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

Rearrangement of α-Aminoketones during Clemmensen Reduction. IX.[1] The Fate of Asymmetry at the α-Carbon[2]

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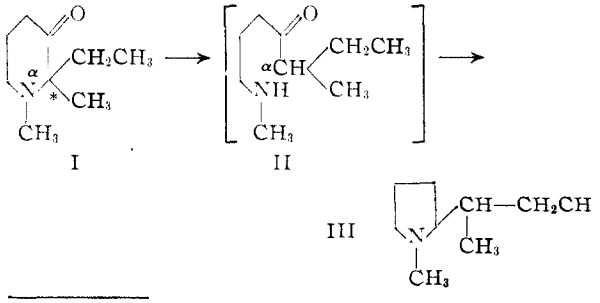
The resolution of 1,2-dimethyl-2-ethyl-3-piperidone has been effected, and the optically active ketone has been subjected to Clemmensen reduction. The product, 1-methyl-2-*s*-butylpyrrolidine, was devoid of optical activity. The loss of optical activity and, hence, of asymmetry at the α-carbon atom during the Clemmensen reduction–rearrangement of this α-aminoketone is consistent with the concept of initial cleavage of the Cα–N bond.

A series of experiments has been devised to test the hypothesis that scission of the Cα–N bond[3,4,5] is the initial step in Clemmensen reductions of cyclic α-aminoketones leading to ring opening and/or rearrangement. Thus, a study of the effect of ring size on the rearrangement of monocyclic α-aminoketones[1] supports this hypothesis. Likewise, a study of the electrolytic reduction of α-aminoketones[6] has indicated clearly that the nature of the products obtained required initial Cα–N cleavage of the α-aminoketone, followed by such further reduction of the resulting intermediate as will occur at the particular cathode employed. The present investigation was undertaken to determine the fate of asymmetry at the α-carbon atom of an α-aminoketone undergoing Clemmensen reduction, since loss of optical activity during the process would be consistent with initial cleavage of the Cα–N bond.

It was necessary to select an α-aminoketone which would not be racemized by hydrochloric acid alone. It was also necessary to ascertain the course of the Clemmensen reduction of the corresponding racemic α-aminoketone before proceeding with the optically active form. The compound 1,2-dimethyl-2-ethyl-3-piperidone (I) satisfied these conditions, since it has no enolizable hydrogen on the 2-carbon and since the racemic form of 1,2-dimethyl-2-ethyl-3-piperidone has been shown to give 1-methyl-2-*s*-butylpyrrolidine (III) on Clemmensen reduction.[7]



I II III

The synthesis of *rac*-1,2-dimethyl-2-ethyl-3-piperidone (I)[7] was improved, and resolution of the aminoketone was accomplished through the use of dibenzoyl-D-tartaric acid. The less soluble form (in 80% ethanol) of the optically active salt of I was recrystallized to nearly constant, maximum rotation and melting point, and was then decomposed to give the free base. It was not established that the (+)-1,2-dimethyl-2-ethyl-3-piperidone thus obtained was the optically pure dextrorotatory enantiomorph, but the liquid exhibited sufficient optical activity ($\alpha = 0.79°$ in a 1-dm. tube) to validate conclusions based upon observed loss or retention of activity during its reduction. The identity of the resolved aminoketone I was checked by elemental analysis and by the infrared absorption maximum at 1712 cm.$^{-1}$, indicative of the presence of the ketone carbonyl. The Clemmensen reduction of (+)-1,2-dimethyl-2-ethyl-3-piperidone yielded 1-methyl-2-*s*-butylpyrrolidine (III), as indicated by microanalysis and by the absence of infrared absorption in the 3 and 6 μ regions. The product was devoid of measurable optical activity, and it was converted in quantitative yield to a picrate which was identical with that of the inactive 1-methyl-2-*s*-butylpyrrolidine obtained from Clemmensen reduction of *rac*-1,2-dimethyl-2-ethyl-3-piperidone.[7] The complete loss of optical activity during the process is consistent with the occurrence of Cα–N bond scission in I to yield as an intermediate the 2°-aminoketone II (or protonated), since such a *s*-butyl ketone, even if asymmetric as initially formed,[8] would be racemized extremely rapidly in the refluxing hydrochloric acid.[9]

Experimental[10]

(±)-1,2-Dimethyl-2-ethyl-3-piperidone.—The general method previously used[7] was followed, with improvements. The yield of **α-methylamino-α-methylbutyronitrile** amounted to 88%, and hydrolysis of this nitrile essentially according to the procedure which Cook and Cox[11] used for hydrolysis of the isomeric α-methylaminovaleronitrile, followed by esterification, afforded **ethyl α-methylamino-α-methylbutyrate** in 52% yield. Condensation of this aminoester with ethyl γ-iodobutyrate in the presence of anhydrous potassium carbonate gave **α-carbethoxy-α-methylpropyl-γ'-carbethoxypropylmethylamine** directly in 82% yield (based on unre-

(1) For article VIII in this series, see N. J. Leonard and R. C. Sentz, THIS JOURNAL, **74**, 1704 (1952).

(2) This work was supported in part by a grant from E. I. du Pont de Nemours and Company, Inc.

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(5) J. H. Brewster, Abstracts of Papers, 12th International Congress of Pure and Applied Chemistry, New York, N. Y., September, 1951, p. 466.

(6) N. J. Leonard, S. Swann, Jr., and H. L. Dryden, Jr., THIS JOURNAL, **74**, 2871 (1952); see also N. J. Leonard, S. Swann, Jr., and J. Figueras, Jr., *ibid.*, **74**, 4620 (1952).

(7) N. J. Leonard and E. Barthel, Jr., *ibid.*, **72**, 3632 (1950).

(8) The hypothesis of Brewster[5] would suggest a sequence proceeding through the enol form of the ketone.

(9) P. D. Bartlett and C. H. Stauffer, THIS JOURNAL, **57**, 2580 (1935), have reported rates for the racemization of various active *s*-butyl ketones in acid solution; see also H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, 2430 (1951).

(10) **Melting points are corrected. The authors are indebted to Mrs. Katherine Pih for microanalyses and to Miss Elizabeth M. Petersen and Miss Helen Miklas for determination of the infrared spectra.**

(11) A. H. Cook and S. F. Cox, *J. Chem. Soc.*, 2334 (1949).

covered starting material). Dieckmann cyclization with sodium ethoxide in toluene, followed by hydrolysis and decarboxylation, gave (±)-1,2-dimethyl-2-ethyl-3-piperidone in 55% yield, b.p. 94–95° (17 mm.), $n^{20}D$ 1.4660. The **hydrochloride**, m.p. 151.5–152°, had an infrared absorption maximum at 1716 cm.$^{-1}$. Two other derivatives had melting points slightly higher than previously reported[7]: **picrate**, m.p. 211.5–212.5° (infrared maximum at 1736 cm.$^{-1}$); **picrolonate**, m.p. 203.5–204°.

Mono-(+)-1,2-dimethyl-2-ethyl-3-piperidone Dibenzoyl-D-tartrate.—A solution of 56.5 g. (0.15 mole) of dibenzoyl-D-tartaric acid monohydrate in 400 ml. of ether was mixed with 27.8 g. (0.15 mole) of (±)-1,2-dimethyl-2-ethyl-3-piperidone dissolved in 100 ml. of ether. The colorless solid which formed was collected by filtration, washed with ether, and recrystallized five times from 80% ethanol. There was obtained 25.1 g. of colorless prisms, m.p. 150° with decomposition; $[\alpha]^{23}D$ −144.5° (*c* 2, methanol).

Anal. Calcd. for $C_{27}H_{31}NO_9$: C, 63.15; H, 6.08; N, 2.67. Found: C, 63.12; H, 6.11; N, 2.63.

(+)-1,2-Dimethyl-2-ethyl-3-piperidone.—A slurry of 25.0 g. of mono-(+)-1,2-dimethyl-2-ethyl-3-piperidone dibenzoyl-D-tartrate and 150 ml. of 3 *N* hydrochloric acid was shaken for 30 minutes. The oil which separated solidified on addition of a few crystals of dibenzoyl-D-tartaric acid monohydrate. The solid was removed by filtration, and the filtrate was cooled and made basic with cold 40% potassium hydroxide solution. The alkaline solution was extracted with ether and the ether extracts were dried. The ether was evaporated and the residual oil was distilled under reduced pressure, yielding 4.8 g. of (+)-1,2-dimethyl-2-ethyl-3-piperidone, b.p. 95–96° (18 mm.), $n^{20}D$ 1.4658; $\alpha^{24}D$ 0.79 ± 0.01° (*l* = 1 dm.).

Anal. Calcd. for $C_9H_{17}NO$: C, 71.01; H, 9.27; N, 9.20. Found: C, 71.09; H, 9.20; N, 9.26.

The infrared absorption spectrum showed a strong band at 1712 cm.$^{-1}$.

Clemmensen Reduction of (+)-1,2-Dimethyl-2-ethyl-3-piperidone.—A solution of 4.6 g. (0.03 mole) of (+)-1,2-dimethyl-2-ethyl-3-piperidone in 40 ml. of concentrated hydrochloric acid was added to 40 g. of zinc amalgam, and the mixture was caused to reflux gently. At two-hour intervals, 15-ml. portions of concentrated hydrochloric acid were added, and after four hours, an additional 20 g. of zinc amalgam was added. Heating was stopped after twelve hours and the solution was concentrated *in vacuo*. The cooled residue was made strongly basic by the addition of 40% potassium hydroxide, and the alkaline mixture was subjected to steam distillation. The distillate was acidified and evaporated to dryness under reduced pressure. The residue was made alkaline by addition of a 40% potassium hydroxide solution, and the basic solution was extracted with ether. The ether extracts were dried, the ether removed, and the residual oil was distilled. There was obtained 2.0 g. (41%) of a colorless oil, b.p. 159–163° (749 mm.), $n^{24}D$ 1.4469; $\alpha^{24}D$ 0.00 ± 0.01° (*l* = 1 dm.).

Anal. Calcd. for $C_9H_{19}N$: C, 76.49; H, 13.56; N, 9.92. Found: C, 76.39; H, 13.39; N, 9.82.

The infrared absorption spectrum confirmed the absence of hydroxyl and carbonyl functions.

Picrate.—One gram of the base gave a quantitative yield of the picrate, m.p. 125–126°. The picrate, when mixed with an authentic sample of the picrate of 1-methyl-2-*s*-butylpyrrolidine, gave an undepressed melting point.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

The Terminal Amino Groups of α- and β-Caseins[2]

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Dinitrofluorobenzene was used to label the amino groups of the α- and β-fractions of casein. The hydrolyzates of these protein derivatives were assayed for the various dinitrophenylamino acids which were shown to be present by chromatographic methods. The arginine derivative and both mono- and diderivatives of lysine were found in each protein. However, the proportions were different in each protein.

The separation of casein by isoelectric precipitation into two distinct fractions, each completely free from the other, was accomplished by Warner.[3] The same fractions were also obtained by Hipp, *et al.*,[4] by precipitation from aqueous alcohol and aqueous urea. The reproducibility of the separation and of the analytical data of the fractions obtained from various preparations indicated that these materials might be sufficiently homogeneous for use in a study of the end groups of casein.

The dinitrofluorobenzene reagent of Sanger[5] was used. However, satisfactory separations of the dinitrophenylamino acids were not obtained by his chromatographic method and a system of paper chromatograms was used for the separation of the ether-extractable dinitrophenylamino acids. Different solvent pairs than those employed by Sanger were necessary to obtain separations on paper. Although silica gel columns were used for the separation of the non-ether-extractable dinitrophenylamino acids, a variation of the procedure of Bailey[6] which uses formaldehyde-treated silica gel gave a much better separation of the ε-lysine and arginine derivatives than the procedure described by Sanger.

Partial decomposition of some of the dinitrophenylamino acids during the hydrolysis of the protein derivatives makes it necessary to run parallel recovery experiments preferably on a synthetic mixture as closely duplicating the actual situation as possible. The correction factors in some instances are quite large and in a few cases (proline, methionine and cystine) practically complete destruction occurs. Small amounts of dinitroaniline and dinitrophenol were obtained in the experiments reported here but an extraction procedure developed recently by Isherwood and Cruickshank satisfactorily removes these materials from the extract.

Experimental

Preparation of Materials.—The 2,4-dinitrophenyl derivatives of the amino acids for use as control substances

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Dept. of Agriculture. Article not copyrighted.

(2) Presented at the 122d Meeting of the American Chemical Society, Atlantic City, N. J., September, 1952.

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