as-triazine[28] (5.08 g, 40 mmol) was added. After 24 hr stirring at 25° Dry Ice was added, and the solution containing some precipitate was concentrated *in vacuo* to 40 ml. After dilution with C_6H_6 the precipitate was removed by filtration and the solution was concentrated to dryness. The residue was vacuum distilled [bp 120° (0.3 mm)] to give pure **14** as crystals (1.58 g, 21%), mp 69–70°.

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.15; H, 4.84; N, 22.44. Found: C, 64.13; H, 4.82; N, 22.31.

2,5-Dihydro-*as*-triazin-3(4*H*)-one (15).—To a solution of **14** (0.561 g, 3 mmol) in DMF (40 ml) was added 5% Pd on charcoal (50 mg), and H_2 was bubbled into the solution for 90 min. The catalyst was then removed by filtration and the solvent was evaporated. The residual white powder was crystallized from EtOH to give **15** (0.18 g, 60.5%), mp 135–136°. Concentration of the EtOH mother liquor yielded an additional 0.065 g (combined yield 82%). An analytically pure sample was obtained by recrystallization from EtOH: mp 136–137°; λ_{max}^{MeOH} 243 nm (ϵ 2440); nmr (D_2O) 7.01 (t, J = 3 Hz), 4.02 (d, J = 3 Hz); mass spectrum molecular ion at m/e 99.

Anal. Calcd for $C_3H_5N_3O$: C, 36.36; H, 5.08; N, 42.40. Found: C, 36.39; H, 5.04; N, 42.30.

Acknowledgment.—The authors wish to thank Mr. E. Banta, Mr. L. T. Larek, and Mr. D. M. Capampangan for the instrumental data.

Registry No.—**3**, 27531-67-5; **4**, 28735-22-0; **5**, 22860-91-9; **6**, 40919-31-1; **7**, 40919-32-2; **8**, 40919-33-3; **10**, 40919-34-4; **11**, 40919-35-5; **12**, 40919-36-6; **14**, 40919-37-7; **15**, 40919-38-8.

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Peripheral Synthesis of Secondary Medium-Ring Nitrogen Heterocycles[1]

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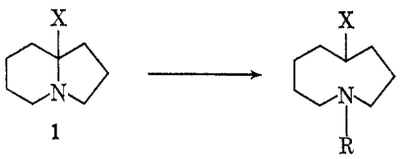
Received January 11, 1973

Three methods for preparing secondary azacyclononanes from 9-substituted indolizidines were investigated. The first method utilized previously developed ring-opening reactions to give *N*-benzylazacyclononanes, which were debenzylated by cleavage with alkyl chloroformates. *N*-Benzyl-5-ethylideneazacyclononane (**8**) was converted to **11** in this way *via* either the ethyl or the 2,2,2-trichloroethyl carbamate. The former group was removed with methyllithium and the latter with zinc dust. Only this latter sequence was successful for debenzylating *N*-benzyl-5-(2′-phenylethylidene)azacyclononane (**12**) to **17**. The second method involved direct cleavage of 9-vinylindolizidine (**3**) and 9-benzylindolizidine (**22**) with ethyl or phenyl chloroformate. Catalytic reduction and hydrolysis of the carbamate from **3** gave **19**. Hydrolysis of the carbamate from **22** caused transannular cyclization back to the starting material. In the final method, **3** was treated with $LiAlH_4$ and $NiCl_2$ to give 9-ethylindolizidine (**20**) and 5-ethyl- (**19**), 5-vinyl- (**10**), and 5-ethylideneazacyclononane (**11**) in varying proportions depending on the reaction conditions. All the secondary amines prepared in this study were converted to the known *N*-methyl homologs.

The peripheral synthesis of medium-ring azacycles as developed in our laboratory[3–5] leads exclusively to compounds in which the ring nitrogen is tertiary (eq 1, R = CH_3). While such compounds are of interest because of their relation to certain alkaloids[6,7] as well as their ability to undergo transannular reactions,[8,9] the availability of the corresponding secondary amines would provide additional possibilities for studies in these areas. At the time this project was initiated the preparation of secondary medium-ring azacycles was limited to two general methods: the ring expansion of cycloalkanones,[10] and the electrolysis of β-keto-1-azabicycloalkanes.[11] Although both of these syntheses are somewhat limited in scope by the availability of starting materials or the reaction conditions, a potentially general route has been described[12] more recently which nicely complements those to be discussed in this paper.

As before[3–5] our method involves the selective cleavage of the central carbon–nitrogen bond of bridgehead-substituted 1-azabicycloalkanes (eq 1), which in the



1 (1)

present study were restricted to the readily available[4,5,13] 9-substituted indolizidines (**1**). Selectivity was assured by the nature of the 9 substituent and the cleavage was facilitated by quaternization of the nitrogen atom. The three methods to be described can be classified according to the character and fate of this quaternary stage: (1) the quaternary compound gives a tertiary amine which is subsequently dealkylated; (2) the quaternary intermediate yields a derivative which can be converted to the secondary amine; or (3) the quaternary intermediate decomposes directly to the secondary amine.

The first method is based on the previously described[3–5] successful synthesis of *tertiary* medium-ring azacycles and requires the selective dealkylation of these compounds to the desired secondary amine. The reaction chosen for this purpose, the chloroformate ester cleav-

(1) Taken in part from the Ph.D. Dissertation of R. G. Daubert, Texas Christian University, 1971.

(2) National Science Foundation Trainee, 1966–1970.

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(12) J. P. Yardley, R. W. Rees, and H. Smith, *J. Med. Chem.*, **10**, 1088 (1967).

(13) An improved preparation of one of the precursors of these starting materials, 9-cyanoindolizidine (**2**), is described in the Experimental Section.

age of tertiary amines to a carbamate and an alkyl chloride (eq 2), is very similar in mechanism and scope

$$R_3N + ClCOOR' \longrightarrow [R_3NCOOR']^+ Cl^- \longrightarrow R_2NCOOR' + RCl \quad (2)$$

to the well-known von Braun cyanogen bromide reaction (eq 3)[14] but has the advantage of permitting

$$R_3N + BrCN \longrightarrow [R_3NCN]^+ Br^- \longrightarrow R_2NCN + RBr \quad (3)$$

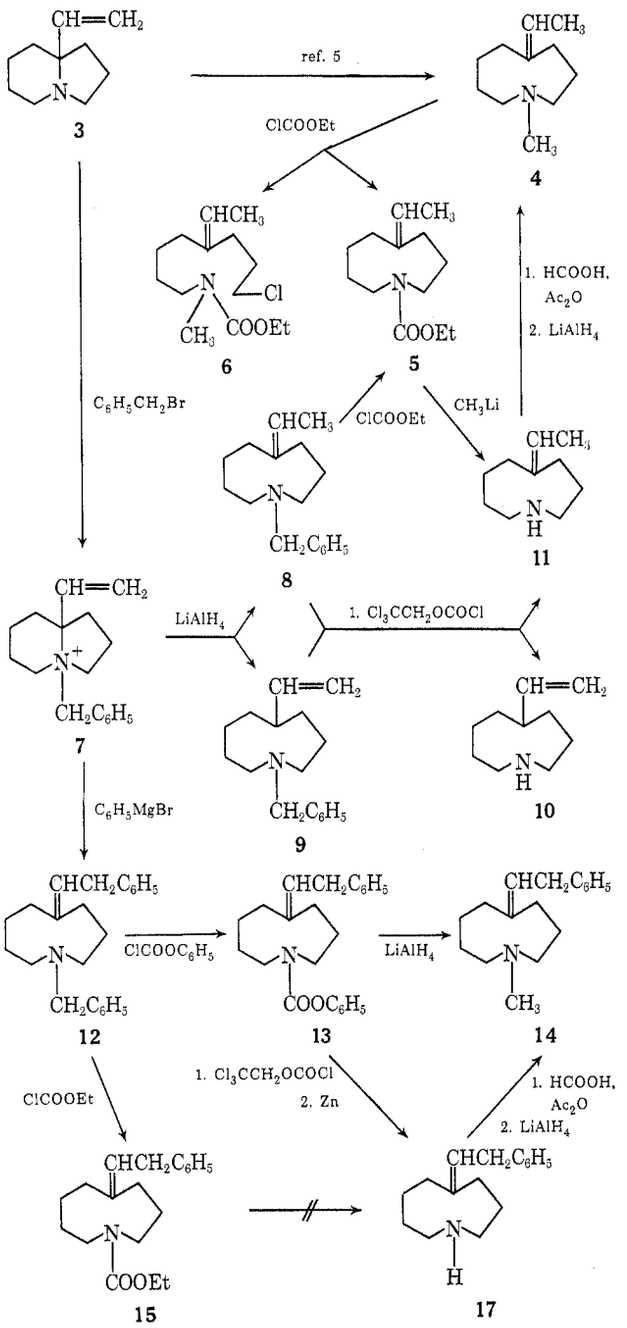
variations in the alcohol moiety (R′) and thus in the method of ultimately converting the carbamate to the secondary amine. Although this chloroformate cleavage has been known for some time in the alkaloid field,[15,16] other applications and studies[17-21] are limited, and therefore the more thoroughly investigated von Braun reaction[14] was used as a model.

The first compound investigated was *N*-methyl-5-ethylideneazacyclononane (**4**), prepared[13] from 9-vinylindolizidine (**3**) by our previously reported[5] methods. Since the von Braun reaction is known to be nonselective for N-demethylation of related compounds,[12] it was not unexpected that the ethyl chloroformate cleavage of **4** gave almost equal amounts of the demethylated product **5** and a ring-opened product (**6** or the other possible isomer).

What is obviously necessary to increase the selectivity of the N-dealkylation is a more labile group on nitrogen. Both the 3,3-ethylenedioxybutyl[12] and the benzyl group[22,23] have been used for this purpose. The former group[12] is cleaved by acid hydrolysis and hydrazinolysis while the latter is removed by hydrogenolysis.[22,23] Although the latter reaction would interfere with the retention of unsaturation in the product, the benzyl group was nevertheless chosen, because it can be introduced more efficiently[12] and because it was anticipated[24] that it could be removed easily by the chloroformate cleavage.

An expected limitation of the *N*-benzyl group was that N-debenzylation would compete with the ring opening of the bicyclic quaternary ammonium salt precursors.[3-5] However, treatment of the *N*-benzyl quaternary salt of 9-vinylindolizidine (**7**) with $LiAlH_4$ gave only a trace of the N-debenzylation product **3**. The major product, 5-ethylidene-*N*-benzylazacyclononane (**8**), was identified from its spectral characteristics, analysis of its benzyl bromide salt, and its ultimate conversion (*vide infra*) to the known[5] *N*-methyl compound **4**. This occurrence of allylic rearrangement during ring opening parallels the behavior of the *N*-methyl analog.[5] A minor product was probably[5] the vinyl isomer **9**, as shown by debenzylation (*vide infra*) of the mixture to a mixture of the 5-vinyl and 5-ethylidene secondary amines **10** and **11**, respectively.

Reaction of **8** with ethyl chloroformate gave the same carbamate, **5**, obtained from cleavage of the *N*-methyl compound **4** but none of the ring-opened isomer **6**. Because of difficulties with transannular ring-closure during the hydrolytic removal of the carbamate group from an unsaturated medium-ring compound (*vide infra*), a method based on the known[25] reaction of amides with lithium reagents was utilized. The desired 5-ethylideneazacyclononane (**11**) was by far the major portion (93%) of the product of **5** and methyllithium, presumably[25] because the secondary amine was tied up as a lithium salt of the carbinolamine intermediate until work-up and hence resistant to cyclization. The structure of **11** was proven by its spectral properties, the analysis of its styphnate, and its conversion to the known[5] *N*-methyl derivative **4** by formylation and reduction. The overall yield of **3** → **11** approaches



(14) H. A. Hageman, *Org. React.*, **7**, 198 (1965).
(15) J. Gadamer and F. Knoch, *Arch. Pharm. (Weinheim)*, **259**, 135 (1921).
(16) J. Knabe, *Arch. Pharm. (Weinheim)*, **289**, 479 (1956).
(17) J. Knabe and H. Gohmert, *Arch. Pharm. (Weinheim)*, **303**, 525 (1970) and previous papers in this series.
(18) J. A. Campbell, *J. Org. Chem.*, **22**, 1259 (1957).
(19) W. B. Wright, Jr., and H. J. Brabander, *J. Org. Chem.*, **26**, 4057 (1961).
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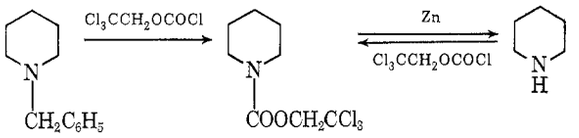
(21) M. M. Abdel-Monem and P. S. Portoghese, *J. Med. Chem.*, **15**, 208 (1972).
(22) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3187 (1968).
(23) N. J. Leonard and T. Sato, *J. Org. Chem.*, **34**, 1066 (1969).
(24) R. Ruggli and G. Geiger, *Helv. Chim. Acta*, **30**, 2035 (1947).
(25) E. A. Evans, *J. Chem. Soc.*, 4691 (1956).

50%, which is highly competitive with methods[12] leading to secondary medium-ring azacycles without the potentially useful transannular unsaturation.

As a further example of the utility of this route, the quaternary salt **7** was treated with phenyl Grignard reagent in an abnormal displacement reaction[5] to give the phenylethylidene derivative **12** in good yield. The structure of **12** follows from its spectral properties, the analysis of its methiodide, and its conversion, by the $LiAlH_4$ reduction of the phenyl carbamate **13**, to the known[5] *N*-methyl compound **14**. The debenzylation of **12** to either the phenyl (**13**) or the ethyl (**15**) carbamate proceeded without any evidence for ring opening. A preliminary experiment indicated, as expected, that acid hydrolysis of **13** gave considerable (*ca.* 70%) cyclization products. Consequently, the methyllithium procedure was applied to the ethyl carbamate **15**. Unfortunately, in this instance considerable polymer and a complex mixture of conjugated and unconjugated olefins were obtained. Presumably the lithium reagent causes isomerization of the double bond of **15** and subsequent polymerization of the resultant styrene derivative.

In order to debenzylate such apparently sensitive olefins as **12** another, more labile, carbamate would be desirable. A recently reported possibility, the β,β,β-trichloroethyl carbamate, can be removed with zinc dust in methanol,[26] conditions which should not affect double bonds. The question of whether the corresponding chloroformate has the same ability to debenzylate tertiary amines as the ethyl and phenyl chloroformates was answered by cleaving *N*-benzylpiperidine to the β,β,β-trichloroethyl carbamate **16** in



16

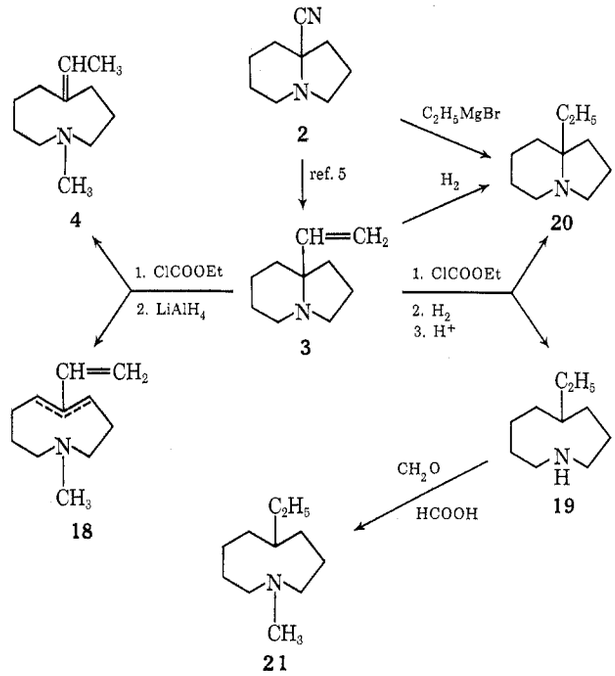
excellent yield. This carbamate, also available from piperidine and the chloroformate, could be cleaved to piperidine by the reported[26] method.

Application of this sequence to the phenylethylidene compound **12** leads to the desired secondary amine **17** in 76% crude yield (71% overall from **3**) as an approximately equal mixture of geometrical isomers. The structure of **17** (mixture) follows from its vpc and spectral data, its analysis, and its conversion in 76% yield to the known[5] *N*-methyl compound **14**, which does not show any evidence of geometrical isomers.

As a final test of this last debenzylation method a mixture of **8** and **9** (86:14) was converted to an 87:13 mixture of the previously prepared secondary amines **11** and **10** in 77% yield. This constitutes an overall yield of *ca.* 63% from the bicyclic precursor **3** and testifies as to the efficiency of this method for the synthesis of unsaturated secondary medium-ring azacycles.

Ring-opening method 2 can be considered a simplified variation of method 1 just described in which the chloroformate cleavage is carried out directly on the indolizidine **1** to give the medium-ring carbamate (eq 1, R = COOR). Based on the von Braun reaction[14] as a model it was anticipated that simple indolizidines would react with chloroformates to open the pyrrolidine ring,[27] but that *N*-allyl groups generally[14] would be cleaved more readily than saturated alkyl groups. Therefore 9-vinylindolizidine (**3**) once again was chosen as a substrate to test the feasibility of this method.

Reaction of **3** with ethyl chloroformate gave a mixture of carbamates which was directly reduced[20] with lithium aluminum hydride to give a 60:40 mixture of N-methylated amines in about 50% overall yield. The minor component was identified as the known[5] ethylidine amine **4** and the spectral characteristics of the major product suggested that it was the conjugated diene **18** presumably formed by elimination of HCl from an intermediate carbamate or quaternary salt. Catalytic reduction of the above carbamate mixture followed by acid hydrolysis gave 5-ethylazacyclononane (**14**) in 47% yield along with a small amount of 9-ethylindolizidine (**20**). The structure of the former compound follows from its analysis, spectral properties, and its conversion to the known[5] *N*-methylamine **21**.



The latter compound was identified as 9-ethylindolizidine (**20**) by comparison of its infrared spectrum with those of samples synthesized by catalytic reduction of the 9-vinyl compound **3** or by the reaction of the ethyl Grignard reagent with the cyano derivative **2**. 9-Ethylindolizidine (**20**) probably arises from the acid-catalyzed cyclization of residual unsaturated secondary amines analogous to the process observed for closely related tertiary amines.[28,29] Substitution of phenyl chloroformate for ethyl chloroformate in the reaction with **3** gave essentially identical results.

In an attempt to direct the apparent tendency toward diene formation noted above in such a way that only a single cleavage product would be produced, the reaction of 9-benzylindolizidine (**22**) with phenyl chloro-

(26) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).

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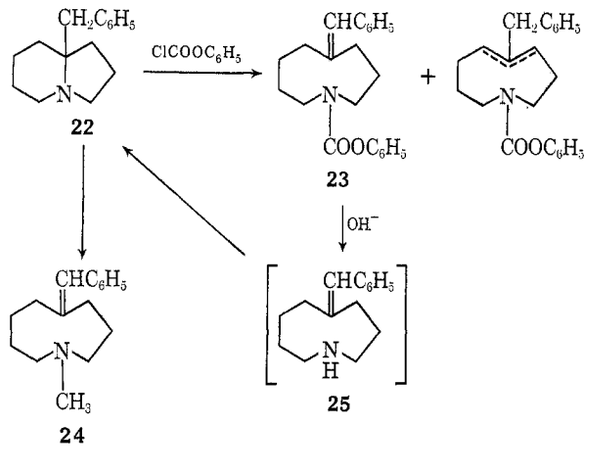
(28) K. Schofield and R. J. Wells, *Chem. Ind. (London)*, 572 (1963).

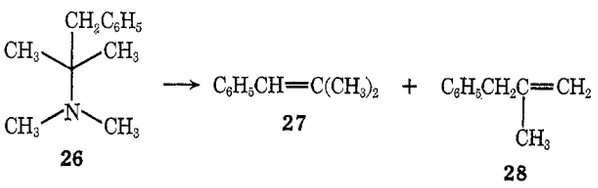
(29) A. J. Sisti and D. L. Lohner, *J. Org. Chem.*, **32**, 2026 (1967).

formate was examined. Once again by analogy to the von Braun reaction[14,30] the tertiary alkyl group should be cleaved preferentially with formation of an olefinic product. This product should consist of the single conjugated olefin **23** as suggested by the exclusive formation of the benzylidene isomer **24** from the β-elimination of **22** MeI.[3,4] Unfortunately, the nmr spectrum of the crude phenylcarbamate from **22** clearly showed the presence of two olefins, a result which was substantiated by the vpc detection of two $LiAlH_4$ reduction products in 70:30 ratio. The phenyl carbamate mixture was treated with strong base on the presumption that isomerization to a single olefin might occur. The only product found, however, was the original starting material **22**, apparently formed by transannular cyclization of an intermediate secondary amine such as **25**.



Analogous anionic additions of amines to phenyl conjugated hydrocarbons are known.[31]

In order to determine if the nonselectivity of the above chloroformate cleavage is inherent in the reaction or peculiar to the ring system, a simple acyclic model, *N*,*N*-dimethyl-α,α-dimethyl-β-phenethylamine (**26**), was treated with phenyl chloroformate. The olefinic product consisted of almost equal amounts of the conjugated and the nonconjugated alkenes, **27** and **28**, thereby establishing that the lack of selectivity of this reaction limits the utility of this second method to the preparation of saturated medium-ring compounds.



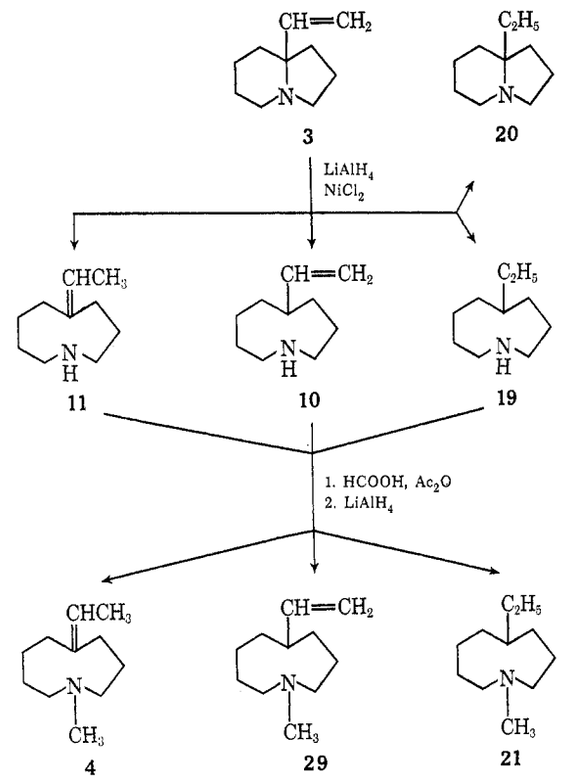
The third and final method investigated for preparing secondary medium-ring amines is based on the reductive cleavage of allyl groups from *N*-allyl-*N*-alkylanilines with lithium aluminum hydride and nickel chloride.[32] Under the reported conditions 9-vinylindolizidine (**3**) failed to react (Table I, no. 1), presumably[32] because of its high basicity compared to anilines. With an increased ratio of nickel chloride to amine, however, reaction did occur to give a mixture of bicyclic (**20**) and medium-ring amines (**10**, **11**, **19**) some of which contained rearranged (**11**) or reduced (**19**) double bonds. The products were identified by comparison with previously prepared samples and by formylation and reduction of the reaction mixture to give a mixture of the known *N*-methyl amines, **4**, **21** and **29**.

TABLE I

REACTIONS OF 9-VINYLINDOLIZIDINE (**3**) WITH $LiAlH_4$ AND $NiCl_2$

No.	Equiv of $LiAlH_4$	Equiv of $NiCl_2$	Time, hr	Rel % of **3**	Rel % of **20**	Rel % of **19**	Rel % of **10**	Rel % of **11**	Wt % yield
1[a]	4.8	0.3	138	100					
2[a]	3.0	0.8	91	55	15		12[b]	18	60
3[a]	7.6	1.2	22		86		10[b]	4	60
4[a]	7.6	1.2	110	15	21		3[b]	61	85
5[a]	10.0	1.2	103		7		88	5	42
6	7.7	2.3	12	37	34	15	4	10	50
7	7.7	2.3	16	30	45	11	3	11	75
8	7.7	2.4	24		74	20[b]		6	80
9	7.6	2.3	113	Trace	41	7	12	40	70
10[c]	7.6	2.4	16			35	8	51	77
11[a,d]	7.7	1.2	112		100				81

[a] Procedure differs in that $LiAlH_4$ was added to refluxing mixture of $NiCl_2$ and THF. [b] Vpc analyses performed with column A which does not separate **10** and **19**. [c] Reactant was 87:13 mixture of **11**:**10**; two unidentified peaks also present in product. [d] Reactant was **20**.



The product distribution from the Tweedie reaction of **3** was very sensitive to the experimental conditions (Table I) and not always reproducible in our hands, probably owing to variations in the nickel catalyst. The unsaturated medium-ring compounds **10** and **11** were never obtained in good yield free of other products, although the saturated amine **19** could be by using a large excess of $LiAlH_4$ (Table I, no. 5). It therefore appears that the utility of this method for preparing

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(31) R. C. Bansal, E. J. Eisenbraun, and P. W. Flanagan, *J. Amer. Chem. Soc.*, **88**, 1837 (1966).
(32) V. L. Tweedie and J. C. Allabashi, *J. Org. Chem.*, **26**, 3676 (1961)

secondary medium-ring amines will also be restricted to saturated examples.

Experimental Section

Melting points and boiling points are uncorrected. Analyses were performed by M-H-W Laboratories, Garden City, Mich. Nmr spectra were determined on a Varian A-60A instrument in CCl_4 or C_2Cl_4 with TMS as an internal standard. Ir spectra were recorded on a Perkin-Elmer 237 infrared spectrophotometer as thin films for liquids or KBr disks for solids. Vpc analyses were performed on a Beckman GC-2A gas chromatograph utilizing column A (4 ft × 0.25 in., 20% SE-30 on Chromosorb W) or column B (15 ft × 0.25 in., 5% KOH and 15% polyphenylether-6-ring on Chromosorb W) unless otherwise noted.

9-Cyanoindolizidine (2).—To a stirred solution of 100 g of mercuric acetate in 400 ml of 5% HOAc at 90° was added 9.0 g of freshly distilled indolizidine.[4,33] After 1 hr the reaction mixture was cooled to 0°, the mercurous acetate was removed by filtration, and a solution of 22.4 g of KCl in 100 ml of H_2O was added to the filtrate. The resulting mercuric chloride complex of the enamine was mixed with 100 ml of H_2O, and 10 ml of concentrated HCl was added followed by a solution of 39.2 g of NaCN in 100 ml of H_2O (*HOOD!*). The resulting solution was extracted with three 50-ml portions of ether which were combined, dried ($CaSO_4$), and concentrated to give 6.6 g (65%) of **2** whose ir spectrum is identical with that of a sample prepared by the lengthier and less efficient method[34] *via* the isolated iminium perchlorate.

Reaction of *N*-Methyl-5-ethylideneazacyclononane (4) with Ethyl Chloroformate.—After a mixture of 1.0 g of **4**[5] and 5.7 g of ethyl chloroformate in 25 ml of benzene had been heated under reflux for 16 hr, it was washed with two 30-ml portions of 4 *N* HCl, dried (K_2CO_3), and concentrated to give 1.2 g of a liquid whose vpc on a 4.5 ft 15% SE-30, 5% Carbowax 20M on Chromosorb W column indicated two products (52:48) of vastly different retention time (5 and 13.5 min at 220°). The former had the same retention time and nmr spectrum as **5**, the product from the ethyl chloroformate cleavage of **8**. The second product (**6**) had the following nmr spectrum: δ 5.2 (m, 1, C=CH_2), 4.0 (q, J = 7 Hz, 2, OCH_2), 3.3 (two overlapping t's, 4, CH_2N and CH_2Cl), 2.8 (s, 3, NCH_3).

***N*-Benzyl-5-ethylideneazacyclononane (8).**—After a mixture of 6.0 g of **3**[5] and 9.5 g of $PhCH_2Br$ had been allowed to react at room temperature for 24 hr, 280 ml of glyme and 6.0 g of $LiAlH_4$ were added and the solution was heated to reflux for 5 days. Excess $LiAlH_4$ was destroyed with H_2O, and the mixture was heated to reflux for 30 min and filtered. The combined filtrate and ether washings of the precipitate were dried (K_2CO_3) and concentrated at reduced pressure to give a liquid which was dissolved in 40 ml of 6 *N* HCl. The acid solution was washed with 25 ml of ether, basified with concentrated NaOH, and extracted with three 20-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated to give 7.6 g (79%) of a liquid, bp 112° (0.25 mm), which gave two peaks (86:14) on vpc analysis (column A). The major product had ir 3090, 3060, 3030, 1655, 1600, 730, 710, 690 cm^{-1}; nmr δ 7.2 (s, 5, PhH), 5.3 (q, J = 7 Hz, 1, C=CH), 3.5 (s, 2, NCH_2Ph). A benzyl bromide salt was prepared, mp 189.5–190.5° when heated at 2°/min.

Anal. Calcd for $C_{24}H_{32}NBr$ (**8**·$PhCH_2Br$): C, 69.55; H, 7.78; N, 3.38. Found: C, 69.76; H, 7.89; N, 3.41.

Reaction of *N*-Benzyl-5-ethylideneazacyclononane (8) with Ethyl Chloroformate. Preparation of 5-Ethylideneazacyclononane (11).—Using the procedure and work-up described above for **4**, 7.6 g of **8** and 16.8 g of ethyl chloroformate were allowed to react for 24 hr to give 8.3 g of **5**: ir 1700 cm^{-1}; nmr δ 5.3 (m, 1, C=CH), 4.1 (q, J = 7 Hz, 2, OCH_2), 3.25 (m, 4, CH_2N), 1.25 (t, J = 7 Hz, 3, CH_3). A solution of 4.1 g of **5** in 100 ml of benzene was added to 100 ml of 2.23 *M* CH_3Li in 100 ml of ether and the mixture was heated to reflux for 23 hr, at which time 70 ml of H_2O was added. The ether layer was extracted with two 25-ml portions of 6 *N* HCl which were basified with concentrated NaOH and extracted with two 50-ml portions of ether. Evaporation of the dried (K_2CO_3) ether extracts gave 1.9 g of a liquid whose major (93%) peak in the vpc had ir 3350 (NH), 1650 cm^{-1} (C=C); nmr δ 5.3 (m, 1, C=CH), 3.2 (m, 4, CH_2N). A styphnate was prepared, mp 151–152° (evacuated capillary).

Anal. Calcd for $C_{16}H_{22}N_4O_8$ (**11** styphnate): C, 48.24; H, 5.57; N, 14.06. Found: C, 48.10; H, 5.43; N, 14.10.

Methylation of 5-Ethylideneazacyclononane (11).—A 0.5-g sample of **11** (93%) was formylated with formic–acetic anhydride mixture and the resulting formamide was reduced with $LiAlH_4$ by the same procedures described (*vide infra*) for the product of the Tweedie reaction of **3**. A vpc of the 0.35 g of product on a 12 ft, 25% PPE on Chromosorb W column showed one major peak (90% of peak area) which was identified as **4** by comparison of its ir spectrum with that of an authentic sample.[5]

***N*-Benzyl-5-(2′-phenylethylidene)azacyclononane (12).**—A mixture of 5.0 g of **3**[5] and 7.4 g of $PhCH_2Br$ was allowed to react for 15 hr at room temperature and the resulting product was dissolved in 16 ml of CH_2Cl_2. This solution and 0.165 mol of PhMgBr in 155 ml of THF were mixed and heated under reflux for 3 days. Concentrated NH_4Cl solution was added until no precipitate remained, and the aqueous layer was extracted with two 50-ml portions of ether. The combined ether and THF solutions were extracted with 60 ml each of 3 *N* and 6 *N* HCl and the combined acid layers were saturated with KCl, basified with concentrated NaOH, and extracted with two 50-ml portions of benzene and 50 ml of ether. The combined organic extracts were dried (K_2CO_3) and concentrated to give 9.8 g (93%) of **12** as a viscous oil: ir 3075, 3050, 3020, 1600, 750, 695 cm^{-1}; nmr δ 7.2 (s, 5, PhH), 7.1 (s, 5, PhH), 5.4 (t, J = 6.5 Hz, 1, C=CH), 3.5 (s, 2, NCH_2Ph), 3.3 (d, J = 6.5 Hz, 2, C=CH**CH_2**Ph). A methiodide, mp 153–154° (evacuated capillary), was prepared.

Anal. Calcd for $C_{24}H_{32}NI$ (**12** MeI): C, 62.47; H, 6.99; N, 3.04. Found: C, 62.79; H, 7.21; N, 2.94.

Attempted N-Debenzylation of 12 with Ethyl Chloroformate and Methyllithium.—Application of the procedure used above for converting **8** to **11** to 9.6 g of **12** gave 5.3 g of a viscous red-brown oil which only partially distilled at 128° (0.25 mm). The distillate gave at least four peaks on vpc analyses and displayed two kinds of olefinic protons in the nmr (δ 6.5 and 5.5). The residue showed no olefinic protons in the nmr.

Reaction of 12 with Phenyl Chloroformate and $LiAlH_4$ to *N*-Methyl-5-(2′-phenylethylidene)azacyclononane (14).—Using the procedure described for **22** (*vide infra*) a 4.2-g sample of **12** and 10.3 g of PhOCOCl were allowed to react to give 6.0 g of crude **13** which was partially purified by passage through a short column of activity I Al_2O_3 with benzene–hexane. The resulting product had ir 3060, 3030, 1725, 1600, 750, and 685 cm^{-1}; nmr δ 7.12 (m, 10, PhH), 5.4 (m, 1, C=CH), 3.32 (m, 6, CH_2N, CH_2Ph).

A 1.5-g sample of **13** was reduced with $LiAlH_4$ as described for the ethyl carbamate of **3** to give 0.5 g of vpc-pure **14** whose ir spectrum was identical with that of an authentic sample.[5]

2,2,2-Trichloroethyl Piperidinecarbamate (16).—A mixture of 2.0 g of *N*-benzylpiperidine[35] and 7.3 g of 2,2,2-trichloroethyl chloroformate in 50 ml of benzene was heated under reflux for 2 days, 50 ml of ether was added, and the whole was washed with two 40-ml portions of 3 *N* HCl and 40 ml of H_2O. The organic layer was dried ($CaSO_4$) and concentrated to give 2.9 g (97%) of **16** as a liquid which crystallized upon standing. A vpc-collected sample (column A) had mp 35.5–37.5°; ir 1720, 850, 820, 775, 750, 715 cm^{-1}; nmr δ 4.8 (s, 2, Cl_3CCH_2[26]), 3.5 (m, 4, CH_2N). Identical spectra were obtained from a sample of **16** prepared from piperidine and the chloroformate.

Anal. Calcd for $C_8H_{12}NO_2Cl_3$ (**16**): C, 36.88; H, 4.64; N, 5.38. Found: C, 36.79; H, 4.45; N, 5.15.

Removal of Carbamate Group from 16.—A solution of 3.2 g of **16** in 50 ml of glacial HOAc and 3.3 g of zinc dust was stirred for 4 hr at room temperature. After removal of the zinc by filtration, the filtrate was basified with concentrated NaOH and extracted with three 50-ml portions of ether. The dried ether extracts were treated with picric acid in ether to give 1.7 g (44%) of piperidine picrate, mp 148.5–150.5°, identified by comparison of its ir spectrum with that of an authentic sample.

5-(2′-Phenylethylidene)azacyclononane (17).—After a solution of 6.0 g of **12** and 12.0 g of Cl_3CCH_2OCOCl in 50 ml of benzene had been heated to reflux for 17 hr, 50 ml of ether was added and the whole was washed with two 40-ml portions of 3 *N* HCl and one 40-ml portion of H_2O. After the organic layer was dried ($CaSO_4$) and concentrated, the 9 g (100%) of residue was dissolved in 30 ml of glacial HOAc and 8.5 g of zinc powder was added. The mix-

(33) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **29**, 1736 (1964).
(34) N. J. Leonard and A. S. Hay, *J. Amer. Chem. Soc.*, **78**, 1984 (1956).
(35) F. Haase and R. Wolffenstein, *Chem. Ber.*, **37**, 3232 (1904).

ture was stirred at room temperature for 4 hr, filtered to remove the zinc, basified with dilute NaOH, and extracted with three 50-ml portions of ether. The dried (K_2CO_3) ether extract was concentrated to give 3.3 g (76%) of **17** as a dark, viscous liquid which gave two overlapping peaks (48:52) on vpc analysis on a 7 ft, 20% SE-54 on Chromosorb W column. A vpc-collected sample of the mixture had ir 3370, 3100–3000, 1650, 1600, 735, and 700 cm^{-1}; nmr δ 7.1 (s, 5, PhH), 5.4 (two t's, 1, C=CH), 2.3 (two d's, 2, CH_2Ph).

Anal. Calcd for $C_{16}H_{23}N$ (**17**): C, 83.78; H, 10.11; N, 6.11. Found: C, 83.80; H, 10.23; N, 6.13.

N-Methylation of 17 to 14.—A 1.0-g sample of **17** (mixture) was formylated and reduced by the same procedure described for the conversion of **11** to **4** to give 0.8 g (76% yield) of **14** as a vpc-pure liquid whose ir spectrum was identical with that of an authentic sample.[5]

N-Debenzylation of 8 with 2,2,2-Trichloroethyl Chloroformate.—A 3.5-g sample of crude **8** containing 14% of an impurity (**9**) from its preparation from **3** described previously was treated with Cl_3CCH_2OCOCl and then zinc (as for the conversion of **12** to **17**) to give 1.7 g (77%) of a liquid which gave two peaks (87:13) on vpc analysis. The major product was identified as **11** and the minor one as **10** by comparison of their ir spectra with those of previously synthesized samples.

Reaction of 9-Vinylindolizidine (3) with Ethyl Chloroformate. A. Followed by $LiAlH_4$ Reduction.—A solution of 0.9 g of **3**[5] and 11.4 g of ClCOOEt in 50 ml of benzene which had been heated under reflux for 19 hr was washed with 20 ml of 4 *N* HCl and 20 ml of H_2O. The benzene solution was dried (K_2CO_3) and concentrated at reduced pressure to give 1.6 g of a liquid which was heated under reflux with 1 g of $LiAlH_4$ in 50 ml of THF for 15 hr. After excess $LiAlH_4$ had been destroyed with H_2O the mixture was filtered and the filtrate was dried (K_2CO_3) and concentrated to give 0.5 g of a liquid which gave two product peaks in the vpc (column A) in a ratio of 60:40. An ir spectrum of a vpc-collected sample of the minor product was identical with that of **4**,[5] while that of the major product had peaks at 3100, 1630, 1600, and 885 cm^{-1} consistent[36] with that of a conjugated diene.

B. Followed by Catalytic Reduction and Hydrolysis.—A solution of 4.3 g of **3**[5] in 25 ml of benzene was added over a period of 30 min to a solution of 4.1 g of ClCOOEt in 50 ml of benzene and the resulting dark-yellow solution was heated at reflux for 10 hr. The cooled reaction mixture was successively washed with 30 ml of H_2O, two 15-ml portions of 4 *N* HCl, and 15 ml of H_2O and then dried (K_2CO_3) and concentrated at reduced pressure. The residue was passed through a short Al_2O_3 column to give 2.2 g of a liquid whose vpc (column A) had two overlapping peaks. An ir spectrum of this material indicated the presence of unsaturation (3090, 1630, 1600 cm^{-1}) and the nmr spectrum clearly showed the presence of two overlapping ethyl groups, δ 4.1 (q, J = 7 Hz), 1.25 (t, J = 7 Hz).

A solution of 2.1 g of the above mixture in 50 ml of glacial HOAc and 1 g of 10% Pd/C was hydrogenated at 50 psi for 23 hr. The catalyst was removed by filtration and washed with 20 ml of glacial HOAc and the filtrate was basified with concentrated NaOH and extracted with three 50-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated to give 1.6 g of a liquid whose vpc (column A) contained only one slightly distorted peak.

A solution of the above liquid in 20 ml of glacial HOAc containing 1 g of $TsOH \cdot H_2O$ was heated under reflux for 5 days. The reaction mixture was concentrated at reduced pressure and 35 ml of H_2O and 50 ml of ether were added. The aqueous layer was basified with concentrated NaOH, saturated with K_2CO_3, and extracted with three 30-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated at reduced pressure to give 0.6 g of a liquid displaying two vpc peaks in a 84:16 area ratio. The minor peak had the same retention time as **20** (*vide infra*) and the major peak was identified as 5-ethylazacyclononane (**19**): micro bp 190–192°; ir 3350 cm^{-1}; nmr δ 2.7 (m, 4, CH_2N).

Anal. Calcd for $C_{10}H_{21}N$ (**19**): C, 77.35; H, 13.63; N, 9.02. Found: C, 77.22; H, 13.65; N, 8.95.

Neither a satisfactory picrate nor a styphnate could be prepared.

Methylation of 5-Ethylazacyclononane (19).—After a solution of 0.3 g of **19**, 2 g of paraformaldehyde, and 0.2 g of *p*-$TsOH \cdot H_2O$ in 10 ml of 88% HCOOH had been heated under reflux for 18 hr, it was washed with 20 ml of ether, basified with dilute NaOH, and extracted with two 30-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated at reduced pressure to give 0.15 g (46%) of **21** identified by comparison of its ir spectrum with that of an authentic sample.[5]

9-Ethylindolizidine (20). A. From 2.—A solution of 14.2 g of **2** in 50 ml of THF was added to 300 ml of THF containing ethylmagnesium bromide prepared from 21.8 g of ethyl bromide prepared from 21.8 of ethyl bromide and 8.1 g of magnesium. After refluxing for 4 hr the reaction mixture was decomposed with 200 ml of concentrated NH_4Cl solution and the organic layer was extracted with two 40-ml portions of 6 *N* HCl. The combined acid extracts were saturated with NaCl, washed with benzene, basified with concentrated NaOH, and extracted with three 50-ml portions of ether. The ether extracts were combined, dried (K_2CO_3), and concentrated to yield 5.1 g (35%) of a vpc-pure liquid: bp 38.5° (0.2 mm); ir no unsaturation; nmr δ 2.75 (m, 4, CH_2N), 2.45 (m, 12, CH_2), 0.8 (t, $J \approx 7$ Hz, 3, CH_3). A picrate was prepared, mp 236–238° dec (evacuated capillary).

Anal. Calcd for $C_{16}H_{22}N_4O_7$ (**20** picrate): C, 50.26; H, 5.80; N, 14.65. Found: C, 50.16; H, 5.73; N, 14.90.

B. From 3.—A solution of 2.2 g of **3**[5] in 30 ml of glacial HOAc containing 0.3 g of 10% Pd/C was hydrogenated at 40 psi for 24 hr. The catalyst was removed by filtration and the solvent by evaporation at reduced pressure to leave a residue which was taken up in concentrated NaOH and extracted with three 25-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and concentrated to leave 1.65 g (75%) of an oil containing one major peak and two trace constituents in the vpc. The ir spectrum of a vpc-collected sample of the former was identical with that of **20** prepared above.

Reaction of 9-Vinylindolizidine (3) with Phenyl Chloroformate.—A mixture of 3.6 g of **3**,[5] 4.0 g of PhOCOCl, and 2.0 g of K_2CO_3 in 65 ml of ether was heated to reflux for 15 min, 3 ml of H_2O was added, and heating was continued for another 50 min. Another 10 ml of H_2O was added, the layers were separated, and the ether layer was washed with two 20-ml portions of 3 *N* HCl and one 20-ml portion of H_2O. The ether was dried (K_2CO_3) and concentrated and the residue was chromatographed on a short column of activity I Al_2O_3 with *n*-hexane–benzene. Evaporation of the eluate left 3.3 g of a viscous liquid: ir 3100, 3000, 1715, 1630, 1600, 750, 675 cm^{-1}; nmr δ 7.1, 6.5–4.7, 3.2, 2.6–1.2 (all m).

A mixture of 2.5 g of the above oil, 1 g of 10% Pd/C, and 50 ml of glacial HOAc was hydrogenated for 20 hr at room temperature and atmospheric pressure. The catalyst was removed by filtration, the solvent by evaporation, and the residue was taken up in 50 ml of ether. The ether was washed with two 20-ml portions of 3 *N* HCl, one 10-ml portion of H_2O, and one 20-ml portion of dilute NaOH. The dried (K_2CO_3) ether solution was evaporated to leave 1.6 g of a liquid: ir 3060, 3040, 1720, 1595, 750, 680 cm^{-1}; nmr δ 7.1, 3.4, 1.4 (all m). Acid hydrolysis of this liquid by the same procedure used for the ethyl carbamate of **19** yielded 0.5 g of a liquid whose major constituent (89%) by vpc on column B was identified as **19** by comparison of its ir spectrum with that of an authentic sample from the EtOCOCl cleavage.

Reaction of 9-Benzylindolizidine (22) with Phenyl Chloroformate.—After a mixture of 6.0 g of **22**[4] and 2.3 g of PhOCOCl in 50 ml of ether had been allowed to react for 14 hr at room temperature, it was washed with two 30-ml portions of 3 *N* HCl and three 30-ml portions of dilute NaOH. Evaporation of the dried (K_2CO_3) ether extracts left 3.3 g of a viscous oil: ir 3060, 3030, 1725, 1630, 1600, 750, 690, 680 cm^{-1}; nmr δ 7.1 (s, PhH), 6.3 (C=CHPh), 5.2 (C=CH), 3.2, 1.9 (all m).

Reduction of a 1-g portion of this oil with $LiAlH_4$ according to the procedure used for the ethyl chloroformate of **3** gave 0.5 g of a liquid whose vpc analysis on column A gave two peaks (70:30) neither of which had the same retention time as **22**.

Another 3.1 g of the oily carbamate mixture was heated to reflux with 2 g of NaOH in 45 ml of EtOH for 16 hr. The solvent was removed at reduced pressure and the residue was taken up in 50 ml of H_2O and extracted with two 50-ml portions of ether. The combined ether extracts were extracted with two 30-ml portions of 4 *N* HCl which were then combined, basified with concentrated NaOH, and extracted with three 30-ml portions of ether. Evaporation of the combined and dried (K_2CO_3) extracts left 0.9 g of a liquid whose vpc displayed one major peak (>99%) which was identified as **22** by comparison of its ir spectrum with that of an authentic sample.

(36) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 40.

1-Phenyl-2-dimethylamino-2-methylpropane (26).—A mixture of 10 g of α,α-dimethylphenethylamine,[37] 5 g of paraformaldehyde, 10 ml of 88% HCOOH, and 0.3 g of *p*-TsOH in 15 ml of H_2O was heated under reflux for 19 hr. The cooled mixture was basified with concentrated NaOH and extracted with two 50-ml portions of ether and the dried (K_2CO_3) ether layers were evaporated at reduced pressure to give 10.3 g (86%) of vpc-pure **26**: micro bp 235°; nmr δ 7.1 (s, 5, ArH), 2.6 (s, 2, CH_2), 2.2 (s, 6, NCH_3), 0.9 (s, 6, CCH_3). A picrate, mp 193–193.5°, was prepared.

Anal. Calcd for $C_{18}H_{22}N_4O_7$ (**26** picrate): C, 53.19; H, 5.45; N, 13.78. Found C, 52.99; H, 5.70; N, 13.73.

Reaction of 26 with Phenyl Chloroformate.—A stirred mixture of 832 mg of **26** and 1.46 g of phenyl chloroformate in 30 ml of ether (white percipitate) was allowed to react at room temperature for 2.5 hr, at which time 350 mg of K_2CO_3 was added. After 14 hr a drop of H_2O was added, and the mixture was stirred for 2.5 hr more and then filtered. The filtrate was washed with two 5-ml portions of 5% HCl and three 5-ml portions of 5% KOH. The dried (K_2CO_3) ether layer was concentrated to give 1.29 g of a clear liquid whose vpc (4.5 ft × 0.25 in., 20% SE-30 on Chromosorb P) contained five peaks, the first two of which (*ca.* 1:1) corresponded to methylallylbenzene and α,α-dimethylsytrene in order of increasing retention time. Positive identification was made by a comparison of the vpc retention times, nmr spectra, and mass spectra (Finnegan Model 1015 SL instrument at 70 eV) with those of authentic samples.[37]

Reaction of 9-Vinylindolizidine (3) with $LiAlH_4$ and $NiCl_2$.—To a stirred solution of 7.6 g of $LiAlH_4$ in 500 ml of THF was slowly added 8.0 g of anhydrous $NiCl_2$ and the resulting mixture was heated to reflux for 30 min, at which time 4.0 g of **3**[5] was introduced. After being refluxed for an additional 16 hr, the reaction mixture was cooled, the excess $LiAlH_4$ was destroyed with methanol, 200 ml of ether was added, and the mixture was heated to reflux for another hour. The cooled mixture was filtered, H_2O was added to the filtrate until precipitation was complete, and the mixture was filtered again. This filtrate, including the ether washings of the precipitates, was extracted with three 30-ml portions of 4 *N* HCl and the combined extracts were saturated with KCl and washed with two 50-ml portions of ether which were then combined, dried (K_2CO_3), and concentrated to give 3 g (~75%) of a yellow oil. Vpc analysis (column B) showed four peaks in addition to unreacted starting material (**3**) and a trace of indolizidine. The products of lowest and highest retention time were identified as 9-ethylindolizidine (**20**) and 5-ethylideneazacyclononane (**11**) by comparison of their ir spectra with those of authentic samples. The remaining two products, whose vpc peaks were not completely resolved, were provisionally identified as 5-ethylazacyclononane (**19**) and 5-vinylazacyclononane (**10**) in order of increasing retention time by, in the first case, spiking with an authentic sample and in the second instance by the spectral characteristics: ir 3350 (NH), 3075 (C=CH), 1625 (C=C), and 900 cm^{-1} ($CH=CH_2$); nmr δ 5.75 (m, 1, HC=C), 4.8 (m, 2, $C=CH_2$), 2.75 (m, 5, CH_2N and NH or CHC=).

Selected variations from the above conditions and product analyses are given in Table I.

N-Methylation of Product from Above Reaction of 3.—The 3 g of product from reaction 7 in Table I was dissolved in 2 ml of formic acid and cooled, and the cooled acetic–formic anhydride mixture previously prepared[38] from 4 ml of formic acid and 8 ml of Ac_2O was added. After sitting for 2 hr at room temperature the solution was treated with ice, basified with concentrated NaOH, and extracted with three 20-ml portions of ether. The combined ether layers were washed with two 20-ml portions of 3 *N* HCl and one 20-ml portion of H_2O, dried over K_2CO_3, and concentrated to give 0.7 g of a neutral liquid.

A stirred mixture of 0.6 g of this liquid and 0.5 g of $LiAlH_4$ in 40 ml of ether and 5 ml of THF was heated at reflux for 21 hr. The excess $LiAlH_4$ was decomposed with H_2O, the mixture was filtered, and the filtrate and ether washings of the precipitate were combined, dried (K_2CO_3), and concentrated to give 0.6 g of a light yellow oil. Vpc analysis of this oil on a 15 ft, 5% KOH, 15% PPE on Chromosorb W column gave three peaks in an area ratio of 15:42:43 which were identified as the *N*-methylamines **21**, **29**, and **4**, respectively, from a comparison of the ir spectra of vpc-collected material with those of authentic samples.[5] The vpc-area ratio of the secondary amines **19**, **10**, and **11** in the reactant was 14:42:44. Similar experiments with mixtures of **19**, **10**, and **11** of different composition also gave mixtures of **21**, **29**, and **4** with unchanged compositions.

Acknowledgment.—This research was generously supported by The Robert A. Welch Foundation, the National Science Foundation,[2] and the TCU Research Foundation.

Registry No.—**2**, 30820-52-1; **3**, 35201-24-2; **4**, 35249-63-9; **5**, 40952-29-2; **6**, 40952-30-5; **8**, 40952-31-6; **8** benzyl bromide salt, 40952-32-7; **11**, 40952-33-8; **11** styphnate, 40952-34-9; **12**, 40952-35-0; **12** methiodide, 40952-36-1; **13**, 40952-37-2; **14**, 40952-38-3; **16**, 40952-39-4; **17**, 40952-40-7; **19**, 40952-41-8; **20**, 40952-42-9; **20** picrate, 40952-43-0; **21**, 40952-44-1; **22**, 4753-49-5; **26**, 40952-46-3; **26** picrate, 40952-47-4; indolizidine, 13618-93-4; NaCN, 143-33-9; ethyl chloroformate, 541-41-3; $PhCH_2Br$, 100-39-0; PhOCOCl, 1885-14-9; *N*-benzylpieripdine, 2905-56-8; 2,2,2-trichloroethyl chloroformate, 17341-93-4; α,α-dimethylphenethylamine, 122-09-8.

(37) Aldrich Chemical Co., Milwaukee, Wis.

(38) W. Stevens and A. Van Es, *Recl. Trav. Chim. Pays-Bas*, **83**, 1287 (1964).