almost two days with 6 g. of sodium hydroxide in aqueous ethanol. The mixture was acidified with hydrochloric acid and then ether extracted. Fractional distillation gave 10 g. (72%) of *cis*-hexahydro-*o*-toluic acid, b. p. 119–121° (9 mm.), $n^{20}D$ 1.4572; reported,[8] b. p. 122–123° (10 mm.), $n^{20}D$ 1.458. A small amount of the acid was heated with thionyl chloride, the excess reagent was removed by distillation and the acid chloride was poured into ice-cold ammonium hydroxide. The amide obtained was recrystallized twice from a methanol-water mixture and melted sharply at 149.5°; reported[8] m. p. 151–153°.

Twelve grams of IX prepared from the adduct of acrylonitrile was placed in 135 ml. of methanol with 50 mg. of Adams catalyst and hydrogenated at room conditions. The platinum was removed by filtration and the filtrate was evaporated to dryness and gave 11.3 g. (93%) of crude amide, m. p. 149°. Treatment with charcoal in a 10% methanol solution gave a product melting sharply at 150°. A mixed melting point with the hexahydroamide prepared from VIII as reported previously showed no depression.

Attempted Ammonolyses of VIII.—All attempts to prepare IX by the action of ammonia on VIII failed. Treatment of VIII with aqueous ammonia or anhydrous ammonia in absolute ethanol with heating failed to give any solid product. Finally the procedure of Fellinger and Audrieth[4] was tried. A solution of 4.8 g. of VIII and 2 g. of ammonium chloride in 120 ml. of liquid ammonia was placed in a 500 ml. Parr bomb and heated at 80–100° for twenty-four hours. The ammonia was allowed to evaporate and the residue was dissolved in 10% methanol and treated with charcoal. After removing the charcoal by filtration and the methanol by evaporation, chilling the solution resulted in the formation of white crystals, 0.1 g. (5%), m. p. 120–122°. Hydrogenation of 52.6 mg. of the substance with 10 mg. of Adams catalyst absorbed slightly more than the theoretical amount of hydrogen which would have been taken up by a tetrahydrotoluamide. Recrystallization of the hydrogenated product gave a white solid, m. p. 141.5°. This does not correspond to the melting point of 155–156° reported for the only known form of hexahydro-*m*-toluamide,[9] and save for an analysis of the hydrogenated material these compounds were not investigated further.

Anal. Calcd. for $C_8H_{15}NO$: N, 9.91. Found: N, 9.70.

***trans*-1,2,5,6-Tetrahydro-*o*-toluamide (X).**—To 120 ml. of liquid ammonia were added 2 g. of sodium hydride and 4.8 g. of VIII. The mixture was heated as before in a Parr bomb, and then the ammonia was allowed to evaporate. The resulting powder was dissolved in water, neutralized with hydrochloric acid, and then ether extracted. Evaporation of the ether gave a gum which was dried on a porous plate and then treated with charcoal and recrystallized from 10% methanol; yield, 0.1 g. (5%), m. p. 166°.

Anal. Calcd. for $C_8H_{13}NO$: N, 10.06. Found: N, 9.75.

***trans*-Hexahydro-*o*-toluamide (XII).**—Twenty-six milligrams of XI was hydrogenated with Adams catalyst in methanol. Slightly more than the theoretical amount of hydrogen was absorbed. Evaporation of the methanol following removal of the catalyst gave a product melting at 178°. Recrystallization from hot water raised the melting point to 180°, reported m. p. for *trans*-hexahydro-*o*-toluamide is 180–181°.[3–8]

Two grams of *cis*-hexahydro-*o*-toluamide, 2 g. of sodium hydride and 100 ml. of liquid ammonia were heated under pressure at 90° for two hours. The material was worked up as in the preparation of XI and 0.3 g. (15%) of amide, m. p. 180°, was obtained. A mixed melting point with the product obtained by hydrogenating XI was not depressed. When 2 g. of X, 2 g. of sodium hydride and 100 ml. of liquid ammonia were allowed to stand together for several hours while the ammonia gradually evaporated, no *trans* amide was obtained.

Acknowledgment.—This work has been supported in part by a grant-in-aid from the Council of Research and Creative Work of the University of Colorado. The sodium hydride used in this work was a gift of the Electrochemical Division of E. I. du Pont de Nemours, Inc., and the thionyl chloride was a gift of the Hooker Electrochemical Company.

Summary

The condensation of piperylene with two negatively unsymmetrically substituted ethylenes, acrylonitrile and methyl acrylate, in the Diels–Alder reaction has been found to give in both cases chiefly the *cis*-ortho isomer. This is in agreement with predictions based upon electronic theories.

BOULDER, COLORADO RECEIVED FEBRUARY 20, 1948

(8) Zelinsky, *Ber.*, **41**, 2676 (1908).

(9) Markownikoff, *J. prakt. Chem.*, [2] **49**, 64 (1894).

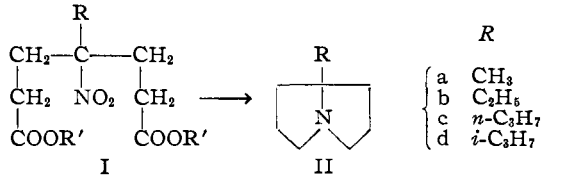
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Synthesis of Pyrrolizidines. II. Basicities of 8-Alkylpyrrolizidines[1]

BY NELSON J. LEONARD AND KARL M. BECK[2]

The 8-alkylpyrrolizidines (II) offer an excellent opportunity for the detection of F-strain[3] in a bicyclic amine system, and the method of synthesis of 8-methylpyrrolizidine (IIa) reported from this Laboratory[1] shows promise of general application. Therefore, the preparation of homologous 8-alkylpyrrolizidines has been investigated so that the relative basicities of the products could be determined.

A favorable yield of 8-methylpyrrolizidine (IIa) had previously been realized in the hydrogenation of diethyl γ-methyl-γ-nitropimelate (Ia) in ethanol over copper chromite at 250–350 atm. and 275°.[1] In extending the method to 8-*n*-propyl-

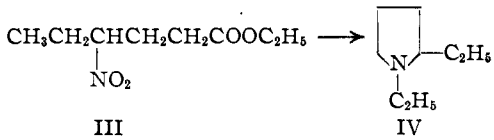


(1) For the first article in the series, see Leonard, Hruda and Long, THIS JOURNAL, **69**, 690 (1947).

(2) Present address: Abbott Laboratories, North Chicago, Illinois.

(3) Brown, THIS JOURNAL, **67**, 374 (1945).

pyrrolizidine (IIc) and 8-isopropylpyrrolizidine (IId), it was found advantageous to employ dioxane as the solvent.[4] The reaction time in dioxane was one-third that required in ethanol. Yields between 60 and 65% were realized. 8-Ethylpyrrolizidine (IIb) was obtained in comparable yield by the one-step catalytic reduction of the condensation product of 1-nitropropane with two moles of ethyl acrylate (Ib). When the condensation product of 1-nitropropane with one mole of ethyl acrylate (III) was hydrogenated in ethanol over copper chromite at 200–300 atm. and 250°, 1,2-diethylpyrrolidine (IV) was obtained in 50% yield. Catalytic hydrogenation gave about the



III IV

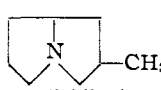
same yield of IV whether the reduction was carried out in one step or by the two-step process with platinum oxide at low pressure followed by copper chromite at high pressure.[1] That N-alkylation occurred is not surprising, since Adkins[5] has cited the N-ethylation of primary and secondary amines with ethanol solvent above 150°, and Barr and Cook[6] have observed N-alkylation in the preparation of certain piperidines by catalytic hydrogenation over copper chromite in methyl, ethyl and butyl alcohols. N-Methylation did not proceed readily in the pyrrolidine series, for when III was hydrogenated in methanol over copper chromite at 200–300 atm. and 250°, none of the expected 1-methyl-2-ethylpyrrolidine could be isolated.

The precursors (Ic,d) of 8-*n*-propyl-and 8-isopropyl-pyrrolizidine were prepared conveniently by the general method of Bruson,[7] through the condensation of methyl acrylate with 1-nitrobutane and 1-nitro-2-methylpropane in the presence of benzyltrimethylammonium hydroxide. Seventy to eighty per cent. of the nitroparaffins was accounted for in the form of condensation products when about 0.07 mole of benzyltrimethylammonium hydroxide was employed per mole of nitroparaffin. From 1-nitrobutane were obtained dimethyl γ-*n*-propyl-γ-nitropimelate (Ic) and methyl γ-nitroheptanoate; from 1-nitro-2-methylpropane, dimethyl γ-isopropyl-γ-nitropimelate (Id) and methyl γ-nitroisoheptanoate. The condensation of nitroisobutane with methyl acrylate gave a predominant yield of the isoheptanoate and only 10% of the pimelate derivative. In further reaction of the methyl γ-nitroisoheptanoate with another mole of methyl acrylate to give dimethyl γ-isopropyl-γ-nitropimelate, diethylamine[8] was found to be superior to benzyltrimethylammonium hydroxide as the condensing agent.

The reduction of the γ-nitropimelate esters furnished a series of alkylpyrrolizidines, for which it was desired to determine the basicity values. The high pK_H value (11.48) for heliotridane, or optically active 1-methylpyrrolizidine, as measured by Adams, Carmack and Mahan,[9] suggested that the fusion of two five-membered rings through a common C–N bond placed the electron pair of the nitrogen in an exposed or sterically freed position. Determination of the *p*H at half neutralization for other alkylpyrrolizidines would indicate whether the unusually high figure for heliotridane was inherent in the pyrrolizidine nucleus. None of our observed pK_H values for alkylpyrrolizidines (see Table I) was in the range of the figure for heliotridane; all exhibited basicity of a much lower order, yet higher than that for analogous acyclic tertiary amines. The higher basicity of cyclic, as compared with acyclic ethers and amines has been ascribed by Brown to B-strain[3] in the acyclic molecules.[10] F-strain[3,11] in the pyrrolizidines should increase with increasing size of the 8-alkyl group attached to the pyrrolizidine nucleus, because the apparent *cis* fusion of the two rings necessitates the protrusion of the 8-alkyl group toward the face of the nitrogen atom. This may be seen by comparing the accompanying photographs of models of the 8-methyl (Fig. 1), 8-ethyl (Fig. 2), 8-isopropyl (Fig. 4), and 8-*n*-propyl (Fig. 3) compounds. The pK_H values determined

TABLE I

BASICITY OF 8-ALKYLPYRROLIZIDINES AND RELATED COMPOUNDS

Compound	Formula	pK_H	BF_3 adduct	Picrate m. p., °C.
2-Methylpyrrolizidine[12]		10.49	....	169–170
8-Methylpyrrolizidine[1]	IIa	10.69	Solid	281
8-Ethylpyrrolizidine[1]	IIb	10.67	Solid	238
8-Isopropylpyrrolizidine	IId	10.70	Solid	228–229
8-*n*-Propylpyrrolizidine	IIc	10.61	None	156–157
1,2-Diethylpyrrolidine	IV	10.02	Liquid	120–121

(4) An amide is the probable last intermediate[1] in the over-all reduction process, and Adkins ("Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937, pp. 95, 112) has recommended the use of dioxane as a solvent for the catalytic reduction of amides.

(5) Adkins, *ibid.*, p. 26.

(6) Barr and Cook, *J. Chem. Soc.*, 438 (1945).

(7) Bruson, U. S. Patent 2,342,119 (Feb. 22, 1944); U. S. Patent 2,390,918 (Dec. 11, 1945).

(8) Kloetzel, THIS JOURNAL, **69**, 2271 (1947), has demonstrated the efficacy of diethylamine as a catalyst for the addition of nitroparaffins to α,β-unsaturated ketones.

(9) Adams, Carmack and Mahan, *ibid.*, **64**, 2593 (1942).

(10) Examples include the following relations in basicity: tetrahydrofuran > dimethyl ether, relative to boron trifluoride [Brown and Adams, *ibid.*, **64**, 2557 (1942)]; pyrrolidine > dimethylamine, relative to trimethylboron [Brown and Taylor, *ibid.*, **69**, 1332 (1947)]; quinuclidine > triethylamine, relative to trimethylboron [Brown, Symposium on the Mechanisms of Organic Reactions, Notre Dame, Indiana, September, 1946].

(11) Examples include the following relations in basicity: pyridine > 2,6-lutidine, relative to boron trifluoride [Brown, Schlesinger and Cardon, *ibid.*, **64**, 325 (1942)]; pyridine > 2-picoline, relative to trimethylboron [Brown and Barbaras, *ibid.*, **69**, 1137 (1947)].

(12) Clemo and Melrose, *J. Chem. Soc.*, 424 (1942).

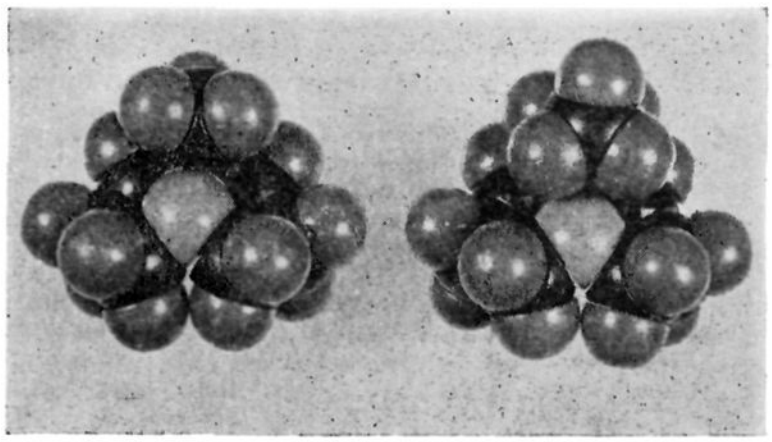


Fig. 1.

Fig. 2.

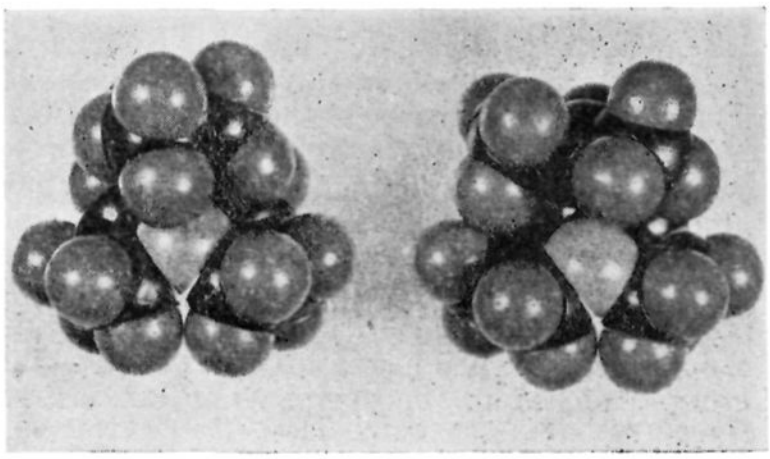


Fig. 3.

Fig. 4.

in 50% aqueous methanol for the series of 8-alkylpyrrolizidines are indicated in Table I, as corrected to 25° and accurate within ±0.01 *p*H unit. In the homologous series of 8-alkylpyrrolizidines, the pK_H values decrease in the order: 8-methyl > 8-ethyl > 8-*n*-propyl, corresponding to the increase in steric hindrance of the 8-alkyl group. The steric effect outweighs the positive inductive effect (+I) of the alkyl group introduced since, in consideration of the polar effect alone, the order of basicities would be the reverse of the observed order. The proximate pK_H values for 8-isopropyl- and 8-methylpyrrolizidine indicate that in IId the increased positive inductive effect of the isopropyl group and the increased steric effect (similar to that in IIb) are about equal in their counteracting influences. The basicity value for 8-methylpyrrolizidine is greater by 0.20 *p*H unit than that for 2-methylpyrrolizidine. This is probably due to the inductive effect of the methyl group, which is only one carbon removed from the nitrogen in the 8-methylpyrrolizidine. A comparison of the effect on basicity of the introduction of a methyl group into the 2- and 8-positions of pyrrolizidine with that of the introduction of a methyl group into the corresponding positions of 1-ethylpiperidine[13] indicates close analogy between the two systems. Thus, the basicity value for 1-ethyl-2-methylpiperidine is greater by 0.22 *p*H unit than that for 1-*n*-propylpiperidine. The basicity value for 1,2-diethylpyrrolidine (IV, Table I) is much lower than that for the pyrrolizidines, a fact which illustrates that the bicyclic bases (five-membered rings) are stronger than analogous monocyclic bases (five-membered ring) with the same number of carbon atoms and the same mode of attachment.

The acid in these determinations of basicity was the proton, since the pK_H values were determined by half-neutralization of the amine with dilute hydrochloric acid. It is apparent from Brown's work[3,10,11] that a bulkier acid, such as boron trifluoride or trimethylboron, would amplify the steric effect of the 8-alkyl substituent on the basicity of the pyrrolizidine nucleus. The results of passing boron trifluoride through the liquid amines are summarized in Table I. Solid adducts of boron trifluoride were formed immediately with IIa, b and d, and a distillable liquid adduct, b.p. 253° (755 mm.), was obtained with IV. No solid product was obtained with IIc, and if any adduct was formed, it was highly unstable since IIc could be distilled from the reaction mixture. Thus the greater F-strain in 8-*n*-propylpyrrolizidine revealed in the reaction with a protonic acid is indicated more strikingly in the reaction with boron trifluoride. An interesting but possibly fortuitous correlation between pK_H values and picrate melting points has also been included in Table I.

Experimental[14]

Methyl γ-Nitroheptanoate and Dimethyl γ-*n*-Propyl-γ-nitropimelate (Ic).—The esters were made from 1-nitrobutane[15] essentially by the procedure described by Bruson[7] for the condensation of 1-nitropropane with methyl acrylate, with the exception that three times the recommended amount of Triton B was employed. The methyl γ-nitroheptanoate was obtained in 51% yield as a colorless liquid, b. p. 102° (2 mm.); $n^{20}D$ 1.4388.

Anal. Calcd. for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 51.18; H, 7.97; N, 7.64.

The dimethyl γ-*n*-propyl-γ-nitropimelate was obtained in 36% yield as a yellow-green oil, b. p. 157° (1 mm.); $n^{20}D$ 1.4612; d^{20}_4 1.133.

Anal. Calcd. for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09; MR_D, 66.57. Found: C, 53.07; H, 7.74; N, 5.29; MR_D, 66.63.

Methyl γ-Nitroisoheptanoate and Dimethyl γ-Isopropyl-γ-nitropimelate (Id).—Using the same procedure, 75.7 g. (0.734 mole) of 1-nitro-2-methylpropane (nitroisobutane)[16] was caused to condense with 130 g. (1.5 moles) of methyl acrylate in the presence of 30 g. of Triton B. The methyl γ-nitroisoheptanoate was obtained as a colorless liquid, b. p. 102° (2 mm.); $n^{20}D$ 1.4397; d^{20}_4 1.115; yield, 82.5 g. (59.3%).

Anal. Calcd. for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 51.08; H, 7.92; N, 7.48.

The dimethyl γ-isopropyl-γ-nitropimelate was obtained as a green oil, b. p. 168° (2 mm.); d^{20}_4 1.138; yield, 19.1 g. (9.5%).

Anal. Calcd. for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 54.09; H, 7.68; N, 4.58.

(13) Adams and Mahan, THIS JOURNAL, **64**, 2588 (1942).

(14) Melting points and boiling points have not been corrected for stem immersion. We gratefully acknowledge the assistance of Donald L. Felley and Gradus L. Shoemaker.

(15) We are indebted to Dr. Robert F. Taylor, Commercial Solvents Corporation, for this material.

(16) Made by the method of Shaw, *Bull. roy. acad. Belg.*, [3] **34**, 1019 (1897), modified by the use of ether solvent in the reaction mixture.

The condensation of 79 g. of methyl γ-nitroisoheptanoate with 40 g. of methyl acrylate in the presence of 30 ml. of *t*-butyl alcohol and 25 g. of Triton B produced 23 g. (20%) of Id, and 69% of the isoheptanoate was recovered. The condensation of 54.2 g. of methyl γ-nitroisoheptanoate with 40 g. of methyl acrylate in the presence of 30 ml. of *t*-butyl alcohol and 30 g. of diethylamine produced 32.5 g. (41%) of dimethyl γ-isopropyl-γ-nitropimelate, and again most of the unreacted monobasic ester was recovered.

1,2-Diethylpyrrolidine (IV)

One-Step Reduction.—A solution of 38 g. (0.2 mole) of ethyl γ-nitrocaproate[7] (b. p. 93° (1 mm.), $n^{20}D$ 1.4358) in 100 ml. of ethanol was reduced with hydrogen in the presence of 20 g. of copper chromite at 250° and 300–350 atm. An exothermic reaction began when the temperature reached 125°, and the theoretical amount of hydrogen was absorbed after five hours at 250°. The catalyst was removed by filtration, 200 ml. of benzene was added, and the benzene–ethanol–water azeotrope was removed at 63–65° followed by solvent at 78–80°. The 1,2-diethylpyrrolidine was collected at 140–141° (750 mm.); $n^{20}D$ 1.4372; d^{20}_4 0.8098; yield 11.2 g. (44%). The analysis and physical properties of the tertiary amine and the analysis of its picrate were consistent with the structure assigned to this product.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01; MR_D, 41.06. Found: C, 75.79; H, 13.72; N, 10.96; MR_D 41.18.

When the same procedure was followed using methanol as the solvent, a high-boiling liquid was obtained, b. p. 230–233° (750 mm.); $n^{20}D$ 1.4535; d^{20}_4 0.9804, the identity of which has not been established.

Anal. Found: C, 62.63; H, 11.25.

Two-Step Reduction.—A solution of 56 g. (0.31 mole) of ethyl γ-nitrocaproate in 125 ml. of ethanol was reduced with hydrogen in the presence of 1 g. of platinum oxide catalyst at 2–4 atm. and 25°. After seven days the theoretical amount of hydrogen for reduction of the nitro group had been absorbed, and the catalyst was removed by filtration. The filtrate was reduced further at 250° and 300 atm. with hydrogen in the presence of 20 g. of copper chromite. After five hours the theoretical amount of hydrogen had been absorbed. Twenty grams (50%) of 1,2-diethylpyrrolidine was isolated in the same manner as in the more convenient one-step hydrogenation of ethyl γ-nitrocaproate in ethanol.

1,2-Diethylpyrrolidine Picrate.—Prepared in and recrystallized from ethanol, the picrate formed yellow needles, m. p. 120–121°. The melting point of a mixture with picric acid was depressed.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: N, 15.72. Found: N, 15.86.

8-*n*-Propylpyrrolizidine (IIc) and 8-Isopropylpyrrolizidine (IId).—Method and yield are similar for these compounds and for IIb, starting with the appropriate γ-alkyl-γ-nitropimelic ester. The synthesis of IId serves as an example. A solution of 46 g. (0.167 mole) of dimethyl γ-isopropyl-γ-nitropimelate (Id) in 90 ml. of purified dioxane was hydrogenated at 250–260° and 200–350 atm. in a high-pressure bomb. Rocking was begun when the temperature in the bomb reached 100°. After fifteen minutes at 125° sufficient hydrogen had been absorbed to reduce the nitro group, and rocking was discontinued until the temperature reached 260°. After seven hours, the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate was fractionated at atmospheric pressure. The colorless, basic fraction distilling at 187–193° (745 mm.) was collected and purified by redistillation; yield, 16.5 g. (64.4%).

8-*n*-Propylpyrrolizidine: b. p. 192° (745 mm.); $n^{20}D$ 1.4632; d^{20}_4 0.8918.

8-Isopropylpyrrolizidine: b. p. 191° (745 mm.); $n^{20}D$ 1.4692; d^{20}_4 0.8899.

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.45; N, 9.14; MR_D, 48.10. Found (IIc): C, 77.99; H, 12.66; N, 8.57; MR_D, 47.35. Found (IId): C, 77.73; H, 12.40; N, 8.52; MR_D, 47.98.

8-*n*-Propylpyrrolizidine Picrate.—Prepared in and recrystallized from ethanol, the picrate formed brilliant yellow needles, m. p. 156–157°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.54; H, 5.75; N, 14.73.

8-Isopropylpyrrolizidine Picrate.—Prepared in and recrystallized from ethanol, the picrate formed brilliant yellow needles which melted, with decomposition, at 228–229°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.10; H, 5.80; N, 14.57.

Determination of Basicity Constants.—The pK_H values were determined by dissolving a weighed portion of freshly distilled amine, calculated to require 15–20 ml. of 0.12 *N* hydrochloric acid, in 90 ml. of aqueous methanol calculated to be about 50% methanol at the end of the neutralization. The amount of 0.1200 *N* hydrochloric acid necessary to react with exactly half of the amine present was then added, and the solution was allowed to stand for twenty minutes. The *p*H of the solution was then measured using a Beckmann model G (laboratory model) *p*H meter with a high *p*H glass electrode (designed for *p*H measurements from 9 to 14). Duplicate or triplicate measurements were made in each case, and the pK_H values were corrected to 25°.[17] The method was checked to determine its accuracy. The pK_H value for one of the amines was determined at one-half the amine concentration used in the series. The identical value observed indicated that activities were not an influential factor in the determination. Also, the *p*H values at one-third and two-thirds neutralization of one of the amines were measured, and the pK_H was calculated by use of the equation $pK_H = pH \pm \log 2$. The identity of the values thus obtained with the *p*H at one-half neutralization was substantial proof that the half-neutralization point was actually being determined by the general procedure employed. The pK_H values are considered accurate within ±0.01 *p*H unit.

Summary

1. The preparation of pyrrolizidines by the one-step catalytic reduction of γ-nitropimelic esters has been extended to the synthesis of 8-*n*-propyl- and 8-isopropyl-pyrrolizidine.

2. Comparison of the pK_H values of 2-methyl-, 8-methyl-, 8-ethyl-, 8-*n*-propyl- and 8-isopropyl-pyrrolizidine have shown that the basicity of the pyrrolizidine is decreased as the length of the 8-alkyl group is increased.

URBANA, ILLINOIS RECEIVED FEBRUARY 26, 1948

(17) Hall and Sprinkle, THIS JOURNAL, **54**, 3469 (1932).