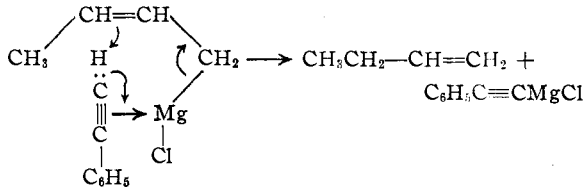
monium chloride in liquid ammonia produced no rearrangement of allylbenzene after three days. All later runs with the modified procedure produced some allylbenzene. This was not the result of incomplete conversion of the original allylbenzene, since an excess of sodamide and longer reaction times had no appreciable effect on the composition of the reaction mixture.

It is significant that a predominance of propenylbenzene is produced at all times. Since these results represent a complete reversal of the results from the hydrolysis of cinnamylmagnesium chloride,[4] using permanganate oxidation for analysis, the hydrolysis of the Grignard reagent was repeated, using precision fractional distillation for analysis of the hydrocarbon mixture. However, the results were in agreement with the previous analysis (75% allylbenzene and 25% propenylbenzene).

The observation that all three of the proton donors used give the same mixture of hydrocarbons with the sodium derivatives of allyl- and propenylbenzene is of considerable interest. With butenylmagnesium chloride, phenylacetylene gives virtually 100% 1-butene,[10] while hydroxylic substances give about 50% 1-butene and 50% 2-butene. This would not be surprising if the initial step in the reaction of the Grignard reagent with phenylacetylene involves a coördination of the magnesium atom with the triple bond of phenylacetylene and this coördination compound then decomposes through the only cyclic process available to give nearly pure 1-butene



Apparently the complex formed from coördination of hydroxylic substances with the magnesium may donate a proton at either the first or the third carbon atom.

This mechanism is substantiated by the observation that sodium allylbenzene, which would not be expected to form coördination complexes, since it is ionic, gives the same mixture of hydrocarbons with both hydroxylic substances and phenylacetylene, as well as with ammonium ion.

Summary

1. The sodium salts of allyl- and propenylbenzene have been prepared and decomposed with methanol, ammonium chloride and phenylacetylene.

2. Addition of a proton to these sodium salts has been shown to give predominantly propenylbenzene.

3. Cinnamylmagnesium chloride, the Grignard reagent analogous to the above salts has been prepared and hydrolyzed. The analysis of the hydrocarbon fraction agrees with values in the literature.

4. A mechanism for the reaction of phenylacetylene with allylic Grignard reagents has been postulated.

(10) Young and Roberts, THIS JOURNAL, **68**, 1472 (1946).

LOS ANGELES, CALIF. RECEIVED AUGUST 31, 1946

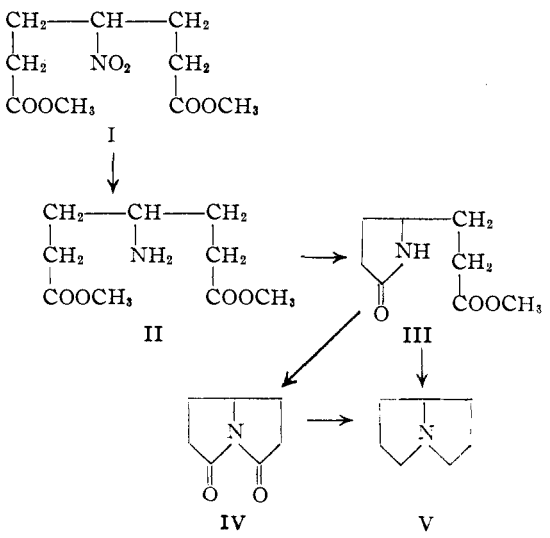
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Pyrrolizidines[1]

BY NELSON J. LEONARD, LILLIAN RUTH HRUDA[2] AND FRANK W. LONG[3]

One method for the synthesis of pyrrolizidine (V) would appear to be a reductive ring-closure of dimethyl γ-aminopimelate (II), which should be readily available from the γ-nitro compound (I). At the outset, the following compounds were regarded as probable intermediates in the course of the reaction: dimethyl γ-aminopimelate (II), 5-β-carbomethoxyethyl-2-pyrrolidone (III), and 3,5-diketopyrrolizidine (IV).

Experiment has shown that the method is not only feasible but also very practical, since pyrrolizidine can be made by a two-step catalytic hydrogenation of dimethyl γ-nitropimelate (I), without necessity for the isolation of intermediates. The

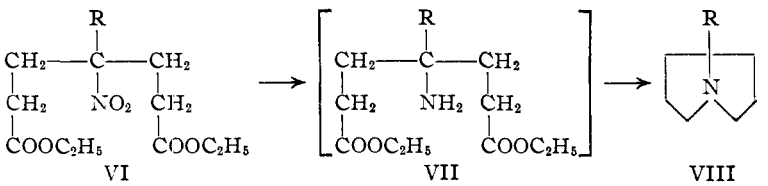


(1) Presented before the Division of Organic Chemistry at the 110th meeting of the American Chemical Society, Chicago, Illinois, September 12, 1946.

(2) Present address: Armour Research Foundation, Chicago, Illinois.

(3) Present address: Department of Chemistry, University of Iowa, Iowa City, Iowa.

over-all yield of pyrrolizidine from I was sixty per cent. 8-Methylpyrrolizidine (VIIIa) and 8-ethylpyrrolizidine (VIIIb) have been synthesized in an analogous manner from the homologous nitropimelic esters (VIa, VIb). The synthesis of the 8-alkylpyrrolizidines is the first example of the preparation of a pyrrolizidine substituted with an angular alkyl group.



a (R = CH_3), b (R = C_2H_5)

By this convenient method of ring-closure, pyrrolizidines, which occur in a number of plant alkaloids, have been made available in a yield exceeding that obtained by any other method for the synthesis of pyrrolizidines. The present method bears little resemblance to the four types of ring-closure which have been applied previously. One such type was the treatment of 2-*s*-butylpyrrolidine and 2-*i*-butylpyrrolidine with sodium hypobromite followed by concentrated sulfuric acid, which led to the formation of 1-methylpyrrolizidine and 2-methylpyrrolizidine, respectively.[4a,4e] The difficulty of obtaining the initial substituted pyrrolidines and the low yield in the ring closure combine to make this a very limited method for the synthesis of pyrrolizidines. The Dieckmann ring-closure has been used for the preparation of a number of substituted pyrrolizidines. 3,5-Dimethylpyrrolizidine was obtained from 2-methylpyrrole in an over-all yield of 2.8 per cent.[4g]; 2-methylpyrrolizidine was made by a synthesis involving seven steps and providing an over-all yield of 1.1%[4h,4i]; 1-methyl-7-ketopyrrolizidine was obtained from 4-methylpiperidine in an eight-step synthesis.[4j] Intramolecular dialkylation of a primary amino group was utilized by Prelog and his co-workers for the synthesis of pyrrolizidine, through a substituted malonic ester intermediate, in an over-all yield of 34%,[4b] and of 1-methylpyrrolizidine, through a Grignard intermediate, in an over-all yield of 33%.[4f] Pyrrolizidine was also prepared by a ring-closure involving internal amide formation followed by electrolytic reduction of this amide.[4c,4d] The over-all yield from pyrrole was 4.6% by this method.

The efficient two-step catalytic hydrogenation of dimethyl γ-nitropimelate (I), first with platinum oxide at low pressure and then with copper chromite at high temperature and pressure to produce pyrrolizidine (V), has the advantage that it requires only compounds which are readily available. The ester I and its homologs VIa and VIb can be prepared conveniently by the method of Bruson[5] through the condensation of acrylic acid esters with nitromethane, nitroethane, and 1-nitropropane in the presence of benzyltrimethyl ammonium hydroxide. From VIa and VIb, 8-methylpyrrolizidine and 8-ethylpyrrolizidine were synthesized by the same two-step catalytic reduction method employed for the parent substance. In the case of 8-methylpyrrolizidine, the process was further simplified by omitting the low pressure hydrogenation over platinum oxide. Diethyl γ-methyl-γ-nitropimelate was hydrogenated directly at high pressure and 275° over copper chromite catalyst, with the production of 8-methylpyrrolizidine in a yield (57%) comparable with that obtained from the stepwise hydrogenation (61%).

Pyrrolizidine was identified by the analysis of its picrate and by the satisfactory agreement of the physical properties of the base and its picrate with those described for pyrrolizidine and pyrrolizidine picrate.[4b,4c] The structures of 8-methylpyrrolizidine and 8-ethylpyrrolizidine were assigned on the basis of analogy to the method of synthesis of pyrrolizidine. The physical properties of the free bases are in accord with the assigned structural formulas, and the analyses of the free bases, their picrates, and picrolonates are in agreement with the molecular formulas $C_8H_{15}N$ (VIIIa) and $C_9H_{17}N$ (VIIIb) required for these structures.

In an attempt to isolate the intermediate II in the synthesis of pyrrolizidine, the reduction of dimethyl γ-nitropimelate was interrupted after the first stage, *i.e.*, low pressure catalytic hydrogenation over platinum oxide. When the theoretical volume of hydrogen had been absorbed, the product which was isolated by distillation was shown by analysis to be the γ-lactam, 5-β-carbomethoxyethyl-2-pyrrolidone (III). This finding is consistent with the behavior of γ-aminoesters on heating. In one experiment when III was subjected to treatment with hydrogen at 300 atmospheres and 250° over copper chromite catalyst, no absorption of hydrogen was observed and an intermediate was obtained which was evidently the result of a thermal reaction. The analysis of the compound isolated was in excellent agreement with the empirical formula of 3,5-diketopyrrolizidine (IV). The analytical figures do not correspond to the other possible intermediates, namely, 5-(γ-hydroxypropyl)-2-pyrrolidone, 3-ketopyrrolizidine, methyl β-2-pyrrolidylpropionate, and 3-(2-pyrrolidyl)-1-propanol. Compound IV was neutral, which fact also eliminates the latter two

(4) (a) Men'shikov, *Ber.*, **69**, 1802 (1936); (b) Prelog and Heimbach, *ibid.*, **72**, 1101 (1939); (c) Galinovsky and Reichard, *ibid.*, **77**, 138 (1944); (d) Galinovsky and Stern, *ibid.*, **77**, 132 (1944); (e) Men'shikov, *Bull. acad. sci. U. S. S. R.*, **5**, 1035 (1937); (f) Prelog and Zalan, *Helv. Chim. Acta*, **27**, 531 (1944); (g) Clemo and Metcalfe, *J. Chem. Soc.*, 606 (1936); (h) Clemo and Melrose, *ibid.*, 424 (1942); (i) Clemo, Morgan and Raper, *ibid.*, 1299 (1936); (j) Adams and Leonard, THIS JOURNAL, **66**, 257 (1944).

(5) Bruson, U. S. Patent 2,342,119.

possibilities and is consistent with the substituted imide configuration assigned.

Isolation of the intermediates in the other reductive ring-closures was not attempted. Since 8-methylpyrrolizidine was obtained in as favorable a yield by a one-step reduction as by a two-step reduction of diethyl γ-methyl-γ-nitropimelate, the most efficient method of synthesizing pyrrolizidine and alkylpyrrolizidines would appear to be the one-step hydrogenation of γ-nitropimelic esters at high temperature and pressure. Studies on this type of reductive ring-closure are continuing.

Experimental[6]

γ-Nitropimelic Acid Esters.—Dimethyl γ-nitropimelate (I), diethyl γ-methyl-γ-nitropimelate (VIa), and diethyl γ-ethyl-γ-nitropimelate (VIb) were prepared from their respective acrylic acid esters and primary nitroalkanes by the method of Bruson.[5]

5-β-Carbomethoxyethyl-2-pyrrolidone (III).—A solution of 20 g. (0.086 mole) of dimethyl γ-nitropimelate in 150 ml. of methanol was hydrogenated at 2–3 atm. and 25° over 0.2 g. of platinum oxide catalyst. During five hours, 0.25 mole of hydrogen was absorbed. After removal of the catalyst, the methanol solution was evaporated under diminished pressure, and the residue (17 g.) was distilled in high vacuum. The fraction which boiled at 150–160° (0.5 mm.) was collected; yield, 9.6 g. (55%). The neutral liquid solidified and was recrystallized from methanol as colorless prisms, m. p. 52–53°.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 56.12; H, 7.65. Found: C, 55.51; H, 7.76.

3,5-Diketopyrrolizidine (IV).—A solution of 0.16 mole of 5-β-carbomethoxyethyl-2-pyrrolidone in 150 ml. of methanol to which 8 g. of copper chromite catalyst had been added was heated at 250° under 300 atm. of hydrogen for thirty hours. In the single experiment, no absorption of hydrogen was observed. From the filtered solution remaining after this treatment, the methanol was removed at reduced pressure and the dark green residual oil was distilled with fractionation in high vacuum. The neutral fraction boiling at 192° (0.5 mm.) solidified on standing and was recrystallized from ethanol as colorless elongated prisms, m. p. 176–177°.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.68; H, 6.80; N, 10.04.

Pyrrolizidine (V).—A solution of 20 g. (0.086 mole) of dimethyl γ-nitropimelate in 150 ml. of methanol was hydrogenated at 2–3 atm. and 25° over 0.2 g. of platinum oxide catalyst. The spent catalyst was removed and 10 g. of copper chromite was added. The material was then subjected to hydrogenation at 250° and 340–410 atm. for eleven hours. After filtration and removal of the methanol from the filtrate, the residual oil was fractionated at atmospheric pressure. The fraction boiling at 142–145° (740 mm.) weighed 5.7 g. (60%) and formed a **picrate** which crystallized as yellow elongated prisms from ethanol. The **picrate** melted with decomposition at 245° and had the correct analysis for pyrrolizidine picrate.[7]

Anal. Calcd. for $C_{13}H_{16}N_4O_7$: C, 45.86; H, 4.74; N, 16.46. Found: C, 46.14; H, 4.69; N, 16.40.

8-Methylpyrrolizidine (VIIIa)

Two-Step Reduction.—A solution of 19.4 g. (0.0706 mole) of diethyl γ-methyl-γ-nitropimelate in 150 ml. of ethanol was hydrogenated at 2–3 atm. and 25° over platinum oxide. During a sixteen-hour period, 0.18 mole of hydrogen was absorbed. The platinum was removed and 10 g. of copper chromite was added. Hydrogenation at 200–340 atm. and 250° was allowed to proceed for twenty hours. The ethanol was evaporated and the residual oil was distilled at atmospheric pressure. The fraction boiling at 148–155° (740 mm.) was collected; yield 5.4 g. (61%); $n^{20}D$ 1.4610. On redistillation, the compound boiled at 152° (740 mm.).

Anal. Calcd. for $C_8H_{15}N$: N, 11.19. Found: 11.21.

One-Step Reduction.—A solution of 29 g. (0.105 mole) of diethyl γ-methyl-γ-nitropimelate in 150 ml. of 95% ethanol was boiled under reflux for one and one-half hours with 4 g. of Raney nickel catalyst. The nickel was removed and 10 g. of copper chromite was added to the solution, which was then hydrogenated at 250–350 atm. and 275°. The theoretical quantity of hydrogen (0.735 mole) was absorbed after nine and one-half hours. The solution was filtered and was distilled very slowly at atmospheric pressure. The fraction boiling at 145–152° (740 mm.) was collected; yield, 7.5 g. (57%).

8-Methylpyrrolizidine Picrate.—Prepared from the base obtained by either reduction method, the picrate was recrystallized from ethanol as yellow plates which melted, with decomposition, at 281°.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.44; H, 5.12; N, 15.81. Found: C, 47.19; H, 5.16; N, 15.79.

8-Methylpyrrolizidine Picrolonate.—Prepared from the base obtained by either reduction method, the picrolonate was recrystallized from ethanol as orange needles which melted, with decomposition, at 198°.

Anal. Calcd. for $C_{18}H_{23}N_5O_5$: C, 55.92; H, 5.95. Found: C, 55.91; H, 6.09.

8-Ethylpyrrolizidine (VIIIb).—A solution of 21.4 g. (0.074 mole) of diethyl γ-ethyl-γ-nitropimelate in 150 ml. of ethanol was subjected to low pressure hydrogenation at 25° over 0.5 g. of platinum oxide, followed by high pressure hydrogenation at 250° over 10 g. of copper chromite. The product boiled at 170–172° (740 mm.); yield 5.2 g. (51%); $n^{20}D$ 1.4670.

Anal. Calcd. for $C_9H_{17}N$: N, 10.06. Found: N, 9.67.

8-Ethylpyrrolizidine Picrate.—Prepared in and recrystallized from absolute ethanol, the picrate formed yellow plates which melted, with decomposition, at 238°.

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47; N, 15.21. Found: C, 49.07; H, 5.65; N, 15.25.

8-Ethylpyrrolizidine Picrolonate.—Prepared in ether and recrystallized from ethanol, the picrolonate formed orange needles which melted, with decomposition, at 222°.

Anal. Calcd. for $C_{19}H_{25}N_5O_5$: C, 56.56; H, 6.25; N, 17.36. Found: C, 56.62; H, 6.37; N, 17.45.

Summary

1. Pyrrolizidine has been prepared in sixty per cent. over-all yield by a two-step catalytic reduction of dimethyl γ-nitropimelate.

2. 8-Methylpyrrolizidine and 8-ethylpyrrolizidine have been synthesized in an analogous manner and yield from diethyl γ-methyl-γ-nitropimelate and diethyl γ-ethyl-γ-nitropimelate, respectively.

3. The possibility of a general simplification of the reduction method has been indicated in the particular case of 8-methylpyrrolizidine, which was synthesized in comparable yield by a one-step hydrogenation over copper chromite at high temperature and pressure.

4. 5-β-Carbomethoxyethyl-2-pyrrolidone and 3,5-diketopyrrolizidine have been isolated as intermediates in the catalytic reduction of dimethyl γ-nitropimelate.

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(6) All melting points above 200° were determined on an aluminum block. The microanalyses were performed by Miss Theta Spoor and one of the authors (Miss L. R. H.).

(7) The physical properties of the base and its picrate are identical with those described for pyrrolizidine and pyrrolizidine picrate.[4b,4c]