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## A Stereoselective Synthesis of Indole Alkaloid Intermediates via *N*-Acylium Cyclizations

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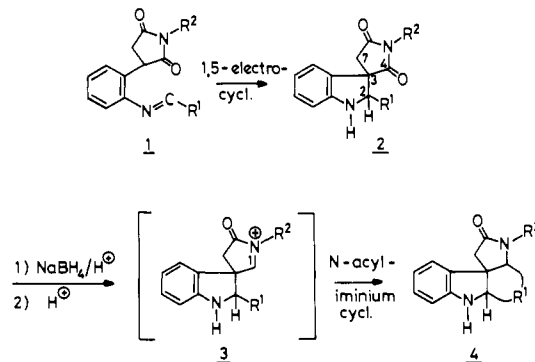
*N*-Acylium ions have been recognized as valuable intermediates in heterocyclic synthesis.<sup>1</sup> Distinct advantages compared to the iminium counterpart include a favorable reactivity,<sup>2</sup> thus allowing carbon-carbon bond formation at ambient temperature and a highly improved stereocontrol<sup>3</sup> in the latter process.

In the course of studies directed to a general and shortened synthesis of indole alkaloids of widely divergent nature, a novel and stereoselective 1,5-dipolar cyclization of imines **1** to dihydroindole 3,3-spiroimidides **2**<sup>4</sup> was discovered. The imides **2** potentially serve as starting materials for the required carbinol lactams which in turn are the direct precursors<sup>3</sup> for the *N*-acylium ions **3**. The latter cationic centers are expected to initiate C-C bond formation with a variety of nucleophilic centers R', thereby affording the annelated lactams **4** (Scheme I).

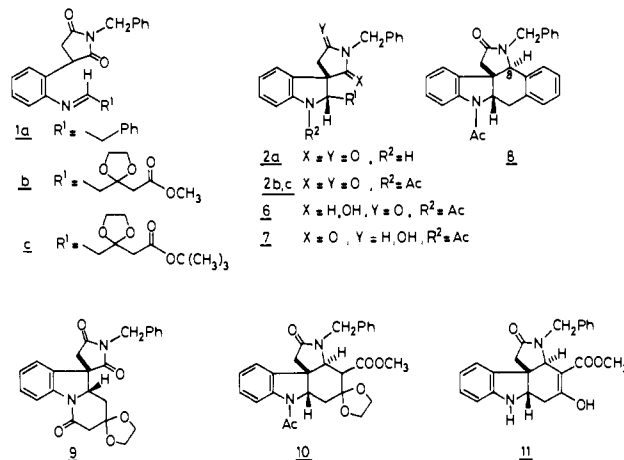
For an evaluation of the feasibility of utilizing a combined 1,5-electrocyclization (**1** → **2**) α-acylium ring closure (**3** → **4**) for the efficient construction of tetracyclic precursors of *Aspidosperma* alkaloids, the imine **1a** derived from phenylacetaldehyde and (*o*-aminophenyl)-*N*-benzylsuccinimide **5**<sup>5</sup> was spirocyclized to **2a**, mp 213.5–214.5 °C, upon treatment with a solution of *t*-BuONa/*t*-BuOH (yield 30%) (Scheme II).

Experimental verification of the *cis* relationship between C-2 benzyl and C-4 imide carbonyl group in **2a** is derived in the following manner. After acylation (Ac<sub>2</sub>O, room temperature) of **2a**, regioselective NaBH<sub>4</sub>/H<sup>+</sup> reduction<sup>6</sup> afforded in 98% yield an epimeric mixture of hydroxy lactams **6a** and **7a** (3:1), easily distinguished on the basis of their <sup>1</sup>H NMR spectra. After fractional crystallization from EtOAc/hexane, **6a**, mp 142–147 °C, was cyclized (HCOOH/room temperature/18 h) to the novel pentacyclic structure **8**, mp 199–202 °C (EtOAc-hexane), in essentially quantitative yield as a single stereoisomer. The latter fact coupled with a prediction made on the basis of model studies of the least hindered cyclization pathway led to the proposed C-8 stereochemistry. Having confirmed the potential applicability of the combined approach, our attention was next focused on the synthesis of the alkaloid intermediate **11** for which the ketal esters **2b** and **2c** proved to be suitable starting materials. Upon spirocyclization of the imine **1b**<sup>7</sup> (*t*-BuONa/*t*-BuOH, room temperature) followed by *N*-acylation (Ac<sub>2</sub>O, room temperature), the dihydroindole **2b**, mp 174–176 °C (EtOH), was obtained in 15%

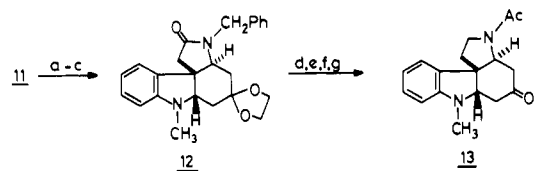
Scheme I



Scheme II



Scheme III<sup>a</sup>



<sup>a</sup> (a) aqueous HCl, (b) H<sup>+</sup>/HOCH<sub>2</sub>CH<sub>2</sub>OH, (c) CH<sub>3</sub>I/NaHCO<sub>3</sub>, (d) LAH, (e) H<sup>+</sup>/H<sub>2</sub>/Pd-C, (f) Ac<sub>2</sub>O, (g) H<sub>3</sub>O<sup>+</sup>.

yield. Due to intramolecular *N*-acylation during the spirocyclization, the lactam **9**, mp 179–180 °C (EtOAc), was isolated as an unwanted byproduct in 45% yield. A solution for preventing the latter problem was found in the use of the *t*-Bu ester and a slight change in the type of base. Thus the imine **1c**<sup>8</sup> underwent cyclization [*t*-BuOLi in *t*-BuOH/THF (1:2)] and *N*-acylation (Ac<sub>2</sub>O, room temperature) to **2c**, mp 150–152 °C (EtOH), in 84% yield.

After regioselective NaBH<sub>4</sub>/H<sup>+</sup> reduction<sup>6</sup> of **2b**, a 2:1 mixture of hydroxy lactams **6b** and **7b** was formed which was separated by silica gel chromatography. The final ring closure of **6b**, mp 145–150 °C (EtOAc-hexane), to **10** was effected in 52% yield (*p*-TsOH-C<sub>6</sub>H<sub>4</sub>-glycol, reflux, 18 h), mp 204–206 °C (EtOAc-hexane). Alternatively **6b** could be converted quantitatively to **11**, mp 170–200 dec, by brief acid treatment (HCl-CH<sub>3</sub>OH, reflux, 30 min). Similarly the hydroxy lactam **6c**, mp 214–219 °C, obtained by fractional crystallization (EtOAc) of the isomer mixture from the NaBH<sub>4</sub>/H<sup>+</sup> reduction of **2c** afforded the enol ester **11** in 70% yield. Its structure was secured by conversion<sup>10</sup>

(8) The aldehyde prepared by selective DIBAH reduction<sup>9</sup> of methyl *tert*-butyl acetonediacarboxylate ethylene ketal was coupled with **5** to afford **1c**.

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(7) The aldehyde prepared by DIBAH reduction<sup>9</sup> of dimethyl acetonediacarboxylate ethylene ketal was coupled with **5** to afford **1b**.

into the known ketone **13**<sup>11</sup> as indicated in Scheme III. Since the latter compound has been converted into Vindorosine,<sup>12</sup> the present synthesis constitutes a formal route to this compound. Most important, however, is the general character of the present approach which may serve to construct a variety of indole alkaloids. Of added practical interest is the fact that the novel intermediate **11** can be prepared in three simple steps on a large scale in an acceptable yield. Studies aimed at alternative applications of the 1,5-electrocyclization/ $\alpha$ -acyliminium route are in progress.

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(10) Selected <sup>1</sup>H NMR values include the following. **8**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  4.63 (1 H, s), 4.43 (1 H, t,  $J = 5$  Hz), 3.06 (2 H, d,  $J = 5$  Hz), 2.82 and 2.68 (2 H, AB,  $J = 17$  Hz), 2.33 (3 H, s). **9**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.25 (1 H, d,  $J = 8$  Hz), 4.65 (2 H, s), 4.37 (1 H, d of d,  $J = 3.5$  and 12.5 Hz), 3.22 and 2.82 (2 H, AB,  $J = 18.5$  Hz), 2.77 (3 H, s). **10**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60 °C)  $\delta$  7.87 (1 H, br d,  $J = 7$  Hz), 5.01 (1 H, d of d,  $J = 5$  and 11.5 Hz), 3.95 (4 H, m), 3.20 (3 H, s). **11**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  12.45 (1 H, br s), 4.72 (1 H, s), 4.19 (1 H, br), 3.84 (1 H, br, NH), 3.49 (3 H, s), 3.20 and 2.69 (2 H, AB,  $J = 19$  Hz). **12**: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.88 (4 H, s), 3.53 (1 H, d of d,  $J = 5$  and 6.5 Hz), 3.37 (1 H, t,  $J = 4.3$  Hz), 2.65 (5 H, s).

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### The Spiro[2.5]oct-4-yl Cation, a Long-Lived Secondary Cyclohexyl Cation<sup>1</sup>

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Tertiary cycloalkyl cations such as the 1-methyl-1-cyclopentyl cation show high stability in strong acid solutions and can be prepared from a variety of precursors.<sup>2,3</sup> While the secondary cyclopentyl cation was observed as a rapidly equilibrating degenerate ion,<sup>4</sup> no secondary cyclohexyl cation has yet been observed in superacid solution.<sup>4,5</sup> In continuation of our studies on cycloalkyl cations,<sup>6</sup> we wish now to report the preparation and <sup>13</sup>C NMR spectroscopic study of the spiro[2.5]oct-4-yl cation (**1**), a long-lived secondary cyclohexyl cation.

The <sup>13</sup>C NMR spectrum of the solution obtained upon ionization of spiro[2.5]octan-4-ol<sup>7</sup> (**2**) in SbF<sub>5</sub>/SO<sub>2</sub>ClF at -78 °C (Figure 1) consists of seven signals<sup>8</sup> at  $\delta$  201.1 (d,  $J_{C-H} = 170.5$  Hz), 95.0 (s), 51.5 (t,  $J_{C-H} = 178.1$  Hz), 34.9 (t), 29.3 (t), 21.0

(1) (a) Part 234. For part 233, see G. A. Olah, A. L. Berrier, and G. K. S. Prakash, *Proc. Natl. Acad. Sci. U.S.A.*, **78**, 1998-2002 (1981); (b) Department of Chemistry, University of Petroleum and Minerals, Dhahran, Saudi Arabia.

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(8) The <sup>13</sup>C NMR chemical shifts are referenced to external capillary tetramethylsilane. These chemical shifts did not show any temperature dependence between -78 and -130 °C, indicating lack of equilibrium of any sort. Also there was no appreciable line broadening in this temperature range.

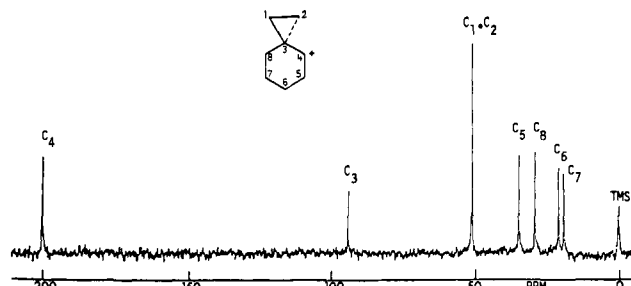
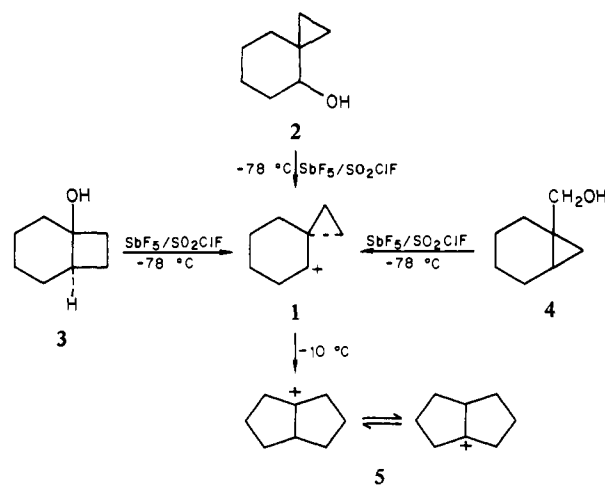


Figure 1. Proton-decoupled <sup>13</sup>C NMR spectrum of the spiro[2.5]oct-4-yl cation in SbF<sub>5</sub>/SO<sub>2</sub>ClF at -80 °C.

(t), and 19.2 (t) (multiplicities are based on the proton coupled spectrum). On the basis of the observed chemical shifts and multiplicities, the spectrum is readily assigned to the spiro[2.5]oct-4-yl cation (**1**). Interestingly the same ion was obtained upon ionization of *trans*-bicyclo[4.2.0]octan-1-ol<sup>9</sup> (**3**) and bicyclo[4.1.0]hept-1-ylcarbinol<sup>10</sup> (**4**) in SbF<sub>5</sub>/SO<sub>2</sub>ClF at -78 or -130 °C. These results are in agreement with the solvolytic studies



on spiro[2.5]oct-4-yl 3,5-dinitrobenzoate and *cis*- or *trans*-bicyclo[4.2.0]oct-1-yl 3,5-dinitrobenzoate in aqueous acetone<sup>9</sup> wherein ion **1** has been postulated as an intermediate. The intermediacy of the ion **1** has been assumed in the acetolysis of *cis*-bicyclo[4.2.0]oct-7-yl tosylate.<sup>11</sup>

In ion **1**, the positive charge is significantly delocalized into the adjacent spiro cyclopropane ring, and correspondingly, the C-3 spiro carbon and C-1 and C-2 methylene carbons are substantially deshielded (<sup>13</sup>C NMR  $\delta$  95.0 and 51.5, respectively). The equivalence of the methylene carbons (although expected in a spiro skeleton) is in accordance with a bisected geometry of the cyclopropane ring with the empty p orbital of the cationic center. The carbocationic center is also highly shielded (<sup>13</sup>C NMR  $\delta$  201.1) for a static secondary carbocation. These trends are, however, in agreement with previous observations on related secondary cyclopropyl carbinyl cations.<sup>6,12</sup> It is also of interest to compare the <sup>13</sup>C NMR chemical shifts of cation **1** with those of the phenonium ion **6**<sup>13</sup> as well as the benzonortricyclyl cation **7**.<sup>14</sup> In the latter two cations the positive charge is, however, delocalized into the 4- $\pi$  framework in addition to the spiro cyclopropane conjugation.

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