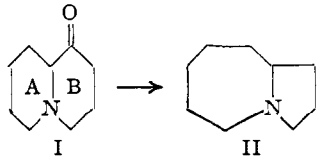
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

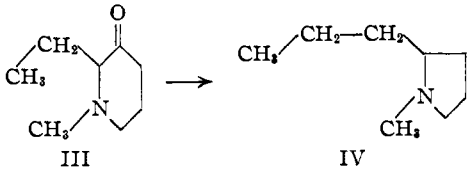
Rearrangement of α-Aminoketones During Clemmensen Reduction. II. Contraction of a Six-membered Ring in the Monocyclic Series

BY NELSON J. LEONARD AND WILLIAM V. RUYLE[1]

In the first article in this series[2] proof was provided that the Clemmensen reduction–rearrangement of 1-ketoquinolizidine (I) to 1-azabicyclo-[5.3.0]decane (II) proceeds through contraction of the six-membered *ketone ring* (B) to a five-membered ring. Since it was also established that contraction is the general fate of the ketonic ring in 1-ketoquinolizidines subjected to Clemmensen reduction, it was of interest to determine if a closely analogous *monocyclic* tertiary α-aminoketone (III) behaved similarly under Clemmensen conditions. Accordingly, the model compound 1-methyl-2-ethyl-3-piperidone (III) has been synthesized and has been subjected to Clemmensen reduction. The fact that the product obtained was 1-methyl-2-*n*-propylpyrrolidine (IV) indicates that the reductive rearrangement is not limited to the bicyclic series, and that ring contraction occurs in the monocyclic series when the amino and carbonyl groups are homocyclic.

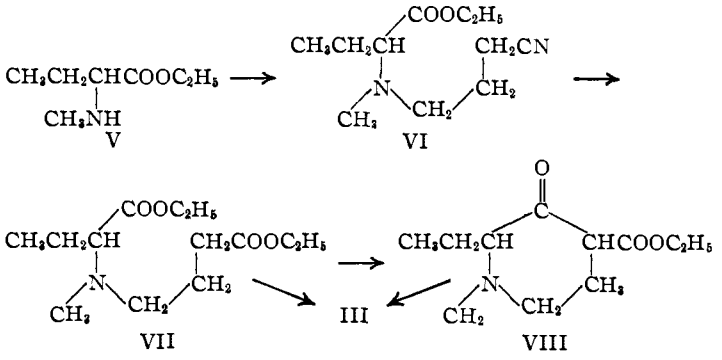


I II



III IV

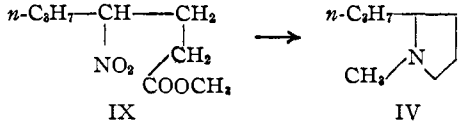
The synthesis of the cyclic aminoketone (III) used in this study was carried out by a series of reactions similar to those employed by Clemo and Ramage[3] in the synthesis of bicyclic aminoketones and by Prill and McElvain[4] in the synthesis of monocyclic aminoketones. Ethyl α-methylaminobutyrate (V) was obtained by condensation of methylamine with α-bromobutyric acid, followed by esterification. Treatment of V with γ-bromobutyronitrile in the presence of anhydrous potassium carbonate furnished α-carbethoxypropyl-γ'-cyanopropylmethylamine (VI), and ethanolysis of VI gave the diester VII.



V VI VII III VIII

Ring closure of the diester (VII) was accomplished by the Dieckmann reaction under two different sets of conditions. When sodium ethoxide was used,[4a] the keto ester (VIII) was isolated as the hydrochloride, which was then hydrolyzed and decarboxylated to give the hydrochloride of III in 60% yield (based on the diester). When potassium was used,[3] the intermediate keto ester (VIII) was not isolated but was immediately hydrolyzed and decarboxylated to give 1-methyl-2-ethyl-3-piperidone (III) in 50% yield. The Clemmensen reduction of 1-methyl-2-ethyl-3-piperidone resulted in a 71% yield of an amine which possessed properties different from those of 1-methyl-2-ethylpiperidine but identical with those of 1-methyl-2-propylpyrrolidine (IV).[5–7]

For direct comparison with the Clemmensen reduction product of III, a sample of 1-methyl-2-propylpyrrolidine (IV) was prepared by the reductive cyclization of methyl γ-nitroheptanoate (IX).[8] The hydrogenation was carried out in dioxane solution over copper oxide–chromium oxide catalyst at 260° and 250 atmospheres. The result was somewhat surprising in that the desired product (IV) was obtained directly, indicating that the process had included N-methylation (by the methanol available from cleavage of the ester).



IX IV

The products of Clemmensen reduction of III and reductive cyclization of IX were identical (see Table I).

As the monocyclic aminoketone III corresponds

(1) Present address: Merck and Company, Inc., Rahway, New Jersey.

(2) Leonard and Wildman, THIS JOURNAL, **71**, 3089 (1949).

(3) Clemo and Ramage, *J. Chem. Soc.*, 437 (1931).

(4) (a) Prill and McElvain, THIS JOURNAL, **55**, 1233 (1933); (b) McElvain, *ibid.*, **46**, 1721 (1924).

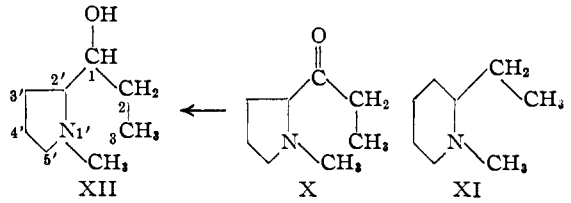
(5) Löffler, *Ber.*, **43**, 2038 (1910).

(6) Hess and Anselm, *ibid.*, **54**, 2110 (1921).

(7) Craig, THIS JOURNAL, **55**, 2543 (1933).

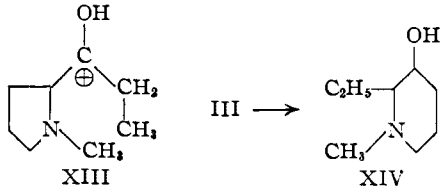
(8) Leonard and Beck, *ibid.*, **70**, 2504 (1948).

to 1-ketoquinolizidine (I) with the non-ketonic ring (A) opened, so the monocyclic aminoketone, 1-methyl-2-propionylpyrrolidine (X), is a model of 1-ketoquinolizidine (or, more accurately, of 1-ketoöctahydropyrrocoline) with the ketonic ring (B) opened. If X were to undergo analogous rearrangement during Clemmensen reduction, the product would be 1-methyl-2-ethylpiperidine (XI), and the process of *non-ketonic ring* expansion from five to six members would effect essentially the reverse of the process (III → IV) of *ketonic ring* contraction from six to five members. 1-Methyl-2-propionylpyrrolidine (X) was prepared



XII X XI

and subjected to Clemmensen reduction. In several runs representing variations in conditions, the only product isolated was 1-(1′-methyl-2′-pyrrolidyl)-1-propanol (XII). Complete reduction did not occur, nor did rearrangement occur. The difference in the behavior of X in the Clemmensen reaction as compared with III (and I)[9] might be rationalized on the basis of the absence in X of the apparently important geometrical directing effect,[2] and thus the carbonium carbon-1 (XIII) may capture a hydride ion (to give XII) before the nitrogen can attack. On a statistical basis, the nitrogen has less opportunity to approach carbonium carbon-1 in X than it does in III where their positions are both fixed by the ring structure. Among the structural features which determine whether rearrangement accompanies reduction, evidently the coexistence of the amino and carbonyl groups in the same ring is important.



XIII XIV

The possibility of the rearrangement (III → IV) proceeding through an ethyleneimonium ion intermediate,[10] formed after Clemmensen conversion of 1-methyl-2-ethyl-3-piperidone (III) to the carbinol (XIV) or corresponding chloro compound, has not been neglected. However, such a sequence seems unlikely since compound XIV was recovered unchanged when subjected to Clemmensen reduction conditions—a behavior similar to that of most secondary alcohols.[11] 1-Methyl-2-ethyl-3-hydroxypiperidine (XIV) as obtained both by catalytic and by sodium and ethanol reduction of III was used in the attempted, unsuccessful conversion (XIV → IV). Our findings are similar to those of von Braun and Weissbach[12] in the α-thiaketone series. These workers found that 4-ketoisothiochroman underwent reduction-rearrangement under Clemmensen conditions to give 1-methyl-1,2-dihydroisothionaphthene, but that 4-hydroxyisothiochroman and 4-chloroisothiochroman did not undergo rearrangement under the same conditions, giving instead isothiochroman. The parallel behavior of the α-amino- and α-thiaketones merits further investigation.

Experimental[13,14]

Ethyl α-Methylaminobutyrate (V).—A mixture of 56 g. (0.34 mole) of α-bromobutyric acid and 1.5 l. of a 35% solution of methylamine in water was stirred at room temperature for four days. The excess methylamine and water were removed by distillation at water pump pressure, with the receiver immersed in a dry ice–ethanol mixture. In this way, 1.34 l. of aqueous methylamine solution (29% methylamine) was recovered. The recovered material was used in a subsequent run without serious diminution of yield. To the residue remaining after removal of the methylamine was added 39 g. of potassium hydroxide in 50% aqueous solution and 200 ml. of 95% ethanol, and the mixture was evaporated to dryness *in vacuo*. In order to effect complete removal of methylamine and water, the residue was treated with 150 ml. of ethanol and was evaporated to dryness *in vacuo*. This process was repeated twice, and the residue at this stage consisted of small colorless crystals suspended in a viscous sirup. The mixture was stirred with 500 ml. of absolute ethanol until the sirupy material was in solution; the crystalline material remained undissolved. The mixture was saturated with dry hydrogen chloride and was allowed to stand overnight. After refluxing for one and one-half hours, the mixture was distilled *in vacuo* almost to dryness. The residue was cooled in an ice–salt-bath and overlayered with 300 ml. of ether. To the well-stirred mixture was added slowly a cold solution of 50 g. of potassium hydroxide in 50 ml. of water, while the temperature was maintained below 10°. The flask was stoppered and shaken vigorously. The yellow ether layer was decanted from the alkaline slurry, which was in turn shaken successively with one 200-ml. portion and three 100-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. After removal of ether by distillation, the product was fractionally distilled, b. p. 64–65.5° (20 mm.); $n^{20}D$ 1.4174; yield, 30.4 g. (63%).

The **picrate** formed slowly in ether solution, and was recrystallized from ether containing a very small amount of methanol, m. p. 103–104.5°.

(9) Prelog and Seiwerth, *Ber.*, **72**, 1638 (1939).

(10) For representative papers on ethyleneimonium ions, see: Cromwell and Cram, THIS JOURNAL, **65**, 301 (1943); Cromwell and Witt, *ibid.*, **65**, 308 (1943); Kerwin, Ullyot, Fuson and Zirkle, *ibid.*, **69**, 2961 (1947); Bartlett, Ross and Swain, *ibid.*, **69**, 2971 (1947); Schultz and Sprague, *ibid.*, **70**, 48 (1948); Fuson and Zirkle, *ibid.*, **70**, 2760 (1948).

(11) It was recognized that existing evidence shows that the Clemmensen reduction of >CO to >CH₂ does not proceed by way of the carbinol (Martin, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 156), but the possibility was not precluded that the α-aminoketones might exhibit unique behavior. The mechanism which was proposed in Paper I for change in ring size in the bicyclic compounds does not require the interim formation of the carbinol and hence continues valid for both bicyclic and monocyclic types.

(12) von Braun and Weissbach, *Ber.*, **62**, 2416 (1929).

(13) All melting points are corrected. Microanalyses were performed by Miss Emily Davis, Mrs. Jane Wood and Mr. Maurice Dare.

(14) The assistance of Dr. Gerhard Leubner is gratefully acknowledged.

Anal. Calcd. for $C_{13}H_{18}N_4O_9$: C, 41.71; H, 4.85; N, 14.97. Found: C, 41.77; H, 4.96; N, 15.04.

α-Carbethoxypropyl-γ'-cyanopropylmethylamine (VI).—A stirred mixture of 59.0 g. (0.407 mole) of ethyl α-methylaminobutyrate, 60.2 g. (0.406 mole) of γ-bromobutyronitrile, and 58.0 g. (0.42 mole) of finely ground anhydrous potassium carbonate was heated in an oil-bath at 100° for one and one-half hours. After cooling, 150 ml. of water was added to the mixture to dissolve the inorganic salts, and the organic layer was separated. The aqueous layer was extracted three times with 30-ml. portions of ether, which were combined with the organic layer. The ethereal solution was dried and the ether was removed. The residue was distilled *in vacuo*. After a considerable forerun, b. p. 28–120° (2 mm.), the product was collected, b. p. 120–122° (2 mm.); yield, 54.6 g. (63.5%); $n^{20}D$ 1.4450. Fractional distillation of the forerun resulted in recovery of approximately 17% of each of the unchanged reactants.

The **picrate**, prepared in ether and recrystallized from ether–ethanol, melted at 78–82°. Repeated recrystallization failed to improve the melting point.

Anal. Calcd. for $C_{17}H_{23}N_5O_9$: C, 46.26; H, 5.25. Found: C, 46.38; H, 5.24.

α-Carbethoxypropyl-γ'-carbethoxypropylmethylamine (VII).—A solution of 54.6 g. (0.257 mole) of α-carbethoxypropyl-γ'-cyanopropylmethylamine in 225 ml. of absolute ethanol, cooled in an ice-bath and protected from moisture, was saturated with dry hydrogen chloride. The solution was warmed to approximately 35° for one and one-half hours and was then heated under reflux for two and one-half hours. After cooling, the ammonium chloride was collected and washed with absolute alcohol. The combined filtrate and washings were concentrated to a small volume *in vacuo*, and the residue taken up in 60 ml. of water. The solution was overlayered with 50 ml. of ether. The mixture was cooled in an ice-bath, and 50% aqueous potassium hydroxide was added until a distinctly alkaline reaction was given. The aqueous layer was extracted three times with 50-ml. portions of ether. The ethereal solution was dried and the ether was removed. The product distilled at 119–120° (2 mm.); yield, 55.9 g. (84%); $n^{20}D$ 1.4391.

Anal. Calcd. for $C_{13}H_{25}NO_4$: C, 60.20; H, 9.72; N, 5.40. Found: C, 60.38; H, 9.85; N, 5.39.

Attempts to prepare the picrate and picrolonate in ether or ethanol failed.

Dieckmann Ring Closure of α-Carbethoxypropyl-γ'-carbethoxypropylmethylamine

A. With Potassium: 1-Methyl-2-ethyl-3-piperidone (III).—Potassium metal (10.0 g., 0.256 gram atom) was powdered under 50 ml. of dry xylene in a 200-ml. round-bottomed, three-necked flask fitted with stirrer, dropping funnel, and reflux condenser protected by a calcium chloride tube. With the temperature of the heating bath maintained at 105–115°, 14.5 g. (0.056 mole) of α-carbethoxypropyl - γ' - carbethoxypropylmethylamine dissolved in 20 ml. of dry xylene was added over a period of fifty minutes while the mixture was stirred rapidly. The mixture was stirred for an additional three hours at the same temperature. After cooling, 15 ml. of absolute ethanol was added cautiously to destroy excess potassium, then 40 ml. of water was added. The layers were separated, and the xylene layer was extracted with three 10-ml. portions of water. To the aqueous extracts was added 70 ml. of concentrated hydrochloric acid, and the mixture was heated under reflux on a steam-bath for two and one-half hours. The mixture was concentrated *in vacuo* to a small volume. The dark red, semi-crystalline residue was taken up in 40 ml. of water and was overlayered with 50 ml. of ether. To the cooled mixture was added with stirring an excess of a saturated aqueous solution of sodium hydroxide. The layers were separated and the aqueous layer was extracted several times with small portions of ether. After drying the ether solution, the ether was removed and the colorless product was distilled at 80–85° (14 mm.); yield, 4.04 g. (51%). A small sample was redistilled for analysis, b. p. 64° (5 mm.); $n^{20}D$ 1.4620.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.04; H, 10.71. Found: C, 67.94; H, 10.94.

The **picrate** was made in ether solution and was recrystallized from absolute ethanol, m. p. 131.5–132.5°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.90; N, 15.13. Found: C, 45.35; H, 5.06; N, 15.05.

The **picrolonate**, prepared similarly, melted with decomposition at 165–166°.

Anal. Calcd. for $C_{18}H_{23}N_5O_6$: C, 53.33; H, 5.72. Found: C, 53.55; H, 5.69.

B. With Sodium Ethoxide: 1-Methyl-2-ethyl-4-carbethoxy-3-piperidone (VIII) Hydrochloride.—Sodium ethoxide[15] was prepared from 2.23 g. (0.097 gram atom) of sodium in a 100-ml. Claisen flask fitted with stirrer, dropping funnel, and receiver, and protected from atmospheric moisture. To the sodium ethoxide was added 25.16 g. (0.097 mole) of the diester. The stirred mixture was heated gradually in an oil-bath. At 120° (bath temp.) ethanol began to distil, and in a period of thirty minutes the temperature was raised to 145° and maintained there for fifteen minutes, after which no more ethanol distilled. The cooled reaction mixture was dissolved in 75 ml. of water, and the solution was made acid to congo red with hydrochloric acid, while the temperature was kept below 10°. The solution was then neutralized to litmus with potassium carbonate, and was extracted with ether until the extracts no longer gave a red color with ferric chloride solution. The combined ether extracts were dried and then concentrated to a volume of about 50 ml. Dry hydrogen chloride was passed into the solution until precipitation of the hydrochloride was complete; yield, 18.71 g. (77%); m. p. 158–160°. After one recrystallization from absolute ethanol–ether mixture, the product melted, with decomposition, at 162–163° and weighed 16.02 g. (66%).

Anal. Calcd. for $C_{11}H_{20}ClNO_3$: C, 52.90; H, 8.07; N, 5.61. Found: C, 53.03; H, 8.32; N, 5.66.

1-Methyl-2-ethyl-3-piperidone Hydrochloride.—1-Methyl-2-ethyl-4-carbethoxy-3-piperidone hydrochloride was hydrolyzed and decarboxylated by heating with 6 *N* hydrochloric acid on a steam-bath for three hours. Removal of excess hydrochloric acid by distillation *in vacuo* and recrystallization of the residue from dry acetone gave a 91% yield of 1-methyl-2-ethyl-3-piperidone hydrochloride, m. p. 133–134°.

Anal. Calcd. for $C_8H_{16}ClNO$: C, 54.08; H, 9.08; N, 7.88. Found: C, 54.35; H, 9.30; N, 7.59.

The **picrate** prepared from this hydrochloride had the same melting point as the picrate prepared from the free base in procedure A, and there was no depression of melting point when the two were mixed.

Reductive Cyclization of Methyl γ-Nitroheptanoate (IX).—Twenty and three-tenths grams of methyl γ-nitroheptanoate (0.1 mole) dissolved in 65 ml. of purified dioxane was hydrogenated in the presence of copper chromite catalyst at 260° and 250 atmospheres.[8] About 65% of the theoretical amount of hydrogen was taken up in four hours. After removal of the catalyst by filtration, the bulk of the dioxane was removed by distillation through a six-inch Fenske column. The product distilled at 138–146°; yield, 4.5 g. (36%). A considerable amount of higher boiling material remained in the distilling flask. A final distillation of the product from metallic sodium yielded 2.8 g. of amine, b. p. 145–146° (742 mm.); $n^{20}D$ 1.4378; d^{15}_4 0.823. The picrate, picrolonate and chloroaurate are described in Table I.

Clemmensen Reduction of 1-Methyl-2-ethyl-3-piperidone Hydrochloride.—Mossy zinc (36 g.) was washed with 5% hydrochloric acid and was then shaken for five minutes with a mixture of water (65 ml.), concentrated hydrochloric acid (4 ml.) and mercuric chloride (4 g.).

(15) Hauser and Hudson, in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 279.

TABLE I

	[a]Product of Clemmensen reduction of 1-methyl-2-ethyl-3-piperidone	[a]Product of Reductive cyclization of methyl γ-nitroheptanoate	Reported for 1-methyl-2-propylpyrrolidine
B. p., °C. (mm.)	146–147 (742)	145–146 (742)	146–147 (761)[5]
Density, 15°	0.825	0.823	0.815[5]
$n^{20}D$	1.4380	1.4378	.....
Picrate, m. p., °C.	123–124	123–124	124,[5] 125[6]
Picrolonate, m. p. °C.	169.5–171	168–169.5	.....
Chloroaurate, m. p., °C.	76–77	75–77	76[5]
Chloroplatinate, m. p., °C.	145–146.5	.....	145–146[4]

[a] Admixture of the corresponding derivatives caused no depression in melting point.

The solution was decanted from the amalgam, which was then washed once with distilled water by decantation. To the amalgam was added cautiously a solution of 1-methyl-2-ethyl-3-piperidone hydrochloride (4.0 g.) in 40 ml. of concentrated hydrochloric acid. After the vigorous initial reaction had subsided, the mixture was heated under reflux for twelve hours. (This period of time was found to be sufficient and was used in subsequent comparative experiments.) At intervals of three hours, 10-ml. portions of concentrated hydrochloric acid were added. After cooling, the solution was decanted, and the residual amalgam was washed with small portions of water. The excess hydrochloric acid was removed from the solution and aqueous washings *in vacuo*. The residual viscous sirup was made strongly alkaline with a solution of 50 g. of potassium hydroxide in 200 ml. of water. The resulting slurry of zinc salts was subjected to steam distillation. The first 40-ml. fraction of distillate appeared to contain most of the organic product, and was collected separately from the subsequent 200 ml. of distillate. The first fraction was saturated with potassium hydroxide with cooling, and was then extracted five times with 10-ml. portions of ether. The ethereal solution was dried and the ether was removed. The product distilled at 143–146° (743 mm.); yield, 1.87 g. (65.3%). Mineral oil was added to the distilling flask, and the last traces of product were forced over by heating strongly. The picrate (4.9% of theory) prepared from this fraction melted at 121–123° without recrystallization, and the melting point was not depressed on admixture with the picrate prepared from the main fraction. A small amount (1.1% of theory) of the same picrate was isolated from the second fraction of steam distillate. The total yield of the product and its picrate was thus 71.3%. A final distillation of the product from metallic sodium furnished material having the physical constants shown in Table I.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.58; H, 13.41; N, 10.74.

Picrate, pale yellow needles from absolute ethanol.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66; N, 15.72. Found: C, 47.45; H, 5.74; N, 15.67.

Picrolonate, small yellow prisms from absolute ethanol.

Anal. Calcd. for $C_{18}H_{25}N_5O_5$: C, 55.23; H, 6.44; N, 17.89. Found: C, 55.06; H, 6.47; N, 17.66.

Catalytic Hydrogenation of 1-Methyl-2-ethyl-3-piperidone Hydrochloride. 1-Methyl-2-ethyl-3-hydroxypiperidine (XIII) Hydrochloride.—The hydrochloride (1.5 g.) of 1-methyl-2-ethyl-3-piperidone was dissolved in 50 ml. of absolute ethanol and was subjected to hydrogenation at 2.5 atmospheres at 25° in the presence of 0.2 g. of platinum oxide catalyst. Slightly more than the theoretical amount of hydrogen was taken up in one hour. After removal of the catalyst by filtration and the solvent by distillation *in vacuo*, the residue was dissolved in hot, dry acetone. Colorless prisms formed slowly on cooling. After a second recrystallization from acetone, the colorless, hygroscopic prisms melted at 109–111°, and weighed 0.62 g. (41%). The compound gave negative Benedict and Tollens tests.

Anal. Calcd. for $C_8H_{18}ClNO$: C, 53.47; H, 10.10; N, 7.80. Found: C, 53.47; H, 10.33; N, 7.68.

The **picrate**, prepared from the hydrochloride by liberating the free base, extracting into ether, and treating the ether solution with ethereal picric acid, crystallized from ethanol–ether as short needles, m. p. 105–108°.

Anal. Calcd. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.25; H, 5.67; N, 15.27.

The mother liquors obtained from the recrystallization of the hydrochloride could not be made to yield more crystalline material. The sirupy residue remaining after removal of solvent gave negative Benedict and Tollens tests. The sirup was converted to the free base, and thence to the **picrate**, which weighed 1.04 g. (33%) and melted at 104–106°. Recrystallization from ethanol–ether mixture raised the melting point to 107–109.5°.

Anal. Calcd. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.19; H, 5.73; N, 15.33.

Admixture of the two picrates (m. p.'s 105–108° and 107–109.5°) gave no depression in melting point. From appearance and solubility characteristics, the two picrates were identical. On occasions, when ethanol–ether solution of the picrate were cooled in the refrigerator for several days, the compound crystallized in the form of small prisms which melted at 113–116°. Admixture with the lower melting form produced a melting range of 105–116°. Although the rather wide melting ranges of these picrates might indicate mixtures of the two possible diastereoisomers, the formation of the two diastereoisomeric entities has not been shown definitely.

Catalytic hydrogenation of the free base, 1-methyl-2-ethyl-3-piperidone, was attempted, but the absorption of hydrogen was much slower and less complete than in the case of the hydrochloride, and the product appeared to contain considerable unchanged ketone.

Reduction of 1-Methyl-2-ethyl-3-piperidone with Sodium and Ethanol.—Three grams of the hydrochloride of 1-methyl-2-ethyl-3-piperidone was converted to the base, and the aminoketone was dissolved in 40 ml. of absolute ethanol contained in a 200-ml. round-bottomed flask bearing a reflux condenser. Sodium (8.0 g.) in small pieces was dropped through the condenser at a rate sufficient to maintain rapid reflux. Toward the end of the addition it was necessary to heat the mixture to cause the sodium to dissolve. Twenty-five milliliters of water was added, and the mixture was subjected to steam distillation. The distillate was collected as long as it showed an alkaline reaction to litmus (approx. 160 ml.), and was then acidified with hydrochloric acid and evaporated to dryness *in vacuo*. The residue was basified with a saturated aqueous solution of potassium hydroxide, extracted into ether, and the extracts were dried. After removal of the ether, the product distilled at 73–77° (4 mm.); $n^{20}D$ 1.4800; yield, 1.4 g. (58%).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.08; H, 11.97. Found: C, 67.37; H, 12.21.

The **picrate**, recrystallized from ethanol–ether mixture, melted at 104.5–108°, and the melting point was not depressed by admixture with the picrate of the catalytic hydrogenation product. The hydrochloride crystallized from acetone as colorless prisms, whose melting point and mixed melting point (109–111°) were the same as the hydrochloride of the catalytic hydrogenation product.

Treatment of 1-Methyl-2-ethyl-3-hydroxypiperidine under Clemmensen Conditions.—The hydrochloride was subjected to the Clemmensen reduction in the same manner as was 1-methyl-2-ethyl-3-piperidone hydrochloride. Sixty per cent. of the starting material was recovered from the reaction mixture as the picrate. No other product was isolated.

The free base obtained from the sodium reduction of the amino-ketone likewise was unchanged when subjected to Clemmensen conditions.

2-Propionylpyrrole.—This compound was prepared by the method of Oddo[16] in a yield of 35%, b. p. 227–230°, m. p. 50–52°.

1-(2′-Pyrrolidyl)-1-propanol.—By sodium and ethanol reduction of 2-propionylpyrrole,[17] a 22% yield of 1-(2′-pyrrolidyl)-1-propanol was obtained, b. p. 97–100° (17 mm.). Recrystallization from petroleum ether gave colorless hygroscopic needles, m. p. 48–50°.

1-Methyl-2-propionylpyrrolidine (X).—By the method of Hess,[18] a 78% yield of the compound was obtained, b. p. 70–72° (12 mm.), $n^{20}D$ 1.4611. The **picrate**, recrystallized from ethanol as orange leaflets, melted at 103–104°. The free base gave a positive Tollens test in the cold, but a negative Benedict test, even when heated.

Clemmensen Reduction of 1-Methyl-2-propionylpyrrolidine.—The free base (1.27 g.), when subjected to the Clemmensen reduction in the usual manner, yielded 0.79 g. (62%) of a liquid which boiled at 79–80° (13 mm.). The boiling point reported for 1-(1′-methyl-2′-pyrrolidyl)-1-propanol (XII) is 83° (14–15 mm.),[19] and the analytical figures were consistent with the assignment of this structure to the product.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.08; H, 11.97. Found: C, 67.18; H, 12.26.

The compound has no effect on Tollens reagent. The **picrate**, recrystallized from ethanol, melted at 149–150.5° with sintering at 145° (reported, 153–154° with sintering at 150°).[17]

Anal. Calcd. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.21; H, 5.68; N, 15.31.

(16) Oddo, *Gazz. chim. ital.*, **39**, I, 649 (1909); *Ber.*, **43**, 1012 (1910).

(17) Hess, *ibid.*, **46**, 3113 (1913).

(18) Hess, *ibid.*, **46**, 4104 (1913).

(19) Hess, Merck and Uibrig, *ibid.*, **48**, 1886 (1915).

Summary

It has been established that Clemmensen reduction of 1-methyl-2-ethyl-3-piperidone results in the formation of the rearrangement product, 1-methyl-2-*n*-propylpyrrolidine.

The Clemmensen reduction–rearrangement of α-aminoketones, which was previously recognized only in the bicyclic series (1-ketoquinolizidines), has thus been shown to occur in the monocyclic series (six-membered ring). It can be said that ring contraction occurs in the monocyclic series when the α-amino and carbonyl groups are homocyclic.

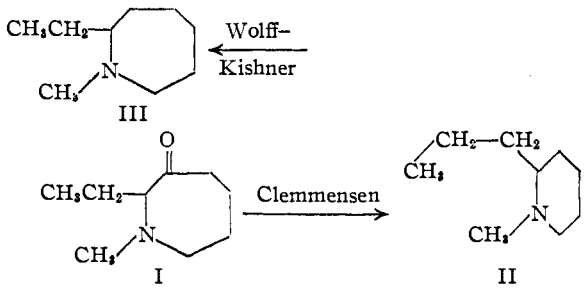
URBANA, ILLINOIS RECEIVED FEBRUARY 21, 1949

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

Rearrangement of α-Aminoketones During Clemmensen Reduction. III. Contraction of a Seven-membered Ring in the Monocyclic Series

BY NELSON J. LEONARD AND ERIC BARTHEL, JR.

Since the fact has been established that under Clemmensen reduction conditions the six-membered ring in 1-methyl-2-ethyl-3-piperidone undergoes contraction to a five-membered ring with the formation of 1-methyl-2-*n*-propylpyrrolidine,[1] we wished to determine whether the seven-membered homolog (I) would undergo contraction to a six-membered ring. This information would constitute the beginning of our knowledge concerning



the possible effect of ring size in limiting the rearrangement process. Accordingly, 1-methyl-2-ethyl-1-azacycloheptan-3-one (I) has been prepared and has been subjected to Clemmensen reduction. The product obtained was identified as the rearranged product, 1-methyl-2-*n*-propylpiperidine (II).

The synthesis of I was accomplished by a method similar to that used by Prill and McElvain[2] for the compound lacking the 2-ethyl group. Ethyl α-methylaminobutyrate[1] was condensed with δ-chlorovaleronitrile to give α-carbethoxypropyl-δ′-cyanobutylmethylamine. Ethanolysis of the cyanoester produced the diester, α-carbethoxypropyl-δ′-carbethoxybutylmethylamine. Dieckmann ring closure of the diester furnished 1-methyl-2-ethyl-1-azacycloheptan-3-one (I), isolated as the hydrochloride in 52% yield. The normal carbonyl reduction product of I, 1-methyl-2-ethylazacycloheptane (III), was obtained by the Wolff–Kishner method; the Clemmensen reduction product of I was isomeric with III. The Clemmensen product and its derivatives had the properties requisite for 1-methyl-2-*n*-propylpiperidine (*dl*-N-methylconiine) (II),[3,4] and identity was fully established by direct comparison with an authentic sample of II.

The results indicate that the Clemmensen reduction-rearrangement of monocyclic α-aminoketones is not limited to contraction of six-membered rings.

Experimental[5]

δ-Chlorovaleronitrile.—Sixty-eight and five-tenths grams of 95% potassium cyanide (1.0 mole) was dissolved

(1) Leonard and Ruyle, THIS JOURNAL, **71**, 3094 (1949).

(2) Prill and McElvain, *ibid.*, **55**, 1233 (1933).

(3) Lukes and Smetackova, *Coll. Czech. Chem. Commun.*, **6**, 231 (1934).

(4) Hess and Eichel, *Ber.*, **50**, 1396 (1917).

(5) All melting points are corrected. Microanalyses were performed by Miss Emily Davis, Mrs. Jane Wood and Mr. Maurice Dare.