Effects of the Alkyl Portion of the Alkoxy Group on the Mass Spectrometric Fragmentation Pathways for the 1-Alkoxy-9-oxabicyclo[3.3.1]nonane System and Comparison with the 1-Alkoxy-9-methyl-9-azabicyclo[3.3.1]nonane System

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The mass spectral fragmentations of the 9-oxabicyclo[3.3.1]nonane nucleus substituted at a bridgehead position with OCH_3 (**1**), OC_2H_5 (**2**), $OCH(CH_3)_2$ (**3**), $OC(CH_3)_3$ (**4**), OH (**5**), and OC_6H_5 (**6**) are reported. The ketals **1** and **2** and hemiketal **5** give rise to their base peaks via α cleavage of the 1,2 bond, loss of ethylene, isomerization to the molecular ion of the corresponding 5-hexenoic acid derivative by means of homolytic scission of the 5,9 carbon–oxygen bond, and a McLafferty rearrangement; a combination of high resolution mass spectral measurements and mass-analyzed ion kinetic energy spectra, as well as the mass spectrum of methyl 5-hexenoate, were utilized to establish the fragmentation sequences leading to the base peaks of **1**, **2**, and **5**. For the branched chain ketals **3** and **4**, a hydrogen from the alkyl portion of the alkoxy group is transferred to an oxygen atom (probably the 9 oxygen atom via a Barton hydrogen-abstraction process within the molecular ion), after which expulsion of the hydrocarbon side chain as an alkene, loss of ethylene, and a McLafferty rearrangement (similar to that observed for compounds **1**, **2**, and **5**) take place. Comparison of the 1-alkoxy-9-oxabicyclo[3.3.1]nonane system with the 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonane system revealed that the pathways leading to the base peaks in each system are unique.

In a recent report from this laboratory, the principal mass spectral fragmentation patterns of the 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonane system were elucidated.[2] It was established that the nature of the alkoxy group exerts considerable influence on the fragmentation processes, particularly those leading to the base peaks. Thus, it was found that for the α-amino bridgehead ethers in which the R group is derived from a *primary* or *secondary* alcohol the base peaks occur without exception at *m/e* 112. Chart I contains the mechanistic pathway proposed to account for the generation of the *m/e* 112 ion. The molecular ion undergoes α cleavage to produce an ammonium ion which then consecutively expels cyclopropane and the R group to provide the base peak. On the other hand, while the *tertiary* alkoxy amines also display intense signals at *m/e* 112, the base ions are at *m/e* 113. Chart II summarizes the sequences presented to rationalize the formations of the *m/e* 113 ions. In a manner analogous to the hydrogen-transfer process of the Hofmann–Loeffler reaction,[3] the molecular ion (an amininium ion) abstracts a hydrogen from the alkoxy side chain and (sometimes simultaneously) expels the alkyl portion of the side chain to give an ammonium alkoxy radical which undergeos α cleavage and expulsion of cyclopropane to afford the base peak. (The *secondary* alkoxy amines also give rise to relatively abundant signals at *m/e* 113 on account of the availability of hydrogens conformationally suitable for abstraction by the initially generated nitrogen radical cation.)

In order to ascertain whether or not the conformational effects of the alkyl portion of the 1-alkoxy group found for the 9-azabicyclo[3.3.1]nonane system can be extended to other heterobicyclic frameworks, the mass spectra of some 1-alkoxy-9-oxabicyclo[3.3.1]nonanes (**1–4**) have been measured, as well as the hemiketal **5** and phenyl ketal **6**. Until now there have been no published reports dealing with the mass spectrometry of the 9-oxabicyclo[3.3.1]nonane skeleton.

Chart I

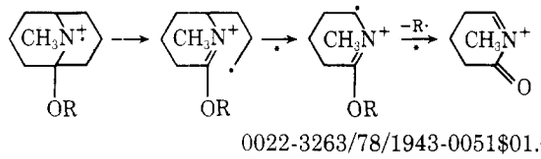
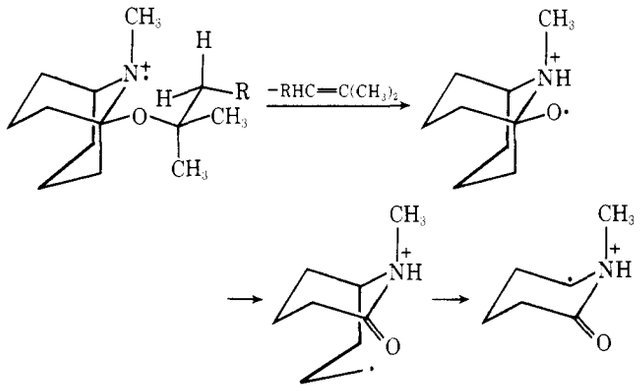
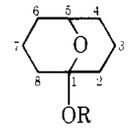


Chart II



Results and Discussion

Table I collects the relative intensity data for the important fragment ions in the mass spectra of compounds **1–6**.[4] Upon



1, R = CH_3 4, R = $(CH_3)_3C$
2, R = CH_3CH_2 5, R = H
3, R = $(CH_3)_2CH$ 6, R = C_6H_5

inspection of the data in Table I, it is seen that the most striking features are: (1) that the ketals **1–4** show only *weak* signals at *m/e* values of 99 and 100, corresponding to the oxa analogues of the terminal aza ions shown in Charts I and II, respectively, which are the most abundant ions in the mass spectra of the 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes;[2,5] and (2) that, while methyl ether **1** has its base peak at *m/e* 74 and its next higher homologue (ethyl ether **2**) gives rise to its base peak at *m/e* 88 (which is consistent with the 14 amu increment resulting from the additional methylene unit), isopropyl ether **3** and *tert*-butyl ether **4** show signals at *m/e* 102 and 116, respectively, with relative intensities *less* than 1%. Clearly, the 9-oxabicyclo[3.3.1]nonane system behaves significantly differently upon electron bombardment than the

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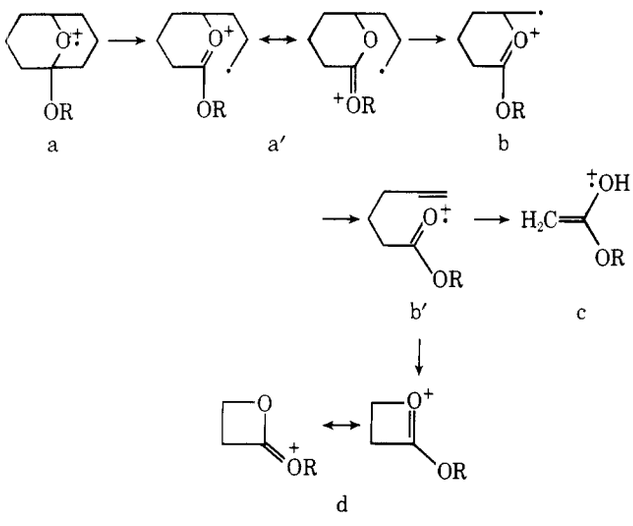
Table I. Relative Intensity Data For Bridgehead-Substituted Ethers

			m/e; ion; %		
1[d]	2[d]	3[d]	4[a,d]	5[d]	6[b,d]
156; a; 29	170; a; 49	184; a; 57	198; a; 4	142; a; 75	218; a; 34
128; b; 12	142; b, e; 16	156; b; 1	170; b; <1	114; b; 90	190; b; <1
87; d; 30	101; d; 39	115; d; 2[c]	129; d; <1	73; d; 54	149; c; 2
74; c; 100	88; c; 100	102; c; <1	116; c; <1	60; c; 90	136; d; <1
125; i; 5	114; f; 8	142; e; 45	142; e; 80	125; i; 5	125; i; 20
99; <1	73; h; 21	114; f; 100	114; f; 74		
100; 2	60; g; 44	73; h; 48	73; h; 35		
	125; i; 9	60; g; 46	60; g; 32		
	99;7	125; i; 20	125; i; 29		
	100; 2	99; 11	99; 8		
		100; 17	100; 9		

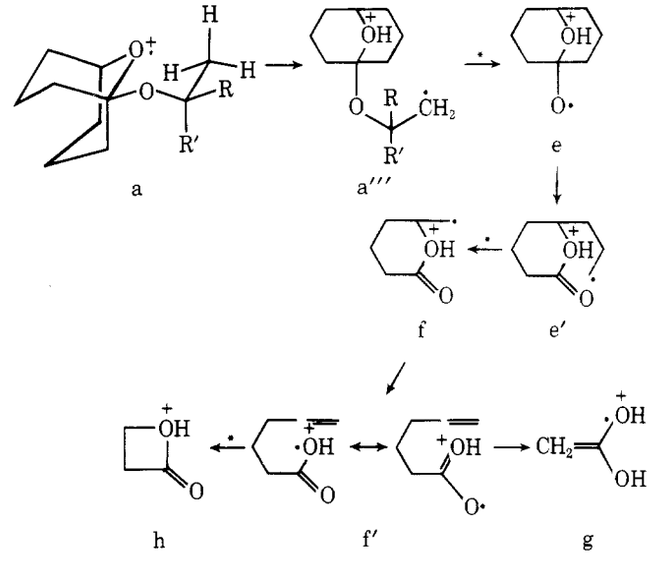
[a] The base peak occurs at *m/e* 41. [b] The base peak occurs at *m/e* 94. [c] Adjusted for the p + 1 contribution of the *m/e* 114 signal. [d] Registry no.: **1**, 63989-34-4; **2**, 63989-35-5; **3**, 63989-36-6; **4**, 63989-37-7; **5**, 37996-41-1; **6**, 63989-38-8.

Chart III



1, R = CH_3
2, R = CH_3CH_2
5, R = H

Chart IV



2, R = R′ = H
3, R = H; R′ = CH_3
4, R = R′ = CH_3

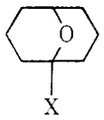
9-methyl-9-azabicyclo[3.3.1]nonane geometry when each framework is substituted at a bridgehead position with an alkoxy group, and (as with the azabicyclic skeleton) the nature of the alkyl portion of the alkoxy group plays a prominent role in the fragmentation pathways, particularly those leading to the formation of the base peaks.

Chart III details the proposed fragmentation scheme leading to the base ions for ketals **1** and **2.** Cleavage of the 1,2 bond in the molecular ion a[6] produces the resonance-stabilized species a′ which expels ethylene to generate b which rearranges via homolytic cleavage of the 5,9 carbon–oxygen bond to the radical cation b′; fragment b′ is structurally (but not necessarily energetically) identical (or nearly so) to the molecular ion of methyl or ethyl 5-hexenoate. Radical cation b′ then takes part in a McLafferty rearrangement (a characteristic feature in the mass spectrometry of aliphatic carboxylic esters[7b]), expelling butadiene to provide the base peak c. Alternatively, intermediate b′ eliminates the relatively stable allyl radical to produce the resonance-stabilized cation d. The mass spectrum of hemiketal **5** (the next lower homologue of ketal **1**) shows several similarities to the mass spectra of its methyl and ethyl ketals **1** and **2**, respectively. Thus, it also contains a substantial (relative intensity = 90%) peak at *m/e* 60 corresponding to ion c (R = H) as well as a strong (relative intensity = 54%) signal at *m/e* 73 corresponding to ion d. Support for the correctness of the interpretations advanced in Chart III comes primarily from a detailed investigation of hemiketal **5.** Thus, the utilization of high-resolution mass spectrometry established unequivocally that the ions at *m/e* 114, 60, and 73 correspond *exclusively* to elemental compositions consistent with ions **5b′–d,** respectively. Moreover, mass-analyzed ion kinetic energy (MIKE) spectra[9] confirmed the actuality of the steps **5a′ → 5b** and **5b′ → 5d.** In addition, the mass spectrum of methyl 5-hexenoate has been recorded;[10] the base peak occurs at *m/e* 74, just as it does for the methyl ketal **1.**[11,12] Therefore, there can be little doubt that the pathways advocated in Chart III are reasonably accurate representations of the fragmentations occurring in the mass spectrometer for hemiketal **5** and ketals **1** and **2.**

As mentioned above, the isopropyl and *tert*-butyl derivatives **3** and **4** do *not* follow the primary paths (Chart III) taken by the methyl and ethyl compounds **1** and **2;** the ions **3b–d** and **4b–d** are present to the extent of less than 2% each. The principle fragmentations for ketals **3** and **4** are, however, *closely related* to the primary paths presented in Chart III for the ketals **1** and **2.** The principal fragmentations for the isopropyl and *tert*-butyl substrates are triggered by an intramolecular transfer of a hydrogen from the alkyl portion of the alkoxy group to the 9-oxygen atom (Chart IV).[6] The side-chain hydrogen is abstracted by the 9-oxyl radical cation to provide the isomeric species a‴ which then loses the side chain as an olefin to afford e which rearranges to e′ and loses ethylene to give f which in turn isomerizes to f′. The a → a‴ step is another

example[13] of the Barton reaction[14] occurring in the mass spectrometer; additional support for the hydrogen abstraction process shown in Chart IV comes from the analogous step established for the 9-azabicyclo[3.3.1]nonane system illustrated in Chart II.[2] Radical cation f′ then goes on to ion g by way of a McLafferty rearrangement analogous to the b′ → c step exhibited by the methyl and ethyl ketals (Chart III); alternatively, f′ also goes on to h upon the elimination of allyl radical. Appropriate metastable peaks for the a‴ → e steps for ketals **3** and **4** were found at *m/e** values of 109.6 and 101.8, respectively; likewise, the mass spectra of **3** and **4** each displayed intense metastable peaks at *m/e** values of 91.5 and 46.7 corresponding to the e′ → f and f′ → h steps. Thus, the fragmentation scheme postulated in Chart IV is supported.[15]

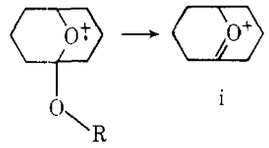
It is important to point out that *none* of the 1-alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes examined previously[2,5] show *m/e* values corresponding to the analogous terminal ions of Charts III and IV with relative intensities greater than 1%. It has also been found that neither the parent ether **7** nor its bridgehead chloride derivative **8** produce ions analogous to



7, X = H
8, X = Cl

ions c and d to any significant extent.[18] Thus, it appears as though the terminal fragmentations of Charts III and IV may be characteristic of 1-alkoxy- and 1-hydroxy-9-oxabicyclo-[3.3.1]nonanes, although further studies will be required to establish the generality of the selectivity found so far, since phenyl ketal **6** does *not* follow the paths outlined in Chart III.

The mass spectrum of phenyl ketal **6** shows an overwhelming base peak at *m/e* 94 which corresponds to the radical cation of phenol; only three other signals occur with relative intensities greater than 15%: the molecular ion (a), the



a i

ion at *m/e* 55, and the cation at *m/e* 125 for which structure i is suggested.[2] Clearly, the phenyl group brings about dramatic changes in the mass spectrometry of the 9-oxabicyclo[3.3.1]nonane system compared to the other ketals studied; such a phenomenon was also observed in the 9-methyl-9-azabicyclo[3.3.1]nonane system.[2]

Conclusions

Two important conclusions emerge from the present investigation: (1) The nature of the alkyl portion of the alkoxy group plays a dominant role in the fragmentation sequences involving the base ions. Thus, in the unbranched side-chain series O–$(CH_2)_nH$ (n = 0, 1, 2), the side chain is retained during the primary fragmentation pathway, while for the ketals bearing side chains derived from secondary or tertiary alcohols a hydrogen from the side chain is transferred to an oxygen atom and the remaining hydrocarbon portion of the side chain is lost during the primary fragmentation scheme. Furthermore, the straight-chain ketals (e.g., **2**) follow only to a minor extent the branched-chain primary fragmentation scheme (Chart IV), and the branched-chain ketals follow to a negligible degree the straight-chain primary fragmentation pathway (Chart III). Therefore, since the primary fragmentation sequences of 1-alkoxy-9-oxabicyclo[3.3.1]nonanes are strongly and highly selectively dependent upon the nature of branching in the 1-alkoxy side chain, mass spectrometry should prove to be extremely valuable in ascertaining the identity of a side chain in this system (and perhaps other related systems such as derivatives of multistriatin and other similar insect pheromone components[19]). In contrast to the alkoxy substrates **1–4**, the primary fragmentation path for phenyl ketal **6** produces the radical cation of phenol. (2) Although the molecular architectures of the 9-oxa- and 9-methyl-9-azabicyclo[3.3.1]nonane geometries are very similar, the primary fragmentation sequence for each system is specific, as evidenced by comparing Chart I with III and Chart II with IV.

Experimental Section

Mass spectra were obtained with an A.E.I. MS-9 mass spectrometer operating at an ionization voltage of 70 eV and a source temperature of about 175 °C. High-resolution measurements, MIKE spectra, and AVS spectra were obtained with a Varian MAT-311 instrument. Proton NMR spectra were measured on a Varian Associates T-60 machine, employing $CDCl_3$ solutions with internal Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer as neat films. All substrates were purified by preparative gas chromatography (with a Varian Aerograph 90-P apparatus equipped with a 5 ft × 0.25 in. stainless-steel column packed with 20% SE-30 on Chromosorb G) immediately prior to mass spectral measurements; the column temperatures employed for sample collection were about 190 °C (which established that the substrates were thermally stable to the conditions used with the mass spectrometer). Elemental analyses were performed by Spang Microanalytical Laboratories. Compounds **1, 2, 4, 5,** and **7–9** were previously known and were prepared according to published procedures.[20] Ketals **3** and **6** are new compounds and were synthesized by the solvolysis reactions of the bridgehead chloride **8** with 2-propanol and phenol, respectively, as described previously for the 9-methyl-9-azabicyclo[3.3.1]nonane system;[2] the spectral properties and analytical results of **3** and **6** (both of which are colorless oils at room temperature) are as follows.

1-(2-Propoxy)-9-oxabicyclo[3.3.1]nonane(3): NMR δ 4.2–4.5 [m, 1 H, bridgehead *H*], 4.22 [m, *J* = 6.5 Hz, 1 H, $CH(CH_3)_2$], 1.3–2.3 [m, 12 H, CH_2 groups], 1.16 [d, *J* = 6.5 Hz, 6 H, $CH(CH_3)_2$]; IR 2965, 2930, 1368, 1179, 1155, 1123, 1115, 1045, 1017 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 72.25; H, 10.96.

1-Phenoxy-9-oxabicyclo[3.3.1]nonane (6). NMR δ 7.3–6.8 [m, 5 H, aromatic *H*], 4.5–4.2 [m, 1 H, bridgehead *H*], 2.3–1.2 [m, 12 H, CH_2 groups]; IR 3050, 3030, 2930, 1595, 1585, 1490, 1370, 1240, 1225, 1215, 1145, 1098, 1015, 942, 898, 885, 778, 705 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.89; H, 8.33.

Registry No.—**8**, 40164-34-9; 2-propanol, 167-63-0; phenol, 108-95-2.

Supplementary Material Available. Bar graphs of the mass spectra of ketals **1–4** (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) The University of Michigan; (b) General Electric Co.; (c) correspondence concerning this manuscript should be directed to H. O. K. at the General Electric Co. address.
(2) H. O. Krabbenhoft, *J. Org. Chem.*, **41**, 1774 (1976).
(3) M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).
(4) Bar graphs of ketals **1–4** appear in the microfilm edition; see paragraph at end of paper regarding supplementary material.
(5) H. O. Krabbenhoft, *J. Org. Chem.*, the preceding article in this issue.
(6) There are two nonequivalent oxygen atoms which can be ionized upon electron impact (a and a″). None the less, several lines of evidence point to the preferential *effective* localization of charge on the 9-oxygen: (i) For ketals **2–4** the M − CH_3 peaks are of very low relative intensities (less than 1%); if the 1-oxyl radical cation a″ were generated, substantially higher intensity signals for the M − CH_3 ions would be expected.[7a] (ii) While abundant peaks are found at *m/e* 124 indicating the loss of the alkoxy group

a a′

in the form of a neutral alcohol and corresponding to the retention of the charge on the bridgehead enol ether, peaks associated with the elimination of a neutral bridgehead olefin and charged alcohols are virtually absent; such a situation also exists for 2-alkoxytetrahydropyrans.[8] (iii) The loss of alkoxy radical from the molecular ion to provide the oxonium ion i requires the 9-oxyl radical cation.

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(15) It is also possible that the hydrogen is transferred to the 9-oxygen atom via a McLafferty rearrangement within a′,[2,16] or to the 1-oxygen atom via the hydrogen migration/olefin elimination process (within a′) characteristic of ethers.[7a,17]
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Synthesis of 1-Azatricyclo[5.2.1.0^{4,10}]decane[1]

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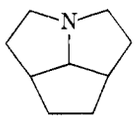
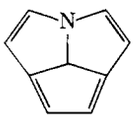
The title compound (**1**) has been synthesized by the reductive cyclization of 2,5-bis(cyanomethyl)cyclopentanone (**5**) with a Raney Ni and, in better yield, with a Raney Co catalyst. The pK_a of **1** is 8.50. Attempts to introduce unsaturation into the system were unsuccessful. Treatment of the *N*-benzyl quaternary salt with butyllithium gave Hofmann elimination and Stevens rearrangement products, but fragmentation occurred with the *N*-methyl quaternary salt. Other cyclopentanone condensation experiments are described.

Our interest in the behavior of quarternary salts of cyclic amines with base[3] and in new heterocyclic, nonalternant, conjugate-unsaturated systems[4] led to consideration of the 1-azatricyclo[5.2.1.0^{4,10}]decane structure (**1**), a possible precursor to 7a*H*-cyclopent[*gh*]-1-azapentalene (**2**) which would



1



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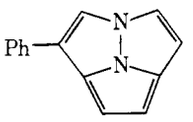

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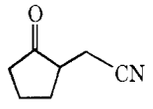
be an azaannulene with a 10 π-electron periphery distorted from planarity by the tetrahedral bridge atom. The closest analogy found was 1-phenyl-8-azacycl[2.2.2]azine (**3**) which was noted to exhibit ^{1}H NMR absorption only in the aromatic region,[5] but which has an unshared electron pair on the central nitrogen.

Leonard and Middleton[6] attempted to prepare **1** and the corresponding 1-azatricyclo[6.2.1.0^{4,11}]hendecane by the high-pressure hydrogenation of the oximes of diethyl cyclopentanone-2,5-diacetate and cyclohexanone-2,6-diacetate, respectively. They attributed the failure of the method to the assigned trans stereochemistry of the carbethoxymethyl groups (introduced by alkylation of the ketone enolate anion), and the formation of the trans product to steric factors. Later, however, Bohlmann et al.[7] showed the cyclohexanone diester to be the cis isomer. Thus, the failure to achieve the tricyclic system was apparently due to the reaction conditions. Subsequently, Mandell et al.[8] prepared *cis*-2,6-bis(cyanomethyl)cyclohexanone using Stork's enamine synthesis[9] and reductively cyclized it to the tricyclic amine in low yield.

Application of Mandell's procedure to the monoalkylation of cyclopentanone with chloroacetonitrile gave a 10% yield of the 2-cyanomethyl derivative (**4**) as compared to 35–45% reported[8] and verified by us for cyclohexanone. A comparable yield disparity has been observed with ethyl bromoacetate as the alkylating agent.[10] The use of dioxane as the solvent and morpholine as the base raised the yield of **4** to ca. 30%, which was still not satisfactory. The procedure of Gutsche et al.[11] of a one-pot reaction of cyclopentanone, pyrrolidine, and one equivalent of chloroacetonitrile was then tried and gave 31% of **4** plus a small amount of **5**. The use of two equivalents of



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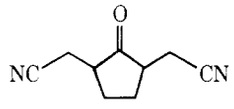
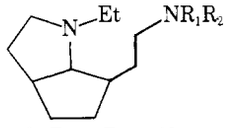


5

chloroacetonitrile and one additional equivalent of triethylamine afforded yields of 42 and 31%, respectively. A two-step procedure with the isolation of **4** gave appreciably lower yields of **5**. Hydrolysis of **5** formed the known corresponding dicarboxylic acid. An attempt to prepare **4** by the alkylation of the anion of *N*-cyclohexyliminocyclopentane[12] gave only tarry products.

High-pressure reduction of **5** in the presence of W-5 Raney nickel catalyst formed **1** (ca. 10%) along with three other compounds which were assigned structures as 1-ethyl-6-(2-aminoethyl)- (**6**), 1-ethyl-6-(2-ethylaminoethyl)- (**7**), and 1-ethyl-6-(2-diethylaminoethyl)cyclopentano[2,3]pyrrolidine (**8**) on the basis of their spectral characteristics. The ethyl groups in **6**–**8** came from the ethanol solvent.[13] Reduction in acetic acid gave essentially no **1**, but the use of glyme as the



6, $R_1 = R_2 = H$
7, $R_1 = H$; $R_2 = Et$
8, $R_1 = R_2 = Et$

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