

vated CO represents but one kind of ligand for which fixation by transition metal hydride reagents merits interest. Work is in progress along these lines.

Acknowledgment. Support from the Research Corporation and Wesleyan University is gratefully acknowledged.

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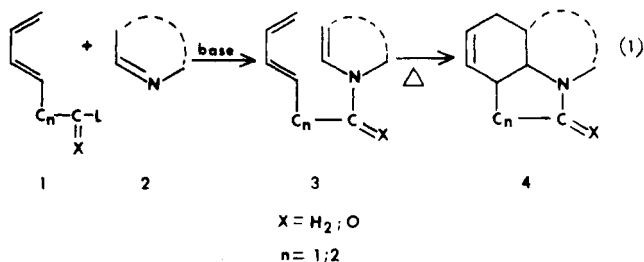
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General Methods for Alkaloid Synthesis via Intramolecular [4 + 2] Cycloaddition Reactions of Enamides. A New Approach to the Synthesis of *Aspidosperma* Alkaloids

Sir:

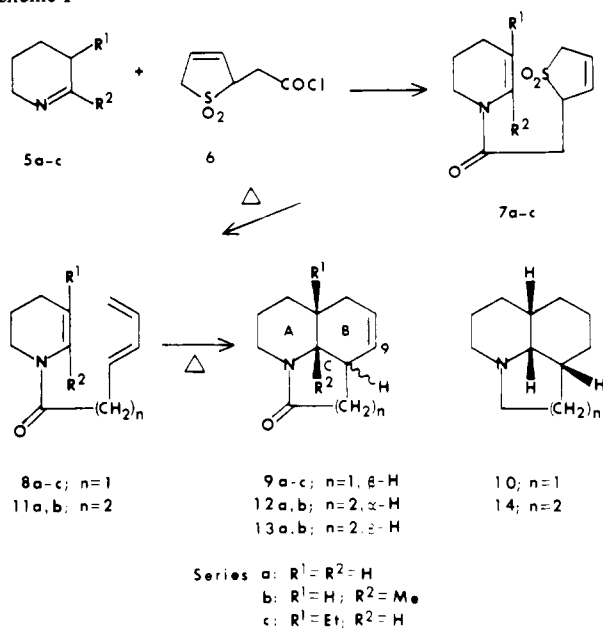
Since substituted hydroindole and hydroquinoline rings are structural elements common to a diverse array of alkaloid natural products, a general synthetic strategy which could be employed for the facile assemblage of functionalized representatives of these important heterocyclic synthons would be highly useful. One entry to these ring systems which seems particularly attractive is depicted in eq 1 and features the in-



tramolecular [4 + 2] cycloaddition reaction of an enamine or an enamide with a suitable diene partner. An important aspect of this novel approach to hydroindoles and hydroquinolines is the ease with which the requisite enamino dienes **3** (X = H₂) and enamido dienes **3** (X = O) may be constructed via a carbon-nitrogen bond forming process in which the imine **2** is coupled with a dienophilic alkylating or acylating agent **1**. While there exist numerous examples of bimolecular¹ and intramolecular^{2,3} Diels-Alder reactions of dienamides with various dienophiles as well as bimolecular [4 + 2] cycloadditions of enamines with electron-deficient dienes,⁴ there appears to be only a single report of the [4 + 2] cycloaddition reactions of enamines or enamides with *unactivated* dienes.^{5,6} We now report that endocyclic enamido dienes related to **3** (X = O; n = 1) and **3** (X = O; n = 2) undergo smooth, intramolecular [4 + 2] cycloadditions to give fused hydroindole and hydroquinoline derivatives, respectively.

To evaluate the feasibility of utilizing intramolecular [4 + 2] cycloaddition reactions for the efficient construction of the hydrolulolidine ring system that is characteristic of the *Aspidosperma* alkaloids and also the hydrojulolidine skeleton which is representative of the *Lycopodium* alkaloids,⁷ our attention was initially focused upon an investigation of the thermal chemistry of the enamido dienes **8a-c** and their homologues **11a,b**. Although the direct coupling of 3,4,5,6-tetrahydropyridine (**5a**)⁸ with 3,5-hexadienoyl chloride gave only exiguous yields of the enamido diene **8a**, the formation of the requisite carbon-nitrogen bond could be readily effected by employing the highly useful expedient of masking the diene moiety as a 2-substituted 2,5-dihydrothiophene 1,1-dioxide (Scheme I). Thus, reaction of **5a** with the acid chloride **6**⁵ (DMF, Et₃N, RT → 50 °C) afforded the latent enamido diene **7a**⁹ (76%) which, upon brief heating in refluxing xylene pro-

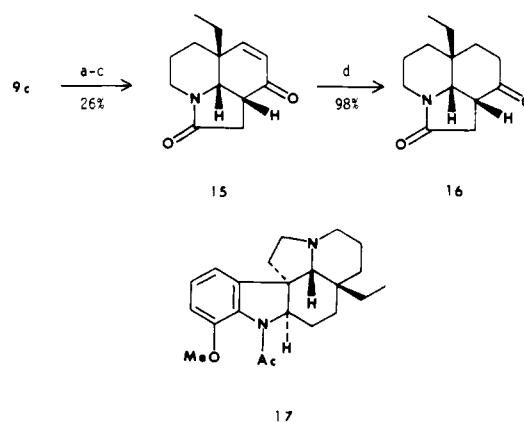
Scheme I



duced the target enamido diene **8a** in virtually quantitative yield. The subsequent thermolysis of **8a** either in a sealed tube (toluene, 260 °C, 20 h) or a vertical, packed column (1% solution in toluene, 600 °C, oven temperature) afforded the hydrojulolidine **9a**¹⁰ (45–55%). Since the isolation of the intermediate enamido diene **8a** appeared to represent an unnecessary inconvenience, a search for other reaction conditions that would allow the direct transformation of **7a** into **9a** was undertaken. As anticipated, the thermolysis of **7a** (sealed tube, toluene, 260 °C, 20 h) proceeded without event to provide **9a**. Somewhat surprisingly, however, the mere passage of a 1% solution of **7a** in toluene through a vertical tube (600 °C, oven temperature) resulted in the sequential cheletropic expulsion of sulfur dioxide followed by an intramolecular Diels–Alder reaction to give **9a** in 64% yield. That the cycloadduct obtained from this reaction was indeed **9a** was readily verified by its transformation into the known hydrojulolidine **10**^{11,12} by catalytic hydrogenation (H_2 , Pd/C, EtOH) and subsequent hydride reduction ($LiAlH_4$, Et_2O).

Since the thermolysis of **8a** appears to form **9a** as the sole cycloadduct, the endo transition state that leads to the production of the *cis*-hydroindole ring system is clearly lower in energy than the alternate exo transition state which would lead to the less stable *trans* B/C ring fusion. It presently seems likely, however, that the endo transition state for this process is preferred as a consequence of its inherently lower strain energy rather than the presence of more favorable, secondary orbital interactions. In partial support of this conjecture, it was shown that the thermolysis (vertical tube, 600 °C) of the homologous enamido diene **11a**, which was prepared in 88% yield by the acylation of **5a** with 4,6-heptadienoyl chloride,¹³ afforded an ~1:2 mixture of the *trans*- and *cis*-hydrojulolidine **12a** and **13a**¹⁴ (48%). This observation is fully in accord with the expectation that the exo transition state leading to the formation of a *trans* B/C ring fusion in a hydrojulolidine ring system should be less strained than the corresponding transition state which would afford a hydrojulolidine possessing a *trans* B/C ring juncture. The structure of the cycloadduct **13a** was unequivocally established by its conversion into the known hydrojulolidine **14** via catalytic hydrogenation (H_2 , Pd/C, EtOH) and subsequent hydride reduction ($LiAlH_4$, Et_2O).^{11,12}

Having confirmed the earlier prediction that endocyclic enamido dienes such as **8a** and **11a** would undergo intramo-

Scheme II^a

^a (a) SeO_2 , AcOH, 100 °C; (b) KOH, aqueous EtOH, RT; (c) H_2CrO_4 ·Pyr, SiO_2 , CH_2Cl_2 , RT; (d) H_2 , Pd/C, EtOH, RT.

lecular [4 + 2] cycloadditions to give fused hydroindoles and hydroquinolines, the thermolyses of the alkyl-substituted substrates **8b**, **8c**, and **11b** were then examined. Thus, reaction of 2-methyl-3,4,5,6-tetrahydropyridine (**5b**)¹⁵ with the acid chloride **6** as previously described produced the masked enamido diene **7b** (53%) which afforded the expected hydrojulolidine **9b**¹⁶ (67%) upon passage through a vertical hot tube (600 °C). Similarly, the cycloadduct **9c**¹⁷ was formed in 58% yield upon thermolysis at 600 °C (oven temperature) of the enamide **7c**, which was prepared by the acylation of 3-ethyl-3,4,5,6-tetrahydropyridine (**5c**)¹⁸ with the acid chloride **6** (57%). Finally, when a solution of **11b**, which was obtained by coupling **5b** with 4,6-heptadienoyl chloride¹³ (75%), in toluene was passed through a vertical hot tube (600 °C), a 43% yield of an ~1:1 mixture of the *trans*- and *cis*-hydrojulolidines **12b** and **13b**, respectively, was obtained.⁹

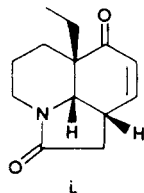
Although the potential of using the intramolecular [4 + 2] cycloaddition reactions of endocyclic enamido dienes for the construction of nitrogen-containing heterocycles has now been convincingly demonstrated, there remains the equally important task of applying this new technology to the total syntheses of alkaloid natural products. Within this context, the hydrojulolidine **16** which was the key intermediate in a synthesis of the *Aspidosperma* alkaloid aspidospermine (**17**)^{7c,19} appeared to be a suitably attractive target.²⁰ The transformation **9c** → **16** is a seemingly prosaic task, but considerable effort was expended prior to the discovery of a suitable method for the introduction of a carbonyl group at C(9) (Scheme II). One successful route to the keto lactam **16** commences with the allylic oxidation of the hydrojulolidine **9c** using freshly prepared selenium dioxide (2 equiv, HOAc, 100 °C, 12 h). Subsequent hydrolysis (KOH, aqueous EtOH, RT) of the intermediate allylic acetates thus obtained followed by oxidation of the resulting allylic alcohols with pyridinium chromate on silica gel²¹ afforded the enone lactam **15** in 26% overall yield.²² The reduction of **15** by catalytic hydrogenation (H_2 , Pd/C, EtOH) proceeded in virtually quantitative yield to give the keto lactam **16**, which was identical with an authentic sample,²³ thereby completing a new formal total synthesis of aspidospermine (**17**).

Inasmuch as the intramolecular [4 + 2] cycloaddition reactions of endocyclic enamido dienes has now been established as a viable strategy for alkaloid synthesis, the extension of this general concept to the syntheses of other alkaloids is under active investigation. Furthermore, the feasibility of employing heteroatom-substituted dienes and dienophiles in these novel reactions to facilitate the incorporation of additional functionality on the cycloadducts is being evaluated, since such a modification of the present methodology should result in highly convergent syntheses of alkaloid natural products.

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- (14) **12a**: NMR (CDCl₃) δ 5.57 (complex, 2 H), 4.32 (m, 1 H), 3.39 (dd, 1 H, J = 5.5, 9 Hz), 1.35–3.15 (complex, 13 H); IR 1620 cm⁻¹. **13a**: NMR (CDCl₃) δ 5.88 (ddd, 1 H, J = 2, 5, 10 Hz), 5.31 (br dd, 1 H, J = 2, 10 Hz), 4.79 (m, 1 H), 3.56 (br d, 1 H, J = 6 Hz), 1.25–2.95 (complex, 13 H); IR 1612 cm⁻¹.
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- (17) NMR (CDCl₃) δ 5.65 (ddt, 1 H, J = 2, 5, 10 Hz), 5.39 (dt, 1 H, J = 3, 10 Hz), 4.05 (m, 1 H), 3.19 (d, J = 7 Hz), 1.00–3.05 (complex, 12 H), 0.88 (t, 3 H, J = 7 Hz); IR 1689 cm⁻¹.
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- (22) An ~20% yield of an isomeric enone which appears to be **i** was also obtained.



- (23) We thank Professor G. Stork for a generous sample of **16**.

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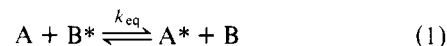
Direct Calculation of Equilibrium Constants for Isotopic Exchange Reactions by Ab Initio Molecular Orbital Theory

Sir:

Equilibrium constants for isotopic exchange reactions may be obtained either by direct measurement or indirectly by the methods of statistical mechanics, in the harmonic approximation, in terms of the normal mode vibrational frequencies of the molecules involved.¹ Because slight errors in observed frequencies lead to large variations in isotope effect, the usual practice has been to fit the experimental spectral data for isotopically substituted molecules to force fields, and from these to calculate the needed frequencies. In principle, frequencies obtained from force fields calculated a priori by molecular orbital theory may be substituted for the quantities derived from spectroscopic measurements. Until recently, however, theoretical force fields of sufficient accuracy were unavailable for any but the smallest molecular species.²

We communicate here preliminary results of our investigations into the performance of simple levels of molecular orbital theory with regard to the calculation of equilibrium constants of isotope exchange processes. Three levels of ab initio molecular orbital theory have been surveyed. The first two are single-determinant Hartree-Fock methods utilizing the 3-21G split-valence³ and 6-31G* polarization⁴ basis sets, respectively. The third and computationally the most complex method also utilizes the 6-31G* basis set⁴ but allows for partial account of electron correlation by way of Møller-Plesset perturbation theory terminated at second order.⁵ Equilibrium geometries have been obtained for all species at each of the three levels of calculation. These have already been reported elsewhere.^{3,5e} Fundamental vibrational frequencies have been evaluated according to Wilson's FG matrix procedure⁶ utilizing force constants obtained in massless symmetry coordinates by numerical second differentiation. Full details will be presented elsewhere.⁷

The equilibrium constant for an isotopic exchange equilibrium



may be written in terms of the ratio of the reduced isotopic partition function ratios for A and B

$$k_{eq} = (s_2/s_1)f[A^*/A]/(s_2/s_1)f[B^*/B]$$

where the $(s_2/s_1)f$'s are expressed in terms of the complete set of normal mode frequencies, ν_i :¹

$$(s_2/s_1)f[A^*/A] = \prod_i \frac{u_i(A^*)}{u_i(A)} \frac{1 - e^{-u_i(A)}}{1 - e^{-u_i(A^*)}} e^{[u_i(A) - u_i(A^*)]/2}$$

$$u_i = \frac{h\nu_i}{kT}$$

By convention A* refers to the heavy isotopically substituted molecule. The effect of symmetry numbers, which is of no particular interest, is omitted here from K_{eq} .¹

Reduced isotopic partition function ratios for hydrogen and for a number of one- and two-heavy-atom hydrides obtained from theoretical harmonic force constants are compared with the corresponding ratios derived from spectroscopic data in Table I. The latter quantities are obtained in one of two ways: (a) by fitting observed frequencies, corrected for anharmonicity, to harmonic force fields (designated "harmonic" in the tables) and (b) by fitting observed uncorrected frequencies to harmonic force fields (designated "anharmonic"). Details concerning the evaluation of these force fields and the calculation of frequencies will be discussed elsewhere.⁸

Table II compares theoretical and spectroscopic equilibrium constants for reactions