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.

(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).

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.

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.

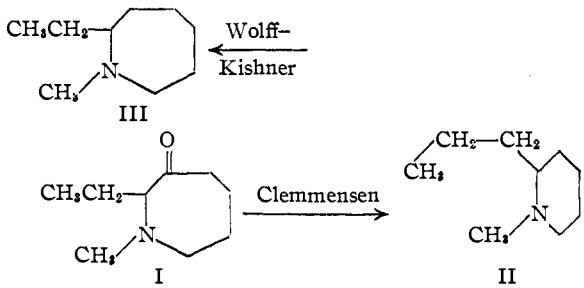
URBANA, ILLINOIS RECEIVED FEBRUARY 21, 1949

[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.

in 1.2 l. of commercial absolute methanol and to this solution was added 660 g. (5.2 moles) of 1,4-dichlorobutane.

The mixture was refluxed on the steam-bath with stirring for seventeen hours. The flask was cooled in an ice-bath and the precipitated salts were collected and washed with absolute methanol. The solvent was removed by distillation and the dark purple residue was subjected to fractional distillation under reduced pressure. 1,4-Dichlorobutane (501 g.), b. p. 61–65° (27–28 mm.), was recovered and the product was collected at 115–118° (28 mm.); $n^{20}D$ 1.4447; yield, 71.7 g. (61% based on potassium cyanide).

α-Carbethoxypropyl-δ'-cyanobutylmethylamine.—A vigorously stirred mixture of 28.4 g. (0.242 mole) of δ-chlorovaleronitrile, 35.1 g. (0.242 mole) of ethyl α-methylaminobutyrate,[1] and 34.5 g. (0.25 mole) of finely ground anhydrous potassium carbonate was heated at 120–130° for twenty-four hours. The mixture was cooled and 100 ml. of water was added to dissolve the inorganic material. The organic layer was separated and the aqueous layer was extracted with three 50-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;* b. p. 110–112° (0.4 mm.); $n^{20}D$ 1.4482; yield, 44.7 g. (82%).

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.97; H, 9.97; N, 12.52.

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

α-Carbethoxypropyl-δ'-carbethoxybutylmethylamine.—A solution of 44.7 g. (0.197 mole) of α-carbethoxypropyl-δ'-cyanobutylmethylamine in 250 ml. of absolute ethanol, cooled in an ice-bath and protected from moisture, was saturated with dry hydrogen chloride. The solution was allowed to stand at room temperature (*ca.* 25°) for two hours and was heated under reflux for two hours. After cooling, the precipitated ammonium chloride was collected and washed with absolute ethanol. The combined filtrate and washings were concentrated to a small volume under reduced pressure. The residue was taken up in 80 ml. of water, the solution was cooled in an ice-bath, and 15% aqueous potassium hydroxide solution was added until the solution was definitely alkaline to litmus paper. The organic layer was separated and the aqueous layer was extracted with two 50-ml. and two 25-ml. portions of ether. The organic layer and ether extracts were combined and dried, and the ether was removed. The product was collected at 125–128° (1.1 mm.); $n^{20}D$ 1.4427; yield, 38.5 g. (71.5%).

Anal. Calcd. for $C_{14}H_{27}NO_4$: C, 61.51; H, 9.96; N, 5.12. Found: C, 61.77; H, 9.77; N, 5.32.

The picrate and picrolonate could not be prepared in ether or ethanol.

Dieckmann Ring Closure of α-Carbethoxypropyl-δ'-carbethoxybutylmethylamine. 1-Methyl-2-ethyl-1-azacycloheptan-3-one (I) Hydrochloride.—Sodium ethoxide[6] was prepared from 3.24 g. of sodium in a 1-l. round-bottomed, three-necked flask fitted with a mercury seal stirrer and a Vigreux fractionating column. A thermometer was inserted in the head of the column and the side arm was attached to a condenser set for downward distillation. The system was protected from moisture. A solution of 38.5 g. (0.141 mole) of the aminodiester in 600 ml. of dry xylene was added. The stirred mixture was heated sufficiently to cause gentle refluxing in the column. Periodically the temperature was raised and the mixture of ethanol and xylene was distilled until the thermometer registered the boiling point of pure xylene. At the end of thirty hours, no more ethanol distilled over. The cooled residue was extracted with four 30-ml. portions of water and was made slightly acid with dilute hydrochloric acid. The xylene layer was extracted with 40-ml. portions of dilute hydrochloric acid until the aqueous extract gave a negative enol test with ferric chloride solution. Concentrated hydrochloric acid (100 ml.) was added to the combined aqueous extracts and the solution was refluxed for two and a quarter hours. A test with ferric chloride solution for the enol function was negative at this time. The reaction mixture was concentrated by evaporation *in vacuo*, cooled in an ice-bath, and made distinctly alkaline to litmus by the slow addition of a saturated aqueous solution of potassium hydroxide. The basic solution was extracted with eight 25-ml. portions of ether. The extracts were combined and dried. Dry hydrogen chloride was passed through the ethereal solution with the formation of a thick, viscous, yellowish gum. The ether was decanted and the residue was recrystallized from ethanol–ether; yield, 14.1 g. (52%) of colorless elongated prisms, m. p. 162.5–163°.

Anal. Calcd. for $C_9H_{18}ClNO$: C, 56.39; H, 9.46; N, 7.31. Found: C, 56.57; H, 9.55; N, 7.07.

The **picrate**, made from the ethereal solution, crystallized from dilute ethanol as bright yellow needles, m. p. 169–169.5°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.25; N, 14.58. Found: C, 47.11; H, 5.24; N, 14.87.

The **picrolonate**, prepared similarly, crystallized as golden-yellow needles, m. p. 164.5–165.5°, from absolute ethanol.

Anal. Calcd. for $C_{19}H_{25}N_5O_8$: C, 54.41; H, 6.01; N, 16.70. Found: C, 54.39; H, 6.22; N, 16.72.

1-Methyl-2-ethyl-1-azacycloheptan-3-one (I).—Four grams (0.029 mole) of anhydrous potassium carbonate dissolved in 10 ml. of water was added to 5 g. (0.026 mole) of the aminoketone hydrochloride in 10 ml. of water. The organic layer which separated was collected in 10 ml. of ether and the aqueous layer was extracted with two additional 10-ml. portions of ether. The extracts were combined and dried and the ether was removed. Distillation of the residue yielded 3.37 g. (84%) of the free base, b. p. 91–92° (13 mm.); $n^{20}D$ 1.4696.

Wolff-Kishner Reduction of 1-Methyl-2-ethyl-1-azacycloheptane-3-one. 1-Methyl-2-ethylazacycloheptane (III).—A mixture of 3.4 g. (0.022 mole) of the aminoketone, 4.2 g. (0.074 mole) of potassium hydroxide, 3 ml. of 85% hydrazine hydrate, and 30 ml. of triethylene glycol was heated at 140–145° under reflux for one hour. The condenser was then set for downward distillation and the temperature of the bath was increased slowly to 250° and was maintained at that point until distillation ceased. The organic matter was removed from the aqueous portion of the distillate by extraction with two 10-ml. portions of ether. After drying, the ether was removed and the residue was distilled, yielding 1.30 g. (42%) of basic material, b. p. 174–175° (755 mm.); $n^{20}D$ 1.4472.

Anal. Calcd. for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 76.96; H, 13.67; N, 10.48.

The **picrate**, formed in ether, crystallized from absolute ethanol as yellow needles, m. p. 166.5–167.5°.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.63; H, 6.07; N, 15.23.

Clemmensen Reduction of 1-Methyl-2-ethyl-1-azacycloheptan-3-one.—Mossy zinc (27 g.) was amalgamated by shaking for five minutes with 3 g. of mercuric chloride, 3 ml. of concentrated hydrochloric acid, and 35 ml. of water. The solution was decanted from the amalgam, which was then washed once with distilled water. Four grams (0.021 mole) of the aminoketone in 40 ml. of concentrated hydrochloric acid was added cautiously to the amalgam. The mixture was heated under gentle reflux for twelve hours. At intervals of two hours, 15-ml. portions of concentrated hydrochloric acid were added and, after seven hours, there was added 20 g. of mossy zinc, amalgamated as before with 2 g. of mercuric chloride, 2 ml. of concentrated hydrochloric acid, and 30 ml. of water. At the end of twelve hours, the aqueous layer was decanted and the residual metal was washed once with distilled water. The solution and washings were concentrated by evaporation *in vacuo*. The resulting viscous sirup was made strongly alkaline to litmus by the addi-

(6) 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-1-azacycloheptan-3-one	Product of Wolff–Kishner reduction of 1-methyl-2-ethyl-1-azacycloheptan-3-one	[a]1-Methyl-2-*n*-propylpiperidine prepared according to Lukes and Smetackova[3]	Reported for 1-methyl-2-*n*-propylpiperidine (*dl*-N-methylconiine)
B. p., °C. (mm.)	163–165 (759)	174–175 (755)	167–168 (757)	175.5[3]; 174[4]
$n^{20}D$	1.4491	1.4472	1.4500	1.4522[3]
Hydrochloride, m. p., °C.	168–168.5	.....	169–169.5	165–167[3]; 165–166[4]
Picrate, m. p., °C.	108.5–109	166.5–167.5	109.3–109.8	112–114[3]; 110.5[4]
Chloroaurate, m. p., °C.	88.5–90.5	.....	88.5–89.5	90[3]; 91[4]
Chloroplatinate, m. p., °C.	194.5–196	.....	196–197	197[3]; 194[4]

[a] The melting points of mixtures of the corresponding derivatives showed no depression.

tion of a saturated aqueous solution of potassium hydroxide. The white slurry thus obtained was subjected to steam distillation until the distillate was no longer basic to litmus paper. The organic layer was separated and the aqueous layer was extracted with four 40-ml. portions of ether. The organic layer and extracts were combined and dried and the ether was removed. Distillation of the residue yielded 1.49 g. (50%) of basic material, b. p. 61–63° (13 mm.); 163–165° (759 mm.); $n^{20}D$ 1.4491.

Anal. Calcd. for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 76.13; H, 13.68; N, 9.99.

The **picrate** was prepared in ether and recrystallized from dilute ethanol as long light-yellow needles, m. p. 108.5–109°.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.75; H, 6.19; N, 15.29.

The **chloroplatinate** was prepared by adding an aqueous solution of the amine hydrochloride to an aqueous solution of platinum chloride and was recrystallized from dilute ethanol as bright orange prisms, m. p. 194.5–196°.

The **chloroaurate** was prepared similarly, yielding greenish yellow needles, m. p. 88.5–90.5°.

The **hydrochloride** was formed in ether and deposited white needles when recrystallized from acetone, m. p. 168–168.5°.

1-Methyl-2-pyridone.—This compound was prepared by the method of Prill and McElvain[7] in a yield of 83%, b. p. 134–136° (18 mm.); $n^{20}D$ 1.5679.

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 419.

1-Methyl-2-piperidone.—Fifty-five and four-tenths grams of 1-methyl-2-pyridone was dissolved in 200 ml. of glacial acetic acid and the solution was hydrogenated at 2–3.5 atmospheres and 26° in the presence of 0.5 g. of platinum oxide catalyst. Slightly more than the theoretical amount of hydrogen was taken up in seventeen hours. The catalyst was removed by filtration and the solvent was removed by evaporation under reduced pressure. Distillation of the residue yielded 50.36 g. (87.5%) of product, b. p. 102–106° (15 mm.); $n^{20}D$ 1.4711.

1-Methyl-2-*n*-propylpiperidine.—The method of Lukes and Smetackova[3] was used in the preparation of this material from 1-methyl-2-piperidone in a yield of 9.7%; b. p. 167–168° (757 mm.); $n^{20}D$ 1.4500. The derivatives of 1-methyl-2-*n*-propylpiperidine were made in the same manner as were the derivatives of the product of the Clemmensen reduction of 1-methyl-2-ethyl-1-azacycloheptan-3-one. They are listed in Table I.

Summary

It has been established that Clemmensen reduction converts 1-methyl-2-ethyl-1-azacycloheptan-3-one to the rearrangement product, 1-methyl-2-*n*-propylpiperidine (*dl*-N-methylconiine). The process involves ring contraction from seven to six members.

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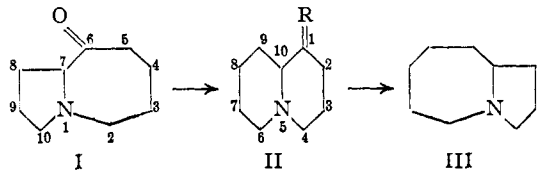
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

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

BY NELSON J. LEONARD AND WILLIAM C. WILDMAN[1]

In a previous communication[2] the authors showed that the rearrangement of 1-ketoquinolizidine (IIb) to 1-azabicyclo[5.3.0]decane (III), under conditions of the Clemmensen reduction, proceeds with contraction of the ketonic ring and expansion of the non-ketonic ring, and a mechanism was suggested for this transformation. Now we have shown that the 1-azabicyclo[5.3.0]decane ring system can be transformed to the quinolizidine ring system by the same process. The Clemmensen reduction of 6-keto-1-azabicyclo[5.3.0]-decane (I) produced the rearrangement product, quinolizidine (1-azabicyclo[4.4.0]decane) (IIa).



I II III

(a, R = H_2; b, R = O)

The synthesis of I was accomplished by the Dieckmann ring closure of ethyl δ-N-(2-carbethoxypyrrolidyl)-valerate (VI) without isolation of the intermediate ketoester. The diester VI was obtained by ethanolysis of δ-N-(2-carbethoxypyrrolidyl)-valeronitrile (V), product of the condensa-

(1) Present address: Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

(2) Leonard and Wildman, THIS JOURNAL, 71, 3098 (1949).