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

Rearrangement of α-Aminoketones during Clemmensen Reduction. VIII. The Fate of an Eight-membered Ring[1,2]

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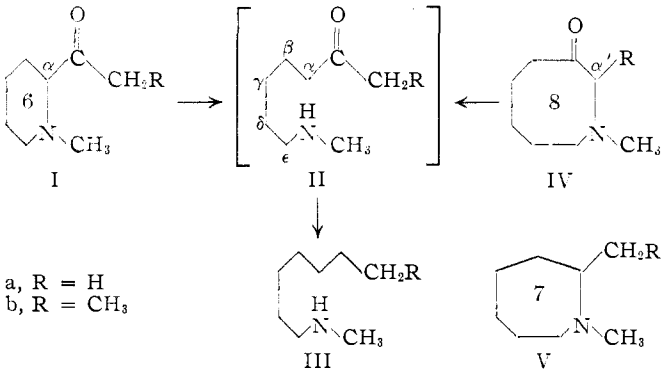
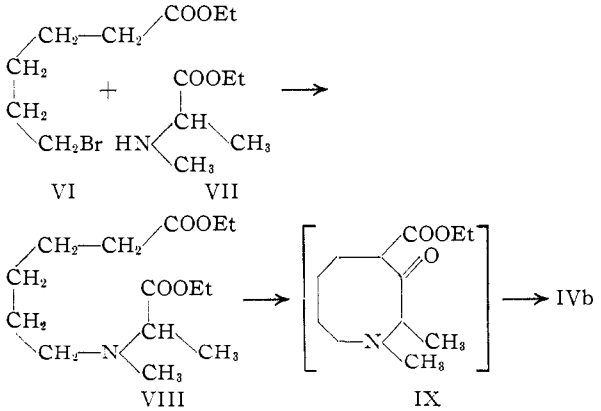
It has been shown that an eight-membered ring α-aminoketone in which the carbonyl and amino groups are homocyclic undergoes Cα–N cleavage under Clemmensen reduction conditions, and that an open-chain structure results. Specifically, the reduction of 1,2-dimethyl-1-azacycloöctan-3-one with zinc amalgam and hydrochloric acid yields N-methyloctylamine. For the synthesis of 1,2-dimethyl-1-azacycloöctan-3-one, the Dieckmann ring closure of α-carbethoxyethyl-ε-carbethoxypentylmethylamine was employed under conditions of high dilution, with potassium *t*-butoxide as the condensing agent. This appears to be the first successful application of the Dieckmann reaction to the closure of an eight-membered ring. The Wolff–Kishner reduction of 1,2-dimethyl-1-azacycloöctan-3-one proceeded anomalously to give N-methyloctenylamine. This finding has led to a new concept of the Wolff–Kishner reduction of certain α-substituted ketones.

Clemo, Raper and Vipond[3] have shown that 1-methyl-2-acetylpiperidine (Ia) gives N-methylheptylamine (IIIa) under Clemmensen reduction conditions, and have suggested as an intermediate the ε-aminoketone IIa (protonated) which would result from initial Cα–N cleavage. If Cα–N



cleavage is indeed the first step in the conversion, the same intermediate ε-aminoketone (IIa) would be expected from IVa and N-methylheptylamine (IIIa) would again be the final reduction product. By contrast, if the Clemmensen reduction–rearrangement observed with α-aminoketones proceeds by a more or less concerted process,[4] the proximity of the carbonyl-carbon and the amino-nitrogen in IV, fixed by the geometry of the eight-membered ring, should be conducive to rearrangement (to V) with ring contraction.[5] An eight-membered-ring α-aminoketone of type IV is thus an especially attractive model for this investigation, and 1,2-dimethyl-1-azacycloöctan-3-one (IVb) was selected for study because of earlier characterization of the possible rearrangement product, 1-methyl-2-ethyl-azacycloheptane (Vb).[5b] The synthesis of IVb in general outline followed the sequence of reactions employed by Leonard and Barthel[5b] for the preparation of the isomeric seven-membered-ring α-aminoketone, 1-methyl-2-ethyl-1-azacycloheptan-3-one. Condensation of ethyl ε-bromocaproate (VI)[6] with ethyl α-methylaminopropionate (VII) in the presence of anhydrous potassium carbonate yielded the aminodiester, α-carbethoxyethyl-ε-carbethoxypentylmethylamine (VIII), requisite for Dieckmann ring closure. Successful closure of the diester to IX was accomplished by employing potassium *t*-butoxide under high dilution conditions. Upon hydrolysis of the crude β-ketoester in 6 *N* hydrochloric acid, followed by decarboxylation, 1,2-dimethyl-1-azacycloöctan-3-one (IVb) was obtained. The overall yield of the aminoketone IVb was a direct function of the length of time used for addition of the aminodiester VIII to the refluxing xylene solution, *e.g.*: 48 hours, 55% yield; 36 hours, 36%; 24 hours, 17%. Attempts to obtain the eight-membered ring under conditions used for the preparation of seven-membered-ring aminoketones[5b,7] were unsuccessful. Attempted cyclizations using sodium ethoxide or sodium hydride[8,9] failed even under conditions of high dilution.[10]



The Clemmensen reduction of 1,2-dimethyl-1-azabicycloöctan-3-one (IVb) gave the open-chain amine, N-methyloctylamine (IIIb), rather than any ring-contracted product (Vb). The identity of the secondary amine was established by direct comparison with an authentic sample of IIIb prepared from methylamine and *n*-octyl bromide. The isolation of exclusively open-chain products

(1) Reported at the Twelfth National Organic Symposium of the American Chemical Society, Denver, Colorado, June 14, 1951.

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

(3) (a) G. R. Clemo, R. Raper and H. J. Vipond, *J. Chem. Soc.*, 2095 (1949); see also (b) E. Barthel, Jr., Ph.D. Thesis, University of Illinois, 1949.

(4) N. J. Leonard and W. C. Wildman, THIS JOURNAL, **71**, 3089 (1949).

(5) (a) N. J. Leonard and E. Barthel, Jr., *ibid.*, **72**, 3632 (1950); (b) N. J. Leonard and E. Barthel, Jr., *ibid.*, **71**, 3098 (1949).

(6) G. B. Brown and C. W. H. Partridge, *ibid.*, **66**, 839 (1944).

(7) E. A. Prill and S. M. McElvain, *ibid.*, **55**, 1233 (1933).

(8) S. M. McElvain and R. E. McMahon, *ibid.*, **71**, 901 (1949).

(9) S. M. McElvain and P. M. Laughton, *ibid.*, **73**, 448 (1951).

(10) R. C. Sentz, Ph.D. Thesis, University of Illinois, 1952.

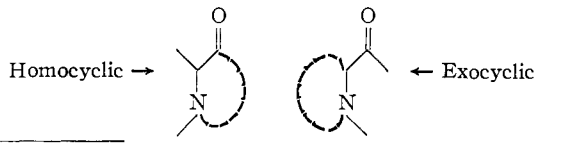
from the Clemmensen reduction of both I and IVb indicates that Cα–N cleavage[3a,11] is the primary step in both reductions. The complete absence of rearranged products (V) would then be attributable to the fact that carbonyl-group reduction of ε-aminoketones (II) takes precedence, in the strongly acid reaction medium, over cyclization accompanied by reduction of the ring-intermediate. Supporting evidence for this viewpoint is found in the work of Gabriel,[12,13] who demonstrated that ε-aminoketones of the type $H_2N(CH_2)_5COR$ (R = CH_3 or C_6H_5) are isolated from mineral acid solution in the open-chain form.[14] Moreover, the picrate derivative of a seven-membered ring generated by the cyclization of ε-aminopentyl methyl ketone under anhydrous conditions reverts back to the open-chain form in aqueous medium.

Thus, it is consistent with the accumulated experimental results to visualize the Clemmensen reduction of α-aminoketones with either homocyclic or exocyclic carbonyl groups (see Table I), whether producing an open-chain amine or effecting a change in ring size, as proceeding with initial Cα–N cleavage. In cases where the open-chain 2°-aminoketone intermediate readily forms a five- or six-membered ring in acid solution, reduction–rearrangement results; where subsequent ring closure is difficult, the reduced acyclic molecule is produced.

TABLE I

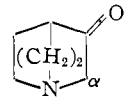
EFFECT OF RING SIZE ON REARRANGEMENT OF MONOCYCLIC α-AMINOKETONES

Ring size	Location of keto group	Product	
4	Exocyclic	?	
5	Homocyclic	?	19,20
5	Exocyclic	6-Membered ring	3a,21
6	Homocyclic	5-Membered ring	5a
6	Exocyclic	Open chain	3
7	Homocyclic	6-Membered ring	5b
7	Exocyclic	?	
8	Homocyclic	Open chain	22



Accordingly, a six-membered ring results from the Clemmensen reduction of a five-membered-ring α-aminoketone with carbonyl exocyclic and also from the reduction of a seven-membered-ring α-aminoketone with carbonyl homocyclic (see Table I). The two types have a common intermediate. A five-membered ring is obtained by reduction of a six-membered-ring α-aminoketone with carbonyl homocyclic, and it is a reasonable supposition that a five-membered ring would also result from the reduction of a 1-alkyl-2-acylazetidine. An open-chain amine results, as we have seen, from the Clemmensen reduction of both a six-membered-ring α-aminoketone with carbonyl exocyclic (I) and an eight-membered-ring α-aminoketone with carbonyl homocyclic (IV). It can be predicted that an open-chain amine would result from similar reduction of a seven (or larger)-membered-ring α-aminoketone with carbonyl exocyclic.[12,13,23,24]

An exception to cleavage of the Cα–N bond occurring during Clemmensen reduction of an α-aminoketone[25] is found in the behavior of 3-ketoquinuclidine (X), which is converted to quinuclidine.[26,27]



X

The fact that Cα–N cleavage does not occur in this instance can be accommodated with the other findings here recorded on the Clemmensen reduction of α-aminoketones if it is assumed that there is a competition between the two reactions, (a) CO→ CH_2 and (b) Cα–N cleavage, and that in this cage-type compound (X) the direct reduction of the carbonyl group takes precedence over cleavage.

The Wolff–Kishner reduction of α-aminoketones, in contrast with the Clemmensen reduction, has heretofore been a reliable method for bringing about the normal conversion of CO to CH_2, without cleavage and without rearrangement.[4,5] When the Wolff–Kishner method, as modified by Huang-Minlon,[28] was applied to 1,2-dimethyl-1-azacyclooctan-3-one (IVb), the main product of the reduction was not 1,2-dimethylazacycloöctane, $C_9H_{19}N$, but an isomeric secondary unsaturated amine. The compounds were partially separated by fractional distillation. The "normal" product, the eight-membered-ring tertiary amine, obtained in

(11) J. H. Brewster (Abstracts of Papers, 12th International Congress of Pure and Applied Chemistry, New York, N. Y., September, 1951, p. 466) considers the cleavage to result from an elimination-type reaction rather than from a hydrogenolysis.[3a]

(12) S. Gabriel, *Ber.*, **42**, 1249 (1909).

(13) S. Gabriel, *ibid.*, **42**, 1259 (1909).

(14) This is in marked contrast to Gabriel's observations on γ- and δ-aminoketones of the type $H_2N(CH_2)_3$ or $_4COR$ (R = CH_3 or C_6H_5).[15] When these aminoketones are generated by hydrolysis of the corresponding phthalimido derivatives, it is impossible to isolate the aminoketone as such or as a salt, because of facile ring closure to a Δ^2-pyrroline or Δ^2-piperidine.[15] Although the existence of an equilibrium between the cyclic and open-chain forms of γ- and δ-aminoketones in acid solution is surmised,[16] evaporation of acidic solutions yields only salts of the cyclic form, and tin reduction of the hydrochloric acid solutions results in the saturated ring compound.[13,17,18]

(15) For leading reference, see S. Gabriel, *Ber.*, **42**, 1238 (1909).

(16) A. Lipp and E. Widnmann, *Ann.*, **409**, 79 (1915).

(17) S. Gabriel and J. Colman, *Ber.*, **41**, 513 (1908).

(18) S. Gabriel, *ibid.*, **41**, 2010 (1908).

(19) N. J. Leonard, F. E. Fischer, E. Barthel, Jr., J. Figueras, Jr., and W. C. Wildman, THIS JOURNAL, **73**, 2371 (1951).

(20) G. R. Clemo and his co-workers have studied the Clemmensen reduction of certain bicyclic α-aminoketones of this type (see E. L. Martin in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 155.)

(21) G. R. Clemo and H. J. Vipond, *Chem. Ind.*, 856 (1949).

(22) Present work.

(23) S. Gabriel, *Ber.*, **42**, 4050 (1909).

(24) S. Gabriel, *ibid.*, **43**, 356 (1910).

(25) Two exceptions were noted in the first article in this series,[4] but one of these was essentially eliminated, *i.e.*, that of the supposed anomaly of 3-ketoquinolizidine, by examination of the stereoisomeric forms of the reduction product (N. J. Leonard and S. H. Pines, THIS JOURNAL, **72**, 4931 (1950)).

(26) G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 1989 (1937).

(27) Dr. S. H. Pines, in this Laboratory, has repeated and confirmed the work of Clemo and Metcalfe and has further determined the absence of both 4-ethylpiperidine (Cα–N cleavage) and 7-methyl-1-azabicyclo[2.2.1]heptane (Cα–N cleavage + rearrangement) in the reduction product.

(28) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

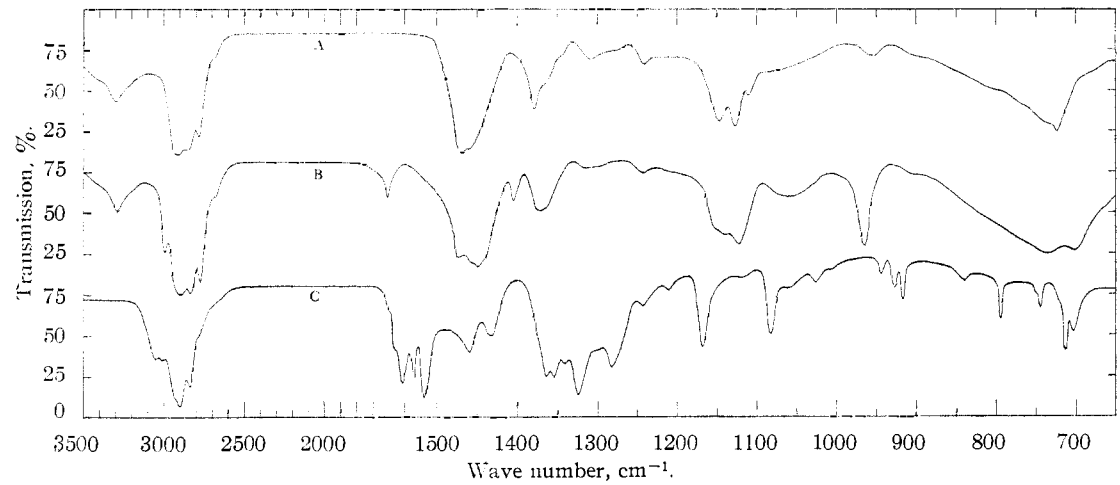
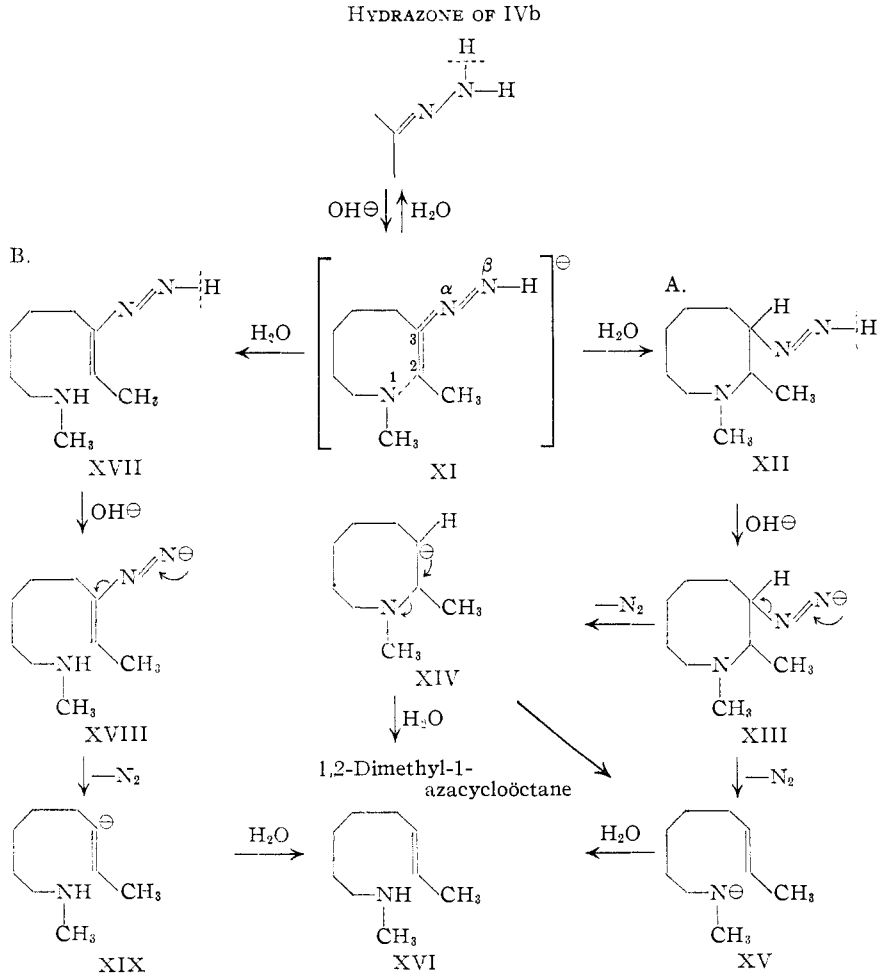


Fig. 1.—Infrared absorption spectra: A, N-methyloctylamine; B, N-methyloctenylamine; C, N-methyloctylamine picrate; (A, B as pure liquids, C in Nujol mull).

less than 1% yield, was isolated and characterized as the picrate, m.p. 197–197.5°.[29] The structure assigned to the major product was that of N-methyloctenylamine, $CH_3NHC_8H_{15}$, on the basis of elemental analysis and the positive infrared (Fig. 1, curve B) and qualitative chemical evidence for the secondary amine function and carbon–carbon unsaturation. Catalytic reduction of the N-methyloctenylamine gave N-methyloctylamine (IIIb), isolated as the picrate, m.p. 98–98.5°. Identity with the picrate of authentic N-methyloctylamine was proved by direct comparison of infrared spectra (Fig. 1, curve C) and melting points. The exact position of the double bond in the N-methyloctenylamine has not been established. The hot alkali used in the Wolff–Kishner reaction would be conducive to shifts in the position of the double bond originally generated. Indeed, the N-methyloctenylamine isolated from the reaction mixture appeared to be a mixture of possibly three double-bond isomers since three pairs of derivatives (picrates and *p'*-hydroxyazobenzene-*p*-sulfonates) were obtainable from the distilled base. The origin of the N-methyloctenylamine can be explained by a simple extension of mechanisms already proposed for the normal Wolff–Kishner reduction.[30] Limiting our consideration to possible ionic mechanisms, the isomeric azo



(29) It has been observed that the picrates of the ring compounds have high melting points compared with those of the picrates of the corresponding open-chain saturated secondary amines.[5]

(30) A. A. Balandin and D. N. Vaskevich, *Zhur. Obshchei Khim*, **6**, 1878 (1936); W. Seibert, *Chem. Ber.*, **80**, 494 (1947); D. Todd in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. IV, 1948, p. 378; E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 275.

form (XII) of the hydrazone of IVb could be attacked by alkali to form the anion XIII (route A). Following the conventional sequence,[30] XIII would lose nitrogen to form the carbanion XIV, which would be stabilized by the acquisition of a proton to form 1,2-dimethyl-1-azacycloöctane. Since the latter is obtained in less than 1% yield, in order to account for the major product (XVI) an alternative fate of the carbanion XIV must be considered: one involving ring opening (XIV → XV). The open-chain anion XV could also result directly from XIII by simultaneous loss of nitrogen and ring opening. Either route of conversion to XV is regarded as irreversible, and would necessarily result from strain in the eight-membered-ring anionic intermediate since homologous five- and six-membered rings are not readily sprung.[5a,19,20,31] Subsequent reaction of the open-chain anion XV with a protonic source (H_2O) would produce XVI (and isomers by subsequent rearrangement).

An alternative and somewhat more attractive hypothesis to account for the formation of N-methyloctenylamine as the major product of the Wolff–Kishner reduction of 1,2-dimethyl-1-azacycloöctan-3-one (IVb) is that designated as route B in the accompanying diagram. The anion formed by abstraction of a proton from IVb hydrazone can be regarded as resonance-stabilized (XI). Addition of a proton can occur at N_β, which would regenerate the hydrazone; at C_3, which would give XII and allow for the eventual formation of the "normal" reduction product, 1,2-dimethyl-1-azacycloöctane; or at N_1, with the springing of the eight-membered ring to form XVII. From the latter, by loss of a proton (XVIII) followed by nitrogen (XIX), could be formed the precursor of N-methyloctenylamine (XVI) (and isomers). Cleavage of the N_1–C_2 bond (as in XI) would generally be expected to occur with proton attack where the ring is readily opened (therefore not in five- and six-membered rings), or where the compound is acyclic.[32]

Experimental[33]

N-Methyloctylamine (IIIb).[34]—The key position of this compound in the investigation, together with the disagreement in physical properties recorded in the literature, necessitated the preparation and characterization of an authentic sample. A pressure bomb charged with 50 g. (0.26 mole) of *n*-octyl bromide (b.p. 88–90° (15 mm.); $n^{20}D$ 1.4526) and 143.9 g. of 34.9% ethanolic methylamine (1.42 moles), prepared by passing gaseous methylamine from a methylamine generator[35] into cold ethanol, was shaken for 16 hours at 180° and then 8 hours at 200°. The reactor was allowed to cool. The contents were transferred to a distillation flask, and the alcohol was removed *in vacuo*. The residue was treated with 100 ml. of 20% aqueous potassium hydroxide, and the organic and aqueous layers were separated. The aqueous layer was extracted with several portions of ether, and the combined extracts and organic layer were dried. Removal of the ether left a colorless basic oil, which gave a positive Duke test[36] for the secondary amine function and boiled at 77.5–80° (17 mm.); $n^{20}D$ 1.4294; yield 32.8 g. (88%). To ensure complete removal of unchanged *n*-octyl bromide, the amine was purified through its hydrochloride salt, hygroscopic colorless plates from acetone, m.p. 184.5–185.5°. The boiling point and refractive index of the purified base were unchanged; d^{20}_4 0.7824.

Anal. Calcd. for $C_9H_{21}N$: C, 75.45; H, 14.78; N, 9.77; MR_D, 47.36. Found: C, 75.43; H, 14.74; N, 9.72; MR_D, 47.24.

The infrared spectrum of the analytically pure material (Fig. 1, curve A) had a strong absorption band at 3294 cm.$^{-1}$ for the N–H function, and a band at 1378 cm.$^{-1}$ for the C–CH_3 function.

The picrate, formed in ether, crystallized from aqueous ethanol as yellow needles, m.p. 98–98.5°.

Anal. Calcd. for $C_{15}H_{24}N_4O_7$: C, 48.38; H, 6.50; N, 15.05. Found: C, 48.47; H, 6.44; N, 15.17.

Ethyl α-Methylaminopropionate (VII).—The hydrochloride of ethyl α-methylaminopropionate was prepared from α-bromopropionic acid (b.p. 91–92° (17 mm.); $n^{20}D$ 1.4754) and 35% aqueous methylamine (Rohm and Haas Company) using the procedure described by Leonard and Ruyle[37] for ethyl α-methylaminobutyrate. Treatment of the crude hydrochloride salt with ammonia dissolved in chloroform, according to the method of Hillmann[38] gave the free ester in an over-all yield of 52%; b.p. 49.5–50° (17 mm.); $n^{20}D$ 1.4145.[39]

Anal. Calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.21; H, 10.03; N, 10.63.

Ethyl ε-Bromocaproate (VI).—The three-step synthesis of Brown and Partridge,[6] involving peroxidation of cyclohexanone, conversion of the resulting crude lactone–ester mixture to ε-bromocaproic acid, and esterification, gave the desired bromoester in 40% over-all yield, b.p. 86.5–87.5° (2.4 mm.); $n^{20}D$ 1.4569. When working on a large scale, it was found helpful to modify the persulfate oxidation procedure derived from the original work of Robinson and Smith[40] by distilling half the ethanol from the reaction filtrate *in vacuo* before diluting with water. This permitted a 50% reduction in the dilution necessary to allow efficient extraction of the mixed lactone–ester product.

α - Carbethoxyethyl - ε - carbethoxypentylmethylamine (VIII).—Condensation of ethyl α-methylaminopropionate with ethyl ε-bromocaproate in the presence of potassium carbonate in the manner described for the preparation of carbethoxymethyl-γ-cyanopropylmethylamine[5a] gave the colorless liquid product in 71% yield; b.p. 110–111° (0.25 mm.); $n^{20}D$ 1.4438.

(31) The 42% Wolff–Kishner conversion of the seven-membered-ring analog, 1-methyl-2-ethyl-1-azacycloheptan-3-one, to 1-methyl-2-ethylazacycloheptane does[5b] not preclude the coformation of some open-chain unsaturated 2°-amine, and the reaction will be reinvestigated.

(32) The experiment suggests that groups such as NR_2, NHR, NH_2, OH, OR, OOCR, SR and the like, when attached to the α-carbon of an alicyclic or open-chain ketone, would be eliminated upon Wolff–Kishner reduction of such ketones. The postulate requires further experimental verification, but isolated examples of olefin formation in the Wolff–Kishner reduction of α-hydroxy- and α-acetoxyketones may be cited: 2,6-dimethyl-2-hydroxyoctan-3-one → 2,6-dimethyloctene-2 (N. Kishner, *J. Russ. Phys. Chem. Soc.*, **45**, 973 (1913)); 3(α),11-dihydroxy-12-ketocholanic acid → 3(α)-hydroxy-Δ⁹-cholenic acid, 3(α),12(β)-dihydroxy-11-ketocholanic acid → 3(α)-hydroxy-Δ¹¹-cholenic acid, 3(α),12(α)-dihydroxy-11-ketocholanic acid → 3(α)-hydroxy-Δ¹¹-cholenic acid, methyl 3(α),11(β)-diacetoxy-12-ketocholanate → 3(α)-hydroxy-Δ¹¹-cholenic acid, methyl 3(α),12(β)-diacetoxy-11-ketocholanate → 3(α)-hydroxy-Δ¹¹-cholenic acid (D. Todd, in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. IV, 1948). ADDED IN PROOF: D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 2752 (1951), have observed and similarly explained the formation of an olefin from an α-methoxyketone.

(33) All melting points are corrected. The authors are indebted to Miss Emily Davis, Mrs. Jean Fortney and Mrs. Katherine Pih for microanalyses and to Miss Elizabeth M. Petersen for determination of the infrared spectra.

(34) (a) E. T. Barrows, B. M. C. Hargreaves, J. E. Page, J. C. L. Resuggan and F. A. Robinson, *J. Chem. Soc.*, 197 (1947); (b) O. Westphal and D. Jerchel, *Ber.*, **73B**, 1002 (1940); (c) F. F. Blicke and F. B. Zienty THIS JOURNAL, **61**, 772 (1939).

(35) R. Mozingo and J. H. McCracken, *Org. Syntheses*, **20**, 35 (1940).

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

(37) N. J. Leonard and W. V. Ruyle, THIS JOURNAL, **71**, 3094 (1949).

(38) G. Hillmann, *Z. Naturforsch.*, **1**, 682 (1946).

(39) The physical constants here reported are more compatible with those observed by E. Barthel, Jr., (Ph.D. Thesis, University of Illinois, 1949) than with those reported by N. D. Zelinskii, A. Annenkov and I. Kulikov (*Z. physiol. Chem.*, **73**, 459 (1911)), and repeated in reference 5a (p. 3635).

(40) R. Robinson and L. H. Smith, *J. Chem Soc.*, 371 (1937).

Anal. Calcd. for $C_{14}H_{37}NO_4$: C, 61.51; H, 9.96; N, 5.12. Found: C, 61.44; H, 9.78; N, 5.18.

Dieckmann Ring Closure of α-Carbethoxyethyl-ε-carbethoxypentylmethylamine.—A diagram of the apparatus used is given in Fig. 2. Attached at A was a three-necked flask (24/40 standard taper joints) containing a stirrer with a vapor-tight seal and an inlet tube for introduction of nitrogen gas below the surface of the reaction mixture. B represents the dilution apparatus.[41,42] A ball joint (C) was included to facilitate the use of the dilution apparatus with flasks bearing necks at different angles. At D was attached a drip-tip condenser, with thermometer, calcium chloride tube and stopcock to allow distillation or reflux. At E a Hershberg dropping funnel[43] was connected. The flask and dilution apparatus were wrapped with asbestos rope. The entire ring-closure process was carried out under an atmosphere of purified nitrogen.

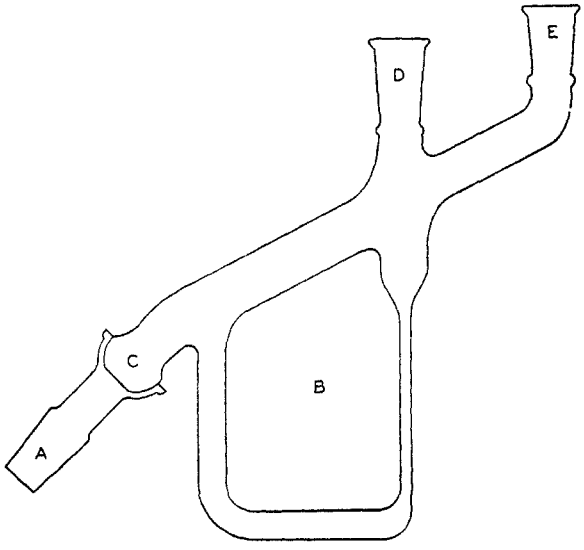


Fig. 2.—Dilution apparatus.

After flushing out the system with nitrogen gas, 4.5 g. (0.12 gram atom) of freshly trimmed potassium, 300 ml. of freshly distilled xylene and 25.5 g. (0.345 mole) of *t*-butyl alcohol, freshly distilled from sodium, were added. The mixture was stirred and warmed below the boiling point of the alcohol–xylene azeotrope until all of the potassium had been converted to potassium *t*-butoxide. Excess alcohol was removed by distillation. Enough dry xylene was introduced to bring the total volume in the flask to 400 ml., and 15 g. (0.055 mole) of α-carbethoxyethyl-ε-carbethoxypentylmethylamine in 125 ml. of dry xylene was added dropwise over a 48-hour period to the reaction mixture, with vigorous stirring and strong refluxing. Alcohol formed during the ring closure accumulated in the condenser where it could be periodically removed by distillation. The temperature of refluxing vapors gave an approximate indication of the amount of alcohol present. A more accurate estimate could be obtained from the refractive index of the distillate. Azeotrope removed served to maintain the volume of xylene in the flask at about 400 ml. After cooling, the orange-colored reaction mixture was extracted with six 20-ml. portions of dilute hydrochloric acid. To minimize product loss due to oxidative decomposition, the acid extraction was carried out promptly after removal of the reaction mixture from the nitrogen atmosphere. One drop of the first extract in 1 ml. of water gave a strong blue-violet ferric chloride test[44] for the enol function. To the combined aqueous extracts was added 70 ml. of concentrated hydrochloric acid, and the solution was boiled under reflux for 2.5 hours (negative ferric chloride test). The solution was concentrated to small volume *in vacuo*, cooled before 5° in an ice-bath, and made strongly alkaline to litmus with a cold saturated aqueous solution of potassium hydroxide. The black basic solution was extracted with ten 30-ml. portions of ether. After drying the combined ether extracts, the ether was removed and the orange-red product was immediately distilled, b.p. 91.5–93° (17 mm.); yield 4.7 g. (55%). The free α-aminoketone could be stored under Dry Ice for an indefinite period without serious oxidative decomposition. Redistillation for analysis gave a yellow-tinted liquid, b.p. 95° (20 mm.); $n^{20}D$ 1.4706. The compound exhibited strong infrared absorption for the carbonyl group at 1706 cm.$^{-1}$. No band was present for any N–H function in the 3294 cm.$^{-1}$ region.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04. Found: C, 69.71; H, 11.15.

The picrate, prepared in ether, crystallized from water as clusters of yellow needles, which began to shrink at 160°, darkened at 165°, and melted at 165.5–166°. Infrared absorption for the carbonyl group was shifted to 1716 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.87; H, 5.25; N, 14.58. Found: C, 46.85; H, 5.41; N, 14.64.

Clemmensen Reduction of 1,2-Dimethyl-1-azacycloöctan-3-one.—Granulated zinc (54 g.) was amalgamated by shaking 5 minutes with 6 g. of mercuric chloride, 6 ml. of concentrated hydrochloric acid and 70 ml. of water. The solution was decanted, and the remaining amalgam was washed twice with distilled water. Concentrated hydrochloric acid (40 ml.) was added to the amalgam and the mixture was heated. When gentle refluxing had started, 7.5 g. (0.048 mole) of freshly distilled 1,2-dimethyl-1-azacycloöctan-3-one dissolved in 40 ml. of concentrated hydrochloric acid was added cautiously. Refluxing was continued for 18 hours. At 2-hour intervals, 30-ml. portions of concentrated hydrochloric acid were added and, after 9 hours, an additional 40 g. of amalgamated zinc was introduced. At the end of 18 hours the reaction liquid was decanted, and the residual amalgam was washed with two 25-ml. portions of water. The combined solution and washings were concentrated *in vacuo*, and the concentrate was made strongly basic by adding a saturated aqueous solution of potassium hydroxide. The resulting white slurry was steam-distilled until 1.4 l. of distillate had been collected. The colorless basic oil floating on the surface of the distillate was removed by adding two 75-ml. portions of ether, and separating the organic and aqueous layers. The aqueous layer was made definitely acid to litmus by adding 6 *N* hydrochloric acid, and the acidic solution was concentrated to 100 ml. by evaporation *in vacuo*. The concentrate was made strongly basic to litmus, and the basic solution was subjected to continuous ether extraction. The combined ether extracts were dried, and the ether was removed by distillation. The remaining basic oil, which weighed 3.2 g. (46% yield), was carefully fractionated through a Holtzmann column. All fractions gave a strongly positive Duke test[36] for secondary amine function. The physical properties of all fractions except the last were shown to agree with those of authentic N-methyloctylamine. The center fraction and authentic N-methyloctylamine had identical infrared spectra (Fig. 1, curve A).

The picrates of all fractions except the last, formed in ether and crystallized from aqueous ethanol as yellow needles, melted at 98–98.5°. Meling points of mixtures with the picrate of authentic N-methyloctylamine and with each other were not depressed.

Anal. Calcd. for $C_{15}H_{24}N_4O_7$: C, 48.38; H, 6.50; N, 15.05. Found: C, 48.63; H, 6.63; N, 15.22.

The final fraction (weight 0.1 g.) was obtained by elevating the column and oil-bath temperatures until the distillation system was dry. The infrared spectrum of the distillate, $n^{20}D$ 1.4314, was essentially like that of N methyloctylamine, but showed the presence of an estimated 5% of impurity having a carbonyl band at 1719 cm.$^{-1}$. Since this is the frequency commonly found for simple aliphatic carbonyl absorption and the impurity was detected only in the highest boiling fraction, the most probable structure for the material was considered to be ε-methylaminopentyl ethyl ketone (IIb). **The picrate** of the last fraction was formed in ether. Efforts to isolate the carbonyl-containing compound for analysis by fractional crystallization of the picrate from aqueous ethanol failed. The only crystalline material obtained in a purified state (0.194 g.) was shown by melting point, mixed melting point, and comparison of in-

(41) A. C. Cope and E. C. Herrick, THIS JOURNAL, **72**, 983 (1950).

(42) K. Ziegler, H. Eberle and H. Ollinger, *Ann.*, **504**, 94 (1933).

(43) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 129.

(44) H. Henecka, *Chem. Ber.*, **81**, 179 (1948).

frared spectra (Fig. 1, curve C) to be the picrate of N-methyloctylamine.

In an attempt to improve the mass balance from the aminoketone used in the reaction, the residue from steam distillation was filtered free from inorganic material, and the solid was washed with two 35-ml. portions of water. No organic material was obtained from continuous ether extraction of the combined filtrate and washings.

Wolff–Kishner Reduction of 1,2-Dimethyl-1-azacyclooctan-3-one.—A mixture of 3.5 g. (0.023 mole) of freshly distilled aminoketone, 4 g. (0.071 mole) of potassium hydroxide, 3 ml. of 85% hydrazine hydrate, and 30 ml. of triethylene glycol was refluxed gently for 1.25 hours. The temperature of the heating-bath was elevated, and volatile material was distilled. When the temperature of the reaction liquid reached 180°, distillation was interrupted, and refluxing was continued for another 3 hours. The bath temperature was then elevated to 250° and distillation of remaining volatile material was completed. The distillate was extracted with four 15-ml. portions of ether. The combined extracts were dried, and the ether was removed. Fractionation of the residual liquid gave four fractions (2.15 g., 67% yield) of colorless, basic product boiling over the range 71–74° (15 mm.). The infrared spectra of all fractions were the same except for an estimated 0.01 g. of impurity in the lowest boiling fraction (fraction 1). All exhibited strong absorption at 3290 cm.$^{-1}$, characteristic for the N–H function; at 966 cm.$^{-1}$, for *trans* double bond C–H bending; at 2995 cm.$^{-1}$, for double bond C–H stretching; and weaker absorption at 1637 cm.$^{-1}$, for C=C stretching and at 1379 cm.$^{-1}$ for the C–CH_3 function (curve B in Fig. 1). That the C=C stretching band is characteristically weak for isolated internal aliphatic double bonds possessing a *trans* configuration was confirmed by the observation of a correspondingly low intensity of C=C absorption at 1637 cm.$^{-1}$ for authentic octene-2 (Connecticut Hard Rubber Company).

All fractions were shown to give a positive bromine test for unsaturation by using equivalent amounts of N-methyloctylamine and basic product in the blank and test solutions, respectively. All fractions gave a strongly positive Duke test[36] for the secondary amine function.

Fraction 4 was redistilled from granulated zinc and was analyzed immediately, b.p. 74.5–75° (16 mm.); $n^{19}D$ 1.4450.

Anal. Calcd. for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 76.42; H, 13.73; N, 10.10.

Analysis of fraction 4, after six or more hours had elapsed from the time of distillation from zinc, gave values for carbon and hydrogen that were 1–2% low, apparently due to absorption of carbon dioxide.

The picrate of fraction 4 melted sharply before recrystallization at 82–83°. Careful fractional crystallization from aqueous ethanol gave successive crops of isomeric picrates, each with a 1–2° melting-point range. Highly fractionated yellow needles, m.p. 78–79°, were analyzed.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.69; H, 6.12; N, 15.04.

Highly fractionated yellow needles, m.p. 87–88°, were analyzed.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.72; H, 6.17; N, 15.25.

Highly fractionated yellow needles, m.p. 92–93°, were analyzed.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.67; H, 6.09; N, 15.04.

The *p*′-hydroxyazobenzene-*p*-sulfonic acid derivative of fraction 4 was prepared in ethanol. Fractional crystallization from ethanol–ether gave successive crops of isomeric salts melting over 1–2° ranges between the temperatures 197 and 211°. Highly fractionated orange needles, m.p. 197.5–199°, were analyzed.

Anal. Calcd. for $C_{21}H_{29}N_3O_4S$: C, 60.12; H, 6.97; N, 10.02. Found: C, 60.07; H, 7.07; N, 9.91.

Highly fractionated orange needles, which softened at 202° and melted at 203–204°, were analyzed.

Anal. Calcd. for $C_{21}H_{29}N_3O_4S$: C, 60.12; H, 6.97; N, 10.02. Found: C, 60.11; H, 6.94; N, 9.79.

Highly fractionated orange needles, m.p. 209–210°, were analyzed.

Anal. Calcd. for $C_{21}H_{29}N_3O_4S$: C, 60.12; H, 6.97; N, 10.02. Found: C, 60.48; H, 7.35.

Too little material remained for further analytical investigation.

The picrate of fraction 1 was formed in ether. The yellow needles as first formed melted at 79–80° to a turbid liquid which did not clear until 145°. Careful fractional crystallization from aqueous ethanol gave 0.0139 g. (0.12% yield) of a picrate, m.p. 191–192.5°. After five additional recrystallizations from ethanol–water the yellow needles, m.p. 197–197.5°, were analyzed.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99. Found: C, 48.76; H, 6.24.

The identity of this picrate was assumed to be that of **1,2-dimethyl-1-azacycloöctane** on the basis of the elementary analysis, the high melting point of the picrate derivative, and the fact that this reaction product was present only in the lowest-boiling fraction.[29] From the mother liquor of the fractional crystallization procedure, 0.4226 g. of yellow needles, m.p. 82–83°, were obtained. This picrate was shown to be the picrate of **N-methyloctenylamine** (see above).

Catalytic Reduction of N-Methyloctenylamine.—Two-tenths of one gram (0.0014 mole) of N-methyloctenylamine dissolved in 30 ml. of ethanol was hydrogenated using 0.02 g. of platinum oxide catalyst at 28° and 3 atm. The catalyst was removed by filtration and the solvent by distillation. The residual basic oil afforded 0.422 g. (80% yield) of **picrate**, which crystallized from aqueous ethanol as yellow needles, m.p. 98–98.5°. Mixtures with the picrate of authentic N-methyloctylamine were not depressed in melting point. The infrared spectra of the reduction product picrate and the picrate of authentic N-methyloctylamine were superposable (curve C in Fig. 1).

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