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New Approaches to the Pyrrolizidine Ring System: Total Synthesis of (±)-Isoretronecanol and (±)-Trachelanthamidine[1,2]

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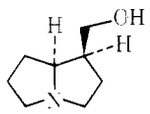
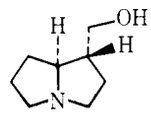
The family of alkaloids containing the pyrrolizidine ring system is attracting much attention[3] because of the wide range of physiological properties exhibited by these compounds.[4] We report the total synthesis of the two simplest members of this series of alkaloids: the diastereomers of 1-hydroxymethylpyrrolizidine, isoretronecanol (1), and trachelanthamidine (2).

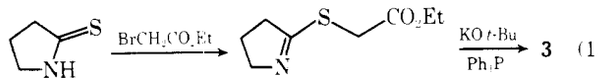


1



2

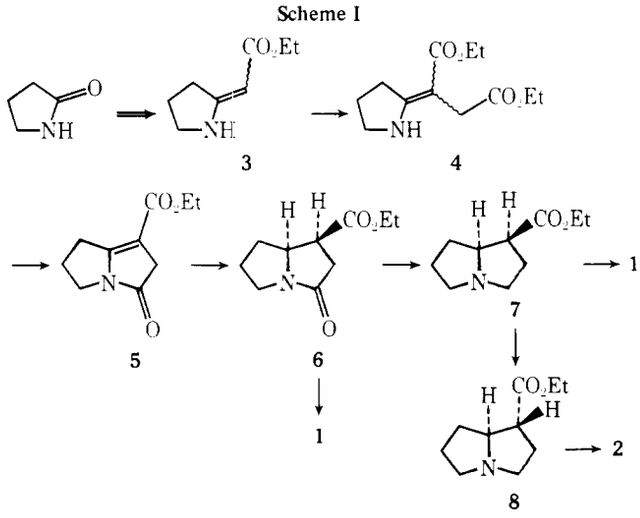
The basic strategy for the syntheses is outlined in Scheme I. Thus, pyrrolidone is converted into thiopyrrolidone which yields the enamine ester **3** by the two-step procedure developed by Eschenmoser[5] (eq 1). Reaction of compound **3** with



(1)

lithium diisopropylamide (LDA) in tetrahydrofuran (THF) followed by ethyl bromoacetate gives the diester **4** in 74% yield.[6] Cyclization with potassium hydride at 0 °C in THF affords the lactam **5** in nearly quantitative yield. Conversion

Scheme I



of this unsaturated lactam into the key intermediate **7** requires reduction of the lactam carbonyl as well as the enamine double bond; however, direct reduction of the lactam carbonyl proves difficult. Fortunately, catalytic reduction proceeds smoothly to give lactam ester **6** which undergoes further reduction with excess lithium aluminum hydride ($LiAlH_4$) to give isoretronecanol.

Selective reduction of lactam **6** would give ethyl isoretronecanolate (**7**) which is reported to epimerize upon heating with base to give the more stable diastereomer **8**[7] which will yield trachelanthamidine after reduction with $LiAlH_4$. Several attempts to carry out this selective reduction (**6** → **7**) with diborane[8] were complicated by the difficulty in destroying the amine–boron complex after the reduction was complete. In every attempt much product was lost during the workup. By using phosphoryl chloride/sodium borohydride[9] instead of diborane, however, this problem was circumvented and **6** was reduced to ester **7** in 66% yield. This completes a formal synthesis of trachelanthamidine.

Experimental Section

Proton nuclear magnetic resonance spectra were recorded on a Varian T-60 instrument. Carbon 13 nuclear magnetic resonance spectra were recorded on a JEOL PFT-100 spectrometer. All chemical shifts are reported in ppm downfield from tetramethylsilane (0.0) as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer and are reported in cm^{-1} (calibration with 1601 cm^{-1} polystyrene peak). Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

Reagent grade THF was distilled from potassium prior to use. Other anhydrous solvents were distilled from CaH_2 and stored over 4A molecular sieves until use.

Combustion analyses were performed by Atlantic Microlabs, Atlanta, Ga.

Preparation of Thiopyrrolidone. Phosphorus pentasulfide (24.4 g, 110 mmol) and 300 mL of anhydrous xylene were mixed in a 1000-mL flame-dried three-neck flask equipped with an efficient mechanical stirrer. Pyrrolidone (42.5 g, 500 mmol) was added in one portion and the solution was allowed to stir at room temperature for 20 min. A dark brown oil separated after the reaction mixture was heated at 130 °C for 30 min with vigorous stirring. The hot solution was filtered through a coarse sintered glass funnel. White crystals formed immediately in the filtrate. Fresh xylene (100 mL) was added to the oily residue and heated to 130 °C for 20 min followed by a hot filtration. This process was repeated once more and the combined xylene was allowed to cool. White crystals were collected by filteration and air dried to give 32.2 g (64%) of thiopyrrolidone: mp 114–115 °C (lit.[5] mp 114–115 °C) after recrystallization from $CHCl_3$/hexane; NMR ($CHCl_3$) 1.95–2.5 (2 H, m), 2.85 (2 H, unsym t, J = 8 Hz), 3.7 (2 H t, J = 8 Hz), 8.5 (1 H, br s); IR (NaCl) 3415 (sharp), 3120 (broad), 1547, 1520 cm^{-1}.

Alkylation of Thiopyrrolidone with Ethyl Bromoacetate. Ethyl bromoacetate (53.2 g, 319 mmol) was added dropwise to thiopyrrolidone (32.2 g, 319 mmol) dissolved in 250 mL of CH_2Cl_2 at 0–10 °C. The reaction mixture was allowed to warm gradually to room temperature and was stirred for 4 h. Solid $NaHCO_3$ was added in portions until further addition did not cause CO_2 evolution. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated to give the thioimino ester (60.0 g, 100%): bp 115–120 °C (1.2 mm); NMR ($CDCl_3$) 1.3 (3 H, t, J = 7 Hz), 1.8–2.4 (2 H, m), 2.5–2.9 (2 H, m), 3.7–4.1 (4 H, m and s), 4.3 (2 H, q, J = 7 Hz); IR (NaCl) 2950, 2850, 1735, 1580 cm^{-1}.

Preparation of Enamine Ester 3. The thioimino ester (60.0 g, 319 mmol), triphenylphosphine (334 g, 1.28 mol), and 550 mL of anhydrous xylene were combined in a flame-dried 1000-mL three-neck flask. A solution of KO-*t*-Bu (3.57 g, 32.0 mmol) in 20 mL of *tert*-butyl alcohol was added dropwise and the reaction mixture was stirred at room temperature for 4 h and then refluxed for 60 h. This was cooled and extracted with 150 mL of 10% HCl three times. The combined aqueous extracts were washed with 50 mL of ether three times, neutralized with solid $NaHCO_3$, and extracted with four 100-mL portions of CH_2Cl_2. The combined CH_2Cl_2 layers were washed twice with 80 mL of brine, dried over $MgSO_4$, and concentrated to give a crude brown solid which was sublimed (40 °C, 0.1 mm) to yield **3** (37.6 g, 76%): mp 62–63 °C; NMR ($CDCl_3$) 1.25 (3 H, t, J = 7 Hz), 2.0 (2 H, t, J = 6 Hz), 2.6 (2 H, t, J = 7 Hz), 3.6 (2 H, t, J = 6 Hz), 4.2 (2 H, q,

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J = 7 Hz), 4.58 (1 H, s), 7.7–8.2 (1 H, br N–H); IR (NaCl) 3375 (s, weak), 3020, 2980, 1700 (strong), 1600 cm^{-1} (strong).

Anal. Calcd for $C_8H_{13}O_2N$: C, 61.94; H, 8.39; O, 20.64; N, 9.03. Found: C, 61.95; H, 8.41; O, 20.61; N, 9.03.

Preparation of Diester 4. *n*-Butyllithium/hexane (102 mL of 2.3 N, 234 mmol) was added dropwise to a flame-dried 1000-mL three-neck flask containing diisopropylamine (25.6 g, 254 mmol) and 700 mL of THF at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was cooled to −78 °C and enamine ester **3** (30.2 g, 195 mmol) in 100 mL THF was added dropwise over 40 min followed by a 30-min stirring period. Ethyl bromoacetate (48.8 g, 293 mmol) was added and stirring was continued for 2 h. The reaction mixture was allowed to warm to 0 °C for 2 h and acidified with 5% HCl. The THF was removed with a rotary evaporator and the residue was washed twice with ether. The aqueous layer was neutralized with excess solid $NaHCO_3$ and then extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were washed twice with brine, dried over $MgSO_4$, and concentrated to give the diester as a brown solid (34.7 g, 74%). This material is adequate for the cyclization to **5** but can be recrystallized from $CHCl_3$/hexane to give analytically pure material: mp 96.5–98 °C; NMR ($CDCl_3$) 1.3 (6 H, t, J = 7 Hz), 1.8–2.3 (2 H, m), 2.7 (2 H, t, J = 7 Hz), 3.25 (2 H, s), 3.6 (2 H, t, J = 7 Hz), 4.2 (4 H, q, J = 7 Hz), 8.1–8.5 (1 H, br s); IR (KBr) 3350 (w), 1720, 1655, 1580 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}O_4N$: C, 59.50; H, 7.85; O, 26.45; N, 6.2. Found: C, 59.87; H, 8.02; O, 26.36; N, 5.75.

Preparation of Lactam 5. Potassium hydride (6.5 g, 39 mmol, of a 24% oil dispersion) was washed four times with benzene in a flame-dried 500-mL three-neck flask and then suspended in 150 mL of anhydrous THF at 0 °C. The diester **4** (7.23 g, 30.0 mmol) in 70 mL of THF was added over a 20-min period and the reaction mixture was stirred at 0 °C for another 25 min. Aqueous 10% HCl was added to pH 6 and the THF was removed with a vacuum pump. The residue was dissolved in 50 mL of water and extracted with three 50-mL portions of $CHCl_3$. The combined $CHCl_3$ layers were washed with water (2 × 250 mL), dried over $MgSO_4$, and concentrated to give the lactam (5.67 g, 97%) as a light brown solid. Recrystallization from $CHCl_3$/hexane gave an analytical sample: mp 88–89 °C; NMR ($CDCl_3$) 1.3 (3 H, t, J = 7 Hz), 2.2–2.6 (2 H, m), 2.8–3.2 (2 H, m), 3.5–3.8 (4 H, m), 4.3 (2 H, q, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.702, 163.553, 161.485, 98.800, 59.620, 41.514, 41.210, 26.640, 25.664, 14.569.

Anal. Calcd for $C_{10}H_{15}O_3N$: C, 61.54; H, 6.67; O, 24.61; N, 7.18. Found: C, 61.61; H, 6.70; O, 24.49; N, 7.20.

Reduction of Lactam 5 to Lactam 6. Lactam **5** (1.16 g, 6.00 mmol) was dissolved in 15 mL of absolute ethanol and a catalytic amount of 10% Pd/C was added. This was maintained under hydrogen at 1 atm and room temperature overnight (20 h) and filtered through celite and the filtrate was concentrated to give 1.15 g (98%) of the lactam: bp 164–165 °C (0.1 mm); NMR ($CDCl_3$) δ 1.3 (3 H, t, J = 7 Hz), 1.7–2.4 (4 H, m), 2.7–2.9 (2 H, unsym d, J = 6 Hz), 3.0–3.9 (3 H, m), 4.0–4.4 (3 H, q and m, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 174.039, 171.600, 62.729, 60.961, 41.697, 39.868, 36.089, 27.432, 26.432, 14.260; IR (NaCl) 2970, 2900, 1730, 1690, 1190 cm^{-1}.

Preparation of Isoretronecanol (1). Lactam **6** (0.788 g, 4.00 mmol) in 5 mL of THF was added over a 5-min period to a flame-dried 50-mL three-neck flask containing $LiAlH_4$ (0.304 g, 8.00 mmol) in 10 mL of THF. The reaction mixture was refluxed for 17 h and the THF was removed by distillation. Ether (10 mL) and water (0.66 mL) were added and the mixture was stirred for 8 h. This was filtered and the filtrate was concentrated and distilled to give 0.35 g (62%) of isoretronecanol as a clear liquid: bp 120–123 °C (0.1 mm); picrate mp 188–189 °C (lit.[10] mp 188–190 °C); NMR ($CDCl_3$) δ 1.4–2.2 (6 H, m), 2.3–2.6 (6 H, m), 3.8 (2 H, d, J = 7 Hz), 4.0–4.5 (1 H, br s, OH); ^{13}C NMR ($CDCl_3$) δ 66.131, 62.571, 55.597, 54.036, 44.379, 27.310, 26.481, 25.945.

Preparation of Ethyl Isoretronecanolate 7. Lactam **6** (1.15 g, 5.80 mmol) was mixed in a flame-dried three-neck flask with phosphoryl chloride (6 mL) at room temperature for 40 min. Excess $POCl_3$ was removed under vacuum and the residue was dissolved in 4 mL of dimethoxyethane at 0 °C. Sodium borohydride (0.444 g, 11.6 mmol) in 18 mL of absolute ethanol was added at such a rate that the reaction remained vigorous. The reaction mixture was allowed to warm up to room temperature for 30 min and then acidified to pH 2 with 5% HCl. The ethanol was removed (rotary evaporator), the reaction mixture was stirred for 30 min, and 25 mL of water was added. This was extracted with three 10-mL portions of ether and the aqueous phase was basified to pH 9 at 0 °C with solid K_2CO_3 and extracted with four 15-mL portions of ether. The combined ether layers were washed with water, dried over $MgSO_4$, concentrated, and distilled to give ethyl isoretronecanolate (0.70 g, 66%) as a clear liquid: bp 113–115 °C (0.1 mm); picrate mp 120–121 °C (lit.[11] mp 119–121 °C); NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 1.8–2.2 (7 H, m), 2.6–3.4 (4 H, m), 3.5–3.9 (1 H, m), 4.2 (2 H, q, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.369, 65.838, 60.181, 55.584, 53.695, 47.452, 28.481, 26.774, 26.384, 14.289.

Registry No.—1, 18929-90-3; 1·picrate, 61259-90-3; **2**, 18929-91-4; **3**, 25219-53-8; **4**, 67800-66-2; **5**, 67800-67-3; **6**, 67800-68-4; **7**, 34951-60-5; **8**, 34951-61-6; thiopyrrolidone, 2295-35-4; ethyl[(3,4-dihydro-2*H*-pyrrol-5-yl)thio]acetate, 4226-71-5; phosphorus pentasulfide, 1314-80-3; pyrrolidone, 616-45-5; ethyl bromoacetate, 105-36-2.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of Yeong-Ho Chang, University of Georgia, 1978.
(2) Presented at the 30th Southeastern Regional Meeting of the American Chemical Society, Savannah, Ga., Nov. 8–10, 1978.
(3) For example, see the following: (a) N. J. Leonard and T. Sato, *J. Org. Chem.*, **34**, 1066 (1969); (b) R. V. Stevens, Y. Luh, and J. T. Sheu, *Tetrahedron Lett.*, 3799 (1976); (c) S. Danishefsky, R. McKee, and R. K. Singh, *J. Am. Chem. Soc.*, **99**, 4783 (1977).
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New Reactions and Reagents. 7. Unusual Reactivity of *N*-Iminoglycyl Peptides. Formation of Substituted Imidazol-4-ones[1]

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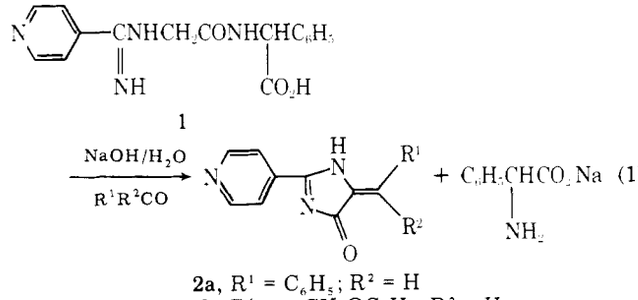
N-(4-Pyridylimino)glycylphenylglycine (**3**) undergoes a novel fragmentation in aqueous alkaline medium which in the presence of a carbonyl compound proceeds to give the corresponding 1,5-dihydro-2-(4-pyridyl)-5-(alkyl- or arylmethylene)-4*H*-imidazol-4-one (**2**) and phenylglycine (eq 1). The structure of **2a–d** is based on IR (–CO–, ~1700 cm^{-1}; –C=N–,



2a, R^1 = C_6H_5; R^2 = H
b, R^1 = *p*-$CH_3OC_6H_4$; R^2 = H
c, R^1 = R^2 = CH_3
d, R^1, R^2 = –$(CH_2)_5$–

~1650 cm^{-1})[2] and ^1H NMR, as well as mass spectral (Table I) and ^{13}C-NMR (Table II) assignments.[3] The formation of **2** from **1** is most likely occurring via the generation of 1,5-dihydro-2-(4-pyridyl)-4*H*-imidazol-4-one (**6**)[4] and its subsequent reaction with the added carbonyl compound (Scheme I).[5,6] It is worthy of note that only one stereoisomer is isolated in the case of **2a,b**.[7] The *Z* stereochemistry assigned for these two compounds is based on close agreement between the calculated and observed shifts for their olefinic protons.[8]

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