Clarke–Eschweiler Cyclization. Scope and Mechanism[1a]

ARTHUR C. COPE AND W. DICKINSON BURROWS[1b]

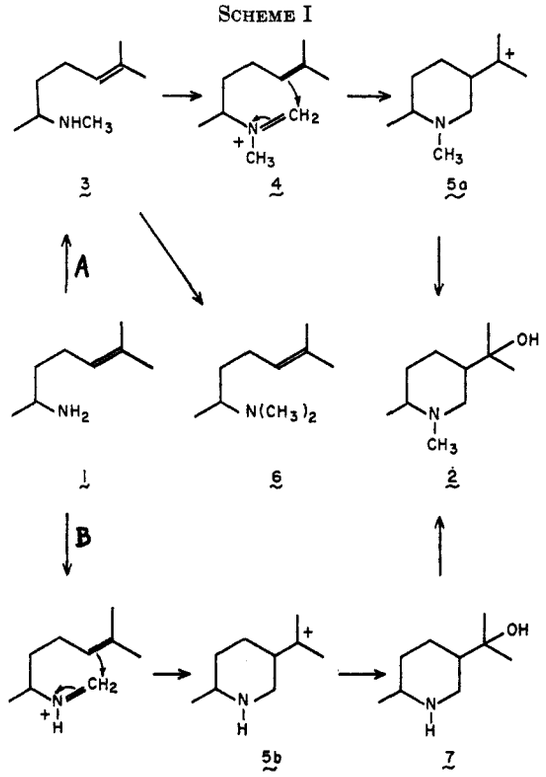
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received April 28, 1966

Cyclization accompanying Clarke–Eschweiler methylation of certain olefinic amines has been investigated further. Cyclization is shown to precede methylation in the case of 1,5-dimethyl-4-hexenylamine. 3-Methyl-3-butenylamine, 4-methyl-3-pentenylamine, 1,4-dimethyl-4-pentenylamine, and 6,6-dimethyl-2-norpineneethylamine also give cyclic products wholly or in part, but not 2-methylallylamine. Results are compared with those of Johnson and Owyang for formolytic cyclization of *p*-nitrobenzenesulfonates.

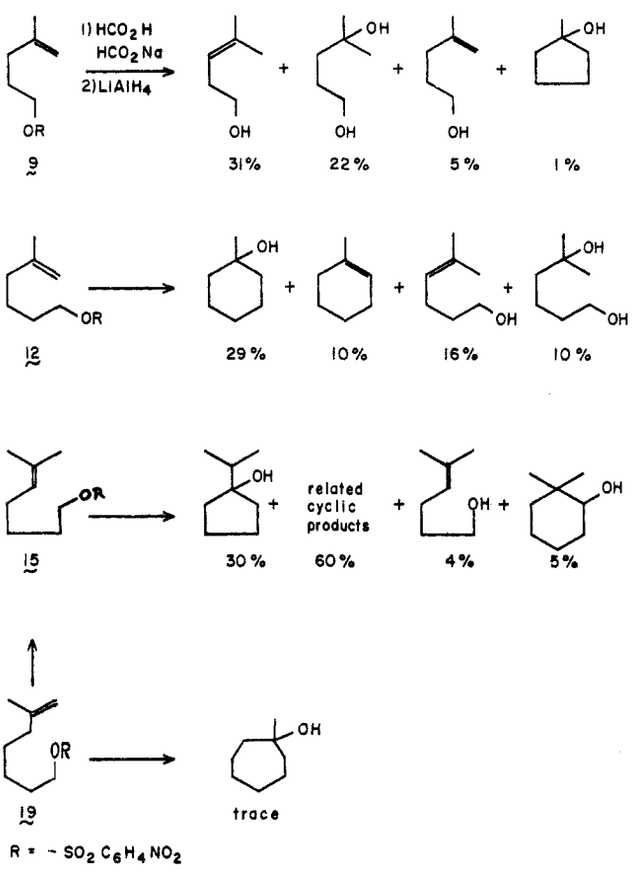
In an earlier paper[2] we reported that 1,5-dimethyl-4-hexenylamine (**1**), on treatment with formaldehyde and formic acid, undergoes cyclization to a mixture of *cis*- and *trans*-α,α,1,6-tetramethyl-3-piperidinemethanol (**2**).[3] It was proposed that the first step is a normal Clarke–Eschweiler reaction, producing the monomethylamine **3**, as in path A. Reaction of **3** with formaldehyde would give the iminium cation **4** which on cyclization would yield the tertiary carbonium ion **5a** and ultimately, with water, **2**. Alternatively cyclization could precede methylation as in path B. When the independently prepared monomethylamine **3** is treated with formaldehyde and formic acid, the normal dimethylamine **6** is produced along with cyclic products. Since **1** gives only cyclic products, pathway B seems to predominate. In confirmation, **1** gives as major product the intermediate piperidinemethanol **7** when treated with a single molar equivalent of formaldehyde in formic acid (Scheme I).

SCHEME I



We were encouraged to extend our investigation of this reaction by the studies of Johnson and Owyang on olefinic cyclizations.[4] We have summarized here the results they report for formolysis of four alkenyl *p*-nitrobenzenesulfonates. It seemed a natural extension of our work to design a series of experiments wherein the iminium cation formed in the Clarke–Eschweiler reaction takes the place of the carbonium ion from nitrobenzenesulfonate formolysis (Scheme II).

SCHEME II



2-Methylallylamine (**8**).—In the reaction analogous to formolysis of 4-methyl-4-pentenyl nitrobenzenesulfonate (**9**), 2-methylallylamine reacts with formaldehyde and formic acid to give almost exclusively the normal product, N,N,2-trimethylallylamine. Failure of the 4-methyl-4-pentenyl derivative of Johnson and Owyang to undergo cyclization is due in large part to

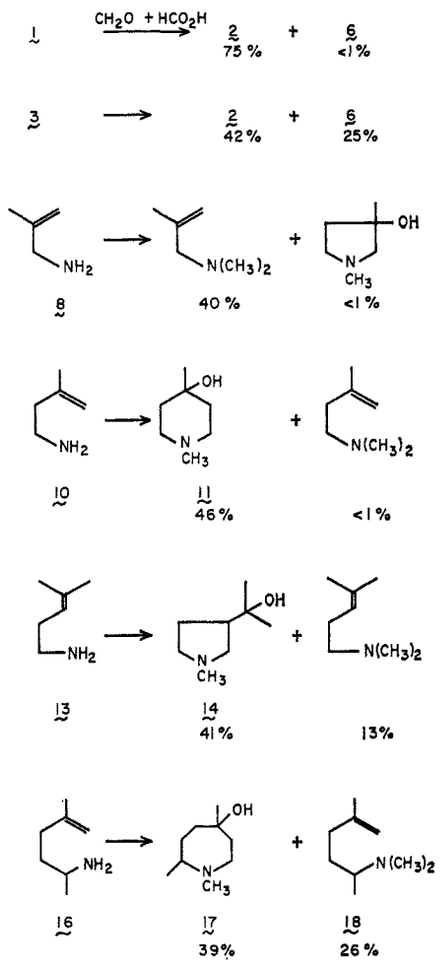
(1) (a) Supported by Merck, Sharp and Dohme Research Laboratories; presented in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965. (b) Inquiries may be addressed to W. D. B.: U. S. Army Natick Laboratories, Natick, Mass.

(2) A. C. Cope and W. D. Burrows, *J. Org. Chem.*, **30**, 2163 (1965).

(3) Cyclization in the course of Clarke–Eschweiler methylation occurs as a special case of the Pictet–Spengler synthesis of tetrahydroisoquinolines from reactive arylethylamines such as mescaline [J. A. Castrillón, *J. Am. Chem. Soc.*, **74**, 558 (1952)], homoveratrylamine [R. Baltzly, *ibid.*, **75**, 6038 (1953)], and ferroceneethylamine [D. Lednicer and C. R. Hauser, *J. Org. Chem.*, **24**, 43 (1959)].

(4) W. S. Johnson and R. Owyang, *J. Am. Chem. Soc.*, **86**, 5593 (1964).

SCHEME III



migration of the terminal double bond. With 2-methylallylamine this does not occur. (See Scheme III.)

3-Methyl-3-butenylamine (10).—The Clarke–Eschweiler reaction of 3-methyl-3-butenylamine gives only the cyclic product, 1,4-dimethyl-4-piperidinol (**11**). The nuclear magnetic resonance (nmr) spectrum of **11** in deuteriochloroform, unusual in that all protons are readily accounted for, exhibits N-methyl and 4-methyl singlets at δ 2.30 and 1.26, respectively, hydroxyl singlet at 3.11, and two triplets at 2.49 and 1.67 (J = 6.0 cps) due to the mutually split α and β protons. In the analogous reaction described by Johnson and Owyang, 5-methyl-5-hexenyl nitrobenzenesulfonate (**12**) gives nearly half acyclic material, again in part because of double-bond migrations.

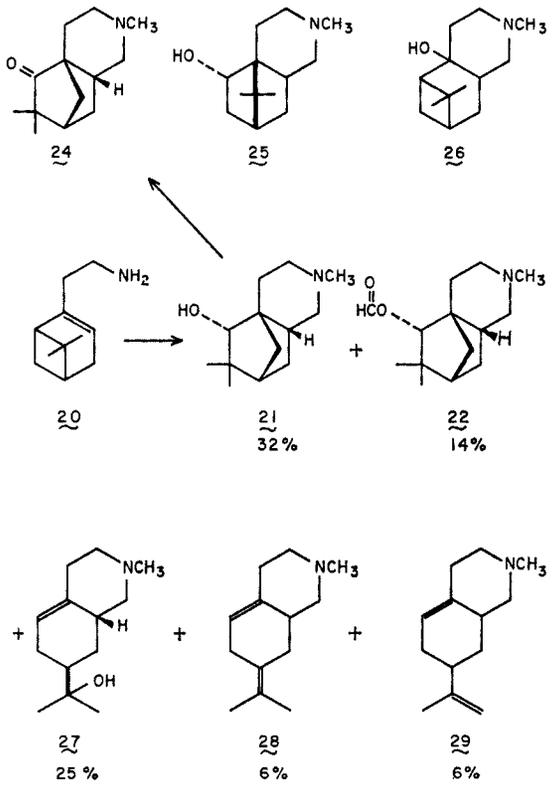
4-Methyl-4-pentenylamine (13).—In the reaction of 4-methyl-4-pentenylamine the cyclic product, α,α,-1-trimethyl-3-pyrrolidinemethanol (**14**), is favored by greater than 3:1 over the normal product. The nmr spectrum of the major methiodide in deuterium oxide displays two α-methyl singlets at δ 1.19 and 1.23 and two N-methyl singlets at 3.13 and 3.19. For the comparable formolysis of the 6-methyl-5-heptenyl system (**15**), Johnson and Owyang report over 90% of cyclic alcohol and products derived therefrom.

1,4-Dimethyl-4-pentenylamine (16).—The most striking contrast with the formolysis reaction is provided by the Clarke–Eschweiler reaction of 1,4-dimethyl-4-pentenylamine, wherein three-fifths of the product is a 1:1 mixture of *cis*- and *trans*-hexahydro-1,4,7-trimethyl-4-azepinol (**17**), the rest being the unrearranged dimethylamine (**18**). The nmr spectrum of the major product in deuteriochloroform shows two overlapping doublets of equal size at δ 0.98 (J = 5.5 cps) and 0.96 (J = 6.0 cps) due to the *cis*- and *trans*-7-methyl groups, singlets at 2.20 and 1.10 due to N-methyl and 4-methyl groups, respectively, and a hydroxyl singlet at 3.41. In the spectrum of the methiodide of **17** in deuterium oxide the 7-methyl resonance becomes a broad doublet at δ 1.48 (J = 7 cps) partially overlapped by the 4-methyl singlet at 1.37, and four overlapping bands appear at 3.26, 3.03, 3.22, and 3.03 due to the N-methyl groups of the two stereoisomers.

Formolysis of 6-methyl-5-heptenyl nitrobenzenesulfonate (**19**), accompanied by double-bond rearrangement, gives only a trace of methylcycloheptanol. It appears that Clarke–Eschweiler cyclization of amines differs from formolytic cyclization of nitrobenzenesulfonates in that double-bond migration is not important, at least not in the cases we have studied, and the products are stable to hot formic acid.

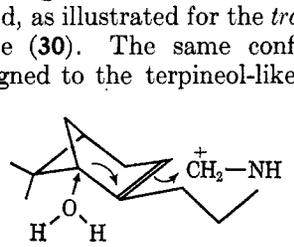
6,6-Dimethyl-2-norpineneethylamine (Nopylamine, 20).—In the earlier paper we suggested that the cyclic intermediate **5a** or **5b** must possess considerable carbonium ion character since 1-methyl-4-pentenylamine, lacking the charge-stabilizing methyl groups, gives only the normal Clarke–Eschweiler product. The generality of the carbonium ion (as opposed to concerted) mechanism finds support in the reaction of nopylamine, from which only rearranged products are isolated. The principal product (**21**) is a crystalline solid. The nmr spectrum of **21** in deuteriochloroform features C-methyl singlets at δ 0.87 and 1.00, a N-methyl singlet at 2.23, and a singlet at 3.21 due to the proton α to the hydroxyl group. The formate (**22**) is also a major product, and can be prepared from **21** by prolonged treatment with hot 75% formic acid. Treatment of **22** with lithium aluminum hydride regenerates **21**. The α-proton singlet is shifted to δ 4.58 in the nmr spectrum of the formate (deuteriochloroform), and the two C-methyl groups and the N-methyl group appear at 0.83, 1.17, and 2.21, respectively. In the spectrum of the acetate (**23**) (deuteriochloroform) of **21** the α proton appears at δ 4.34, the C-methyls at 1.12 and 0.79, and the N-methyl at 2.22. Alcohol **21** is cleanly oxidized to the ketone (**24**) by Jones reagent. In the nmr spectrum of **24** (deuteriochloroform) the C-methyl singlets are both shifted downfield from their position in **21** to δ 1.03, and the N-methyl peak appears at 2.22. Principal product **21** is thus shown to be a secondary alcohol structurally related to α-fenchol rather than the borneol (**25**) or unrearranged pinanol (**26**) related product. The third major product (**27**) is related to α-terpineol. The nmr spectrum of **27** (deuteriochloroform) displays a six-proton singlet at δ 1.18 due to the dimethylcarbinol group, an N-methyl singlet at 2.27, and a one-proton multiplet at 5.5 due to the single olefinic proton. The infrared spectrum of **27** in chloroform exhibits a weak band at 1680 cm^{-1} due to the trisubstituted double bond. Prolonged treatment with hot 65% formic acid effects partial dehydration of **27** to **28** and **29**, the two minor products of the Clarke–Eschweiler reaction. The former is related to terpinolene, since it exhibits only the same weak double-bond band at 1675 cm^{-1}

SCHEME IV



(chloroform) as **27**; **29** has the weak band at 1675 and a strong band at 1645 cm^{-1} characteristic of a terminal methylene group and is thus related to limonene. (See Scheme IV.)

The unrearranged product **26** was not detected and, since other Clarke–Eschweiler cyclization products are quite stable to hot formic acid, was probably not formed in significant concentration. If **26** is not an intermediate in the formation of **21** (and there are additional stereochemical reasons for believing it is not) the configuration at 5 and 8a results from Walden inversion following attack of the iminium cation at the double bond, as illustrated for the *trans*-decalin-like transition state (**30**). The same configuration at 7 and 8a is assigned to the terpineol-like product (**27**),



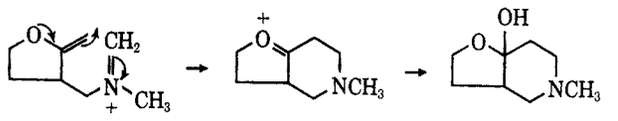
30

but with less certainty; **27** could also have been formed by attack of the iminium cation on the opposite face of the double bond, although this would be expected to result in formation of the borneol-like product (**25**) as well.[5]

Husson, Potier, and Le Men have provided an example (here abbreviated) from the steroid field of Clarke–Eschweiler cyclization involving a vinyl ether linkage.[6]

(5) W. D. Burrows and R. H. Eastman [*J. Am. Chem. Soc.*, **81**, 245 (1959)] found that *cis*-methylnopinol (2-pinanol) gave bornyl and terpinyl acetates on acetolysis; *trans*-methylnopinol gave α-fenchyl and terpinyl acetates.

(6) We thank Dr. Potier for sharing his results with us in advance of publication; H. P. Husson, P. Potier, and J. Le Men, *Bull. Soc. Chim. Trans.*, 948 (1966).



Experimental Section

Instrumental.—Analysis by vapor phase chromatography (vpc) and collection of samples for combustion and spectroscopic analyses were accomplished using the F & M Model 720 chromatograph equipped with 2-ft columns of silicone rubber (20%) on Chromosorb W. For infrared spectra the Perkin-Elmer Model 237B was used, for nmr spectra the Varian Model A-60 was used, and for mass spectra the Hitachi Perkin-Elmer RMU-6D was used. Tetramethylsilane or the sodium salt of γ-trimethylsilylpropanesulfonic acid were the internal standards for nmr spectra. Melting points were taken with a Kofler–Reichert microhot stage apparatus and are uncorrected.

3-Methyl-3-butenylamine (10).[7]—To 100 g of magnesium turnings and 100 ml of ether was added 4 ml of ethyl bromide. With the reaction proceeding vigorously, 800 ml of ether was added, followed by a 1:1 solution of 181 g of redistilled methallyl chloride in ether, dropwise with stirring. The reaction vessel was cooled in an ice bath during the 3 hr of addition and for 3 hr of stirring after addition was complete. The Grignard solution was saturated with formaldehyde prepared by passing nitrogen through a flask containing paraformaldehyde heated at 190–200°. The mixture was heated to reflux for 1 hr, then was decomposed with ice and dilute hydrochloric acid. The ether layer and additional ether extracts were combined, evaporated, and distilled, yielding 55 g (32%) of 3-methyl-3-buten-1-ol, bp 125–135°.

The alcohol was converted in 40% yield to 4-chloro-2-methyl-1-butene by treatment with thionyl chloride and tributylamine as previously described.[7] The chloride (15 g), potassium phthalimide (29 g), and 100 ml of dimethylformamide were sealed in a Pyrex tube and heated at 120° for 8 hr. The tube was inverted once every hour during heating. The cooled mixture was poured into ice–water, and the solid that precipitated was collected by filtration, washed with water, and dried. The yield of phthalimide derivative was 25 g (81%). This material was treated with 8 g of 85% aqueous hydrazine hydrate in 200 ml of refluxing methanol for 6 hr, then half the methanol was removed by distillation, and 200 ml of 6% aqueous sodium hydroxide was added. After the mixture was heated at reflux for 2 hr, the amine was removed by steam distillation. Ether extraction of the distillate gave on evaporation and distillation of the extract 9.4 g of a 2:1 mixture of the desired amine and hydrazine. Using a 35-cm semimicrodistilling column a sample of 90% purity was obtained: bp *ca.* 45° (80–85 mm).

4-Methyl-3-pentenylamine (13).—4-Chloro-2-methyl-2-butanol was prepared according to the method of Campbell and Campbell by addition of ethyl 4-chlorobutyrate to an ether solution of methyl magnesium iodide.[8] The crude chlorohydrin (100 g) was treated with 90 g of potassium phthalimide in 500 ml of dimethylformamide at 120° for 14 hr. The cooled mixture was poured into ice–water and filtered to remove phthalimide. The phthalimide was washed with chloroform and the aqueous portion was extracted with chloroform. Combined chloroform extracts were washed with dilute aqueous sodium hydroxide and several times with water; then they were dried and evaporated. The yield of crude phthalimide derivative was 38 g (21%).

The phthalimide derivative, dissolved in 75 ml of pyridine, was added to a chilled solution of 40 g of phosphorus oxychloride in 75 ml of pyridine and allowed to stand for 48 hr at 25°. The mixture was then poured into ice–water and extracted with chloroform. The extract was washed with dilute hydrochloric acid, dried, and evaporated, yielding 31 g (88%) of oil which by vpc and infrared analysis was *ca.* 90% pure. An analytical sample was prepared by vpc.

Anal.[9] Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.05; H, 6.56; N, 6.10.

(7) The preparation of this amine is described by E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts [*J. Am. Chem. Soc.*, **83**, 2719 (1961)], but, because we experienced considerable difficulty in following their abbreviated description, our procedure is described in detail.

(8) B. K. Campbell and K. N. Campbell, *ibid.*, **60**, 1372 (1938).

(9) Scandinavian Microanalytical Laboratory, Herlev, Denmark.

The crude phthalimide was converted to 6.5 g (55%) of amine, bp 60–62° (60 mm), by treatment with hydrazine as described above for 3-methyl-3-butenylamine. Infrared and vpc analysis showed the product to be a 2:1 mixture of 4-methyl-3-pentenylamine and 4-methyl-4-pentenylamine.[10]

1,4-Dimethyl-4-pentenylamine (16).—The oxime, bp 100–107° (15 mm), of 2-methyl-1-hexen-5-one was prepared in 91% yield by treatment of the ketone with hydroxylamine hydrochloride and potassium carbonate in aqueous methanol. To 31 g of lithium aluminum hydride in 500 ml of tetrahydrofuran (THF) was added dropwise with cooling 103 g of the oxime in 100 ml of THF. After the initial reaction had subsided the mixture was heated to reflux for 6 hr. Work-up in the usual way provided 35 g (38%) of amine, bp *ca.* 70° (70 mm). The picrate, recrystallized from ethanol, had mp 124–128°.

Anal. Calcd for $C_{13}H_{18}N_4O_7$: C, 45.61; H, 5.30; N, 16.37. Found: C, 45.75; H, 5.34; N, 16.33.

2-(2-Chloroethyl)-6,6-dimethyl-2-norpinene (Nopyl Chloride).—To a solution of 83 g of 6,6-dimethyl-2-norpinene-2-ethanol (nopol)[11] and 93 g of tributylamine in 150 ml of ether chilled in an ice bath was added 11.9 g of thionyl chloride, dropwise with stirring during 2 hr. After 3 hr additional standing in the ice bath, the mixture was shaken with ice–water and with 5% aqueous sodium hydroxide. The ether layer was dried, evaporated, and distilled, yielding 74 g (80%) of colorless oil, bp 56–60° (0.8 mm).

6,6-Dimethyl-2-norpinene-2-ethylamine (Nopylamine 20).—A mixture of nopyl chloride (45 g) and potassium phthalimide (47 g) in 250 ml of dimethylformamide was heated at 120–130° for 9 hr, then poured into ice–water, and extracted with chloroform. The extract, washed with water and with 5% aqueous sodium hydroxide, gave on evaporation 66 g of dark oil. The phthalimide derivative was converted to the free amine by treatment with hydrazine as described above for 3-methyl-3-butenylamine. The yield was 25.5 g (63%), bp 60–70° (0.2 mm). The picrate, recrystallized from ethanol, had mp 170–175° dec.

Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.62; N, 14.21. Found: C, 51.69; H, 5.80; N, 14.08.

N,N,6,6-Tetramethyl-2-norpinene-2-ethylamine (Dimethylnopylamine).—Nopyl chloride (10 g) was dissolved in 21 g of anhydrous dimethylamine and heated in a sealed Pyrex tube for 144 hr at 90°. The contents of the tube were treated with aqueous sodium hydroxide and extracted with ether. Evaporation and distillation of the dried extract gave 9.4 g (90%) of colorless oil, bp 60–70° (0.6 mm).[12] The methiodide, recrystallized from isopropyl alcohol–ether, had mp 255–260° dec.

Anal. Calcd for $C_{14}H_{26}IN$: C, 50.15; H, 7.82; N, 4.18. Found: C, 50.20; H, 7.86; N, 4.04.

The Clarke–Eschweiler Reaction.—Except where otherwise noted, the amine was treated with 3 molar equiv of 37% aqueous formaldehyde in 5 molar equiv of 90% formic acid and heated on a steam bath for 6 hr after the initial reaction had subsided. The mixture was then poured into ice–water and made strongly basic with solid sodium hydroxide. The product was isolated by ether extraction.

The Clarke–Eschweiler Reaction with N,1,5-Trimethyl-4-hexenylamine (3).—N,1,5-Trimethyl-4-hexenylamine was prepared in 85% yield by reductive amination of 2-methyl-2-hepten-6-one according to the method of Klavehn,[13] as elaborated by Laforge, Whitehead, Keller, and Hummel.[14] To 5.0 g of the amine in 7 g of 90% formic acid was added 6 g of 37% aqueous formaldehyde. When evolution of carbon dioxide had largely ceased the mixture was heated on a steam bath for 3 hr. Work-up in the usual way provided 4.2 g of material, shown by vpc to comprise three major products: *cis*- (14%) and *trans*- (47%) α,α,1,6-tetramethyl-3-piperidinemethanol (**2**) and a more volatile amine, 39%, bp 75–79° (12 mm). Infrared and nmr analysis of the last material indicated it to be a 4:1 mixture of N,N,1,5-tetramethyl-4-hexenylamine and N,N,1,5-tetramethyl-5-hexenylamine (**6**), possibly containing other double-bond isomers. Hydrogenation of the mixed amines over prereduced platinum oxide in methanol provided a saturated material with an infrared spectrum identical with that of authentic N,N,1,5-tetramethylhexylamine, described below.

N,N,1,5-Tetramethylhexylamine.—N,1,5-Trimethylhexylamine, bp 78–80° (30 mm), was prepared by hydrogenation of N,1,5-trimethyl-4-hexenylamine (**3**) over prereduced platinum oxide in methanol. Clarke–Eschweiler methylation of 10 g of the saturated amine gave 9.7 g (89%) of colorless oil, bp 83–85° (27 mm). The methiodide, recrystallized from acetone–ether, had mp 220–224° dec.

Anal. Calcd for $C_{11}H_{26}IN$: C, 44.15; H, 8.76; N, 4.68. Found: C, 44.05; H, 8.79; N, 4.69.

α,α,6-Trimethyl-3-piperidinemethanol (7). The Interrupted Clarke–Eschweiler Reaction of 1,5-Dimethyl-4-hexenylamine (1).—To 6.35 g of amine in 10 g of formic acid was added 4 g (1 molar equiv) of 37% aqueous formaldehyde. After bubbling had ceased the mixture was heated on a steam bath for 90 min. Work-up in the usual way gave 1.3 g of low-boiling material which was not further investigated, and a fraction with bp 70–90° (1 mm) (3.3 g) which largely crystallized. This material, which was shown by vpc to contain 10–15% α,α,1,6-tetramethyl-3-piperidinemethanol (**2**), was recrystallized from THF–ether to mp 104–105°. This material was completely converted by formaldehyde and formic acid to *trans*-**2**.

1,4-Dimethyl-4-piperidinol (11). The Clarke–Eschweiler Reaction of 3-Methyl-3-butenylamine (10).—A 2.2-g sample of the amine containing 10% hydrazine gave 1.4 g (46%) of the cyclic product, but no trace of the normal product. A sample recrystallized from pentane and sublimed had mp 66–68° (lit.[15] mp 66.4–68°).

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.05; H, 11.65; N, 10.94.

α,α,1-Trimethyl-3-pyrrolidinemethanol (14). The Clarke–Eschweiler Reaction of 4-Methyl-3-pentenylamine (13).—A 9.0-g sample of amine containing 33% 4-methyl-4-pentenylamine (see above) afforded 6.8 g of oil. By vpc 30% of the product consisted of a 1:1 mixture of volatile amines, most reasonably N,N,4-trimethyl-3-pentenylamine and N,N,4-trimethyl-4-pentenylamine. The remainder consisted of a 3:1 mixture of cyclization products, bp 100–110° (30 mm). The methiodide of the major product, recrystallized six times from isopropyl alcohol, had mp 175–182°.

Anal. Calcd for $C_9H_{20}INO$: C, 37.90; H, 7.07; N, 4.91. Found: C, 37.84; H, 7.00; N, 4.91.

Hexahydro-1,4,7-trimethyl-4-azepinol (17) and N,N,1,4-Tetramethyl-4-pentenylamine (18). The Clarke–Eschweiler Reaction of 1,4-Dimethyl-4-pentenylamine.—The crude product from 33.9 g of amine was distilled, yielding 11 g (26%) of the normal product, bp 70–75° (40 mm), and 19.3 g (39%) of the cyclic product, bp 95–100° (8 mm). An analytical sample of the latter was prepared by vpc.

Anal. Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.59; H, 12.21; N, 9.00.

The methiodide of **17**, recrystallized from acetone–methanol, had mp 225–232°.

Anal. Calcd for $C_{10}H_{22}INO$: C, 40.14; H, 7.41; N, 4.68. Found: C, 39.96; H, 7.41; N, 4.54.

The methiodide of the volatile product (**18**), recrystallized from acetone, had mp 160–167°.

Anal. Calcd for $C_{10}H_{22}IN$: C, 42.41; H, 7.83; N, 4.95. Found: C, 42.41; H, 7.85; N, 4.70.

Octahydro-2,6,6-trimethyl-7H-4a,7-methanoisoquinolin-5-ol (21) and Formate (22), 1,2,3,4,6,7,8,8a-Octahydro-α,α,2-trimethyl-7-isoquinolinemethanol (27), 1,2,3,4,6,7,8,8a-Octahydro-7-isopropylidene-2-methylisoquinoline (28), and 1,2,3,4,6,7,-8,8a-Octahydro-7-isopropenyl-2-methylisoquinoline (21). The Clarke–Eschweiler Reaction of Nopylamine (20).—Filtration of the crude product from 8.2 g of nopylamine gave 1.8 g of **21** as crystalline solid which, recrystallized from ether–THF, had mp 174–175°.

(10) It was attempted to synthesize the pure amine from 5-bromo-2-methyl-2-pentene, the preparation of which is described by L. Ruzicka and M. Liguori [*Helv.*, **15**, 6 (1932)], but the dehydrobromination of 2,5-dibromo-2-methylpentane gave, in our hands, a 55:45 mixture of the 2-pentene and 1-pentene derivatives. Other methods of preparing **18**, in particular methods based on the Wittig reaction, were unsuccessful.

(11) Kindly provided by the Glidden Co., Organic Chemicals Division, Jacksonville, Fla.

(12) A patent [Rohm and Haas Co., British Patent 730,031 (May 18, 1955)] claims that dimethylnopylamine is prepared by treatment of β-pinene with formaldehyde and ammonium chloride in a mixture of acetic and phosphoric acids, but the properties described in no way resemble those of the amine that we prepared.

(13) W. Klavehn, U. S. Patent 1,972,450 (Sept 4, 1934).

(14) R. A. Laforge, C. R. Whitehead, R. B. Keller, and C. E. Hummel, *J. Org. Chem.*, **17**, 457 (1952).

(15) S. M. McElvain and R. S. Berger, *J. Am. Chem. Soc.*, **77**, 2848 (1955).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.75; H, 11.09; N, 6.56.

The alcohol **21** underwent 70% conversion to the formate (**22**) by prolonged (7 days) treatment with 75% (but not 90%) aqueous formic acid at 100°. The formate was reconverted to **21** by treatment with lithium aluminum hydride in ether. An analytical sample of **22** was prepared by vpc.

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 71.21; H, 9.90; N, 5.88.

The acetate (**23**) was prepared by heating alcohol **21** and acetic anhydride for 16 hr at 100°. An analytical sample was prepared by vpc.

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.79; H, 10.04; N, 5.41.

Analysis by vpc of the filtrate of the Clarke–Eschweiler product showed five major components constituting, in order of increasing retention times, 7.5%, 7%, 19%, 33%, and 22% of the total of 7.8 g. By retention times, the third proved to be the crystalline amino alcohol **21** and the fifth the formate thereof (**22**). Treatment of the entire sample with lithium aluminum hydride cleaved the formate, and on prolonged standing in concentrated ether solution most of alcohol **21** crystallized. Chromatography of the remaining liquid portion on Merck acid-washed alumina and elution first with ether, then with methanol, separated the two more volatile products from the major component (**27**). An analytical sample of **27** was prepared by vpc.

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.01; H, 11.06; N, 6.53.

The methiodide of **27**, recrystallized from isopropyl alcohol–THF, had mp 170–178°.

Anal. Calcd for $C_{14}H_{26}NOI$: C, 47.86; H, 7.46; N, 3.99. Found: C, 47.72; H, 7.60; N, 3.85.

On treatment with 65% formic acid for 90 hr at 100°, **27** was half converted to a mixture of the original two volatile products, **28** and **29**, the longer retained (**28**) predominating by 3:2. An analytical sample of **28**, prepared by vpc, had mp 28–32°.

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.82. Found: C, 81.00; H, 10.97; N, 7.38.

An analytical sample of **29** was prepared by vpc.

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06; N, 7.82. Found: C, 81.31; H, 10.93; N, 7.37.

Octahydro-2,6,6-trimethyl-7H-4a,7-methanoisoquinolin-5-one (**24**).—To 0.25 g of amino alcohol **21** in 4 ml of acetone was added dropwise with cooling 1 ml of Jones reagent, prepared by adding 12.5 g of chromic anhydride and 10.5 ml of concentrated sulfuric acid to 36 ml of water. The oxidation mixture was stirred for 1 hr, then made basic with sodium hydroxide, and extracted with ether. Evaporation of the extract left 0.25 g of colorless oil, by vpc a single material.

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.22; H, 10.20; N, 6.54.

Mass Spectra.—Mass spectra were obtained routinely and were of major importance in confirming assigned structures; in particular, all cyclic Clarke-Eschweiler products gave strong molecular ion peaks. In Table I are listed the major peaks of higher mass for the cyclic products. We shall not speculate here on the nature of the fragmentation products, but it will be seen that the fragmentation patterns are consistent with the structures assigned.

TABLE I

Compd	Molecular ion	Other major peaks
trans-**2**	171	156, 138, 112
11	129	128, 114, 112, 111, 110, 96
trans-**7**	157	142, 124, 110, 98
14	143	142, 128, 126, 110, 84, 82
17	157	155, 142, 124, 112
21	209	208, 207, 206, 194, 190, 180, 179, 178, 148
22	237	236, 209, 194
23	251	250, 248, 208, 192, 190
27	209	194, 192, 191, 190, 176, 151, 150, 148
28	191	190, 176, 148, 134, 122
29	191	190, 176, 148, 123, 122

Acknowledgment.—We gratefully acknowledge the contribution of Dr. Elizabeth P. Burrows, who determined all of the mass spectra.

The Synthesis of Some Substituted 3-Nitro-1,5-pentanediamines[1]

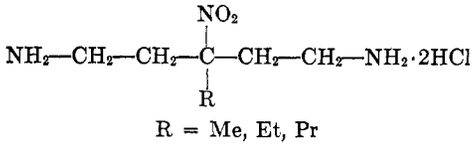
JOHN M. PATTERSON, MICHAEL W. BARNES, AND RICHARD L. JOHNSON[2]

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Received April 25, 1966

Alkyl-substituted 3-nitro-1,5-pentanediamines were synthesized from the corresponding substituted heptanediamides using the Hofmann reaction and from the substituted heptanedioic acids using the Curtius reaction. The expected piperidine was not obtained on pyrolysis of the dihydrochloride of 3-nitro-3-methyl-1,5-pentanediamine.

A limitation to the classical Ladenburg[3] synthesis of piperidine from the hydrochloride of pentanediamine is the availability of the starting diamines. In an attempt to extend this procedure to the synthesis of 4-substituted 4-nitropiperidines, we have synthesized a series of 3-nitro-3-alkylpentanediamines (I) and have examined



R = Me, Et, Pr

the behavior of one of these under pyrolytic conditions. The properties of these diamine dihydrochlorides and their precursors are summarized in Table I.

(1) Presented at the Southeast-Southwest Regional Meeting of the American Chemical Society, Memphis, Tenn., Dec 1965.

(2) Abstracted in part from the M.S. Thesis of R. L. Johnson, University of Kentucky, 1962.

The diamines were obtained from the 4-nitro-4-alkylheptanediamides using the Hofmann reaction and from the 4-nitro-4-alkylheptanedioic acids using the Curtius reaction. The acid did not produce the diamine when Schmidt reaction conditions were used. The diacids and diamides in turn were obtained from reaction of an acrylic acid derivative with the appropriate nitroalkane.

The disubstituted heptanediamides reacted smoothly with alkaline sodium hypobromite to yield the 3-alkyl-3-nitro-1,5-pentanediamines (I) isolated as the dibenzoyl derivatives. Attempts to isolate the free amine directly from the reaction mixture failed.

The acid hydrolysis of the dibenzoyl derivatives of the 3-alkyl-3-nitro-1,5-pentanediamines (I) becomes increasingly difficult with increasing size of the alkyl group. Thus, the methyl compound is hydrolyzed with

(3) A. Ladenburg, *Ber.*, **17**, 388, 513 (1884).