The Peripheral Synthesis of Medium-Ring Nitrogen Heterocycles by Displacement Reactions[1]

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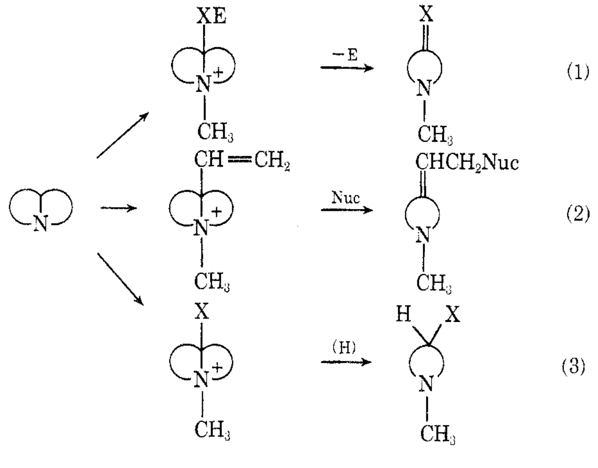
A series of 5-substituted *N*-methyl-1-azacyclononanes has been prepared by the selective cleavage of the central carbon–nitrogen bond of 9-substituted indolizidines with Grignard reagents, $LiAlH_4$, and alkali metals in liquid ammonia. 9-Vinylindolizidine (**3**) reacts *via* its methiodide with ethyl or phenyl Grignard reagents in an abnormal displacement reaction to give the butylidene and phenylethylidene derivatives **4a** and **4b** in high yield. The ethylidene and vinyl compounds **6** and **7** are produced from $LiAlH_4$ and **3** MeI in varying proportions depending on the solvent. Reduction of either **6** or **7** gives the 5-ethyl derivative **8**. Both **6** and **4a** can be oxidized to *N*-methyl-1-azacyclonona-5-one (**5**). 9-Ethynylindolizidine (**9**) is efficiently converted with $LiAlH_4$ to the 5-allenyl compound **10**, which can also be reduced to **8**. The metal–ammonia cleavage of the methiodides of **3** and **9**, as well as those of 9-phenyl- (**12**) and 9-acetylindolizidine (**18**), also leads to 5-substituted *N*-methylazacyclononanes in good to excellent yields. The phenyl compound ring opens normally to **14**, **3** undergoes a double bond shift during the process to give **6**, which is also the major product from **9**, and **18** gives in addition to **20** some of the corresponding alcohol **21**. The synthesis of the starting materials, structure proof of the products, and some mechanistic implications of the cleavage reactions are discussed.

The peripheral synthesis of medium-ring azacycles as developed in our laboratory[2,3] involves the selective cleavage of the central carbon–nitrogen bond of a fused 1-azabicycloalkane. This was achieved in the preceding paper[3] by introduction of a bridgehead substituent containing a group E which could be induced to leave, without its bonding electrons, in a β-elimination reaction (eq 1). The present paper describes a second ring-opening method in which an unsaturated group is placed at the bridgehead and ring opening occurs by either abnormal (eq 2) or normal (eq 3) displacement reactions with Grignard reagents, $LiAlH_4$, or alkali metals in liquid ammonia (Emde cleavage).[4]



As a prototype for the ring opening shown in eq 2, the reactions of 9-vinylindolizidine (**3**) were investigated. In common with the reactions of other ternary iminium salts with Grignard reagents,[5,6] vinylmagnesium chloride failed to add directly to $\Delta^{4(9)}$-dehydroindolizidinium perchlorate (**1**) to give **3**. This compound was obtained in 94% yield, however, by first converting **1** to the tertiary α-aminonitrile **2**, a type of compound which undergoes a facile displacement of the cyano group by the alkyl moiety of Grignard reagents.[5-9] The structure of **3** follows from elemental analysis and the presence of characteristic vinyl group absorptions in its infrared and nmr spectra.

Treatment of **3** methiodide with ethylmagnesium bromide gave **4a** in 92% yield as a colorless oil which contained only one olefinic hydrogen peak in its nmr and gave the appropriate analytical values. Further proof for the assigned structure was obtained by the oxidative cleavage of the carbon–carbon double bond of **4a** to give the known[3] amino ketone **5** and *n*-butyraldehyde, isolated as their perchlorate and 2,4-DNP derivatives, respectively.

In an analogous reaction, phenylmagnesium bromide was added to the vinyl group of **3** methiodide to give the ring-opened product **4b** in 96% yield. The double bond was assigned to the nonconjugated position on the basis of the nmr spectrum of **4b**, which shows one olefinic proton coupled to two benzylic protons.

The cleavage of quaternary ammonium salts with Grignard reagents is a well-known reaction[10,11] which usually proceeds by normal displacement of a group attached to nitrogen. The occurrence of abnormal displacement had been considered previously for the metal salt catalyzed reaction of Grignard reagents with allyltrimethylammonium bromide,[11] but no unambiguous examples were available. The possibility that the uncatalyzed abnormal displacements described above are restricted to those heterocyclic ring systems examined in this paper has been discounted by other studies in our laboratory.[12]

On the assumption that the attacking species is a nucleophile (eq 2) rather than a radical,[11] a second ring-opening reagent, $LiAlH_4$, was investigated. The preparation of nine- and ten-membered azacycles by the reaction of quaternary ammonium salts with $LiAlH_4$

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[1] Taken from the Ph.D. Dissertation of R. F. Francis, Texas Christian University, 1967.

[2] M. G. Reinecke, L. R. Kray, and R. F. Francis, *Tetrahedron Lett.*, 3549 (1965).

[3] M. G. Reinecke, L. R. Kray, and R. F. Francis, *J. Org. Chem.*, **37**, 3489 (1972).

[4] H. Emde and H. Kull, *Arch. Pharm.* (*Weinheim*), **272**, 469 (1934).

[5] N. J. Leonard and A. S. Hay, *J. Amer. Chem. Soc.*, **78**, 1984 (1956).

[6] H. Zinnes, R. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 105 (1965).

[7] P. Van Daele, *Meded. Vlaam. Chem. Ver.*, **23**, 163 (1961).

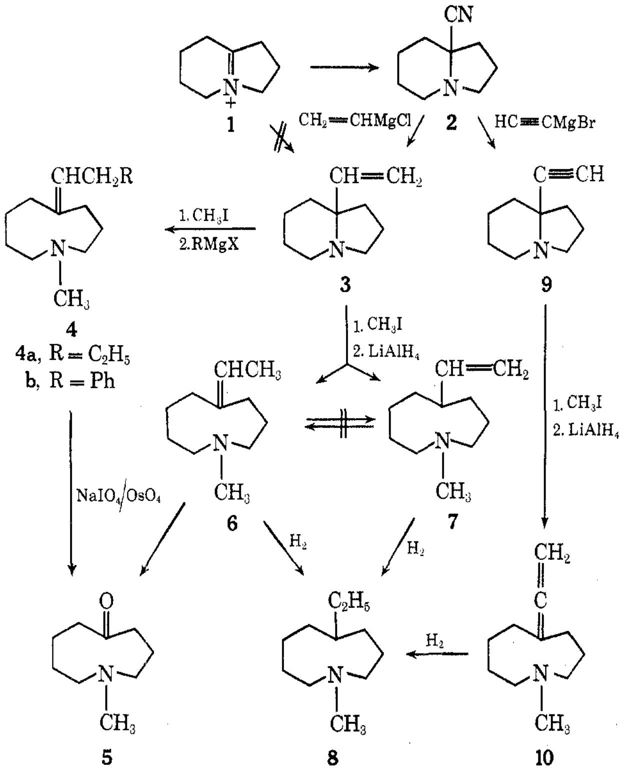
[8] B. Hermans, P. van Daele, C. van de Westeringh, C. Van der Eycken, J. Boey, and P. Janssen, *J. Med. Chem.*, **8**, 851 (1965).

[9] J. Yoshimura, Y. Ohgo, and T. Sato, *Bull. Chem. Soc. Jap.*, **38**, 1809 (1965).

[10] J. Brewster and E. Eliel, *Org. React.*, **7**, 99 (1953).

[11] M. Kharasch, G. Williams and W. Nudenberg, *J. Org. Chem.*, **20**, 937 (1955).

[12] M. G. Reinecke, M. Ready, and W. Bennett, unpublished results.



is known,[13,14] but requires the presence of an appropriately placed active hydrogen atom in the molecule, since the mechanism probably involves an elimination–addition process.[14] Even when this prerequisite is filled, however, the reaction is not general.[14b,15]

Reaction of **3**-methiodide with $LiAlH_4$ leads to two products, **6** and **7**, the former predominating in THF and the latter predominating in ether. The assigned structures are based on analytical and spectral data; the nmr spectrum of **6** shows one olefinic hydrogen peak coupled to an allylic methyl group, while both the nmr and infrared spectra of **7** display characteristic vinyl group absorptions. Further proof was obtained by the oxidation of **6** to the amino ketone **5** and by catalytic reduction of **6** and **7** to the same saturated amine **8**.

The formation of two products (**6** and **7**) in the reaction of **3** methiodide with $LiAlH_4$ may be due to competition between normal (eq 3) and abnormal (eq 2) displacement, respectively. Alternatively, this may represent complete or partial equilibration of **6** and **7** under the reaction conditions. This latter possibility was shown to be incorrect by resubjecting pure **6** or a 30:70 mixture of **6** and **7** to the reaction conditions and recovering them unchanged. The marked solvent effect on the product distribution (Table I) is probably due to a complex interplay of solubility and concentration effects which was not unraveled in this study.

As a second substrate for the ring-opening sequence in eq 2, 9-ethynylindolizidine (**9**) was prepared in 96% yield from the reaction of ethynylmagnesium bromide and the aminonitrile **2**. Similar replacements of the cyano group of aminonitriles by an ethynyl group are known.[16] The structure of **9** follows from its analysis and infrared spectrum.

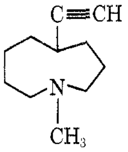
TABLE I

REACTIONS OF **3** MeI WITH $LiAlH_4$

Reactants				Products		
	mmol			Mole ratios		wt, %
Solvent (ml)	**3** MeI	$LiAlH_4$	Time, hr	**6** :	**7**	**3** MeI
THF (75)	20	10	12	100	0	46
THF (100)	10	5	72	97	3	24
THF (150)	10	50	48	85	15	0
THF (25)	20	60	72	67	33	0
THF (25)	10	50	48	70	30	0
Et_2O (75)	20	50	12	16	84	82
Et_2O (50)	15	50	72	17	83	73

Treatment of **9** methiodide with $LiAlH_4$ in either THF or ether gave a single product in 96% yield which was assigned the allene structure **10** on the basis of its analysis and the presence of characteristic allene absorptions in its infrared and nmr spectra.[17] Substantiating evidence for structure **10** was obtained from its catalytic reduction to the same saturated amine **8** obtained from the alkenes **6** and **7**.

Since only one product (**10**) is obtained from the ring opening of **9** methiodide, it is not possible to say if it is formed directly by an abnormal displacement or indirectly by rearrangement of the normal displacement product **11**. It is not unreasonable to assume that the same factors which stabilize endocyclic *vs.* exocyclic olefins in medium-ring compounds[18] would also favor the allene **10** over the acetylene **11** in an equilibration. On the other hand, the not unrelated $LiAlH_4$ dehalogenation of some propargyl halides also gives only allenes to the exclusion of acetylenes and has been formulated as an abnormal displacement reaction.[19]



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A third reaction utilized for ring opening in this study is the reductive cleavage of quaternary ammonium salts by means of alkali metals. This 85-year-old reaction[20] was developed by Emde[4] into a useful alkaloid degradation which can lead to medium-ring compounds according to eq 3. Recent applications of this reaction to various β-carboline[14a,15,21] and isoquinoline[15a,22] derivatives have culminated[13b,23] in the synthesis of several medium-ring containing alkaloids. The only examples of medium rings prepared by this method which do not contain other fused rings (and hence are better suited for the study of transannular

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[13] (a) L. J. Dolby and S. Sakai, *J. Amer. Chem. Soc.*, **86**, 1890 (1964); (b) J. Kutney, N. Abdurahman, C. Gletsos, P. LeQuesne, E. Piers, and I. Vlattas, *ibid.*, **92**, 1727 (1970).

[14] (a) L. J. Dolby and D. Booth, *J. Org. Chem.*, **30**, 1550 (1965); (b) P. Aeberli and W. Houlihan, *ibid.*, **34**, 1720 (1969).

[15] (a) D. Herbst, R. Rees, G. Hughes, and H. Smith, *J. Med. Chem.*, **9**, 864 (1966); (b) L. J. Dolby and G. Gribble, *J. Org. Chem.*, **32**, 1391 (1967); (c) A. Kubo, *Yakugaku Zasshi*, **90**, 224 (1970).

[16] D. Lednicer and J. Babcock, *J. Org. Chem.*, **27**, 2541 (1962).

[17] E. Snyder and J. D. Roberts, *J. Amer. Chem. Soc.*, **84**, 1582 (1962).

[18] A. Cope, D. Ambros, E. Ciganek, C. Howell, and Z. Jacura, *ibid.*, **82**, 1750 (1960).

[19] T. L. Jacobs and R. Wilcox, *ibid.*, **86**, 2240 (1964).

[20] C. M. Thompson and J. T. Curdall, *J. Chem. Soc.*, **53**, 781 (1888).

[21] E. Wenkert, S. Garratt, and K. G. Dave, *Can. J. Chem.*, **42**, 489 (1964).

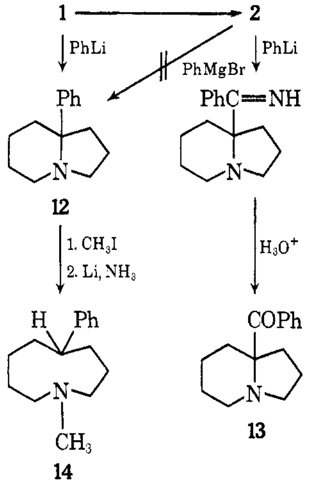
[22] M. Winn and H. E. Zaugg, *J. Org. Chem.*, **33**, 3779 (1968).

[23] J. P. Kutney, W. J. Cretney, P. LeQuesne, B. McKague, and E. Piers, *J. Amer. Chem. Soc.*, **92**, 1712 (1970); J. Harley-Mason, Atta-Ur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1966).

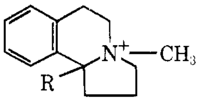
interactions)[24] are those of Arata, *et al.*,[25] and nicely complement those described in this paper.

Selective cleavage of the central carbon–nitrogen bond by the Emde reaction, as in eq 3, requires that the group X be able to preferentially stabilize an intermediate carbanion or radical[26] at the bridgehead carbon atom. At the time this study was initiated[1] only aromatic rings (phenyl[4,15a,22] or indolyl[4,14a,15,21]) had been used for this purpose, although subsequently[25] carboxamido and cyano groups also were utilized. For this reason ring opening was initially investigated with 9-phenylindolizidine (**12**).

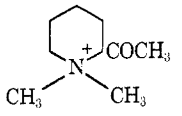
Since phenyl Grignard reagents do not react with ternary iminium salts,[5,6] the preparation of **12** *via* the α-aminonitrile **2** was attempted. Although this procedure succeeded for the preparation (*vide supra*) of the vinyl and ethynyl analogs (**3** and **9**) it failed for **12**. Phenyllithium did react with **2** but by addition to, rather than displacement of, the nitrile function to give the benzoylamine **13** after hydrolysis. Similar additions by lithium reagents to tertiary α-aminonitriles are known.[8,9] Treatment of the iminium salt **1** directly with phenyllithium finally gave the desired precursor **12** in 47% yield.



Emde cleavage of **12** MeI with lithium in liquid ammonia[15a] proceeded in 80% yield to give the azacyclononane (**14**) which was identified from its spectral and analytical properties. Products from the cleavage of the peripheral carbon–nitrogen bonds were not detected. This contrasts with the behavior of other indolizidines,[22] which suggested that two activating benzene rings as in **15** were required for completely selective fission of the central carbon–nitrogen bond. The fact that **12** MeI but not **16**[22] cleaves exclusively to an azacyclononane indicates that a single phenyl group can elicit this selectivity if it is at a bridgehead but not if it is a fused position.



15, R = Ph
16, R = CH_3



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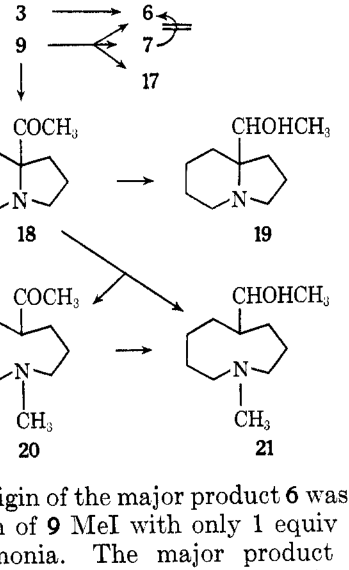
Reductive cleavage of allyl groups under Emde conditions from both oxygen[27] and nitrogen[28] is known. In the present study the reaction of 9-vinylindolizidine methiodide (**3** MeI) with either sodium or lithium in liquid ammonia[15a] gave a single product in nearly quantitative yield which proved to be identical to *N*-methyl-5-ethylideneazacyclononane (**6**). The possibility that **7** might be the initial cleavage product which then rearranged to the probably more stable[18] **6** was eliminated by subjecting a sample of **7** to the reaction conditions and recovering it unchanged. Rearrangements accompanying the reductive cleavage of allyl groups from oxygen are often observed and have been rationalized as arising from kinetically controlled protonation of an intermediate, resonance-stabilized anion.[29] A similar mechanism could be operative for the reaction **3** MeI → **6**, but additional factors may be involved[30] as well. From a synthetic point of view it is clear that the Emde cleavage is preferred over the $LiAlH_4$ ring opening (*vide supra*) of **3** MeI for the preparation of **6**.

The reverse is true for the ring opening of the methiodide of the ethynylamine **9** which gives only the allene **10** in high yield with $LiAlH_4$ (*vide supra*) but which gives a variety of products under Emde conditions. With 2 or 3 equiv of lithium, three products are obtained in a ratio of ~8:1:1 (vpc). The major product was identified as the ethylidene compound **6** and one of the minor components was identified as the vinyl isomer **7**. The remaining compound, **17**, has absorptions in the infrared at 3110, 1702, and 1600 cm^{-1} which are not present in the infrared spectrum of the crude reaction product, and it is therefore probably an artifact. This view is supported by the fact that these infrared peaks appear at the expense of ones at 3300 and 2100 cm^{-1} after the crude reaction product is passed through the vpc.



A possible origin of the major product **6** was suggested by the reaction of **9** MeI with only 1 equiv of lithium in liquid ammonia. The major product was once again **6** but substantial quantities of the allene **10**

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[24] A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev. Chem. Soc.*, **20**, 119 (1966).

[25] (a) Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.*, **17**, 1363 (1969); (b) Y. Arata, T. Kobayashi, M. Nakamura, and T. Yasuda, *Yakugaku Zasshi*, **90**, 1424 (1970).

[26] H. Smith, "Organic Reactions in Liquid Ammonia," Interscience, New York, N. Y., 1963, pp 151–153.

[27] Ref 26, pp 158–166.

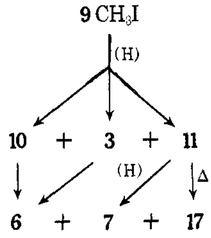
[28] S. Bhattacharji, A. J. Birch, A. Brack, A. Hoffmann, H. Kobel, D. C. C. Smith, H. Smith, and J. Winter, *J. Chem. Soc.*, 421 (1962).

[29] Ref 26, pp 158–159.

[30] E. Grovenstein, Jr., and R. W. Stevenson, *J. Amer. Chem. Soc.*, **81**, 4850 (1959).

were present according to the nmr and ir spectra of the reaction mixture. Allene **10** may be the source of **6**, since upon reaction with 2 equiv of lithium in liquid ammonia it gave only **6** in 91% yield. Other partial reductions of allenes with metal–ammonia systems have been observed,[31] but, since the partial reduction of acetylenes to olefins with lithium in liquid ammonia is also a well known process,[32] the possibility that **6** arises from **9** MeI *via* **3** MeI cannot be excluded.

Emde cleavage of **9** MeI must proceed by still another path, however, since neither **10** nor **3** MeI give any of the vinyl amine **7** on treatment with lithium in liquid ammonia, nor does **10** decompose in the vpc to give **17**. A reasonable source of **7** and **17** would be the acetylene **11** formed by cleavage of **9** MeI without rearrangement. This compound could account for the infrared absorptions in the crude reaction mixture at 3300 and 2100 cm^{-1} and would be likely[32] to be reduced to **7** under the reaction conditions. The possibility that **9** was formed by demethylation during the Emde cleavage and then decomposed to **17** in the vpc was eliminated by its complete stability to this process. The following scheme therefore summarizes the probable course of the Emde cleavage of **9** MeI.



As a final example of ring opening by reductive cleavage (eq 3), the reaction of a compound with a carbonyl activating group was investigated. The desired substrate, 9-acetylindolizidine (**18**), was prepared in 82% yield by the mercuric salt catalyzed hydration of the ethynylamine **9**. More than an equivalent of $HgSO_4$ was actually required, apparently because the basic nitrogen atom complexes with the mercuric ions.[33] The structure of **18** was deduced from its spectral and analytical properties as well as from those of the corresponding alcohol **19** prepared by $LiAlH_4$ reduction in 90% yield.

The Emde cleavage of **18** MeI with either lithium or sodium in liquid ammonia gave two products. Spectral and analytical values indicated that the major product was the ring-opened ketone **20**, and that the minor product was an alcohol different from **19**, probably **21**. Reduction of **20** with $LiAlH_4$ gave this same alcohol in 94% yield, thus substantiating its structure as **21**. That the alcohol **21** probably originates from overreduction of **20** during the Emde fission was shown by the formation of only **21** when the original product mixture was resubjected to the reaction conditions.

A recent study of the Emde cleavage of α-amino ketones[34] also reveals that the intervening carbon–nitrogen bond is selectively ruptured and the ketone is reduced to an alcohol. Interestingly the carbonyl group must be exocyclic to the nitrogen-containing ring as in **22** or **18**, otherwise simple demethylation occurs. This rather surprising observation is reminiscent of the situation with the phenyl-substituted compounds **12**, **15**, and **16** (*vide supra*) and suggests that the Emde cleavage of activated quaternary ammonium salts may have specific stereochemical requirements.

Experimental Section

Melting points and boiling points are corrected. Analyses were performed by M-H-W Laboratories, Garden City, Mich. Nmr spectra were determined on a Varian A-60 instrument as 30–40% solutions in CCl_4 for liquids and 10–20% solutions in $DCCl_3$ for solids with TMS as an internal standard. Ir spectra were recorded on Beckman IR-10 or Perkin-Elmer 237 spectrophotometers as thin films or KBr disks. Vpc analyses were obtained on an Aerograph A-700 chromatograph with a 20 ft × $^5/_8$ in. column of 30% SE-30 on Chromosorb W unless otherwise noted.

9-Vinylindolizidine (3).—A mixture of 3 g (20 mmol) of 9-cyanoindolizidine (**2**)[5] in 50 ml of THF and 44 ml of 0.0091 *N* vinylmagnesium chloride[35] in THF was heated to reflux for 3 hr with the usual precautions against air and water. The excess Grignard reagent was decomposed with wet ether and the mixture was continuously extracted with ether for 48 hr. The ether extracts were dried (K_2CO_3) and concentrated on a rotary evaporator to give 2.9 g (94%) of **3** as a light-yellow oil which produced only one peak on vpc analysis and could be collected as a colorless oil: bp 66–67° (3.9 mm); ir 3070, 1655, 995, 908 cm^{-1}; nmr τ 3.47 (m, 3, vinyl H). A crystalline methiodide was prepared: mp 265–265.5°; nmr τ 3.9 (m, 3, vinyl H), 6.22 (m, 4, CH_2N), 6.8 (s, 3, NCH_3).

Anal. Calcd for $C_{11}H_{20}NI$ (**3** MeI): C, 45.07; H, 6.87; N, 4.78. Found: C, 44.89; H, 7.05; N, 4.49.

***N*-Methyl-5-butylidene-1-azacyclononane (4a).**—A mixture of 0.1 mol of ethylmagnesium bromide in 150 ml of THF and 5.86 g (0.02 mol) of **3** MeI was heated to reflux for 12 hr with the usual precautions against air and moisture. Excess Grignard reagent was destroyed with 20 g of ice and the resulting mixture was continuously extracted with ether for 24 hr. The ether extracts were dried (K_2CO_3) and the solvent was removed by distillation and at reduced pressure with a rotary evaporator to leave 3.31 g (92%) of **4a** as a colorless oil. A vpc collected sample (no other peaks except traces of solvent) had bp 62–63° (0.55 mm); ir 3017 and 1665 cm^{-1}; nmr τ 4.76 (t, 1, J = 6.2 Hz, vinyl H), 7.77 (s, 3, NCH_3).

A crystalline methiodide was prepared: mp 159–160°; nmr τ 4.52 (t, 1, J = 6.2 Hz, vinyl H), 6.57 (s, 6, NCH_3).

Anal. Calcd for $C_{14}H_{28}NI$ (**4a** MeI): C, 49.85; H, 8.37; N, 4.15. Found C, 50.01; H, 8.35; N, 4.14.

Oxidation of 4a.—A mixture of 2 g of **4a**, 50 mg of OsO_4, 35 ml of dioxane, and 12 ml of H_2O was stirred at 25° for 15 min. To the resulting dark brown mixture was added 4.4 g of $NaIO_4$ in small portions over a period of 40 min. After an additional 3 hr, the solid present was dissolved with 6 *M* HCl and the solution was extracted with four 50-ml portions of ether. The combined ether extracts were dried (Na_2SO_4), shown to give only one peak in the vpc beside solvent, and distilled through a 4-cm Vigreux column. The fraction of bp 70–100°, was treated with 2,4-dinitrophenylhydrazine to give 250 mg (10%) of butyraldehyde DNP, mp 122.5–123.5° (lit.[36] 122–122.5°).

The acid solution was basified (40% NaOH) and extracted with four 50-ml protions of ether. The extracts were dried (K_2CO_3), concentrated by distillation, and shown to contain only one product besides solvent by vpc analysis. The residue was dissolved in 1:1 ether–absolute EtOH and 1:1 absolute EtOH–70% $HClO_4$ added until no more solid formed. The 620 mg (24%) of *N*-methyl-9-hydroxyindolizidinium perchlorate (**5** $HClO_4$) thus formed was identical in melting point, mixture melting point, and ir spectra with an authentic sample.[3]

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[31] D. Devaprabhakara and P. D. Gardner, *J. Amer. Chem. Soc.*, **85**, 648 (1963).

[32] Ref 26, pp 213–216.

[33] J. W. Smith, in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, pp 198–200.

[34] E. A. Mistryukov and G. Katvalyan, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2800 (1969); *Chem. Abstr.*, **72**, 78821z (1970).

[35] H. Ramsden, J. Leebrick, S. Rosenberg, E. Miller, J. Walburn, A. Blaint, and R. Cserr, *J. Org. Chem.*, **22**, 1602 (1957).

[36] M. S. Newman and W. Edwards, *J. Amer. Chem. Soc.*, **76**, 1840 (1954).

***N*-Methyl-5-(2′-phenylethylidene)-1-azacyclononane (4b).**—A mixture of 0.1 mol of PhMgBr in 100 ml of THF and 5.86 g (0.02 mol) of **3** MeI was heated to reflux for 48 hr with the exclusion of air and moisture. The mixture was poured on 20 g of ice, acidified with 3 *M* HCl, and extracted with 100 ml of ether. The ether extract was washed with four 50-ml portions of 3 *M* HCl, and the combined acid solutions were basified with 50% NaOH and continuously extracted with ether for 48 hr. The resulting ether extract was dried (K_2CO_3) and concentrated by distillation and rotary evaporation to leave 3.49 g (96%) of **4b** as a vpc pure colorless oil. A vpc collected sample had bp 104–105° (0.13 mm); ir 3090, 3060, 3040, 1601, 1488, 725, 685 cm^{-1}; nmr τ 2.61 (s, 5, ArH), 4.35 (t, 1, J = 7.5 Hz, vinyl H), 6.52 (d, 2, J = 7.5 Hz, $ArCH_2$), 7.7 (s, 3, NCH_3). A crystalline methiodide, mp 165–166°, was obtained.

Anal. Calcd for $C_{18}H_{28}NI$ (**4b** MeI): C, 56.11; H, 7.32; N, 3.63. Found: C, 56.32; H, 7.64; N, 3.77.

Reaction of 3 MeI with $LiAlH_4$.—A mixture of **3** MeI and $LiAlH_4$ in either THF or ether was heated to reflux. The quantities used are found in Table I. At the end of the specified reaction times the excess $LiAlH_4$ was destroyed with wet ether, 100 ml of additional ether was added, and the solids were removed by filtration and washed with three 10-ml portions of ether.

The precipitate was titurated with three 30-ml portions of boiling EtOH. Addition of ether to the EtOH precipitated unreacted starting material (**3** MeI) identified by melting point and ir data.

The filtrate was dried (K_2CO_3), and the solvent was removed by distillation and a rotary evaporator to leave a colorless oil (85–95% yield) which was analyzed by vpc (see Table I for product analyses). Pure samples of the two products were obtained by preparative vpc.

N-Methyl-5-ethylidene-1-azacyclononane (**6**) had bp 39–41° (0.26 mm); ir 3020, 1658 cm^{-1}; nmr τ 4.68 (q, 1, J = 6.5 Hz, vinyl H), 7.76 (s, 3, NCH_3), 8.4 (d, 3, J = 6.5 Hz, CCH_3). A crystalline methiodide was formed, mp 177–177.5°.

Anal. Calcd for $C_{12}H_{24}NI$ (**6** MeI): C, 46.64; H, 7.77; N, 4.53. Found: C, 46.48; H, 7.94; N, 4.59.

N-Methyl-5-vinyl-1-azacyclononane (**7**) had bp 42–43° (0.6 mm); ir 3070, 1635, 986, 900 cm^{-1}; nmr τ 4.36 (m, 3, vinyl H), 7.63 (s, 3, NCH_3). A methiodide had mp 173.5–174°.

Anal. Calcd for $C_{12}H_{24}NI$ (**7** MeI): C, 46.64; H, 7.77; N, 4.53. Found: C, 46.89; H, 7.73; N, 4.62.

***N*-Methyl-5-ethyl-1-azacyclononane (8).**—A mixture of 1.4 g (9 mmol) of **6**, 50 ml of glacial HOAc, and 0.5 g of PtO_2 was hydrogenated in a Parr apparatus until there was no further pressure drop (24 hr). The solution was decanted from the catalyst, which was washed with three 10-ml portions of glacial HOAc. The acid solution was basified (40% NaOH), saturated with K_2CO_3, and extracted with three 50-ml portions of ether. The extracts were dried (K_2CO_3) and concentrated by distillation and rotary evaporation to afford 1.5 g (89%) of **8** as a colorless oil which gave only one peak on vpc analysis and did not display olefinic protons in either its nmr or ir spectra. A methiodide was prepared: mp 195.5–196°; nmr τ 6.58 (s, 6, NCH_3).

Anal. Calcd for $C_{12}H_{26}NI$ (**8** MeI): C, 46.31; H, 8.42; N, 4.49. Found: C, 46.19; H, 8.58; N, 4.49.

Reduction of a mixture of 67% **6** and 33% **7**, as described above, also produced only **8** (90% yield), identified by its vpc retention time, infrared, and nmr spectra.

Oxidation of 6.—Using the procedure described above for the oxidation of **4a**, a sample of **6** was treated with OsO_4–$NaIO_4$ to give **5** $HClO_4$ in 32% yield, identified by comparison of its melting point, mixture melting point, and infrared and nmr spectra with those of an authentic sample.[3]

Attempted Interconversion of 6 and 7.—A 30:70 mixture of **6**:**7** was treated with $LiAlH_4$ in THF under the conditions which produce a 67:33 mixture of **6**:**7** (Table I). Upon work-up, a 93% recovery of **6** and **7** (identified from the ir spectra of vpc collected samples) was obtained with the mole ratios unchanged.

9-Ethynylindolizidine (9).—To a solution of 40 mmol of ethynylmagnesium bromide[37] in 70 ml of THF was added 3 g (20 mmol) of **2** in 5 ml of THF, and the mixture was heated to reflux for 6 hr with stirring and the usual precautions against air and moisture. The mixture was treated with 20 g of ice and extracted with three 100-ml portions of ether, and the ether extracts were dried (K_2CO_3) and concentrated by distillation and rotary evaporation to leave 2.87 g (96%) of **9** as a vpc pure liquid. A vpc collected sample had bp 42–44° (2.7 mm); ir 3300 and 2080 cm^{-1}; nmr τ 7.6 (s, 1, ethynyl H). The methiodide of **9** had mp 250–251.5° dec.

Anal. Calcd for $C_{11}H_{18}NI$ (**9** MeI): C, 45.39; H, 6.18; N, 4.81. Found: C, 45.72; H, 6.43; N, 4.98.

***N*-Methyl-5-allenyl-1-azacyclononane (10).**—A mixture of 5.82 g (20 mmol) of **9** MeI, 30 mmol of $LiAlH_4$, and 150 ml of THF was heated under reflux for 48 hr. Sufficient wet ether was added to decompose the excess $LiAlH_4$, the solids were removed by filtration, and the filtrate was dried (K_2CO_3) and concentrated by distillation and rotary evaporation to leave 1.59 g (95%) of **10** as a vpc pure colorless oil. A sample of **10** collected by preparative vpc had bp 55–56° (0.1 mm); ir 3033 and 1950 cm^{-1}; nmr τ 5.33 (q, 2, J = 2.8 Hz, allenyl H),[17] 7.75 (s, 3, NCH_3). The methiodide had mp 229–230°.

Anal. Calcd for $C_{12}H_{22}NI$ (**10** MeI): C, 46.91; H, 7.22; N, 4.56. Found: C, 46.82; H, 7.25; N, 4.57.

An identical reduction using ether instead of THF led to **10** in 96% yield.

Reduction of 10.—Using the same procedure described above for the reduction of **6** to **8**, a sample of **10** was converted to **8** (vpc, ir, nmr) in 89% yield.

9-Phenylindolizidine (12).—A mixture of 0.2 mol of PhLi (prepared from 2.8 g of Li wire and 31.4 g of PhBr)[38] in 250 ml of ether, 2.24 g (10 mmol) of the iminium perchlorate **1**,[39] and 100 ml of dry benzene was heated to reflux for 72 hr. The cooled reaction mixture was decomposed with water and acidified with 3 *M* HCl, and the organic portion was extracted with four 50-ml portions of 3 *M* HCl. The combined acid extracts were basified with 40% NaOH and extracted with four 50-ml portions of ether, and the ether extracts were dried (K_2CO_3) and evaporated to leave 1.8 g of yellow oil which darkened on standing. Vpc analysis indicated that the oil consisted of a 13:87 mixture of Δ^8-dehydroindolizidine (identified by comparison of its ir spectrum with that of an authentic sample)[39,40] and **21** (47% yield) which was collected by preparative vpc from a 4 ft × 0.25 in. column as a viscous yellow oil: bp 83–84° (0.25 mm); ir 3060, 3020, 1600, 760, 700 cm^{-1}; nmr τ 2.66 (m, 5, ArH), 7.52 (m, 4, CH_2N), 8.53 (m, 10). A crystalline methiodide, mp 184–185°, was formed.

Anal. Calcd for $C_{15}H_{22}NI$ (**12** MeI): C, 52.49; H, 6.46; N, 4.08. Found: C, 52.43; H, 6.84; N, 4.10.

9-Benzoylindolizidine (13).—The reaction and work-up described above, but utilizing 0.4 mol of PhLi and 3 g of 9-cyanoindolizidine (**2**)[6] instead of **1**, gave 4.2 g (92%) of **13** as a vpc pure, viscous, yellow oil. A sample collected by preparative vpc had: bp 112–113° (0.3 mm); ir 3060, 1675, 775, 705 cm^{-1}; nmr τ 1.64 (m, 2, *o*-ArH), 2.66 (m, 3, ArH). A methiodide, mp 164–165°, was obtained.

Anal. Calcd for $C_{16}H_{22}NOI$ (**13** MeI): C, 51.76; H, 5.97; N, 3.77. Found: C, 51.79; H, 6.12; N, 3.76.

When the above reaction was repeated without the use of acid in the work-up (decomposition of PhLi with water, ether extraction, drying, evaporation), a viscous yellow oil was obtained which had infrared peaks at 3174 (NH) and 1611 cm^{-1} (C=N) and which, on dissolution in 3 *M* HCl, yielded only **13**.

9-Acetylindolizidine (18).—To a stirred mixture of 1.27 ml of concentrated H_2SO_4, 40 g of 60% HOAc, and 5.44 g (18 mmol) of $HgSO_4$ at 80° was added a solution of 2.17 g (15 mmol) of 9-ethynylindolizidine (**9**) in 10 ml of 60% HOAc. After the mixture had been stirred at 80° for 4 hr, it was cooled with ice, basified with 40% NaOH, and extracted with three 50-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated by distillation to give 2 g (82%) of vpc pure **18** as a light yellow oil: bp 69–70° (1.4 mm); ir 1707 cm^{-1}; nmr τ 7.06 (m, 4, CH_2N), 7.92 (s, 3, CH_3CO). A methiodide was prepared: mp 238–239°; nmr τ 5.9 (m, 4, CH_2N), 6.60 (s, 3, NMe), 7.56 (s, 3, CH_3CO).

Anal. Calcd for $C_{11}H_{20}NOI$ (**18** MeI): C, 42.74; H, 6.52; N, 4.53. Found: C, 42.65; H, 6.72; N, 4.56.

9-(1′-Hydroxyethyl)indolizidine (19).—To a solution of 1.6 g (10 mmol) of **18** in 30 ml of ether was slowly added a solution of 20 mmol of $LiAlH_4$ in 40 ml of ether and the mixture was heated to reflux overnight with the usual precautions against air and

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[37] E. R. H. Jones, L. Skattebøl, and M. C. Whiting, *J. Chem. Soc.*, 4765 (1956).

[38] L. A. Walter, *Org. Syn.*, **23**, 83 (1943).

[39] N. J. Leonard, W. J. Middleton, P. D. Thomas, and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956).

[40] M. G. Reinecke and L. R. Kray, *ibid.*, **31**, 4215 (1966).

moisture. The cooled reaction mixture was treated with wet ether and filtered, and the filtrate was dried (K_2CO_3) and evaporated to give 1.52 g (90%) of **19** as a colorless oil: bp 68–70° (0.62 mm); ir 3390 cm^{-1}; nmr τ 6.14 (m, 2, CHOH), 7.16 (m, 4, CH_2N), 9.18 (d, 3, J = 7 Hz, CH_3). The crystalline methiodide melted at 263–264° dec.

Anal. Calcd for $C_{11}H_{22}NOI$ (**19** MeI): C, 42.45; H, 7.12; N, 4.49. Found: C, 42.51; H, 7.31; N, 4.43.

General Procedure for Metal–Ammonia Emde Cleavage.—To a 1000-ml three-necked Morton flask equipped with a gas inlet tube, a mechanical stirrer, a cold-finger condenser containing Dry Ice–acetone, and a $CaCl_2$ tube at the exit to the atmosphere was added 300 ml of liquid NH_3, the compound to be reduced, and an equivalent amount of either ethanol (A) or 1-methoxy-2-propanol (B).[15a] The mixture was rapidly stirred as the Li or Na was added in small pieces to give a blue color which sometimes was discharged immediately and sometimes remained until NH_4Cl was added after 10–15 min. Work-up consisted of adding 100 ml of ether, allowing the NH_3 to evaporate, and drying (K_2CO_3) and evaporating the ether. Any ether-insoluble residue in the reaction flask was taken up in hot ethanol to recover unreacted starting material. Reactant and product compositions are listed in Table II. Identification of **6** and **7** was made by comparison with authentic samples and **14**, **20**, and **21** from the analytical and spectral data given below.

5-Phenyl-*N*-methylazacyclononane (**14**) had bp 118–119° (1.8 mm); ir 3060, 3020, 1600, 745, 695 cm^{-1}; nmr τ 2.9 (s, 5, ArH), 7.67 (s, 3, NMe). The crystalline methiodide melted at 187.5–188°.

Anal. Calcd for $C_{16}H_{26}NI$ (**14** MeI): C, 53.49; H, 7.29; N, 3.89. Found: C, 53.55; H, 7.33; N, 3.90.

5-Acetyl-*N*-methylazacyclononane (**20**) had bp 68–69° (0.6 mm); ir 1705 cm^{-1}; nmr τ 7.6 (m, 4, CH_2N), 7.72 (s, 3, NMe), 7.98 (s, 3, CH_3CO). A methiodide was prepared, mp 172.5–173.5°.

Anal. Calcd for $C_{12}H_{24}NOI$ (**20** MeI): C, 44.31; H, 7.44; N, 4.30. Found: C, 44.45; H, 7.61; N, 4.38.

5-(1′-Hydroxyethyl)-*N*-methylazacyclononane (**21**) had bp 79–80° (1.7 mm); ir 3360 cm^{-1}; nmr τ 6.45 (s, 1, OH), 7.67 (m, 4, CH_2N), 7.74 (s, 3, NMe), 8.92 (d, 3, J = 7 Hz, CH_3C). The methiodide had mp 199–200°.

Anal. Calcd for $C_{12}H_{26}NOI$ (**21** MeI): C, 44.05; H, 8.01; N, 4.28. Found: C, 44.17; H, 8.14; N, 4.31.

Reduction of 20.—With the same procedure used to reduce **18** to **19**, 370 mg of **20** was converted to 350 mg (94%) of vpc pure **21** identified by comparison of its ir spectrum with that of a sample prepared as above.

TABLE II

REACTANT AND PRODUCT COMPOSITIONS FOR EMDE CLEAVAGE

Reactant (mmol)	Alcohol	Metal (mmol)	Products (%)
12 MeI (10)	A	Li (20)	**14** (59); **12** MeI (37)
3 MeI (15)	B	Li (30)	**6** (92)
3 MeI (15)	A	Li (30)	**6** (95)
3 MeI (15)	B	Na (30)	**6** (96)
7 (10)	A	Li (20)	**7** (100)
9 MeI (20)	B	Li (40)	**7**, **6**, **17** (6:84:10)[a]
9 MeI (20)	B	Li (60)	**7**, **6**, **17** (12:80:8)[a]
9 MeI (15)	B	Li (15)	**6**, **10**[b]
10 (10)	A	Li (20)	**6**, (91)
18 MeI (10)	A	Li (20)	**20** (68), **21** (28)[c]
18 MeI (10)	A	Na (20)	**20** (78), **21** (17)[c]
20 + **21** (4:1) (10)	A	Li (20)	**21** (94)

[a] In order of increasing retention time; **17** appears to be an artifact formed from probably **11** during vpc treatment at 150°, 200 cm^3/min (see discussion). [b] Spectral analysis of the crude product showed, in addition to absorptions for **6** and **11**, characteristic peaks for **10** at 1950 cm^{-1} in the ir and τ 5.33 (q, J = 2.8 Hz) in the nmr. [c] Separated on a 15 ft × 0.25 in. 15% Carbowax 20M on Chromosorb W column.

Registry No.—**3**, 35201-24-2; **3** MeI, 10478-78-1; **4a**, 35201-26-4; **4a** MeI, 35201-27-5; **4b**, 35201-02-6; **4b** MeI, 35201-03-7; **6**, 35249-63-9; **6** MeI, 35201-04-8; **7**, 35201-05-9; **7** MeI, 35201-06-0; **8** MeI, 35201-07-1; **9**, 35201-08-2; **9** MeI, 35201-09-3; **10**, 35201-10-6; **10** MeI, 35201-11-7; **12**, 35201-12-8; **12** MeI, 35201-13-9; **13**, 35201-14-0; **13** MeI, 35249-64-0; **14**, 35201-15-1; **14** MeI, 35201-16-2; **18**, 35201-17-3; **18** MeI, 35249-65-1; **19**, 35201-18-4; **19** MeI, 35201-19-5; **20**, 35201-20-8; **20** MeI, 35201-21-9; **21**, 35201-22-0; **21** MeI, 35201-23-1.

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2*H*-Cyclopenta[*d*]pyridazines. Acylation with Trifluoroacetic Anhydride[1,2]

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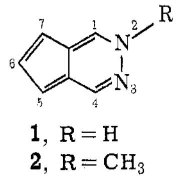
2-Methyl-2*H*-cyclopenta[*d*]pyridazine (**2**) reacts with 1 equiv of trifluoroacetic anhydride in the absence of a catalyst to give the 5- and 7-trifluoroacetyl derivatives (**4**, **5**) in a ratio of *ca.* 1:3. Compounds **4** and **5** react more slowly with the anhydride to form the 5,7-bis(trifluoroacetyl) derivative (**8**). 2-Phenyl-2*H*-cyclopenta[*d*]pyridazine (**3**) also gives the 5,7-disubstituted compound **10**, but the parent molecule **1** gives only the 7-monosubstituted product **9**. Hydrolysis and esterification of **4** and **5** provide the first route to the corresponding acids (**12**, **14**) and esters (**13**, **15**). Methylation of the anion of **9** occurs only at the 2 position to yield **5**. The nmr and electronic spectra of **4** and **5** are described and discussed.

Subsequent to the demonstration[5] that 2*H*-cyclopenta[*d*]pyridazine (**1**) and its 2-methyl (**2**) and 2-phenyl (**3**) derivatives exhibited spectra and protonation characteristics analogous to those of azulene and simple π-excessive heteroanalogs of azulene, attention



1, R = H
2, R = CH_3
3, R = C_6H_5

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