mixed oxidation products) were combined and examined individually. The fastest moving material (22 mg) showed R_f 0.76 on thin layer chromatography (1:2 ether–benzene), melted at 247–249°, and produced a pale-blue fluorescence under ultraviolet light. This product, which could be the naphthalene hexacarboxylate, was not investigated further. The fraction with R_f 0.51 weighed 16 mg and showed mp 138–140°; the fraction with R_f 0.35 weighed 44 mg and showed mp 187–188°. Direct thin layer chromatographic and mixture melting point comparisons with authentic samples of the methyl esters of 1,2,4,5-benzenetetracarboxylic acid, benzenepentacarboxylic acid (R_f 0.44), and benzenehexacarboxylic acid identified the material with R_f 0.51 as the tetraester of acid **19**, and the material with R_f 0.35 as the hexaester of acid **18**. No pentaester could be detected among the oxidation products.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Registry No.—**1**, 41580-44-3; **2**, 41580-45-4; **8**, 41580-46-5; **9**, 41580-47-6; **10**, 41580-48-7; **12b**, 41580-49-8; **14**, 41580-50-1; **15**, 41580-51-2; **16**, 41580-52-3; **17**, 41580-53-4; 1,4-nonadiyne, 6088-94-4.

Synthesis of DL-Slaframine

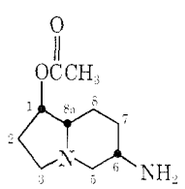
WALTER J. GENSLER* AND MAE W. HU

Department of Chemistry, Boston University, Charles River Campus, Boston, Massachusetts 02215

Received March 10, 1973

A stereoselective synthesis of slaframine is described. Ethyl *N*-(β-carbethoxyethyl)-5-oxopyrrolidine-2-carboxylate was obtained conveniently from glutamic acid and acrylonitrile. Dieckmann cyclization of this pyrrolidine diester followed by hydrolysis, decarboxylation, and catalytic hydrogenation furnished 2-(β-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride. *N*-Alkylation with methyl bromoacetate led to a mixture of the lactone and the methyl ester of *N*-(carbomethoxymethyl)-2-(β-carboxyethyl)-3-hydroxypyrrolidine, which could be cyclized by a second Dieckmann process. Subsequent hydrolysis, decarboxylation, and acetylation gave 1-acetoxy-6-oxoindolizidine, which, after conversion into the oxime, was hydrogenated to DL-slaframine.

Slaframine (**1**), an alkaloid first detected as the result of its property of stimulating excess salivation in livestock foraging on fungus-infected red clover, has been isolated in low yield from cultures of *Rhizoctonia leguminicola*.[1,2] The proposed indolizidine structure **1**,[3,4] as revised in 1968,[5] has been confirmed by synthesis.[6] Since slaframine is of interest as a possible research tool for locating acetylcholine receptor sites and as an agent relieving the symptoms of cystic fibrosis,[7-9] we were led to investigate alternative approaches. The present paper describes our work on a direct and stereoselective synthesis of DL-slaframine (**13**).



1

The starting point was ethyl *N*-(β-carbethoxyethyl)-5-oxopyrrolidine-2-carboxylate (**3**), which can be prepared conveniently from L-(+)-glutamic acid (**2**) and acrylonitrile.[10] Cyclization with sodium ethoxide produced ethyl 1,5-dioxopyrrolizidine-2-carboxylate (**4**). Although pyrrolidone **3** still showed optical activity, pyrrolizidine **4** was completely racemized. Decarboxylation of the pyrrolizidine **4** in hot hydrochloric acid was accompanied by lactam ring hydrolysis, so that the product was the 3-oxopyrrolidine acid **5**. The corresponding alcohol methyl ester **6** was obtained (46% from **3**) by hydrogenating the keto group over a platinum catalyst in methanol solvent.

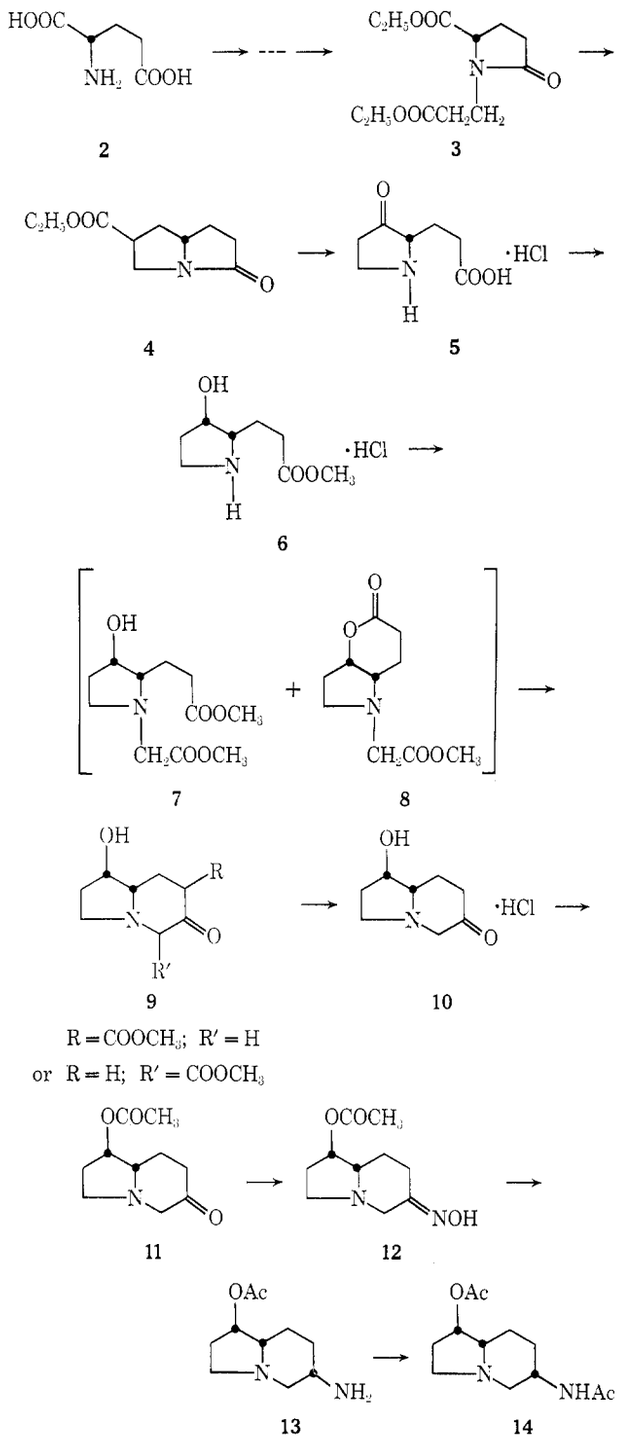
To attach the fused six-membered rings as in slaframine (**1**), the sequence continued by alkylating hydroxypyrrolidine **6** on nitrogen with methyl bromoacetate. The expected diester **7** was obtained mixed with the equally useful lactone **8** (40 and 23%, respectively). The relation between the two products was established by allowing lactone **8** to methanolize, whereupon dimethyl ester **7** was produced. Dieckmann cyclization of a mixture of diester **7** and ester lactone **8** gave rise to indolizidine **9**. Although there is no steric barrier to direct ring closure of lactone **8** as a first step, whether this occurs or whether there is prior *in situ* methanolysis that converts the lactone into the diester **7** was not ascertained. The unstable Dieckmann product **9** was decarboxylated with acid to give 1-hydroxy-6-oxoindolizidine hydrochloride (**10**), which was first acetylated to **11** and then converted into the relatively stable oxime **12**.

With the hope of providing milder conditions in the decarboxylation stage (**9** to **10**), *tert*-butyl bromoacetate was substituted for methyl bromoacetate in the *N*-alkylation of pyrrolidine **6**. Although a pair of products analogous to diester **7** and lactone **8** was obtained in good yield, the next two steps with these *tert*-butyl esters was found to offer no advantages over the methyl esters.

The oxime **12** emerged as a mixture of syn and anti forms, which could be separated and characterized. The last step proceeded by hydrogenating the mixed

(1) D. P. Rainey, E. B. Smalley, M. H. Crump, and F. M. Strong, *Nature*, **205**, 203 (1965).
(2) S. D. Aust and H. P. Broquist, *Nature*, **205**, 204 (1965).
(3) S. D. Aust, H. P. Broquist, and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **88**, 2879 (1966).
(4) B. J. Whitlock, D. P. Rainey, N. V. Riggs, and F. M. Strong, *Tetrahedron Lett.*, 3819 (1966).
(5) R. A. Gardiner, K. L. Rinehart, Jr., J. J. Snyder, and H. P. Broquist, *J. Amer. Chem. Soc.*, **90**, 5639 (1968).
(6) D. Cartwright, R. A. Gardiner, and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **92**, 7615 (1970).
(7) S. D. Aust, *Biochem. Pharmacol.*, **18**, 929 (1969).
(8) S. D. Aust, *Biochem. Pharmacol.*, **19**, 427 (1970).
(9) *Cf. Chem. Eng. News*, **46**, 43 (July 15, 1968).
(10) L. L. McKinney, E. H. Uhing, E. A. Setzkorn, and J. C. Cowan, *J. Amer. Chem. Soc.*, **72**, 2599 (1950); J. F. Cavalla, J. Davoll, M. J. Dean, C. S. Franklin, D. M. Temple, J. Wax, and C. V. Winder, *J. Med. Pharm. Chem.*, **4**, 1 (1961).

oximes to the final product, DL-slaframine (**13**). Neither the hygroscopic dihydrochloride of slaframine **13** nor the free base itself was as convenient to work with as the dipicrate, so that we generally relied on the dipicrate for product isolation and for purification. The identity of our product as DL-slaframine was proved by the correspondence in properties of the dihydrochloride, dipicrate, free base, and *N*-acetyl derivative **14**



of the synthetic material with those of the natural alkaloid. Tables I, II, and III give the details.

The two steps in our synthesis that determine the configuration, *i.e.*, **5** to **6** and **12** to **13**, are both platinum-catalyzed hydrogenations in acidic media. In this kind of process the hydrogen generally favors in-

TABLE I

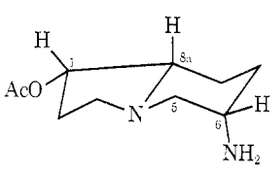
COMPARISON OF DIPICRATES FROM SYNTHETIC AND NATURAL SLAFRAMINE

	Synthetic, 215–221° dec	Natural, 180–184°
Mp[a]		
Ir[b]	3000, 1738, 1634, 1368, etc., cm^{-1}	3000, 1738, 1634, 1364, etc., cm^{-1}
Nmr[c]	δ 8.60, 8.10 (broad), 5.35 ($W_{1/2}$ = 13 Hz), 4.12–2.86 (m), 2.32–1.57 (m) ppm	δ 8.59, 8.12 (broad), 5.35 ($W_{1/2}$ = 13 Hz), 4.12–2.88 (m), 2.30–1.57 (m) ppm
Tlc	R_f[d] 0.87, 0.66 R_f[e] 0.63, 0.68	R_f[d] 0.87, 0.66 R_f[e] 0.63, 0.68

[a] The mixture melting point was 180–195°. The different melting points represent the only discrepancy in properties. We suggest that the racemic derivative is a molecular compound of the two enantiomers. [b] The ir curves, taken with KBr pellets, were superposable. [c] The curves were determined with the dipicrates dissolved in DMSO-d_6, with both curves showing a prominent singlet at 2.10 ppm. The low solubility in DMSO made integration difficult. The dipicrate was only slightly soluble in F_3CCOOH, D_2O, or $CDCl_3$. [d] The solvent system here was 7:7:3 chloroform–methanol–17% ammonium hydroxide. The yellow R_f 0.66 spots were identified as dissociated picric acid and the R_f 0.87 spot as dissociated free base by separate determinations of picric acid and of slaframine on the same plate. The dissociation of amine picrates during thin layer chromatography has been observed by H. B. Henbest, E. R. H. Jones, and G. F. Smith, *J. Chem. Soc.*, 3796 (1953), and by P. A. Plattner and A. S. Pfau, *Helv. Chim. Acta*, **20**, 224 (1937). The slaframine with R_f 0.87 came out as a brown spot with iodine vapor or as an orange-red spot with a spray of aqueous hydrochloric acid containing bismuth subnitrate and potassium iodide (Dragendorff mixture). [e] These results were obtained with 7:7:1 chloroform–methanol–17% ammonium hydroxide, with R_f 0.63 corresponding to the free base and R_f 0.68 to picric acid.

sertion into the unsaturation from the less hindered side,[11] and, since in both substrates scale models suggest clearly which side is the less hindered, we had a good basis from which to predict the stereochemical outcome. This led us to expect the hydrogen atoms at positions 1, 8a, and 6 of slaframine (**1**) to appear on the same side of the molecule. Thus, the earlier assignment for the slaframine configuration, as in **1**,[5] receives independent support.

Several spectroscopic data also agree with this configuration as well as with the conformation shown in **15** for slaframine. So far as the ring fusion in **15** is



15 = **13**

concerned, the relatively intense infrared absorption peaks observed in the 2800–2700-cm^{-1} region point to the trans arrangements.[12,13] These same peaks are also noted in indolizidine intermediates **9**, **10**, **11**, **12** (syn and anti) as well as in *N*-acetylslaframine (**14**). The relative configurations at positions 1 and 8a are

(11) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, pp 46, 86, 101; E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 119; S. Siegel, *J. Amer. Chem. Soc.*, **75**, 1317 (1953).

(12) H. S. Aaron, C. P. Radar, and G. E. Wicks, Jr., *J. Org. Chem.*, **31**, 3502 (1966).

(13) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); H. S. Aaron, *Chem. Ind. (London)*, 1338 (1965); C. P. Rader, R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **30**, 1536 (1965).

TABLE II

COMPARISON OF SYNTHETIC AND NATURAL SLAFRAMINE BASES

	Synthetic	Natural
Ir[a]	1734, 1242 cm^{-1}	1734, 1242 cm^{-1}
Nmr[b]	δ 5.22, 2.09 ppm	δ 5.22, 2.09 ppm
Tlc[c]	R_f 0.66,[d] 0.64, 0.12	R_f 0.66,[d] 0.64, 0.12
Glc,[e,g] retention time (area, appearance)	7.3 min (3%, broad), 11.1[f] (79, slight distortion), 18.2 (1, broad), 24.8 (12, broad), 31.1 (5, broad)	7.6 min (3%, broad), 11.1[f] (67, slight distortion), 18.2 (19, broad), 24.8 (5, broad), 31.6 (6, broad)

[a] The two infrared absorption curves, both taken with CCl_4 solutions, were identical. [b] Samples recovered from the infrared determinations were used here. Although all features of the two curves matched very well, the inadequate integration results allowed no comparison on this basis. The solvent used was $CDCl_3$. [c] Different solvent systems gave different R_f values, although in no case was more than one spot noted. Exposure to iodine vapor gave brown spots; exposure to acid bismuth subnitrate plus potassium iodide gave orange-red spots with the same R_f values. [d] The decreasing R_f values were obtained respectively with 7:6:2 chloroform–1-propanol–29% aqueous ammonia, with 7:7:1 chloroform–1-propanol–17% aqueous ammonia, and with 7:7:0.1 chloroform–1-propanol–29% aqueous ammonia. [e] The comparisons utilized a 6-ft column of methyl phenyl silicone supported on an acid-washed calcined diatomite support at 140° (1.5% OV 17 supported on Chromosorb W). [f] Tentatively, the 11.1-min peak is assceiated with the slaframine; the other peaks may arise as the result of decomposition at the port or on the column. [g] To get some idea of the nature of the synthetic slaframine base *before* purification, it was isolated from its hydrochloride directly out of a hydrogenation run and examined by glc. The following features appeared: 4.2 min (18%, sharp peak), 6.7 (8%, broad), 8.9 (1%, broad), 11.1 (71%, slightly distorted), 25.0 (1%, broad), and 31.5 (1%, broad). The area of the large peak at 11.1 min compared favorably with the purer samples.

TABLE III

COMPARISON OF *N*-ACETYL DERIVATIVES OF SLAFRAMINE

	Synthetic	Natural
Mp[a]	143–146°	143–146°
Ir[b]	3426, 1735, 1663, 1509 cm^{-1}	3420, 1735, 1663, 1510 cm^{-1}
Nmr[c]	δ 5.20 ($W_{1/2}$ = 13 Hz), 4.20 ($W_{1/2}$ = 8 Hz)	δ 5.31 ($W_{1/2}$ = 13 Hz), 4.24 ($W_{1/2}$ = 8 Hz)
Mass spectrum[d]	*m/e* 240 (M), 181 (M − $AcNH_2$), 121 (M − $AcNH_2$ − AcOH)	*m/e* 240, 181, 121
Tlc[e]	R_f 0.60,[f] 0.49, 0.25	R_f 0.60,[f] 0.49, 0.25
Glc,[g] retention time	4.5, 15.1 min	4.5, 15.1 min

[a] The mixture melting point was 143–146°. [b] The curves were taken from chloroform solutions, with the curve for the natural material sent to us by Dr. Aust.[3] The two curves were essentially identical. [c] The nmr spectrum for the natural material as furnished by Aust[3] was essentially the same as the one obtained here with the synthetic material. Data for the nmr absorption of the hydrochloride of *N*-acetylslaframine are also available.[5] [d] The two mass spectra, determined on a Hitachi Perkin-Elmer RMU-6E instrument, were virtually superposable. [e] In each case only one spot was seen. Comparisons performed by Aust in his laboratory, using samples of our synthetic *N*-acetylslaframine, independently established the identify of the synthetic and natural materials. [f] The decreasing R_f values were obtained with the following solvents, in order: 7:6:0.1 chloroforom–1-propanol–29% aqueous ammonia, 7:7:0.1 chloroform–1-propanol–29% ammonia, and 16:4:0.5 ether–ethanol–29% ammonia. [g] Single peaks were noted, with the shorter retention time obtained at 220° and the longer at 185°. Comparisons made by Rinehart in his laboratory using a sample of our synthetic *N*-acetylslaframine independently confirmed the identity.

supported by nuclear magnetic resonance measurements. The curve for indolizidine **9** shows a signal for H_1 at δ 4.12 ppm with $W_{1/2}$ = 11 Hz. The same signal with about the same bandwidth is seen for both oxime acetates **12** ($W_{1/2}$ = 13 Hz) as well as for *N*-acetylslaframine (**14**) ($W_{1/2}$ = 13 Hz). With the help of scale models built according to **15**, the bandwidths can be estimated[14] to be 13 Hz for cis (H_{8a}, H_1) and 18.4 Hz for trans (H_{8a}, H_1). Thus the cis geometry is preferred.[15] So far as the configuration at position 6 is concerned, *N*-acetylslaframine (**14**) shows a nuclear magnetic resonance signal for H_6 with $W_{1/2}$ = 8 Hz (N–H coupling removed). This value corresponds more closely to the $W_{1/2} \sim$ 12 Hz calculated for equatorial H_6 (as assigned for slaframine) than for $W_{1/2} \sim$ 22 Hz calculated for axial H_6.

Experimental Section

General Information.—All proton magnetic resonance spectra were determined at 60 MHz. Temperature readings are uncorrected. The concentrations of solutions used for optical rotation readings are given in grams per 100 milliliters. All thin layer chromatography runs used polyethylene terephthalate supported layers of silica gel 0.1 mm thick. Analyses for elements were reported either by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Werby Laboratories, Inc., Boston, Mass.

Ethyl *N*-(β-Carbethoxyethyl)-5-oxo-2-pyrrolidinecarboxylate (3).—*N*-(β-Cyanoethyl)-5-oxo-2-pyrrolidinecarboxylic acid, prepared from 147 g of L-(+)-glutamic acid (**2**) and acrylonitrile,[10] was esterified by refluxing with absolute ethanol (698 ml) containing concentrated sulfuric acid (207 g) for 18 hr. Precipitated inorganic salts were removed from the cooled mixture, and the clear solution was concentrated at 30°. After adjusting the concentrate to pH 5 with 10% bicarbonate, product was collected by repeated extractions with chloroform. The combined extracts were rinsed with small volumes of 10% bicarbonate and saturated salt solution, dried, and concentrated. Distillation afforded 140 g (55% from glutamic acid) of the desired diester **3**: bp 134–135° (0.07 mm); $[\alpha]^{25}D$ −12.3° (*c* 1.41, C_2H_5OH); ir ($CHCl_3$) 1740 (ester C=O) and 1740 cm^{-1} (lactam C=O); nmr ($CDCl_3$) δ 4.25 (q, *J* = 7 Hz, OCH_2CH_3), 3.90–3.60 (m, pyrrolidine no. 2 H), 3.42 (t, *J* = 7 Hz, $N-CH_2CH_3$), 2.56 (distorted t, ring CH_2C=O), 2.40–1.80 (m, ring no. 3 CH_2 plus acyclic CH_2C=O), 1.28 and 1.22 ppm (2 t, *J* = 6–7 Hz, 6, 2 $-OCH_2CH_3$'s). The integration ratio for the signals at δ 4.25–3.42 and at 2.56–1.84 ppm was 7:6 as required. This ethyl *N*-(β-carbethoxyethyl)-5-oxo-2-pyrrolidenecarboxylate (**3**) was homogeneous according to both thin layer chromatography (2:1 ether–hexane) and gas–liquid chromatography (neopentyl glycol succinate column at 180°).

Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.06; H, 7.59; N, 5.64. Found: C, 56.01; H, 7.46; N, 5.44.

1,5-Dioxo-2-carbethoxypyrrolizidine (4) from Ethyl *N*-(β-Carbethoxyethyl)-5-oxo-2-pyrrolidenecarboxylate (3).—A solution of 50.3 g (0.196 mol) of diester **3** in 50 ml of absolute ethanol was added dropwise to a room temperature solution of sodium

(14) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965; N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 79, 80; also see F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(15) Note that the H_1 signal for 1-hydroxyindolizidine itself has been reported with $W_{1/2}$ = 11.5 Hz and $W_{1/2}$ = 21 Hz for the cis and trans forms, respectively.[12]

(6.2 g, 0.27 g-atom) in absolute ethanol (125 ml). With pure nitrogen blanketing the reaction mixture throughout, it was allowed to stand overnight and then concentrated at temperature below 40° under reduced pressure. Adding 280 ml of dry ether transformed the residual yellow oil to the solid sodium enolate of cyclization product **4**, which could then be collected conveniently by filtration. A solution of the solid in 125 ml of water (5°) was brought to pH 5 with hydrochloric acid and then extracted with chloroform. Straightforward processing furnished 42 g of oily pyrrolizidine product **4** showing one spot on a thin layer chromatographic plate (3:8:1 chloroform–methanol–hexane); ir ($CHCl_3$) 1765 (cyclopentanone C=O), 1727 (ester C=O), 1695 (γ-lactam C=O), and 1614 cm^{-1} (enol). This material was suitable for use in the next step in the preparation of pyrrolidine **5**. A sample was purified by slow short-path distillation at 100–110° (10^{-3} mm); decomposition was noted at 140°. The water-white distillate of 1,5-dioxo-2-carbethoxypyrrolizidine (**4**) moved with exactly the same R_f value as the unpurified material and gave the same infrared absorption curve; the ferric chloride test developed a purple color. The product showed $[\alpha]^{25}D$ 0.0° (*c* 0.5, C_2H_5OH); nmr ($CDCl_3$) δ 5.15 (broad, enol OH), 4.70–3.64 (m, with a quartet evident at 4.26, J = 7 Hz), 2.48–1.82 (m, 4, γ-lactam ring 2 CH_2), 1.32 and 1.28 ppm (two sets of t's, J = 7 Hz, 3, CH_2CH_3). Integration of the signals at δ 5.15 and at 4.70–3.64 ppm totaled to 6 protons, in the ratio 0.5:5.4; the 5.15 signal disappeared when a drop of D_2O was added.

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.58; H, 6.08; N, 6.40.

2-(β-Carboxyethyl)-3-oxopyrrolidine Hydrochloride (5).—Warming the pyrrolizidine product **4** (40 g) in 420 ml of 15% hydrochloric acid at 75° for 6 hr resulted in release of carbon dioxide. After about 10 hr at room temperature, the acid mixture was concentrated *in vacuo* (temperatures no higher than 60°), and the residual light-orange oil was allowed to stand at 5° under a layer of ether. The resulting solid hydrochloride of 2-(β-carboxyethyl)-3-oxopyrrolidine (**5**), after washing on the funnel with a small volume of cold alcohol, weighed 30 g (80%), developed to a single spot on thin layer chromatography (7:3:0.05, chloroform–methanol–acetic acid), and showed ir (mineral oil) 1758 (cyclopentanone C=O) and 1726 cm^{-1} (acid C=O). A sample recrystallized from ethanol plus ether solvent gave a positive silver nitrate test for chloride and melted at 152–157°: $[\alpha]^{25}D$ 0.0° (*c* 0.5, C_2H_5OH); nmr (DMSO-d_6) δ 10.30 (broad, 1, COOH), 3.60 (m, 3, pyrrolidine H's at 2 and 5), 2.52 (m, 6, CH_2 at pyrrolidine 4 plus CH_2COOH plus $-N^+H_2-$), 2.05 ppm (m, 2, CH_2CH_2COOH). The carboxylic H signal at δ 10.3 ppm disappeared on addition of D_2O; a clear-cut change at 3.60 was difficult to establish.

Anal. Calcd for $C_7H_{12}ClNO_3$: C, 43.42; H, 6.25; N, 7.23. Found: C, 43.17; H, 6.18; N, 7.26.

A convenient derivative was prepared by ketalizing the keto group as follows. The oxopyrrolidinium chloride **5** (0.5 g) was added to a solution of thionyl chloride (0.34 mg) in absolute methanol (0.7 g) at 0°, and the mixture was allowed to stand at 35–40° for 2 hr. After removing all volatiles, trituration of the gummy residue with a small volume of cold ethanol afforded a solid, which on recrystallization from ethanol–ether gave the white, crystalline hydrochloride of 2-(β-carbomethoxyethyl)-3,3-dimethoxypyrrolidine: mp 134–135°; ir (mineral oil) 1730 cm^{-1} (ester C=O); nmr (D_2O) showed signals at *ca.* δ 3.23 (two s's, 6, $CH_3O-\underset{\diagdown\ \diagup}{C}-OCH_3$) and 3.63 ppm (s, 3, $COOCH_3$).

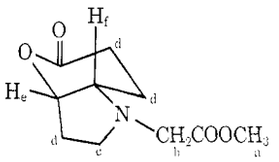
Anal. Calcd for $C_{10}H_{20}ClNO_4$: C, 47.33; H, 7.95; N, 5.52. Found: C, 47.37; H, 7.86; N, 5.47.

This ester–ketal could be reconverted into the keto acid **5** by treatment with 10% hydrochloric acid at 95°.

2-(β-Carbomethoxyethyl)-3-hydroxypyrrolidine Hydrochloride (6) by Hydrogenation of 2-(β-Carboxyethyl)-3-oxopyrrolidine Hydrochloride (5).—Keto pyrrolidine hydrochloride **5** (20.6 g) in 250 ml of methanol was hydrogenated for 3 days at atmospheric pressure over 1.1 g of platinum oxide catalyst. Removal of solids followed by concentration of the solution *in vacuo* at ~40° left a yellow oil that solidified when scratched under ether at −80°. Crystallization of the product from methanol afforded 12.7 g (61%) of 2-(β-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride (**6**) in the form of white needles, melting at 120–125° and showing only one spot on thin layer chromatography (7:3:0.05, chloroform–methanol–acetic acid); ir (KBr) 1726 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 5.50 (d, J = 3.8 Hz, 1, OH), 4.25 (broad band, $W_{1/2}$ = 12 Hz, 1, H–C–OH), 3.66 (s, $COOCH_3$), 3.23 (m, pyrrolidine ring H's at 2 and 5), 2.53 (m, 4, $CH_2CH_2COOCH_3$ plus $^+NH_2$), 1.95 ppm (m, 4, pyrrolidine H's at 4 plus $CH_2CH_2COOCH_3$) (together, the integration values of the δ 3.66 and 3.23 ppm signals came to 6 H's as required); nmr (D_2O) δ 4.34 (m, 1, HCOD), 3.68 (s, 1, $COOCH_3$), 3.4 (m, 3, pyrrolidine H's at 2 and 5), 2.48 (q, 2, pyrrolidine H's at 4), 2.12 ppm (t, 4, $CH_2CH_2COOCH_3$). These chemical shifts may be compared with those reported for hydroxyproline.[16] The yield of crystallized hydroxy product **6** over the three steps from the oxo diester **3** came to 46%. A sample of 2-(β-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride prepared for analysis by two recrystallizations from methanol showed mp 123–127° and $[\alpha]^{25}D$ 0.0° (*c* 0.5, CH_3OH).

Anal. Calcd for $C_8H_{16}ClNO_3$: C, 45.78; H, 7.69; N, 6.68. Found: C, 45.65; H, 7.55; N, 6.53.

***N*-Alkylation of Pyrrolidine Derivative 6 with Bromoacetate Esters.**—A solution of 11 g (0.053 mol) of 2-(β-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride (**6**) in 200 ml of dry methanol was treated with sodium carbonate (6.7 g, 0.063 mol) and methyl bromoacetate (11.8 g, 0.077 mol), and the mixture was stirred at 60° for 2 days. The reaction mixture was filtered at room temperature, and the filtrate was stripped of volatiles. The residue was triturated with chloroform (200 ml), solids were removed, and the chloroform solution was again freed of solvent. Chromatography of the residual oil through an 80-g column of silica gel with 2:1 hexane–ether as elution solvent allowed the two main constituents to be separated. The faster moving material, which proved to be lactone **8**, was obtained as crystals (2.9 g, 23%), mp 52–55°, homogeneous according to thin layer chromatography (8:1 ether–hexane). The next fraction through the column was taken as diester **7**, an oil (5.5 g, 40%) containing a trace of lactone **8** by thin layer chromatography.



8

Lactone **8** showed the following properties: ir ($CHCl_3$) 1730 (ester and lactone C=O's) with no significant absorption above 3100 cm^{-1}; nmr ($CDCl_3$) δ 4.84 (q, J = 5 Hz, 1, H_e), 3.68 (s, 3, CH_3-a), 3.50–2.86 (m for H_e including a pronounced peak at 3.42 for H_b, 4), 2.87–1.77 ppm (m, 7, H's at d and f). A single crystallization from ether–hexane brought the melting point of lactone **8** to 58–60°.

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.07; H, 6.97; N, 6.47.

Dimethyl ester **7** was obtained with ir ($CHCl_3$) 3400 (OH) and 1729 cm^{-1} (ester C=O's); nmr ($CDCl_3$ plus 10% D_2O) δ 4.70–3.90 (m, $W_{1/2}$ = 12 Hz, 1, CHOD), 3.66 and 3.62 (two s's, 6, 2 $COOCH_3$), 3.42 (s) and 3.20 (m) (3, NCH_2COOCH_3 plus pyrrolidine H at 2), 2.40 and 1.85 ppm (two sets of m's, 8, pyrrolidine H's at 4 and 5 plus $CH_2CH_2COOCH_3$).

Converting lactone **8** into the dimethyl ester **7** established the relation between the two. Thus, when a solution of homogeneous lactone **8** (27 mg) in 5 ml of methanol was allowed to stand at room temperature for 2 weeks, the resulting product (still with traces of lactone **8** plus an unidentified spot, possibly from the corresponding carboxylic acid) gave R_f values as well as infrared and nuclear magnetic resonance spectra identical with those obtained from dimethyl ester **7**.

When *tert*-butyl bromoacetate was substituted for methyl bromoacetate in the N-alkylation using essentially the same procedure, the homogeneous *tert*-butyl ester lactone analogous to **8** was obtained (49%) as a solid, mp 48–50°; and the *tert*-butyl methyl diester analogous to **7** was obtained in about 30% yield as a colorless oil still containing a trace of lactone. The *tert*-butyl lactone ester showed ir ($CHCl_3$) 1732 (ester and lactone C=O's), no maxima above 3100 cm^{-1}; nmr ($CDCl_3$) essentially the same as that of the methyl lactone ester **8** except that the three-proton singlet at δ 3.68 for $COOCH_3$ has changed to a nine-proton singlet at 1.48 ppm for $COOC(CH_3)_3$. One crystalliza-

(16) R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, **5**, 195, 513 (1962).

tion from ether–hexane furnished *tert*-butyl lactone ester with mp 50–52°.

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.66; H, 8.29; N, 5.49. Found: C, 61.22, H, 8.41; N, 5.60.

The oily *tert*-butyl methyl diester showed ir ($CHCl_3$) 3400 (OH), 1734 cm^{-1} (ester C=O's); nmr ($CDCl_3$) δ 4.02 (m, $W_{1/2}$ = 3 Hz, 2, HCOH), 3.65 (s, 3, $COOCH_3$), 3.35 and 3.15 (s and m, 3, NCH_2COO plus pyrrolidine H at 2), 2.40 and 1.87 (two sets of multiplets, 8, pyrrolidine H's at 3 and 4 plus $CH_2CH_2COOCH_3$), 1.46 ppm (s, 9, $COOC(CH_3)_3$). The hydroxyl group of this *tert*-butyl methyl diester could be acetylated at room temperature with acetic anhydride and pyridine. Chromatography followed by a single crystallization from ether–hexane gave the expected *N*-(*tert*-butyloxycarbonylmethyl)-2-(β-carbomethoxyethyl)-3-acetoxypyrrolidine, mp 39–39.5°.

Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.22; H, 8.28; N, 4.35.

1-Acetoxy-6-oxoindolizidine (11) by Dieckmann Cyclization of Pyrrolidines 7 and 8, Decarboxylation, and Acetylation.—A mixture of lactone **8** and dimethyl ester **7** was prepared as described above. No separation was attempted; instead, after chromatography through a short column, solvent was removed completely, and the colorless oily mixture was used directly in the Dieckmann process.

Sodium hydride in oil, as a 57% suspension, was rinsed free of heavy solvent with dry ether. A vigorously stirred suspension of this sodium hydride (3.0 g, 0.070 mol) with 20 ml of dry benzene was treated at room temperature over a 1-hr period with a solution of mixed lactone and diester **8** and **7** (8.1 g) in 50 ml of benzene containing 0.05 ml of methanol. Pure nitrogen protected the reaction mixtures throughout. Thin layer chromatography (19:1 chloroform–methanol) of the condensation mixture after 6 hr of stirring at room temperature revealed no unchanged starting materials. Adding 10% hydrochloric acid brought the mixture to pH 5. The resulting two-phase system was used directly for decarboxylation to **10** (see below) or, in a similar run with sodium methoxide in place of sodium hydride, was processed to isolate cyclic keto ester **9**. The latter experiment involved evaporating the aqueous phase, triturating the dry residue with 1:20 methanol–chloroform to separate inorganic salts, and chromatographing the soluble material through silica gel with 1:19 methanol–chloroform as solvent. The pale yellow product (purple color with ferric chloride solution), when crystallized from chloroform–hexane at −80°, was obtained as pale yellow solid keto ester **9**: mp 99–102°; ir ($CHCl_3$) 3608 (sharp, free OH), 3396 (broad, H-bonded OH), 1721, 1666, and 1629 (ester and ketone C=O's and the enolic system), 2806, 2751, 2704 cm^{-1}; nmr ($CDCl_3$) δ 9.48 (m, 1, O=C—CH—C=O), 4.12 (broad, $W_{1/2}$ = 11 Hz, 1, HCOH), 3.70 (s, 3, $COOCH_3$), 3.54–2.45 (m, 4), 2.45–1.56 ppm (m, 6). The δ 9.48-ppm signal disappeared when D_2O was added to the tube. Keto ester **9** proved to be very unstable, turning brown after standing a few hours either in air or sealed under argon.

For the decarboxylation of Dieckmann product **9** to hydroxy ketone **10**, the neutralized condensation mixture described above was mixed with concentrated hydrochloric acid (23 g) and water (32 ml) and the two-phase system was stirred and heated at 85°. After 6 hr, when none of the starting material **9** could be detected by thin layer chromatography, the aqueous acid layer was washed twice with benzene and then evaporated at 45° to remove all volatiles. The dark residual hydrochloride of indolizidine **10** was either acetylated directly to **11** (see below) or in other experiments was worked up at this point for the free indolizidine **10** by basification, extraction with chloroform, and preparative layer chromatography of the chloroform-soluble product (1:19, methanol–chloroform). The resulting partially purified still somewhat colored 1-hydroxy-6-oxoindolizine (**10**) was obtained as an unstable material in *ca.* 34% yield calculated from the **7** and **8** reactant mixture: ir ($CHCl_3$) 3410 (OH), 1717 (C=O), 2801, 2742, 2709 cm^{-1}. The Dieckmann cyclization with sodium methoxide or with potassium *tert*-butoxide using either the methyl or the *tert*-butyl compounds followed by decarboxylation offered no advantages; nor did decarboxylation in glacial acetic acid containing a trace of *p*-toluenesulfonic acid.

In order to obtain 1-acetoxy-6-oxoindolizidine (**11**), the unpurified hydrochloride of 1-hydroxy-6-oxoindolizidine (**10**) described above was mixed under nitrogen with pyridine (13 ml), acetic anhydride (6.4 g) was added dropwise, and the mixture was allowed to stand at room temperature for 3 hr. After stripping off volatiles, the residue was treated at temperatures below 0° with 10 ml of water followed by 10% sodium hydroxide solution to pH 8. The product was taken up in chloroform, and the chloroform solution was rinsed with aqueous bicarbonate, dried, and freed of all solvent. The acetylated product **11** so obtained weighed 2.6 g (estimated 38% from **7** + **8**) and was suitable for conversion into the oxime **12**.

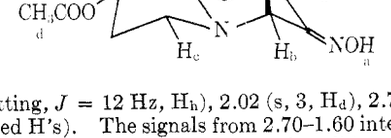
An experiment that was used to prepare pure 1-acetoxy-6-oxoindolizidine (**11**) utilized 5.0 g of the lactone–ester mixture (**8** and **7**) in a cyclization with sodium methoxide. Subsequent acid decarboxylation (**9** to **10**) followed by a 1-day exposure of the 1-hydroxy-6-oxoindolizine (**10**) to the action of acetic anhydride (3 g) plus pyridine (10 ml) as described above gave the unpurified acetyl derivative **11**, which was fractionated by chromatography through 24 g of neutral alumina (1:1, ether–hexane). The light-yellow material emerging as a thin layer chromatographically homogeneous product (8:1, ether–hexane) was taken as the desired 1-acetoxy-6-oxoindolizidine (**11**): mp 32–35°; ir ($CHCl_3$) 2795, 2744, 2721, 1732 (ester C=O) and no maxima at 4000–3500 cm^{-1}; nmr ($CDCl_3$) δ 2.03 ppm [s, —C(=O)CH_3]. One crystallization from ether–hexane at −80° brought the melting point to 42–44°.

The analysis for elements was performed with minimum delay, since indolizidine **11** deteriorated rapidly at room temperature. It could be stored however at Dry Ice temperature.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.66; N, 7.10. Found: C, 60.72; H, 7.85; N, 6.87.

Oximes 12 from 1-Acetoxy-6-oxoindolizidine (11).—A mixture of 1-acetoxy-6-oxoindolizidine (2.6 g) with pyridine (20 ml), ethanol (40 ml), and hydroxylamine hydrochloride (3.1 g) in a nitrogen atmosphere was stirred at 85–95° under a reflux condenser for 4 hr. After standing overnight, the mixture was stripped of volatiles. The residue was brought to pH 8 with 10% aqueous sodium hydroxide, and the mixture was extracted thoroughly with chloroform. The dried combined chloroform extracts were stripped of solvent at temperatures no higher than 40°, and the residual oxime product (two spots on thin layer chromatography) was passed through a 25-g silica gel chromatography column using 50 ml of hexane, 500 ml of 1:7 ether–hexane, and finally 2 l. of 1:1 ether–hexane as developing solvents. A fraction emerging with the 1:1 ether–hexane solvent and showing a single thin layer chromatography spot (R_f 0.47 with 9:0.4 ether–ethanol), when stripped of solvent, appeared as a colorless oil; layered under 1:2 ether–hexane at 0°, the oil crystallized to give colorless oxime **12A** (81 mg), mp 129–132°. This fraction was followed by a mixture of the two oximes **12A** and **12B** (R_f 0.47 and 0.31), mp 68–74°, weighing 230 mg, and finally by the homogeneous oxime **12B** (R_f 0.31), mp 95–97°, weighing 91 mg (total ~14%).

The oxime isomer **A**, mp 129–132°, showed ir ($CHCl_3$), 3590 (free OH), 3304 (H-bonded OH), 1730 (ester C=O), 1657 (C=N), 2800, 2751, 2719 cm^{-1}; nmr ($CDCl_3$) δ 8.58 (broad, H_a, disappears on addition of D_2O), 5.08 (broad d, J = 13 Hz, 1, H_e), 4.48 (d, J = 13 Hz, 1, H_b), 3.06 (m, 2, H_c + H_g), 2.28 (d with



further splitting, J = 12 Hz, H_h), 2.02 (s, 3, H_d), 2.70–1.60 ppm (m, unlabeled H's). The signals from 2.70–1.60 integrated to 11 H's as required. Crystallization from ether did not change the melting point of oxime **12A**.

Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.48; H, 7.62; N, 13.18.

Oxime isomer **B**, mp 95–97°, showed ir ($CHCl_3$) 3590 and 3294 (OH), 1730 (ester C=O), 1658 (C=N), 2800, 2751, 2719 cm^{-1}; nmr ($CDCl_3$) δ 8.60 (broad, H_a), 5.08 (broad, $W_{1/2}$ = 13 Hz, 1, H_e), 3.55 (d, J = 13 Hz, 1, H_b), 3.06 (m, 2, H_g + H_c), 2.57 (d, J = 12 Hz, 1, H_h), 2.02 (s, 3, H_d), 2.40–1.60 ppm (unlabeled H's). Signal integration showed 10 H's from δ 2.40–1.60 ppm. Crystallization of this oxime **12B** from ether–hexane raised the melting point to 97–99°.

Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.31; H, 7.82; N, 13.07.

The overall yield of oximes **12** obtained in the several steps from 2-(β-carbomethoxyethyl)-3-hydroxypyrrolidine hydrochloride (**6**) was in the order of 3.5%.

Hydrogenation of Oxime 12 to DL-Slaframine (13).—A mixture of 81 mg of oxime **12A**, mp 130°, 7.2 ml of absolute ethanol, 0.5 ml of 36.5% aqueous hydrochloric acid, and 96 mg of platinum oxide was shaken at room temperature under hydrogen (40 psi) for 6 hr. Catalyst and solvent were then removed, and the residue was pumped at room temperature (0.1 mm) to give 109 mg of slaframine dihydrochloride (**13** 2HCl) as a foamed, very hygroscopic solid. This dihydrochloride showed ir (KBr) 3120–2500 ($^+NH_3$) and 1732 cm^{-1} (C=O); nmr (D_2O) δ 5.5 (broad, H-C-OAc), 2.16 ppm (s, $OCOCH_3$).[3]

To obtain slaframine base (**13**) the dihydrochloride was stirred at 0° for 15 min in methanol containing solid sodium carbonate. Removal of solids and then solvent left a residue, which was triturated with carbon tetrachloride. The carbon tetrachloride-soluble slaframine, freed of solvent (30°; vacuum), was obtained as an oil homogeneous according to thin layer chromatography (R_f 0.43 with 12:3:5 1-butanol–acetic acid–water and R_f 0.30 with the same solvents in the ratio 4:1:1) using a 1:1 mixture of 1.1% potassium iodide and 0.14% chloroplatinic acid to bring out the spots. The product gave a positive ninhydrin test for primary amine:[3] ir (CCl_4) 1734 (ester C=O), 1242 cm^{-1} (acetate); gas–liquid chromatography with a 6-ft column of supported methyl phenyl silicone at 140° indicated a major component (71%) at 11.1 min accompanied by several much smaller peaks.

The minimum yield of slaframine, judging from the yield of pure dipicrate (34%) or *N*-acetyl (40%) derivatives obtained from the hydrogenation product (see below), is in the order of 30–40%.

Dipicrate and *N*-Acetyl Derivatives of Synthetic Slaframine (13).—The mixed syn and anti oximes **12** (168 mg) were hydrogenated essentially as described above. A small aliquot of the resulting slaframine dihydrochloride was processed as before to recover the free base **13**, which proved to be homogeneous by thin layer chromatography (with the same R_f value as before) and which gave essentially the same kind of gas–liquid chromatography pattern. The bulk of the dihydrochloride hydrogenation product was diluted with water to 40 ml and used for the preparation of derivatives.

The dipicrate was obtained by removing all solvent from 5 ml of this stock solution, dissolving the residue (31 mg) in 0.5 ml of water, and adding saturated aqueous picric acid dropwise until no more precipitate formed. Crystallization of the solids (35 mg) from 20% aqueous alcohol gave slaframine dipicrate (21.3 mg, 34%) as yellow needles: mp 215–221° dec; ir (KBr) 3000, 2700–2250 ($^+NH_3$), 1738 (ester C=O), 1634, 1609, 1365 cm^{-1}.

Anal. Calcd for $C_{22}H_{24}N_8O_{16}$: C, 40.28; H, 3.63; N, 16.90; Found: C, 40.24; H, 3.68; N, 17.07.

N-Acetylslaframine (**14**) was obtained by stripping solvent from the remaining 35 ml of dihydrochloride stock solution and stirring the residue at room temperature with acetic anhydride (1.2 g) under a nitrogen atmosphere for 18 hr. Water (5 ml) was added at 0°, followed by 10% sodium hydroxide to pH 8. The *N*-acetylslaframine product was extracted repeatedly with chloroform, and the dried extracts ($MgSO_4$) were stipped of solvent to leave 143 mg of a light brown residue. Gas–liquid chromatography results suggested that at this stage the *N*-acetylslaframine (**14**) was 94% homogeneous; thin layer chromatography produced one heavy spot accompanied by two faint spots. Chromatography through a 36-cm column of neutral alumina (14 g) with ether–hexane mixture as solvents (300 ml of 1:4, 300 ml of 3:7; 5 l. of 1:1) furnished a one-spot fraction, which on crystallization from hexane at −80° gave 72 mg (40%) of white, crystalline *N*-acetylslaframine, mp 142–144°. This material showed one spot on thin layer chromatography (R_f 0.41 with 8:1 ether–alcohol) and produced a single peak on gas–liquid chromatography: ir ($CHCl_3$) 3426 (N–H), 1734 (ester C=O), 1663 (amide C=O), 1509 (N–H), 2900, 2750 cm^{-1}; nmr ($CDCl_3$) δ 6.28 (m, 1, N–H; disappears when D_2O added), 5.20 (m, $W_{1/2}$ = 13 Hz, 1, H–C–OAc), 4.20 (m, $W_{1/2}$ = 16 Hz before, and 8 Hz, after, adding D_2O, 1, H–C–NHAc), 3.00 (m, 2, H_{eq}–C–N–C–H_{eq}), 2.75–1.20 ppm (m, 15, all other protons, including two prominent singlets at 2.02 and 2.10 assigned respectively to CH_3COO and CH_3CONH). One crystallization from ethanol–hexane brought the melting point of the *N*-acetylslaframine (**14**) to 143–146°, $[\alpha]^{25}D$ 0.0°.

Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.81; H, 8.27; N, 11.58.

Comparison Samples of Slaframine and Derivatives. A. Synthetic Slaframine Dihydrochloride.—A partially purified sample of the synthetic material was used. Although natural slaframine dihydrochloride was not available for comparison in our laboratories, copies of its infrared absorption curve (KBr) and its nuclear magnetic resonance curve (D_2O)[3] were sent to us by Dr. Aust. The corresponding pairs of curves were found to be identical.

B. Natural Slaframine Dipicrate.—A sample of the dipicrate from slaframine isolated from *R. leguminicola* was furnished by Dr. Aust. Table I compares this material with the synthetic material described above.

C. Slaframine Base.—The synthetic dipicrate (11 mg) in 5 ml of 10% hydrochloric acid was shaken several times with ether to remove the picric acid. Adding 10% sodium hydroxide solution to the aqueous layer until pH 10 released the slaframine, which was extracted thoroughly with chloroform. The dried extracts ($MgSO_4$) were freed of all solvent at reduced pressures at temperatures no higher than 30° to leave *ca.* 2 mg (*ca.* 60%) of oily DL-slaframine (**13**).

Natural slaframine base (3 mg, 64% yield) was obtained in the same way from its dipicrate. Table II gives the comparison results.

D. *N*-Acetylslaframine from the Natural Material.—A 0.5-mg sample supplied to us showed mp 138–144°. Purified by sublimation at 100° (0.1 mm), the sample was obtained as white needles, mp 143–146°. The comparison between this material and synthetic *N*-acetylslaframine appears in Table III.

Acknowledgment.—We are indebted to Professor Steven D. Aust, Michigan State University, for spectra and for samples of slaframine dipicrate and *N*-acetylslaframine prepared from natural slaframine. His help in other ways, as well as the help of Professor Kenneth L. Rinehart, Jr., of the University of Illinois, is also appreciated.

Registry No.—**1**, 6582-81-6; 1 dipicrate, 6582-82-7; 1 *N*-acetyl deriv., 41563-75-1; **3**, 41563-76-2; **4**, 41563-77-3; **5**, 41563-78-4; **6**, 41563-79-5; **7**, 41563-80-8; **7** *N*-*tert*-butyl ester analog, 41563-81-9; **8**, 41563-82-0; **8** *tert*-butyl ester analog, 41563-83-1; **9** (R = $COOCH_3$, R′ = H), 41563-84-2; **9** (R = H, R′ = $COOCH_3$), 41563-85-3; **10**, 41563-86-4; **11**, 41563-87-5; *syn*-**12**, 41563-88-6; *anti*-**12**, 41563-89-7; **13**, 30591-15-2; **13** 2HCl, 41563-91-1; **13** dipicrate, 41563-92-2; **14**, 41563-93-3; *N*-(β-cyanoethyl)-5-oxo-2-pyrrolidinecarboxylic acid, 41563-94-4; 2-(β-carbomethoxyethyl)-3,3-dimethoxypyrrolidine HCl, 41563-95-5; methyl bromoacetate, 96-32-2; *tert*-butyl bromoacetate, 5292-43-3; *N*-*tert*-butyloxycarbonylmethyl)-2-(β-carbomethoxyethyl)-3-acetoxypyrrolidine, 41563-97-7.