melting point, and infrared spectrum) with an authentic sample of the ethyl ester of V.

**Phthalidin-2-propionic Acid (VI).**—A solution of 3.5 g (0.018 mole) of 2-hydroxy-3-methyl-1,4-naphthoquinone (IV) in 30 ml of concentrated sulfuric acid was cooled to 0°. To this solution was added 1.7 g (0.026 mole) of sodium azide at such a rate as to maintain the reaction temperature between 5 and 10°. The resulting solution was then allowed to warm to room temperature and stand for an additional 2 hr. The reaction solution was then poured into water causing the precipitation of a yellow solid. This mixture was immediately filtered. The collected solid was mainly unreacted quinone, recovered in excess of 1.5 g. The lactone, VI, precipitated from the mother liquor as a white crystalline solid. Recrystallization from ethanol gave 300 mg (8.3% yield), mp 253° (lit.[10] mp 248°).

*Anal.* Calcd for $C_{11}H_8O_4$: C, 64.70: H, 3.92. Found: C, 64.71; H, 4.11.

**Nmr Spectroscopy.**—The nmr spectra were recorded on a Varian Associates high resolution spectrometer (A-56/60) at a frequency of 60 Mcps. Chemical shifts are expressed as shielding values, $\tau$, as defined by G. V. D. Tiers.[12]

**Registry No.**—III, 83-72-7; IV, 483-55-6; V, 4403-34-3; VI, 14120-20-8; VIII, 14120-21-9; IX, 577-56-0; X, 14120-22-0; XIII, 14120-23-1.

**Acknowledgment.**—The authors are grateful to the National Science Foundation for partial support of this work from Grant GP 5945.

(12) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

# Small Charged Rings. X.[1] Expansion of the Aziridinium Ring by Reaction with Nitrones[2]

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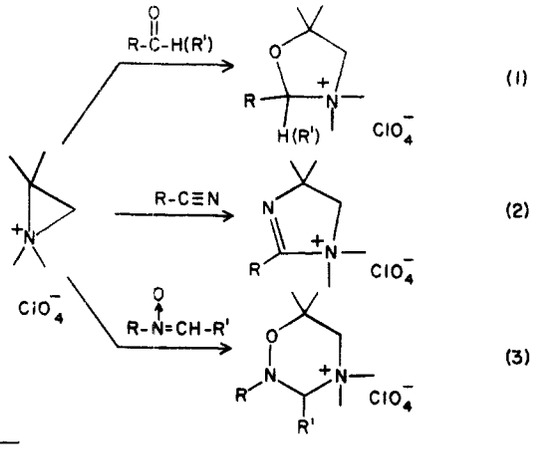
*Received June 19, 1967*

1,1,2,2-Tetramethylaziridinium perchlorate (**3**) has been shown to react with substituted $\Delta^1$-pyrroline 1-oxides (**2**) to yield 1:1 adducts (**4**) containing the 2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane ring system. The ring expansion thus effected is representative of a new type, expressed as ③$^+$ + 3 → ⑥$^+$, in which a three-membered charged ring combines with a 1,3-dipolar moiety to form a six-membered charged ring. The structures of the adducts were established by catalytic hydrogenolytic cleavage of the 5,6 bond, followed by reductive cleavage of the 1,2 bond with zinc and acetic acid, with attendant spectroscopic and chemical identification of the sequential degradation products. Similar adducts (**15**) were obtained from 1-benzyl-1-ethyl-1-azoniaspiro[2.5]octane perchlorate (**14**) and substituted $\Delta^1$-pyrroline 1-oxides. In this case, cleavage of the 5,6 bond in the adduct was effected with lithium aluminum hydride and cleavage of the 1,2 bond with zinc and acetic acid to complete the establishment of structure.

Previous papers in this series[5] have described the expansion of the aziridinium ring with aldehydes and ketones to form oxazolidinium salts (eq 1) and with nitriles to form imidazolinium salts (eq 2). These reactions may be represented generally by the expression ③$^+$ + 2 → ⑤$^+$, descriptive of a broad type in which a charged, three-membered cycle is increased in size to a charged, five-membered cycle.[6-8] They appear to proceed by opening of the aziridinium ring to the more stable of two possible tertiary β-aminocarbonium ions, which combines with the polarized carbonyl or nitrile group to form the appropriate five-membered heterocycle. We now report an extension of the scope of such ring enlargements to include a new type, ③$^+$ + 3 → ⑥$^+$, where the adding group is a 1,3-dipole in general, a nitrone (azomethine N-oxide) in this particular case (eq 3). The 1,3-dipolar cycloaddition of nitrones to olefinic and acetylenic bonds to form isoxazolidine derivatives is well documented.[9-12] We be-




(1) For preceding article in this series, see N. J. Leonard and B. Zwanenburg, *J. Am. Chem. Soc.*, **89**, 4456 (1967).

(2) This investigation was supported by Research Grant GP 2012 from the National Science Foundation, to whom we are pleased to acknowledge our thanks.

(3) Lubrizol Corp. Fellow, 1964–1965; National Science Foundation Cooperative Fellow, 1965–1967.

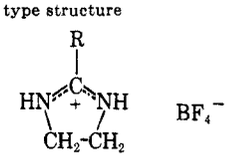
(4) On leave from Central Research Laboratory, Daiichi Seiyaku Co., Ltd., Edogawa-ku, Tokyo, Japan, 1964–1965.

(5) For pertinent references and a general summary of work in this field, see N. J. Leonard, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **26**, 211 (1966).

(6) N. J. Leonard, J. V. Paukstelis, and L. E. Brady, *J. Org. Chem.*, **29**, 3383 (1964).

(7) N. J. Leonard and L. E. Brady, *ibid.*, **30**, 817 (1965).

(8) E. Pfeil and U. Harder, *Angew. Chem.*, **77**, 505 (1965). The tautomeric structure and the name used in this reference to represent the product of reaction of a nitrile with unsubstituted aziridinium tetrafluoborate are very likely in error, since the vigorous conditions employed by Pfeil and Harder would certainly be expected to bring about equilibration to the more stable, symmetrical amidinium type structure



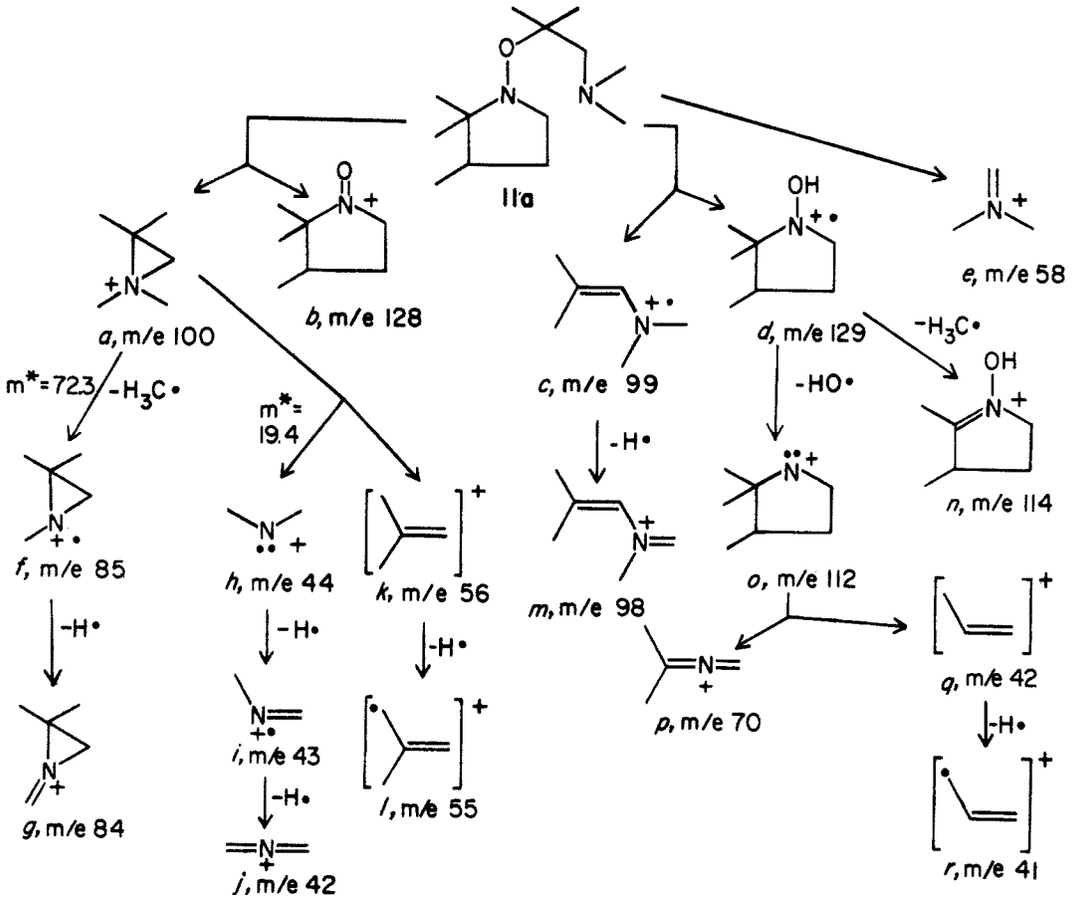

(9) For two recent reviews of the chemistry of nitrones, see (a) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964); (b) G. R. Delpierre and M. Lamchen, *Quart. Rev.* (London), **19**, 329 (1965).

(10) (a) N. A. LeBel and J. J. Whang, *J. Am. Chem. Soc.*, **81**, 6334 (1959); (b) N. A. LeBel, G. M. J. Slusarczuk, and L. A. Spurlock, *ibid.*, **84**, 4360 (1962); (c) N. A. LeBel, M. E. Post, and J. J. Whang, *ibid.*, **86**, 3759 (1964).

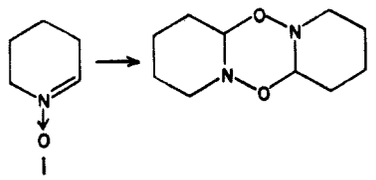
(11) (a) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963); (b) R. Huisgen, *ibid.*, **2**, 633 (1963).

(12) I. Brüning, R. Grashey, H. Hauck, R. Huisgen, and H. Seidl, *Org. Syn.*, **46**, 127 (1966).

SCHEME I



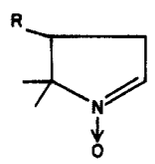

lieve that the reaction with aziridinium salts described herein constitutes the first example of a cycloaddition of a nitrone to what presumably may be represented as a 1,3 *polar* moiety as the aziridinium ring is opened.



1

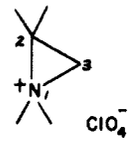
The reported cyclodimerization[13] of $\Delta^1$-piperideine 1-oxide (**1**) bears some resemblance to the above reaction type, but in that case the nitrone adds to a 1,3 *dipolar* species.

4,5,5-Trimethyl-$\Delta^1$-pyrroline 1-oxide (**2a**) and 5,5-dimethyl-$\Delta^1$-pyrroline 1-oxide (**2b**) were chosen as representative nitrones, since these compounds could be



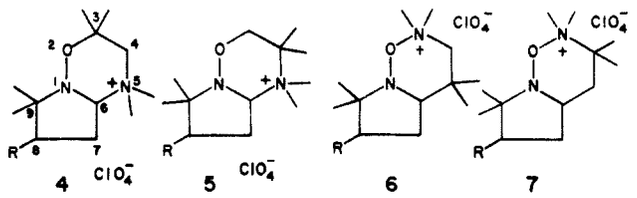
**2a**, R=CH$_3$

**2b**, R=H



**3**

synthesized conveniently,[14] are reasonably stable, and are known to be monomeric. When an intimate mixture of 1,1,2,2-tetramethylaziridinium perchlorate (**3**)[6] and either nitrone was allowed to stand for several days at room temperature, a product having the correct analysis for a 1:1 adduct was isolated in good yield. Assuming that one of the aziridinium ring C–N$^+$ bonds had been broken during the reaction, we considered four possible structures (**4**–**7**) for the adducts.[15] *A priori* we tended to favor structure **4** for two reasons. Bond dissociation energy calculations



**4** **5** **6** **7**

**a**, R=CH$_3$

**b**, R=H

indicated that **4** and **5** should be more stable than **6** and **7** by approximately 23 kcal/mole. Moreover, on the basis of our previous experience with aziridinium salts, it was expected that in the process of ring expansion the 1,2 bond of the aziridinium moiety would be broken in preference to the 1,3 bond. Unfortunately, the infrared and nmr spectra of the adducts were not sufficiently definitive to permit a decision regarding structure; accordingly, we resorted to chemical degradation.

(13) J. Thesing and H. Mayer, *Chem. Ber.*, **89**, 2159 (1956).

(14) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959).

(15) Possible structures containing a tertiary amine N-oxide grouping were eliminated on the basis of the absence of a strong band in the 950–970-cm$^{-1}$ region in the infrared spectra of these adducts; see R. Mathis-Noel, R. Wolf, and F. Gallais, *Compt. Rend.*, **242**, 1873 (1956).

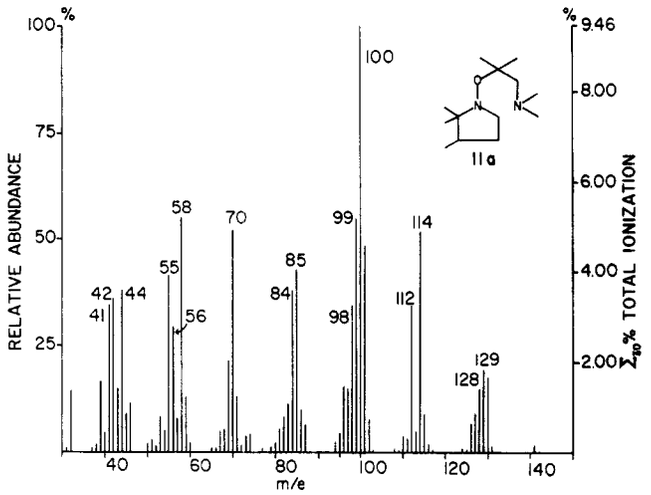



Figure 1.—Mass spectrum of N-[2-methyl-2-(2′,2′,3′-trimethylpyrrolidin-1′-oxy)propyl]dimethylamine at 70 ev.

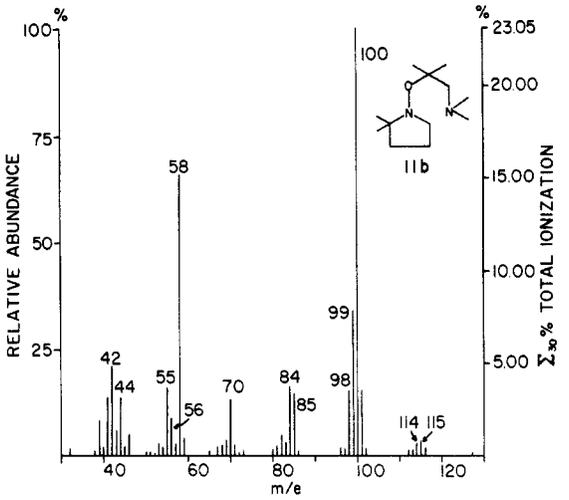
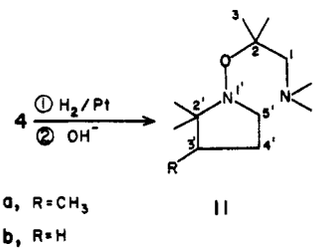



Figure 2.—Mass spectrum of N-[2-(2′,2′-dimethylpyrrolidin-1′-oxy)-2-methylpropyl]dimethylamine at 70 ev.

Catalytic hydrogenolysis of the adduct obtained from **2a** and **3**[16] resulted in the uptake of 1 mole of hydrogen per mole of compound. The product (**8a**) proved to be a tertiary amine perchlorate, as evidenced by an infrared band at 3100 $cm^{-1}$ for $\rightarrow N^+H$. Treatment with aqueous base liberated a free amine which was homogeneous by glpc analysis. The infrared spectrum of this amine showed no bands attributable to O–H or N–H, indicating that an N–O bond had not been cleaved in the hydrogenolysis. The nmr spectrum of the amine *vis-à-vis* that of its salt was instructive. A six-proton singlet in deuteriochloroform ($\tau$ 7.72) became a doublet in trifluoroacetic acid ($\tau$ 6.80, $J$ = 4.5 cps), indicating the presence of a $(CH_3)_2N$ group in the molecule. Further information was obtained from a consideration of the nmr spectra of the two isomeric amino alcohols **9** and **10**. In deuteriochloroform, **9** exhibited singlets at $\tau$ 7.65 and 7.72 for $(CH_3)_2N-$ and $-CH_2-N<$, respectively, while **10** had singlets at $\tau$ 7.79 and 6.67 for $(CH_3)_2N-$ and $-CH_2O-$, respectively. The spectrum of the amine from **8a** in deuteriochloroform exhibited singlets at $\tau$ 7.72 (six protons) (mentioned above) and 7.75 (two protons), suggesting the presence of the $(CH_3)_2NCH_2$ moiety. These data, together with other features of the spectra, effectively eliminated all possible structures for the free amine except **11a**, N-[2-methyl-2-(2′,2′,3′-trimethylpyrrolidin-1′-oxy)propyl]dimethylamine. Thus, it followed that **8a** was simply the perchlorate of **11a** and the structure of the original adduct had to be **4a**, 3,3,5,5,8,9,9-heptamethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane perchlorate (and **4b**, 3,3,5,5,9,9-hexamethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane perchlorate).

**9** **10**

For further confirmation of the assigned structures **11a** and **11b** (N-[2-(2′,2′-dimethylpyrrolidin-1′-oxy)-2-methylpropyl]dimethylamine), mass spectra (70 ev) were obtained for both of these compounds (Figures 1 and 2). The proposed fragmentation process for **11a** is outlined in Scheme I; a similar sequence appears to hold for **11b**. The ease with which these highly




branched molecules undergo fragmentation is evidenced by the absence of a discernible molecular ion peak in both spectra, even when the ionizing voltage was reduced to 12 ev. Osmometric determination of the molecular weights, however, gave values well in agreement with the calculated values. There appear to be three primary modes of fragmentation. One involves the well-documented[17] cleavage $\alpha$–$\beta$ to the tertiary amine function to yield the intense fragment *e* (*m/e* 58), a result diagnostic for the $(CH_3)_2NCH_2$ moiety. Both of the other modes involve cleavage of the C–O bond to yield either fragments *a* (*m/e* 100) and *b* (*m/e* 128) or *c* (*m/e* 99) and *d* (*m/e* 129). In view of the fact that the *m/e* 99 peak is greatly enhanced relative to the *m/e* 100 peak when the sample is heated in the inlet system, it appears that the process giving rise to fragments *c* and *d* is largely thermal in nature. The remaining structures in Scheme I are postulated as being derived from the primary ions through relatively straightforward fragmentation sequences, two of which were confirmed by the presence of metastable peaks. In the case of **11b**, the empirical formulas of the fragments were established by means of high-resolution mass spectroscopy.

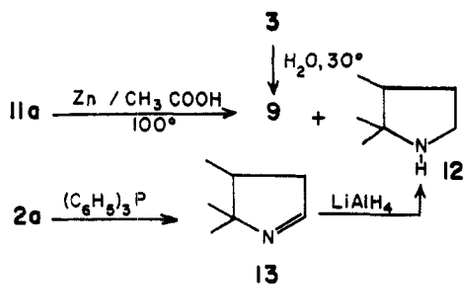
The stability of the N–O bond in **4** toward hydrogenolysis is somewhat surprising in view of the fact that such bonds in isoxazolidine derivatives are reported to be cleaved easily to form amino alcohols[18,10c] under conditions similar to those which we applied to

(16) The structure proof for the adduct from **2b** and **3** follows similar lines and will not be discussed in detail here; pertinent spectra are given in the Experimental Section.

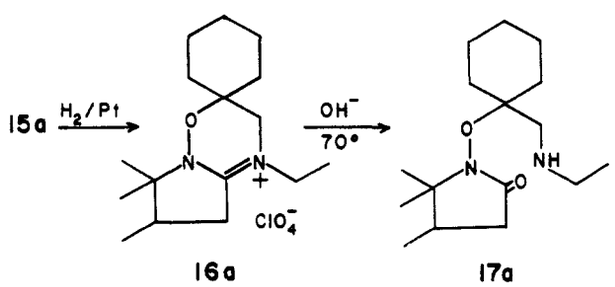
(17) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, p 63.

(18) R. Grashey, R. Huisgen, and H. Leitermann, *Tetrahedron Letters*, No. 12, 9 (1960).

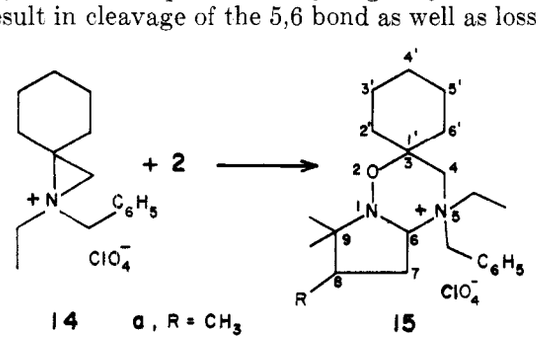
4. Attempts to reduce **11a** or **11b** further by means of hydrogenolysis in ethanol at room temperature or in aqueous hydrochloric acid at 60° were unsuccessful. In addition, treatment of **11a** with lithium aluminum hydride[10c,19] in refluxing dimethoxyethane resulted in no detectable reaction after 6 days. Successful cleavage of the N–O bond in **11a** was finally achieved through the use of zinc dust and aqueous acetic acid at 100° as the reducing medium. Separation of the product mixture by preparative glpc yielded two components, which proved to be identical with 1-dimethylamino-2-methyl-2-propanol (**9**) and 2,2,3-trimethylpyrrolidine (**12**) in both spectral characteristics and glpc retention time. For comparison purposes, authentic **9** was conveniently prepared by hydrolysis, at room temperature, of the aziridinium salt **3**.[20] The synthesis of authentic **12** involved deoxygenation of nitrone **2a** with triphenylphosphine[21] followed by reduction of the intermediate 4,5,5-trimethyl-$\Delta^1$-pyrroline (**13**) with lithium aluminum hydride.[22] Although it is still not readily apparent why **11** is so resistant to reduction, other than that there is hindering substitution about the N–O bond, the successful cleavage of this bond firmly establishes **4** as the type of structure resulting from the nitrone–aziridinium salt reaction.

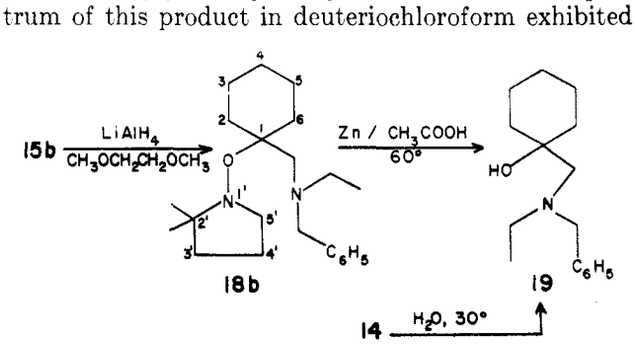



Further generality of the ⑧$^+$ + 3 → ⑥$^+$ ring expansion was demonstrated by the fact that 1-benzyl-1-ethyl-1-azoniaspiro[2.5]octane perchlorate (**14**)[7] also reacts smoothly with nitrones **2a** and **2b** to form 1:1 adducts (**15**) in good yield. (Compound **15a** is named 5-benzyl-5-ethyl-8,9,9-trimethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane-3-spiro-1′-cyclohexane perchlorate and **15b** is named 5-benzyl-9,9-dimethyl-5-ethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane-3-spiro-1′-cyclohexane perchlorate.) From our experience with adduct **4**, it was anticipated that hydrogenolysis of **15** would result in cleavage of the 5,6 bond as well as loss of the benzyl group. When the actual reduction was carried out, however, an anomalous product was obtained. For example, catalytic hydrogenolysis of **15a** yielded a perchlorate (**16a**) having the correct analysis for $C_{16}H_{29}ClN_2O_5$, indicating that the elements constituting toluene had been lost during the reaction. The product exhibited a strong infrared band at 1680 cm$^{-1}$ and an ultraviolet maximum at 228 mμ (ε ~7000). The absence of infrared bands attributable to $\rightarrow N^+H$ or $>N^+H_2$ suggested that the salt was truly quaternary and not the conjugate acid of an amine. Upon heating in aqueous base at 70°, **16a** was gradually converted into an immiscible oil (**17a**) which was ether soluble. This material exhibited a strong infrared band at 1710 cm$^{-1}$ and a medium band at 3300 cm$^{-1}$, the latter being indicative of a secondary amine. On the basis of these limited data, we suggest that under the heterogeneous equilibrium conditions of the catalytic hydrogenolysis, **15a** loses not only the benzyl group but also an additional hydrogen to form a 5,6-iminium bond which may be stabilized by conjugation with the nitrogen at the bridgehead position of the fused ring system. Subsequent basic hydrolysis of this iminium bond in **16a** would be expected to liberate the corresponding N-alkoxypyrrolidinone derivative (**17a**). The nmr spectrum of **17a** is consistent with, albeit not definitive for, the structure assigned. Further study would be necessary to confirm fully these postulated structures.




In view of the problems associated with the hydrogenolysis approach to degradation of **15**, an alternate method was employed. Treatment of **15b** with lithium aluminum hydride in refluxing dimethoxyethane brought about a cleavage of the 5,6 bond to yield **18b**, N-[1-(2′,2′-dimethylpyrrolidin-1′-oxy)cyclohexanemethyl]-N-ethylbenzylamine. The nmr spectrum of this product in deuteriochloroform exhibited peaks for both N-benzyl and N-ethyl, as well as a singlet at $\tau$ 7.48 for $-CH_2N<$, indicating that the $-CH_2N(C_2H_5)CH_2C_6H_5$ grouping was indeed present. Cleavage of the N–O bond in **18b** was effected through the use of zinc dust and aqueous acetic acid at 60°. Chromatography of the product mixture afforded 1-(N-benzyl-N-ethylaminomethyl)-1-cyclohexanol (**19**),




(19) G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, 4693 (1963).

(20) Hydrolytic ring opening of similarly substituted aziridinium salts has been studied previously in this laboratory and has been found to involve predominant cleavage at the 1,2 bond.

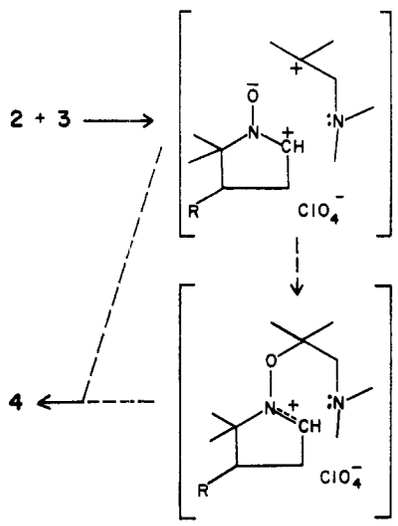
(21) F. Agolini and R. Bonnett, *Can. J. Chem.*, **40**, 181 (1962).

(22) R. Bonnett, V. M. Clark, A. Giddey, and A. Todd, *J. Chem. Soc.*, 2087 (1959).

identified by comparison with an authentic sample prepared by hydrolysis, at room temperature, of aziridinium salt **14**.

With regard to the mechanism of this ③$^+$ + 3 → ⑥$^+$ reaction, it appears likely that the aziridinium ring opens initially at the 1,2 bond to the corresponding tertiary β-aminocarbonium ion, which is shown in Scheme II in correct orientation with respect to the

SCHEME II




1,3-polarized nitrone. From this stage, at least two pathways may be envisioned. If C–O bond formation proceeds at essentially the same rate as C–N bond formation, the process becomes in effect a concerted "1,3-*polar–dipolar* cycloaddition." In the other pathway, a relatively fast attack by the nitrone oxygen on the tertiary β-aminocarbonium ion could result in an intermediate resonance-stabilized oxoiminium ion which would undergo subsequent intramolecular attack by the amino function to complete the formation of the 1,2,4-oxadiazinium ring.

The ③$^+$ + 3 → ⑥$^+$ reaction presented in this paper provides an addition to the growing list of small charged heterocyclic ring expansions. In addition, the method represents a facile synthetic route to a novel heterocyclic system. Preliminary studies with suitably substituted azetidinium salts indicate that these four-membered charged rings also form 1:1 adducts with nitrones, a reaction that may well prove to be representative of a new type, ④$^+$ + 3 → ⑦$^+$.

## Experimental Section[23,24]

**1,1,2,2-Tetramethylaziridinium perchlorate (3) and 1-benzyl-1-ethyl-1-azoniaspirol[2.5]octane perchlorate (14)** were prepared as described previously[6,7] by the addition of diazomethane to the corresponding iminium perchlorate in an appropriate solvent at 0°. To prevent hydrolysis, these aziridinium salts were stored in a vacuum desiccator at room temperature.

**4,5,5-Trimethyl-Δ$^1$-pyrroline 1-oxide (2a) and 5,5-dimethyl-Δ$^1$-pyrroline 1-oxide (2b)** were prepared by reductive cyclization of the corresponding γ-nitroaldehydes according to the method of Bonnett, *et al.*[14] The nitrones were stored at 5° under nitrogen to minimize decomposition.

**General Procedure for the Formation of Nitrone–Aziridinium Salt Adducts.**—The appropriate aziridinium salt was added in portions to an excess of nitrone and the two reactants were mixed as thoroughly as possible. Cooling of the flask with tap water was employed during the addition in order to dissipate the heat evolved. After standing for 5 days at room temperature, the intimate mixture was treated with ethyl acetate to precipitate the crude product. Usually one recrystallization from isopropyl alcohol or acetonitrile–ether was sufficient to provide an analytically pure sample of the adduct.

From 23.4 g (0.117 mole) of 1,1,2,2-tetramethylaziridinium perchlorate (**3**) and 25.8 g (0.20 mole) of 4,5,5-trimethyl-Δ$^1$-pyrroline 1-oxide (**2a**) there was obtained 30.4 g (80%) of **3,3,5,5,8,9,9-heptamethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane perchlorate (4a)**. An analytical sample, colorless prisms from acetonitrile–ether, had mp 176–180°; no infrared maxima corresponding to O–H or N$^+$–H; nmr (in $CDCl_3$), with satisfactory integration, at τ 5.70 (m, $NCHN^+$), 6.28 and 6.87 (AB system, $J$ = 14.0 cps, $CH_2$–$N^+$), 6.72 and 6.87 (s,s, $(CH_3)_2N^+$), 7.6–8.2 (m, $CH_3CH$ and $CCH_2C$), 8.43 and 8.72 (s,s $(CH_3)_2CO$), 8.82 and 9.08 (s,s, $(CH_3)_2CN$), and 8.93 (d, $J$ = 7.0 cps, $CH_3CH$).

*Anal.* Calcd for $C_{13}H_{27}ClN_2O_5$: C, 47.77; H, 8.33; N, 8.57. Found: C, 47.95; H, 8.38; N, 8.30.

A mixture of 5.00 g (25 mmoles) of aziridinium salt **3** and 5.65 g (50 mmoles) of 5,5-dimethyl-Δ$^1$-pyrroline 1-oxide (**2b**) yielded 5.90 g (76%) of **3,3,5,5,9,9-hexamethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane perchlorate (4b)**. The analytical sample, colorless prisms from acetonitrile–ether, had mp 199–200° dec; no O–H or N$^+$–H bands in the infrared spectrum; nmr (in DMSO-$d_6$) at τ 5.64 (m, $NCHN^+$), 6.37 and 6.80 (AB system, $J$ = 13.5 cps, $CH_2N^+$), 6.81 and 6.98 (s,s, $(CH_3)_2N^+$), 7.7–8.4 (complex multiplet, $CH_2$–$CH_2$), 8.52 and 8.81 (s,s, $(CH_3)_2CO$), and 8.81 and 8.95 (s,s, $(CH_3)_2CN$).

*Anal.* Calcd for $C_{12}H_{25}ClN_2O_5$: C, 46.08; H, 8.06; N, 8.96. Found: C, 46.33; H, 8.06; N, 8.96.

From 4.95 g (15 mmoles) of 1-benzyl-1-ethyl-1-azoniaspiro-[2.5]octane perchlorate (**14**) and 4.45 g (35 mmoles) of nitrone **2a** there was obtained 6.11 g (89%) of **5-benzyl-5-ethyl-8,9,9-trimethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane-3-spiro-1′-cyclohexane perchlorate (15a)**. An analytical sample, colorless prisms from acetonitrile–ether, had mp 149–150°; no infrared maxima corresponding to O–H or N$^+$–H: nmr (in $CDCl_3$) at τ 2.50 (s, $C_6H_5$), 5.52 (s, $ArCH_2N^+$), 5.6–6.0 (m, $NCHN^+$), 6.0–6.6 (unresolved multiplet, $CH_3CH_2N^+$), 6.27 and 6.97 (AB system, $J$ = 14.0 cps, $CCH_2N^+$), 7.5–8.2 (m,m, $CH_3CH$ and $CCH_2C$), 8.2–8.7 (unresolved multiplet, $(CH_2)_5$ and $CH_3CH_2N^+$), 8.83 and 9.16 (s,s, $(CH_3)_2CN$), and 9.0–9.2 (partially hidden doublet, $CH_3CH$).

*Anal.* Calcd for $C_{23}H_{37}ClN_2O_5$: C, 60.45; H, 8.16; N, 6.13. Found: C, 60.28; H, 8.15; N, 5.98.

A mixture of 4.95 g (15 mmoles) of aziridinium salt **14** and 3.96 g (35 mmoles) of nitrone **2b** yielded 5.57 g (84%) of **5-benzyl-9,9-dimethyl-5-ethyl-5-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane-3-spiro-1′-cyclohexane perchlorate (15b)**. The analytical sample, colorless plates from acetonitrile–ether, had mp 149–150°; no O–H or N$^+$–H bands in the infrared spectrum; nmr (in $CDCl_3$) at τ 2.50 (s, $C_6H_5$), 5.51 (s, $ArCH_2N^+$), 5.6–6.0 (m, $NCHN^+$), 6.1–6.7 (unresolved multiplet, $CH_3CH_2N^+$), 6.30 and 7.00 (AB system, $J$ = 14.0 cps, $(CCH_2N^+)$, 7.5–8.3 (m, $CH_2$–$CH_2$), 8.3–8.7 (unresolved multiplet, $(CH_2)_5$ and $CH_3CH_2N^+$), and 8.77 and 8.98 (s,s, $(CH_3)_2CN$).

*Anal.* Calcd for $C_{22}H_{35}ClN_2O_5$: C, 59.65; H, 7.96; N, 6.32. Found: C, 59.91; H, 7.95; N, 6.55.

**Hydrogenolysis of Adducts 4a and 4b.**—A solution of 9.80 g (30 mmoles) of adduct **4a** in 300 ml of 1:1 methanol–acetic acid was shaken under 3 atm of hydrogen for 36 hr in the presence of 1.0 g of Adams' catalyst. The mixture was then filtered and the catalyst washed with methanol. Evaporation of the solvents *in vacuo* yielded 9:30 g (94%) of **N-[2-methyl-2-(2′,2′,3′-trimethylpyrrolidin-1′-oxy)propyl]dimethylamine perchlorate**

(23) All melting points are corrected; boiling points are uncorrected. In all cases involving drying of an ethereal solution of an amine during work-up, anhydrous potassium carbonate was employed as the drying agent. Infrared spectra were obtained with Perkin-Elmer grating spectrophotometers, Models 521 or 337. Nmr spectra were obtained on a Varian Associates Model A-60 or A-60A spectrometer using tetramethylsilane as an internal standard. Glpc analyses were carried out on an F & M Model 300 gas chromatograph using 0.25-in. columns—1 m 20% Carbowax 20M on Anakrom ABS (column A) or 8-ft 20% diisodecyl phthalate on Chromosorb W (column B). The preparative glpc separation was carried out on a Nester–Faust Prepkromatic instrument using a 0.75-in. biwall column. Mass spectra were obtained on a Consolidated Model CEC-110 double-focusing mass spectrometer.

(24) We are indebted to Dr. W. W. Hargrove of Eli Lilly and Co., Indianapolis, for obtaining the mass spectra and determining $pK_a$ values for compounds **11a** and **11b**.

(**8a**). Recrystallization from ethyl acetate–ether afforded an analytical sample as colorless needles: mp 144.5–145.5°; $\nu_{max}^{CHCl_3}$ 3100 cm$^{-1}$ ($N^+$–H).

*Anal.* Calcd for $C_{13}H_{29}ClN_2O_5$: C, 47.48; H, 8.89; N, 8.52. Found: C, 47.76; H, 9.03; N, 8.40.

The perchlorate salt was converted to a free amine by treatment with 6% aqueous sodium hydroxide and extraction into ether. The combined extracts were then dried, filtered, and evaporated *in vacuo*. Distillation of the residual liquid through a 12-in. spinning-band column yielded **N-[2-methyl-2-(2′,2′,3′-trimethylpyrrolidin-1′-oxy)propyl]dimethylamine** (**11a**) as a clear colorless liquid: bp 61.0–62.5° (1.0 mm); p$K_a$ 8.6 (in 66% dimethylformamide);[24] no O–H or N–H bands in the infrared spectrum; nmr (in $CDCl_3$) at $\tau$ 6.8–7.3 (unresolved multiplet, $CH_2NO$), 7.72 s, $(CH_3)_2N$), 7.75 (s, $(CH_3)_2NCH_2$), 8.1–8.6 (m, $CH_3CH$ and $CCH_2C$), 8.82 (s, $(CH_3)_2CO$), 8.97 and 9.20 (s,s, $(CH_3)_2CN$), 9.14 (d, $CH_3CH$); nmr (in $CF_3COOH$) at $\tau$ 6.80 (d, $J$ = 4.5 cps, $(CH_3)_2N^+H$).

*Anal.* Calcd for $C_{13}H_{28}N_2O$: C, 68.37; H, 12.36; N, 12.27; mol wt, 228. Found: C, 68.34; H, 12.61; N, 12.33; mol wt, 230 (osmometric, in benzene), 236 (from p$K_a$ determination).

In a manner similar to that described above, a solution of 3.44 g (11 mmoles) of adduct **4b** in 120 ml of 1:1 methanol–acetic acid was hydrogenated in the presence of 500 mg of Adams' catalyst to yield 3.37 g (97%) of **N-[2-(2′,2′-dimethylpyrrolidin-1′-oxy)-2-methylpropyl]dimethylamine perchlorate** (**8b**). An analytical sample, colorless needles from ethyl acetate–ether, had mp 150–152°, $\nu_{max}^{CHCl_3}$ 3080 cm$^{-1}$ ($N^+$–H).

*Anal.* Calcd for $C_{12}H_{27}ClN_2O_5$: C, 45.78; H, 8.65; N, 8.90. Found: C, 45.59; H, 8.63; N, 8.78.

The free amine was liberated and distilled as described above to yield **N-[2-(2′,2′-dimethylpyrrolidin-1′-oxy)-2-methylpropyl]dimethylamine** (**11b**) as a clear colorless liquid: bp 70–72° (2.2 mm); p$K_a$ 8.5 (in 66% dimethylformamide);[24] no O–H or N–H bands in the infrared spectrum; nmr (in $CDCl_3$) at $\tau$ 6.7–7.2 (unresolved multiplet, $CH_2NO$), 7.73 (s, $(CH_3)_2N$, 7.77 (s, $(CH_3)_2NCH_2$), 8.1–8.5 (m, $CCH_2CH_2C$), 8.82 (s, $(CH_3)_2CO$), 8.97 (s, $(CH_3)_2CN$); nmr (in $CF_3COOH$) at $\tau$ 6.79 (d, $J$ = 4.5 cps, $(CH_3)_2N^+H$).

*Anal.* Calcd for $C_{12}H_{26}N_2O$: C, 67.24; H, 12,23; N, 13.07; mol wt, 214. Found: C, 67.13; H, 12.36; N, 13.05; mol wt, 224 (osmometric, in chloroform), 236 (from p$K_a$ determination).

**1-Dimethylamino-2-methyl-2-propanol** (**9**).—A solution of 16.1 g (81 moles) of 1,1,2,2-tetramethylaziridinium perchlorate (**6**) in 75 ml of water was allowed to stand at room temperature for 5 days. The water was then evaporated *in vacuo* and the residual oil was shaken with ether. The resulting hygroscopic solid (16.2 g, 92%; mp 68–71°) was treated with 10% aqueous sodium hydroxide and the mixture was extracted with ether. The combined extracts were dried and filtered and the ether was removed by slow distillation through a 6-in. Vigreux column. Distillation of the pot residue through a 12-in. spinning-band column yielded the desired amino alcohol as a clear colorless liquid: bp 128.0–128.5° (lit.[25] bp 129.5–131.5°); $\nu_{max}^{film}$ 3440 (O–H), 1145 cm$^{-1}$ (C–O); nmr (in $CDCl_3$) at $\tau$ 6.80 (s, OH), 7.65 (s, $(CH_3)_2N$), 7.72 (s, $(CH_3)_2NCH_2$), and 8.82 (s, $(CH_3)_2C$–O).

*Anal.* Calcd for $C_6H_{15}NO$: C, 61.49; H, 12.90; N, 11.95. Found: C, 61.68; H, 13.03; N, 11.74.

**2-Dimethylamino-2-methyl-1-propanol** (**10**), available from Aldrich Chemical Co., Inc., was purified by distillation through a 6-in. Vigreux column: bp 61.5–63.0° (19 mm) (lit.[20] bp 158–160°); $\nu_{max}^{film}$ 3410 (O–H), 1055 cm$^{-1}$ (C–O); nmr (in $CDCl_3$) at $\tau$ 6.53 (s, OH), 6.67 (s, $CH_2OH$), 7.79 (s, $(CH_3)_2N$), and 9.01 (s, $(CH_3)_2C$–N).

**Unsuccessful Attempts to Reduce 11a and 11b.**—A solution of 465 mg (2.2 mmoles) of **11b** in 50 ml of ethanol was shaken under 3 atm of hydrogen for 44 hr in the presence of 600 mg of Adams' catalyst. The mixture was then filtered and the catalyst was washed with ethanol. Following acidification of the filtrate with ethereal hydrogen chloride, the ethanol was removed *in vacuo*. The residue was then treated with 10% aqueous sodium hydroxide and extracted with ether. The extracts were dried, filtered, and evaporated *in vacuo* (no heating bath). Glpc analysis (column A, 70–200°) of the residual liquid indicated that little or no reaction had taken place. Recovery of starting material was 355 mg (75%).

A solution of 344 mg (1.5 mmoles) of **11a** in 40 ml of 10% aqueous hydrochloric acid was shaken under 3 atm of hydrogen at 60° for 45 hr in the presence of 300 mg of Adams catalyst. After filtering the mixture and washing the catalyst with additional aqueous acid, the filtrate was evaporated *in vacuo*. The residue was treated with excess 20% aqueous sodium hydroxide and extracted with ether. The extracts were then dried and filtered and the ether was removed by slow distillation through a 6-in. Vigreux column. The residual liquid was subjected to glpc analysis (column A, 70–200°) but proved to be only starting material (301 mg, 88% recovery).

A solution of 3.32 g (14.5 mmoles) of **11a** in 25 ml of 1,2-dimethoxyethane was added with stirring to a slurry of 2.84 g (75.0 mmoles) of lithium aluminum hydride in 75 ml of dimethoxyethane and the resulting mixture was heated under reflux for 6 days. Work-up was effected by the dropwise addition of 2.8 ml of water, 2.8 ml of 15% aqueous sodium hydroxide, and 8.4 ml of water. After the precipitated salts had been filtered and washed with hot solvent, the filtrate was dried and the solvent was removed by distillation through a 12-in. spinning-band column. A glpc analysis (column A, 70–200°) of the residual liquid showed it to be starting material, 3.23 g (97% recovery).

**Zinc–Acetic Acid Reduction of 11a.**—To a solution of 1.71 g (7.5 mmoles) of **11a** in 50 ml of 50% aqueous acetic acid was added in portions 6.0 g (92 mg-atoms) of activated zinc dust.[26] The mixture was heated with vigorous stirring at 100° for 45 hr. At the end of this time, the residual zinc was filtered and washed with water. The combined filtrates were acidified by the addition of 4 ml of concentrated hydrochloric acid and were evaporated *in vacuo*. Treatment of the residual oil with 25% aqueous sodium hydroxide liberated an amine mixture which was extracted into ether. The combined extracts were then dried and filtered and the ether was removed by slow distillation through a 6-in. Vigreux column. Glpc analysis (column B, 100°) of the residual liquid showed two components in addition to ether. The retention times of these components were identical with those determined for authentic samples of 1-dimethylamino-2-methyl-2-propanol (**9**) and 2,2,3-trimethylpyrrolidine (**12**). Yields of the amino alcohol and trimethylpyrrolidine were calculated by integration of the glpc trace to be 97 and 80%, respectively.[27] Separation of the mixture was achieved by means of preparative glpc on a 12-ft column of 20% diisodecyl phthalate on Chromosorb W (HMDS treated) at 100°. The two amines thus collected exhibited infrared and nmr spectra identical in all respects with those of authentic **9** and **12**.

**2,2,3-Trimethylpyrrolidine** (**12**).—A mixture of 9.5 g (75 mmoles) of 4,5,5-trimethyl-$\Delta^1$-pyrroline 1-oxide (**2a**) and 25.0 g (95 mmoles) of triphenylphosphine in a 100-ml flask was heated gently over a free flame. The volatile product thus formed was distilled through a short Vigreux column and collected up to 150° as a yellow liquid. A solution of this crude **4,5,5-trimethyl-$\Delta^1$-pyrroline** (**13**) in 100 ml of ether was dried over anhydrous potassium carbonate, filtered, and added dropwise with stirring to a cold slurry of 3.8 g (0.10 mole) of lithium aluminum hydride in 50 ml of ether. The mixture was then heated under reflux for 30 hr and subsequently decomposed through the dropwise addition of 7.6 ml of water and 6.1 ml of 10% aqueous sodium hydroxide. Following filtration and ether washing of the precipitated salts, the combined filtrates were dried and the ether was removed by slow distillation through a 6-in. Vigreux column. Distillation of the residual liquid through a 12-in. spinning-band column afforded 2.02 g (24%) of the desired trimethylpyrrolidine as a clear colorless liquid: bp 123–127° (lit.[22] bp 128–132°); $\nu_{max}^{film}$ 3270 cm$^{-1}$ (N–H); nmr (in $CDCl_3$) at $\tau$ 7.09 (unsymmetrical triplet, $CH_2NH$), 7.8–8.7 (complex multiplet, $CCH_2CH(C)C$), 8.45 (s, NH), 8.87 and 9.07 (s,s, $(CH_3)_2C$–N), and 9.07 (d, $J$ = 6.0 cps, $CH_3CH$).

**Hydrogenolysis of Adducts 15a and 15b.**—A solution of 1.00 g (2.19 mmoles) of adduct **15a** in 125 ml of ethanol was shaken under 3 atm of hydrogen for 24 hr in the presence of

(25) I. F. Halverstadt, W. R. Hardie, and A. R. Williams, *J. Am. Chem. Soc.*, **81**, 3618 (1959).

(26) Fisher reagent grade zinc dust was treated successively with 2% aqueous hydrochloric acid, water, 95% ethanol, and ether. The activated metal was then dried in a vacuum desiccator.

(27) An integrated glpc trace was also obtained for a known mixture of authentic **9** and **12** in order to correct for the difference in detector response toward the two components.

250 mg of Adams' catalyst. Employing the usual work-up procedure, 760 mg (95%) of crude product (**16a**) was isolated. Recrystallization from ethyl acetate–ether afforded an analytical sample as colorless needles: mp 125–127°; $\nu_{max}^{CHCl_3}$ 1680 cm$^{-1}$ (strong), no $N^+$–H or $N^+H_2$ bands; $\lambda_{max}^{EtOH}$ 228 m$\mu$ ($\epsilon$ ~7000).

*Anal.* Calcd for $C_{16}H_{29}ClN_2O_5$: C, 52.67; H, 8.01; N, 7.68. Found: C, 52.66; H, 7.99; N, 7.94.

Upon heating **16a** in 10% aqueous sodium hydroxide at 70° for 2 hr, the salt was gradually converted to an immiscible oil. This was extracted into ether, the combined extracts were dried, and the ether was removed *in vacuo*. The residual oil (**17a**) had $\nu_{max}^{film}$ 3300, 1710 cm$^{-1}$ (strong); nmr (in $CDCl_3$) at $\tau$ 7.22 (s, 2 H), 7.35 (q, 2 H), 7.5–8.7 (complex multiplet, 13 H), 8.74 (s, 3 H), 8.89 (t, 3 H), and 8.97 (singlet over doublet, 6 H).

In a similar fashion, 443 mg (1.0 mmole) of adduct **15b** underwent hydrogenolysis to yield 274 mg (78%) of crude product (**16b**). The analytical sample, colorless needles from ethyl acetate–ether, had mp 167–170°; $\nu_{max}^{CHCl_3}$ 1680 cm$^{-1}$ (strong), no $N^+$–H or $N^+H_2$ bands; $\lambda_{max}^{EtOH}$ 227 m$\mu$ ($\epsilon$ ~8000).

*Anal.* Calcd for $C_{15}H_{27}ClN_2O_5$: C, 51.34; H, 7.75; N, 7.98. Found: C, 51.25; H, 7.90; N, 7.60.

**Lithium Aluminum Hydride Reduction of Adduct 15b.**—To a slurry of 380 mg (10.0 mmoles) of lithium aluminum hydride in 25 ml of 1,2-dimethoxyethane was added 885 mg (2.0 mmoles) of adduct **15b**. After 28 hr of heating under reflux, the mixture was treated dropwise with 0.76 ml of water and 0.61 ml of 10% aqueous sodium hydroxide. The precipitated salts were filtered and washed with hot solvent. The filtrate was then acidified with aqueous hydrochloric acid and evaporated *in vacuo*. Treatment of the residue with 10% aqueous sodium hydroxide followed by extraction with ether and the usual isolation procedure afforded 623 mg (91%) of crude *N-[1-(2',2'-dimethylpyrrolidin-1'-oxy)cyclohexanemethyl]-N-ethylbenzylamine* (**18b**) as a yellow oil; nmr (in $CDCl_3$) at $\tau$ 2.68 (m, $C_6H_5$), 6.27 (s, $ArCH_2N$), 6.7–7.2 (unresolved multiplet, $CH_2NO$), 7.46 (q, $CH_3CH_2N$), 7.48 (s, $CH_2N(C_2H_5)CH_2C_6H_5$), 8.1–8.8 (m, $CCH_2CH_2C$ and $(CH_2)_5$), 8.96 (s, $(CH_3)_2CN$), and 9.03 (t, $CH_3CH_2N$).

**Zinc–Acetic Acid Reduction of 18b.**—A mixture of 480 mg (1.4 mmoles) of **18b** and 1.0 g of activated zinc dust[26] in 20 ml of 50% aqueous acetic acid was heated at 60–65° with vigorous stirring for 22 hr. At the end of this period, the residual zinc was filtered and washed with ethanol. The filtrate was then acidified with aqueous hydrochloric acid and the solvents were evaporated *in vacuo*. Basification of the residue with 30% aqueous sodium hydroxide followed by extraction with ether and the usual work-up procedure yielded a yellow oil. Chromatography on silica gel using ether–pentane for elution afforded 106 mg (31%) of *1-(N-benzyl-N-ethylaminomethyl)-1-cyclohexanol* (**19**): nmr (in $CDCl_3$) at $\tau$ 2.70 (s, $C_6H_5$), 6.29 (s, $ArCH_2N$), 7.01 (s, OH), 7.45 (q, $CH_3CH_2N$), 7.52 (s, $CH_2N(C_2H_5)CH_2C_6H_5$), 8.52 (unresolved multiplet, $(CH_2)_5$), and 9.00 (t, $CH_3CH_2N$).

**1-(N-Benzyl-N-ethylaminomethyl)-1-cyclohexanol** (**19**).—A mixture of 3.3 g (10 mmoles) of 1-benzyl-1-ethyl-1-azoniaspiro[2.5]octane perchlorate (**14**) and 50 ml of water was allowed to stand at room temperature for 9 days. Subsequent treatment with 10% aqueous sodium hydroxide liberated a free amine which was extracted into ether. The combined extracts were dried, filtered, and evaporated *in vacuo* to yield the crude amino alcohol as a yellow oil. The nmr spectrum of this material proved to be identical with that of the product from the zinc–acetic acid reduction of **18b**.

**Registry No.**—**4a**, 14172-85-1; **4b**, 14172-86-2; **8a**, 14123-46-7; **8b**, 14123-47-8; **9**, 14123-48-9; **10**, 7005-47-2; **11a**, 14123-50-3; **11b**, 14123-51-4; **12**, 14123-52-5; **15a**, 14123-53-6; **15b**, 14123-54-7; **16a**, 14123-55-8; **16b**, 14123-56-9; **17a**, 14123-57-0; **18b**, 14123-58-1; **19**, 14123-59-2.

# Nucleophilic Displacements of 3 Substituents in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridines

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The substitution reactions at the 3 position of 3-substituted 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridines occur without participation of the heterocyclic nitrogen. Attempts to study the role of the allylic system in the displacement by deuterium labeling was hindered since the allylic cation formed readily, leading to a scrambling of the isotopic label.

The reactions of 3-halopiperidines and 3-piperidyl esters often occur with the participation of the nitrogen atom, forming an aziridinium ion, and with some ring contraction to the pyrrolidine.[2-6] A similar participation of the double bond of an allylic system would be anticipated. Thus the nucleophilic displacement reaction with 3-substituted 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridines could go by a variety of mechanisms, SN1, SN2, and SN2′ of the allylic system or by nitrogen participation. The product analysis of solvolysis reactions of 1-methyl-4-phenyl-3-halo-1,2,3,6-tetrahydropyridine (**1b** and **d**) should give indication of any nitrogen participation, and the location of a deuterium label after reactions of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-$d_5$ (**1c**-$d_5$) should indicate the role of the double bond.

**Preparation of the 1-Methyl-3-halo-4-phenyl-1,2,3,6-tetrahydropyridines.**—The reaction of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1a**) hydrobromide with bromine was reported to give 1-methyl-3,4-dibromo-4-phenylpiperidine hydrobromide (**2**).[7] On heating **2** was converted into a new compound whose properties were consistent with the structure 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine hydrobromide (**1b**). The identical compound could be prepared by reaction of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (**1c**)[8] with phosphorus tribromide. The corresponding chloro derivative, **1d**, was obtained by treatment of **1c**, as the hydrochloride, with thionyl chloride. 1-Methyl-3-chloro-4-phenyl-1,2,3,6-tetrahy-

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