The structures were proved by degradation to known compounds. In these reactions it was observed that the 4-amino group in 2,4-diaminopteridines was readily converted to hydroxyl.

Anaerobic alkaline treatment of I resulted in the formation of pteroylglutamic acid, thus constituting a new synthesis of the latter compound.

The previously reported reaction of methylglyoxal with 2,4,5,6-tetraminopyrimidine was investigated, and it was found that in 0.25 *N* hydrochloric acid 2,4-diamino-7-methylpterin was the chief product while in sodium sulfite solution at *p*H 7 the 6-methyl isomer predominated.

BOUND BROOK, NEW JERSEY
RECEIVED DECEMBER 8, 1948

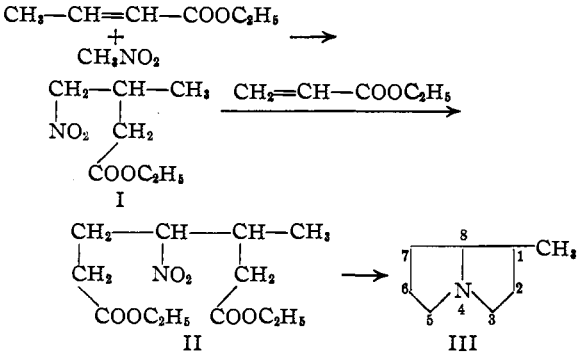
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Pyrrolizidines. III. Condensation of Nitromethane with Ethyl Crotonate and Subsequent Formation of 1-Methylpyrrolizidine (Heliotridane, Pseudoheliotridane)[1]

BY NELSON J. LEONARD AND DONALD L. FELLEY

The compound 1-methylpyrrolizidine (III) occupies an important position in alkaloid chemistry because it has been obtained, in the optically active form called *l*-heliotridane, as a degradation product of a large number of alkaloids found in the *Senecio*, *Heliotropium*, *Crotalaria*, *Erechtites*, and *Trichodesma* genera. Men'shikov[2] first showed that *l*-heliotridane probably possessed structure III, and Adams and Rogers[3] established this structure unequivocally. More recently, Men'shikov and Borodina[4] have shown that *l*-pseudoheliotridane, from the alkaloids of *Trachelanthus korolkovi*, is probably the diastereoisomer of *l*-heliotridane. The first synthesis of 1-methylpyrrolizidine (III) was effected by Men'shikov[5] in amount sufficient only to characterize the product as its picrate. Prelog and Zalan[6] have since synthesized this compound by a five-step procedure, starting with γ-ethoxypropyl bromide and γ-phenoxy-α-methylbutyronitrile, in a 22% over-all yield. In both syntheses, apparently only one of the two expected diastereoisomeric racemates, "*dl*-heliotridane," was obtained.

The reductive cyclization of diethyl β-methyl-γ-nitropimelate (II), by the method developed in this Laboratory for the synthesis of pyrrolizidines,[1] suggested itself as a more convenient and efficient method for the synthesis of 1-methylpyrrolizidine. This method has been found to be practical, and 1-methylpyrrolizidine has been synthesized, starting with ethyl crotonate and nitromethane, in an over-all yield of 26%. It was found that the addition of nitromethane to ethyl crotonate to yield ethyl β-methyl-γ-nitrobutyrate (I) could not be effected using either the method of Bruson[7] for acrylic esters or the method of Kohler and Engelbrecht[8] for certain more highly activated α,β-unsaturated esters. With diethylamine as a catalyst,[9] in the method used by Kloetzel[10] for the condensation of nitroparaffins with α,β-unsaturated ketones, a yield of 15% of I was obtained. It seemed possible that the use of diisopropylamine as a catalyst might result in a better yield of the product since this amine is of commensurate strength with diethylamine[11] but would probably not be as active in the competing reaction of addition of the amine to the ethyl crotonate.[12] Using diisopropylamine in the condensation of nitromethane with ethyl crotonate, a 25% yield of I was obtained. Other amines were studied as catalysts in this condensation but the best yield (55%) was obtained by the use of benzyltrimethylammonium butoxide in butanol at 75–80°.



The condensation of ethyl β-methyl-γ-nitrobutyrate (I) with ethyl acrylate to give diethyl β-

(1) For the first two papers in this series, see (a) Leonard, Hruda and Long, THIS JOURNAL, **69**, 690 (1947); (b) Leonard and Beck, *ibid.*, **70**, 2504 (1948).

(2) (a) Men'shikov, *Ber.*, **66**, 875 (1933); (b) **68**, 1051 (1935); (c) **69**, 1799 (1936); (d) **69**, 1802 (1936); (e) *J. Gen. Chem.* (U. S. S. R.), **7**, 1632 (1937).

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

(4) (a) Men'shikov and Borodina, *J. Gen. Chem.* (*U. S. S. R.*), **15**, 225 (1945); (b) **16**, 1311 (1946).

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

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

(7) Bruson, U. S. Patent 2,342,119, Feb. 22, 1944.

(8) Kohler and Engelbrecht, THIS JOURNAL, **41**, 764 (1919).

(9) Worrall and Bradway, *ibid.*, **58**, 1607 (1936).

(10) Kloetzel, *ibid.*, **69**, 2271 (1947).

(11) Hall and Sprinkle, *ibid.*, **54**, 3469 (1932).

(12) Hromatka, *Ber.*, **75**, 131 (1942), found that diisopropylamine does not react with ethyl acrylate, while Flürscheim, *J. prakt. Chem.*, [2] **68**, 348 (1903), found that diethylamine reacts with ethyl acrylate at reflux temperature to give a quantitative yield of ethyl β-diethylaminopropionate after one hour.

methyl-γ-nitropimelate (II) was best effected (in 63% yield) with benzyltrimethylammonium hydroxide, following a modification of the general Bruson method.[7] Reductive cyclization of the nitro diester (II) by the one-step method previously described[1] gave 1-methylpyrrolizidine in 75% yield. The physical properties of the product and its derivatives indicated that the 1-methylpyrrolizidine obtained was predominantly the "*dl*-heliotridane" previously synthesized by Men'shikov[5] and Prelog and Zalan.[6]

Experimental[13]

Ethyl β-Methyl-γ-nitrobutyrate

Benzyltrimethylammonium Butoxide as Catalyst.—To a stirred solution of 139 g. (2.28 mole) of nitromethane and 35 g. of benzyltrimethylammonium butoxide (25% solution in butanol, Rohm and Haas Co.) was added 65 g. (0.57 mole) of ethyl crotonate. The reaction mixture was stirred for eighty hours at 75–80°, and additional 12-g. portions of catalyst were added at twenty-four hour intervals. The product was acidified with 1 *N* hydrochloric acid and was dissolved in an equal volume of ethylene dichloride. The ethylene dichloride layer was washed with water, separated, and the solvent and unreacted material were removed at reduced pressure (40 mm.). The residual oil was distilled in vacuum, and the colorless fraction boiling at 84–86° (1 mm.) was collected; yield 55.4 g. (55%); $n^{20}D$ 1.4350; d^{20}_4 1.097.

Anal. Calcd. for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00; MR_D, 41.81. Found: C, 48.17; H, 7.45; N, 7.89; MR_D 41.66.

Other Catalysts.—When nitromethane and ethyl crotonate were allowed to stand at 30° in the presence of diethylamine, a maximum yield of 15% of ethyl β-methyl-γ-nitrobutyrate was realized after twenty days. In the presence of diisopropylamine, a maximum yield of 25% was realized after twenty-eight days at 30°, or after forty-eight hours at the reflux temperature. Other amines give inferior yields.

Diethyl β-Methyl-γ-nitropimelate.—To a stirred solution of 15.4 g. (0.088 mole) of ethyl β-methyl-γ-nitrobutyrate and 4 g. of benzyltrimethylammonium hydroxide (40% solution in water, Rohm and Haas Co.) was added 8.8 g. (0.088 mole) of ethyl acrylate. After the initially exothermic reaction had subsided, the mixture was stirred for forty-eight hours at 50–55°. The product was isolated as in the case of the ethyl β-methyl-γ-nitrobutyrate and was purified by fractional distillation in vacuum; b. p. 143–144° (1 mm.); yield, 15.2 g. (63%); $n^{20}D$ 1.4488; d^{20}_4 1.109.

Anal. Calcd. for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09; MR_D, 66.55. Found: C, 52.37; H, 7.88; N, 5.31; MR_D, 66.56.

The diester was obtained in 46% yield when a solution of one mole each of ethyl β-methyl-γ-nitrobutyrate, ethyl acrylate, and diisopropylamine was allowed to stand at 25° for twenty-nine days.

1-Methylpyrrolizidine.—A solution of 31 g. (0.113 mole) of diethyl β-methyl-γ-nitropimelate in 150 ml. of purified dioxane was hydrogenated over copper chromite catalyst at 265° and 200–250 atm. during eight hours. The catalyst was removed by filtration, and the filtrate was fractionated at reduced pressure. The colorless, basic fraction boiling at 55–57° (16 mm.) was collected and purified by redistillation; yield, 10.6 g. (75%). The boiling point at atmospheric pressure was 161–162° (749 mm.). Values reported for *l*-heliotridane are 165–166°,[3] 167–168.5°,[2b] and 169–170°;[2a] for *l*-pseudoheliotridane, 159–160°.[4]

1-Methylpyrrolizidine Picrate.—Prepared in ether and recrystallized from methanol, the picrate formed yellow needles which melted, with decomposition, at 233–234°. Prelog and Zalan[6] reported 234–236° and Men'shikov[5] reported 236° as the melting point of "*dl*-heliotridane" picrate; Men'shikov and Borodina[4] reported 232–233° as the melting point of *l*-pseudoheliotridane picrate.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.46; H, 5.12; N, 15.81. Found: C, 47.61; H, 5.22; N, 15.78.

1-Methylpyrrolizidine Picrolonate.—Prepared in ether and recrystallized from methanol, the picrolonate formed orange needles which melted at 167–169°, after sintering at 163°. Prelog and Zalan[6] reported 162–163° for "*dl*-heliotridane" picrolonate; Men'shikov and Borodina[4] reported 162–163° for *l*-pseudoheliotridane picrolonate.

Anal. Calcd. for $C_{18}H_{23}N_5O_5$: C, 55.52; H, 5.95; N, 17.99. Found: C, 55.61; H, 6.08; N, 17.98.

Summary

1-Methylpyrrolizidine has been synthesized conveniently starting with nitromethane and ethyl crotonate by a three-step method involving two Michael condensations followed by reductive cyclization.

URBANA, ILLINOIS RECEIVED NOVEMBER 1, 1948

(13) Melting points are corrected for both emergent stem and thermometer errors. Microanalyses by Mrs. Jane Wood and Mr. Maurice Dare.