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The Flash Vacuum Thermolysis of (–)-Cocaine

Nicholas J. Sisti and Frank W. Fowler*

Department of Chemistry
State University of New York at Stony Brook
Stony Brook, New York 11790

Joanna S. Fowler

Department of Chemistry
Brookhaven National Laboratory
Upton, New York 11973

Summary: (–)-Cocaine is thermally labile and, in a series of remarkable thermal reactions, is cleanly partitioned among benzoic acid, N-methylpyrrole and methyl 3-butenoate.

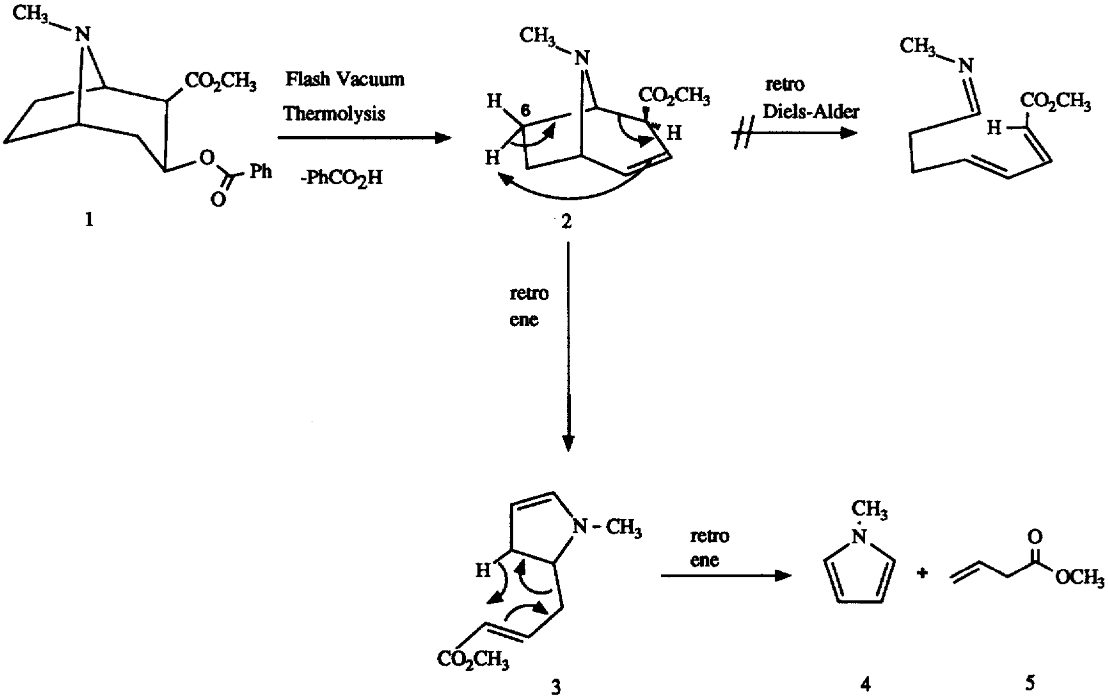
Unimolecular thermal behavior occupies a position of fundamental importance among those reactions that describe the chemistry of a molecular system. All organic molecules have thermal chemistry and few reactions can rival the conceptual simplicity of adding thermal energy to a molecular system until a chemical transformation occurs. The thermal chemistry of a molecular system can often provide important information with respect to structure-reactivity relationships as well as being of value in organic synthesis.[1]

Because of complications arising from bimolecular reactions, the unimolecular thermal chemistry is best studied by taking advantage of the conditions of very high dilution of the gas phase. However, the difficulty with using the gas phase for molecules with a high degree of complexity is that heat is usually required for their evaporation. The application of heat to many compounds, even under conditions of high vacuum, often results in their decomposition into intractable tars before evaporation occurs. We have discovered that this problem can be considerably alleviated by using a solvent to co-sublime the substrate at low temperatures.[2] We now report the application of this method to some tropane alkaloids.

An important member of the tropane alkaloids is (–)-cocaine **1** whose abuse has created a number of complex and interacting social, economic, political and medical problems resulting in an urgent need for more scientific information on the biology and chemistry of this substance.[3] The thermal processes associated with (–)-cocaine may be particularly important because heat is often used as a mode of drug delivery.[4] Surprisingly, there is little information in the literature on the gas phase thermolysis of (–)-cocaine.[5]

The most obvious thermal reaction available to (–)-cocaine **1** is the *cis* elimination of benzoic acid[8] to produce the methyl ester of ecgonidine **2**.[9] Ecgonidine **2** has the structural features necessary for two modes of pericyclic reactivity. The presence of the double bond in a six membered ring suggests the possibility of the *retro* Diels-Alder reaction. This possibility is suggested by photochemical studies on tropidine which resulted primarily in this mode of reactivity.[10]

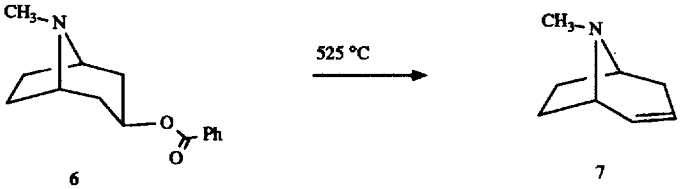
The second type of pericyclic reaction available to ecgonidine **2** is the *retro* ene reaction.[11] The structural features necessary for this reaction is a double bond and the availability of γ-hydrogen atoms. These features are present in ecgonidine **2** but, because of structural constraints, only the *endo* γ-hydrogen atom on C-6 of ecgonidine **2** is available to participate in a *retro* ene reaction.



At an oven temperature of 500 °C the sublimation (–)-cocaine, using a technique previously described,[2] produced thermal products along with 65% of unreacted (–)-cocaine. Raising the temperature of the thermolysis oven to 550 °C resulted in the complete conversion of (–)-cocaine into its thermal products. However, ecgonidine **2** was not detected among the other thermal products.

The proton nmr spectrum shows the presence of two new absorptions characteristic of O- and N-methyl groups. The absence of other significant O- or N-methyl absorptions is supportive of the presence of one major thermal pathway for (–)-cocaine. Inspection of the proton nmr spectrum led to the conclusion that, in addition to benzoic acid, two thermal products were formed whose structures were N-methylpyrrole **4** and methyl 3-butenoate **5**.[12] This conclusion was confirmed by a comparison of the pyrolysis products with authentic samples.[13]

Although ecgonidine **2** was not observed it the thermolysis of (–)-cocaine, it is its participation in series of *retro* ene reactions that is most consistent with the formation of thermal products, N-methylpyrrole and methyl 3-butenoate. The *retro* ene reaction of ecgonidine **2** would initially produce the pyrroline derivative **3**. A second *retro* ene reaction of this compound would give the observed products. Important driving forces for these processes are the formation of the aromatic pyrrole nucleus as well as the favorable $T\Delta S$ term of the total free energy of the process at the high reaction temperature. The failure to detect ecgonidine **2** strongly suggests that the carboxylic acid elimination is the slowest, least favorable thermal reaction leading to the final products.



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It is interesting to compare the above result with the benzoate derivative of tropine **6**. The evaporation of **6** at 525 °C resulted in the formation of tropidine (**7**). There was no indication of a *retro* ene reaction occurring at 525 or 550 °C, suggesting that the carboxyl substituent plays an important role in lowering the activation energy of the *retro* ene reaction. Although substituent effects are well established for the Diels-Alder reaction, less is known about their role for the ene reaction.[11]

These studies suggest that two consecutive ene reactions initiating with methyl 4-butenoate and a suitable pyrrole derivative[14] could provide access to the tropane ring system. This possibility is presently being explored.

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REFERENCES AND NOTES

* Author to whom correspondence should be addressed.

(1) There have been a number of recent reviews on various aspects of gas-phase flow thermolysis: (a) Karpf, M. *Angew. Chem., Internat. Ed.* **1986**, *25*, 414. (b) Wiersum, U. E. *Aldrichimica Acta* **1984**, *17*, 31. (c) Wiersum, U. E. Recl. Trav. Chim Pays-Bas **1982**, *101*, 317 and 365. (d) Seybold, G. *Angew. Chem., Internat. Ed.* **1977**, *16*, 365. For a recent monograph on this subject see:(e) Brown, R. F. C."Pyrolytic Methods in Organic Chemistry", Academic Press, 1980.

(2) The application of heat to introduce compounds into the gas phase frequently results in their decomposition. This problem has historically limited the general application of flash vacuum thermolysis to compounds of interest. We have observed that co-sublimation of a sample with a volatile solvent can be an effective solution to this problem. (Magrath, J.; Fowler, F.W. *Tetrahedron Lett.* **1988**, *29*, 2171). The sublimation of a 10% solution of (–)-cocaine in benzene-d_6 was used to introduce (–)-cocaine into the thermolysis oven. Because (–)-cocaine is reasonably volatile, it can be directly evaporated into the thermolysis oven without the aid of co-sublimation. Although the product mixture is more complex, qualitatively we observe the same result. Benzoic acid, methyl 3-butenoate and N-methylpyrrole were the major products.

(3) Koob, G. F.; Bloom, F. E. *Science* **1988** *242*, 715.

(4) Snyder, C. A.; Wood, R. W.; Graefe, J. F.; Bowers, A.; Magar, K. *Pharm. Biochem. Behavior* **1988**, *29*, 9395.

(5) Previous studies on the thermolysis of (–)-cocaine are contradictory. One study[6] has reported a low conversion to methyl 4-(3-pyridyl)butyrate. The second study did not report the formation of methyl 4-(3-pyridyl)butyrate but did observe the formation of a number of products including the isomeric methyl cycloheptatrienecarboxylates.[7] These studies were not as concerned with unraveling the unimolecular thermal chemistry of (–)-cocaine as they were with determining whether (–)-cocaine decomposed under the conditions of drug delivery.

(6)(a) Novák, M;. Salemink, S. A. *Bull. Narc.* **1984**, *36*, 79. (b) Novák, M.; Salemink, C. A. *Tetrahedron* **1989**, *45*, 4287.

(7) Cook, C. E.; Jeffcoat, A. R.; Perez-Reyes, M. in *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs*, Biomedical Publications: Foster City, CA, 1984, p. 48.

(8) Smith, G. G.; Kelly, F. W. *Prog. Phys. Org. Chem.* **1971** *8*, 75.

(9) There was some confusion in the literature regarding structure **2**. (Findlay, S. P. *J. Amer. Chem.* Soc., **1953**, *75*, 1033) There are two isomeric ecgonidines, one with the double bond a, b and the other with the double bond b, g to the ester group (**2**). It now appears that compound **2**, almost assuredly the first gas phase thermolysis product of (–)-cocaine, has never been characterized.

(10) Srinivasan, R.; Studebaker, J.; Brown, K. *Tetrahedron Lett.* **1979**, *22*, 1955.

(11) The retro ene is a common reaction occurring in the gas phase (see reference 3). It is the reverse transformation of the well known ene reaction (Oppolzer, W. *Angew. Chem., Int. Ed. Eng.* **1984**, *23*, 876).

(12) The yields of benzoic acid (100%), N-methylpyrrole (74%) and methyl 3-butenoate (60%) were estimated from the pmr spectrum of the product mixture using cyclohexane as an internal standard.

(13) The methyl 3-butenoate was prepared from 3-butenoic acid using diazomethane. The N-methyl pyrrole and 3-butenoic acid are commercially available from Aldrich Chemical Company, Milwaukee, WI.

(14) The known Diels-Alder reactivity of N-carbomethoxypyrrole would suggest it as a suitable pyrrole derivative.

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