Novel Synthesis of 5,6,7,8-Tetrahydroindolizines[1]

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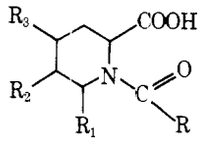
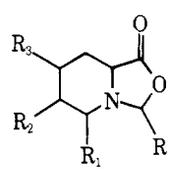
Several synthesis of 5,6,7,8-tetrahydroindolizines (THI) and octahydroindolizines (OHI) were developed in the past, with limitations in yields or substituents.[2]

We wish to report a new route to THI that allows the introduction of the desired substituents in all positions but 2. Since OHI can be obtained by reduction of THI this is also a new method of synthesis of OHI, some of which are biologically active natural compounds.[3-6]

The key step is the cycloaddition of ethyl propiolate to the easily available *N*-acyl-2-piperidinecarboxylic acid through a 1,3-dipolar intermediate[7,8] of type **2**. The cycloaddition of





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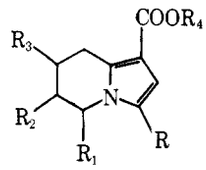
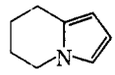
1, R = R_1 = R_2 = R_3 = H
3, R = R_1 = H; R_2–R_3 = C_6H_4
4, R = R_2 = R_3 = H; R_1 = COOH
5, R = CH_3; R_1 = R_2 = R_3 = H



6, R = R_1 = R_2 = R_3 = H; R_4 = C_2H_5
7, R = R_1 = H; R_2–R_3 = C_6H_4; R_4 = C_2H_5
8, R = CH_3; R_1 = R_2 = R_3 = H; R_4 = C_2H_5
9, R = R_2 = R_3 = H; R_1 = $COOC_2H_5$; R_4 = C_2H_5
10, R = CH_3; R_2 = R_3 = H; R_1 = $COOC_2H_5$; R_4 = C_2H_5
11, R = R_1 = R_2 = R_3 = R_4 = H



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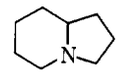

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propiolic esters to oxazolones has been described by Huisgen[7] as giving mixtures of 3- and 4-substituted pyrroles. Therefore, the cycloaddition of ethyl propiolate to substituted *N*-acyl-2-piperidinecarboxylic acids was expected to give 1- and 2-substituted THI, but as we found in pyrrolizidine synthesis[8] the reaction is regiospecific since only one isomer was isolated.

The NMR spectra of compounds **6** and **9** showed the presence of an AB quartet with $\Delta\nu$ values of 8 and 10 Hz, respectively, and therefore both are 1-substituted THI. We have found a smaller $\Delta\nu$ value for 1-carboethoxy-6,7-dihydropyrrolizidine (5 Hz),[8] and compound **7** has the same chemical shift for both protons as similar compounds reported in the literature.[9]

Decarboethoxylation of **6** was accomplished in 80% yield by hydrolysis and decarboxylation (**11** and **12**). A diester is isolated (**9, 10**) when the substituent on the 2-piperidinecarboxylic acid is a second carboxylic group because transesterification occurs owing to the sevenfold molar excess of ethyl propiolate.

By using this sequence of reactions δ-coniceine (**13**) (octahydroindolizine) was prepared in 67% overall yield after five steps, starting from commercially available 2-piperidinecarboxylic acid.

Experimental Section

Melting points were measured on a Kofler micro hot stage apparatus; infrared spectra were recorded using a Perkin-Elmer 735 B spectrometer. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R 12 spectrometer. Microanalyses were performed by Mrs. Martha Casanello of this university. Thin layer chromatography (TLC) and preparative thick layer chromatography were performed on silica gel GF-254.

***N*-Formyl-2-piperidinecarboxylic Acid (1).** Acetic anhydride (35 g) was added dropwise to a stirred and cooled (0–5 °C) solution of 2-piperidinecarboxylic acid (6.45 g, 0.05 mol) in 50 ml of formic acid (98%). Stirring was continued for 1 h at room temperature. Water (40 ml) was added and the solution evaporated to dryness to give 7.89 g (98%) of crystalline **1**. Recrystallization from ethanol gave analytically pure **1**: mp 85–87 °C; NMR ($CDCl_3$) δ 8.85 (s, 1, –COOH), 8.15 (s, 1, –COH), 5.30–3.30 (m, 3, protons on C_2 and C_6), 2.50–1.50 (m, 6, protons on C_3, C_4, and C_5); IR (Kbr) 1720, 1710 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 6.36; N, 8.91. Found: C, 53.40; H, 6.20; N, 9.03.

2-Formyl-3-carboxy-1,2,3,4-tetrahydroisoquinoline (3) was prepared in 98% yield by the same procedure, starting from 3-carboxy-1,2,3,4-tetrahydroisoquinoline prepared by us according to the procedure of Julian et al.[10] (recrystallized from ethanol): mp 114–116 °C; NMR ($CDCl_3$) δ 9.60 (s, 1, –COOH), 8.60 (s, 1, –CHO), 7.30 (s, 4, aromatic protons), 5.25 (t, 1, J = 6 Hz, proton on C_3), 4.90 (s, 2, protons on C_2), 3.45 (d, 2, J = 6 Hz, protons on C_4); IR (KBr) 1715, 1720 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_3 \cdot H_2O$: C, 59.1; H, 5.90; N, 5.95. Found: C, 59.10; H, 6.10; N, 6.05.

***N*-Formyl-2,6-piperidindicarboxylic acid (4)** was prepared in 96% yield by the same procedure, starting from 2,6-piperidinedicarboxylic acid prepared by us according to Andersson and Soine[11] (recrystallized from ethanol), mp 190–192 °C. Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.47; N, 6.96. Found: C, 47.65; H, 5.60; N, 6.83.

***N*-Acetyl-2-piperidinecarboxylic Acid (5).** The solution of 0.645 g (5 mmol) of 2-piperidinecarboxylic acid in 10 ml of acetic anhydride was stirred for 1 h. Water (10 ml) was added and the solution evaporated to dryness to give an oil. Chromatography on silica gel (15 g) and elution with dichloromethane–methanol (9:1) afforded **5** as a colorless oil (509 mg, 64%): NMR ($CDCl_3$) δ 8.60 (s, 1, COOH), 5.70–4.20 (m, 3, protons on C_2 and C_6), 3.70 (m, 2, protons on C_3), 2.30 (s, 3, CH_3–), 2.05–1.30 (m, 4, protons on C_4 and C_5). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.14; H, 7.60; N, 8.19. Found: C, 56.23; H, 7.68; N, 8.08.

Ethyl 5,6,7,8-Tetrahydroindolizine-1-carboxylate (6). A solution of 1.1 g (7 mmol) of **1** and 4.3 ml (50 mmol) of ethyl propiolate in 9 ml of acetic anhydride was heated for 2 h at 120 °C under a nitrogen atmosphere. The excess reagents were stripped to give an oil. Purification by column chromatography on 30 g of silica gel (elution with benzene–ethyl acetate, 1:1) gave 1.12 g (82%) of **6**: NMR ($CDCl_3$) δ 6.42 (AB quartet, 2, $\Delta\nu$ = 8, J = 3 Hz, olefinic protons), 4.25 (q, 2, J = 7 Hz, $-OCH_2-$), 3.88 (broad t, 2, protons on C_5), 3.05 (broad t, 2, protons on C_8), 1.85 (m, 4, protons on C_6 and C_7), 1.35 (t, 3, J = 7 Hz, $-CH_3$). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 67.00; H, 7.60; N, 7.10. Found: C, 67.20; H, 7.50; N, 6.80.

Ethyl benz[*f*]-5,10-dihydroindolizine-1-carboxylate (7) was prepared from **2** as **5** from **1**, but the reaction was carried out at 90 °C. The residue was purified by TLC (CH_2Cl_2) giving a 70% yield of **7**: NMR (D_2O) δ 7.30 (m, 4, aromatic protons), 6.68 (s, 2, olefinic protons), 5.08 (s, 2, protons on C_5), 4.35 (m, 6, $-OCH_2-$ and protons on C_{10}), 1.40 (t, 3, $-CH_3$). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 75.20; H, 6.09; N, 5.69. Found: C, 75.35; H, 6.14; N, 5.50.

Ethyl 3-Methyl-5,6,7,8-tetrahydroindolizine-1-carboxylate (8). A solution of 171 mg (1 mmol) of **5** and 0.5 ml (5 mmol) of ethyl propiolate in 1.5 ml of acetic anhydride was heated for 3 h at 120 °C under a nitrogen atmosphere. Solvents were evaporated to dryness giving an oily residue that was chromatographed on 5 g of silica gel (elution with dichloromethane) to give 130 mg (67%) of **8**: NMR ($CDCl_3$) δ 6.70 (s, 1, olefinic proton on C_2), 4.35 (q, 2, J = 7 Hz, $-OCH_2-$), 3.80 (m, 2, protons on C_5), 3.15 (m, 2, protons on C_8), 2.15 (s, 3, $-CCH_3$), 1.85 (m, 4, protons on C_6 and C_7), 1.4 (t, 3, J = 7 Hz, $-CH_3$). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.59; H, 8.26; N, 6.76. Found: C, 69.70; H, 8.40; N, 6.80.

Diethyl 5,6,7,8-Tetrahydroindolizine-1,5-dicarboxylate (9). The procedure for the preparation of **9** was the same as the one described above, except that the residue was purified by TLC (CH_2Cl_2) affording 45% of the diester **9**: oil; NMR ($CDCl_3$) δ 6.50 (AB quartet,

2, $\Delta\nu$ = 10, J = 3 Hz, olefinic protons), 4.80 (t, 1, J = 4 Hz, proton on C_5), 4.40 (2 q superposed, 4, J = 7 Hz, $-OCH_2-$), 3.15 (m, 2, protons on C_8), 2.05–1.60 (m, 4, protons on C_6 and C_7), 1.35 (2 t superposed, 6, $-CH_3$). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 68.57; H, 7.75; N, 5.71. Found: C, 68.42; H, 7.80; N, 5.60.

Diethyl 3-Methyl-5,6,7,8-tetrahydroindolizine-1,5-dicarboxylate (10). It was prepared in 70% yield from 2,6-piperidinedicarboxylic acid as described for **9**. An analytical sample was obtained by TLC (CH_2Cl_2): NMR ($CDCl_3$) δ 6.30 (s, 1, proton on C_2), 4.80 (m, 1, proton on C_5), 4.25 (q, 4, J = 7 Hz, $-OCH_2-$), 3.40–1.60 [m, 9, $-CH_3$ and $-(CH_2)_3-$], 1.35 (t, 6, J = 7 Hz, $-CH_3$). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.52; H, 7.52; N, 5.01. Found: C, 64.60; H, 7.75; N, 5.10.

5,6,7,8-Tetrahydroindolizine-1-carboxylic Acid (11). A solution of 386 mg (2 mmol) of **6** and 700 mg of KOH in 9 ml of methanol–water (2:1) was refluxed for 3 h, cooled, diluted with water (20 ml), and acidified to pH 1. The precipitate was filtered and dried giving 300 mg (90%) of **11** as colorless crystals. After recrystallization from ethanol it showed mp 151–153 °C dec; NMR ($CDCl_3$) δ 11.00 (broad s, 1, exchangeable with D_2O= –COOH), 6.68 (AB quartet, 2, $\Delta\nu$ = 10, J = 3 Hz, olefinic protons), 4.08 (broad t, 2, protons on C_5), 3.23 (broad t, 2, protons on C_8), 1.85 (m, 4, protons on C_6 and C_7). Anal. Calcd for $C_9H_{11}NO_2$: C, 66.45; H, 6.66; N, 8.48. Found: C, 66.20; H, 6.69; N, 8.45.

5,6,7,8-Tetrahydroindolizine (12). A thin-walled glass tube containing 820 mg (5 mmol) of **11** was introduced in a bath at 240 °C until gas evolution ceased (5 min), leaving a brown oil. Chromatography on 60 g of silica gel using benzene as eluent afforded 520 mg (88%) of **12** as a colorless oil, which was homogeneous on TLC (benzene–ethyl acetate, 1:1): NMR ($CDCl_3$) δ 6.50 (d, 1, proton on C_1), 6.10 (t, 1, proton on C_2), 5.80 (d, 1, proton on C_3), 3.95 (broad t, 2, protons on C_5), 2.80 (broad t, 2, protons on C_8), 1.85 (m, 4, protons on C_6 and C_7). This compound was not stable enough to be analyzed.

Octahydroindolizine (δ-Coniceine, 13). A solution of 242 mg (2 mmol) of **12** in 20 ml of ethanol was hydrogenated for 24 hr at 3 atm using 200 mg of 10% palladium on carbon. The catalyst was filtered off and the filtrate evaporated, giving 240 mg (98%) of pure **13**. The picrate, recrystallized from methanol, had mp 225–228 °C (lit.[4] 224–228 °C). Anal. Calcd for $C_{14}H_{18}N_4O_7$: C, 47.20; H, 5.60; N, 15.7. Found: C, 47.30; H, 5.50; N, 15.8.

Registry No.—**1**, 54966-20-0; **2**, 61009-74-3; **3**, 61047-23-2; **4**, 61009-75-4; **5**, 61009-76-5; **6**, 61009-77-6; **7**, 61009-78-7; **8**, 61009-79-8; **9**, 61009-80-1; **10**, 61009-81-2; **11**, 61009-82-3; **12**, 13618-88-7; **13**, 13618-93-4; **13** picrate, 5210-66-2; 2-piperidinecarboxylic acid, 535-75-1; ethyl propiolate, 623-47-2; 3-carboxy-1,2,3,4-tetrahydroisoquinoline, 35186-99-3; 2,6-piperidinedicarboxylic acid, 499-82-1.

References and Notes

(1) This investigation was supported by grants from the National Research Council (Argentina).
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A Convenient Synthesis of (±)-Glaziovine and (±)-*N*-Methyloreoline

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Preferential O-demethylation of isoquinolines with mineral acids under controlled conditions has provided access to a variety of phenolic isoquinoline alkaloids.[1] However, this process cannot be applied directly to proaporphine alkaloids containing a dienol or dienone system since these rearrange in the presence of strong acids to aporphines; e.g., pronuciferine (**1**) undergoes the dienone–phenol rearrangement in aqueous sulfuric acid to give 1,2-dimethoxy-10-hydroxyaporphine (**2**).[2] We have found that selective O-demethylation of amuronine (**3**) and tetrahydropronuciferine (**7**) proceeds smoothly in refluxing hydrochloric acid to furnish the corre-