Synthesis in the Pyrrolizidine Class of Alkaloids. *dl*-Supinidine[1]

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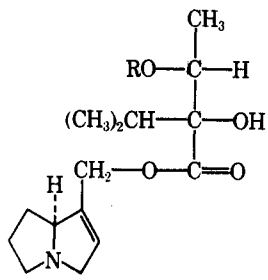
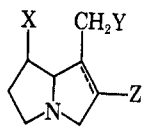
A nitrone based entry to the pyrrolizidine class of alkaloids is described. The synthesis of supinidine (**3**), the necine base obtained from supinine (**1a**) and heleurine (**1b**), illustrates the approach used.

Pyrrolizidine alkaloids, also referred to as the Senecio alkaloids, occur naturally in various plant species and have been the subject of several excellent reviews.[2-5] Many of the alkaloids of this class are toxic, causing liver tumors and lung damage in animals feeding on plants containing these compounds. The alkaloids usually consist of a pyrrolizidine ("necine") base and a carboxylic ("necic") acid coupled by an ester linkage (cf. **1**).



1a, R = H
b, R = CH_3



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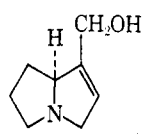

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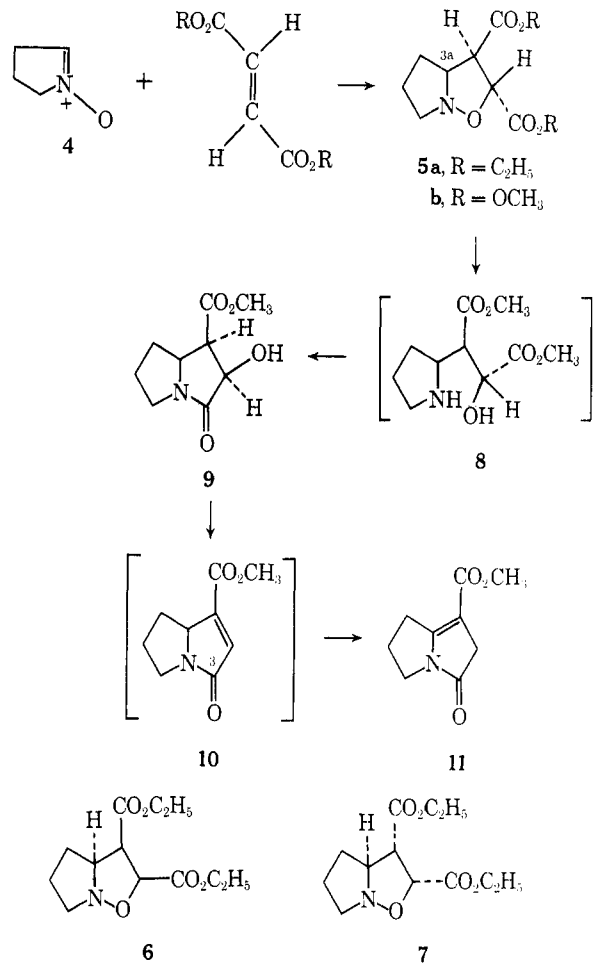
The necine bases embody a pyrrolizidine nucleus with a one-carbon side chain and usually one or more hydroxyl groups positioned as shown in structure **2**, where X, Y, and Z may be H or OH, and a double bond is frequently located (i.e., when Z = H) at the position indicated by a dotted line. It is the unsaturated pyrrolizidine alkaloids that are principally involved in the hepatotoxicity of these compounds.[5] Although considerable synthetic effort has been directed toward the pyrrolizidine bases, the synthesis of supinidine[6] (**3**), the necine base derived from supinine (**1a**) and heleurine (**1b**), was not achieved[7-10] at the outset of this work.[7]

Synthetic Approach. Initially, we sought a nitrone based approach to supinidine which would involve an addition to a symmetrical dipolarophile, thereby avoiding any potential problems involving the regioselectivity of the cycloaddition. Toward this end, we examined the reaction of 1-pyrroline 1-oxide (**4**) with both diethyl fumarate and diethyl maleate. Each reaction provided two isomeric adducts in a 2:1 ratio (e.g., **6** and **7** from diethyl maleate and **4**). The stereochemistry of the hydrogen at C_{3a} in adduct **5a** is unspecified in Chart I. In an effort to simplify the NMR spectra of the adducts, the cycloaddition of the nitrone **4** with dimethyl fumarate was investigated. Once more a mixture of two isomeric adducts was produced with properties similar to those observed for the diethyl fumarate adducts. No effort was made to separate these adducts since both isomers would, by the synthetic plan, lead to the same target. Hydrogenolysis of the nitrogen–oxygen bond in the dimethyl maleate adduct mixture led to the formation of hydroxylactam **9**, presumably as a mixture of two stereoisomeric adducts. This mixture was dehydrated via the corresponding tosylate according to the procedure of Nair and Adams.[9] A solid unsaturated ester (i.e., **11**) was obtained which did not exhibit olefinic protons in its NMR spectrum but which did have spectral properties identical with those of **11** previously reported by Goldschmidt.[10] Thus, the

Chart I

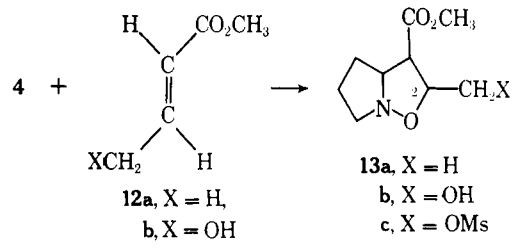


elimination apparently proceeded through the intermediacy of the desired cross conjugated keto ester **10** on the way to the undesirable vinylogous lactam **11**.

Several attempts were made to dehydrate **9** directly. Geissman's method[11] (employing barium hydroxide), phosphorus pentoxide in benzene, or *p*-toluenesulfonic acid in benzene did not lead to readily identifiable material.

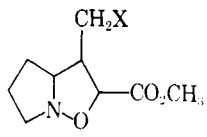
The facility of the isomerization of **10** → **11**, coupled with the failure of a similar dehydration to occur in Geissman's retronecine synthesis,[11] suggests that the cross conjugated nature of **10** may be responsible for its facile transformation into **11**. Thus, we sought to explore synthetic possibilities which precluded the existence of a carbonyl group at C_3 in **10**. This led us to explore the reaction of 1-pyrroline 1-oxide (**4**) with unsymmetrical dipolarophiles.

Unsymmetrical Dipolarophiles. The major difficulty envisioned with the use of unsymmetrical dipolarophiles, such as γ-substituted crotonates (e.g., **12**), was the possibility of a substantial stereochemical preference for the undesirable α-oxy ester isomer **14**.[12,13]



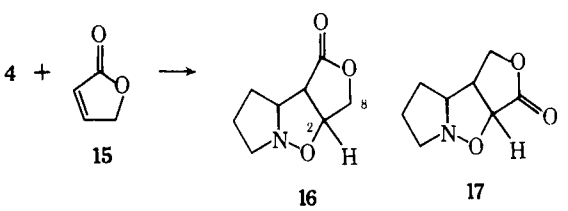
12a, X = H,
b, X = OH

13a, X = H
b, X = OH
c, X = OMs



14a, X = H
b, X = OH

Our initial regiochemical probe was 1-butenolide[14] (**15**). Reaction of nitrone **4** with **15** resulted in the isolation of a single adduct, **16**, the orientation of which encouraged further exploration of this approach. The orientation was assigned on the basis of a spin decoupling experiment. The NMR spectrum of **16** exhibits a seven-line pattern at 4.9 ppm, attributed to the proton at C_2. Double irradiation of this signal caused the signal due to the adjacent methylene protons at 4.4 ppm to collapse to a singlet. Similarly, double irradiation of the methylene signal caused the multiplet at 4.9 ppm to collapse to the expected doublet ($J_{2,3}$ = 7, $J_{2,8e}$ = 5 Hz). Clearly, one would expect H_2 for the alternate adduct **17** to be a doublet prior to irradiation, and the downfield methylene protons should not have been coupled to the proton at C_2. While efforts to convert **16** into supinidine met with difficulty, the regiochemistry of the cycloaddition involving 1-butenolide encouraged us to pursue similar chemistry using substituted crotonates of the type **12**. We found that the addition of methyl crotonate (**12a**) to nitrone **4** afforded **13a**, consistent with similar findings of Murray and Turner[15] in a related reaction. Hydrogenolytic cleavage of **13a** gave a compound which exhibited a positive iodoform test. In addition, the NMR spectrum of **13a** shows the H_2 proton signal to be a multiplet ($J_{2,3}$ = 8.6, $J_{2,8}$ = 6.1 Hz) rather than the doublet anticipated for **14a**.



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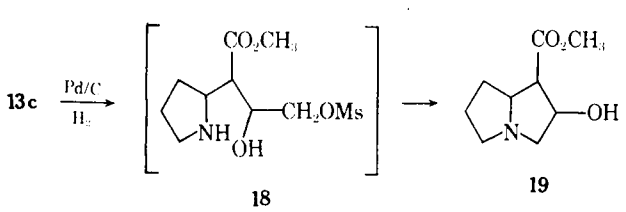
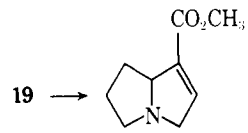
The cyclization was studied using methyl γ-hydroxycrotonate (**12b**). A light yellow liquid was obtained in 80% yield which, upon chromatography through Florisil, afforded the adduct **13b** as colorless crystals. The NMR spectrum of this adduct contained a six-line pattern at 4.23 ppm integrating for one proton, strongly suggesting that the adduct had the orientation depicted by **13b**, and not by **14b**. Conversion to the methanesulfonate proceeded in 94% yield. Hydrogenolysis occurred over 10% palladium on carbon to give β-hydroxy ester **19** as a white solid in 95% yield, presumably via the amino alcohol **18**. Thus, the pyrrolizidine system has been assembled with functionality appropriate for the subsequent elaboration into supinidine. To effect this transformation, **19** was subjected to dehydration conditions with phosphorus oxychloride in pyridine at 20° or below. A pale yellow liquid was isolated which exhibited an olefinic stretching band at 6.08 μ in its ir spectrum and a band at λ_{max} (ethanol) 214 nm (ε 7375) in its uv spectrum. The NMR spectrum contained a one-proton multiplet at δ (Me_4Si, carbon tetrachloride) 6.7 ppm attributed to the vinyl proton in **20**. The β-vinyl protons in methyl crotonate, methyl γ-hydroxycrotonate, methyl γ-chlorocrotonate, and methyl 1-cyclopentenecarboxylate fall in the range (Me_4Si) 6.7–7.0 ppm in carbon tetrachloride solution.



18 19



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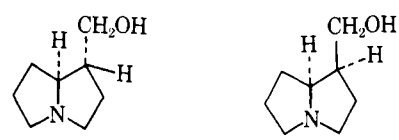
Finally, the unsaturated ester **20** was converted into *dl*-supinidine (**3**) using a mixed hydride reagent prepared from lithium aluminum hydride and aluminum chloride.[17] Reduction with lithium aluminum hydride also led to extensive reduction of the double bond.[18] The mixed hydride method led to a 3:2:6 mixture, the major constituent of which was *dl*-supinidine, purified by preparative gas–liquid phase chromatography, as determined by spectral comparisons with authentic material. The *dl*-supinidine (**3**) so obtained possessed NMR, ir, and mass spectra virtually identical with those of supinidine obtained by hydrolysis of supinine (**1a**). The other constituents of the reduction mixture were presumably trachelanthamidine (**21**) and isoretronecanol (**22**). The infrared spectra of both compounds were very similar to the published spectrum[8] of 1-hydroxymethylpyrrolizidine. A mass spectrum of the major saturated isomer was virtually identical with the corresponding spectrum of trachelanthamidine (**21**).



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Experimental Section

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on the Beckman IR-5a spectrophotometer and calibrated using the 6.24-μ band of polystyrene. Proton magnetic resonance spectra were obtained using a Varian A-60 spectrometer using tetramethylsilane as the internal standard. Notations s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Mass spectra were recorded on a CEC-120 spectrometer at an ionization potential of 77.5 V. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer.

1-Pyrroline 1-Oxide (4). 1-Pyrroline 1-oxide was prepared according to the method of Thesing and Sirrenberg[20] in an overall yield of 40%: bp 74–76° (0.1 mm) [lit.[20] bp 65° (0.07 mm)]; ir (film) 6.32 (s), 7.98 μ (s).

Addition of 1-Pyrroline 1-Oxide to Diethyl Maleate. A 1.3-g (15 mmol) sample of 1-pyrroline 1-oxide was dissolved in 150 ml of chloroform and to this was added 2.53 g (15.3 mmol) of diethyl maleate. The solution was stirred at 25° for 1 hr. A 10% excess of diethyl maleate was then added and the solution was refluxed for 1 hr. Evaporation of the chloroform under reduced pressure afforded a light yellow liquid. Distillation gave 1.17 g (24% yield) of a clear liquid, bp 95–97° (4 mm). Chromatography ofthe liquid through Florisil afforded two fractions, both liquids, which appeared to be isomers. Isomer A obtained from elution with 1:1 ether–acetone gave an analytical sample with ir (film) 5.75–5.80 (s), 8.3–8.55 μ (s);

λ_{max} (EtOH) 206 nm (ϵ 383); NMR (CCl_4) δ 4.7 (d, 1), 4.15 (cp, 5), 2.95–3.25 (j, 3), 1.6–2.2 (m, 4), and 1.15–1.45 ppm (two overlapping triplets, 6).

Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found (isomer A): C, 56.24; H, 7.66; N, 5.78. Found (isomer B): C, 55.90; H, 7.41; N, 5.75.

Addition of 1-Pyrroline 1-Oxide to Diethyl Fumarate. To a well-stirred solution of 6.65 g (78 mmol) of 1-pyrroline 1-oxide and 75 ml of chloroform was added 13.4 g (78 mmol) of diethyl fumarate and the resulting solution was refluxed for 1 day. Evaporation of the chloroform under reduced pressure followed by distillation of the liquid residue gave a light yellow liquid: 18 g, 90% yield; bp 116–117° (0.4 mm); ir (film) 5.71–5.75 (s), 8.3–8.35 μ (s); NMR (CCl_4) δ 4.75 (d, J = 5 Hz) and 4.55 ppm (d, J = 8 Hz) in a 1:2 area ratio, respectively, corresponding to H_2 of two different stereoisomers. No attempt was made to separate the isomers.

Dimethyl Hexahydropyrrolo[1,2-*b*]isoxazole-2,3-carboxylate (5b). Dimethyl fumarate (2.1 g, 15 mmol) was added to a stirred solution of 25 ml of chloroform and 1.3 g (15 mmol) of 1-pyrroline 1-oxide. A 24-hr reflux period afforded a light yellow solution. The chloroform was evaporated under reduced pressure and the remaining liquid distilled under vacuum. A yellow liquid was obtained: 2.17 g, 62% yield; ir (film) 5.69–5.76 μ (s); NMR ($CDCl_3$) δ 1.6–2.25 (cp, 4), 2.83–3.55 (cp, 3), 3.75–4.18 (cp, 7), and 4.58–4.98 (cp, 1).

Methyl 2-Hydroxy-3-oxopyrrolizidine-1-carboxylate (9). A solution of 2 g (8.7 mmol) of dimethyl hexahydropyrrolo[1,2-*b*]isoxazole-2,3-carboxylate (**5b**) in 60 ml of methanol was hydrogenated for 4 hr using 100 mg of 10% palladium on carbon. Filtration through Celite followed by removal of the methanol under reduced pressure afforded a greenish-white solid. Recrystallization from acetone–hexane gave a brownish solid: mp 118–128°; ir 2.96 (m), 5.75 (s), and 5.92 μ (2).

Dehydration of Methyl 2-Hydroxy-3-oxopyrrolizine-1-carboxylate. Following the procedure of Nair and Adams,[9] 500 mg (2.5 mmol) of methyl 2-hydroxy-3-oxopyrrolizidine-1-carboxylate (**9**) in 5 ml of pyridine was cooled to −10°. To this was added 477 mg (2.5 mmol) of toluenesulfonyl chloride in one portion and the resulting solution was stored at 0° for a short time. Small pieces of ice were slowly added until ca. 25 ml of water had been introduced. The solution was then acidified with 20% HCl and extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate. Evaporation of the chloroform under reduced pressure afforded a brown liquid which was chromatographed through alumina (Woelm). Elution with 50:50 ether–chloroform gave a pale yellow solid: uv λ_{max} (ethanol) 218 nm (ϵ 4600) and 289 (12700) [lit.[10] λ_{max} (ethanol) 218 nm (ϵ 4600) and 288 (12000)]; ir ($CHCl_3$) 5.84 (s), 5.98 (s), and 6.02 μ (m), very similar to that reported by Goldschmidt.[10]

Methyl γ-Bromocrotonate. A well-stirred mixture of 20.5 g (0.205 mol) of methyl crotonate, 110 ml of carbon tetrachloride, 29.1 g (0.164 mol) of *N*-bromosuccinimide, and a small amount (ca. 10 mg) of benzoyl peroxide was refluxed for 48 hr. Filtration and evaporation of the carbon tetrachloride under reduced pressure afforded a yellow liquid. Distillation of the liquid gave a clear liquid: 23 g, 80% yield; bp 92–95° (10 mm) [lit.[19] bp 83–85° (13 mm)]; ir (film) 5.77 (s), 5.97 (w), 10.22 μ (m); NMR (CCl_4) δ 3.72 (s, 3), 409 (q, 2), 606 (m, 1), 7.0 (m, 1).

1-Butenolide (15). The unsatured lactone 1-butenolide was prepared in a two-step synthesis according to the method of Judge and Price[14] in an overall yield of 16%: ir (film) 5.63 (s), 5.73 (s), 6.20 μ (w); NMR (CCl_4) δ 4.95 (q, 2), 6.15 (m, 1), 7.8 (m, 1); bp 88–89° (2 mm) [lit.[14] bp 94–98° (2 mm)].

Hexahydro-2-(hydroxymethyl)pyrrolo[1,2-*b*]isoxazole-3-carboxylate Lactone (16). A stirred solution of 2.7 g (3.3 mmol) of 1-pyrroline 1-oxide, 2.7 g (3.3 mmol) of 1-butenolide, and 70 ml of chloroform was refluxed for 8 hr and stirred at 25° for 24 hr. Evaporation of the chloroform under reduced pressure left a brown solid. Recrystallization using hexane afforded white needles: 2.3 g, 43% yield; mp 87–89°; ir (film) 5.59–5.66 (s), 8.46 μ (s); uv λ_{max} (MeOH) 206 nm (ϵ 422); NMR ($CDCl_3$) δ 1.5–2.4 (cp, 4), 3.0–3.58 (cp, 3), 3.68–4.02 (broad triplet, 1), 4.35–4.5 (t, 2), 4.8–5.08 (m, 1).

Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 57.08; H, 6.58; N, 8.26.

Methyl Hexahydro-2-methylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (13a). A solution of 2.7 g (31 mmol) of 1-pyrroline 1-oxide and 10 g of methyl crotonate was stirred at 25° for 24 hr. The excess methyl crotonate was removed under reduced pressure and the remaining liquid was distilled under vacuum. A clear liquid, 5.0 g (87% yield), was obtained: bp 77–79° (0.2 mm); ir (film) 5.74 (s), 8.31 μ (s); NMR (CCl_4) δ 4.25 (m, 1), 3.6–4.0 (m, 1), 3.7 (s, 3), 3.05 (m, 3), 1.5–2.0 (cp, 4), and 1.25 ppm (d, 3, J = 7 Hz).

Methyl 2-(Pyrrolidin-2-yl)-3-hydroxybutyrate. Catalytic hydrogenation using 160 mg of 10% Pd/C was carried out on a solution of 4.4 g (24 mmol) of methyl hexahydro-2-methylpyrrolo[1,2-*b*]isoxazole-3-carboxylate in 150 ml of methanol for 6 hr. The methanol was removed under vacuum and the residue taken up in ether and dried over calcium chloride. Evaporation of the ether under reduced pressure afforded a yellow liquid: 4.3 g, 96% yield; ir (film) 2.97 (m), 5.77 (s), 9.04 μ (s); NMR (CCl_4) δ 1.05 (d, 30), 1.4–1.97 (cp, 4), 2.32–2.96 (cp, 3), 3.18–3.38 (cp, 2), 3.56 (s, 3), 3.77–4.32 (cp, 2). The OH proton signal at 3.77–4.32 ppm disappeared on shaking with D_2O. The product also gave a positive iodoform test.

Methyl γ-Hydroxycrotonate (12b). An adaptation of the method of Rambaud[16] was employed. To a well-stirred mixture of 105 ml of water and 11.6 g (0.05 mol) of silver oxide was added 17.9 g (0.1 mol) of methyl γ-bromocrotonate. The mixture was stirred for 24 hr at 25° and then heated for 6 hr at 60°. Filtration and evaporation of the water under reduced pressure gave a liquid residue which was distilled under vacuum. A clear liquid was obtained: 6.0 g, 51%; bp 77–80° (0.3 mm) [lit.[16] bp 118° (15 mm)]; ir (film) 2.9 (s), 5.77 (s), and 5.98 μ (m); NMR (CCl_4) δ 3.65 (s, 3), 4.8 (s, 3), 6.0 (m, 1), 7.0 (m, 1).

Methyl Hexahydro-2-hydroxymethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (13b). To a stirred solution of 19 g (0.164 mol) of methyl γ-hydroxycrotonate in 65 ml of chloroform was added 14 g (0.164 mol) of 1-pyrroline 1-oxide under a nitrogen atmosphere. The mixture became warm on addition and was stirred for 4 hr at 25°, then refluxed for 12 hr. The chloroform was evaporated under vacuum and the residue chromatographed through 340 g of silica gel. Elution with chloroform, ethyl acetate, and acetone, respectively, afforded a yellow liquid: 26.4 g, 80%; ir (film) 2.96 (s), 5.73 (s), 6.91 μ (s); NMR (CCl_4) δ 1.5–2.25 (cp, 4), 3.0–3.4 (cp, 2), 3.45–4.1 (cp, 7), 4.2–4.5 (sextet, 1), 4.75 (s, 1, a hydroxyl proton). Careful chromatography of a small amount of this liquid through Florisil afforded a white, crystalline material on elution with benzene–ether. Recrystallization of the solid using ether afforded white prisms: mp 61–63°; ir (KBr) 3.12 (m), 5.75 (s), 6.94 μ (m); the NMR spectrum of the solid was the same as that of the liquid; NMR ($CDCl_3$) δ 4.35 (m, 1), 4.15 (s, 1, OH), 3.70 (s, 3) 3.50–4.00 (cp, 4), 3.18 (cp, 2), and 1.5–2.3 (cp, 4).

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.14; N, 6.96. Found: C, 53.42; H, 7.17; N, 7.20.

The Methanesulfonate of Methyl Hexahydro-2-hydroxymethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (13c). Methyl hexahydro-2-hydroxymethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (**13b,** 5 g; 24.8 mmol) was dissolved in 50 ml of anhydrous pyridine and the solution was cooled to −15°. To this solution was added 3.1 g (27.5 mmol) of methanesulfonyl chloride and the solution was kept at 0° for 3 hr. Small pieces of ice were then introduced until ca. 10 ml of water had been added. Ice–water (50 ml) was then added and the resulting aqueous solution was extracted with four 125-ml portions of chloroform. The combined chloroform extracts were shaken with 200 ml of a sodium bicarbonate solution. The chloroform layer was dried over anhydrous magnesium sulfate. Evaporation of the chloroform and pyridine under vacuum afforded a light yellow liquid: 6.5 g, 94% yield; ir (film) 5.75 (s), 6.92 (m), 7.38 (s), 8.50 μ (s); NMR ($CDCl_3$) δ 1.45–2.3 (cp, 4), 2.9–4.15 (cp, includes two singlets, 10), 4.2–4.4 (d, 2), 4.42–4.8 (cp, 1).

Methyl 2-Hydroxypyrrolizidine-1-carboxylate (19). Compound **13c,** the methanesulfonate of methyl hexahydro-2-hydroxymethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (6.58 g, 24 mmol), was dissolved in 50 ml of methanol and to this was added 300 mg of 10% Pd/C. The mixture was hydrogenated for 24 hr and filtered and the methanol was removed under vacuum. A light yellow oil remained which was dissolved in chloroform (150 ml) and shaken with 35 ml of a 1 *N* sodium hydroxide solution. The chloroform layer was dried over anhydrous magnesium sulfate. Evaporation of the chloroform left 4.2 g (95% crude yield) of a white solid. Recrystallization from hexane gave white crystals, mp 97–101°. Sublimation, followed by two successive recrystallizations, afforded white, powdery needles: mp 100–101°; ir (KBr) 2.90 (m), 5.77 (s), 8.61 μ (s); NMR ($CDCl_3$) δ 1.6–2.2 (cp, 4), 2.7–3.5 (cp, 5), 3.65–4.0 (cp, includes a singlet, 4), 4.35–4.65 (cp, 1), and 5.85 (s, 1, OH proton); mass spectrum *m/e* 185, 154, 136, 126, 108, 98, 83 (100), 70, and 55.

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.03; H, 8.31; N, 7.04.

Methyl Pyrrolizid-1-ene-1-carboxylate (20). To an ice-cooled, stirred solution of 11 g (50 mmol) of methyl 2-hydroxypyrrolizidine-1-carboxylate (**19**) in 100 ml of anhydrous pyridine was slowly added 11.3 g (73 mmol) of phosphorus oxychloride over a 15-min period. The dark brown solution was stirred for 12 min at 0° and the pyridine was then removed under reduced pressure, leaving a dark brown oil. This material was dissolved in 15 ml of ice-cold water and the solution made basic with potassium carbonate. The basic solution was then extracted with six 150-ml portions of ether and the combined ether extracts were dried over magnesium sulfate. Evaporation of the ether under vacuum afforded a dark brown liquid which distilled at reduced pressure. A light yellow liquid was obtained, bp 61–62° (0.05 mm), which was 90% pure as determined by GLC analysis using a 4 ft × 0.25 in. 15% QF-1 column at 140°: yield 3.7 g (35%); ir (film) 5.79 (s), 6.08 (m), 6.92 (m), 7.91 (s), 12.90 (m), 13.42 μ (m); uv λ_{max} (EtOH) 214 nm (ϵ 7375); NMR ($CDCl_3$) δ 6.70 (m, 1), 4.3 (m, 1), 3.75 (s, 3), 1.0–4.0 ppm (m, 8); picrate, mp 160–161° (methanol).

Anal. Calcd for picrate $C_{15}H_{16}N_4O_9$: C, 45.46; H, 4.07; N, 14.14. Found: C, 45.64; H, 4.26; N, 14.45.

***dl*-Supinidine (3).** A mixture of 700 mg of lithium aluminum hydride, 600 mg of aluminum chloride, and 50 ml of anhydrous ether was prepared according to the method of Jorgenson.[17]

To this cooled, stirred solution was slowly added 2.1 g (12.5 mmol) of methyl pyrrolizid-1-ene-1-carboxylate in 10 ml of ether. The mixture was then stirred for 15 min at room temperature and the excess hydride destroyed by adding successive portions of 1 ml of water, 2 ml of 10% sodium hydroxide solution, and 2 ml of water. The ether solution was then filtered and dried over magnesium sulfate. Evaporation of the ether afforded a light yellow liquid which was distilled through a short-path distillation apparatus to give 900 mg of a clear liquid which turned yellow on exposure to air. Gas–liquid chromatographic analysis using a 6 ft × 0.25 in. 20% FFAP-4% KOH column at 160° showed the material to be 50% *dl*-supinidine. The *dl*-supinidine was separated and collected using this column. The infrared spectrum was identical with that of natural supinidine. The NMR spectrum and the mass spectrum were also identical with those of the natural material: ir (neat) 3.2, 3.5, 6.8, 7.5, 8.4, 8.6, 9.0, 9.2, 9.5, 9.8, 11.2, 11.6, 12.4, and 12.7 μ; NMR ($CDCl_3$) 5.8 (br s, 1, OH), 5.50 (m, 1), 2.3–4.5 (cp, 7), 1.3–2.2 ppm (cp, 4); MS *m/e* 139, 138, 122, 111, 108, 94, and 80 (100); picrate mp 124–126° (methanol).

Anal. Calcd for picrate $C_{14}H_{16}N_4O_8$: C, 45.60; H, 4.38; N, 15.21. Found: C, 45.60; H, 4.42; N, 15.22.

Also separated on the above column, under the same conditions, were two compounds in a 3:2 ratio, which afforded ir spectra virtually identical with the published[8] spectrum of 1-hydroxymethylpyrrolizidine. A mass spectrum of the major constituent was virtually identical with the mass spectrum of trachelanthamidine (**21**).[21]

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Registry No.—**3**, 23185-51-5; **3** picrate, 56783-26-7; **4**, 24423-88-9; **5a** isomer A, 56783-27-8; **5a** isomer B, 56816-53-6; **5b** isomer A, 56783-28-9; **5b** isomer B, 56816-54-7; **6**, 56816-55-8; **7**, 56816-56-9; **9** isomer A, 56783-29-0; **9** isomer B, 56783-30-3; **11**, 56783-09-6; **12a**, 18707-60-3; **12b**, 4508-99-0; **13a**, 56783-10-9; **13b**, 32790-65-1; **13c**, 56783-11-0; **15**, 497-23-4; **16**, 56783-12-1; **19**, 56783-13-2; **20**, 56783-14-3; **20** picrate, 56783-15-4; diethyl maleate, 141-05-9; diethyl fumarate, 623-91-6; dimethyl fumarate, 624-49-7; methyl γ-bromocrotonate, 1117-71-1; *N*-bromosuccinimide, 128-08-5; methyl 2-(pyrrolidin-2-yl)-3-hydroxybutyrate, 56783-16-5; methanesulfonyl chloride, 124-63-0.

References and Notes

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