640 mg of dione **37** recrystallized from acetone–water: mp 180–183 °C; ν_{max} 1700 cm^{-1}; NMR τ 9.15 (CH_3-18), 8.73 (CH_3-19).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.3; H, 10.1.

Reduction of Diones 3, 4, and 37. Standard conditions, as described in the third epxeriment, were employed in the reduction of the title ketones. The 3,17a-dione *3* (150 mg) gave *D*-homo-5α-androstane-3β,17aβ-diol (**38**, 135 mg) [mp 199–202 °C (lit.[4] 219–220 °C; NMR τ 9.18 (CH_3-19 and CH_3-18), 6.80 (m, $W_{1/2}$ = 14 Hz, H-17a), 6.50 (m, $W_{1/2}$ = 24 Hz, H-3)], and 350 mg of the 3,17-dione **4** gave after separation on PLC *D*-homo-5α-androstane-3β,17β-diol (**39**, 155 mg) from acetone–hexane [mp 220–222 °C; ν_{max} 3600 cm^{-1}; NMR τ 9.20 (CH_3-19), 8.93 (CH_3-18), 6.30 (m, $W_{1/2}$ = 18 Hz, H-3), 6.00 (m, $W_{1/2}$ = 8 Hz, H-17) (Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.1. Found: C, 78.0; H, 11.0.)] together with 65 mg of *D*-homo-5α-androstane-3β,17α-diol (**40**) from acetone–hexane: mp 176–178 °C; ν_{max} 3600 cm^{-1}; NMR τ 9.20 (CH_3-19 and CH_3-18), 6.50–6.00 (H-3 and H-17) (Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.1. Found: C, 78.2; H, 11.3.). Finally 130 mg of 3,7-dione **37** gave *D*-homo-5α-androstane-3β,7α-diol (**41**, 90 mg) recrystallized from methanol: mp 205–208 °C; ν_{max} 3600 cm^{-1}; NMR τ 9.20 (CH_3-19), 9.19 (CH_3-18), 6.37 (m, $W_{1/2}$ = 18 Hz, H-3), 6.00 (m, $W_{1/2}$ = 8 Hz, H-7) (Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.4; H, 11.1. Found: C, 77.9; H, 11.1.).

Registry No.—**1**, 26729-16-8; **2**, 51057-15-9; **3**, 61231-79-6; **4**, 20377-71-3; **5**, 61258-86-4; 71aα-**6**, 61231-80-9; 17aβ-**6**, 61277-41-6; 17aα-**7**, 61249-41-0; 17aβ-**7**, 61231-81-0; 17aα-**8**, 61231-82-1; 17aβ-**8**, 61231-83-2; **9**, 30040-16-5; **10**, 26729-18-0; **11**, 61277-42-7; **12**, 61231-84-3; **13**, 29172-67-6; **15**, 29172-56-3; **16**, 61231-85-4; **17**, 61231-86-5; **18**, 61231-87-6; **19**, 61231-88-7; **20**, 61231-89-8; **21**, 60243-73-4; **22**, 61231-90-1; **23**, 61231-91-2; **24**, 61231-92-3; **25**, 61231-93-4; **26**, 61231-94-5; **27**, 61231-95-6; **28**, 61231-96-7; **29**, 61231-97-8; **30**, 61231-98-9; **31**, 61231-99-0; **32**, 31552-74-6; **33**, 61232-00-6; **34**, 61232-01-7; **35**, 61232-02-8; **36**, 61232-03-9; **37**, 61232-04-0; **38**, 60269-01-4; **39**, 61232-05-1; **40**, 61232-06-2; **41**, 61232-07-3; benzaldehyde, 100-52-7; acetic anhydride, 108-24-7; *p*-toluenesulfonyl chloride, 98-59-9; 3β-hydroxy-*D*-homoandrost-5-ene, 31552-60-0; *D*-homo-5α-androstane-3β,6β-diol, 61231-97-8; *D*-homo-5β-androstane-3β,6β-diol, 61232-08-4; oxalic acid, 144-62-7.

References and Notes

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A New Synthesis of the Pyrrolizidine Alkaloids (±)-Isoretronecanol and (±)-Trachelanthamidine[1]

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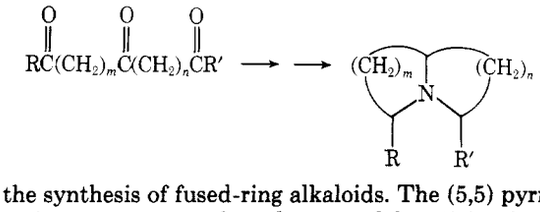
The pyrrolizidine alkaloids (±)-isoretronecanol (**1a**) and (±)-trachelanthamidine (**1b**) were synthesized using as a key step the oxidation of a carbon–carbon double bond and subsequent in situ reductive amination with sodium cyanoborohydride. 2-Carbethoxycyclohept-4-en-1-one (**2b**) was synthesized via three independent routes and was utilized as the key intermediate. Ozonolysis followed by reduction of the ozonide and reaction with NH_4NO_3–$NaBH_3CN$ afforded carbethoxypyrrolizidines **5a** and **5b** in 7% yield along with pyrrole **6** in 14% yield. Reductive amination of **2b** to give amino esters **6a** and **6b** followed by OsO_4–$NaIO_4$ oxidation and $NaBH_3CN$ reductive cyclization gave **4a** and **4b** in 35% yield. Reduction of **4a** and **4b** with $LiAlH_4$ gave the alkaloids (±)-isoretronecanol (**1a**) and (±)-trachelanthamidine (**1b**), respectively.

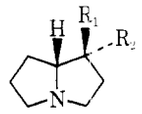
The reaction of aldehydes and ketones with an amine and sodium cyanoborohydride ($NaBH_3CN$) has been described as a general method for the synthesis of substituted amines,[2,3] and it has been applied to the formation of nitrogen-containing rings in alkaloid syntheses.[4,5] We were interested to know whether this method could be generalized to the insertion of nitrogen via reductive amination into an acyclic tricarbonyl compound, viz.



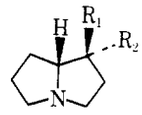
for the synthesis of fused-ring alkaloids. The (5,5) pyrrolizidine ring system was selected as a model, anticipating that intramolecular reactions in a polyfunctional acyclic precursor would be maximized for the five-membered rings. We report here a successful example of this synthetic approach applied to (±)-isoretronecanol (**1a**)[6] and (±)-trachelanthamidine (**1b**).[7]

Results and Discussion

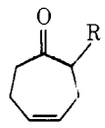
The synthesis was based on β-keto ester **2b** as the key intermediate, inasmuch as appropriate oxidation of the olefin would provide the necessary keto dialdehyde with which to test the reductive cyclization reaction. The diastereomeric pyrrolizidines thus formed would contain the requisite substituent for facile reduction to **1a** and **1b**. Cyclohept-4-en-1-one (**2a**) was prepared by two separate routes based on published procedures.[8–12] However, the relative complexity and poor overall yields from these routes prompted investigation of a more direct route to β-keto ester **2b** utilizing the alkylation of a β-keto ester dianion.[13] Reaction of the dianion of methyl acetoacetate[13] with excess 1,4-dichloro-*cis*-2-butene[14] in THF at 0 °C afforded a 25% yield of monoalkylated product **3**. Cyclization of keto ester **3** by gradual addition over



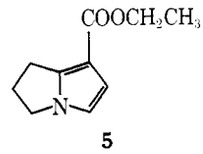
1a, R_1 = H; R_2 = CH_2OH
b, R_1 = CH_2OH; R_1 = H_A



4a, R_1 = H; R_2 = $COOCH_2CH_3$
b, R_1 = $COOCH_2CH_3$; R_2 = H



2a, R = H
b, R = $COOCH_2CH_3$
c, R = $COOCH_3$



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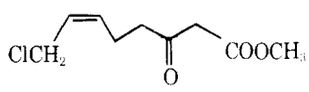
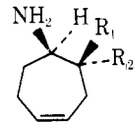


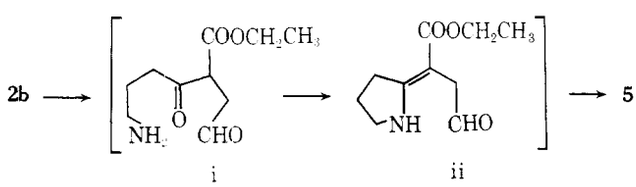
3



6a, R_1 = H; R_2 = $COOCH_2CH_3$
b, R_1 = $COOCH_2CH_3$; R_2 = H

24 h to sodium methoxide in refluxing methanol led to the desired keto ester **2c** in 60% yield. When this alkylation–cyclization sequence was repeated using 1,4-dichlorobutane as the alkyl halide, the corresponding cycloheptanone was not obtained, suggesting that the cis double bond is essential to this reaction.

Having available a two-step sequence for the preparation of the 2-carbethoxycyclohept-4-en-1-ones, attention was directed to the oxidation of the carbon–carbon double bond to generate the desired tricarbonyl intermediate. Reaction of **2b** with osmium tetroxide–sodium metaperiodate at 0 °C, followed by treatment of the crude product with excess ammonium nitrate and sodium cyanoborohydride, afforded no isolable products. However, when keto ester **2b** was ozonized in methanol at −78 °C and the crude ozonide reduced with dimethyl sulfide and then reacted with ammonium nitrate and sodium cyanoborohydride, a basic fraction was obtained from which the pyrrolizidine esters **4a** and **4b** were isolated as a 1:1 mixture in 7% yield. Workup of the nonbasic fraction from this reaction afforded a nitrogen-containing compound in 14% yield which was identified as the known pyrrole **5**[15] on the basis of spectroscopic data. Hydrogenation of **5** over 5% ruthenium–alumina afforded a single product whose structure was assigned pyrrolizidine **4a**; this structure was confirmed by reduction of this product with lithium aluminum hydride to give isoretronecanol, picrate mp 188–190 °C.[15] Pyrrole **5** presumably arises via initial reductive amination of the C-7 aldehyde group to give i; subsequent cyclization leads to a stabilized (and slowly reducible[2]) enamine ii which eventually closes to the corresponding pyrrole.



i ii

In order to improve the yields of **4a** and **4b** and to block the formation of the pyrrole, the amino group was introduced at the ketone carbon prior to oxidation. This was readily accomplished by reaction of **2b** with ammonium nitrate–$NaBH_3CN$[2] to give a mixture of amino esters **6a** and **6b** in 48% yield. Attempts to separate the two stereoisomers at this stage led to extensive decomposition. When a mixture of **6a** and **6b** was oxidized with osmium tetroxide–sodium metaperiodate and subsequently reacted with sodium cyanoborohydride, a mixture of **4a** and **4b** was obtained in 35% yield. Purification by preparative TLC afforded pure **4a** (picrate mp 122–123 °C[15]) and **4b** (picrate mp 149–151 °C). A sample of the initial mixture of **4a** and **4b** was reduced with lithium aluminum hydride to give **1a** and **1b**. GLC analysis revealed that **1a** and **1b** were formed in a ratio of 1:2, suggesting that reductive amination of **2b** produced amino esters **6a** and **6b** in a 1:2 ratio since subsequent stereochemistry should be preserved. Pyrrolozidine esters **4a** and **4b** were separately reduced with lithium aluminum hydride in ether to give respectively (±)-isoretronecanol (**1a**) (picrate mp 188–189 °C[11]) and (±)-trachelanthamidine (**1b**) (picrate mp 170–172 °C[11]). Each product had IR, NMR, and mass spectra identical with those reported.[11]

Experimental Section

General. Melting points were determined on a Kofler hot stage or on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on either a Beckman Model 33 or IR-18 spectrophotometer. Proton magnetic resonance (^1H NMR) spectra were measured on a Varian Associates T-60 instrument with chemical shifts given in parts per million (δ) downfield from tetramethylsilane as internal standard. Mass spectra were obtained at 70 eV on an AEI MS-30 instrument. Elemental analyses were determined by M-H-W Laboratories, Garden City, Mich. GLC data were obtained with either a Varian Aerograph Model A90-P3 or Perkin-Elmer 900 gas chromatograph using helium at a flow rate of 60 ml/min. Unless otherwise specified, the column used was a 10 ft × 0.25 in. stainless steel column packed with 15% FFAP on Chromosorb W. Tetrahydrofuran (THF) was dried just prior to use by sequential distillation from calcium hydride and lithium aluminum hydride under nitrogen. Methanol was dried by distillation from magnesium metal.

2-Carbethoxycyclohept-4-en-1-one (2b). A solution of 4-cyclohepten-1-one (**2a**, 4.4 g, 40 mmol) in diethyl carbonate (5 ml) was added dropwise to a stirred suspension of sodium hydride (4.0 g as 50% dispersion in mineral oil, 85 mmol) in diethyl carbonate (50 ml). The rate of addition was adjusted to maintain continuous evolution of hydrogen, and stirring was continued after the addition was complete until hydrogen evolution ceased. The reaction mixture was poured into a mixture of ether (50 ml), ice water (50 ml), and glacial acetic acid (12 ml). The organic layer was separated, and the aqueous layer was extracted with ether (4 × 40 ml). The combined organic layers were washed with 5% sodium bicarbonate (2 × 150 ml) and saturated salt solution (100 ml), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. Distillation afforded 4.27 g (59%) of **2b**: bp 100–104 °C (0.4 mm); IR (neat), 1750, 1720, 1650 cm^{-1}; ^1H NMR ($COCl_3$) δ 5.8 (m, 2 H, C=CH), 4.3 (q, 2 H, OCH_2–), 3.8 (m, 1 H, methine), 2.7 (m, 6 H, $-CH_2-$), 1.3 (t, 3 H, $[OCH_2CH_3]$); mass spectrum *m/e* 182 (molecular ion). GLC analysis showed a single peak (5 ft × 0.25 in., 3% SE-30 on Chromosorb W, 120 °C, 7.5 min).

Methyl 3-Oxo-8-chloro-*cis*-6-octenoate (3). Methyl acetoacetate (11.6 g, 0.1 mol) was added over 30 min to a stirred suspension of sodium hydride (5.4 g of 50% dispersion in mineral oil, 0.11 mol) in dry THF at 0 °C. *n*-Butyllithium (48 ml of a 2.23 M solution in hexene, 0.11 mol) was then added at 0 °C over 20 min. The resulting solution was rapidly added to a stirred solution of 1,4-dichloro-2-butene (45 g, 0.36 mol) in THF (100 ml) at 0 °C. The resulting mixture was quenched with 3 N HCl (100 ml), and ether (150 ml) was added. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 80 ml). The combined organic layers were washed with saturated salt solution (100 ml) and dried ($MgSO_4$), and the solvent was removed in vacuo. Distillation afforded 6.1 g (30%) of crude **3**: bp 115–123 °C (0.4 mm); IR 1750, 1725, 1650, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.7 (m, 2 H, C=CH), 4.2 (d, 2 H, CH_2Cl), 3.8 (s, 3 H, OCH_3), 3.5 (s, 2 H, $COCH_2CO$), 2.6 (m, 4 H, methylene). This crude product was used without further purification below.

2-Carbomethoxycyclohept-4-en-1-one (2c). A solution of chloro keto ester **3** (425 mg, 2.1 mmol) in 40 ml of methanol was added via a high-dilution apparatus[16] over 24 h to a gentle refluxing solution of sodium methoxide (from 115 mg of sodium, 5 mmol) in 100 ml of methanol. The reaction mixture was cooled, the methanol removed in vacuo, and water (50 ml) added. The solution was acidified with 12 N HCl and extracted with ether (3 × 60 ml). The combined extracts were washed with saturated salt solution (50 ml) and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product (400 mg) was purified by preparative TLC (silica gel, 20 × 20 cm × 1.5 mm

plate, 1:4 ethyl acetate–benzene, R_f 0.6) to give 210 mg (60%) of **2c**: IR (neat) 1750, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.8 (m, 2 H, C=CH), 3.9 (m, 1 H, methine), 3.8 (s, 3 H, OCH_3), 2.6 (m, 6 H, methylene).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.30; H, 7.14. Found: C, 64.46; H, 7.24.

1-Amino-2-carbethoxy-4-cycloheptenes (6a and 6b). A solution of keto ester **2b** (3.1 g, 17 mmol), ammonium nitrate (7.2 g, 90 mmol), and sodium cyanoborohydride (400 mg, 6.3 mmol) in methanol (200 ml) was stirred at room temperature for 48 h. The methanol was removed in vacuo and the residue was dissolved in water (80 ml), acidified to pH ~2 with 12 N HCl, and washed with ether (3 × 50 ml). The aqueous layer was made basic by saturation with solid sodium carbonate. The resulting solution was extracted with ether (4 × 50 ml), the combined extracts were washed with saturated salt solution (50 ml), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. Distillation afforded 1.51 g (48%) of **6a** and **6b**: bp 82–85 °C (0.1 mm); IR (neat) 3430, 3360, 1730, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.73 (m, 2 H, C=CH), 4.13 (q, 2 H, OCH_2), 3.4 (m, 1 H, –CHN), 1.5 (s, 2 H, NH_2), 1.22 (t, 3 H, OCH_2CH_3).

Anal. Calcd for $C_{10}H_{17}O_2N$: C, 65.53; H, 9.35; N, 7.64. Found: C, 65.25; H, 9.59; N, 7.83.

1-Carbethoxypyrrolizidines (4a and 4b). Method A. A solution of **2b** (550 mg, 3 mmol) in 25 ml of methanol was ozonized at −70 °C until the solution turned blue, and dimethyl sulfide (1 ml) was added. The resulting solution was allowed to stir at 0 °C for 1 h, and a chilled solution of ammonium nitrate (1.5 g, 19 mmol) and sodium cyanoborohydride (300 mg, 4.8 mmol) in methanol (15 ml) was added. The mixture was stirred at 0 °C for 5 h and then at room temperature for 48 h. The methanol was removed in vacuo, and water (20 ml) was added to the residue. The solution was acidified with 6 N HCl and extracted with ether (3 × 40 ml). The combined extracts were washed with saturated salt solution and dried ($MgSO_4$), and the solvent was removed in vacuo to give 220 mg of nonbasic product. Preparative TLC (20 × 20 cm × 1.5 mm silica gel plate, 2:3 ethyl acetate–benzene, R_f 0.6) afforded 75 mg (14%) of the known[15] pyrrole **5** as a colorless oil: UV (95% EtOH) λ_{max} 256 nm (ϵ 9800), 237 (14 000); ^1H NMR ($CDCl_3$) δ 6.67 (2 d, 2 H, C=CH), 4.33 (q, 2 H, OCH_2), 4.0 (τ, 2 H, CH_2N), 3.1 (τ, 2 H, CH_2C=), 2.6 (m, 2 H, $-CH_2-$), 1.3 (τ, 3 H, OCH_2CH_3); mass spectrum *m/e* 179, 150, 132, 106 (reported[15] 179, 150, 134, 106).

The acidic aqueous solution was made basic with solid potassium carbonate and extracted with ether (4 × 40 ml). The combined extracts were washed with saturated salt solution and dried ($MgSO_4$), and the solvent was evaporated in vacuo to give 100 mg of crude basic product. The crude products from three identical runs were combined and subjected to short-path distillation (pot temperature 100 °C, 0.4 mm) to give 155 mg (7%) of **4a** and **4b** as a colorless oil: IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.18 (q, 2 H, OCH_2), 3.7 (m, 1 H, H-8 pyrrolizidine ring),[17] 1.23 (t, 3 H, OCH_2CH_3); mass spectrum *m/e* 183, 154, 138, 110, 83.

Anal. (picrate) Calcd for $C_{16}H_{20}N_4O_9$: C, 46.60; H, 4.89; N, 13.59. Found: C, 46.40; H, 4.87; N, 13.41.

Method B. To a stirred solution of amino esters **6a** and **6b** (1.5 g, 8.2 mmol) in ether (40 ml) and water (40 ml) at 0 °C was added 50 mg of osmium tetroxide in ether (10 ml). Sodium metaperiodate (3.8 g, 17 mmol) was then added in one portion. The resulting mixture was stirred at 0 °C for 3 h and then added to a chilled solution of sodium cyanoborohydride (2.8 g, 44 mmol) in methanol (300 ml). The resulting mixture was allowed to stand at 0–5 °C for 4 days. Most of the solvent was removed in vacuo, and 1 N HCl (40 ml) was added. This solution was washed with ether (2 × 50 ml), made basic with solid potassium carbonate, and extracted with ether (4 × 50 ml). The extracts were combined, washed with saturated salt solution, dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo. Distillation through a short-path apparatus afforded 520 mg (35%) of **4a** and **4b** as a colorless oil, bp 82–87 °C (1.5 mm). IR, ^1H, NMR, and mass spectra were indistinguishable from those of the sample obtained via method A. GLC analysis showed a single broad peak which could not be resolved on a variety of columns. However, preparative TLC (three 20 × 20 cm × 1.5 mm silica gel plates, THF saturated with ammonia, developed three times) afforded 150 mg of **4a**, R_f 0.25, picrate mp 122–123 °C (reported[15] 119.5–120 °C), and 320 mg of **4b**, R_f 0.5, picrate mp 149–151 °C.

(±)-Isoretronecanol (1a). A solution of **4a** (250 mg, 1.4 mmol) in ether (5 ml) was added over 5 min to a solution of lithium aluminum hydride (53 mg, 1.4 mmol) in ether (15 ml). The resulting solution was refluxed for 3 h, cooled, and treated sequentially with water (60 μl), sodium hydroxide solution (60 μl, 15%), and water (180 μl). The solid was removed by filtration, and the ether was removed in vacuo to give 180 mg (93%) of **1a**, picrate mp 188–190 °C (reported[15] 190–192 °C). GLC analysis (5 ft × 0.25 in., 15% OV-1 on Gas-Chrom P, 150 °C) showed a single peak. A portion was purified by preparative GLC; IR, NMR, and mass spectra were in accord with reported values.[15]

(±)-Trachelanthamidine (1b) was prepared from **4b** in 86% yield exactly as described above, picrate mp 170–172 °C (reported[15] 173–174 °C). GLC analysis (5 ft × 0.25 in., 15% OV-1 on Gas-Chrom P, 150 °C) showed a single peak different from and with shorter retention time than **1a**. A portion was purified by preparative GLC; IR, NMR, and mass spectra were in accord with reported values.[15]

High-Resolution Mass Spectrum. Calcd for $C_8H_{15}NO$: 141.1153. Found: 141.1142.

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Registry No.—**1a**, 18929-90-3; **1a** picrate, 61259-90-3; **1b**, 18929-91-4; **1b** picrate, 61259-91-4; **2a**, 19686-79-4; **2b**, 61267-54-7; **2c**, 61259-92-5; **3**, 61259-93-6; **4a**, 34951-60-5; **4a** picrate, 61259-94-7; **4b**, 34951-61-6; **4b** picrate, 61259-95-8; **5**, 34951-59-2; **6a**, 61259-96-9; **6b**, 61259-97-0; diethyl carbonate, 105-58-8; methyl acetoacetate, 105-45-3; 1,4-dichloro-2-butene, 1476-11-5; sodium methoxide, 124-41-4; ammonium nitrate, 6484-52-2.

References and Notes

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(16) For a description of this high-dilution apparatus, see N. J. Leonard and R. C. Sentz, *J. Am. Chem. Soc.*, **74**, 1704 (1952).
(17) The chemical shift of this ring-junction proton is characteristics for these carbethoxypyrrolizidines; see B. Luning and H. Trankner, *Acta Chem. Scand.*, **22**, 2324 (1968).