ture of stereoisomers. This mixture was promptly subjected to oxidative cleavage with lead tetraacetate[10] (EtOAc/pyridine, 25 °C, 20 min) and, after purification by chromatography on silica (elution with 1:1 benzene-ethyl acetate), a 54% yield (based on **12**) of **14** (3500, 1728, 1708 cm^{-1}; δ 1.50 (9 H, s), 2.18 (6 H, s), 6.58 (1 H, d, J = 16 Hz), 6.64 (1 H, d, J = 16 Hz), 6.96 (1 H, d, J = 16 Hz), 7.06 (1 H, d, J = 16 Hz)) was obtained. Mild hydrolysis of **14** (TFA, 0 °C, 15 min) furnished the highly polar carboxylic acid **15**, which provided the substrate for subsequent lactonization studies.

Virtually all lactonization methods currently in vogue entail activation of the carboxyl group, followed by nucleophilic attack by hydroxyl.[11] Although this tactic has enjoyed noteworthy success in macrolide synthesis,[2,12] the sensitive ene-dicarbonyl functions in **14** frustrated all attempts to construct suitably activated ester derivatives. Consequently, we turned to an approach in which the roles of carboxyl and hydroxyl partners are reversed, adopting the principle of hydroxyl activation in the presence of a carboxyl group as nucleophile.[13] Thus, treatment of **14** in benzene with triphenylphosphine, followed by diethyl azodicarboxylate with vigorous stirring (25 °C, 2 days),[14] gave, after preparative thin-layer chromatography on silica, a 15% yield of (±)-vermiculine (**1**), identical by infrared, NMR, mass spectral, and chromatographic comparison with authentic material. A slightly more polar, chromatographic fraction corresponding to the unnatural, trans isomer of **1** was also isolated.

Although the yield of **1** from **14** is disappointingly low, the lactonization method demonstrated here provides a potentially useful alternative to the conventional carboxyl-activation methodologies.[15] Considerable refinement of this "reverse activation" technique may be anticipated.[16]

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(16) This work was supported financially by the National Institutes of Health (AI 10964).
(17) Recipient of a National Institutes of Health Research Career Development Award.

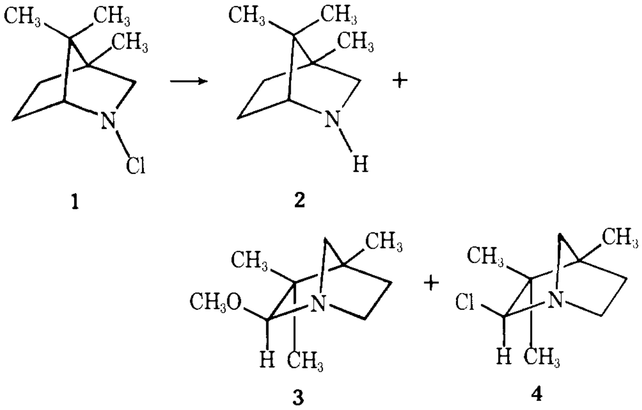
Yoshiyasu Fukuyama, Curtis L. Kirkemo, James D. White*[17]
Department of Chemistry, Oregon State University
Corvallis, Oregon 97331
Received October 15, 1976

A Comparison of the Heterolytic vs. Homolytic Cleavage of the Nitrogen–Chlorine Bond

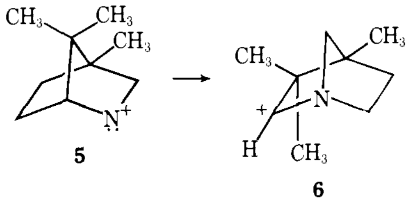
Sir:

Over the last decade, we have carried out a detailed study of the reactions and properties of nitrenium ions (divalent positive nitrogen species).[1] As part of these investigations, we described the heterolytic cleavage of the N–Cl bond of *N*-chloramines in both silver ion promoted and purely solvolytic ionization reactions. However, recently it was stated that "Nitrenium ions *are not* generated from simple secondary chloramines in the presence of silver ions at room temperature."[2] Extrapolations of this statement[3] have prompted us to thoroughly establish the difference between the heterolytic and homolytic cleavage of the N–Cl bond of chloramines. We now wish to report the details of this study.

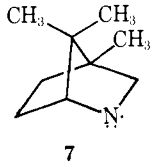
In our early work on the rearrangement of *N*-chloramines, we established that both the silver-ion promoted and noncatalyzed solvolysis of **1** in methanol gave a mixture of **2**, **3**, and **4**.[4] It was proposed that the formation of **3** and **4**, which constituted greater than 90% of the product mixture arose via Wagner–Meerwein rearrangement of the initially generated nitrenium ion **5** to yield the carbonium ion **6**. Addition of solvent or internal return of chloride would then give **3** or **4**, respectively. In order to distinguish between a homolytic and a heterolytic cleavage of the N–Cl bond, it became necessary to generate the amino radical, **7**, and to compare the products derived from **7** with those arising from the solvolytic reactions previously studied. Three approaches were taken to the generation of **7**. These were (1) photolysis of the tetrazene **8**, (2) photolysis of **1**, and (3) benzoyl peroxide promoted decomposition of **1** in methanol.



1 **2** **3** **4**

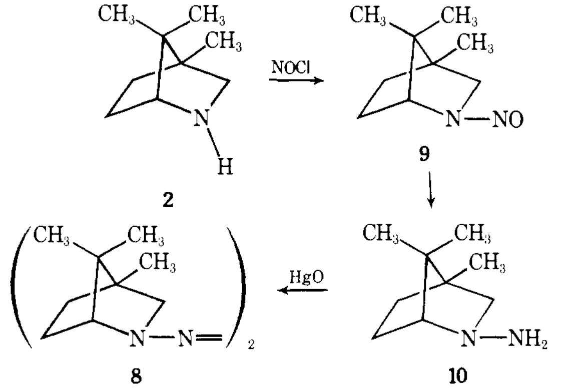


5 **6**

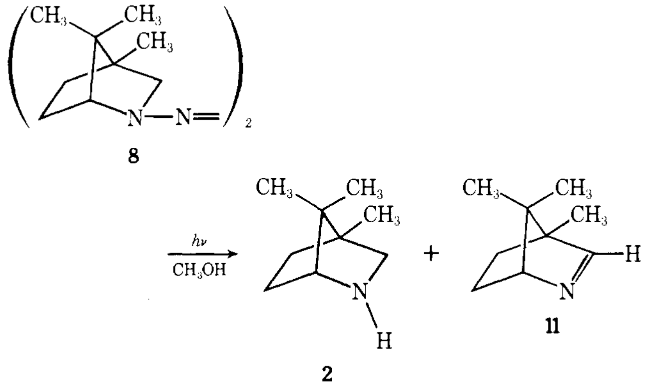


7

Tetrazenes are well-established sources of nitrogen radicals.[5] In order to prepare the tetrazene necessary for the production of **7**, **2** was treated with nitrosyl chloride to give **9**,[6] which on lithium aluminum hydride reduction gave the hydrazine **10**.



Oxidation of **10** with mercuric oxide gave the tetrazene **8** in 60% overall yield. Irradiation of a methanolic solution of **8** at room temperature with a Hanovia 450-W high pressure mercury lamp gave only **2** and **11** in 63 and 34% yields, respectively. *No products derived from skeletal rearrangement could be detected.* The structure of **2** was established through comparison with an authentic sample. The structure of **11** was assigned on the basis of its NMR spectrum (single olefinic proton at δ 7.50) and through comparison with an authentic sample prepared from **1** by treatment with sodium methoxide.



Photolysis of **1** in methanol with a 450-W Hanovia source gave as major products 37% of **2**, 33% of **11**, and 10% of **4**.[7] The formation of **4** in this reaction indicated that some solvolysis was competing with the homolytic cleavage. The difference in the ratio of **2** to **11** may be attributed to the generation of a pair of amino radicals plus nitrogen in the irradiation of **2**, vs. the formation of a chlorine-amino radical pair in the photolysis of **1**. Since the precursors are different in the two experiments being compared, it is also conceivable that the generated amino radicals might not exist in identical solvent cages and, hence, may react with the solvent cage at slightly different rates and in slightly different manners.

From the photochemical decomposition of **8** and **1**, it became obvious that **11** was a major product of the photochemically generated radical **7**. However, it was not established whether the formation of **11** depended on **7** having its origin in an excited state reaction. In order to answer this question, we carried out the methanolysis of **1** in the presence of 0.1 equiv of benzoyl peroxide. This reaction gave 10% of **2**, 5% of **3**, 26% of **4**, and most significantly 21% of **11**. Again, a combination of homolytic and heterolytic processes was involved. However, the formation of **11** in this reaction firmly established that **11** could arise from a nonphotochemically generated nitrogen radical. These results clearly indicate that the benzoyl peroxide-induced decomposition of **1** in methanol has a radical-chain component.

In summary, we have demonstrated that nitrogen radicals can follow reaction paths, which are very diverse from those of nitrenium ions. Specifically, in the case studied, we have shown that while the imine **11** was completely absent in the methanolysis of **1**, it was a major product of all of the reactions, which should proceed via the nitrogen radical **7**. This indicates that both the silver ion promoted and noncatalyzed methanolysis of **1** proceed via heterolytic cleavage of the N-Cl bond as previously proposed.[4,8]

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(8) These results raise questions concerning the role of "heavy atom solvent effects" in the interconversion of singlet and triplet nitrenium ions.[1] Since the amino radical **7** clearly yielded both **2** and **11**, the failure to identify **11** as a major product of the decomposition (solvolysis) of **1** in heavy atom solvents indicated that a major difference existed between the cationic nitrogen diradical (nitrenium ion triplet), the nitrogen cation radical (previously postulated as an intermediate in the reaction of triplet nitrenium ions with hydrogen donating solvents), and amino radicals such as **7**. Further studies of these differences and of the general concept of "heavy atom effects" in nitrenium ion chemistry are currently under investigation.

(9) Inquiries concerning this study should be sent to P.G.G. at the University of Minnesota.

Paul G. Gassman,*[9] Kenji Uneyama, Jerry L. Hahnfeld
Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455 and
Department of Chemistry, The Ohio State University
Columbus, Ohio 43210

Received August 2, 1976

Biosynthesis of the Isoquinuclidine Moiety of Dioscorine. Incorporation of [5,6-$^{13}C_2$]Nicotinic Acid Established by Means of ^{13}C Nuclear Magnetic Resonance

Sir:

Dioscorine (**2**)[1] is an alkaloid found in the tropical yam, *Dioscorea hispida*, Dennst. and related species. We have previously[2] established that the administration of [1-^{14}C] acetate to this plant yielded radioactive dioscorine, which was labeled on alternate carbons (C-5, 10, and 12) of the unsaturated lactone ring. This result led us to suggest that dioscorine is formed by a condensation between Δ^1-piperideine (**1**) (which is formed from lysine in higher plants[3]) with a branched 8-carbon unit derived from four acetate units (route A, Scheme I). Spenser[4] suggested a slight modification in which pelle-