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

The Kishner Reduction–Elimination. I. Cyclic and Open Chain α-Aminoketones[1,2]

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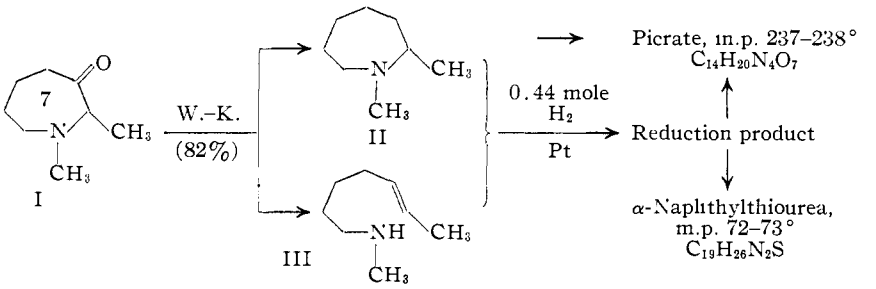
The extent to which α-amino group elimination with olefin formation occurs during the Wolff–Kishner reduction of cyclic α-aminoketones has been shown to be dependent upon ring size (8- > 7->>>>6-membered ring). The generality of occurrence of the reduction–elimination reaction—first observed by Kishner for an aliphatic α-hydroxyketone—has been demonstrated by a study of the reduction of a series of open chain α-aminoketones.

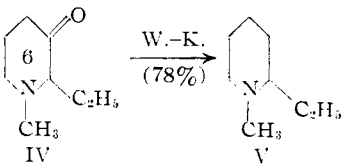
At the time of his discovery, contemporaneously with Wolff, of a method for the reduction of a carbonyl to a methylene group, Kishner[4] also noted one example of attendant elimination: the conversion of an α-hydroxyketone (2,6-dimethyl-2-hydroxy-3-octanone) to an olefin (2,6-dimethyl-2-octene). We have recently provided an instance of the elimination of an amino group upon reduction of an α-aminoketone[5] under the Huang-Minlon conditions,[6] and have predicted generality for olefin formation from ketones having a variety of α-substituents.[7]

The finding that the reduction of the eight-membered ring α-aminoketone, 1,2-dimethyl-1-azacycloöctan-3-one, yields less than 1% of the "normal" reduction product, 1,2-dimethyl-1-azacycloöctane, and at least 65% of a mixture of isomeric N-methyloctenylamines[5] encouraged a study, in the first place, of the effect of ring size on the extent of the reduction–elimination reaction. In particular, it seemed desirable to determine the degree to which the analogous seven- and six-membered ring α-aminoketones undergo ring opening during attempted Wolff–Kishner reduction. The relative yields reported for the Wolff–Kishner reduction of 1-methyl-2-ethyl-1-azacycloheptan-3-one to 1-methyl-2-ethyl-1-azacycloheptane (42%)[8] and of 1,2,2-trimethyl-3-piperidone to 1,2,2-trimethylpiperidine (74%)[9] were suggestive of the results which might be expected in experiments where the simultaneous formation of anomalous products was anticipated.



The reduction of 1,2-dimethyl-1-azacycloheptan-3-one (I)[8] and of the other α-substituted ketones described herein was carried out according to the following sequence: a mixture of the aminoketone, excess hydrazine, potassium hydroxide and triethylene glycol[6] was heated until hydrazone formation was complete; further heat was applied until a temperature favorable for the decomposition of the hydrazone was reached; the reaction mixture was distilled; the products were isolated from the distillate and also from the still residue by extraction. Evidence for the "normal" reduction product (II) of I was obtained by the isolation, directly from the crude distillate, of a high melting picrate[10] which had the correct analysis for 1,2-dimethyl-1-azacycloheptane picrate. Although the distillate furnished no low melting isomeric picrate, the presence of a secondary amine was indicated by a positive Duke test[11] and by the infrared absorption maximum at 3280 cm.$^{-1}$. The presence of unsaturation was indicated by the absorption peaks at 1655 and 966 cm.$^{-1}$. A quantitative catalytic hydrogenation of the distillate mixture provided an estimate that approximately 44% of the total Wolff–Kishner product consisted of unsaturated isomers, of which III is representative. 1,2-Dimethyl-1-azacycloheptane (II) picrate was isolated from the catalytic hydrogenation mixture, and the presence of N-methylheptylamine was shown by the formation of its α-naphthylthiourea derivative, thus revealing the N-methylheptenylamines to be precursors for this final reduction.

Although good yields of normal products had been obtained in the Wolff–Kishner reduction of a variety of five- and six-membered cyclic α-aminoketones, the reduction of 1-methyl-2-ethyl-3-piperidone (IV) was studied in order to determine whether the formation of olefinic products had previously been overlooked. We obtained, in 78% yield, a reduction product of constant boiling point and refractive index. A Duke test[11] for the secondary amine function was negative and no absorption



(1) N. J. Leonard, *Chimia*, **7**, 93 (1953); see also S. Gelfand, Ph.D. Thesis, University of Illinois, 1953.

(2) N. J. Leonard and S. Gelfand, Abstracts of Papers, 124th Meeting, American Chemical Society, Chicago, Illinois, September 6–11, 1953, p. 15-O.

(3) U. S. Rubber Company Fellow, 1952–1953.

(4) N. Kishner, *J. Russ. Phys. Chem. Soc.*, **45**, 973 (1913).

(5) N. J. Leonard and R. C. Sentz, THIS JOURNAL, **74**, 1704 (1952).

(6) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(7) Ref. 5, footnote 32.

(8) N. J. Leonard and E. Barthel, Jr., THIS JOURNAL, **71**, 3098 (1949).

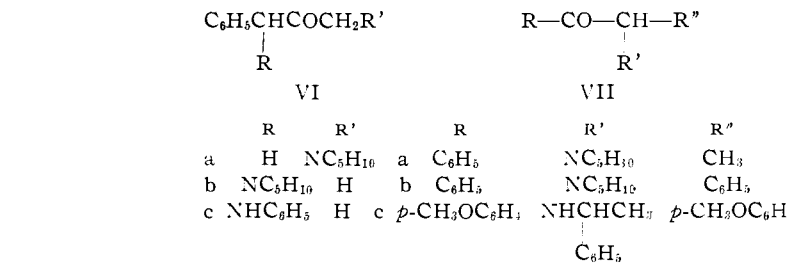
(9) N. J. Leonard and E. Barthel, Jr., *ibid.*, **72**, 3632 (1950).

(10) Ref. 5, footnote 29.

(11) F. R. Duke, *Ind. Eng. Chem., Anal. Ed.*, **17**, 196 (1945).

could be detected in the 3 or 6 μ region of the infrared. The picrate, which was formed in nearly quantitative yield, was identified as that of 1-methyl-2-ethylpiperidine (V). It is therefore apparent that a reduction–elimination reaction of the type first observed by Kishner does not occur with the cyclic α-aminoketone of six members, occurs to the extent of nearly 50% with that of seven, and predominates with that of eight members. On this basis, it is to be expected that in similar reductions of cyclic α-aminoketones of larger ring size, ring opening would also predominate.

Our findings on the cyclic α-aminoketones prompted an examination of the behavior of open chain α-aminoketones, since it was obvious that olefin formation should be a competing reaction, hitherto unnoticed, with the normal CO to CH_2 conversion.[12] A random selection was made of α-aminoketones (VI, VII) which had varying degrees and types of substitution in order to show the expected generality[7] of occurrence of the Kishner re-



duction–elimination. The relative yields of olefinic and normal reduction products are given in Table I. A known olefin was produced in each case. The identity of the normal reduction product was provided by elemental analysis of the amine or suitable derivatives. The possibility of rearrangement during the formation or reduction of the three isomeric α-piperidinoketones (VIa, b, VIIa) was eliminated by direct comparison of the picrates of the normal reduction products. The Wolff–Kishner reduction product of α-phenyl-α-N-piperidylacetophenone (VIIb) was accompanied by a considerable amount of N-benzylpiperidine, as a result of the known basic cleavage of α-substituted phenyl ketones[13–15]; by contrast, no product corresponding to this course of reaction was observed in the reduction of α-N-piperidylpropiophenone (VIIa). The neutral product which was isolated in the reduction of VIIc and identified as p,p'-dimethoxybibenzyl rather than p,p'-dimethoxystilbene probably results from a deamination reaction similar to that observed by Letsinger and Collat[12] with the *o*- and *p*-hydroxydimethylaminoacetophenones.

The Wolff–Kishner reduction of two representative open chain α-alkoxyketones, benzoin ethyl ether and 1-amyloxy-3-phenyl-2-propanone (n-$C_5H_{11}OCH_2COCH_2C_6H_5$), was also included in this investigation. Both were found to yield olefins as the major products (Table I), in accord with two other examples of α-alkoxyketone reduction.[16,17]

(12) *E.g.*, R. L. Letsinger and R. Collat, THIS JOURNAL, **74**, 621 (1952).

(13) P. Rabe, W. Schuler, G. Suszka and E. Federer, *Ber.*, **81**, 139 (1948).

(14) P. Rabe and W. Schneider, *Ann.*, **365**, 377 (1909).

(15) D. B. Sharp and B. L. Miller, THIS JOURNAL, **74**, 5643 (1952).

Experimental[18]

Wolff–Kishner Reduction of 1-Methyl-2-ethyl-3-piperidone (IV).—A mixture of 10.0 g. (0.078 mole) of freshly distilled 1-methyl-2-ethyl-3-piperidone,[19] 15.9 g. (0.283 mole) of potassium hydroxide, 12 ml. of 85% hydrazine hydrate and 30 ml. of triethylene glycol was heated at 110–120° for two hours. The condenser was then set for downward distillation and the temperature inside the reaction flask was increased to 200°, where it was maintained until distillation ceased. The distillate and the water-diluted reaction mixture were each extracted with four 25-ml. portions of ether, saturated with potassium carbonate, and extracted again. The combined extracts were dried, the ether was removed, and the residue was distilled through a Holzman column,[20] b.p. 152–154° (745 mm.), $n^{19.5}D$ 1.4482; yield 7.1 g. (78%). A Duke test[11] for a secondary amine function was negative, and no absorption band indicative of C=C or NH could be detected in the infrared spectrum of the liquid sample.

The **picrate** was obtained from an absolute ethanol solution in nearly quantitative yield, m.p. 174.5–175°[21,22] after one recrystallization from 95% ethanol. Mixtures with authentic **1-methyl-2-ethylpiperidine picrate**[23] were not depressed. No trace of low melting picrate could be detected.

Wolff–Kishner Reduction of 1,2-Dimethyl-1-azacycloheptan-3-one (I).—Reduction of 1,2-dimethyl-1-azacycloheptan-3-one,[9] b.p. 72–73° (11 mm.), $n^{20}D$ 1.4700, under the same conditions gave a product (83% yield) which was collected in four fractions ($n^{20}D$ 1.4419–1.4470). All fractions gave a positive Duke test[11] for the secondary amine function and exhibited infrared absorption bands at 3280, characteristic of NH, at 1655 (C=C), and at 966 cm.$^{-1}$ (*trans* —CH=CH—).

The **picrate of the "normal" product, 1,2-dimethyl-1-azacycloheptane**, separated readily from ether, m.p. 237–238° after one recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{20}N_4O_7$: C, 47.19; H, 5.66. Found: C, 47.09; H, 5.66.

The attempted isolation of a low melting, more soluble picrate corresponding to the "abnormal" reduction product was unsuccessful.

The total reduction product (above) was redistilled without fractionation and a sample of distilled material was subjected to quantitative hydrogenation over platinum in absolute ethanol. The product (1.4748 g., 11.68 mmoles) took up 115.8 ml. (5.17 mmoles) of hydrogen (S.T.P.), indicating the presence of 44% unsaturated isomer (one double bond). The catalyst and solvent were removed and the residue was distilled over the range 135–150°; $n^{20}D$ 1.4381. 80% recovery. The picrate which separated from an ether solution was identical with that obtained from the amine mixture prior to reduction. The **α-naphthylthiourea**[24] prepared directly from the reduction mixture and recrystallized four times from aqueous ethanol, m.p. 72–73°, had the correct analysis for the derivative of N-methylheptylamine.[25]

Anal. Calcd. for $C_{19}H_{26}N_2S$: C, 72.56; H, 8.34. Found: C, 72.13; H, 8.38.

Aminoketones. 1-Phenyl-3-N-piperidyl-2-propanone (VIa) had b.p. 126–128° (0.8 mm.), $n^{25}D$ 1.5210, hydrochloride, m.p. 182–183°.[26]

(16) D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 2752 (1951).

(17) T. D. Perrine and L. F. Small, *J. Org. Chem.*, **17**, 1540 (1952).

(18) Melting points are corrected and boiling points are uncorrected. We are indebted to Miss Helen Miklas for determination of the infrared spectra and to Mrs. Katherine Pih, Mrs. Esther Fett, Mrs. Lucy Chang and Mr. Joseph Nemeth for the microanalyses.

(19) N. J. Leonard and W. V. Ruyle, THIS JOURNAL, **71**, 3094 (1948).

(20) G. W. Gould, Jr., G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

(21) A. Lipp, *Ber.*, **33**, 3513 (1900).

(22) M. Heidrich, *ibid.*, **34**, 1889 (1901).

(23) E. Barthel, Jr., Ph.D. Thesis, University of Illinois, 1949.

(24) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," third edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 179.

(25) N. J. Leonard, S. Swann, Jr., and Hugh L. Dryden, Jr., THIS JOURNAL, **74**, 2871 (1952).

(26) We are indebted to Eli Lilly and Company for a sample of this compound.

TABLE I

WOLFF–KISHNER REDUCTION PRODUCTS

From	Normal product	%	%	Olefin
1-Phenyl-3-N-piperidyl-2-propanone (VIa)	N-(γ-Phenylpropyl)-piperidine[a]	75	14[b]	Propenylbenzene[c]
1-Phenyl-1-N-piperidyl-2-propanone (VIb)	N-(α-Phenylpropyl)-piperidine[d]	74	19[b]	Propenylbenzene[c]
1-Anilino-1-phenyl-2-propanone (VIc)	N-(α-Phenylpropyl)-aniline[e]	70	6	Propenylbenzene
α-N-Piperidylpropiophenone (VIIa)	N-(α-Methyl-β-phenylethyl)-piperidine[f]	40	37	Propenylbenzene[c]
α-Phenyl-α-N-piperidylacetophenone (VIIb)	N-(1,2-Diphenylethyl)-piperidine[g]	5[h]	34	Stilbene[i]
4-Methoxy-α-4′-methoxyphenyl-α-(α′-phenylethylamino)-acetophenone (VIIc)	.....	..	34[j]	p,p′-Dimethoxybibenzyl[j]
Benzoin ethyl ether[45]	.....[k]	..	44	Stilbene[i]
1-Amyloxy-3-phenyl-2-propanone	n-Amyl γ-phenylpropyl ether[l]	18	70	Allylbenzene[m] and propenylbenzene[c]

[a] B.p. 151–154° (19–21 mm.) (reported[35] 149° (15 mm.)); $n^{22}D$ 1.5172; hydrochloride, m.p. 182–185° (184–185°)[35]; methiodide, m.p. 133–135° (134–135°)[35]; picrate, m.p. 102°. *Anal.* Calcd. for $C_{20}H_{24}N_4O_7$: C, 55.55; H, 5.59; N, 12.96. Found: C, 55.60; H, 5.49; N, 12.99. [b] Equivalent yield of piperidine, phenylthiourea derivative, m.p. 99.5–100° (101°).[36] [c] Converted to the dibromide, m.p. 65–66.5° (65–66°).[37] [d] B.p. 128–129° (11 mm.); $n^{20}D$ 1.5227; picrate, m.p. 140–141°. *Anal.* Calcd. for $C_{20}H_{24}N_4O_7$: C, 55.55; H, 5.59; N, 12.96. Found: C, 55.69; H, 5.85; N, 12.92. [e] B.p. 117–118° (0.5 mm.) (172° (9 mm.)),[38] $n^{20}D$ 1.5907; hydrochloride, m.p. 177–179°. *Anal.* Calcd. for $C_{15}H_{18}ClN$: C, 72.71; H, 7.32. Found: C, 72.89; H, 7.35. [f] B.p. 153–155° (22 mm.) (143–145° (14 mm.))[39]; picrate, m.p. 134–135°. *Anal.* Calcd. for $C_{20}H_{24}N_4O_7$: C, 55.55; H, 5.59; H, 12.96. Found: C, 55.77; H, 5.51; N, 12.95. [g] Identified as the picrate, m.p. 166–168°.[40] *Anal.* Calcd. for $C_{25}H_{26}N_4O_7$: C, 60.72; H, 5.30; N, 11.33. Found: C, 60.43; H, 5.53; N, 11.44. [h] Plus N-benzylpiperidine (25% yield), b.p. 63.0–64.5° (0.3–0.4 mm.)[41–43]; picrate, m.p. 179–181°. *Anal.* Calcd. for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99. Found: C, 53.46; H, 5.12. [i] Identified by m.p. 123–124°, and mixed m.p. with an authentic sample. [j] Neutral product was the bibenzyl rather than the stilbene, m.p. 127–127.5°, identical in infrared spectrum and m.p. with an authentic sample.[44] [k] The residue obtained after separation of stilbene had no C–O or CH_3 infrared absorption. [l] B.p. 153–154° (30 mm.). *Anal.* Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 82.01; H, 10.43. [m] Dibromide, b.p. 77° (0.1 mm.).[46]

1-Phenyl-1-N-piperidyl-2-propanone (VIb) was obtained from 1-bromo-1-phenylacetone[27,28] and piperidine in 80% yield following the general method,[13] b.p. 99° (0.5 mm.); d^{20}_4 1.017, $n^{20}D$ 1.5293.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45; MR_D, 65.0. Found: C, 77.37; H, 8.65; N, 6.66; MR_D, 65.8.

1-Anilino-1-phenyl-2-propanone (VIc), m.p. 89.5–90.5°, was prepared by the method of Verkade and Janetzky.[28]

α-N-Piperidylpropiophenone (VIIa), b.p. 94–96° (0.3 mm.); $n^{22.5}D$ 1.5373; picrate, m.p. 177–178° (reported[13] 172–173°), was prepared by the method of Rabe, Schuler, Suszka and Federer.[13] The **hydrazone** was made by heating the α-N-piperidylpropiophenone at the reflux for 4 hours in a mixture of hydrazine and sufficient ethanol to form a homogeneous solution, b.p. 127–128° (0.5 mm.).

Anal. Calcd. for $C_{14}H_{21}N_3$: C, 72.68; H, 9.15; N, 18.17. Found: C, 72.52; H, 9.04; N, 18.26.

α-Phenyl-α-N-piperidylacetophenone (VIIb), m.p. 82–83°, was obtained in nearly quantitative yield.[29,30] **4-Methoxy-α-4′-methoxyphenyl-α-(α′-phenylethylamino)-acetophenone (VIIc)** was available as the hydrochloride.[26]

1-Amyloxy-3-phenyl-2-propanone.—The Grignard reagent, prepared from 12.15 g. (0.5 gram atom) of magnesium and 56 ml. of freshly distilled benzyl chloride,[31] was cooled in an ice–salt bath, and a solution of 63.5 g. (0.5 mole) of n-amyloxyacetonitrile[32–34] in 50 ml. of dry ether was added dropwise. The reaction mixture was stirred for an additional hour and then allowed to stand at room temperature for 12 hours before it was poured on a mixture of ice and hydrochloric acid. The ethereal layer was separated, washed with water, dried and the ether was removed. The product was distilled through a Holzman column, b.p. 102° (0.15 mm.), $n^{24.5}D$ 1.4926, yield 58 g. (53%).

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.23; H, 9.16.

The infrared spectrum of the pure liquid showed bands at 1727 (C=O), 1150 (C–O–C) and 698 cm.$^{-1}$ (mono-substituted phenyl).

Wolff–Kishner Reductions.—The reduction of each of the α-substituted ketones described above was carried out in the manner reported for 1-methyl-2-ethyl-3-piperidone. Following ether extraction of the distillate and the residual reaction mixture, neutral and basic constituents were separated, isolated by distillation or crystallization, and identified. The results are assembled in Table I.

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(27) A. von Wacek, K. Kratzl and A. von Bézard, *Ber.*, **75**, 1348 (1942).

(28) P. E. Verkade and E. F. J. Janetzky, *Rec. trav. chim.*, **62**, 775 (1943).

(29) R. E. Lutz, J. A. Freek and R. S. Murphey, THIS JOURNAL, **70**, 2015 (1948).

(30) P. Rabe, *Ber.*, **45**, 2163 (1912).

(31) H. Gilman and W. E. Catlin, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 471.

(32) C. F. H. Allen and J. A. VanAllan, *J. Org. Chem.*, **14**, 754 (1949).

(33) S. Rovira, *Ann. Chim. Paris*, [11] **20**, 660 (1945).

(34) See also A. J. Hill and D. T. Keach, THIS JOURNAL, **48**, 257 (1926).

(35) C. Mannich, K. Handke and K. Roth, *Ber.*, **69**, 2112 (1936).

(36) Ref. 24, p. 234.

(37) G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949).

(38) C. M. Rosser and J. J. Ritter, THIS JOURNAL, **59**, 2179 (1937).

(39) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

(40) A. Christiaen, *Bull. soc. chim. Belg.*, **33**, 483 (1924).

(41) E. Ochiai and H. Kataoka, *J. Pharm. Soc. Japan*, **62**, 241 (1942).

(42) I. Scriabine, *Bull. soc. chim. France*, [5] **14**, 454 (1947).

(43) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

(44) E. Späth, *Monatsh.*, **34**, 1965 (1913).

(45) E. Bergmann and J. Hervey, *Ber.*, **62**, 893 (1929).

(46) M. Ageva, *J. Russ. Phys. Chem. Soc.*, **37**, 662 (1905).