Quaternizations in the 8-Azabicyclo[4.3.0]non-3-ene Series

Rodney D. Otzenberger, Kenneth B. Lipkowitz, and Bradford P. Mundy*

Department of Chemistry, Montana State University, Bozeman, Montana 59715

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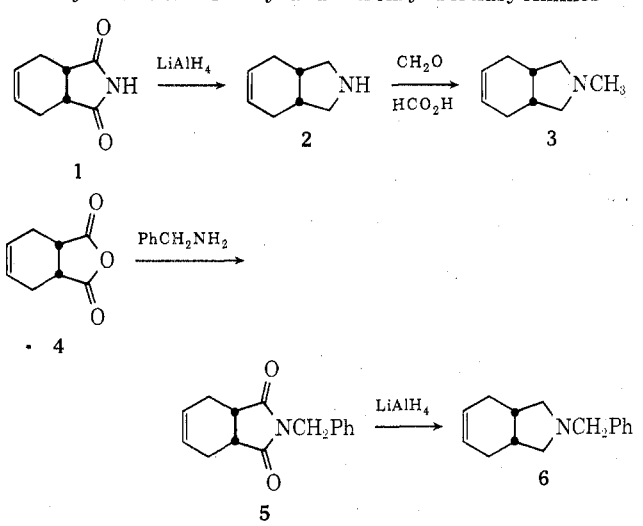
The stereochemistry of quaternization of 8-methyl and 8-benzyl-*cis*-8-azabicyclo[4.3.0]non-3-ene has been investigated. The results correlate with those for simple tertiary pyrrolidines and piperidines.

There has been considerable activity in studies relating to quaternization of tertiary amines, particularly in attempting to understand the factors which control stereoselectivity.[1] Most of the contributions, to date, have been concerned with the piperidine system,[2] and the little attention focused on the pyrrolidine system has not considered 3,4-disubstituted pyrrolidines.

In analyzing the steric course of quaternization of 2-methylpyrrolidines, McKenna concluded that N-alkylation occurred preferentially cis to the 2-methyl group.[3] Analysis of the chemical shift data demonstrated that the *N*-alkyl groups cis to the 2-alkyl group in quaternary salts of the 2-alkylpyrrolidine series were found at higher field.[4] A recent examination of the quaternization of 2-phenylpyrrolidines has resulted in the conclusion that alkylation with small alkylating groups will generally occur cis to the phenyl group with larger groups alkylating trans.[5] The nmr data are consistent with data in the other 2-alkylpyrrolidine series.[4]

As part of our continuing study of the effects of heteroatoms in a five-membered ring on conformation and reactivity,[6] we undertook the investigation of quaternizations in the *cis*-8-azabicyclo[4.3.0]non-3-ene series. These compounds are prepared according to the reactions delineated in Scheme I. The available tetrahydrophthalimide (**1**) was reduced to **2** with lithium aluminum hydride. Methylation of **2** was accomplished in good yield to give **3**. The *N*-benzyl amine **6** was prepared from **4** by first converting the anhydride to the imide **5**, which was in turn reduced to **6** with lithium aluminum hydride.

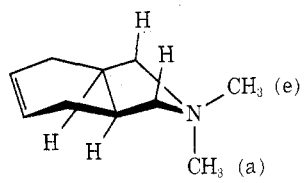
Scheme I
Synthesis of *N*-Methyl and *N*-Benzyl Tertiary Amines



Quaternizations were carried out by mixing the tertiary amine with the alkyl halide in ether. The salts from these reactions were then subjected to the scrutiny of nmr spectroscopy.

Methylation of **3** gave a quaternary salt having distinguishable methyl signals at δ 3.52 and 3.60. Substitution of deuteriomethyl iodide as the alkylating agent removed the upfield methyl signal by 93%, demonstrating considerable stereoselectivity in the alkylation. However, the reasons for this high stereoselectivity were not obvious, since Drieding models did not appear to suggest any special factors which might be controlling the direction of addition.

In the piperidine series, higher field nmr signals have been assigned to axial substituents; however, it is sometimes more difficult to consider axial or equatorial positions in the five-ring series. These structural problems were alleviated with the completion of an X-ray structure analysis of the methyl quaternary salt of **3**. This structure, completed as part of a separate problem,[7] clearly demonstrated the nonidentity of the two methyl groups. A model, prepared by adjusting bond lengths and bond angles to fit those determined from the X-ray structure, is represented by 7.



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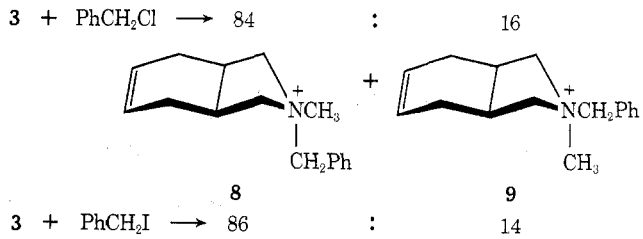
From this structure, it is evident that we can consider an axial and an equatorial methyl group.[8] Continuing this train of thought, the methyl signal at δ 3.52 can be tentatively assigned as the axial methyl, which requires that methylation of **3** must occur primarily as an axial alkylation. This is consistent with observations in the 2-alkylpyrrolidine series where preferential alkylation cis to the 2-alkyl group can most readily be appreciated as axial alkylation.

If we suggest treating quaternization of pyrrolidines to be similar to the piperidine series, several additional tests are possible. As a first test, benzylation has been demonstrated to be less stereoselective than methylation, and an increasing percentage of equatorial alkylation is observed.[9] Treating **3** with benzyl halide gave two products, **8** and **9** (Scheme II). In the quaternizations of **3** with benzyl chloride, two distinct methylene signals from the benzyl groups could be observed in the nmr spectrum of the isomer mixture at δ 5.03 and 5.13 (assigned to **8** and **9**, respectively). However, no separate, distinguishable methyl

Scheme II
Benzylation Studies



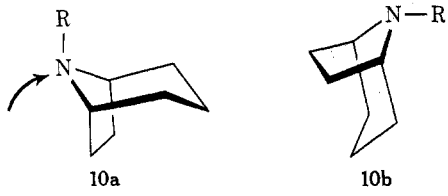
signals could be seen. The iodide salts mixture, on the other hand, exhibited distinct methyl signals at δ 3.32 and 3.27 and methylene signals at δ 4.95 and 5.10 (for **8** and **9**, respectively).

These data again show consistency with the assumption that the pyrrolidine salts can be analyzed similarly to piperidine salts in that (a) higher field signals correspond to axial substituents and (b) an increased percentage of equatorial alkylation is observed with the benzyl halides. These data are also consistent with the studies reported for benzylation of the 2-phenylpyrrolidines.[5]

It has been demonstrated that a quaternary salt can be thermally equilibrated.[10] Thus, a piperidine quaternary salt possessing an axial *N*-benzyl group can be isomerized to a mixture enriched in the isomer having an equatorial *N*-benzyl group. Attempting this isomerization on the chloride salts of **8** and **9** (84:16 mixture) resulted in considerable decomposition; however, the resulting mixture was 62:38 of **8** and **9**. Whether this was an artifact due to preferred decomposition of **8** could not be determined. A similar study on the iodide salts resulted in much less decomposition, and the 60% recovered salts were shown to consist of a 27:73 mixture of **8** and **9**. These results can only reflect isomerization. A similar analysis with pure **9** resulted in no isomer change. These results, too, support the assignments of structure for **8** and **9**, and lend additional credibility to treating pyrrolidines with methods successfully used for piperidines.

A last test is possible. The direction of alkylation of tertiary piperidines has been suggested by examining the stereoselectivity of "inverse alkylations."[9] Results from our studies are presented in Table I. In general, if the methylation is more selective than another alkylation, the major product from the methylation reaction is presumably derived from axial alkylation. This analysis is consistent with our studies, since the sterically smaller methyl group should give more axial attack.

These combined studies allow us to consider that alkylation of tertiary pyrrolidines can be studied using the methodologies which have proven so effective for the piperidines. Further, it has not escaped our attention that these results can be applied to the tropane series (**10**). When considered as a substituted piperidine (**10a**), N-alkylation has to be considered as primarily equatorial,[11] in contrast to the wealth of data demonstrating that piperidines undergo preferential axial alkylation. This anomaly can be eliminated, however, by considering tropane as a 2-substituted pyrrolidine (**10b**). In this series we can expect preferential axial alkylation.



10a **10b**

Consideration of a model of tropane reveals that the steric interactions on the pyrrolidine ring side of the molecule are considerably less than on the piperidine side. Since quaternizations are affected by subtle steric interactions, it is not surprising that the pyrrolidine ring dominates the tropane chemistry.[12]

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer, using tetramethylsilane as an internal standard and deuteriochloroform as solvent. Melting and boiling points are uncorrected. Ratios of quaternary salt isomers were determined from integration of particular peak areas in the spectra of the salt mixtures, and can be considered to be ±5%.

Table I
Inverse Alkylation Studies

$$\mathbf{3} \xrightarrow{PhCH_2I} 86{:}14\ (\mathbf{8}+\mathbf{9})$$

$$\mathbf{6} \xrightarrow{CH_3I} 8{:}92$$

Table II

Amine	Alkyl Halide	Yield, %	Mp (crude isomer °C mixtures)
3	CH_3I	78	215–216
3	CD_3I	71	216–218
3	$PhCH_2Cl$	90	175–177
3	$PhCH_2I$	74	130–145
4	CH_3I	73	200 (pure **9**) 143–148 (50:50 **8**:**9**)

cis-**8-Azabicyclo[4.3.0]non-3-ene (2).** A solution of *cis*-1,2,3,6-tetrahydrophthalimide (30.2 g, 0.2 mol) in dry THF was added dropwise to a mixture of lithium aluminum hydride (15.6 g, 0.4 mol) and dry THF (500 ml). The resulting reaction mixture was refluxed for 7 hr. Work-up and distillation gave 10.0 g (41%) of the colorless *cis*-8-azabicylco[4.3.0]non-3-ene, bp 77–80° (10 mm) [lit.[13] bp 79–81° (15 mm)].

8-Methyl-*cis*-8-azabicyclo[4.3.0]non-3-ene (3). The amine (1.23 g, 0.01 mol) from the previous reaction was treated with 90% formic acid (2.6 g) and 37% formaldehyde. The reaction mixture was heated at 90–100°. Evolution of carbon dioxide was observed, and heat was removed until this ceased, after which time the reaction mixture was heated for an additional 8 hr. After this time, the product was removed by extraction with 5 ml of 4 *N* hydrochloric acid, and evaporation of water yielded the crude hydrochloride salt. The free base was liberated by adding aqueous base to the salt and extracting with benzene. Distillation gave 0.9 g (66%) of the colorless *N*-methyl amine (**3**), bp 68–71° (10 mm) [lit.[14] bp 62–88° (10 mm)].

8-Benzyl-*cis*-8-azabicyclo[4.3.0]non-3-ene (6). *cis*-1,2,3,6-Tetrahydrophthalic anhydride (20 g) was mixed with benzyl amine (15 ml) in 40 ml of xylene, resulting in an instantaneous exothermic reaction. This reaction mixture was heated for an additional 2 hr, after which time it was cooled. Product (16.8 g) crystallized from the reaction mixture (*m/e* 241), and this crude product was treated, without further purification, with 5.5 g of lithium aluminum hydride in dry THF (175 ml). The reduction mixture was refluxed for 18 hr. The reaction mixture was hydrolyzed with water, and, after cooling, the tetrahydrofuran was decanted. The salts were washed with ether and the combined ethers were concentrated. Distillation yielded 11.8 g (79%) of the *N*-benzyl amine **6**, bp 140–160° (4 mm), characterized as the methiodide salt, mp 200°.

Anal. Calcd for $C_{16}H_{22}IN$: C, 54.09; H, 6.25. Found: C, 54.35; H, 6.38.

Preparation of Quaternary Amine Salts. The salts were prepared by adding the alkyl halide to an ether solution of the amine. Reactions using methyl iodide and benzyl iodide took place readily at room temperature. Reaction of benzyl chloride required refluxing for 5 hr. The crude salt mixtures precipitated from the ether as they were formed. These salts were filtered, washed with ether, and dried. The benzyl chloride salts were hygroscopic and required drying in a vacuum desiccator. Where necessary, recrystallization was from methylene chloride. See Table II.

Isomer **9** could be separated from **8** by recrystallization from methylene chloride.

Thermal Equilibration of Quaternary Salt Isomers. A solution of the mixed iodide salts **8** and **9** (0.106 g) in chloroform (10 ml) was sealed in a glass tube and heated at 75–80° for 138 hr. Reisolation yielded 60% recovery of the salt mixture, whose nmr spectrum indicated a 27:73 ratio of **8** and **9**. Similar treatment of pure **9** (75° for 120 hr) resulted in a 50% recovery of **9** with no **8**.

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David Smith and Charles N. Caughlan for their help in the X-ray analysis.

Registry No.—**1**, 1469-48-3; **2**, 2144-87-8; **3**, 49558-71-6; **4**, 935-79-5; **6**, 49558-73-8; **7**, 43208-79-3; **7** (a)-CD_3 analog, 49558-75-0; **7** (e)-CD_3 analog, 49558-76-1; **8**, 49559-22-0; **9**, 49559-23-1.

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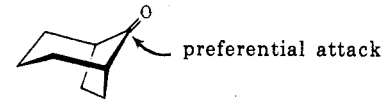
(7) G. D. Smith, R. D. Otzenberger, B. P. Mundy, and C. N. Caughlan, *J. Org. Chem.*, **39**, 321 (1974).
(8) It has been suggested by a referee that one might better consider these as exo and endo methyl groups, and that further consideration of the preferred course of alkylation might better be discussed in these terms.
(9) D. R. Brown, R. Lygo, J. McKenna, J. M. McKenna, and B. G. Hutley, *J. Chem. Soc. B*, 1184 (1967).
(10) See ref 9. Decomposition is noted to accompany isomerization, so that it is essential in these studies to demonstrate the per cent of recovered product so that there can be assurance that a relative increase of one isomer is not, in fact, a preferential decomposition of the other isomer.
(11) (a) For a recent review of some problems in the tropane series, see G. Fodor, D. Frehel, M. J. Cooper, and N. Mandavar in "Conformational Analysis—Scope and Present Limitations," G. Chirudoglu, Ed., Academic Press, New York, N. Y., 1971, pp 73–92. (b) A recent X-ray analysis demonstrates the propensity of tropanes toward equatorial alkylation. See V. O. de la Camp, A. T. Bottini, C. C. Thut, J. Gal, and A. G. Bellettini, *J. Org. Chem.*, **37**, 324 (1972), and leading references.
(12) This suggestion is compatible with the observed dominating effect of the cyclopentane ring in controlling the course of reduction of bicyclo[3.2.1]octan-8-one.[15]



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Crystal and Molecular Structure of *cis*-8-Azabicyclo[4.3.0]non-3-ene Methiodide Quaternary Salt, $C_{10}H_{18}NI$

G. D. Smith, R. D. Otzenberger, B. P. Mundy, and C. N. Caughlan*

Department of Chemistry, Montana State University, Bozeman, Montana 59715

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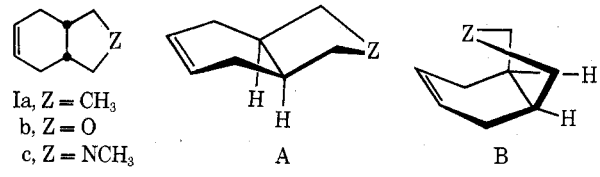
The crystal and molecular structure of the methiodide quaternary salt of *cis*-8-azabicyclo[4.3.0]non-3-ene has been determined by X-ray analysis. The crystals are orthorhombic, space group *Pbca*, with a = 11.673 (6), b = 11.718 (4), and c = 17.142 (12) Å. The structure was solved from the Patterson and refined by full-matrix least squares to R = 3.7% for 616 observed reflections. Owing to distortions in the five-membered heterocyclic ring, one of the methyl groups is in a pseudo-axial position while the other methyl group is in a pseudo-equatorial position. Bond distances around nitrogen range from 1.48 (2) to 1.52 (2) Å while angles range from 100.0 (1) to 112.0 (1)°.

There is a paucity of data relating to structural analysis in the *cis*-bicyclo[4.3.0]non-3-ene series (I). Examination of Drieding models suggests two major conformational types (Ia and Ib), both possessing a boat cyclohexene moiety.

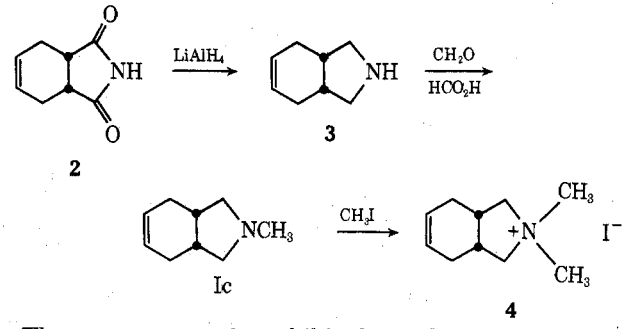


By indirect chemical methods alone, Ia was suggested to possess conformation B.[1] Using the same tests, and buttressed by nmr data, Ib was shown to exist as A.[2] Additional evidence supporting product assignments in chemical studies with Ib has recently been reported.[3]

The difficulty in obtaining solid derivatives of Ia and Ib has precluded the use of X-ray analysis for these systems. However, the potential for preparing quaternary salts of Ic makes this more amenable to scrutiny by X-ray methods.

As part of a continuing study on the effects of heteroatoms in determining conformation and reactivity,[4] the preparation of the methiodide salt of *cis*-8-methyl-8-azabicyclo[4.3.0]non-3-ene (4) was undertaken (Scheme I).

Scheme I
Synthesis of the Methiodide Salt of *cis*-8-Methyl-8-azabicyclo[4.3.0]non-3-ene



The nmr spectra of **4** exhibited two distinct methyl signals at δ 3.52 and 3.60.[5] Consideration of the two most likely conformations, **5** and **6**, prompted us to suggest **6** as the more likely. A conformation of this type would be con-