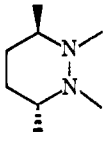
Table I. "Lone Pair" Pes Ionizations for Hexahydropyridazine Derivatives

Compound	I_{p1}, eV (area[a])	I_{p2}, eV (area[a])	I_{p3}, eV (area[a])	$\Delta_{1,2}$[b]	$\Delta_{1,3}$[c]
1	7.77 (2.6)	8.86 (1)	10.08 (2.1)	1.09	2.31
3	7.78 (0.9)	8.63 (1)	9.76 (0.02)	0.85	1.98
4	7.82 (0.9)	8.68 (1)	9.76 (0.04)	0.86	1.94
5	7.81 (1)	8.77 (1)	9.96 (0.2)	0.98	2.15

[a] Estimated area under the ionization peak relative to that of peak 2 (taken as 1.00); since peaks 1 and 2 overlap badly, these estimates are quite crude. [b] $I_{p2} - I_{p1}$. [c] $I_{p3} - I_{p1}$.

1c (Δ = 1.09) also being easily detectable. Although the areas under pes peaks may not necessarily be exactly proportional to the number of electrons ionized[4] and future work will be necessary to see how quantitative such data can be made, the presence of both types of conformers and preponderance of the e,e conformer **1a** seems to us the most reasonable interpretation of the data.

In contrast, *trans*-3,6-dimethyl-1,2-dimethylhexahydropyridazine (**3**) gave large pes peaks separated by 0.85 eV and only a tiny peak 1.98 eV higher than I_{p1} (area relative to I_{p2} about 0.02), which is consistent with very little of the e,e conformation **3a** being present.



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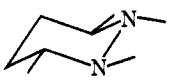
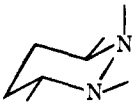
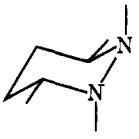


3a



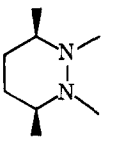
3b



3c

The nmr spectrum of **3** in CF_2Cl_2 at $-120°$ showed two equal NCH_3 singlets (δ 2.34, 2.10) and two equal intensity $CHCH_3$ doublets (δ 0.97, 0.91), consistent only[5] with **3b**. Conformations **3a**, **3b**, and **3c** cannot interconvert by processes which avoid forcing vicinal methyl groups past each other, and so these conformations should be "frozen out" at low temperature, in contrast to **1a–1c**.[2] We observed only a single asymmetric conformation, which cannot be **3a** or **3c**. The nmr spectrum of **3** is consistent with the pes; **3b** is almost exclusively present.

The *cis*-tetramethyl compound **4** also showed only a tiny pes peak attributable to the e,e conformation **4a**, suggesting that **4b** is the major conformation present. Here we also saw only one conformation by low-temperature nmr, but, since the molecule lacks any symmetry, a structure could not be assigned unambiguously. The pes of **5** shows a more substantial amount of the large Δ (e,e) conformer relative to e,a conformers of either **3** or **4**; for **5** the relative areas were 0.2:1. The nmr spectrum showed two sets of $CHCH_3$ doublets in 70:30 ratio in $CDCl_3$ ($-60°$) and 90:10 ratio in CF_3Cl_2 ($-65°$). We did observe another rate process starting to "freeze out" at very low temperatures, but were unable to obtain resolved spectra at the low-temperature limit. The lack of symmetry again prevents us from assigning conformational structures from the nmr data, but the fact that two important conformations were observed by nmr as well as pes is consistent with our assumption that the relative amounts of conformations present may be estimated by areas under pes curves is at least semiquantitatively correct.



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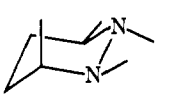
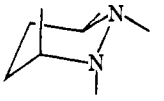
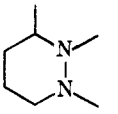


4a



4b



5

Our pes and nmr data agree satisfactorily, where testable, and show that a definite preference for the axial, equatorial distribution of *N*-methyl substituents in the hexahydropyridazene system occurs in the presence of a methyl group on the 3 position, although the equatorial, equatorial disposition is preferred without a flanking methyl group. The pes and nmr data complement each other and show that pes can be useful for conformational analysis, particularly in compounds of lower symmetry, and also because the experiment is performed in the absence of solvation effects.

Acknowledgment. We thank the National Science Foundation for generous support of this research (GP-34488) and the major instrument program of NSF for funds used in purchasing the IEE.15 and XL-100 spectrometers used in this work.

S. F. Nelsen,* J. M. Buschek, P. J. Hintz
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706
Received November 29, 1972

(4) J. A. Kisinger and J. W. Taylor, *Int. J. Mass Spectrom. Ion Phys.*, **10** (4), 445 (1973), and references therein.

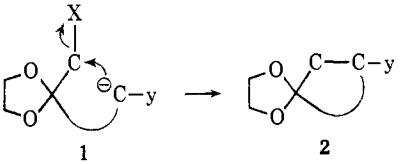
(5) We rule out structures with 1,3 diaxial methyl–methyl interactions as reasonable possibilities throughout.

Haloketal Cyclization. A General Method for the Synthesis of Functionalized Cis Bicyclic Ketones

Sir:

Cyclization reactions are especially valuable when the resulting rings bear functional groups in predictable relationships. When they are used to fuse a new ring onto a preexisting one ("annelation"), it is, of course, desirable that they lead to specific and predictable stereochemistry.

We now report a new, apparently general, reaction which meets both requirements. This is illustrated schematically by **1** to **2**

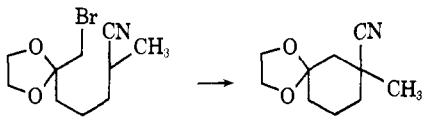


1 **2**

It is noteworthy that the low reactivity of α-haloketals in displacement reactions[1] causes no difficulty in the cyclization processes and may indeed be a help (*vide infra*).

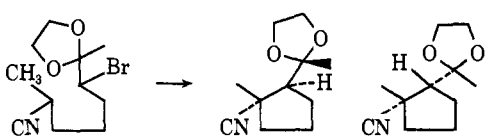
The most generally useful conditions for cyclization involve the use of 1–3 equiv of potassium hexamethyldisilazane[2] in benzene. The reaction is either allowed to stand at room temperature for 8–20 hr or refluxed for 1–4 hr.[3] The cyclization reactions can be carried out on α-chloro- as well as α-bromoketals, although the former cyclize, of course, somewhat more slowly.[4] The yield of distilled or recrystallized material was between 70 and 85% in all cases reported in this communication.[5]

The formation of monocyclic systems may be illustrated by the cyclization of the ketal nitrile **3** which readily gave the corresponding cyclohexanone derivative **4**.[6] It is of some interest that the resistance of α-



3 **4**

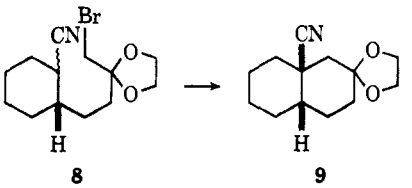
haloketals to solvolytic processes makes the cyclization possible even with a secondary halide; the bromoketal **5** was cyclized, using sodium hexamethyldisilazane, to



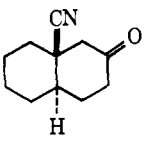
5 **6** **7**

the acetyl cyanocyclopentane derivative **6** (evaporatively distilled at 110° (1 mm)). It is of potential synthetic utility that the isomer formed is the less stable one (**6**:**7** = 92:8) as shown by the fact that hydrolysis of the ketal and reketalization leads to the isomer **7** (**6**:**7** = 3:97).[7]

It is in the area of polycyclic systems that the haloketal cyclization should prove most useful. For instance, cyclization of **8** gave a 9-cyano-2-decalone which proved to be largely (83%) the cis compound **9**, while similarly the haloketal *ester* **10** gave the ethylene ketal of *cis*-methyl 2-decalone-9-carboxylate **11** (mp 54–56°).[8] The Nagata sequence,[9] using either the alu-



8 **9**



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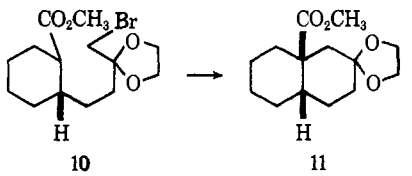
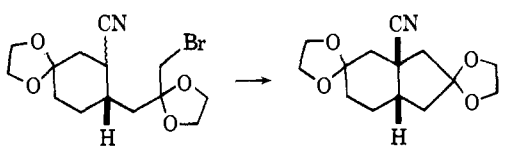


10 **11**

minum cyanide reagents or potassium cyanide–ammonium chloride, is known to give largely the trans isomer **12**.

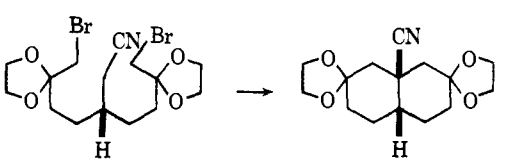
Hydrindan systems can, of course, also be made by this method For instance, the bromoketal **13** was



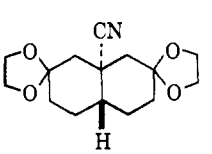
13 **14**

cyclized as usual to the diketal nitrile **14**, mp 93–94° (from ether at −20°).[10] The total cyclization mixture in this case consisted almost entirely of the cis isomer.[11]

It is also possible to form two rings at once. The cyano dibromoketal **15** was cyclized to a mixture con-



15 **16**



17

sisting of 95% of the *cis*-decalin diketal (**16**), mp 108–109°, accompanied by 5% of the trans isomer **17**, mp 163–164° (both from ether).[12]

(1) M. Kuhn, *J. Prakt. Chem.*, **156**, 103 (1940).

(2) This was made by the procedure described by V. Wannagat and H. Niedersprum, *Ber.*, **94**, 1540 (1961), for the related sodium derivative.

(3) Higher yields and stereospecificity were obtained under room temperature conditions.

(4) Two general methods were used for the synthesis of the terminal α-halo ketones: α-chloro ketones were usually made by the well known diazo ketone synthesis from the corresponding carboxylic acids; α-bromo ketones were often derived from the appropriate terminal olefins and aqueous *N*-bromosuccinimide–DMSO (*cf.* D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Amer. Chem. Soc.*, **90**, 5498 (1968)).

(5) All the substances mentioned in this communication gave satisfactory ir, nmr, and mass spectral data.

(6) The structure of **4** was confirmed by correlation with an independently synthesized authentic sample.

(7) The stereochemistry follows from the nmr signal of the methyl group adjacent to the acetyl group (after removal of the ketal); in the ketones corresponding to **6** and **7**, the ring methyls appear at 73 and 90 cps, respectively (*cf.*, N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry. Illustration from the Steroid Field," Prentice-Hall, San Francisco, Calif., 1964).

(8) The structures of **9** and **11** were proved by comparison of the corresponding ketones (50% acetic acid, 1 hr on steam bath) with authentic specimens derived from the minor isomer of the KCN–NH_4Cl sequence, starting with $\Delta^{1,9}$-2-octalone, described by Nagata.[9] The stereochemical result implies that the nitrile anion is more spatially demanding than methyl at the transition state.

(9) W. Nagata, M. Yoshioka, and T. Terasawa, *J. Amer. Chem. Soc.*, **94**, 4672 (1972).

(10) The structure and stereochemistry of this molecule were established by eventual correlation with the *cis*-decalin **16** (R. Boeckman, unpublished work in this laboratory).

(11) Bromoketals **13** and **15** were prepared in the course of another synthetic project. Their synthesis will be detailed in due course.

(12) The cis isomer is eluted from silica gel with 5% ethyl acetate–benzene; the trans follows with 10% ethyl acetate–benzene. The stereochemistry derives from correlation with the known *cis*-9-methyl-2-decalone (A. J. Birch and R. Robinson, *J. Chem. Soc.*, 501 (1943). It is also supported by the nmr of the dioxolane protons which appear as a broad singlet in the cis isomer **16** and as a multiplet in **17**.

To the extent that *cis*-decalin systems can be obtained *via* the α-haloketal cyclization, the process is complementary to the Nagata process;[9] *cis*-9-cyano-2-decalones are available by our method and the trans isomers by Nagata's.

We consider in an accompanying communication[13] the factors which lead to *cis*-decalin stereochemistry and the situations in which this result can be altered or reversed.[14]

(13) Gilbert Stork and Robert K. Boeckman, Jr., *J. Amer. Chem. Soc.*, 95, 2016 (1973).

(14) We thank the National Science Foundation and the National Institutes of Health for their support of this work.

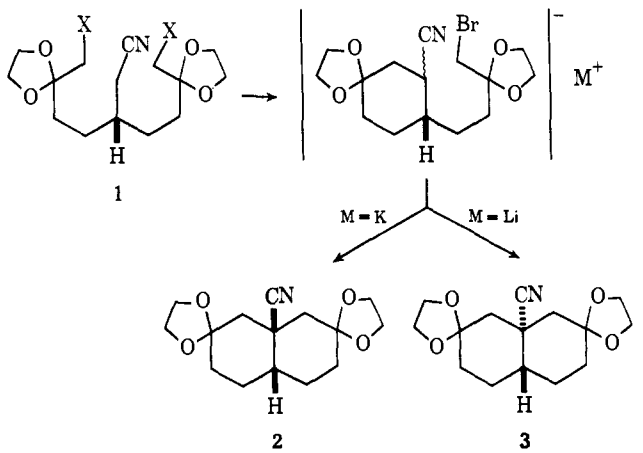
Gilbert Stork,* John O. Gardner
Robert K. Boeckman, Jr., Kathlyn A. Parker
Department of Chemistry, Columbia University
New York, New York 10027
Received November 1, 1972

Mechanism and Stereochemical Control in the α-Haloketal Cyclization. A Remarkable Effect of Metal Cations

Sir:

We report in an accompanying communication[1] that *cis*-decalin and hydrindan systems are formed in high yields from suitable α-haloketal nitriles and esters (Scheme I).

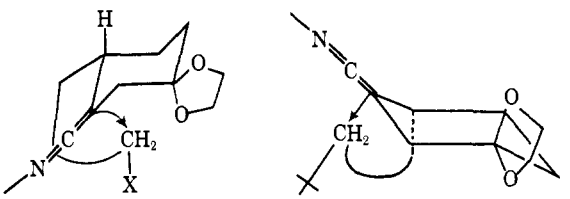
Scheme I



We have made the surprising observation that whereas, as previously reported,[1] the cyclization of **1** (X = Br) with *potassium* hexamethyldisilazane in benzene leads, in high yield, to a mixture consisting of 95% of the *cis*-decalin (**2**), mp 108–109°, the use of *lithium* hexamethyldisilazane, also in benzene, leads to a complete reversal of stereochemistry and the formation of a mixture which now consists of 95% of the *trans*-decalin (**3**), mp 163–164°. This is, to our knowledge, the most dramatic effect yet encountered of the metal cation on the stereochemistry of an alkylation.

Before passing to a discussion of the mechanism of the cyclization, we draw attention to further remarkable observations relating to the control of stereochemistry in the formation of **2** and **3**. First, changing the departing group in **1** from chloride to bromide to iodide had very little effect on the stereochemical result, with either the potassium or sodium base. Even with the lithium base, we only observed a change in product composition from 70% trans from **1** (X = Cl) to 90% trans from the corresponding dibromide or diiodide. In striking contrast, cyclization of the ditosylate **1** (X = OTs) with the same lithium base changed the product composition to 90% *cis*-decalin (**2**). Second, cyclization of the bis(chloroketal) with the lithium base in tetrahydrofuran, rather than in benzene, changes the product ratio from 70:30 in favor of the *trans*-decalin (**3**) to 80:20 in favor of the *cis*-decalin (**2**).

In considering the mechanism of these cyclizations, two possibilities come to mind. If the chain is equatorial at the transition state, the formation of a *cis*-decalin requires that it enter from the axial side at the nitrile α carbon (*cf.* **4**). Conversely, if the transition-state



4 **5**

conformation of the chain is axial (*cf.* **5**), the formation of a *cis*-decalin requires equatorial side connection to that same α carbon.

The first possibility is, *a priori*, unlikely because closure of the chain would produce strong 1,3-diaxial interaction with one of the ring ketal oxygens as shown in **4**. In spite of this, cyclization of the bromoketal **6**, in

6 **7**

which axial entry would not be subject to such an interaction, actually gives *less* cis cyclization (to **7**) than is obtained from **1** (X = Br) under the same conditions (cis:trans ratio = 83:17 and 95:5, respectively).

The second possibility was demonstrated to be the correct one by showing that no *cis*-decalin results when the cyclizing chain is constrained to an equatorial position. This is achieved in the bicyclic bromoketal **9**, synthesized as shown in Scheme II,[2] in which there is a considerable barrier to axial orientation of the chain since such an orientation would require a boat (or twist) conformation of the ring to which it is attached.[3,4]

Cyclization of **9** with potassium hexamethyldisilizane in benzene, conditions which give very largely *cis*-deca-

(1) G. Stork, J. O. Gardner, R. K. Boeckman, Jr., and K. A. Parker, *J. Amer. Chem. Soc.*, 95, 2014 (1973).

(2) The starting enone **8** was made by pyrrolidine enamine annelation of *trans*-2-decalone (G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 85, 207 (1963)), followed by enolate trapping (G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *ibid.*, 87, 275 (1965)) with acetic anhydride (*cf.* G. Stork, M. Nussim, and B. August, *Tetrahedron Suppl.*, 8, 105 (1966)), ozonolysis to the aldehyde acid, and transformation of the related nitrile acid to **13** *via* the diazoketone route. This sequence was selected to establish rigorously the stereochemistry of the chain in **9**.

(3) This barrier might be of the order of 5–6 kcal/mol; *cf.* E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 206.

(4) For the use of this approach, albeit in a mechanistically unrelated case, *cf.* P. T. Lansbury, P. C. Briggs, T. R. Demmin, and G. E. DuBois, *J. Amer. Chem. Soc.*, 93, 1311 (1971).