methyl isocyanate and mucochloric acid but no well-defined product could be isolated.

Mucochloric Anhydride.—Mucochloric acid (84 g., 0.5 mole), 100 ml. of benzene, 50 ml. of dioxane and 1 g. of benzenesulfonic acid were refluxed for twenty hours under a Dean and Stark trap while 9 cc. of water was removed. Ten grams of crystals were removed from the hot solution by filtration. This fraction was recrystallized twice from a mixture of benzene and dioxane (using Nuchar for decolorization) to give 5 g. of white crystals of the β-isomer of mucochloric anhydride, m. p. 180°.

The mother liquor from the hot filtration was evaporated to small volume and cooled to give 45 g. of crystals, m. p. 140–143°. Several recrystallizations from alcohol and from a mixture of benzene and hexane gave the α-isomer in slightly purer form, m. p. 141–143°.

Anal. Calcd. for $C_8H_2Cl_4O_5$: C, 30.0; H, 0.63; Cl, 44.3. Found for α-isomer: C, 30.1; H, 0.70; Cl, 44.4. Found for β-isomer: C, 30.1; H, 0.90; Cl, 43.8.

Similar products were obtained by the action of sulfuric acid or oleum on mucochloric acid in chlorobenzene solution at 0–20°. The α-isomer was also isolated as a by-product in the preparation of mucochloryl chloride below.

Mucochloryl Chloride.—Mucochloric acid (254 g., 1.5 moles) and 354 g. (330 cc., 4.5 moles) of thionyl chloride were mixed but gave very little evidence of reaction at room temperature. One gram of zinc chloride was then added and the solution was refluxed vigorously for two days after which time the evolution of hydrogen chloride and sulfur dioxide had abated. Distillation gave 145 g. (52%) of mucochloryl chloride; b. p. 109° (21 mm.), $n^{25}D$ 1.5252. Hill[4] reports b. p. 101° (15 mm.) for a preparation made from mucochloric acid and phosphorus pentachloride. The absorption spectrum, Fig. 2, indicates that mucochloryl chloride is predominantly 3,4,5-trichloro-2-(5)-furanone, the principal maximum being at 235 mμ. However, a minor absorption band at 270 mμ indicates the possibility of some α,β-dichloro-β-formylacrylyl chloride impurity.

From a higher boiling fraction, b. p. 180–185° (1 mm.), there was obtained 60 g. (26%) of mucochloric α-anhydride. This melted at 141–143° after recrystallization from a mixture of benzene and hexane.

Mucochloryl chloride was found to be relatively inert in several attempted reactions. It did not attack magnesium in refluxing ether or dioxane in the presence of traces of iodine or methylmagnesium iodide. It was largely recovered unchanged after lengthy stirring with equimolar quantities of benzene and aluminum chloride in carbon tetrachloride, carbon disulfide or nitrobenzene at temperatures up to 70°. Over 50% recovery was also observed after heating at 200° for five hours with excess cuprous cyanide. Only intractable tars resulted from longer or more drastic treatment.

Acknowledgments.—The author is indebted to Mr. D. R. Beasecker and Miss Rosella Ulm of this Laboratory for measurements of the ultraviolet absorption spectra.

Summary

The methyl, allyl, vinyl, *n*-amyl and *n*-dodecyl esters of mucochloric acid have been prepared and characterized as 3,4-dichloro-5-alkoxy-2(5)-furanones. Mucochloric acid has been dehydrated to its anhydride which has been isolated in two stereoisomeric forms. The acid has also been treated with acetic anhydride, with benzoyl chloride and with phenyl isocyanate to give the corresponding mixed anhydrides. Several observations on mucochloryl chloride have been noted.

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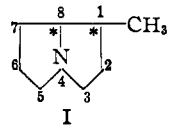
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

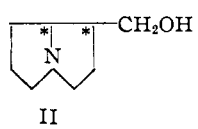
The Synthesis of Pyrrolizidines. VI. Stereochemical Correlation of 1-Methyl- and 1-Hydroxymethylpyrrolizidine Isomers with Certain Alkaloid Products[1]

BY NELSON J. LEONARD AND DONALD L. FELLEY[2]

With the development of a convenient method for the synthesis of 1-methylpyrrolizidine (I),[3] it became possible to proceed to the separation of this product into its racemic modifications and, following this, to the resolution of the racemates. The realization of both separation and resolution now permits elucidation of the stereochemistry of the alkaloid products *l*-heliotridane and *l*-pseudoheliotridane. It has also been possible to effect the synthesis of 1-hydroxymethylpyrrolizidine (II), the structure represented in diastereoisomeric forms by the alkaloid products *l*-isoretronecanol and *l*-trachelanthamidine.



I



II

In the synthesis of 1-methylpyrrolizidine (I) starting with nitromethane and ethyl crotonate by a three-step method involving two Michael condensations followed by reductive cyclization,[3] both asymmetric centers (carbons 1 and 8) have been established prior to the reduction step, which might otherwise be stereospecific. The immediate precursor of I, diethyl β-methyl-γ-nitropimelate, results from two Michael reactions and hence should represent a mixture of two racemates. Reduction of such a mixture would be expected to yield the two diastereoisomeric racemates of I, yet in our previously described synthesis,[3] only one of the racemates was obtained pure. This isomer which predominated was apparently identical with the sole 1-methylpyrrolizidine racemate obtained by the syntheses of Men'shikov[4] and Prelog and Zalan[5] and named by them "*dl*-heliotridane." In order to obtain both

(1) For paper V in this series, see Leonard and Shoemaker, THIS JOURNAL, **71**, 1762 (1949).

(2) Rohm and Haas Co., Philadelphia, Pennsylvania.

(3) Leonard and Felley, THIS JOURNAL, **71**, 1758 (1949).

(4) Men'shikov, *Bull. acad. sci. U. S. S. R., Classe sci. math. nat., Sér. chim.*, **5**, 1035 (1937).

(5) Prelog and Zalan, *Helv. Chim. Acta*, **27**, 531 (1944).

racemates of I in pure form, we have repeated our synthesis of 1-methylpyrrolizidine on a larger scale. The separation of the product into racemic forms was then accomplished both by chromatography and by fractional distillation.

The product obtained (in 75% yield) by reductive cyclization of diethyl β-methyl-γ-nitropimelate was subjected to chromatographic adsorption on activated alumina. The course of the chromatography was followed by evaporation of successive percolate fractions and conversion of each residue to a picrate. Two picrates were thus obtained: A, m. p. 234–236°; B, m. p. 243–244°. Since 1-methylpyrrolizidine (I) is the $C_8H_{15}N$ product which results from this method of synthesis and since both picrates had the correct analysis for 1-methylpyrrolizidine picrate, one of the derivatives was necessarily *dl*-heliotridane picrate and the other, *dl*-pseudoheliotridane picrate.[6] Picrate B was identified as ***dl*-heliotridane picrate** on the basis of physical properties, including infrared absorption. Two samples[9,10] of authentic *l*-heliotridane picrate[11] were found to melt at 243–244°,[12] with decomposition. Authentic *l*-heliotridane picrate was similar in crystal form to picrate B, gave no melting point depression when mixed with it, but was depressed in melting point on admixture with picrate A. The infrared absorption spectra, as determined in solution, were identical for picrate B and *l*-heliotridane picrate, and different for picrate A. Picrate A was accordingly called ***dl*-pseudoheliotridane picrate,** as the picrate of the second racemate of 1-methylpyrrolizidine.

The separation of the racemates of 1-methylpyrrolizidine was effected on a larger scale by fractional distillation, a method which was suggested by the difference between the boiling points reported for the active diastereoisomers, *l*-heliotridane[9,13,14,15] and *l*-pseudoheliotridane.[7] The higher-boiling racemate, b. p. 168–170° (748 mm.), was readily identified as ***dl*-heliotridane** by its conversion to picrate B and to a picrolonate, m. p. 152–154°, which agreed closely in physical properties with the picrolonate of active heliotridane.[9,14] *dl*-Heliotridane was present to the extent of about 5% in the $C_8H_{15}N$ product. The lower-boiling racemate, b. p. 155–157° (748 mm.), which constituted about 95% of the product, was convertible to picrate A and was therefore called ***dl*-pseudoheliotridane.**

For satisfactory identification of the lower-boiling synthetic isomer as the racemate of the alkaloid product *l*-pseudoheliotridane, it was considered necessary to resolve the racemate and to compare the properties of an active form with those reported for *l*-pseudoheliotridane.[7] Resolution employing *d*-tartaric acid was the most effective method tried, and a pure, optically active base was liberated from the *d*-tartrate salt. The specific rotation observed for the active 1-methylpyrrolizidine was $[\alpha]_D$ + 6.94° (homogeneous), as compared with the value, −8.25° (homogeneous), observed by Men'shikov and Borodina[7] for *l*-pseudoheliotridane. The similarity in range of rotation is at least suggestive, since the specific rotation of *l*-heliotridane has been reported to be more than ten times as great.[9,16,17] Assuming that *l*-pseudoheliotridane is a 1-methylpyrrolizidine, the discrepancy between the specific rotation values may be due either to our inability to effect complete resolution or to contamination of *l*-pseudoheliotridane with some of the higher rotating *l*-heliotridane due to the method employed[7,8] for obtaining the product from *l*-trachelanthamidine (II).[18] A comparison of the properties of the derivatives of our resolved form with those reported for the derivatives of *l*-pseudoheliotridane is somewhat more rewarding. The melting points of the picrates are identical, as are those of the picrolonates (see Table I). Thus, it appears that the product obtained by this method of resolution of the lower-boiling 1-methylpyrrolizidine is *d*-pseudoheliotridane. The infrared absorption spectra of *d*-pseudoheliotridane and *l*-heliotridane are recorded in Fig. 1 for purposes of present and future comparison.

On the basis of the foregoing observations, the following conclusions seem justified: (a) Our method of synthesis of 1-methylpyrrolizidine gives a mixture of *dl*-heliotridane and *dl*-pseudoheliotridane, with the latter present in much greater amount. (b) The 1-methylpyrrolizidine synthesized by Prelog and Zalan[5] was not entirely "*dl*-heliotridane" (picrate, m. p. 234–236°; picrolonate, m. p. 162–163°) as they concluded but was probably predominantly *dl*-pseudoheliotridane.[19] (c) Men'shikov's conclusion that *l*-pseudoheliotridane is a 1-methylpyrrolizidine and a diastereoisomer of *l*-heliotridane appears to be correct.

(6) On the assumption that the structural assignment of *l*-pseudoheliotridane as a 1-methylpyrrolizidine[7,8] is correct.

(7) Men'shikov and Borodina, *J. Gen. Chem.* (*U. S. S. R.*), **15**, 225 (1945).

(8) Men'shikov, *ibid.*, **16**, 1311 (1946).

(9) Adams and Rogers, THIS JOURNAL, **63**, 228 (1941).

(10) Adams and Mahan, *ibid.*, **65**, 2009 (1943).

(11) We are indebted to Dr. Roger Adams for providing us with authentic samples of material.

(12) Corrected, as are all of the melting points reported in this paper. The authors suggest emergent stem and thermometer errors as possible sources of the discrepancy between our observed value for the melting point of *l*-heliotridane picrate and that reported in reference 9.

(13) Men'shikov, *Ber.*, **66**, 875 (1933).

(14) Konovalova and Orekhov, *Bull. soc. chim.*, [5] **4**, 1285 (1937).

(15) Konovalova and Orekhov, *Ber.*, **69**, 1908 (1936).

(16) Men'shikov, *ibid.*, **68**, 1051 (1935).

(17) Men'shikov, *ibid.*, **66**, 875 (1933).

(18) This method involved replacement of the primary hydroxyl of trachelanthamidine by chlorine to give $C_8H_{14}ClN$ and removal of the chlorine by reduction, first with sodium and isoamyl alcohol, then with hydrogen over platinum catalyst, to give $C_8H_{15}N$ (b. p. 159–160°; picrate, m. p. 232–233°; picrolonate, m. p. 162–163°; aurichloride, m. p. 183–184°). If any unsaturation at the 1-carbon were to be created during the process, the final hydrogenation might allow contamination of the *l*-pseudoheliotridane with its diastereoisomer.

(19) In reference 3, therefore, for "*dl*-heliotridane" throughout read *dl*-pseudoheliotridane.

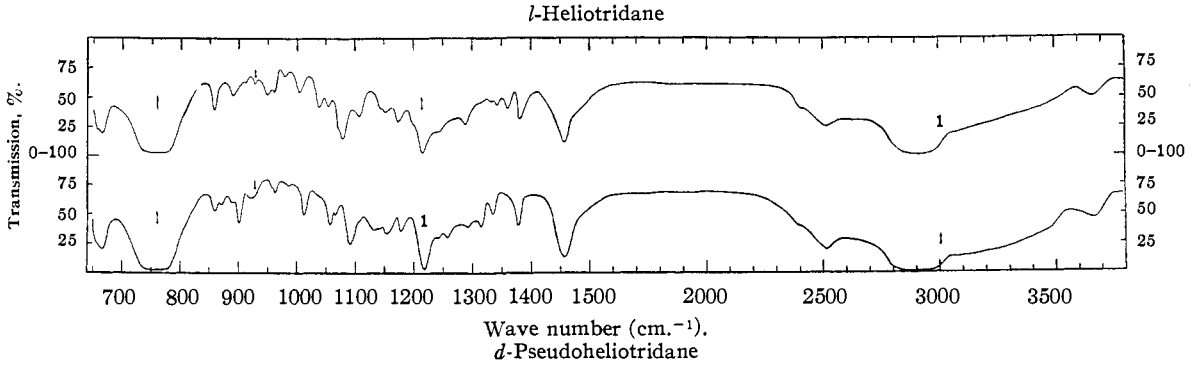
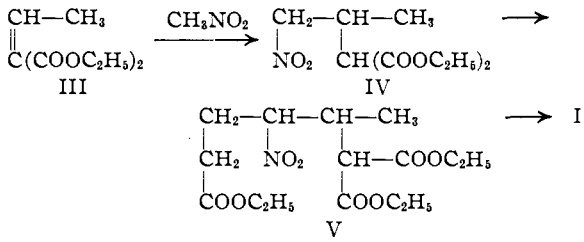


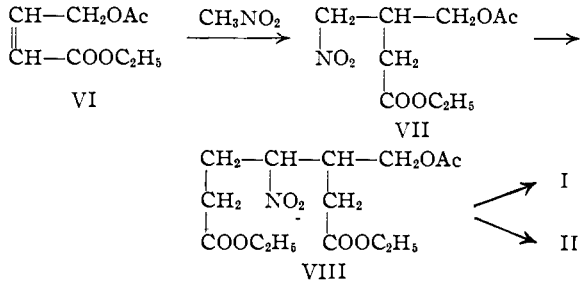
Fig. 1.

With the object of trying to vary the proportion of the diastereoisomeric racemates obtained in the synthesis of 1-methylpyrrolizidine (I), different intermediates were selected for a similar sequence of reactions. The main departure from the previous synthesis[3] was the substitution of diethyl ethylidenemalonate (III) for ethyl crotonate.



It was expected that diethyl ethylidenemalonate would be more reactive than ethyl crotonate in the Michael condensation with nitromethane, due to the presence of the additional activating carbethoxyl group. This was found to be so, since the addition of nitromethane to the ethylidenemalonic ester (III) proceeded readily in the presence of benzyltrimethylammonium hydroxide at 50° to give a 69% yield of ethyl α-carbethoxy-β-methyl-γ-nitrobutyrate (IV). The condensation of IV with ethyl acrylate to give diethyl α-carbethoxy-β-methyl-γ-nitropimelate (V) was effected (in 65% yield) under the same conditions, which constituted a modification of the general Bruson method.[20] Reductive cyclizations of certain substituted malonic esters have been shown to proceed with complete loss of one carbethoxyl group,[21] and diethyl α-carbethoxy-β-methyl-γ-nitropimelate (V) was found to behave in like manner. Hydrogenation of V in dioxane in the presence of copper chromite catalyst at 265° and 250–350 atmospheres[1] produced 1-methylpyrrolizidine (I). Although the yield in the reductive cyclization step was lower (25%) than that obtained by the reductive cyclization of diethyl β-methyl-γ-nitropimelate,[3] our object was partially realized in that the proportion of the two racemates present in the final product was altered. A chromatographic separation indicated that *dl*-heliotridane was present to the extent of at least 13% of the total 1-methylpyrrolizidine.

Compounds with the related structure, 1-hydroxymethylpyrrolizidine (II), have been obtained from a number of alkaloids, and the diastereoisomeric active forms are known as *l*-isoretronecanol,[22] corresponding in configuration to *l*-heliotridane, and *l*-trachelanthamidine,[7,8,23] corresponding in configuration to *l*-pseudoheliotridane. A logical approach to the synthesis of 1-hydroxymethylpyrrolizidine appeared to be a series of reactions analogous to those used in the synthesis of 1-methylpyrrolizidine, but with the substitution of fumaric ester for the crotonic or ethylidenemalonic ester. However, Kloetzel[24] has shown that adducts of the nitroparaffins with fumaric ester are not stable in the presence of base and lose the nitro group as nitrous acid. Consequently, further attempts to condense either nitromethane or methyl γ-nitrobutyrate with dimethyl fumarate gave only the unsaturated esters resulting from loss of nitrous acid from the expected adduct, or products resulting from further condensation of the original nitro compound with these unsaturated esters. Ethyl γ-acetoxycrotonate (VI) was found to be a satisfactory intermediate for the series of reactions (VI → VII → VIII → II) leading to the formation of 1-hydroxymethylpyrrolizidine.



Addition of nitromethane to this ester (VI)

(20) Bruson, U. S. Patent 2,342,119, February 22, 1944.

(21) Boekelheide and Rothchild, THIS JOURNAL, **69**, 3149 (1947); **71**, 879 (1949).

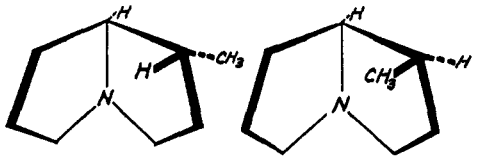
(22) Adams and Hamlin, *ibid.*, **64**, 2597 (1942).

(23) Guerevich and Men'shikov, *J. Gen. Chem.* (*U. S. S. R.*), **17**, 1714 (1947).

(24) Kloetzel, THIS JOURNAL, **70**, 3571 (1948).

in the presence of benzyltrimethylammonium butoxide gave ethyl β-nitromethyl-γ-acetoxybutyrate (VII) in 65% yield, and further condensation with ethyl acrylate gave diethyl β-acetoxymethyl-γ-nitropimelate (VIII) in 67% yield. Hydrogenation of VIII over copper chromite at 265°, the temperature normally employed for these reductive cyclizations, gave mainly 1-methylpyrrolizidine (I). The hydrogenolysis probably occurred due to the presence of the 1,3-aminoalcohol linkage after reduction of the nitro group. This type of cleavage is common with 1,3-glycols and 1,3-aminoalcohols undergoing hydrogenation at high temperature and pressure over copper chromite,[25] but recent work[26] has shown that hydrogenation at lower temperatures may prevent the hydrogenolysis of 1,3-glycols. Accordingly, the reduction step was carried out at 180–200° using an equal part by weight of copper chromite catalyst. 1-Hydroxypyrrolizidine (II) was thereby obtained, but in very low yield. It was necessary to subject the product to chromatographic adsorption on alumina for purification and using this method, the amine was isolated as the picrate. The greater portion of the product was an intractable oil consisting of incompletely reduced material. The low temperature necessary to ensure against hydrogenolysis was apparently insufficient to effect complete reductive cyclization. The picrate obtained (m. p. 174–175°) was identical in melting point with that reported by Men'shikov and Borodina[7] for *l*-trachelanthamidine picrate (m. p. 174°). The synthetic picrate differed in melting point and crystal form from *l*-isoretronecanol picrate,[11] an authentic sample of which was observed to melt at 193–194°. On the basis of the melting point behavior and by analogy to the predominant isomer obtained in the synthesis of 1-methylpyrrolizidine, it appears that the predominant isomer of 1-hydroxymethylpyrrolizidine herewith synthesized is probably *dl*-trachelanthamidine.[26a]

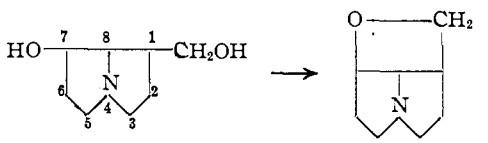
There has been no correlation of evidence reported concerning the absolute configuration of the 1-methylpyrrolizidine (I) isomers, that is, whether the 1-methyl group in heliotridane is *cis* (IX) or *trans* (X) to the 8-hydrogen atom. However, certain conclusions regarding the configuration can be drawn by examination of earlier work on the *Senecio* alkaloids and some of their degradation products. The structure of platynecine (active) was finally determined as XI



IX X

(a, CH_2OH in place of CH_3)

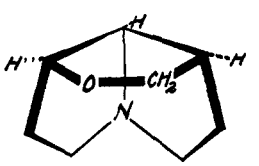
and that of anhydroplatynecine, as XII, when the position of the secondary hydroxyl group was established as being at the 7-position throughout the series of *Senecio* alkaloid products.[27] Anhydroplatynecine (XII) is readily formed from platynecine by the treatment of XI with a variety



XI XII

(a, CH_3 in place of CH_2OH)

of reagents (sulfuric acid, thionyl chloride, phosphorus trichloride, phosphorus pentachloride or phosphorus oxychloride).[15,28] Examination of scale molecular models of XII indicates that it can exist only in the configuration shown in formula XIII (and its mirror image), that is, with the 1,7-methyleneoxy bridge *trans* with respect to the 8-hydrogen atom. Nothing definite can be



XIII

said concerning the configuration of the 7-hydroxyl as originally present in platynecine, since it cannot be readily ascertained whether retention or inversion of configuration at C-7 occurs in ether formation (XI→XII) as effected by such a variety of reagents. However, it appears certain that these reagents would not cause any change in configuration at the 1-carbon, and therefore that the 1-CH_2OH group is *trans* to the 8-hydrogen in platynecine. Since platynecine (XI) has been converted to *l*-isoretronecanol (II)[22] and retronecanol (XIa) has been converted to *l*-heliotridane (I)[9] under conditions unlikely to affect the C_1–CH_2OH or C_1–CH_3 bonds, and since platynecine has also been degraded to *l*-heliotridane,[15] it can be concluded that the 1-methyl group in heliotridane is *trans* to the 8-hydrogen atom, so that *l*-heliotridane is represented by structure X (or its mirror image) and *l*-isoretronecanol, by structure Xa (or its mirror image). One of the optically active forms of *dl*-pseudoheliotridane would then be represented by IX

(25) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 88.

(26) Adkins and Billica, THIS JOURNAL, **70**, 3121 (1948).

(26a) It appears now from the work of Galinovsky, Goldberger and Pöhm (*Monatsh.*, **80**, 550 (1949)) that this product which we have synthesized may also be regarded as DL-*laburnine*, or the racemic form of the alkaloid laburnine, which was recently isolated from *Cytisus laburnum*. Galinovsky and his coworkers have pointed out that Men'shikov's trachelanthramidine[1] and their laburnine may well be optical antipodes, since the properties of the derivatives are similar (picrate, m. p. 172–173°; picrolonate, m. p. 181–182°), and the optical rotations are approximately equal and opposite (added in proof, April 28, 1950).

(27) Adams and Leonard, THIS JOURNAL, **66**, 257 (1944).

(28) Orekhov, Konovalova and Tiedebel, *Ber.*, **68**, 1886 (1935).

TABLE I

PHYSICAL CONSTANTS OF THE DIASTEREOISOMERIC 1-METHYLPYRROLIZIDINES AND THEIR DERIVATIVES

	l-Heliotridane	*dl*-Heliotridane[a]	"*dl*-Heliotridane" of Prelog and Zalan[5]	*dl*-Pseudoheliotridane[a]	*l*-Pseudoheliotridane[7]	*d*-Pseudoheliotridane[a]
B. p., °C.	165–166,[9] 165–167,[14] 169–170,[13] 169–171[15]	168–170 (748 mm.)	.....	155–157 (748 mm.) 65–66 (32 mm.)	159–160	155–157 (748 mm.)
$n^{20}D$	1.4648,[9] 1.4641[9]	.....	1.4638	1.4620	.....	1.4616
$[\alpha]D$ (homogeneous)	−92.06,[9] −91.27,[9] −68,[13] −51.03[15]	.....	.....	.....	−8.25	+6.94
Picrate, m. p. dec., °C.	243–244,[a] 237–238,[14,15] 236,[9,13] 233–234,[14] 232[9]	243–244	234–236	234–236	232–233	234–236
Picrolonate, m. p. dec., °C.	153–154,[15] 152–153[14]	152–154	162–163	163[8] (sintering)	162–163	162–163
Methiodide, m. p. dec., °C.	240–250[13]				>275	323–325

[a] Present investigation.

and one of the active forms of *dl*-trachelanthamidine, by IXa.

Experimental[29]

Separation of Racemates of 1-Methylpyrrolizidine. A. By Chromatography.—A column 27 cm. in length and 12 mm. in diameter was packed with 25 g. of activated alumina (Aluminum Ore Co.). Twenty ml. of petroleum ether (b. p. 37–49°) was put through the column, and then a solution of 1 g. of 1-methylpyrrolizidine[3] in 250 ml. of petroleum ether, followed in order by 400 ml. of a 1:1 solution of benzene and petroleum ether, 100 ml. of benzene, and finally 225 ml. of ether. Under atmospheric pressure, the solvent came through at the rate of 10 ml. per min. The first 20 ml. of percolate was discarded, and each succeeding 50 ml. was collected separately. The solvent was removed by distillation at atmospheric pressure, and the residue was treated with a saturated solution of picric acid in ether. The resulting picrates were recrystallized from methanol and the melting points were determined. The picrate made from the benzene-petroleum ether percolates of the column separated from methanol as elongated prisms, m. p. 234–236°, and constituted 89% of the total yield of 1-methylpyrrolizidine picrate. The picrate made from the diethyl ether percolates separated from methanol as fine needles, m. p. 243–244°, and constituted 3% of the total picrate. The remaining 8% was a mixture of the two picrates and was observed to melt at an intermediate temperature (237–239°). Samples of authentic *l*-heliotridane picrate,[9,10,11] m. p. 243–244°, caused no depression in the melting point of the racemic picrate of the same melting point. A mixture of *l*-heliotridane picrate with the racemic picrate of m. p. 234–236° melted at an intermediate temperature (237–239°).

***dl*-Heliotridane Picrate.**—The picrate crystallized from methanol as fine yellow needles which melted, with decomposition, at 243–244°.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12. Found: C, 47.54; H, 5.41.

***dl*-Pseudoheliotridane Picrate.**—The picrate crystallized from methanol as yellow elongated prisms which melted, with decomposition, at 234–235°.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12. Found: C, 47.45; H, 5.26.

B. By Fractional Distillation.—Twenty-five grams of 1-methylpyrrolizidine[3] was fractionally distilled through a 15-in., jacketed column, packed with glass helices and fitted with a total condensation, variable take-off distilling head. The pressure was controlled at about 30 mm. by means of a manostat, and a reflux ratio of 10:1 was employed. Cuts of the distillate were made regularly throughout the distillation and were identified by refractive index and by melting point of the recrystallized picrates made from each cut. After collection of 20 g. of *dl*-**pseudoheliotridane** (b. p. 65–66° (32 mm.); $n^{20}D$ 1.4620; picrate, m. p. 234–236°), the distilling pot was practically dry, and the distillation was stopped. When the column was allowed to cool and drain, about 3 g. of a dark residue was obtained. When the helices were washed with ether and a picrate was made from the ether washings, it was found to melt, with decomposition, at 240–242°, after recrystallization from methanol. The column hold-up was therefore impure *dl*-heliotridane. Pure *dl*-**heliotridane** (1.1 g.) was obtained by distillation of the 3-g. residue through a Vigreux column; b. p. 168–170° (748 mm.); picrate, fine needles from methanol, m. p. 242–243° (dec.). ***dl*-Heliotridane picrolonate**, made from this fraction in the usual manner, crystallized from methanol as orange needles, which melted, with decomposition, at 152–154°. In crystal form and melting point, this derivative closely resembled *l*-heliotridane picrolonate (see Table I).

Infrared Absorption Spectra of 1-Methylpyrrolizidine Picrates.—Infrared absorption spectra were determined for the following 1-methylpyrrolizidine picrates in chloroform solution: (1) *dl*-pseudoheliotridane picrate, m. p. 234–236° (dec.); (2) *dl*-heliotridane picrate, m. p. 242–243° (dec.); (3) *l*-heliotridane picrate, m. p. 243–244° (dec.).[10] The curves for the second two samples were identical and different from that for sample (1) in that they had characteristic absorption bands at 952 and 1043 $cm.^{-1}$, which were not present in the spectrum of (1).

Resolution of *dl*-Pseudoheliotridane.—A solution of 13.72 g. (0.0914 mole) of *d*-tartaric acid (Eastman Kodak Co.) in 150 ml. of hot solvent consisting of 100 ml. of ethyl acetate and 50 ml. of 95% ethanol was added to a solution of 11.42 g. (0.0914 mole) of *dl*-pseudoheliotridane in 150 ml. of the same solvent. The *dl*-pseudoheliotridane *d*-bitartrate precipitated immediately. The mixture was heated to boiling, and solution was effected by the addition of 25 ml. of solvent to the total. By effecting very gradual cooling of the solution from 70 to 25°, 12.5 g. of salt separated in clusters of long, stout, colorless prisms. After crushing on a clay plate or allowing the salt to dry for twenty-four hours *in vacuo* over calcium chloride and phosphorus pentoxide, the bitartrate melted at 69–71°. After drying for a further forty-eight hour period, with intermittent crushing and stirring, the melting point was raised to 111–113°, and the salt was converted from lustrous crystals to a chalky powder.

Anal. Calcd. for $C_{12}H_{21}NO_6$: C, 52.34; H, 7.69. Found: C, 52.21; H, 7.67.

Fractional crystallization from ethyl acetate–95% ethanol did not alter the melting point, and after six recrystallizations the specific rotation had reached a constant maximum of $[\alpha]^{25}D$ 19.7 ± 0.2° (*c*, 3.95, water). A mixture of 4.87 g. of *d*-pseudoheliotridane *d*-bitartrate with 20 ml. of 10% aqueous sodium hydroxide was extracted with three 25-ml. portions of ether. The combined ether extracts were dried, the ether was removed by distillation through an 8-in. helices-packed column, and the residual oil was fractionally distilled. The main frac-

(29) The authors are indebted to Miss Elizabeth M. Petersen for determination of infrared absorption spectra.

tion boiling at 153–155° was fractionally distilled twice more, yielding 0.4 g. of *d*-pseudoheliotridane; b. p. 155–157° (748 mm.); $n^{20}D$ 1.4616; $d^{20}D$ 0.896; *MR*D, calcd. 38.23, found 38.36; $[\alpha]^{25}D$ +6.94° (homogeneous).

***d*-Pseudoheliotridane Picrate.**—Prepared in ether and recrystallized from methanol, the picrate formed fragile, elongated plates which melted, with decomposition, at 234–236°.

***d*-Pseudoheliotridane Picrolonate.**—Prepared in ether and recrystallized from methanol, the picrolonate formed fine orange needles which melted, with decomposition, at 162–163°.

***d*-Pseudoheliotridane Methiodide.**—Prepared in ether and recrystallized from acetone, the methiodide formed colorless rhombic prisms which melted, with decomposition, at 323–325°, after preliminary darkening at 310°.

Infrared Absorption Spectra of *l*-Heliotridane and *d*-Pseudoheliotridane.—The infrared absorption spectra were determined for solutions of *l*-heliotridane and resolved *d*-pseudoheliotridane of equal concentration in chloroform. The spectra indicated clearly the difference between these diastereoisomeric amines (Fig. 1).

Synthesis of 1-Methylpyrrolizidine Starting with Diethyl Ethylidenemalonate

Ethyl α-Carbethoxy-β-methyl-γ-nitrobutyrate.—To a stirred solution of 61 g. (1.0 mole) of nitromethane and 10 g. of aqueous benzyltrimethylammonium hydroxide (Rohm and Haas Co.) with 25 ml. of *t*-butyl alcohol was added dropwise over a period of one-half hour 46.5 g. (0.25 mole) of diethyl ethylidenemalonate. The reaction was initially exothermic, and when the temperature began to fall, the reaction mixture was stirred at 50° for forty-eight hours. An additional 5-g. portion of "Triton B" was added after the first twenty-four hours. The product was isolated as in the case of ethyl β-methyl-γ-nitrobutyrate[3] and collected as an oil, b. p. 118–120° (1.2 mm.); yield 42.5 g. (69%); $n^{20}D$ 1.4426; d^{20}_4 1.151.

Anal. Calcd. for $C_{10}H_{17}NO_6$: C, 48.57; H, 6.93; N, 5.67; *MR*D, 56.90. Found: C, 48.84; H, 7.05; N, 5.89; *MR*D, 57.32.

Diethyl α-Carbethoxy-β-methyl-γ-nitropimelate.—To a stirred solution of 45.8 g. (0.185 mole) of ethyl α-carbethoxy-β-methyl-γ-nitrobutyrate and 8 g. of benzyltrimethylammonium hydroxide solution with 25 ml. of *t*-butyl alcohol was added dropwise over a period of one-half hour 18.5 g. (0.185 mole) of ethyl acrylate. The reaction mixture was stirred at 50° for twenty-four hours and worked up in the usual manner. The product was distilled *in vacuo*, b. p. 158–170° (0.9–1.1 mm.); yield 41.7 g. (65%). A portion was redistilled for analysis, and the colorless fraction boiling at 152–153° (0.8 mm.) was collected; $n^{20}D$ 1.4510; d^{20}_4 1.146.

Anal. Calcd. for $C_{15}H_{29}NO_8$: C, 51.86; H, 7.25; N, 4.03; *MR*D, 81.68. Found: C, 52.37; H, 7.53; N, 4.70; *MR*D, 82.07.

The high nitrogen and carbon values are due possibly to partial loss of a carbethoxyl group during the distillation. The values found for C, H and N lie between those calculated for the desired product and those calculated for diethyl β-methyl-γ-nitropimelate. Even using a short-path distillation apparatus, considerable decomposition took place continuously during the distillation.

1-Methylpyrrolizidine.—A solution of 27 g. (*ca.* 0.08 mole) of diethyl α-carbethoxy-β-methyl-γ-nitropimelate in purified dioxane was hydrogenated over copper chromite catalyst at 265° and 250 atmospheres during four and one-half hours. After removal of the catalyst by filtration, the solvent was removed by distillation through a 10-in. helices-packed column. The residual oil was fractionally distilled at reduced pressure, and the colorless, basic fraction boiling at 67–68° (24 mm.) was collected; yield 2.7 g. (25%). The higher boiling fractions were not identified. A picrate made from the distillate and recrystallized from methanol melted at 235–236° with decomposition. The chromatography of 1 g. of 1-methylpyrrolizidine was carried out in the same manner as with the 1-methylpyrrolizidine synthesized from ethyl crotonate, and the percolate fractions were converted to picrates. The total amount of picrate obtained was 1.11 g., of which 0.80 g. (72%) was the low melting form, *dl*-pseudoheliotridane picrate, m. p. 234–236°. This was obtained from the benzene–petroleum ether percolates. The higher melting picrate, *dl*-heliotridane picrate, m. p. 243–244° (0.14 g., 13%), was obtained from final ethanol percolation of the alumina column. The remaining 15% of the total picrate obtained was intermediate in melting point. The two pure picrates were in every way identical with the two picrates obtained from the 1-methylpyrrolizidine synthesized from ethyl crotonate.

Pyrrolizidine. One-Step Reduction.—The two-step synthesis of pyrrolizidine from the diester of γ-nitropimelic acid[11] has been previously described.[30] It has also been possible to obtain pyrrolizidine by the general one-step reductive cyclization process developed in this Laboratory[31]; b. p. 140–142° (750 mm.); yield 47%.

8-Ethylpyrrolizidine.[32] One-Step Reduction.—This compound was also produced by the one-step reductive cyclization method from diethyl γ-ethyl-γ-nitropimelate[20] in dioxane over copper chromite with hydrogen at 260° and 300 atm.; yield 55%. The higher-boiling fractions were not identified.

8-Methyl-3,5-diketopyrrolizidine.—In one experiment in which a solution of 20 g. (0.074 mole) of diethyl γ-methyl-γ-nitropimelate[20] in 150 ml. of 95% ethanol was hydrogenated over copper chromite at 260° and 250 atm., the reaction stopped after absorption of only two-thirds of the theoretical amount of hydrogen and, upon removal of the catalyst, it was found to be poisoned. Attempted distillation of the residue gave only a neutral fraction, b. p. 160–165° (3 mm.), which crystallized in the condenser and receiver. Purification of the solid was effected by recrystallization from 95% ethanol, from which it separated as colorless plates, m. p. 160–161°.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.81; H, 6.67; N, 9.30.

The structure was assigned on the basis of analysis, infrared spectrum and analogy to the 3,5-diketopyrrolizidine[30] obtained from dimethyl γ-nitropimelate in attempted pyrrolizidine synthesis. The independent synthesis of 3,5-diketopyrrolizidine by Lukeš and Šorm[33] indicated that the structure we had proposed[11] was correct. The $C_8H_{11}NO_2$ product presently obtained must be the 8-methyl homolog. The infrared absorption spectra of the two compounds were similar and exhibited the characteristic imide frequencies present in the spectrum of succinimide.

Methyl γ-Nitrobutyrate.[20]—To a stirred solution of 244 g. (4.0 moles) of nitromethane and 15 g. of aqueous 40% benzyltrimethylammonium hydroxide solution in 75 ml. of *t*-butyl alcohol was added over a period of one hour 86 g. (1.0 mole) of methyl acrylate. External cooling was necessary to maintain the temperature at 35–40°. After addition of the methyl acrylate was complete, an additional 7-g. portion of the basic catalyst was added and the reaction mixture was stirred at 30° for four hours. The nitro ester was worked up in the usual manner; b. p. 67–70° (0.3 mm.); yield 52.0 g. (35%); $n^{20}D$ 1.4375.

Anal. Calcd. for $C_5H_9NO_4$: N, 9.52. Found: N, 9.47.

Ethyl γ-Acetoxycrotonate.—A mixture of 75 g. (0.38 mole) of ethyl γ-bromocrotonate, prepared by the method of Ziegler and his co-workers,[34] as modified by Schmid and Karrer,[35] 37.2 g. (0.38 mole) of potassium acetate and 68.5 g. (1.14 moles) of glacial acetic acid was heated at the reflux temperature for twelve hours. Approximately 30 ml. of acetic acid was removed by distillation at atmos-

(30) Leonard, Hruda and Long, THIS JOURNAL, **69**, 690 (1947).

(31) *E. g.*, Leonard and Shoemaker, *ibid.*, **71**, 1760 (1949).

(32) Leonard and Beck, *ibid.*, **70**, 2504 (1948).

(33) Lukeš and Šorm, *Coll. Czechoslov. Chem. Commun.*, **12**, 278 (1947).

(34) Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).

(35) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

pheric pressure, and the residue was poured into 250 ml. of ice-water. The mixture was extracted with two 75-ml. portions of ether, and the ether extracts were combined and dried. The ether was removed and the residue was fractionally distilled in vacuum, b. p. 61–63° (0.5 mm.); yield 48 g. (74%); $n^{20}D$ 1.4455 (Kirrmann and Rambaud reported for ethyl γ-acetoxycrotonate, $n^{20}D$ 1.4445).[36]

Ethyl β-Nitromethyl-γ-acetoxybutyrate.—To a stirred solution of 53 g. (0.875 mole) of nitromethane and 12 g. of freshly prepared benzyltrimethylammonium butoxide in butanol (25% solution) was added dropwise over one-half hour 30 g. (0.175 mole) of ethyl γ-acetoxycrotonate. The reaction mixture was stirred for forty-eight hours at 60–65°, with the addition of 5-g. portions of catalyst after sixteen and thirty-two hours. The product was isolated in the usual manner. Fractional distillation gave 26.3 g. (65%) of ethyl β-nitromethyl-γ-acetoxybutyrate, b. p. 116–119° (0.4–0.5 mm.); $n^{20}D$ 1.4490; d^{20}_4 1.185.

Anal. Calcd. for $C_9H_{15}NO_6$: C, 46.35; H, 6.48; N, 6.01; *MR*D, 52.70. Found: C, 46.42; H, 6.59; N, 5.84; *MR*D, 52.77.

Diethyl β-Acetoxymethyl-γ-nitropimelate.—To a stirred solution of 22.7 g. (0.097 mole) of ethyl β-nitromethyl-γ-acetoxybutyrate and 4 g. of aqueous 40% benzyltrimethylammonium hydroxide solution with 10 ml. of *t*-butyl alcohol was added 9.7 g. (0.097 mole) of ethyl acrylate. The mixture was stirred for forty-eight hours at 55–60° and was then worked up in the usual manner. The product was distilled through a short-path distillation apparatus and was obtained as a light yellow oil, b. p. 157–160° (0.3 mm.); yield 21.7 g. (67%); $n^{20}D$ 1.4562; d^{20}_4 1.173.

Anal. Calcd. for $C_{14}H_{23}NO_8$: C, 50.44; H, 6.95; N, 4.20; *MR*D, 77.45. Found: C, 50.39; H, 6.88; N, 4.43; *MR*D, 77.30.

Reductive Cyclization of Diethyl β-Acetoxymethyl-γ-nitropimelate

A. At 265°.—Hydrogenation of VIII in dioxane at 265° and 250 atm. over copper chromite resulted in absorption of more than the theoretical amount of hydrogen necessary for conversion to 1-hydroxymethylpyrrolizidine. Isolation and purification of the product gave at least a 40% yield of 1-methylpyrrolizidine. Treatment with picric acid gave a picrate, m. p. 234–236° (dec.), identical with *dl*-pseudoheliotridane picrate. Attempts to form derivatives of the higher-boiling fraction were unsuccessful.

B. At 180–200°.—A solution of 21.7 g. of VIII in 130 ml. of dioxane was hydrogenated at 180–200° and 200–250 atm. over 22 g. of copper chromite catalyst during three and one-half hours. After filtration of the catalyst and removal of the solvent, it was possible to distil only a small portion of the residue *in vacuo*. A fraction (0.1 g.) was collected at 60–65° (21 mm.) and was converted to a picrate, m. p. 234–236° (dec.) which did not depress the melting point of *dl*-pseudoheliotridane picrate. A second fraction (1.2 g.) was collected at 93–96° (0.5 mm.) and was subjected to purification by chromatographic adsorption on alumina. Ether percolation of the column gave a small amount of basic oil, after evaporation of the ether, which formed a picrate that melted, with decomposition, at 174–175°. By melting point and analysis, the picrate could be ***dl*-trachelanthamidine picrate** (Men'shikov and Borodina[7] reported 174° as the melting point of *l*-trachelanthamidine picrate). A mixture of this picrate with *l*-isoretronecanol picrate (m. p. 193–194°)[11] melted, with decomposition, at 174–175°. Two recrystallizations of *dl*-trachelanthamidine picrate from ethanol–ether failed to alter the melting point of the fine yellow needles.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.42; H, 4.91; N, 15.01.

(36) Kirrmann and Rambaud, *Compt. rend.*, **194**, 1168 (1932).

Summary

1. 1-Methylpyrrolizidine has been separated into its racemic forms, *dl*-heliotridane and *dl*-pseudoheliotridane, with the latter predominating in the Leonard and Felley[3] method of synthesis.

2. 1-Methylpyrrolizidine has also been synthesized starting with nitromethane and diethyl ethylidenemalonate by a three-step method involving two Michael condensations followed by reductive cyclization.

3. *dl*-Pseudoheliotridane has been resolved and the active form isolated is probably the enantiomorph of the alkaloid product "*l*-pseudoheliotridane."[7,8]

4. 1-Hydroxymethylpyrrolizidine has been synthesized by a reductive cyclization method, and the predominant racemate obtained is apparently *dl*-trachelanthamidine.

5. The absolute stereochemical configuration of the naturally occurring 1-substituted pyrrolizidines has been discussed.

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The Synthesis of Pyrrolizidines. VII. Use of the Pyrrole Mannich Base

BY NELSON J. LEONARD AND EMMETT H. BURK, JR.[1]

A general method has been developed[2] for the synthesis of pyrrolizidine (I) and substituted pyrrolizidines by reductive cyclization of the corresponding γ-nitropimelic esters. The possibility of the development of a second general method for the synthesis of pyrrolizidines was envisaged as a result of the use of the pyrrole Mannich base II. Herz, Dittmer and Cristol[3] have reported the synthesis of diethyl (2-pyrrylmethyl)-malonate (III) by alkylation of diethyl malonate with 2-dimethylaminomethylpyrrole (II) and the synthesis of the lactam IV by the use of acetamidomalonic ester. The structure of these products and their ready availability suggested that catalytic hydrogenation of such intermediates might be a practical method for the synthesis of pyrrolizidines, especially 2-substituted pyrrolizidines. Accordingly the method has been

(1) Present address: Sherwin-Williams Co., Chicago, Illinois.

(2) (a) Leonard, Hruda and Long, THIS JOURNAL, **69**, 690 (1947); (b) Leonard and Beck, *ibid.*, **70**, 2504 (1948); (c) Leonard and Felley, *ibid.*, **71**, 1758 (1949); (d) Leonard and Shoemaker, *ibid.*, **71**, 1760 (1949); (e) **71**, 1762 (1949); (f) Leonard and Felley, *ibid.*, **72**, 2537 (1950).

(3) Herz, Dittmer and Cristol, *ibid.*, **70**, 504 (1948).