The Peripheral Synthesis of Medium-Ring Nitrogen Heterocycles *via* β-Elimination Reactions[1]

MANFRED G. REINECKE,*[2] LOUIS R. KRAY, AND ROBERT F. FRANCIS

Departments of Chemistry, University of California, Riverside, California 92502, and Texas Christian University, Fort Worth, Texas 76129

Received March 21, 1972

A series of 5-substituted *N*-methylazacyclononanes have been prepared from several $\Delta^{4(9)}$-dehydroindolizidines by (i) nucleophilic addition to the ternary iminium group, (ii) quaternization with methyl iodide, and (iii) selective cleavage of the central carbon–nitrogen bond by β elimination. α-Picolyllithium, benzylmagnesium chloride, allylmagnesium bromide, and the ethyl bromoacetate–zinc reagent were used as nucleophiles, and ring opening was accomplished with sodium amide, sodium ethoxide, *n*-butyllithium, or by a thermal aminodecarboxylation. The structures of the products were proven by nmr and ir and in one case by oxidative cleavage of the carbon–carbon double bond to a nine-membered ring amino ketone **17** which displayed the anticipated transannular reactions and interactions and could be reduced to *N*-methylazacyclononane.

Interest in medium-sized carbocyclic and heterocyclic rings originates from common sources; both undergo transannular reactions[3-6] and both occur in important natural products.[7-9] Unfortunately the ready availability of the former series[10,11] is not paralleled for the latter.

The preparation of medium-ring nitrogen heterocycles by ring expansion,[12] cyclization,[13,14] or peripheral synthesis,[15] while valuable for specific compounds, is limited in scope either by the availability of the starting materials or the reaction conditions. The goal of the research described in this and subsequent papers[16,17] was to develop an efficient, general synthesis of such compounds, particularly those with functional groups transannular to nitrogen.

Peripheral synthesis, in which the medium ring is first constructed on the periphery of a bicyclic system of normal-sized rings and the central bond is then cleaved (**1** → **2**), was selected as the most suitable

1 **2**

method of preparation since it would circumvent undesirable transannular effects and also would permit the unambiguous prior placement of substituents. This concept is based on early structural studies of the berberine alkaloids[18] and was first utilized to synthesize the protopine alkaloids allocryptopine,[19] protopine,[20] and cryptopine.[21] Recognition of the more general utility of this method is due to Leonard[15] and Wharton[22] in the azacyclic and carbocyclic series, respectively, and has led to many recent applications directed at the synthesis of sesquiterpenes,[23] indole alkaloids,[8,24] and medium-ring heterocycles in general.[25] Bicyclic precursors (**1**) with bridged[25a] or fused [25b-f] ring systems containing various functional groups and heteroatoms in various positions have been utilized. Our own method[25b] is based on the biogenetic relationship of the berberine and the protopine alkaloids[26] in that it begins with fused 1-azabicycloalkanes (**3**) and requires selective cleavage of the central carbon–nitrogen bond. Although the details of this cleavage in nature remain obscure,[26,27] the hypothetical sequence,[28] oxidation (**3** → **4**), hydration (**4** → **5**), methylation (**5** → **6**), and elimination (**6** → **7**), serves as a useful model for these synthetic studies.

Fused 1-azabicycloalkanes (**3**) are readily available[29] and their oxidation to iminium salts (**4**) with mercuric acetate is well known.[29-31] The fact that nucleophiles will add to ternary iminium groups[32] and that structures such as **6** and **7** are easily interconvertible[3] provides the remaining analogies for this scheme. The

(1) Taken from the Ph.D. Dissertations of (a) L. R. Kray, University of California, Riverside, 1965, and (b) R. F. Francis, Texas Christian University, 1967.

(2) To whom inquiries should be sent at Texas Christian University.

(3) N. J. Leonard, *Rec. Chem. Progr.*, **17**, 243 (1956).

(4) V. Perlog, *ibid.*, **18**, 247 (1957).

(5) J. Sicher, *Progr. Stereochem.*, **3**, 202 (1962).

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

(7) F. Sorm, *Pure Appl. Chem.*, **2**, 533 (1961).

(8) J. Kutney, E. Piers, and R. Brown, *J. Amer. Chem. Soc.*, **92**, 1700 (1970).

(9) R. Manske, *Alkaloids*, **4**, 147 (1954).

(10) G. Schrauzer, *Advan. Catal. Relat. Subj.*, **18**, 373 (1968).

(11) P. Heimback, P. Jolly, and G. Wilke, *Advan. Organometal. Chem.*, **8**, 29 (1970).

(12) L. Ruzicka, M. Kobelt, O. Häfliger, and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).

(13) N. J. Leonard, R. Fox, and M. Oki, *J. Amer. Chem. Soc.*, **76**, 5708 (1954).

(14) N. J. Leonard, M. Oki, and S. Chiavarelli, *ibid.*, **77**, 6234 (1955).

(15) N. J. Leonard, S. Swann, and J. Figueras, *ibid.*, **74**, 4620 (1952).

(16) M. G. Reinecke and R. Francis, *J. Org. Chem.*, **37**, 3494 (1972).

(17) M. G. Reinecke and R. Daubert, to be submitted.

(18) F. L. Pyman, *J. Chem. Soc.*, **103**, 817 (1913).

(19) R. D. Haworth and W. H. Perkin, Jr., *ibid.*, 445 (1926).

(20) R. D. Haworth, W. H. Perkins, Jr., and T. S. Stevens, *ibid.*, 1764 (1926).

(21) R. D. Haworth and W. H. Perkins, Jr., *ibid.*, 1769 (1926).

(22) P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961).

(23) J. A. Marshall, *Rec. Chem. Progr.*, **30**, 3 (1969).

(24) (a) L. J. Dolby and S. Saki, *J. Amer. Chem. Soc.*, **86**, 1890 (1964); (b) E. Wenkert, S. Garratt, and K. Dave, *Can. J. Chem.*, **42**, 489 (1964); Harley-Mason, Atta-ur-Rahman, and J. Beisler, *Chem. Commun.*, 743 (1966); (d) J. Kutney, W. Cretney, P. LeQuesne, B. McKague, and E. Piers, *J. Amer. Chem. Soc.*, **92**, 1712 (1970).

(25) (a) L. Paquette and L. Wise, *ibid.*, **87**, 1561 (1965); (b) M. G. Reinecke, L. R. Kray, and R. F. Francis, *Tetrahedron Lett.*, 3549 (1965); (c) D. Herbst, R. Rees, G. Hughes, and H. Smith, *J. Med. Chem.*, **9**, 864 (1966); (d) M. Winn and H. Zaugg, *J. Org. Chem.*, **33**, 3779 (1968); (e) P. Aeberli and W. Houlihan, *ibid.*, **34**, 1720 (1969); (f) Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.*, **17**, 1363 (1969).

(26) A. R. Battersby, R. J. Francis, M. Hirst, R. Southgate, and J. Staunton, *Chem. Commun.*, 602 (1967).

(27) (a) R. Manske, *Alkaloids*, **4**, 5 (1954); (b) S. Prasad, A. Wahi, and S. Ghosal, *J. Indian Chem. Soc.*, **46**, 371 (1969); (c) E. Brochmann-Hanssen, A. Leung, K. Hirai, and G. Zanati, *Planta Med.*, **18**, 366 (1970).

(28) H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961, p 347.

(29) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **29**, 1736 (1964); modifications of this method better suited for large-scale preparations are described in the Experimental Section of this paper.

(30) N. J. Leonard, A. Hay, R. Fulmer, and V. Gash, *J. Amer. Chem. Soc.*, **77**, 439 (1955).

(31) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **31**, 4215 (1966).

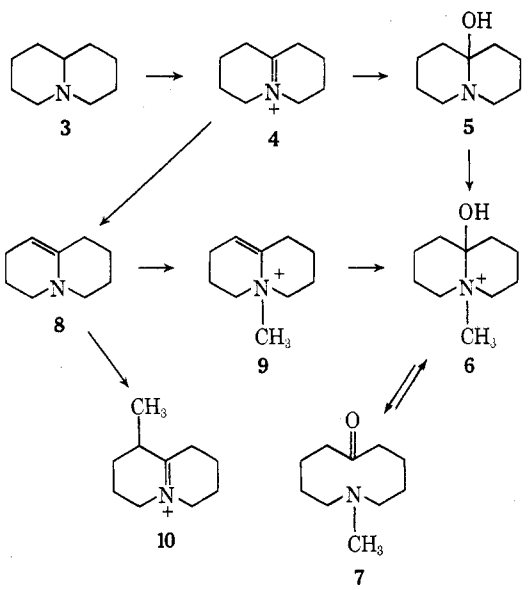
(32) N. J. Leonard and A. Hay, *J. Amer. Chem. Soc.*, **78**, 1984 (1956).

TABLE I
STRUCTURES AND YIELDS IN RING-OPENING SEQUENCE

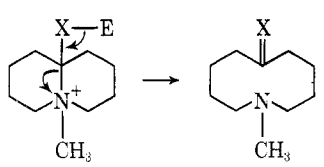
Series	R_1	R_2	X	M	B	% yields 13 → 14	→ 14 MeI	→ 15
a	H	H	α-Pyridyl	Li	$NaNH_2$	64	93	25
b	H	H	Phenyl	MgCl	$NaNH_2$	93	94	100
c	CH_3	H	Phenyl	MgCl	$NaNH_2$	90	89	90
d	H	H	Vinyl	MgBr	$NaNH_2$	97	93	96
e	H	H	COOEt	ZnBr	NaOEt	87	87	84[a]
f	H	CH_3	COOEt	ZnBr	NaOEt	88	89	89[b]
g	H	Et	COOEt	ZnBr	NaOEt	83	85	80

[a] One of the isomers **20** (see Results and Discussion). [b] Mixture of **15f** and **21** (see Results and Discussion).

key to extending the scope of this method is the use of nucleophiles other than the hydroxide ion which, *in vitro*, doesn't add to **4** at all but gives the enamine **8**.[30,31] The preparation of **6** from **8** *via* the quaternary enammonium salt **9** is not generally possible since enamines such as **8** sometimes undergo methylation on carbon[33] (**8** → **10**) as well as on nitrogen (**8** → **9**).[30]

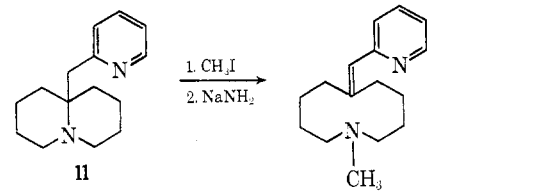


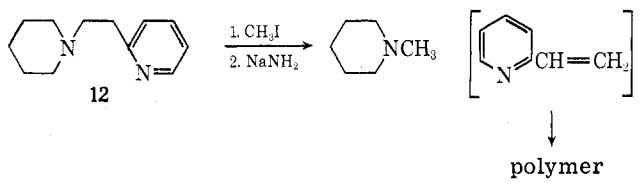
In the present study the nucleophile (XE) was selected so as to facilitate cleavage of the central carbon–nitrogen bond by the β elimination of a group E without its bonding electrons. Subsequent papers[16,17] deal with other ring-opening reactions and hence other nucleophiles are necessary.



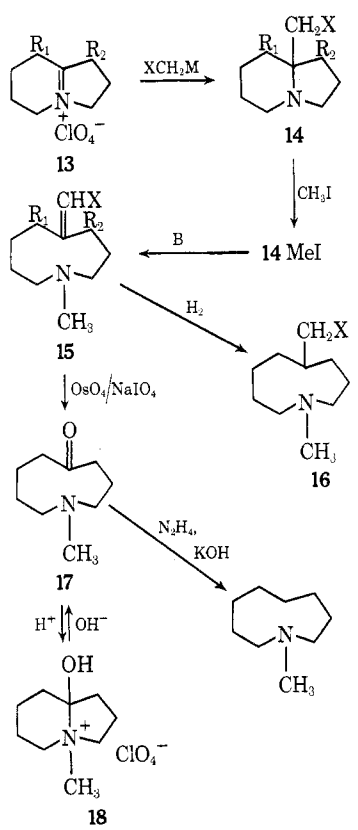
Results and Discussion

Initially, ring opening was attempted on the known[32] methiodide of **11** available from dehydroquinolizidine and α-picolyllithium. Although the sodium amide induced elimination of the model methiodide of **12** proceeded smoothly as shown, the product from **11** was obtained in low yield as an unstable, uncharacterizable mixture. The methiodide of the related indolizidine **14a** (Table I) was prepared from dehydroindolizidine





13a analogously to **11** and also gave a low yield of an unstable product **15a**, but in this case pure crystalline



derivatives were obtained. The nmr spectrum of **15a** displayed only one olefinic proton peak, indicating that the central and not one of the peripheral carbon–nitrogen bonds had been cleaved. This conclusion was substantiated by the clean catalytic reduction of **15a** to a dihydro compound **16a**, whose nmr spectrum contains neither vinyl hydrogen nor *C*-methyl peaks.

(33) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **30**, 3671 (1965).

The double bond in **15a** was assigned to the conjugated position as shown on the basis of infrared (1630 cm^{-1}) and nmr (no vicinal coupling of vinyl-hydrogen singlet) evidence. The fact that the uv spectrum of **15a** was more like that of 2-ethyl, rather than 2-vinylpyridine, while perhaps due to steric effects, suggested that additional evidence might be desirable. Attempted oxidative cleavage of the double bond of **15a** gave no characterizable products, however.

While extension of this ring-opening sequence with α-picolyllithium to the substituted indolizidine **13c** failed at the very first step (68% recovery of **13c**), both **13b** and **13c** reacted readily with benzylmagnesium chloride as the nucleophile. Furthermore, in contrast to the **a** series, stable products were produced throughout the **b** and **c** series in high yield (Table I) and purity. The assigned structures **15b,c** follow from analytical and spectral evidence similar to that cited for the **a** series (Tables II and III). Catalytic reduction of **15b** gave a dihydro compound **16b**, while oxidation of either **15b** or **c** with OsO_4/HIO_4 led to benzoic acid as the only isolable product. With $OsO_4/NaIO_4$ as the oxidizing agent, **15b** gave benzaldehyde (90% yield) and an amino ketone **17** (98% yield) whose spectral properties, in particular[3] the disappearance of the infrared carbonyl absorption at 1686 cm^{-1} on formation of the salt **18**, support the indicated structure. Final proof of the presence of a nine-membered ring in these compounds comes from the Wolff–Kishner reduction of **17** to *N*-methylazacyclononane.

The sequence **13b** → **17** has been repeated[34] as well as extended[35] to the quinolizidine series by Sisti and Lohner with the same excellent yields as obtained in our laboratory (Table I). Substitution of an allyl for a benzyl group (**d** series) also has no adverse effects on the course of reaction. The resulting diene **15d** is a stable colorless liquid displaying diene absorptions in the infrared and peaks for four vinyl hydrogens in the nmr.

In an extension of the analogy[32] between carbonyl and ternary iminium groups, a Reformatsky reaction was carried out on the indolizidinium salts **13e–g** as well as on $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate. The resulting amino esters (**14e–g**, **19**) were obtained in good yields (Table I) as stable colorless liquids. Ring opening of the indolizidine methiodides occurs readily with sodium ethoxide to give **15e–g**. Spectral properties indicate that **15g** has the structure shown (nonconjugated vinyl hydrogen peak in the nmr and a conjugated carbonyl group in the infrared), that **15e** is actually one of the nonconjugated isomers **20** (triplet vinyl hydrogen peak in nmr and nonconjugated carbonyl in infrared), and that **15f** is a mixture of *ca.* 30% **15f** and 70% **21** (two kinds of vinyl hydrogens in the nmr and two carbonyls in the infrared).

The formation of the more stable[36] endocyclic olefins **20** and **21** suggests that, in contrast to sodium amide, sodium ethoxide induced ring opening leads to isomerization of the initially formed conjugated olefins **15**. Some support for this view comes from the formation

TABLE II

PHYSICAL PROPERTIES OF AZACYCLONONANES AND THEIR DERIVATIVES

Compd	Mp, or bp, °C (mm)	Calcd, % C	Calcd, % H	Found, % C	Found, % H
15a	135–136 (0.05)	78.21	9.62	77.97	10.32
15a picrate	203–204	47.09	4.09	47.21	4.33
15a MeI	143–145	50.27	6.59	50.34	6.81
15b	94–95 (0.1)	83.78	10.10	83.76	10.14
15b MeI	169–170.5	54.98	7.07	55.05	7.25
15b TNBS[a]	143–144	50.57	5.02	50.58	5.31
15c MeI	200–203 dec	56.10	7.32	56.07	7.50
15d	40–41 (0.6)				
15d MeI[b]	138–139	48.60	7.53	48.78	7.64
20	75–77 (1.0)				
20 MeI	97.5–100	45.78	7.16	45.93	7.44
20 TNBS[a]	132–133 dec	44.01	5.05	43.77	4.91
15g	80–82 (1.0)				
15g TNBS[a]	140–142	46.08	5.50	46.09	5.41
22 MeI	184–185	54.99	9.22	55.29	9.07
24	38–39 (0.12)				
24 picrate[c]	305 dec	50.25	5.79	50.27	5.82
16a MeI	113–115	52.73	7.06	52.97	6.76
16b TNBS[a]	204–206 dec	53.88	4.99	53.81	4.81
18	272–273 dec[d]	42.28	7.09	42.40	7.10

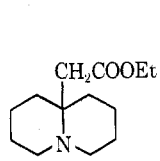
[a] 2,4,6-Trinitrobenzenesulfonate.[39] [b] % N: calcd, 4.36; found, 4.43. [c] % N: calcd, 14.65; found, 14.51. [d] Lit.[34] 270°; % N: calcd, 5.48; found, 5.59.

TABLE III

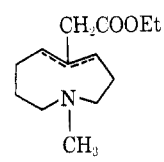
SELECTED SPECTRAL PROPERTIES OF AZACYCLONONANES

Compd	Nmr, δ	Ir, cm^{-1}
15a[a]	6.35 (s, 1)	1630 (w)
15b	6.32 (s, 1)	1650 (w)
15c	6.35 (s, 1), 1.05 (d, 3, J = 9 Hz)	1650 (w)
15d	5.84 (m, 4)	1631 (s), 1585 (w)
15d MeI	6.00 (m, 4)	
20	5.32 (t, 1, J = 9.6 Hz)	1735
20 MeI	5.55 (t, 1, J = 9.5 Hz)	1740
15f + **21**	5.60 (s, 0.3), 5.3 (m, 0.7)	1710, 1735
15g	5.60 (s, 1)	1715
22	5.14 (d, 1, $J \approx 1$ Hz)	1645 (w)
24	5.23 (d, 2, J = 4.4 Hz)	1640, 880
17[b]		1686[c]
18		3420, 3170, 3040[d]

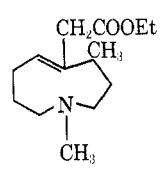
[a] Uv max (95% EtOH) 261 mμ (ε 3660); 2-ethylpyridine, 261 mμ (ε 5780); 2-vinylpyridine, 235, 277 mμ (ε 5640). [b] Mass spectrum *m/e* (rel intensity) 155 (47), 140 (10), 126 (11), 112 (17), 99 (68), 98 (100), 84 (88), 71 (53), 70 (72), 57 (82). We would like to thank Professor Carl Djerassi for obtaining this spectrum for us. [c] Lit. 1675 cm^{-1}; *N*-methylazacycloocta-5-one (**25**), 1683 cm^{-1};[14] *N*-methylazacyclodecan-6-one (**26**), 1694 cm^{-1}.[14] [d] Lit. HBr salt, 3180 cm^{-1}; **25** $HClO_4$, 3380 cm^{-1};[14] **26** $HClO_4$, 3400 cm^{-1}.[14]



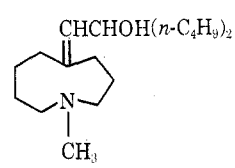
19



20



21

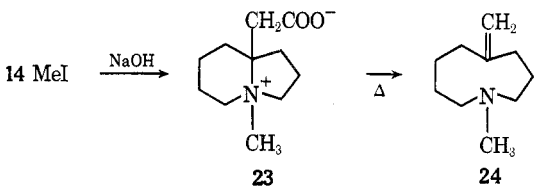


22

(34) D. Lohner, Ph.D. Dissertation, Adelphi University, 1966.
(35) A. Sisti and D. Lohner, *J. Org. Chem.*, **32**, 2026 (1967).
(36) A. Cope, D. Ambros, E. Ciganek, C. Howell, and Z. Jacura, *J. Amer. Chem. Soc.*, **82**, 1750 (1960).

of the exocyclic olefin **22** from the ring opening of **14e** MeI with *n*-butyllithium. Presumably before the initially formed **15e** can isomerize to **20**, it reacts further at the carbonyl group, thereby deactivating the molecule to base-catalyzed isomerization. The variation of isomer composition with the nature of R_2 in **15e–g** reflects a steric effect either on the stability of the various olefins or on the ease of their formation.

A final example of ring opening by β elimination was carried out in the absence of base, thus permitting the preparation of a medium-ring nitrogen heterocycle containing the less stable[36] exocyclic methylene group. Treatment of **14e** MeI with 1 equiv of sodium hydroxide led to the betaine **23** which, when heated to



23 **24**

200° in a dry state, gave **24**. A similar aminodecarboxylation has been reported for the morphine alkaloid metaphanine.[37]

Experimental Section

Melting points and boiling points are corrected. Analyses were performed by Mr. C. F. Geiger, Ontario, Calif., and by M-H-W Laboratories, Garden City, Mich. Nmr spectra were determined on a Varian A-60 instrument using $DCCl_3$ (for solids) and CCl_4 (for liquids) as solvents and TMS as an internal standard. Infrared spectra were measured on Perkin-Elmer 421, 237 or Beckman IR-10 instruments as films (liquids) or KBr disks (solids). A Cary Model 15 spectrophotometer was used to obtain the uv spectra.

Iminium Salts (13).—These compounds were prepared as described previously[29,31,38] by $Hg(OAc)_2$ oxidation of the corresponding 1-azabicycloalkanes which, in turn, were synthesized by the two-step reductive cyclization[29] of the appropriate pyridyl alcohols modified as follows for the large-scale preparation of indolizidine. The catalytic reduction of the pyridine ring[29] was replaced by a chemical reduction.[39] Although the yields by this procedure were lower (75 *vs.* 92%), an overall saving of time and/or expense was possible since: (i) the Pt catalyst in the original method[29] had to be either regenerated or discarded after several runs; (ii) a simpler work-up procedure not requiring hydrolysis of the intermediate acetate ester[29] was possible; and (iii) scale-up was not as limited by the size of the equipment.

Reactions of Iminium Compounds with Nucleophiles. A. With α-Picolyllithium.—Following the procedure of Leonard and Hay[32] $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate[38] was converted to 10-(α-picolyl)quinolizidine (**11**) in 55% yield, $\Delta^{4(9)}$-dehydroindolizidinium perchlorate (**13a**)[38] was converted to 9-(α-picolyl)-indolizidine (**14a**) in 64% yield, and $\Delta^{4(9)}$-dehydro-8-methylindolizidinium perchlorate (**13c**)[29] failed to react (68% recovery of **13c**). The properties of the products **11** and **14a** and their methiodides are found in Table IV.

B. With Benzylmagnesium Chloride.—To a solution of 108 mmol of $PhCH_2MgCl$ in 300 ml of ether was slowly added 36 mmol of the dried (55°, P_2O_5, *in vacuo*) iminium salts **13b**[38] or **13c**.[29] After the vigorous reaction had subsided, the mixture was heated to reflux for 4 hr, cooled, and treated with 100 ml of 6 *M* HCl. The separated aqueous layer was washed with two 150-ml portions of ether, basified with 48 g of NaOH in 150 ml of H_2O, and subjected to continuous liquid–liquid extraction with ether for 48 hr. The ether extract was dried (K_2CO_3) and concentrated on a rotary evaporator to give 9-benzylindolizidine (**14b**) or 9-benzyl-8-methylindolizidine (**14c**) as viscous colorless oils in 93 and 90% yields, respectively. Vpc analysis[40] of **14b** showed only one peak; so the derivatives in Table IV were prepared from undistilled material.

TABLE IV
PROPERTIES OF BRIDGEHEAD SUBSTITUTED 1-AZABICYCLOALKANES AND THEIR DERIVATIVES

Compd	Mp or bp, °C (mm)	Calcd, % C	Calcd, % H	Found, % C	Found, % H
11	140–142 (1.0)[a]				
11 picrate	152–153[b]				
11 MeI	212–213[c]				
14a	125–126 (1.5)				
14a picrate	138.5–140 dec	53.93	5.20	54.08	5.07
14a MeI	204–205	50.28	6.47	50.23	6.61
14b	97–98 (0.25)				
14b picrate	167–168.5 dec	56.75	5.44	57.05	5.52
14b TNBS[d]	180–182	49.60	4.75	49.90	4.95
14b MeI	300–302	53.78	6.77	54.00	7.06
14c picrate	138–139	57.85	5.72	57.66	5.50
14c TNBS[d]	164–166 dec	50.38	4.83	50.40	4.85
14c MeI	230–232 dec	54.99	7.06	55.22	7.28
14d	61–62 (1.3)				
14d MeI[e]	216.5–218	46.91	7.22	46.92	7.42
14e	95–97 (1.0)	68.20	10.01	68.01	9.94
14e MeI	145–147	44.20	6.85	44.18	7.01
14f	100–102 (1.0)				
14f MeI	170–171	45.78	7.13	45.48	7.12
14g	101–104 (1.0)				
14g MeI	174–175	47.13	7.38	47.25	7.55
19	99–102 (1.0)				
19 MeI	180–182 dec	45.78	7.13	45.48	7.41

[a] Lit.[23] 137 (0.3). [b] Lit.[32] 152.5–153.5. [c] Lit.[32] 212–213. [d] TNBS = 2,4,6-trinitrobenzenesulfonate.[29] [e] % N: calcd, 4.56; found, 4.56.

C. With Allylmagnesium Bromide.—Application of the above procedure to 40 mmol of allylmagnesium bromide and 20 mmol of **13d**[38] led to 9-allylindolizidine (**14d**) (97%) as a light yellow oil which slowly darkened on exposure to air and gave only one peak in the vpc.[40] The properties of **14d** and its methiodide are listed in Table IV.

D. With Ethyl Bromoacetate and Zinc.—In a 500-ml three-necked Morton flask fitted with a mechanical stirrer, reflux condenser, and gas inlet tube was placed 18.5 g of powdered zinc (previously washed with 1 *M* HCl and acetone and dried at 100°), 100 ml of dry ether, 6.68 g (40 mmol) of ethyl bromoacetate, 40 mmol of the appropriate iminium perchlorate (**13e**,[38] **13f**,[29] **13g**,[31] or $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate[38]), and a crystal of iodine. The mixture was heated to reflux with rapid stirring and five 18.5-g portions of zinc and an iodine crystal were added at 45-min (12 hr for **13f** and **13g**) intervals. During the second (fourth for **13f** and **13g**) addition, another 6.68 g of ethyl bromoacetate was added. Heating was continued for another 12 hr, 20 ml of H_2O was slowly added, and the zinc was removed by decantation and washed with four 50-ml portions of 1 *M* HCl. The washings and decantate were intimately mixed, and the aqueous portion was separated, washed with two 100-ml portions of ether, basified with K_2CO_3, and extracted with three 100-ml portions of ether. These latter extracts were combined and dried(K_2CO_3), and the solvent was removed on a rotary evaporator to leave the amino esters **14e**, **14f**, **14g**, and **19** in 87, 89, 85, and 90% yields, respectively, as pale green oils which were distilled at reduced pressure before conversion to the methiodides (Table IV).

Ring Opening of Indolizidine Methiodides (14 MeI) to Azacyclononanes (15). A. With Sodium Amide.—In a 500-ml three-necked Morton flask equipped with a mechanical stirrer, gas inlet tube, and a Dry Ice–acetone filled cold-finger condenser was prepared[41] 76 mmol of $NaNH_2$ in 200 ml of liquid NH_3. One of the dried solid methiodides of **14a–d** was added (40 mmol) and the mixture was stirred for 2 hr, at which time 200 ml of

(37) H. deWaal, B. Prinsloo, and R. Arndt, *Tetrahedron Lett.*, 6169 (1966).
(38) N. J. Leonard, W. Middleton, P. Thomas, and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956).
(39) C. S. Marvel and W. Lazier, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1944, p 93.
(40) Aerograph A-700; 20 ft × ⅜ in. column of 30% SE-30 on Chromosorb W.
(41) F. Bergstrom, *Org. Syn.*, **20**, 86 (1940).

ether was cautiously added. The NH_3 was allowed to evaporate overnight in a stream of N_2 and 50 ml of H_2O was then added. The ether layer was combined with two additional 75-ml portions of ether used to extract the H_2O, dried (K_2CO_3), and concentrated on a rotary evaporator to give **15a** as a dark viscous oil and **15b–d** as colorless liquids. Three successive molecular distillations of **15a** gave a colorless liquid (30% yield) which darkened rapidly on exposure to air, did not give satisfactory analytical values, but could be converted to crystalline derivatives. In a similar reaction with the methiodide of the quinolizidine **11**, more tars, less product, and no crystalline derivatives were formed. The physical and spectral properties of **15a–d** are found in Tables II and III, respectively.

B. With Sodium Ethoxide.—A solution of 33 mmol of NaOEt and 30 mmol of one of the methiodides of **14e–g** was heated under reflux under N_2 for 4 hr. The solution was cooled, acidified with 1:1 concentrated HCl in EtOH, and evaporated to dryness on a rotary evaporator. A solution of the residue in 50 ml of H_2O was basified with 4 *M* NaOH and extracted with three 50-ml portions of ether. The extracts were dried (K_2CO_3) and the ether was removed on a rotary evaporator to leave the amino esters **20**, **15f** + **21**, and **15g** as pale green oils which gave colorless liquids on vacuum distillation and whose properties are listed in Tables II and III.

C. With *n*-Butyllithium.—A mixture of 1.0 g (2.8 mmol) of **14e** MeI, 11.2 mmol of *n*-BuLi in 7 ml of hexane, and 50 ml of anhydrous ether was heated under reflux for 6 hr. The excess *n*-BuLi was destroyed with water and the organic layer was separated and dried (K_2CO_3), and the solvent was removed on a rotary evaporator to leave 0.64 g (80%) of **22** as a viscous, pale green oil which was purified by molecular distillation. The spectral properties of **22** are listed in Table III and the physical properties of its methiodide are listed in Table II.

D. By Aminodecarboxylation.—A solution of 10.7 g (30 mmol) of **14e** MeI and 1.4 g (35 mmol) of NaOH in 50 ml of H_2O was heated under reflux for 3 hr. Removal of the water with a rotary evaporator and drying of the residue over P_2O_5 in a vacuum for 12 hr gave the betaine **23** as a glassy solid whose ir displayed characteristic COO^- absorption at 1490 and 1590 cm^{-1}. The dry **23** was placed in a 50-ml distillation flask connected to a vacuum pump *via* a sidearm test tube serving as a collector. The flask was evacuated and immersed in an oil bath. Between 180–200°, 2.9 g (63%) of **24** distilled over as a colorless liquid whose vpc[40] contained only one peak. The spectral properties of **24** are listed in Table III and its physical properties and those of its picrate are listed in Table II.

Preparation of 12 MeI and Its Reaction with $NaNH_2$.—The known[42] amine **12** was converted to its methiodide, a hygroscopic white powder, mp 120–121°.

Anal. Calcd for $C_{13}H_{21}N_2I$: C, 46.99; H, 6.37. Found: C, 46.79; H, 6.60.

Reaction of **12** MeI with $NaNH_2$ and work-up as described above led to a polymeric mass which was triturated with three 100-ml portions of H_2O. Extraction of this aqueous solution with ether, drying (K_2CO_3), and distillation gave 2.5 g (61%) of *N*-methylpiperidine: bp 106° (lit.[43] 105.5°); picrate mp 220–222° (lit.[43] 223–224°).

Catalytic Reduction of Azacyclononanes 15a–b.—A MeOH solution of **15a** or **15b** was hydrogenated at 1 atm and 25° in the presence of PtO_2 until H_2 uptake ceased (30–60 min, 90% theoretical). Removal of the catalyst by filtration and the solvent by evaporation left **16a** and **16b** in quantitative yield as viscous colorless oils which were converted to a monomethiodide and a TNBS derivative, respectively, whose physical properties are listed in Table II. The nmr and infrared spectra of **16a** and **16b** were devoid of vinyl hydrogen or C=C absorptions.

Oxidation of *N*-Methyl-5-benzylideneazacyclononane (15b).—A mixture of 1.5 g (6.5 mmol) of **15b**, 50 mg of OsO_4, 25 ml of dioxane, and 15 ml of H_2O was stirred for 15 min at 25°. To the now dark brown mixture was added 2.8 g of $NaIO_4$ in small portions over a period of 30 min. After being stirred at 25° for an additional 3 hr, the mixture was treated with enough 3 *M* HCl to dissolve the solids present and extracted with three 100-ml portions of ether. The extracts were dried (Na_2SO_4), the ether was removed by distillation, and the residue was distilled to give 0.62 g (90%) of benzaldehyde (comparison of infrared spectrum and retention time with those of an authentic sample).

The acid solution was basified with 40% NaOH and continuously extracted with ether for 48 hr. The ether was dried (K_2CO_3) and removed with a rotary evaporator to leave 1 g (98%) of **17** as an oil. A sample collected by preparative vpc[40] for spectral analysis (Table III) was a low melting white solid.

The perchlorate salt **18** of **17** was prepared in 1:1 ether–absolute EtOH with 1:1 absolute EtOH–70% $HClO_4$ and recrystallized from EtOH–ether. The properties of **18** are listed in Tables II and III.

Reduction of *N*-Methylazacyclonona-5-one (17).—A solution of 1.0 g of **17**, 2.0 g of 95% $N_2H_4 \cdot H_2O$, and 5 ml of diethylene glycol was heated under reflux for 5 hr, distilled until the boiling point reached 200°, at which time 2 g of KOH were added, and then heated for an additional 5 hr. The reaction was steam distilled, the distillate was saturated with K_2CO_3 and extracted with three 75-ml portions of ether, and the extracts were dried (K_2CO_3) and evaporated on a rotary evaporator to afford 0.3 g (30%) of *N*-methylazacyclononane identified by comparison of its nmr and infrared spectra and the melting point and mixture melting point of its picrate with those of an authentic sample.[44]

Registry No.—**12** MeI, 35225-83-3; **14a**, 35225-84-4; **14a** picrate, 35225-85-5; **14a** MeI, 35225-86-6; **14b**, 4753-49-5; **14b** picrate, 4870-83-1; **14b** TNBS, 4795-24-8; **14b** MeI, 5588-55-6; **14c** picrate, 35225-90-2; **14c** TNBS, 35225-91-3; **14c** MeI, 35225-92-4; **14d**, 35225-93-5; **14d** MeI, 35225-94-6; **14e**, 35225-95-7; **14e** MeI, 35225-96-8; **14f**, 35225-97-9; **14f** MeI, 35225-98-0; **14g**, 4753-53-1; **14g** MeI, 4795-26-0; **15a**, 35226-01-8; **15a** picrate, 35226-02-9; **15a** MeI, 35226-03-0; **15b**, 4753-50-8; **15b** MeI, 4795-25-9; **15b** TNBS, 4753-51-9; **15c**, 35226-07-4; **15c** MeI, 35261-97-3; **15d**, 35226-08-5; **15d** MeI, 35261-98-4; **15f**, 35226-09-6; **15g**, 4753-54-2; **15g** TNBS, 4870-85-3; **16a** MeI, 35212-74-9; **16b** TNBS, 35212-75-0; **17**, 4753-52-0; **18**, 35212-77-2; **19**, 35212-78-3; **19** MeI, 35212-79-4; **20**, 11-141-121; **20** MeI, 11-141-143; **20** TNBS, 11-141-132; **21**, 35212-80-7; **22**, 35212-81-8; **22** MeI, 35212-82-9; **24**, 35212-83-0; **24** picrate, 35212-84-1.

Acknowledgments.—This research was generously supported by The Robert A. Welch Foundation, the T. C. U. Research Foundation, and by NIH and NSF fellowships to L. R. K.

(42) H. Reich and R. Levine, *J. Amer. Chem. Soc.*, **77**, 4913 (1955).
(43) R. Lukes, *Collect. Czech. Chem. Commun.*, **12**, 71 (1947).
(44) R. Lukes and J. Malek, *Chem. Listy*, **45**, 72 (1951); *Chem. Abstr.*, **45**, 9523c (1951).