New Type of Intramolecular Imino-Ene Cyclization during Pyrolysis of (-)-Cocaine

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Abstract: Pyrolysis of (-)-cocaine resulted in an unprecedented, complex sequence of reactions, including a new type of imino-ene reaction.

As a consequence of a new practice of cocaine abuse, cocaine base smoking, 1.2 there is a recent increase of interest in the thermal behaviour of cocaine.³⁻⁵ In our previous work^{6,7} the formation of methyl 4-(3-pyridyl)butanoate, a volatile having a characteristic odour of oak wood, by pyrolysis of (-)-cocaine in a stream of nitrogen at 600°C has been described. We now wish to report on a new type of intramolecular imino-ene cyclization which occurs as one of the reactions involved in a complex sequence of reactions of remarkable diversity (see Scheme 1) by which the methyl pyridylbutanoate is formed. To the best of our knowledge, the imino-ene reaction⁸⁻¹⁰ in which the olefin acts as a hydrogen acceptor has not been described.

Labelled starting material (-)-cocaine- $[N-CD_3]$ 1⁷ was used to unravel the thermal reaction pathway leading to labelled methyl pyridylbutanoate 6. Assuming *cis*-elimination of benzoic acid^{3,7} as the first step, followed by retro-Diels-Alder reaction,¹¹ a reaction pathway was proposed as shown in Scheme 1. Evidence for the imino-ene reaction of compound 3 was taken from the place of the label in the butanoate chain of compound $6.^{12}$ Further support for the occurrence of the imino-ene reaction was given by the detection of diene-ester 7^{13} in the pyrolysate, as a degradation product of imine 4, see Scheme 2.

The position of the deuterium label in the pyridine nucleus of compound 6^{12} was indicative of the occurrence of a 2-aza-Cope rearrangement. To establish this sequence of reactions, a second labelling study was undertaken using (-)-cocaine- $[N-^{13}CH_3]$ 9 as starting material. In accordance with the proposed reaction pathway, the α -labelled methyl pyridylbutanoate 10^{13} was isolated from the pyrolysate (see Scheme 3).

a Dedicated to the memory of our father Dr. Gustav Novák.





Scheme 2



The 2-aza-Cope rearrangement,¹⁴ in the non-cationic fashion,¹⁵ is a rather uncommon reaction. In Scheme 1, we describe the first example of this rearrangement occurring in the gas phase. This is in contrast to the 1-aza-Cope¹⁶ and 3-aza-Cope¹⁷ rearrangements which are known to occur in the gas phase.





Following the logic and numbering of a 1,5-H shift,¹⁸ we propose a notation for the heteroene reaction (see Scheme 4), also including cationic types of this reaction. Within this classification all the possible imino-ene reactions can be distinguished by name. Thus the above mentioned imino- ene reaction (see Scheme 1) should be named 2-aza-ene reaction. The known imino-ene reactions should then be named: 5-aza-ene reaction^{8a,b,d} and 4-aza-ene reaction.^{8c}

Detailed labelling study of the several H-shifts and of the dehydrogenation step, as well as the extension of the reaction sequence to cocaine-analogues are underway.

References and Notes

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- Compound 6: ¹H NMR (200 MHz, CDCl₃) δ 8.45 (m, 1H), 7.5 (m, 1H), 7.2 (m, 1H), 3.7 (s, 3H), 2.65 (m, 1H), 2.3 (m, 2H), 1.95 (m, 2H). The assigned structure 6 is in agreement with ¹³C NMR and mass spectral data.
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