was carried out under the auspices of the Netherlands Foundation for Chemical Research (SON) and with financial support from the Netherlands Organization for Advancement of Pure Research (ZWO).

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

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Received February 19, 1981

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

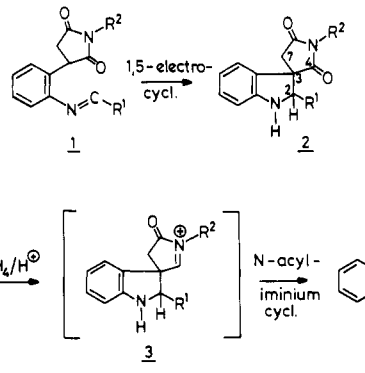
In the course of studies directed to a general and shortened synthesis of indole alkaloids of widely divergent nature, a novel and stereoselective 1,5-dipolar cyclization of imines **1** to dihydroindole 3,3-spiroimides **2**[4] was discovered. The imides **2** potentially serve as starting materials for the required carbinol lactams which in turn are the direct precursors[3] for the *N*-acyliminium 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-acyliminium 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**[5] was spirocyclized to **2a**, mp 213.5–214.5 °C, upon treatment with a solution of *t*-BuONa/*t*-BuOH (yield 30%) (Scheme II).

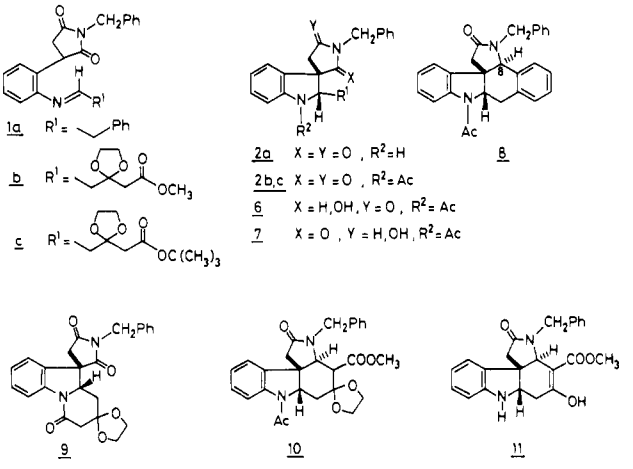
Experimental verification of the cis relationship between C-2 benzyl and C-4 imide carbonyl group in **2a** is derived in the following manner. After acylation (Ac_2O, room temperature) of **2a**, regioselective $NaBH_4/H^+$ reduction[6] afforded in 98% yield an epimeric mixture of hydroxy lactams **6a** and **7a** (3:1), easily distinguished on the basis of their ^1H 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**[7] (*t*-BuONa/*t*-BuOH, room temperature) followed by N-acylation (Ac_2O, room temperature), the dihydroindole **2b**, mp 174–176 °C (EtOH), was obtained in 15% 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**[8] underwent cyclization [*t*-BuOLi in *t*-BuOH/THF (1:2)] and N-acylation (Ac_2O, room temperature) to **2c**, mp 150–152 °C (EtOH), in 84% yield.

After regioselective $NaBH_4/H^+$ reduction[6] 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_6H_6–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_3OH, reflux, 30 min). Similarly the hydroxy lactam **6c**, mp 214–219 °C, obtained by fractional crystallization (EtOAc) of the isomer mixture from the $NaBH_4/H^+$ reduction of **2c** afforded the enol ester **11** in 70% yield. Its structure was secured by conversion[10]

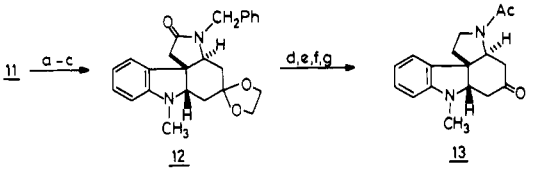
Scheme I



Scheme II



Scheme III[a]



[a] (a) aqueous HCl, (b) $H^+/HOCH_2CH_2OH$, (c) $CH_3I/NaHCO_3$, (d) LAH, (e) $H^+/H_2/Pd$–C, (f) Ac_2O, (g) H_3O^+.

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(7) The aldehyde prepared by DIBAH reduction[9] of dimethyl acetonedicarboxylate ethylene ketal was coupled with **5** to afford **1b**.

(8) The aldehyde prepared by selective DIBAH reduction[9] of methyl *tert*-butyl acetonedicarboxylate ethylene ketal was coupled with **5** to afford **1c**.

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into the known ketone **13**[11] as indicated in Scheme III. Since the latter compound has been converted into Vindorosine,[12] 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/α-acyliminium route are in progress.

Acknowledgment. We express our appreciation to Professor S. Takano for sending us an authentic sample of **17**. The present investigation was carried out under the auspices of the Netherlands Foundation for Chemical Research (SON) and with financial support from the Netherlands Organization for Advancement of Pure Research (ZWO).

(10) Selected ^{1}H NMR values include the following. **8**: ^{1}H NMR ($CDCl_3$) δ 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**: ^{1}H NMR ($CDCl_3$) δ 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**: ^{1}H NMR ($CDCl_3$, 60 °C) δ 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**: ^{1}H NMR ($CDCl_3$) δ 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**: ^{1}H NMR ($CDCl_3$) δ 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[1]

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Received February 5, 1981

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.[2,3] While the secondary cyclopentyl cation was observed as a rapidly equilibrating degenerate ion,[4] no secondary cyclohexyl cation has yet been observed in superacid solution.[4,5] In continuation of our studies on cycloalkyl cations,[6] we wish now to report the preparation and ^{13}C NMR spectroscopic study of the spiro[2.5]oct-4-yl cation (**1**), a long-lived secondary cyclohexyl cation.

The ^{13}C NMR spectrum of the solution obtained upon ionization of spiro[2.5]octan-4-ol[7] (**2**) in SbF_5/SO_2ClF at −78 °C (Figure 1) consists of seven signals[8] at δ 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 (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[9] (**3**) and bicyclo[4.1.0]hept-1-ylcarbinol[10] (**4**) in SbF_5/SO_2ClF 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[9] 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.[11]

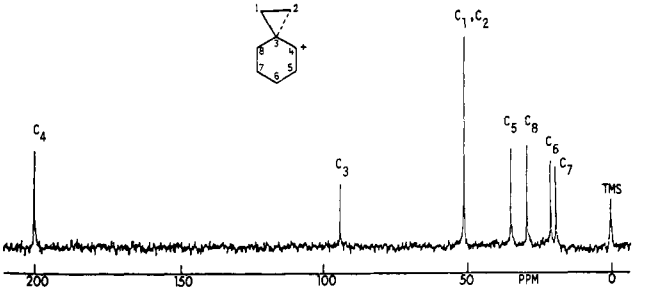
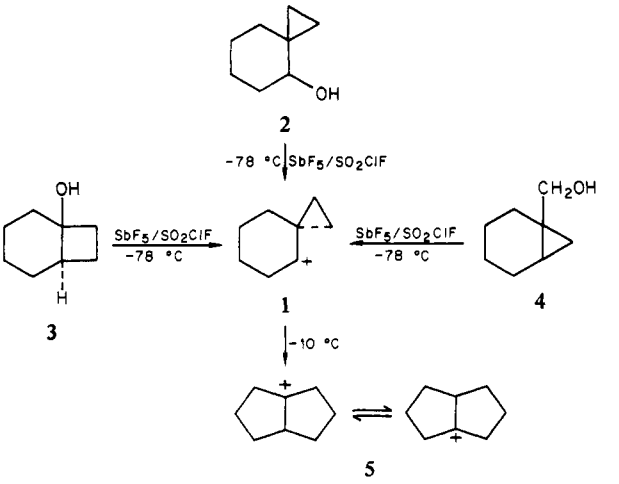


Figure 1. Proton-decoupled ^{13}C NMR spectrum of the spiro[2.5]oct-4-yl cation in SbF_5/SO_2ClF at −80 °C.



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 (^{13}C NMR δ 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 (^{13}C NMR δ 201.1) for a static secondary carbocation. These trends are, however, in agreement with previous observations on related secondary cyclopropyl carbinyl cations.[6,12] It is also of interest to compare the ^{13}C NMR chemical shifts of cation **1** with those of the phenonium ion **6**[13] as well as the benzonortricyclyl cation **7**.[14] In the latter two cations the positive charge is, however, delocalized into the 4-π framework in addition to the spiro cyclopropane conjugation.

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