Pyrrolizidines

The general procedure for the reductive cyclization of γ-nitropimelic esters to pyrrolizidines is illustrated below in the specific directions for the preparation of 2,6,8-trimethylpyrrolizidine.

2,6,8-Trimethylpyrrolizidine.—A solution of 21.4 g. (0.067 mole) of dimethyl α,α',γ-trimethyl-γ-nitropimelate in 110 ml. of purified dioxane was reduced with hydrogen in the presence of 10 g. of copper chromite catalyst at 260° and 300–350 atmospheres. Rocking was continuous from the time that heat was applied. At 130°, rapid exothermic reduction of the nitro group occurred and the theoretical amount of hydrogen was absorbed after three hours at 255–260°. The catalyst was removed by filtration and the filtrate was fractionated at reduced pressure. The colorless, basic fraction boiling at 86–88° (40 mm.) was collected and purified by redistillation; yield 8.5 g. (71%).

Summary

The conditions for bringing about the condensation of nitroparaffins with methyl methacrylate have been explored.

A number of 2-alkyl-, 2,6-dialkyl-, 2,8-dialkyl- and 2,6,8-trialkylpyrrolizidines have been synthesized in good yield by the method comprising Michael condensations and reductive cyclization.

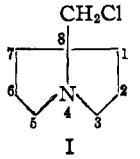
URBANA, ILLINOIS RECEIVED NOVEMBER 1, 1948

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

The Synthesis of Pyrrolizidines. V. 8-Hydroxymethylpyrrolizidine and 8-Chloromethylpyrrolizidine[1]

BY NELSON J. LEONARD AND GRADUS L. SHOEMAKER[2]

The availability of 8-chloromethylpyrrolizidine (I) through a convenient method of synthesis offers an excellent opportunity for testing the typical β-chloroamine rearrangement in the bicyclic series. The rearrangement of β-chloroamines through an ethyleneimonium ion intermediate has been observed in the acyclic series (2-dialkylamino-1-chloropropane → 1-dialkylamino-2-chloropropane)[3] and in the monocyclic series (2-chloromethyl-1-ethylpyrrolidine → 3-chloro-1-ethylpiperidine).[4] It would be expected that 8-chloromethylpyrrolizidine could not undergo rearrangement under analogous conditions because of the constraint which the ring structure places on the formation of the necessary rearrangement intermediates. Compound I has now been synthesized and has been found to be stable.



I

The general method for the synthesis of pyrrolizidines[5,6] has been applied successfully to the preparation of 8-hydroxymethylpyrrolizidine (IV), and this compound has been converted, through its hydrochloride, to the hydrochloride of 8-chloromethylpyrrolizidine. The first step in the synthesis of IV was the Michael condensation of ethyl nitroacetate with ethyl acrylate in the presence of benzyltrimethylammonium hydroxide to give diethyl α-nitroglutarate (II) and diethyl γ-carbethoxy-γ-nitropimelate (III). The diester II could be converted to the triester III by further condensation with ethyl acrylate. 8-Hydroxymethylpyrrolizidine (IV), a position isomer of the *Senecio* alkaloid product, isoretronecanol,[7] was obtained by catalytic hydrogenation of III over copper chromite at high temperature and pressure.[6] 8-Hydroxymethylpyrrolizidine hydrochloride (V) was converted to 8-chloromethylpyrrolizidine hydrochloride (VI) by means of thionyl chloride. The ring structure of these compounds was established by catalytic hydrogenation of VI to give VII, which was identical with an authentic sample of 8-methylpyrrolizidine.[5]

If compound I could undergo rearrangement in a manner analogous to the acyclic and monocyclic β-chloroamines,[3,4] the product would be 5-chloro-1-azabicyclo[3.3.1]nonane(X). However, no rearranged product was obtained following the methods which have been employed for bringing about such rearrangements: (a) heating the β-chloroamine hydrochloride above its melting point, and (b) freeing the β-chloroamine from its salt through the action of alkali. The resistance of compound I to rearrangement is not due to di-α-substitution in the β-chloroamine since Kerwin, Ullyot, Fuson and Zirkle found that a compound with two alkyl groups on the α-carbon undergoes rearrangement (XI → XII).[3] The reason why compound I remains unchanged appears rather to be due to the fact that the necessary ethyleneimonium ion (VIII) or carbonium ion (IX) intermediate cannot be formed. Even if the ethyleneimonium ion (VIII) could be formed by methylenic linkage between positions 4 and 8 of the inflexible pyrrolizidine nucleus, the subsequent formation of the coplanar carbonium ion (IX) would be impossible

(1) For paper IV in this series, see Leonard and Shoemaker, THIS JOURNAL, 71, 1760 (1949).

(2) Present address: Department of Chemistry, Rutgers University, New Brunswick, New Jersey.

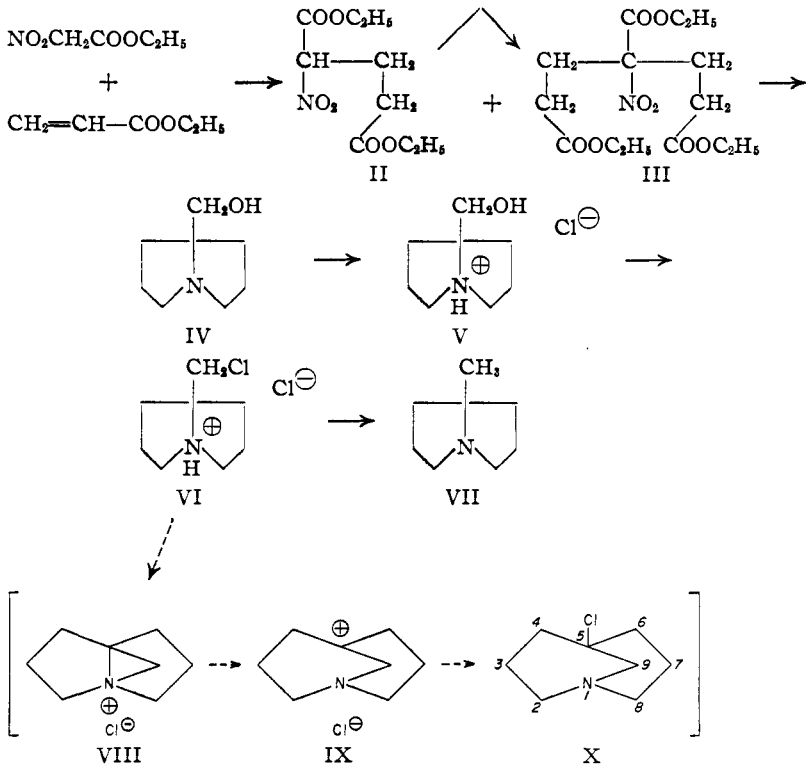
(3) Kerwin, Ullyot, Fuson and Zirkle, THIS JOURNAL, 69, 2961 (1947).

(4) Fuson and Zirkle, *ibid.*, 70, 2760 (1948).

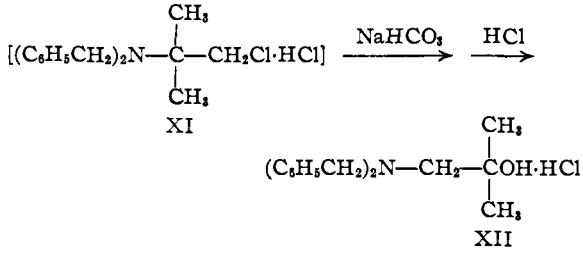
(5) Leonard, Hruda and Long, *ibid.*, 69, 690 (1947).

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

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



due to the excessive strain requisite for its formation.



Experimental

Diethyl α-Nitroglutarate and Diethyl γ-Carbethoxy-γ-nitropimelate.—To a stirred solution of 13.3 g. (0.1 mole) of ethyl nitroacetate[8] (b. p. 82–85° (10 mm.); $n^{20}D$ 1.4230) and 3 ml. of 40% aqueous benzyltrimethylammonium hydroxide in 20 ml. of dioxane was added slowly 20 g. (0.2 mole) of ethyl acrylate. The temperature was maintained at 60–65° for twenty-four hours. An equal volume of ethylene dichloride was added to the reaction mixture. The mixture was acidified with 1 *N* hydrochloric acid, and the ethylene dichloride layer was washed three times with 75-ml. portions of water. The solvents and unreacted materials were removed by distillation, and the residual oil was fractionated. Diethyl α-nitroglutarate distilled at 109–112° (1 mm.); $n^{20}D$ 1.4417; d^{20}_4 1.1670; yield, 12.8 g. (55%).

Anal. Calcd. for $C_9H_{15}NO_6$: N, 6.01; MR_D, 52.70. Found: N, 6.22; MR_D, 52.85.

Diethyl γ-carbethoxy-γ-nitropimelate was collected as the fraction boiling at 181–183° (2 mm.); $n^{20}D$ 1.4525; d^{20}_4 1.1572; yield, 7.25 g. (22%).

Anal. Calcd. for $C_{14}H_{23}NO_8$: N, 4.20; MR_D, 77.45. Found: N, 4.40; MR_D, 77.78.

(8) Steinkopf, *Ann.*, **434**, 21 (1923).

If the same quantities of reactants were caused to condense in the presence of 10 ml. of 40% aqueous benzyltrimethylammonium hydroxide, no diethyl α-nitroglutarate was formed, but 22.7 g. (68%) of diethyl γ-carbethoxy-γ-nitropimelate was produced. If the diester was caused to react with more ethyl acrylate in the presence of a proportionate amount of Triton B, approximately the same yield of triester was obtained.

8-Hydroxymethylpyrrolizidine.—A solution of 20 g. (0.06 mole) of diethyl γ-carbethoxy-γ-nitropimelate in 130 ml. of dioxane was hydrogenated in the presence of 7 g. of copper chromite at 300–350 atm. and 260°. The theoretical amount of hydrogen was absorbed in three hours. The solutions resulting from two such runs were combined, the solvent was removed, and the residual oil was fractionally distilled *in vacuo*. The 8-hydroxymethylpyrrolizidine was collected between 72 and 80° (3 mm.) in a yield of 12.2 g. (72%), and was redistilled at 70–71° (2.8 mm.); $n^{20}D$ 1.4882; d^{20}_4 1.0150.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92; MR_D, 40.38. Found: C, 68.02; H, 11.07; N, 10.16; MR_D, 40.43.

The **hydrochloride** was precipitated by dissolving the 8-hydroxymethylpyrrolizidine in dry toluene and saturating the solution at 0° with dry hydrogen chloride. Small, clear prisms were obtained after decolorization and recrystallization from ethyl acetate–chloroform solution, m. p. 282–283°.

Anal. Calcd. for $C_8H_{16}ClNO$: C, 54.07; H, 9.08. Found: C, 54.29; H, 9.24.

The **picrate** of 8-hydroxymethylpyrrolizidine was prepared in and recrystallized from ethanol. The short, yellow needles melted, with decomposition, at 292–293°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.47; H, 5.18; N, 15.15.

8-Chloromethylpyrrolizidine Hydrochloride.—A solution of 5.9 g. (0.042 mole) of 8-hydroxymethylpyrrolizidine in 50 ml. of dry chloroform was saturated at 0° with dry hydrogen chloride. To the cooled and stirred solution of 8-hydroxymethylpyrrolizidine hydrochloride was added 5.95 g. (0.05 mole) of thionyl chloride in 5 ml. of dry chloroform. Stirring was continued at 25° for forty minutes, and after this time the solution was heated under reflux for one and one-half hours. Removal of the solvent left a dark crystalline solid. A solution of the solid in acetone–ethanol was decolorized, concentrated and cooled, with the resulting separation of 0.62 g. (10%) of light tan flakes. After two recrystallizations from acetone–ethanol, the 8-chloromethylpyrrolizidine hydrochloride was obtained as colorless leaflets, m. p. 210–212°.

Anal. Calcd. for $C_8H_{15}Cl_2N$: C, 48.99; H, 7.71; N, 7.14. Found: C, 49.24; H, 7.61; N, 7.10.

Attempts to obtain more crystalline product by further concentration of the mother liquor were unsuccessful. Of the approximately 15 ml. of mother liquor, 0.5 ml. was added to a saturated ethanolic solution of picric acid. Yellow platelets (0.18 g.) separated, which melted with decomposition at 227–228° after three recrystallizations from ethanol. The sample of **8-chloromethylpyrrolizidine picrate** obtained from the crystalline 8-chloromethylpyrrolizidine hydrochloride and picric acid had an identical melting point but crystallized from ethanol in the form of needles. The picrates from the crystalline material and

from the mother liquor gave no melting point depression when mixed, and their infrared spectra in chloroform solution were identical. On the basis of the **picrate** isolated from 0.5 ml. of mother liquor, the presence of an additional 2.71 g. of 8-chloromethylpyrrolizidine was indicated, or an over-all yield of 3.33 g. (53%).

Anal. Calcd. for $C_{14}H_{17}ClN_4O_7$: C, 43.25; H, 4.41; N, 14.41. Found: C, 43.44; H, 4.36; N, 14.22.

Conversion of 8-Chloromethylpyrrolizidine to 8-Methylpyrrolizidine.—Five milliliters of the mother liquor from the crystallization of 8-chloromethylpyrrolizidine hydrochloride and 3 g. of anhydrous sodium acetate were dissolved in 25 ml. of glacial acetic acid. The solution was hydrogenated at 3 atm. and 25° in the presence of 5 g. of 10% palladium on carbon. The theoretical quantity of hydrogen was absorbed after one-half hour. The reaction mixture was made strongly basic with potassium hydroxide and was steam-distilled. The distillate, about 50 ml., was added to 50 ml. of ether and was made basic with sodium hydroxide. The ether extract was dried and was added to an ethereal solution of picric acid. About 1.1 g. of **picrate** separated and after two recrystallizations from ethanol, yellow needles (0.62 g.) were obtained which melted at 277–280° with preliminary darkening. A mixture of this picrate with an authentic sample of 8-methylpyrrolizidine picrate[6] gave no melting point depression, and infrared spectra of the two picrates were identical.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.44; N, 5.12. Found: C, 47.49; H, 5.26.

The **picrolonate** prepared from a similar hydrogenolysis run was recrystallized from methanol as needles, m. p. 197–198°, which did not depress the melting point of an authentic sample of 8-methylpyrrolizidine picrolonate.[5]

Attempted Rearrangement of 8-Chloromethylpyrrolizidine.—In previous work with β-chloroamines, rearrangement has been obtained by two methods: (a) heating the amine hydrochloride above its melting point, and (b) freeing the amine from its salt through the action of alkali.[3,4] Both were attempted with 8-chloromethylpyrrolizidine hydrochloride.

(a) In the determination of the melting point of 8-chloromethylpyrrolizidine hydrochloride, no change in the melting point was observed during either rapid or slow heating. When 10 mg. of the amine hydrochloride was heated in a sealed tube for one hour at 200–230°, slight decomposition was observed and the melting point was depressed by 10–15°. However, when the contents of the tube was converted to the picrate, the product was identical with 8-chloromethylpyrrolizidine picrate in melting point (227–228°, with decomposition) and infrared absorption spectrum.

(b) A solution of 90 mg. of the chloroamine hydrochloride in 1 ml. of water was treated with 0.5 g. of sodium hydroxide in 2 ml. of water. The liberated amine was removed by extraction with three 5-ml. portions of ether. The ethereal extract was treated with picric acid in ether, with the production of 150 mg. of picrate. Long yellow needles, m. p. 227–228°, were obtained after recrystallization from ethanol. 8-Chloromethylpyrrolizidine picrate did not depress this melting point, and the infrared spectra of the two picrates were identical.

tris-(2-Carboxyethyl)-nitromethane.—To 220 ml. of concentrated hydrochloric acid was added 74 g. (0.33 mole) of tris-cyanoethylnitromethane prepared by the method of Bruson and Riener,[9] and the solution was boiled under reflux for twelve hours. The white solid obtained after evaporation to dryness was recrystallized from water; m. p. 182–184°; yield, 65.1 g. (70.5%). The same acid had been made previously by Beck,[10] in somewhat lower yield, by the alkaline hydrolysis of crude tris-(2-carbomethoxyethyl)-nitromethane.[11]

Anal. Calcd. for $C_{10}H_{15}NO_8$: C, 43.32; H, 5.45; N, 5.05. Found: C, 43.36; H, 5.60; N, 4.95.

Synthesis and Attempted Reductive Cyclization of tris-(2-Carbomethoxyethyl)-nitromethane.—A solution of 55 g. (0.20 mole) of tris-(2-carboxyethyl)-nitromethane, 150 ml. of methanol, 350 ml. of dry benzene, and 5 g. of *p*-toluenesulfonic acid was placed in a round-bottomed flask fitted with an esterification column for methyl esters, and was heated at the reflux for sixty hours. The cooled solution was washed with 300 ml. of cold 3 *N* sodium hydroxide, and the benzene layer was washed several times with water and dried. The solvent was removed at reduced pressure. The light brown oil which remained, supposedly tris-(2-carbomethoxyethyl)-nitromethane, contained some unesterified acid functions as indicated by a methoxyl determination. To complete the esterification, an ether solution of diazomethane, approximately 0.2 mole in 300 ml. of ether,[12] was added to the brown oil dissolved in 150 ml. of ether. The solution was allowed to stand at 25° for eighteen hours, after which the ether was removed. The light brown oil (54.7 g., 86%) could not be distilled or induced to crystallize. When this unpurified tris-(2-carbomethoxyethyl)-nitromethane was subjected to hydrogenation in dioxane over copper chromite at 350 atm. and 260°, in an attempt to prepare 8-(γ-hydroxypropyl)-pyrrolizidine, no pure product could be isolated.

Summary

8-Hydroxymethylpyrrolizidine, a position isomer of isoretronecanol, has been synthesized conveniently from ethyl nitroacetate and ethyl acrylate by a Michael condensation followed by reductive cyclization.

It has been found that 8-chloromethylpyrrolizidine is unchanged under conditions which cause the rearrangement of analogous monocyclic and acyclic β-chloroamines.

URBANA, ILLINOIS RECEIVED JANUARY 14, 1949

(9) Bruson and Riener, THIS JOURNAL, **65**, 23 (1943).

(10) Beck, Thesis, Doctor of Philosophy, University of Illinois, 1948.

(11) Bruson, U. S. Patent 2,342,119 (February 22, 1944); U. S. Patent 2,390,918 (December 11, 1945).

(12) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.