomerism of Dihydropyrimidines: The Influence of the 2- and 5-Substituents on the Observation of Tautomers[1]

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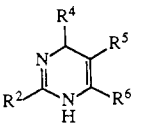
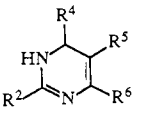
Tautomerism in the dihydropyrimidine system has not been sufficiently investigated to date. The location of the tautomeric double bond is not clearly indicated in most papers. Namely, the tautomeric compounds were drawn as either tautomer **a** or **b** or as an unspecified form without sufficient investigation.[3]

We recently carried out the X-ray crystallographic analysis of 4-(2-chlorophenyl)-5-(ethoxycarbonyl)-2,6-dimethyldihydropyrimidine and found it to exist as the 1,4-dihydro form **a** in the crystalline state.[4] Regarding the dihydro form in solution, Van der Plas et al.[5] and Girke[6] independently studied the behavior of a variety of dihydropyrimidines. They attempted to obtain the NMR spectra in deuteriochloroform ($CDCl_3$) of each of the tautomers (type a and type b), but even at temperature below 0 °C this was not possible. Weis carefully studied the tautomerism

Chart I



a



b

	R^2	R^4	R^5	R^6
1	CF_3	2-NO_2-C_6H_4	COOiPr	CH_3
2	SMe	2-NO_2-C_6H_4	COOiPr	CH_3
3	NMe_2	2-NO_2-C_6H_4	COOiPr	CH_3
4	H	2-NO_2-C_6H_4	COOiPr	CH_3
5	Me	2-NO_2-C_6H_4	COOiPr	CH_3
6	iPr	2-NO_2-C_6H_4	COOiPr	CH_3

of 4-methyl-2,6-diphenyldihydropyrimidine and observed two individual tautomers (type a and type b) at −50 °C in a dilute $CDCl_3$ solution (0.001–0.003 M).[7]

Recently, Kashima observed the tautomeric equilibrium between dihydropyrimidines in the 2-(dimethylamino)-4,6,6-trimethyldihydropyrimidine system. However, in the proton NMR experiment the location of the tautomeric double bonds could not be clearly determined.[8] We synthesized a variety of 2-substituted-5-(alkoxycarbonyl)-4-(2-nitrophenyl)-6-methyldihydropyrimidines but usually observed an averaged broad NMR (270 MHz) spectrum, as the rate of proton transfer from one nitrogen to the other was very fast in most solvents (especially in $CDCl_3$) at ambient temperature (25 °C). However, we succeeded in observing two individual tautomers with compounds **1** and **2** at ambient temperature even in a highly concentrated $CDCl_3$ solution as well as in C_6D_6 as shown below.

Because a substituent at position-2 should have an influence on the electron densities of the *N*-1, *C*-2, *N*-3 system, we expected that this substituent would affect the tautomeric equilibrium. Moreover, we supposed that the ester group at position-5 may have a role in affecting the tautomerism. Thus, compounds with six different substituents at position-2 (X = CF_3, SMe, NMe_2, H, Me, and *i*-Pr) were synthesized.[9] In the case of compounds **4**, **5**, and **6**, we could not observe tautomers by NMR (100–360 MHz, $CDCl_3$, 25 °C), but the averaged spectra were obtained instead. It is of interest that two distinct tautomers **a** and **b** were successfully observed at ambient temperature in $CDCl_3$ with compounds **1** and **2**. This finding means that the rate of proton exchange in the dihydropyrimidine system is sometimes very slow on the NMR time scale (100–270 MHz).

The equilibrium constants k can be calculated from the data obtained from the NMR measurement. Generally, if there are two tautomers A and B in solution as shown in Scheme I, the equilibrium constants k_A and T_{1A} can be calculated from the simultaneous eq 2. In a similar manner, k_B and T_{1B} can be obtained.[10]

Scheme I[a]

$$[A] \underset{k_B}{\overset{k_A}{\rightleftharpoons}} [B] \qquad k_A[A] = k_B[B] \tag{1}$$

$$M_A/M_{0A} = 1/(1 + k_A T_{1A}) \qquad 1/T_{1Aeff} = 1/T_{1A} + k_A \tag{2}$$

[a] [A], concentration of tautomer **a**; [B], concentration of tautomer **b**; M_A/M_{0A}, ratio of remaining magnetization under saturation transfer conditions; T_{1Aeff}, observable longitudinal relaxation time; T_{1A}, theoretical longitudinal relaxation time.

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