A Transannular Route for Stereospecific Synthesis. (±)-Isoretronecanol[1]

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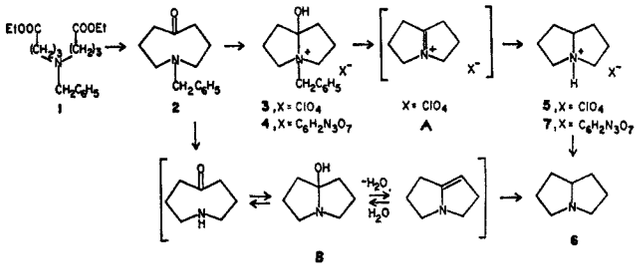
A transannular reaction has been utilized effectively for the stereospecific synthesis of the pyrrolizidine alkaloid derivative (±)-isoretronecanol. The keto ester, ethyl 1-benzyl-1-azacyclooctan-5-one-4-carboxylate, resulting from the high-dilution Dieckmann cyclization of diethyl γ,γ′-benzyliminobisbutyrate, was converted into its transannular salt, ethyl 4-benzyl-8-hydroxypyrrolizidine-1-carboxylate perchlorate. Hydrogenation of this compound using palladium-on-charcoal catalyst produced ethyl (±)-isoretronecanolate perchlorate, from which the base was liberated and reduced to (±)-isoretronecanol with lithium aluminum hydride. 1-Benzyl-1-azacyclooctan-5-one perchlorate could be hydrogenolyzed to pyrrolizidine perchlorate, 1-benzyl-1-azacyclooctan-5-one to pyrrolizidine, ethyl 1-benzyl-1-azacyclooctan-5-one-4-carboxylate to a mixture of ethyl (±)-isoretronecanolate and the corresponding $\Delta^{1,8}$-dehydro ester, and 1-benzyl-1-azacyclodecan-6-one to quinolizidine. The use of the transannular salt as an intermediate in the catalytic hydrogenation step is more efficient than the use of the corresponding base.

We have been intrigued with the possibility of the application of a transannular reaction[2,3] to pyrrolizidine alkaloid[4,5] synthesis, especially due to the X-ray determination by Wunderlich,[6a] which indicated that a retusamine salt exists in the *O*-protonated transannular form, and the finding that otonecine-derived alkaloids show strong $N-C_{CO}$ interaction.[6b,c] We therefore addressed our efforts to the synthesis of 1-hydroxymethylpyrrolizidine in the hope of realizing a stereospecific synthesis of one of the racemates, (±)-isoretronecanol. Formula **12** indicates the absolute stereochemistry of (−)-isoretronecanol, 1β-hydroxymethyl-(8α)-pyrrolizidine, and lindelofidine is its enantiomer, 1α-hydroxymethyl-(8β)-pyrrolizidine; formula **16** corresponds to trachelanthamidine, 1α-hydroxymethyl-(8α)-pyrrolizidine, and laburnine is its enantiomer, 1β-hydroxymethyl-(8β)-pyrrolizidine.[7] Previous syntheses have produced a mixture of the racemates of 1-hydroxymethylpyrrolizidine;[8–13] a racemate of unspecified stereochemistry;[14] (±)-trachelanthamidine;[13,15–17] and (±)-isoretronecanol.[18–20]

The feasibility of the transannular synthetic route was first tested with the synthesis of the unsubstituted bicyclic system, pyrrolizidine (**6**). Diethyl γ,γ′-benzyliminobisbutyrate (**1**), prepared from benzylamine and ethyl γ-iodobutyrate, was subjected to Dieckmann cyclization with potassium *t*-butoxide under high dilution conditions.[21] 1-Benzyl-1-azacyclooctan-5-one (**2**), which was obtained in 62% yield, exhibited infrared absorption (CCl_4) at 1693 cm^{-1}, indicative of transannular interaction between tertiary amino nitrogen and ketone carbonyl.[2,21] Transannular reaction occurs in the protonation of **2** (Scheme I). Perchlorate **3** and

SCHEME I



picrate **4** salts of 1-benzyl-1-azacyclooctan-5-one are in the transannular form, as evidenced by the lack of infrared absorption in the carbonyl region and by the presence of absorption in the hydroxyl region.[22] Quantitative hydrogenation of 1-benzyl-1-azacyclooctan-5-one perchlorate (**3**) in methanol at 25° and atmospheric pressure using 10% palladium-on-charcoal catalyst resulted in the smooth absorption of 2 mol equiv of hydrogen during 1 hr. Pyrrolizidine **6** obtained was converted into its picrate (**7**) for identification[23] (93% over-all yield). When the hydrogenation was run on a larger scale at 3 atm, pyrrolizidine perchlorate (**5**) could be isolated directly.

The yield of pyrrolizidine (**6**) was somewhat lower when the base, 1-benzyl-1-azacyclooctan-5-one (**2**), was treated with hydrogen and palladium on charcoal. For the production of pyrrolizidine the initial reaction in either case is necessarily hydrogenolysis of the benzyl–nitrogen bond. In the perchlorate case (**3**),

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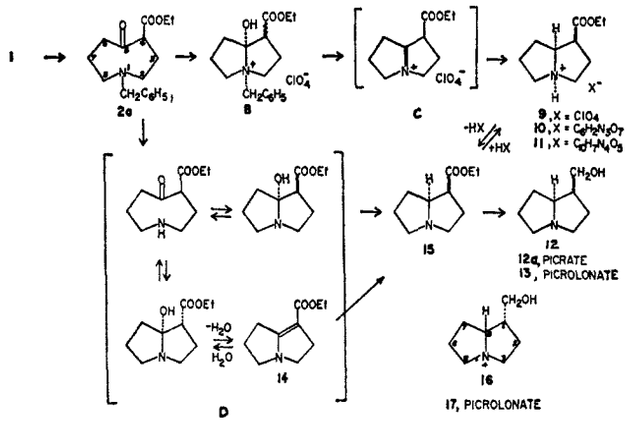
the iminium salt A[22a] is the logical intermediate. When the free base **2** is used, the intermediate 1-azacyclooctan-5-one would be expected to equilibrate with bicyclic forms (B), the carbinolamine which can potentially undergo hydrogenolysis[24] and the enamine which can undergo hydrogenation to the saturated product (**6**). Intermediates were not isolated along either pathway, and the rate of hydrogen absorption showed no break at 1 mol equiv.

Since the conversion of **3** to **5** was very efficient, the method was applied to the synthesis of ethyl (±)-isoretronecanolate perchlorate (**9**, one enantiomer shown). To obtain this product, the material resulting from the Dieckmann cyclization of **1** was isolated at the stage of ethyl 1-benzyl-1-azacyclooctan-5-one-4-carboxylate (**2a**), which was converted directly into its oily perchlorate (Scheme II). Transannular formula-

SCHEME II



tion of this salt as ethyl 4-benzyl-8-hydroxypyrrolizidinium-1-carboxylate perchlorate (**8**, 4,8-*cis*, 1,8-*cis* and/or -*trans*) was indicated by the absence of a ketone C=O band in the infrared spectrum and by the presence of OH bands at 3550 and 3370 cm^{-1}. Perchlorate **8** was obtained in 89% yield from diethyl γ,γ-benzyliminobisbutyrate (**1**). Catalytic reduction of perchlorate **8** in ethanol at 1–3 atm using 10% palladium on charcoal resulted in the absorption of 2 mol equiv of hydrogen and the isolation, in 69% yield, of ethyl (±)-isoretronecanolate perchlorate (**9**), mp 128–128.5°. Tentative identification at this stage was made by conversion into picrate **10** which had the correct melting point, 119.5–120°, for this derivative as previously described by Kochetkov and Likhosherstov.[18] Picrolonate **11**, mp 187–188°, has not been described previously.

Ethyl (±)-isoretronecanolate (**15**) was liberated from perchlorate **9** and was reduced with lithium aluminum hydride in ether[18] to (±)-isoretronecanol (**12**, one enantiomer is shown). Conversion into picrate **12a**, mp 189.5–190°, and picrolonate (**13**), mp 176–177°, both with known physical properties[18,19] which differ markedly from those for the corresponding derivatives of the other 1-hydroxymethylpyrrolizidine racemate, (±)-trachelanthamidine (**16**, one form is shown), provided final identification of the structure and stereochemistry of product **12**. A mixture of **13** with a sample of (±)-isoretronecanol picrolonate previously synthesized[19] gave no melting point depression.

The purity of the (±)-isoretronecanol prepared by the sequence **1** → **2a** → **8** → **9** → **15** → **12** was checked by liberating the base from picrate **12a** and subjecting it to gas–liquid partition chromatography on 30% Apiezon L on Gas-Chrom P. This system was used effectively by Červinka, Felz, and Jirkovsky[13] for the separation of (±)-isoretronecanol and (±)-trachelanthamidine, on which system the latter, as the less polar racemate, moved more rapidly.[25,26] The synthetic (±)-isoretronecanol was at least 98% pure. Under the conditions employed, it would have been possible to detect as little as 2–3% of (±)-trachelanthamidine. The ratio of the retention times observed for a pure, homogeneous sample of the latter[16] and for (±)-isoretronecanol was 1.00:1.14.

Since the major final product (**12**) in the transannular synthetic sequence was shown to have *cis*-1,8-hydrogens,[4,5] compound **9** (**15**) was confirmed as having the same stereochemistry. Initial hydrogenolysis of the benzyl-nitrogen bond in perchlorate **8** would be expected to be followed by dehydration of the protonated carbinolamine ester to the more stable iminium intermediate C (parallel to the formation of A above). Addition of hydrogen to the iminium grouping of C would be expected to occur on the less hindered side of the molecule, *trans* to the carbethoxyl group, thus providing the specific stereochemistry observed in **9** (**15**). The final result in this sequence does not depend necessarily upon the stereochemistry of intermediate **8**, formed under reversible protonation conditions, in which the 4 and 8 substituents are *cis* to each other but the 1-carbethoxyl group is either *trans* (*endo* with respect to the folded ring system) or *cis* of these.[27]

That the substituent on nitrogen must be initially hydrogenolyzable was readily tested by catalytic hydrogenation of 1-*p*-tolyl-1-azacyclooctan-5-one perchlorate, which is known to exist in the transannular form (**3**, *p*-$CH_3C_6H_5$ in place of $C_6H_5CH_2$).[28] This compound absorbed 3 mol equiv of hydrogen in 1.5 hr, but only with the reduction of the aromatic ring to give the corresponding 4-methylcyclohexyl derivative. Thus the C-8 hydroxyl bond was not hydrogenolyzed while the aryl or cycloalkyl group remained attached to the quaternary nitrogen. Moreover, the perchlorate salt of an N-ethyl compound, 1-ethyl-1-azacyclononan-5-ol-6-one, which is in the transannular form,[21] was inert to hydrogenation over palladium-on-charcoal catalyst.

The stereochemical result of synthesis of 1-hydroxymethylpyrrolizidine from the base, ethyl 1-benzyl-1-azacyclooctan-5-one-4-carboxylate (**2a**), was also investigated. Catalytic hydrogenation in ethanol over

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(25) A. H. Chalmers, C. C. J. Culvenor, and L. W. Smith [*J. Chromatogr.*, **20**, 270 (1965)] have reported a specific retention time for isoretronecanol, 1β-hydroxymethyl-8α-pyrrolizidine, under different, standardized conditions, but the diastereomer was not among the compounds they studied.

(26) The same order of polarity, and hence of chromatographic elution, was observed in the separation of these racemates by alumina column chromatography.[11]

(27) In the absence of the bulky 4 and 8 substituents, the position of greater stability for a 1 substituent on pyrrolizidine is normally *exo* with respect to the folded ring system,[4,5] a fact which served as the basis for the synthesis of (±)-trachelanthamidine (**16**, one enantiomer shown) from γ,γ′-iminobisbutyraldehyde at pH 7.[16] See also analysis of the stereochemistry of the *cis*-bicyclo[3.3.0]octane system by A. C. Cope, M. Brown, and H. E. Petree, *J. Amer. Chem. Soc.*, **80**, 2852 (1958).

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palladium on charcoal ceased completely after 2.5 hr with the absorption of less than 2 mol equiv of hydrogen. The product had physical properties corresponding to a mixture of ethyl (±)-isoretronecanolate (**15**) and the unsaturated ester **14**. The hydrogenation of the latter to **15** had been reported by Kochetkov and Likhosherstov[18] using platinum in acetic acid, but it is likely that under these acidic conditions the iminium salt (C, CH_3COO^- for ClO_4^-) is the entity actually being reduced (see above). When these conditions were applied to the mixture of **14** and **15**, the formation of the latter was checked by conversion to perchlorate and picrate derivatives which were identical with those described earlier. In this sequence, **2a** → **14** + **15** → **15**, following the initial hydrogenolysis of the N-benzyl bond over palladium on charcoal, the ethyl 1-azacyclooctan-5-one-4-carboxylate produced thereby can equilibrate with the bicyclic forms (D).[29] The racemic carbinolamine ester in which the C-8 hydroxyl and C-1 hydrogen are *trans* is stereochemically susceptible to dehydration, catalyzed by the indigenous base, to give **14**. The reduction of the conjugated unsaturated ester **14** may not proceed to completion using palladium on charcoal, whereas with platinum in acetic acid[18,20] reduction is complete. The racemic carbinolamine ester in which the C-8 hydroxyl and C-1 hydrogen are *cis* could serve as a precursor for **15** if C–O hydrogenolysis were to occur (with retention of relative configuration).

The essentially four-step synthetic sequence [diethyl γ,γ′-benzyliminobisbutyrate (**1**) → ethyl 1-benzyl-1-azacyclooctan-5-one-4-carboxylate perchlorate (**8**) → ethyl (±)-isoretronecanolate (**15**) → (±)-isoretronecanol (**12**, only one enantiomer shown at each stage)] proceeds stereospecifically in reasonable over-all yield from readily available materials and is preferred over the route **2** → **14** + **15** → **15**, which required additional isolation and hydrogenation stages. The concept of utilizing a transannular reaction to construct a bicyclic system may be applied additionally to ring sizes nine and ten. As a preliminary example, the catalytic hydrogenation of 1-benzyl-1-azacyclodecan-6-one produced quinolizidine.

Experimental Section[30]

Diethyl γ,γ′-Benzyliminobisbutyrate (1).—A mixture of 195 g (0.82 mol) of ethyl γ-iodobutyrate,[31,32] 44 g (0.41 mol) of benzylamine, and 121 g (0.82 mol) of anhydrous potassium carbonate in 500 ml of ethanol was heated under reflux for 5 hr. Following filtration the filtrate was concentrated and taken into ether, which was washed with water and dried. Following removal of the ether the residue was fractionally distilled: bp 163–167° (0.025 mm); $n^{25}D$ 1.4916; ν_{max}^{film} 1750 cm^{-1} (ester C=O).

Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.73; N, 4.18. Found: C, 68.29; H, 8.51; N, 4.33.

1-Benzyl-1-azacyclooctan-5-one (2).—To a boiling slurry made from 14 g (0.36 g-atom) of potassium and *t*-butyl alcohol in 2 l. of xylene, stirred at high speed under nitrogen,[33] was added during 55 hr 55 g (0.16 mol) of diethyl γ,γ′-benzyliminobisbutyrate (**1**) in 400 ml of xylene. The mixture was stirred and heated at reflux for 1 additional hr following the addition. The cooled reaction mixture was neutralized with 3 *N* hydrochloric acid, and then the whole was extracted five times with 100-ml portions of 6 *N* hydrochloric acid. The combined acid solutions were filtered and heated under reflux for 4 hr. The mixture resulting from the hydrolysis–decarboxylation was treated with activated charcoal and then cautiously basified with concentrated potassium hydroxide solution at ice-bath temperature. Ether extraction followed by removal of the ether left a residue which solidified on distillation: bp 137° (0.25 mm); $n^{25}D$ 1.5452; mp 34–35°, colorless prisms; $\nu_{max}^{CCl_4(10\%)}$ 1693 cm^{-1} (C=O); yield 22 g (62%).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45; mol wt, 217.3. Found: C, 76.99; H, 8.90; N, 6.45; mol wt, 201 (osmometric).

Perchlorate 3, mp 144–144.5°,[22] in acetone was treated under different conditions with excess 2,2-dimethoxypropane[34] in an attempt to form the *O*-methyl compound: (1) at 25° for 1.5 hr, (2) at reflux for 3.5 hr, and (3) at 25° for 12 hr, in the presence of a small amount of *p*-toluenesulfonic acid, but none of these attempts brought about replacement of hydroxyl by methoxyl, and starting material was recovered unchanged.

Picrate 4, mp 207–208°,[22b] was similar to the perchlorate in showing no infrared maximum in the carbonyl stretching region.

Hydrogenolysis of 1-Benzyl-1-azacyclooctan-5-one Perchlorate (3).—The reaction was first carried out on a quantitative basis. A mixture of 0.92 g (2.9 mmol) of 1-benzyl-1-azacyclooctan-5-one perchlorate, 0.35 g of palladium-on-charcoal (10%) catalyst, and 40 ml of absolute methanol was hydrogenated at 25° and atmospheric pressure. The theoretical amount for 2 mol equiv of hydrogen (130 ml) was absorbed within 1 hr. The methanol was removed from the filtered solution. Aqueous sodium hydroxide and ether were added to the residue. The ether extracts were used to form the picrate, identified as crude **pyrrolizidine picrate,**[23] yield 0.92 g (93% over-all).

The hydrogenation was carried out on a larger scale employing 3 atm pressure of hydrogen with palladium on charcoal at 25°. Direct isolation of **pyrrolizidine perchlorate (5)** [mp 71–72°, ν_{max}^{Nujol} 3160 cm^{-1} (>N$^+$H)] was possible in 80% yield. The nmr spectrum provided further characterization with proton resonance signals ($CDCl_3$) at τ 5.56 (1 H, m, CHN$^+$), 6.53 (4 H, two groups of multiplets), 7.88 (7.2 H, center of m). The salt was very hygroscopic.

Anal. Calcd for $C_7H_{14}ClNO_4$: C, 39.67; H, 6.67; N, 6.62. Found: C, 38.52; H, 6.54; N, 6.56.

This hygroscopic perchlorate was shaken with ether and aqueous potassium hydroxide. **Pyrrolizidine picrate 7** was obtained directly from the combined and dried ether extracts and was recrystallized from ethanol, yellow plates, mp 258–260° dec.

Anal. Calcd for $C_{13}H_{16}N_4O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 45.94; H, 4.85; N, 16.34.

Complete Hydrogenation of 1-Benzyl-1-azacyclooctan-5-one (2).—A mixture of 1.3 g (6 mmol) of 1-benzyl-1-azacyclooctan-5-one, 1 g of palladium on charcoal (10%) and 30 ml of ethanol was hydrogenated at 25° and atmospheric pressure until 2 mol equiv of hydrogen was absorbed. From the concentrated filtrate the picrate was obtained as yellow plates, mp 255–256° dec, weighing 1.45 g (71%), recrystallized from ethanol and identified as **pyrrolizidine picrate (7)**, mp 259–260° dec.

Perchlorate of Ethyl 1-Benzyl-1-azacyclooctan-5-one-4-carboxylate (2a). Ethyl 4-Benzyl-8-hydroxypyrrolizidinium-1-carboxylate Perchlorate (8).—The Dieckmann cyclization of diethyl γ,γ-benzyliminobisbutyrate (**1**) was carried out under the special conditions described above leading to the isolation of 1-benzyl-1-azacyclooctan-5-one. To the cooled reaction mixture was added acetic acid, water, and saturated potassium carbonate solution. The xylene solution was dried over magnesium sulfate and the residue was used directly for the formation of the perchlorate salt by addition of ether and then aqueous ethanolic perchloric acid. The oily perchlorate **8**, after washing with ether until neutral to Congo red and removing the ether *in vacuo*,

(29) The position of equilibrium between the forms with *cis* and *trans* stereochemistry at C-1 and C-8 (**D**) will probably differ from that (**8**) where the N$^+$ benzyl substituent is present.

(30) Melting points are corrected. We are grateful to Mr. Josef Nemeth and his associates at the University of Illinois for the microanalyses. We also take pleasure in expressing appreciation to our colleagues Dr. Joseph V. Paukstelis and Dr. Michael J. Martell, Jr., for important confirmatory experiments.

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(34) N. J. Leonard and C. R. Johnson, *ibid.*, **84**, 3701 (1962).

showed infrared maxima at 3550, 3370, 1740 and 1100 cm^{-1}, but no ketone C=O band, yield 89%.

Anal. Calcd for $C_{17}H_{24}ClNO_7$: C, 52.37; H, 6.21; N, 3.59. Found: C, 52.41; H, 6.64; N, 3.40.

Hydrogenolysis of Ethyl 4-Benzyl-8-hydroxypyrrolizidinium-1-carboxylate Perchlorate (8). Ethyl (±)-Isoretronecanolate Perchlorate (9).—A mixture of 10 g (0.026 mol) of ethyl 4-benzyl-8-hydroxypyrrolizidinium-1-carboxylate, 250 ml of absolute ethanol, and 4 g of palladium on charcoal (10%) was hydrogenated under 3 atm for 3 hr. Filtration and concentration yielded 5.1 g (69%) of salt, recrystallized from ethanol as colorless plates: mp 128–128.5°; ν_{max}^{Nujol} 3250 (N^+H), 1750 (ester C=O) and 1100 cm^{-1} (ClO_4^-).

Anal. Calcd for $C_{10}H_{18}ClNO_6$: C, 42.33; H, 6.39; N, 4.94. Found: C, 42.20; H, 6.44; N, 4.91.

The hydrogenolysis carried out at atmospheric pressure on a quantitative basis indicated the absorption of 2.0 mol equiv of hydrogen within 1 hr.

Ethyl (±)-Isoretronecanolate Picrate (10).—An aqueous solution of the perchlorate (above) was treated with a saturated aqueous solution of picric acid. The yellow needles were recrystallized from ethanol: mp 119.5–120° (lit.[18] 118–118.5°); ν_{max}^{KBr} 2700 (N^+H) and 1730 cm^{-1} (ester C=O); $\nu_{max}^{CHCl_3(5\%)}$ 2550 and 1732 cm^{-1}; yield 91%.

Anal. Calcd for $C_{16}H_{20}N_4O_9$: C, 46.60; H, 4.98; N, 13.59. Found: C, 46.37; H, 4.85; N, 13.50.

Ethyl (±)-Isoretronecanolate Picrolonate (11).—The picrolonate, made from the perchlorate in aqueous solution, was recrystallized from ethanol, yellow prisms: mp 187–188°; $\nu_{max}^{CHCl_3(5\%)}$ 2540 and 1732 cm^{-1}.

Anal. Calcd for $C_{20}H_{25}N_5O_7$: C, 53.68; H, 5.63; N, 15.65. Found: C, 53.63; H, 5.60; N, 15.83.

(±)-Isoretronecanol Picrate (12a).—Ethyl (±)-isoretronecanolate (**15**) was liberated from 2 g (7.1 mmol) of the perchlorate salt by treatment with 2 g of sodium hydroxide in 5 ml of water containing sodium chloride followed by continuous ether extraction. To the dried ethereal solution (about 70 ml) was added 350 mg (9.2 mmol) of lithium aluminum hydride, and the reduction was carried out at reflux temperature during 3 hr. The reaction mixture was decomposed by the sequential addition of 0.35 ml of water, 0.35 ml of 15% aqueous sodium hydroxide, and 1 ml of water, which afforded a granular precipitate. The filtered ethereal solution was dried and treated with picric acid. The picrate, mp 185–186°, was recrystallized from ethanol, which raised the melting point of the yellow needles to 189.5–190° (lit. mp 188–189°,[13,19] 185.5–186.5°,[18] 186.5–187.5°),[11] yield 1.45 g (55%); ν_{max}^{Nujol} 3550 cm^{-1} (OH).

Anal. Calcd for $C_{14}H_{15}N_4O_8$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.65; H, 5.15; N, 14.95.

The base was liberated from the picrate and its purity checked by glpc. The sample was injected as a solution in ether. The column used was 30% Apiezon L on Gas-Chrom P[13] (base washed). The (±)-isoretronecanol (**12**) was at least 98% pure. Under the conditions employed (3 atm; flow rate of 45 ml/min; temperature 210°; block 265°; injection port 255°) it would have been possible to detect as little as 2–3% of (±)-trachelanthamidine (**16**).

(±)-Isoretronecanol Picrolonate (13).—The lithium aluminum hydride reduction product of ethyl (±)-isoretronecanolate (**15**) was treated with picrolonic acid in ether. The picrolonate was recrystallized from ethanol, yellow needles, mp 176–177° (lit.[19] mp 175.5–176°), mmp 175.5–176° (with Nair and Adams' sample).

Anal. Calcd for $C_{18}H_{23}N_5O_6$: C, 53.33; H, 5.72; N, 17.28. Found: C, 53.04; H, 5.55; N, 17.45.

Hydrogenation of 1-*p*-Tolyl-1-azacyclooctan-5-one Perchlorate (3, *p*-$CH_3C_6H_5$ in place of $C_6H_5CH_2$).—A mixture of 500 mg of this salt,[28] 350 mg of palladium on charcoal (10%), and 40 ml of methanol was hydrogenated for 1.5 hr while 3 mol equiv of hydrogen was consumed. The oily perchlorate was made basic and extracted with ether. The ether extract showed $\nu_{C=O}$ 1690 cm^{-1} and was converted into the corresponding picrate, $C_{20}H_{28}N_4O_8$, mp 130–131°, yield 400 mg (57%). Recrystallization gave yellow plates, mp 133–134°, of **1-(4-methylcyclohexyl)-1-azacyclooctan-5-one picrate.**

Anal. Calcd for $C_{20}H_{28}N_4O_8$: C, 53.33; H, 5.82; N, 12.44. Found: C, 53.09; H, 6.24; N, 12.38.

Attempted Hydrogenation of 1-Ethyl-1-azacyclononan-5-ol-6-one Perchlorate.—This salt[28,33] was inert to hydrogenation, and the picrate which was made following the attempt was identical with the one made directly from the acyloin itself, yellow plates, mp 237–238° dec.

Anal. Calcd for $C_{16}H_{22}N_4O_9$: C, 46.37; H, 5.35; N, 13.52. Found: C, 46.80; H, 5.38; N, 13.43.

Hydrogenation of the Dieckmann Cyclization Product of Diethyl γ,γ′-Benzyliminobisbutyrate.—The crude keto ester corresponding to 0.052 mol of starting diester **1** in 100 ml of absolute ethanol was hydrogenated over 2 g of palladium on charcoal (10%) at atmospheric pressure and 25°. After 2.5 hr the reaction ceased completely with the absorption of 1.5 l. (0.067 mol) of hydrogen. The filtrate was concentrated, and the residue was fractionally distilled as a colorless oil: bp 130–145° (15 mm); $n^{25}D$ 1.4780–1.4823, weight 3.7 g; $\nu_{max}^{CCl_4}$ 1726, 1674, and 1621 cm^{-1}. This was regarded as a mixture of **14** [lit.[18] bp 78–81° (2 mm), $n^{18}D$ 1.4893] and **15** [lit.[18] bp 78–80° (2 mm), $n^{20}D$ 1.4715; yield 39% from **1**].

The hydrogenation of **14** plus **15** in acetic acid was effected in 2 hr with platinum oxide catalyst at 3 atm and 25°. The product was a constant boiling fraction, bp 124° (12 mm), which gave a single peak in glpc on Carbowax 20 (10 ft): nmr (CCl_4) τ 5.92 (2 H, q, CH_2O), 6.42 (1 H, m, CHN), 6.8–8.6 (10.5+, H, complex signals), 8.76 (3 H, t, CH_3). The ethyl (±)-isoretronecanolate was converted into the perchlorate and picrate, identical respectively with those derivatives described above.

Diethyl δ,δ′-Benzyliminobisvalerate.—A mixture of 210 g (0.82 mol) of ethyl δ-iodovalerate, 44 g (0.41 mol) of benzylamine, and 121 g (0.82 mol) of potassium carbonate in 500 ml of ethanol was stirred under reflux for 5 hr.[33] The filtered solution was concentrated, and the residue was dissolved in ether. The ethereal solution was washed with water and dried over magnesium sulfate. Fractionation gave a nearly colorless oil [bp 173–178° (0.025 mm); yield 40 g (37%)] which was redistilled: bp 165° (0.025 mm); $n^{23}D$ 1.4914; $\nu_{max}^{CCl_4}$ 1733 cm^{-1}.

Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.33; H, 8.94; N, 4.05.

1-Benzyl-1-azacyclodecan-6-one.—The Dieckmann cyclization of diethyl δ,δ′-benzyliminobisvalerate was run under the high dilution conditions (45 hr) described for **2**. The product was a solid, 2.5 g (9.3%), which was distilled at 140° (0.1 mm). The distillate was recrystallized from benzene–petroleum ether (bp 30–60°), colorless prisms: mp 113°; $\nu_{max}^{CCl_4}$ 1697 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.31; H, 9.45; N, 5.71; mol wt 245.4. Found: C, 78.26; H, 9.50; N, 5.99; mol wt 233 (osmometric).

The perchlorate was made in ether and recrystallized from ethanol as colorless prisms: mp 187–189°; ν_{max}^{Nujol} 3365 cm^{-1}, but no C=O maximum.

Anal. Calcd for $C_{16}H_{24}ClNO_5$: C, 55.56; H, 6.97; N, 4.05. Found: C, 55.23; H, 6.96; N, 4.09.

The picrate was made in and recrystallized from acetone–ether as yellow plates: mp 171–172°; ν_{max}^{Nujol} 3060 cm^{-1} (sh) but no C=O maximum.

Anal. Calcd for $C_{22}H_{26}N_4O_8$: C, 55.69; H, 5.52; N, 11.81. Found: C, 55.96; H, 5.61; N, 12.21.

Both salts were in the transannular form under the infrared examination conditions.

Hydrogenation of 1-Benzyl-1-azacyclodecan-6-one.—A mixture of 1 g of palladium on charcoal (10%) and 35 ml of absolute ethanol was stirred under hydrogen and to this was added 1 g (4.08 mmol) of 1-benzyl-1-azacyclodecan-6-one in a small amount of ethanol. The mixture was hydrogenated at room temperature and atmospheric pressure for 55 min, by which time the absorption of hydrogen had practically stopped. It was further stirred for 15 min until 179 ml of hydrogen was absorbed (183 ml theoretical for 2 mol equiv). The mixture was filtered and the catalyst was washed with ethanol. The combined filtrates were concentrated after drying over magnesium sulfate. The picrate was made directly from the concentrate, yellow plates from ethanol, mp 199–200°, yield 0.89 g (59%).

On admixture with authentic **quinolizidine picrate,**[23] mp 198.5–199°, the melting point was not depressed.

Anal. Calcd for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 49.29; H, 5.43; N, 15.09.

(±)-Trachelanthamidine [(±)-Laburnine] (16).—γ,γ′-Im-

inobisbutyraldehyde tetraethyl diacetal (8 g, 26.4 mmol) was converted into the dialdehyde and allowed to self-condense.[18] Nine such runs were made simultaneously and after reduction the residues were pooled and distilled through a micro-spinning-band column. Four fractions were collected with the following boiling points (at 0.8 mm) and $n^{25}D$: (1) 97.5–98.5°, 1.4964; (2) 97.5°, 1.4969; (3) 97.5°, 1.4970; (4) 97.5–98.5°, 1.4970; total distilled material 7.76 g (23%). Paper chromatography (water–butanol–acetic acid) showed all four fractions to be identical and homogeneous: $\nu_{max}^{CHCl_3}$ 3400, 1625, 1610, 1565, 1362, 1317, 1270, 1160, and 1075 cm^{-1}.

The picrate was formed in 95% yield in ether and recrystallized several times from tetrahydrofuran–ether: mp 174–175° (lit. mp 174–175°,[15] 170.5°,[11] 172–173°[13,17]).

Anal. Calcd for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.20; H, 4.77; N, 15.26.

Picrolonate **17** was made in ether and recrystallized from ethanol, microcrystalline yellow solid, mp 161–162°.

Anal. Calcd for $C_{18}H_{23}N_5O_6$: C, 53.33; H, 5.72; N, 17.28. Found: C, 53.55; H, 5.91; N, 17.29.

Registry No.—**1,** 18944-80-4; **2,** 16853-08-0; **5,** 18927-50-9; **7,** 14129-07-8; **8,** 18927-52-1; **9,** 18968-32-6; **11,** 18927-53-2; **12,** 18929-90-3; 1-(4-methylcyclohexyl)-1-azacyclooctan-5-one picrate, 18927-74-7; 1-ethyl-1-azacyclononan-5-ol-6-one picrate, 18927-75-8; diethyl δ,δ′-benzyliminobisvalerate, 18944-93-9; 1-benzyl-1-azacyclodecan-6-one, 18944-94-0; 1-benzyl-1-azacyclodecan-6-one perchlorate, 18927-76-9; 1-benzyl-1-azacyclodecan-6-one picrate, 18927-77-0; **16,** 18929-91-4; **17,** 18929-92-5.

The Synthesis of *dl*-Deethylibogamine[1]

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The synthesis of deethylibogamine lactam (**22**) which was previously converted to deethylibogamine is described. Dihydrohomocarbostyril (**3**) was converted by acylation, reduction, and oxidation into the amido acid **12**. Further oxidation and hydrolysis gave the amino ketone **18**. Hydrogenation of the amino benzoic acids **13** and **18** over ruthenium gave the isoquinuclidones **14** and **19**, respectively. Oxidation of **19** followed by phenylhydrazone formation and Fisher indole synthesis gave **22**.

In recent years the efforts which have been expended on the synthesis of ibogamine (**1a**) have culminated in a number of reports of the preparation of this compound[3] and related species.[4] Prior to the publication of these results we had initiated a research program which was directed toward the syntheses of **1a** by way of the tricyclic ketone **2**.[5] The following discussion is concerned with the results of this work which led to the synthesis of deethylibogamine (**1b**) as well as the incorporation of an ethyl group onto a key reaction intermediate.

Homodihydrocarbostyril (**3**) was considered the ideal starting material for this synthesis since not only was it readily available from α-tetralone[6] but also the presence of the aromatic ring would permit the incorporation of a potential corboxylic acid function at a, oxidation of the benzylic position, b, and insertion of an ethyl group at c (Chart I). Hydrogenation of the aromatic ring would be expected to give the required all-*cis* product[7] and cyclization of the amino acid would give the desired tricyclic compound.

Friedel–Crafts acylation of **3** using aluminum chloride and acetyl chloride in carbon disulfide gave a 75% yield of the ketone **4**. The ultraviolet (uv) spectrum of **4** was essentially the same as that reported for *p*-acetamidoacetophenone but was quite different from those of the *ortho* and *meta* isomers.[8] Conjugation of the nitrogen with the ketone group lowered the reactivity of the latter and made the preparation of the ketal, **5**, more difficult than usual. Refluxing **4** in toluene with dry ethylene glycol and a trace of *p*-toluenesulfonic acid did not give any **5** under the common azeotropic distillation conditions. However, when **4** was treated with ethylene glycol in the presence of triethyl orthoformate and sulfuric acid, an 87% yield of **5** was obtained.

Lithium aluminum hydride reduction of **5** in tetrahydrofuran followed by acetylation of the crude amine gave a colorless oil, the infrared (ir) spectrum of which showed a single carbonyl stretching band at 1655 cm^{-1} but no adsorption in the 1040-cm^{-1} region which would be expected for a ketal.[9] The nmr spectrum of this product also showed that the doublet at δ 3.93 associated with the dioxolane protons was absent and, instead, a three-proton triplet at 1.26 and a two-proton quartet at 2.68 were observed. These data indicated that the ketal had been cleaved during the reduction of the lactam and that the product obtained was the ethyl tetrahydrobenzazepine, **7**. Since no other example of ketal cleavage by lithium aluminum hydride in the

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