H [OH]), 2.47 (dd, J = 16.4, 6.2 Hz, 1 H), 2.26 (br d, J = 16.4 Hz, 1 H), 2.12 (br d, J = 16.5 Hz, 1 H), 1.97 (pseudoquintet, J = 6 Hz, 1 H), 1.38 (complex multiplet, 4 H), 0.81 (t, J = 7.0 Hz, 3 H), and 0.79 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (50.3 MHz) δ 144.7, 121.8, 71.9, 44.7, 42.0, 41.2, 25.83, 25.78, 11.89, 11.84; IR (thin film) 3348, 3060, 1640 cm^{-1}; high-resolution mass spectrum calculated for $C_{10}H_{18}O$ 154.135 76, found (EI) 154.136 39. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.04; H, 12.02.

3-Cyclohexylcyclopent-3-en-1-ol (3e): bp 68–76 °C (0.1 mmHg); ^{1}H NMR (250 MHz) δ 5.23 (br s, 1 H), 4.40 (m, 1 H), 2.7–2.5 (m, 2 H), 2.3–2.15 (m, 2 H), 1.96 (m, 1 H), 1.85–1.6 (m, 5 H), 1.51 (br s, 1 H [OH]), 1.3–1.1 (m, 5 H); ^{13}C NMR (62.9 MHz) δ 147.7, 118.3, 72.0, 43.4, 42.6, 39.7, 31.9, 31.8, 26.4; IR (thin film) 3359, 3062, 1651 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.19; H, 10.60.

3-(3-Methylpent-3-yl)cyclopent-3-en-1-ol (3f): bp 57–64 °C (0.1 mmHg); ^{1}H NMR (200 MHz) δ 5.27 (br t, 1 H), 4.46 (m, 1 H), 2.67 (br dd, J = 17, 6 Hz, 1 H), 2.55 (br dd, J = 17, 6 Hz, 1 H), 2.30 (br d, J = 16.6 Hz, 1 H), 2.16 (br d, J = 16.6 Hz, 1 H), 2.1 (br s, 1 H [OH]), 1.37 and 1.33 (overlapping quartets, J = 7.5 and 7.5 Hz, total 4 H), 0.77 (t, J = 7.5 Hz, 3 H), and 0.73 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (50.3 MHz) δ 148.0, 121.2, 72.2, 42.3, 41.5, 39.4, 31.9, 21.7, 8.5; IR (thin film) 3353, 3061, 1634 cm^{-1}; high-resolution mass spectrum calculated for $C_{11}H_{20}O$ 168.151 41, found (EI) 168.150 56. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.32; H, 12.12.

3-Carbethoxycyclopent-3-en-1-one (4b): oil; ^{1}H NMR (250 MHz) δ 5.91 (br s, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 3.22 (s, 2 H), 2.88 (br s, 4 H), 1.30 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (62.9 MHz) δ 215.6, 170.2, 134.6, 125.4, 60.7, 45.1, 43.6, 37.6, 14.0; IR (thin film) 3060, 1740 (br), 1652 cm^{-1}.

3-(Methoxymethyl)cyclopent-3-en-1-one (4c). This compound was not characterized and was converted directly to compound **5c**.

3-(3-Pentyl)cyclopent-3-en-1-one (4d): oil; ^{1}H NMR (200 MHz) δ 5.70 (m, 1 H), 2.91 (br s, 2 H), 2.73 (br s, 2 H), 2.02 (br quintet, J = 6.5 Hz, 1 H), 1.5 (complex multiplet), 4 H), 0.83 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (50.3 MHz) δ 217.3, 144.9, 122.0, 46.0, 43.3, 42.0, 25.6, 11.9; IR (thin film) 3062, 1744, 1632 cm^{-1}.

3-Cyclohexylcyclopent-3-en-1-one (4e): oil; ^{1}H NMR (200 MHz) δ 5.60 (m, 1 H), 2.81 (br s, 2 H), 2.76 (br s, 2 H), 2.02 (br t, 1 H), 1.7 (m, 5 H), 1.2 (m, 5 H); ^{13}C NMR (50.3 MHz) δ 217.5, 147.4, 118.6, 43.7, 43.5, 40.3, 31.3, 26.22, 26.18; IR (thin film) 3060, 1740, 1628 cm^{-1}.

3-(3-Methylpent-3-yl)cyclopent-3-en-1-one (4f): oil; ^{1}H NMR (200 MHz) δ 5.70 (m, 1 H), 2.85 (br s, 2 H), 2.70 (br s, 2 H), 1.29 (overlapping q, J = 7 Hz, total 4 H), 0.67 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (50.3 MHz) δ 217.7, 147.9, 121.2, 43.7, 42.2, 40.1, 31.6, 21.0, 8.5; IR (thin film) 3064, 1748, 1626 cm^{-1}.

3-(Carbethoxymethyl)cyclopent-2-en-1-one (5b) (bp 78–82 °C, 0.025 mmHg): ^{1}H NMR (200 MHz) δ 6.02 (br s, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.38 (s, 2 H), 2.64–2.60 (AA′ multiplet, 2 H), 2.38–2.34 (BB′ multiplet, 2 H), 1.20 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (50.3 MHz) δ 209.0, 172.5, 168.5, 132.2, 61.1, 38.6, 35.2, 31.4, 13.9 ppm; IR (neat) 3070, 1735, 1700, 1617 cm^{-1}; MS (EI) m/z 168 (M$^+$). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.20. Found: C, 64.29; H, 7.18.

3-(Methoxymethyl)cyclopent-2-en-1-one (5c) (bp 41–44 °C, 0.1 mmHg): ^{1}H NMR (200 MHz) δ 6.03 (br m, 1 H), 4.2 (br s, 2 H), 3.3 (s, 3 H), 2.54–2.49 (AA′ multiplet, 2 H), 2.36–2.30 (BB′ multiplet, 2 H); ^{13}C NMR (50.3 MHz) δ 209.1, 177.9, 128.9, 71.9, 58.9, 34.7, 28.2; IR (neat) 3053, 1690, 1622 cm^{-1}; MS (EI) m/z 126 (M$^+$). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.47; H, 8.19.

3-(3-Pentyl)cyclopent-2-en-1-one (5d) (bp 48–52 °C, 0.1 mmHg): ^{1}H NMR (200 MHz) δ 5.88 (br m, 1 H), 2.47 (AA′ m, 2 H), 2.35 (BB′ m, 2 H), 2.26 (pseudo quintet, J = 6.9 Hz, 1 H), 1.50 (pseudo octet, J = 7.0 Hz, 4 H), 0.78 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (50.3 MHz) δ 210.2, 186.2, 130.6, 46.8, 35.1, 28.8, 26.0, 11.8; IR (neat) 3065, 1703, 1600 cm^{-1}; MS (EI) m/z 152 (M$^+$). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.83; H, 10.71.

3-Cyclohexylcyclopent-2-en-1-one (5e) (bp 69–72 °C, 0.1 mmHg): ^{1}H NMR (200 MHz) δ 5.85 (m, 1 H), 2.53 (AA′ m, 2 H), 2.32 (BB′ m, 2 H), 2.22 (m, 1 H), 1.9–1.5 (m, 5 H), 1.3–0.9 (m, 5 H); ^{13}C NMR (50.3 MHz) δ 210.4, 187.6, 128.0, 42.0, 35.1, 31.3, 29.6, 26.06, 26.00; IR (neat) 3060, 1697, 1598 cm^{-1}; MS (EI) m/z 164 (M$^+$). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.26; H, 9.83.

3-(3-Methylpent-3-yl)cyclopent-2-en-1-one (5f) (bp 52–56 °C, 0.1 mmHg); ^{1}H NMR (200 MHz) δ 5.86 (t, J = 1.7 Hz, 1 H), 2.46 (AA′ m, 2 H), 2.32 (BB′ m, 2 H), 1.48 and 1.45 (overlapping q, J = 7.0 Hz, total 4 H), 1.02 (s, 3 H), 0.70 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (50.3 MHz) δ 210.2, 188.9, 130.4, 42.2, 35.2, 32.0, 27.7, 21.6, 8.4; IR (neat) 3077, 1705, 1597 cm^{-1}; MS (EI) m/z 166 (M$^+$). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.25; H, 10.58.

Acknowledgment. We would like to thank the Natural Sciences and Engineering Research Council for financial support of this work.

Registry No. **1a** (regioisomer 1), 69248-36-8; **1a** (regioisomer 2), 69248-37-9; **1b** (regioisomer 1), 32379-35-4; **1b** (regioisomer 2), 66612-56-4; **1c** (regioisomer 1), 2619-28-5; **1c** (regioisomer 2), 2619-29-6; **1d** (regioisomer 1), 58569-53-2; **1d** (regioisomer 2), 126457-97-4; **1e** (regioisomer 1), 126457-78-1; **1e** (regioisomer 2), 126457-98-5; **1f** (regioisomer 1), 126457-79-2; **1f** (regioisomer 2), 108776-45-0; **2a**, 7301-16-8; **2b**, 3141-04-6; **3a**, 126457-80-5; **3b**, 126457-81-6; **3c**, 126457-82-7; **3d**, 126457-83-8; **3e**, 126457-84-9; **3f**, 126457-85-0; **4a**, 126457-91-8; **4b**, 126457-96-3; **4c**, 126457-92-9; **4d**, 126457-93-0; **4e**, 126457-94-1; **4f**, 126457-95-2; **5a**, 67100-39-4; **5b**, 126457-86-1; **5c**, 126457-87-2; **5d**, 126457-88-3; **5e**, 126457-89-4; **5f**, 126457-90-7; EtC(O)Et, 96-22-0; cyclopentadiene, 542-92-7.

Free-Radical Reactions of Retronecine and Heliotridine Derivatives. The Synthesis of (-)-Supinidine[1]

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The pyrrolizidine alkaloids, ubiquitous throughout the plant world, are endowed with a vast array of biological activities. Many of the $\Delta^{1,2}$-unsaturated 1-methylpyrrolizidines functionalized by hydroxyl or ester moieties have been associated with hepatotoxic, mutagenic, antimitotic, or carcinogenic properties.[2] Because of their cytotoxic and antimitotic activity, pyrrolizidine alkaloids attracted interest as potential antitumor agents many years ago.[3,4] One of the alkaloids, indicine *N*-oxide, progressed to clinical studies as an anticancer drug, but the mechanism of its activity is still unclear.[5-8] Relationships be-

(1) Previously communicated: Gruszecka-Kowalik, E.; Zalkow, L. H. 40th American Chemical Society Southeast Regional Meeting; Atlanta, GA, November 9–11, 1988.

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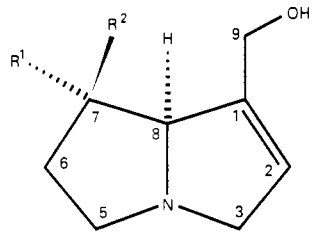
tween the pharmacological activity of pyrrolizidine alkaloids and their structural and chemical features are not yet fully understood. In order to better understand structure–activity relationships necessary for antitumor activity, new pyrrolizidine alkaloid analogues, modeled after indicine *N*-oxide, have been prepared by semisynthetic methods and several have shown excellent results in screening in the in vivo tumor panel at NCI.[9-11] As part of our continuing structure–activity studies of semisynthetic pyrrolizidine alkaloid *N*-oxides, we decided to examine the derivatives of the monohydroxylated, unsaturated necine base, (−)-supinidine (1).

Much effort has been expended on developing syntheses of the necine bases, including the synthesis of racemic supinidine,[12] but relatively little has been reported on approaches to the synthesis of the natural (−)-supinidine.[13] Thus (−)-supinidine was not available in useful quantities either from reported synthetic procedures or by isolation and hydrolysis of readily available natural alkaloids containing (−)-supinidine as the necine. The selective deoxygenation of more readily available dihydroxylated, unsaturated necines such as retronecine (2) or heliotridine (3) appeared to offer a solution to our problem. As previously reported, retronecine was easily obtained, in large quantities, by the hydrolysis of the pyrrolizidine alkaloid, monocrotaline, readily available from the seeds of *Crotalaria spectabilis*.[9] A similar natural source of heliotridine could not be found, but an efficient synthesis of heliotridine from retronecine was accomplished by nucleophilic displacement of the 7-mesylate, in the 7-mesyl-9-benzoate of retronecine with cesium propionate followed by hydrolysis.[14]

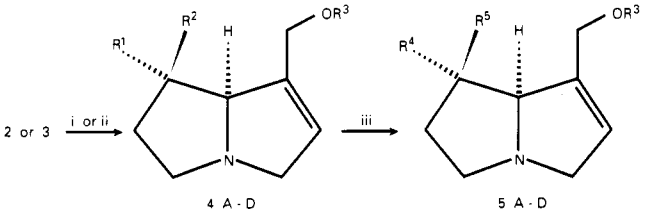


1, $R^1 = R^2 = H$ (-)-Supinidine

2, $R^1 = H$, $R^2 = OH$ (+)-Retronecine

3, $R^1 = OH$, $R^2 = H$ (+)-Heliotridine

Scheme I



4A, $R^1 = H$, $R^2 = OH$, $R^3 = SiMe_2t\text{-}Bu$ 88%

4B, $R^1 = OH$, $R^2 = H$, $R^3 = SiMe_2t\text{-}Bu$ 87%

4C, $R^1 = H$, $R^2 = OH$, $R^3 = C(O)Ph$ 94%

4D, $R^1 = OH$, $R^2 = H$, $R^3 = C(O)Ph$ 46%

i: 1) NaH, THF; 2) $t\text{-}BuMe_2SiCl$, THF

ii: $PhCO_2H$, CDI, THF

iii: PhOCSCl, 4-DMAP, CH_3CN

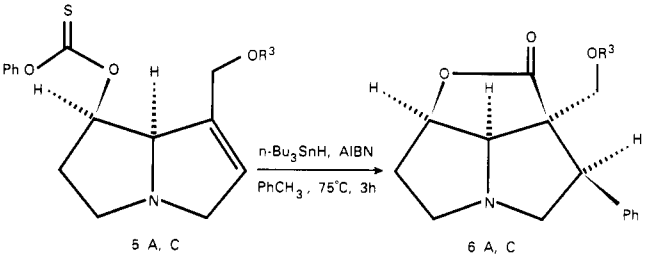
5A, $R^4 = H$, $R^5 = OC(S)OPh$, $R^3 = SiMe_2t\text{-}Bu$ 50%

5B, $R^4 = OC(S)OPh$, $R^5 = H$, $R^3 = SiMe_2t\text{-}Bu$ 58%

5C, $R^4 = H$, $R^5 = OC(S)OPh$, $R^3 = C(O)Ph$ 58%

5D, $R^4 = OC(S)OPh$, $R^5 = H$, $R^3 = C(O)Ph$ 62%

Scheme II



6A, $R^3 = SiMe_2t\text{-}Bu$ 48%

6C, $R^3 = COPh$ 60%

Conventional methods for the replacement of OH groups by H have involved the reduction of suitable alcohol derivatives such as tosylates, mesylates, sulfates, etc., or the nucleophilic displacement of the hydroxy group by halogen or thiolate with subsequent reductive dehalogenation or desulfurization. In 1962, Culvenor and Smith[15] reported the conversion of the C-9 methyl ether of retronecine into the methyl ether of supinidine by prior treatment with thionyl chloride followed by reduction with cuprous chloride. Others in our laboratory have found this procedure, even after extensive experimentation, not a useful and practical method for obtaining (−)-supinidine.[16]

The deoxygenation of secondary alcohols by tin hydride reduction of appropriate thiocarbonyl derivatives is a preparatively useful reaction.[17,18] For the purpose of preventing possible formation of byproducts during reduction, thiono ester intermediates[19,20] prepared from phenoxythiocarbonyl chloride have been used. Our synthetic strategy was based on preparation of C-9 site specifically protected, C-7 *O*-(phenoxythiocarbonyl) unsaturated necines followed by treatment with tri-*n*-butyltin hydride, and finally deprotection to yield the desired (−)-supinidine.

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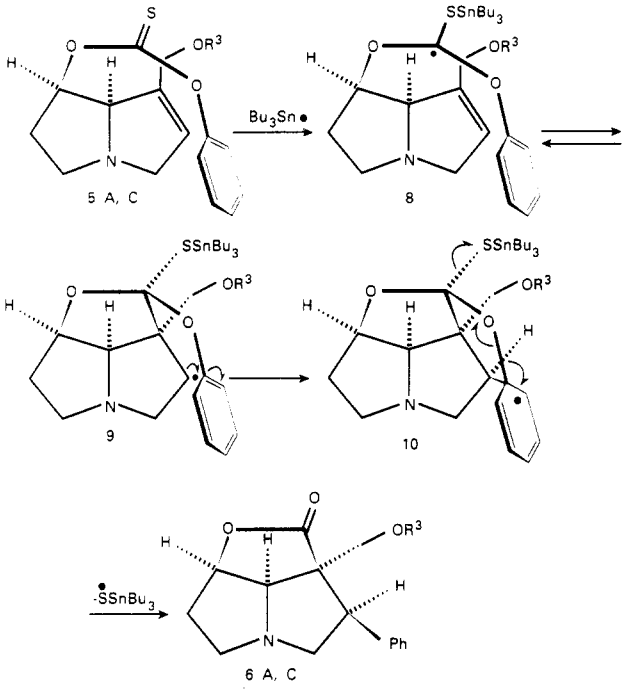
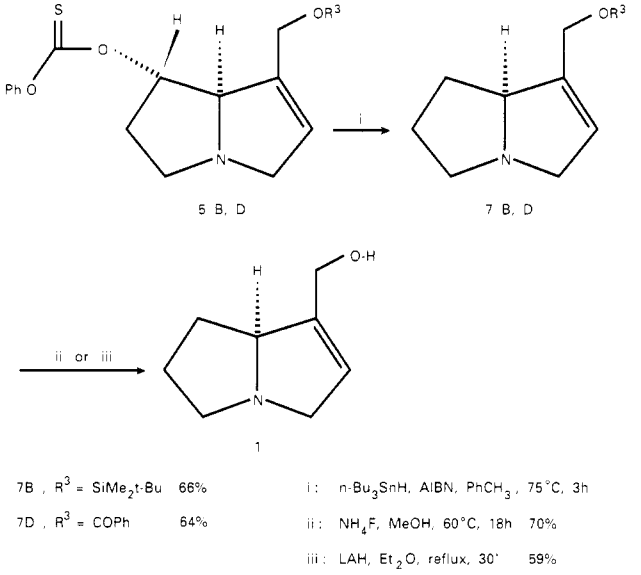
Scheme III



Scheme IV



Thus, optically pure (+)-retronecine and (+)-heliotridine[21] were selectively protected at their primary hydroxy groups (C-9), as *tert*-butyldimethylsilyl ethers or benzoate esters (Scheme I, **4A–D**). Monosilylation of the monosodium salts of retronecine or heliotridine was site specific, in each case, resulting in high yields of the C-9 derivatives. While coupling of benzoic acid with retronecine using 1,1′-carbonyldiimidazole[10] was found to be highly site specific for the C-9 position, heliotridine under the same conditions gave a mixture of the C-7 and C-9 monoesters and the C-7, C-9 diester in a ratio 1:8:9, respectively. Use of lower temperatures and inverse addition resulted in a mixture of the C-7 and C-9 monoesters and the C-7, C-9 diester in a ratio of 1:8:3, respectively. These latter results are consistent with those reported earlier,[11] which illustrate the less hindered environment of the C-7 hydroxy group in heliotridine as compared to retronecine. In the preparation of the silyl ethers, the greater site specificity is probably due to a combination of factors such as acidity of the C-9 OH group, size and selectivity of the reagent, etc.

Treatment of 9-O-protected retronecine (**4A** and **4C**) or heliotridine (**4B** and **4D**) with excess phenoxythiocarbonyl chloride in the presence of 4-(dimethylamino)pyridine (DMAP) as a catalyst gave the corresponding phenyl thionocarbonates **5A–D**, isolated in good yields as illustrated in Scheme I, after column chromatography or preparative TLC. The thionocarbonates prepared from retronecine (**5A** and **5C**) were then heated with tri-*n*-butyltin hydride in toluene at 75 °C for 3 h, in the presence of AIBN (Scheme II). Spectral analysis of the products (**6A** and **6C**), obtained after chromatography on silica gel, indicated the absence of the C=C bond and the presence of a phenyl group and a carbonyl group absorbing at high frequency characteristic of a γ-lactone. Using ^1H–^1H (COSY) and ^1H–^{13}C (HETCOR) correlated 2D NMR, structures **6A** and **6C** were indicated for these products. The structures were confirmed by a single-crystal X-ray analysis of **6A**.[22]

Formation of the tricyclic products **6A** and **6C** could conceivably arise by a mechanism similar to that outlined in Scheme III. An analogous mechanism, describing work apparently done after ours, was recently suggested for the formation of an α-diphenylmethyl γ-lactone from 4-phenylbut-3-enyl phenyl thionocarbonate upon treatment with tri-*n*-butyltin hydride.[23] X-ray analyses of rectronecine and heliotridine,[24] and of many pyrrolizidine alkaloids containing these necines, clearly demonstrate that the five-membered rings of the necines are inclined together (envelope conformations) at angles of 115–130°.[24] This places the β-oriented substituents attached to the C-7 OH group in retronecine derivatives directly over the inside face (endo) of the C-1, C-2 double bond. By contrast, the α-oriented substituents attached to the C-7 OH group in heliotridine derivatives are located on the outside face (exo) pointing away from the C-1, C-2 double bond. Thus, intermediate radicals such as **8**, obtained when the phenyl thionocarbonates **5A** and **5C**, derived from retronecine, react with tri-*n*-butyltin hydride, are ideally positioned to attack the carbon–carbon double bond at C-1, and the resulting stereochemistry at C-1 in **6A** and **6C** is, therefore, controlled by the stereochemistry at C-7 in the precurosrs **5A** and **5C**, respectively. The regiospecificity observed (attack at C-1) is an example of a 5-*exo-trig* [*endo*-5] radical cyclization process for which there is precedent.[25] Intramolecular addition of **9** onto the phenolic ring gives the spirohydroaromatic system **10**. Finally, rearomatization with concomitant elimination of $Bu_3SnS^•$ leads to γ-lactones **6A** and **6C**. The resulting stereochemistry at C-2 in **6A** and **6C** is, of course, determined by the stereochemistry at C-1 since only supraficial transfer of the phenyl ring is sterically possible from intermediate **9**.

(21) (+)-Retronecine was prepared by hydrolysis of monocrotaline and showed $[\alpha]^{27}_D$ = +55.2° (*c* 1.62, EtOH) [lit.[24] $[\alpha]^{25}_D$ = +55.0° (*c* 1.0, EtOH)]. (+)-Heliotridine was prepared from (+)-retronecine as described in the literature[14] and showed $[\alpha]^{27}_D$ = +31.3° (*c* 1.25, EtOH) [lit.[25] $[\alpha]^{25}_D$ = +31.0° (*c* 1.0, EtOH)].

(22) We thank Dr. Donald VanDerveer for determining the crystal structure of **6A**. The paper concerning the X-ray structure of **6A** is in preparation.

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Analysis of the products derived from similar radical-initiated homolytic deoxygenation of *O*-(phenoxythiocarbonyl) derivatives of heliotridine (Scheme IV, **5B** and **5D**) suggested structures of supinidine derivatives **7B** and **7D**. Thus, the ^{1}H NMR spectra showed the disappearance of aromatic peaks characteristic of the thiono substituent and the absence of signals for the C-7 proton in heliotridine derivatives. The appearance of characteristic sets of triple signals in the range of 1.51–2.02 ppm corresponding to the C-6 and C-7 protons in supinidine derivatives was evident. In the thionocarbonates from heliotridine, the carbon–carbon double bond is not accessible to attack by the intermediate radicals, and the reaction takes the usual course.

Deprotection of 9-*O*-(*tert*-butyldimethylsilyl)supinidine (**7B**) was effected by using ammonium fluoride, while the ester moiety in 9-*O*-benzoylsupinidine (**7D**) was reductively removed with lithium aluminum hydride. Chromatographically homogeneous supinidine (**1**), identical in all respects with previously reported material, was obtained by purification on preparative plates of silica gel.

In conclusion, a practical four-step conversion of heliotridine to supinidine has been developed, which involves the selective protection of heliotridine as its 9-*O*-(*tert*-butyldimethylsilyl) or 9-*O*-(benzoyl) derivative followed by phenoxythiocarbonylation of its hydroxy group at C-7 and finally AIBN-initiated homolytic deoxygenation with tri-*n*-butyltin hydride, and deprotection of the 9-*O*-(*tert*-butyldimethylsilyl) or 9-*O*-(benzoyl) products with ammonium fluoride or lithium aluminum hydride, respectively. The method offers optically pure material, of known absolute configuration, from optically pure starting material. Syntheses, in optically active form, of natural or unnatural pyrrolizidine alkaloids containing the necine (−)-supinidine are presently underway in our laboratory. By contrast, 7-*O*-(phenoxythiocarbonyl)-9-*O*-protected-retronecine derivatives, under similar conditions, yield tricyclic actones (**6A** and **6C**).

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Bruker WM-300 spectrometer equipped with an Aspect 2000 data system. Chemical shifts are reported relative to internal Me_4Si (δ 0.00) or $CDCl_3$ (δ 7.24). The ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer. The two-dimensional correlated nuclear magnetic resonance spectra, ^{1}H–^{1}H homonuclear shift correlated NMR (COSY) and ^{1}H–^{13}C heteronuclear shift correlated NMR (HETCOR) were recorded on the Varian XL-400 spectrometer. IR spectra were recorded on a Perkin-Elmer 299 spectrophotometer. Mass spectra were obtained by using a Varian MAT 112S spectrometer interfaced with an SS 200 data system. Optical rotations were taken on a JASCO DIP-360 digital polarimeter. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed with EM Science precoated silica gel 60 F-254 plates or EM Science precoated aluminum oxide 150 F-254 plates. Spots were detected with shortwave UV light or by iodine vapor, the bases were located with the modified Dragendorff reagent spray.[26] Preparative TLC was performed on 2 mm thick plates of EM Science aluminum oxide 60 PF-254 or EM Science silica gel 60 PF-254. Column chromatography was carried out with ICN Industries, Inc., 60–200 μm silica gel or alumina, neutral Brockman activity 1 (80–200 mesh). Solvents were dried according to procedures reported by Perrin et al.[27] All yields reported refer to chromatographically homogeneous products.

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Selective Protection of the C-9 Hydroxyl Function of Retronecine and Heliotridine. 9-*O*-(*tert*-Butyldimethylsilyl)retronecine (4A). Sodium hydride (0.324 g of 60% suspension, 10.0 mmol) was suspended in dry THF (100 mL) after being washed with hexane. Retronecine (1.55 g, 10.0 mmol) was added to this mixture at room temperature and stirred for 1 h under nitrogen. *tert*-Butyldimethylsilyl chloride (1.51 g, 10.0 mmol) was then added, and stirring was continued for 3 h. The mixture was poured into ether (200 mL), washed with 10% aqueous K_2CO_3 (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel, using chloroform followed by chloroform/methanol (95/5) mixtures as eluents, to afford 2.37 g (88%) of **4A** as an oil crystallizing upon refrigeration: TLC (silica gel, ethyl acetate–methanol, 9:2) R_f 0.47; ^{1}H NMR ($CDCl_3$) δ 5.71 (bs, 1 H, H-2), 4.34 (d, J = 11.1 Hz, 1 H, H-9), 4.22 (t, J = 3.7 Hz, 1 H, H-7), 4.10 (m, 2 H, H-8, H-9), 3.85 (dd, J = 15.6, 2.2 Hz, 1 H, H-3α), 3.40 (dd, J = 15.7, 5.6 Hz, 1 H, H-3β), 3.33 (bs, 1 H, OH), 3.22 (t, J = 7.8 Hz, 1 H, H-5α), 2.71 (m, 1 H, H-5β), 1.99 (dd, J = 12.9, 5.5 Hz, 1 H, H-6α), 1.92 (m, 1 H, H-6β), 0.90 (s, 9 H, Si-t-Bu), 0.11 (s 6 H, $SiMe_2$); IR (CCl_4) ν 3510, 3490, 2960, 2940, 2900, 2860, 1471, 1465, 1438, 1392, 1372, 1362, 1335, 1320, 1308, 1251, 1203, 1175, 1135, 1120, 1050, 1015, 995, 945, 935 cm^{-1}; EIMS m/e (relative intensity) 39 (11), 41 (28), 45 (13), 53 (13), 57 (13), 59 (15), 67 (16), 73 (46), 75 (67), 80 (28), 89 (17), 93 (84), 94 (100), 106 (16), 118 (11), 120 (54), 136 (21), 138 (90), 168 (22), 182 (74), 212 (30), 225 (7), 254 (1), 269 (M^+, 0.8).

9-*O*-(*tert*-Butyldimethylsilyl)heliotridine (4B). **4B** was obtained following the procedure described above for the preparation of **4A**. The crude oil was chromatographed on silica gel (chloroform gradually changed to a mixture of chloroform/methanol, 4/1) to give in 87% yield pure **4B** as an oil crystallizing upon refrigeration: mp 62–64 °C; TLC (silica gel, chloroform–methanol, 4:1) R_f 0.28; ^{1}H NMR ($CDCl_3$) δ 5.51 (bs, 1 H, H-2), 4.41 and 4.29 (d + d, J = 13.1 Hz, 2 H, H-9), 4.01 (dt, J = 8.0, 5.7 Hz, 1 H, H-7), 3.88 (m, 2 H, H-3α, H-8), 3.34 (m, 2 H, H-3β, H-5α), 2.64 (td, J = 9.5, 6.0 Hz, 1 H, H-5β), 2.06 (dtd, J = 10.1, 6.0, 4.0 Hz, 1 H, H-6α), 1.89 (m, 1 H, H-6β), 0.92 (s, 9 H, Si-t-Bu), 0.11 (s, 6 H, $SiMe_2$); IR (CCl_4) ν 3525, 2960, 2935, 2885, 2860, 1470, 1463, 1390, 1361, 1350, 1315, 1290, 1252, 1197, 1162, 1155, 1122, 1084, 1074, 1047, 1000, 938 cm^{-1}; EIMS m/e (relative intensity) 39 (16), 41 (30), 53 (18), 55 (24), 57 (13), 59 (14), 62 (12), 67 (16), 73 (53), 75 (59), 80 (40), 89 (20), 93 (84), 94 (100), 106 (17), 111 (22), 120 (41), 136 (15), 138 (97), 168 (25), 182 (80), 212 (48), 225 (11), 254 (3), 269 (M^+, 1); CIMS m/e (relative intensity) 106 (6), 120 (12), 138 (42), 182 (9), 212 (30), 252 (7), 270 (M^+ + 1, 100).

9-*O*-Benzoylretronecine (4C). This compound was prepared according to the procedure previously described by Zalkow et al.[10] All of the properties were identical with those reported.

9-*O*-Benzoylheliotridine (4D). 1,1′-Carbonyldiimidazole (CDI) (1.12 g, 6.9 mmol) and benzoic acid (0.73g, 6.0 mmol) were dissolved in 40 mL of dry THF under nitrogen. The mixture was stirred at room temperature for 45 min. This solution was added dropwise at 0–5 °C to the solution of heliotridine (0.93 g, 6.0 mmol) in dry THF (40 mL). The addition was continued over 30 min, after which the reaction mixture was allowed to warm to room temperature and stirred for an additional 20 h. The solvent was removed in vacuo, and the residue was partitioned between chloroform and water. The chloroform layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography on alumina using first a mixture of ethyl acetate and hexane (2:1 by volume) followed by ethyl acetate and next a mixture of ethyl acetate and 2-propanol (9:1 by volume). The middle fraction was separated by preparative TLC on alumina developing with a mixture of ethyl acetate and 2-propanol (9:1 by volume). Chromatographically pure C-9 monoester **4D** was isolated from a mixture of the C-7 and C-9 monoesters and the C-7, C-9 diester in 46% yield: TLC (alumina, chloroform–2-propanol, 9:1) R_f 0.67; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2 H, ortho aromatic) 7.58 (t, J = 7.4 Hz, 1 H, para aromatic), 7.45 (t, J = 7.5 Hz, 2 H, meta aromatic), 5.78 (bs, 1 H, H-2), 5.09 and 4.93 (d + d, J = 13.0 Hz, 2 H, H-9), 4.23 (dt, J = 5.4, 2.2 Hz, 1 H, H-7), 3.99 (bs, 1 H, H-8), 3.91 (d, J = 15.0 Hz, 1 H, H-3α), 3.31 (m, 2 H, H-3β, H-5α), 2.66 (m, 2 H, H-5β, OH), 1.98 (sextet, J = 6.5 Hz, 1 H, H-6α), 1.84 (sextet, J = 6.5 Hz, 1 H, H-6β); IR (CCl_4) ν 3530, 2970, 2935, 2880, 1730, 1452,

1372, 1315, 1270, 1178, 1110, 1070, 1026, 907 cm^{-1}; EIMS *m/e* (relative intensity) 39 (19), 41 (21), 43 (11), 51 (24), 53 (19), 67 (11), 77 (41), 80 (25), 93 (100), 105 (30), 126 (10), 137 (28), 154 (12), 259 (M^+, 1.1).

Conversion of 9-O-Protected Retronecine and Heliotridine to Their 7-*O*-(Phenoxythiocarbonyl) Derivatives, Respectively. The following general procedure was used: To 1 equiv of dried 9-O-protected retronecine or heliotridine was added anhydrous acetonitrile (50 mL/g of pyrrolizidine alkaloid derivative), 1.5 equiv of 4-(dimethylamino)pyridine (DMAP), and 2.6 equiv of phenoxythiocarbonyl chloride. The solution was stirred at room temperature for 2 days, after which the solvent was evaporated in vacuo and the residue was treated with ethyl acetate (50 mL/g of pyrrolizidine alkaloid derivative). The solid was removed by filtration and washed with ethyl acetate, and the filtrate was evaporated as before. In each case, the resulting oily products were purified by column chromatography or preparative TLC. The following properties were obtained for the corresponding 7-*O*-(phenoxythiocarbonyl) derivatives.

7-*O*-(Phenoxythiocarbonyl)-9-*O*-(*tert*-butyldimethylsilyl)retronecine (5A). This compound was purified by column chromatography on silica gel using ethyl acetate as eluent. Evaporation of appropriate fractions gave **5A**, as an oil, in 50% yield: TLC (silica gel, ethyl acetate–triethylamine, 5:1) R_f 0.46; ^1H NMR ($CDCl_3$) δ 7.39 (t, J = 8.0 Hz, 2 H, meta aromatic), 7.27 (t, J = 7.3 Hz, 1 H, para aromatic), 7.05 (d, J = 7.3 Hz, 2 H, ortho aromatic), 5.73 (t, J = 3.3 Hz, 1 H, H-7), 5.61 (d, J = 1.7 Hz, 1 H, H-2), 4.38 (bs, 1 H, H-8), 4.31 and 4.22 (d + d, J = 14.0 Hz, 2 H, H-9), 3.87 (dd, J = 14.8, 4.5 Hz, 1 H, H-3α), 3.28 (m, 2 H, H-3β, H-5α), 2.60 (ddd, J = 12.1, 9.3, 5.7 Hz, 1 H, H-5β), 2.34 (dd, J = 13.8, 5.6 Hz, 1 H, H-6α), 2.17 (ddd, J = 12.1, 8.0, 4.1 Hz, 1 H, H-6β), 0.93 (s, 9 H, Si-t-Bu), 0.10 (s, 6 H, $SiMe_2$).

7-*O*-(Phenoxythiocarbonyl)-9-*O*-(*tert*-butyldimethylsilyl)heliotridine (5B). The resulting crude material was chromatographed on silica gel, eluting with ethyl acetate, followed by a mixture of ethyl acetate and 2-propanol (8:1 gradually changed to 7:1). Chromatographically pure **5B** was obtained as an oil in 58% yield: TLC (silica gel, ethyl acetate–2-propanol, 5:3) R_f 0.54; ^1H NMR δ ($CDCl_3$) 7.43 (t, J = 7.6 Hz, 2 H, meta aromatic), 7.30 (t, J = 7.5 Hz, 1 H, para aromatic), 7.10 (d, J = 7.8 Hz, 2 H, ortho aromatic), 5.70 (d, J = 1.8 Hz, 1 H, H-2), 5.55 (d, J = 4.9 Hz, 1 H, H-7), 4.43 and 4.31 (d + d, J = 14.7 Hz, 2 H, H-9), 4.29 (bs, 1 H, H-8), 3.99 (m, 1 H, H-3α), 3.37 (m, 1 H, H-3β), 3.25 (td, J = 11.4, 5.4 Hz, 1 H, H-5α), 2.91 (m, 1 H, H-5β), 2.01 (m, 2 H, H-6), 0.91 (s, 9 H, Si-t-Bu), 0.08 (s, 6 H, $SiMe_2$); IR (CCl_4) ν 2960, 2930, 2885, 2860, 1593, 1492, 1472, 1464, 1363, 1316, 1273, 1255, 1201, 1168, 1100, 1025, 995 cm^{-1}; EIMS *m/e* (relative intensity) 41 (12), 45 (24), 62 (10), 73 (51), 75 (23), 77 (19), 89 (18), 93 (21), 106 (100), 118 (28), 120 (93), 136 (14), 151 (14), 194 (17), 226 (10), 251 (73), 274 (9), 348 (1), 405 (M^+, 1); CIMS *m/e* (relative intensity) 73 (14), 89 (11), 95 (19), 106 (45), 120 (100), 195 (20), 252 (92), 390 (23), 406 ($M^+ + 1$, 90); high-resolution mass spectrum, *m/e* 405.1802 ($C_{21}H_{31}O_3NSSi$ requires 405.1794).

7-*O*-(Phenoxythiocarbonyl)-9-*O*-benzoylretronecine (5C). Purification of this material was achieved by column chromatography on alumina eluting with a mixture of ethyl acetate and hexane (first 1:1 by volume followed by 3:2 by volume); the yield of oily **5C** was 58%: TLC (alumina, ethyl acetate–hexane, 3:2) R_f 0.72; ^1H NMR ($CDCl_3$) δ 8.07 (d, J = 7.6 Hz, 2 H, ortho aromatic for benzoyl ester), 7.57 (t, J = 7.5 Hz, 1 H, para aromatic for benzoyl ester), 7.44 (t, J = 7.8 Hz, 2 H, meta aromatic for benzoyl ester), 7.36 (t, J = 7.9 Hz, 2 H, meta aromatic for thiono ester), 7.26 (t, J = 7.6 Hz, 1 H, para aromatic for thiono ester), 7.00 (d, J = 7.3 Hz, 2 H, ortho aromatic for thiono ester), 5.83 (d, J = 1.3 Hz, 1 H, H-2), 5.78 (t, J = 3.7 Hz, 1 H, H-7), 4.95 (bs, 2 H, H-9), 4.50 (bs, 1 H, H-8), 3.92 (d, J = 15.0 Hz, 1 H, H-3α), 3.33 (m, 2 H, H-3β, H-5α), 2.66 (ddd, J = 12.1, 9.4, 5.8 Hz, 1 H, H-5β), 2.42 (dd, J = 13.9, 5.6 Hz, 1 H, H-6α), 2.18 (ddd, J = 11.7, 8.0, 4.0 Hz, 1 H, H-6β); IR (CCl_4) ν 2970, 2935, 2880, 1730, 1490, 1454, 1315, 1272, 1204, 1178, 1108, 1070, 1027 cm^{-1}; EIMS *m/e* (relative intensity) 77 (33), 93 (55), 105 (40), 108 (21), 119 (72), 120 (100), 136 (42), 241 (12), 273 (5), 290 (4), 395 (M^+, 14).

7-*O*-(Phenoxythiocarbonyl)-9-*O*-benzoylheliotridine (5D). The crude compound was purified by preparative TLC on alumina; development with a mixture of hexane and ethyl acetate (7:2 by volume) gave **5D** (62%) as a chromatographically homogeneous oil: TLC (alumina, ethyl acetate–hexane, 1:1) R_f 0.67; ^1H NMR ($CDCl_3$) δ 8.06 (d, J = 7.2 Hz, 2 H, ortho aromatic for benzoyl ester), 7.56 (t, J = 7.3 Hz, 1 H, para aromatic for benzoyl ester), 7.40 (m, 4 H, meta aromatic), 7.27 (t, J = 7.4 Hz, 1 H, para aromatic for thiono ester), 7.02 (d, J = 7.3 Hz, 2 H, ortho aromatic for thiono ester), 5.88 (bs, 1 H, H-2), 5.68 (t, J = 2.4 Hz, 1 H, H-7), 5.06 (bs, 2 H, H-9), 4.46 (bs, 1 H, H-8), 4.05 (d, J = 15.8 Hz, 1 H, H-3α), 3.43 (ddd, J = 15.8, 5.1, 1.9 Hz, 1 H, H-3β), 3.30 (dd, J = 11.4, 5.8 Hz, 1 H, H-5α), 2.92 (m, 1 H, H-5β), 2.07 (m, 2 H, H-6); IR (CCl_4) ν 2980, 2940, 2885, 1730, 1670, 1485, 1452, 1313, 1270, 1202, 1135, 1100, 1068, 1025 cm^{-1}; EIMS *m/e* (relative intensity) 77 (20), 93 (16), 105 (20), 119 (100), 136 (18), 241 (43), 395 (M^+, 1.3).

Reductive Deoxygenation of Phenyl Thionocarbonate Esters of 9-O-Protected Retronecine and Heliotridine. The following general procedure was used. One equivalent of phenyl thionocarbonate ester **5A–D** was dissolved in dry toluene (100 mL/g of compound) and 0.2 equiv of 2,2′-azobis(2-methylpropionitrile) (AIBN), and 1.5 equiv of tri-*n*-butyltin hydride was added. Rigorous anerobic conditions were kept during the reaction. The reaction mixture was heated at 75 °C for 3 h. Solvent was evaporated in vacuo, and the residue was purified. The following properties were obtained for the products.

(5*R*)-1-Aza-3(*R*)-phenyl-4(*S*)-(((*tert*-butyldimethylsilyl)oxy)methyl)-4(*S*)-carboxy-6(*R*)-hydroxybicyclo[3.3.0]octane Lactone (6A). The crude compound was chromatographed on silica gel using first a mixture of ethyl acetate and hexane (1:1 by volume) followed by ethyl acetate. Evaporation of the ethyl acetate fractions containing alkaloid gave **6A** as a white solid in 48% yield: mp 134–135 °C; $[\alpha]^{23}_D$ +57.92° (*c* 1.25, $CHCl_3$); TLC (silica gel, ethyl acetate) R_f 0.43; The ^1H and ^{13}C NMR assignments reported here were made using proton–proton correlated 2D NMR (COSY), and proton–carbon-13 correlated 2D NMR (HETCOR). The structure of this compound was determined by X-ray crystallography;[22] ^1H NMR ($CDCl_3$) δ 7.30 (m, 3 H, meta, para aromatic), 7.14 (m, 2 H, ortho aromatic), 4.86 (dt, J = 5.4, 2.4 Hz, 1 H, H-7), 4.14 (d, J = 5.0 Hz, 1 H, H-8), 3.93 and 3.79 (d + d, J = 9.4 Hz, 2 H, H-9), 3.65 (dd, J = 12.4, 6.4 Hz, 1 H, H-2), 3.44 (dd, J = 9.3, 6.4 Hz, 1 H, H-3α), 3.21 (ddd, J = 11.5, 8.3, 6.2 Hz, 1 H, H-5α), 3.01 (m, 2 H, H-3β, H-5β), 2.43 (m, 1 H, H-6α), 2.26 (m, 1 H, H-6β), 0.86 (s, 9 H, Si-t-Bu), 0.05 (s, 3 H, SiMe), 0.00 (s, 3 H, SiMe); ^{13}C NMR ($CDCl_3$) δ 176.73 (C=O), 134.78, 129.21, 128.37 and 128.01 (C aromatics), 82.51 (C-7), 75.32 (C-8), 65.49 (C-9), 61.44 (C-1), 59.34 (C-3), 53.34 (C-5), 52.50 (C-2), 33.12 (C-6), 26.02 ($SiC(CH_3)_3$), 18.38 ($SiC(CH_3)_3$), 5.37 and 5.33 ($Si(CH_3)_2$); IR (CCl_4) ν 2960, 2935, 2860, 1783, 1465, 1380, 1350, 1252, 1183, 1140, 1110, 1040, 983 cm^{-1}; EIMS *m/e* (relative intensity) 42 (11), 73 (13), 75 (12), 82 (20), 198 (52), 212 (15), 286 (20), 298 (11), 316 (100), 358 (3), 373 (M^+, 0.2); CIMS *m/e* (relative intensity) 133 (3), 198 (5), 212 (2), 235 (2), 316 (28), 358 (4), 374 ($M^+ + 1$, 100).

(5*R*)-1-Aza-3(*R*)-phenyl-4(*S*)-(benzoylmethyl)-4(*S*)-carboxy-6(*R*)-hydroxybicyclo[3.3.0]octane Lactone (6C). Purification of this material was achieved by column chromatography on silica gel eluting with ethyl acetate to give oily, chromatographically homogeneous **6C** in 60% yield: $[\alpha]^{23}_D$ = +65.29° (*c* 2.19, $CHCl_3$); TLC (silica gel, ethyl acetate) R_f 0.19; ^1H NMR δ 7.97 (d, J = 8.2 Hz, 2 H, ortho aromatic for benzoyl ester), 7.58 (t, J = 7.5 Hz, 1 H, para aromatic for benzoyl ester), 7.44 (t, J = 7.7 Hz, 2 H, meta aromatic for benzoyl ester), 7.35 (m, 3 H, meta, para aromatic for phenyl), 7.22 (m, 2 H, ortho aromatic for phenyl), 4.97 (dt, J = 5.4, 2.2 Hz, 1 H, H-7), 4.67 and 4.55 (d + d, J = 11.0 Hz, 2 H, H-9), 4.19 (d, J = 4.9 Hz, 1 H, H-8), 3.82 (dd, J = 12.4, 6.4 Hz, 1 H, H-2), 3.51 (dd, J = 9.4, 6.4 Hz, 1 H, H-3α), 3.23 (ddd, J = 11.5, 8.3, 6.1 Hz, 1 H, H-5α), 3.06 (m, 2 H, H-3β, H-5β), 2.48 (m, 1 H, H-6α), 2.30 (m, 1 H, H-6β); IR ($CHCl_3$) ν 2970, 2930, 2890, 1775, 1727, 1603, 1450, 1357, 1316, 1265, 1195, 1114, 1070, 1025, 920; EIMS *m/e* (relative intensity) 42 (30), 51 (17), 77 (48), 82 (100), 91 (10), 105 (45), 115 (12), 129 (10), 196 (13), 197 (19), 228 (11), 363 (M^+, 18); high-resolution mass spectrum, *m/e* 363.1460 ($C_{22}H_{21}O_4N$ requires 363.1471).

9-*O*-(*tert*-Butyldimethylsilyl)supinidine (7B). The desired product was prepared from **5B** and purified by preparative TLC on silica gel using a mixture of chloroform and methanol (6:1 by volume) as eluent for developing. Pure supinidine ether **7B** was obtained as an oil in 66% yield: $[\alpha]^{27}_D$ = −4.5° (*c* 1.00, $CHCl_3$);

TLC (silica gel, chloroform–methanol, 6:1) R_f 0.33; ^{1}H NMR ($CDCl_3$) δ 5.49 (dd, J = 3.5, 1.8 Hz, 1 H, H-2), 4.21 (bs, 2 H, H-9), 4.11 (bs, 1 H, H-8), 3.87 (ddt, J = 15.4, 4.6, 2.3 Hz, 1 H, H-3α), 3.33 (dtd, J = 15.3, 4.3, 2.1 Hz, 1 H, H-3β), 3.11 (dt, J = 9.8, 4.9 Hz, 1 H, H-5α), 2.49 (ddd, J = 9.7, 7.8, 6.5 Hz, 1 H, H-5β), 1.94 (m, 1 H, H-7α), 1.75 (m, 2 H, H-6), 1.51 (ddd, J = 14.6, 11.8, 7.8 Hz, 1 H, H-7β), 0.91 (s, 9 H, Si-t-Bu), 0.08 (s, 6 H, $SiMe_2$); IR (CCl_4) ν 2965, 2940, 2905, 2865, 1474, 1465, 1447, 1392, 1376, 1364, 1345, 1322, 1307, 1252, 1198, 1172, 1122, 1089, 1074, 1023, 1001, 948, 940, 909 cm^{-1}; EIMS m/e (relative intensity) 41 (22), 53 (12), 57 (15), 59 (12), 73 (24), 75 (16), 80 (15), 89 (12), 93 (23), 108 (24), 120 (47), 122 (100), 196 (37), 221 (12), 225 (11), 238 (25), 252 (36), 254 (M^+, 64).

9-*O*-Benzoylsupinidine (7D). This compound was obtained from **5D** and purified by preparative TLC on aluminia using a mixture of hexane and chloroform (1:1 by volume) as eluent for developing. **7D** was obtained as an oil in 64% yield: $[\alpha]^{24}_D$ = −10.56° (c 1.25, $CHCl_3$); TLC (alumina, ethyl acetate) R_f 0.48; ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.2 Hz, 2 H, ortho aromatic), 7.57 (t, J = 7.3 Hz, 1 H, para aromatic), 7.45 nt, J = 7.7 Hz, 2 H, meta aromatic), 5.70 (d, J = 1.6 Hz, 1 H, H-2), 4.92 (bs, 2 H, H-9), 4.22 (bs, 1 H, H-8), 3.92 (bd, J = 15.8 Hz, 1 H, H-3α), 3.39 (ddd, J = 15.7, 4.8, 1.9 Hz, 1 H, H-3β), 3.14 (quintet, J = 5.0 Hz, 1 H, H-5α), 2.51 (ddd, J = 10.0, 8.2, 5.9 Hz, 1 H, H-5β), 2.02 (m, 1 H, H-7α), 1.77 (m, 2 H, H-6), 1.59 (ddd, J = 14.9, 11.7, 7.9 Hz, 1 H, H-7β); IR (CCl_4) ν 2970, 2940, 2875, 1730, 1453, 1316, 1270, 1198, 1178, 1110, 1070, 1027 cm^{-1}; EIMS m/e (relative intensity) 41 (11), 51 (13), 77 (39), 80 (23), 93 (57), 105 (45), 108 (42), 110 (37), 120 (100), 122 (80), 138 (26), 243 (M^+, 11); CIMS m/e (relative intensity) 93 (2), 105 (1), 108 (2), 110 (1), 120 (14), 122 (46), 244 (M^+ + 1, 100); high-resolution mass spectrum, m/e 243.1257 ($C_{15}H_{17}O_2N$ requires 243.1259).

Deprotection of Supinidine Derivatives. (−)-Supinidine (1): Method I. A mixture of 9-*O*-(*tert*-butyldimethylsilyl)supinidine (**7B**) (0.75 g, 2.96 mmol) and ammonium fluoride (0.22g, 5.92 mmol) in dry methanol (60 mL) was stirred and kept at 60 °C for 18 h. The solvent was removed under reduced pressure to give a pale-yellow residual oil that was purified by preparative TLC on 2-mm silica gel plates (three times), developing with a mixture of chloroform/methanol/concentrated ammonium hydroxide (10/4/1, respectively). Supinidine (1) was extracted from the silica gel with methanol, and the solvent was removed under reduced pressure. The residues were then taken up in chloroform or acetone, which resulted in the precipitation of small amounts of silica gel that were removed by filtration. Evaporation of the solvent under reduced pressure gave chromatographically homogeneous product 1 in 70% yield.

Method II. A mixture of 9-*O*-benzoylsupinidine (**7D**) (0.21 g, 0.86 mmol) and lithium aluminum hydride (0.066 g, 1.73 mmol) in dry ether (10 mL) was heated under reflux for 30 min. To the resulting solution was sequentially added 0.062 mL of water, 0.062 mL of 3 N aqueous NaOH, and 0.088 mL of water. The mixture was filtered, and the filtrate was dried (anhydrous $MgSO_4$) and concentrated in vacuo to give a pale-yellow liquid, which was purified by preparative TLC as described above to yield **1** as a chromatographically homogeneous product supinidine (1) in 59% yield: mp (picrate) 139–141 °C (MeOH) [lit.[13b] mp 143–144 °C (EtOH)]; $[\alpha]^{26}_D$ = −10.4° (c 2.64, EtOH),[28] after distillation at reduced pressure to remove last traces of solvent; TLC (silica gel, chloroform–methanol–concentrated ammonium hydroxide, 10:4:1) R_f 0.49; ^{1}H NMR ($CDCl_3$) δ 5.52 (bs, 1 H, H-2), 4.31 (bs, 1 H, H-8), 4.25 and 4.16 (d + d, J = 14.3 Hz, 2 H, H-9), 3.98 (bd, J = 15.3 Hz, 1 H, H-3α), 3.36 (ddd, J = 15.4, 4.3, 2.1 Hz, 1 H, H-3β), 3.19 (td, J = 10.9, 5.0 Hz, 1 H, H-5α), 2.58 (td, J = 10.3, 6.9 Hz, 1 H, H-5β), 2.03 (ddd, J = 13.7, 12.2, 6.0 Hz, 1 H, H-7α), 1.81 (quintet, 2 H, H-6), 1.57 (ddd, J = 14.5, 11.8, 7.1 Hz, 1 H, H-7β); IR ($CHCl_3$) ν 3620, 3350, 2970, 2880, 1605, 1450, 1385, 1290, 1190, 1115, 1085, 1040; EIMS m/e (relative intensity) 39 (16), 41 (31), 43 (14), 45 (12), 53 (16), 55 (13), 68 (21), 80 (100), 94 (12), 108 (41), 110 (28), 120 (11), 122 (53), 138 (18), 139 (M^+, 69); high-resolution mass spectrum, m/e 139.1013 ($C_8H_{13}ON$ requires 139.0997).

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Registry No. **1**, 551-59-7; **2**, 480-85-3; **3**, 520-63-8; **4A**, 82485-07-2; **4B**, 126253-89-2; **4C**, 95363-37-4; **4D**, 126191-51-3; **5A**, 126191-48-8; **5B**, 126191-52-4; **5C**, 126191-53-5; **5D**, 126191-54-6; **6A**, 126191-49-9; **6C**, 126191-55-7; **7B**, 126191-50-2; **7D**, 126191-56-8.

(28) Several different values have been reported for the specific rotation of synthetic $[[\alpha]^{25}_D$ = −9.7° (c 2.5, EtOH);[13a] $[\alpha]^{18}_D$ = −8.3° (c 2.0, EtOH)[13b]] and natural $[[\alpha]^{18}_D$ = −10.3° (c 1.65, EtOH)[29]] supinidine. The NMR spectrum of our synthetic (−)-supinidine run in the presence of the chiral shift reagent Eu(hfc)$_3$ did not reveal any splitting of peaks. Requests for authentic samples of (±)-supinidine were unfruitful.

(29) Culvenor, C. C. J. *Aust. J. Chem.* **1954**, *7*, 287.

Intermolecular Decomposition of *N*-Acylcyanamides

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In efforts to synthesize acyl derivatives as prodrugs of cyanamide (1, $H_2NC{\equiv}N$),[1] a potent aldehyde dehydrogenase inhibitor which is used therapeutically as an alcohol deterrent agent,[2] we discovered that certain *N*-acylcyanamides, viz., *N*-(benzyloxycarbonyl)cyanamide (**2a**) and *N*-acetylcyanamide (**2b**), the latter a major urinary metabolite of cyanamide in rodents, dog, and humans,[3] were unstable in their free states and gradually decomposed at room temperature. We now report our investigations on the nature of the decomposition products of these *N*-acylcyanamides, and by deduction, propose a pathway for these reactions.

Results and Discussion

When *N*-(benzyloxycarbonyl)cyanamide (**2a**) was stored at room temperature for 1 week, the originally clear liquid was converted to a semisolid. By TLC analysis, the residue was found to contain unchanged **2a**, **1**, and some other UV-quenching substances. Two crystalline compounds were isolated from the above mixture by solvent extractions followed by column chromatography, etc. The spectral data for the first suggested it to be *N*-(benzyloxycarbonyl)-*N'*-cyanoguanidine (**5a**), and this was confirmed by acylation of cyanoguanidine (dicyanodiamide) with (benzyloxy)carbonyl chloride in aqueous base to give a product with physicochemical and spectral properties identical with those of **5a**. The IR and NMR spectral data for the second compound suggested it to be *N*,*N*-bis(benzyloxycarbonyl)cyanamide (**3a**), and this was confirmed by its elemental analysis.

N-Acetylcyanamide (**2b**) was similarly converted to a semisolid under the same conditions. By TLC analysis, the residue was shown to contain unchanged **2b**, cyanoguanidine, and a number of UV-quenching substances. The spectral data for a minor product isolated from the above mixture by preparative TLC suggested it to be *N*-acetyl-*N'*-cyanoguanidine (**5b**), again proven by acetylation of cyanoguanidine to a product with identical physicochemical and spectral properties.

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