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Artigo

TEMPERATURE-DEPENDENT BENZOIC ACID ELIMINATION MECHANISMS IN PYROLYSIS OF (–)-COCAINE

Michal Novák*
Bijvoet Center, Department of Organic Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands

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The thermal elimination of benzoic acid from (–)-cocaine is shown to be temperature-dependent. In the temperature range of 200-500 °C only a *trans*-elimination is observed leading to methylecgonidine. Above ca. 500 °C a second mechanism, the *cis*-elimination, comes up yielding a novel alkaloid methylisoecgonidine which has been characterized by means of mass spectrometry. At 600 °C the *cis*-elimination predominates. The *trans*-elimination is postulated a two-step process consisting of a 1,7- and a 1,5-hydrogen shift. The chemistry of cocaine base smoking is explained using the theory of chemical activation.

Keywords: cocaine base smoking; (+)-pseudococaine; 1,3-methoxyl shift.

INTRODUCTION

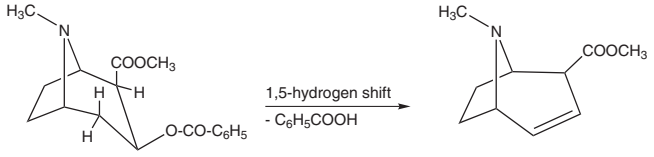
Cocaine base (crack) smoking is a highly addictive form of drug abuse.[1] In this process heating is used to volatilize the free base for inhalation. However, the application of heat causes some degradation of (–)-cocaine (**1**). Methylecgonidine (anhydroecgonine methyl ester) (**2**) and benzoic acid are the major degradation products during cocaine base smoking which takes place at ca. 260 °C. Methylecgonidine (**2**) shows biological activity on the heart,[2] lung[3] and liver,[4] and probably has addictive potential.[5]

During gas chromatographic analysis of (–)-cocaine (**1**) a small amount (0.1-2.6%) of methylecgonidine (**2**) is very often being formed by elimination of benzoic acid from the parent molecule.[6-8] Methylecgonidine (**2**) was found as the main thermal decomposition product of (–)-cocaine (**1**) at 180-200 °C[9] and at 210-290 °C.[10] The literature regarding the thermal elimination mechanism of benzoic acid from (–)-cocaine (**1**) contains some contradictory statements. Although never studied in detail, the mechanism of this thermal process has been described twice as a *trans*-elimination[7,10] and twice as a *cis*-elimination.[8,9]

There is also contradiction concerning the first gas-phase pyrolytic product of (–)-cocaine (**1**). One study[9] postulates methylecgonidine (**2**) as the primary pyrolysate, while other studies[11,12] claim the unconjugated isomer of methylecgonidine, which we name methylisoecgonidine (**3**), as the first gas-phase thermolysis product of (–)-cocaine (**1**). The hypothetical intermediate methylisoecgonidine (**3**) was not detected by these authors. It is important to note that methylecgonidine (**2**) is obtained at temperatures of 180-290 °C, while methylisoecgonidine (**3**) is believed to be formed at 500-550 °C. This difference in temperature ranges led us to the idea that two different mechanisms are operating in the thermal elimination of benzoic acid from (–)-cocaine (**1**).

RESULTS AND DISCUSSION

In our previous work on cocaine base smoking[13] we found that at 600 °C pyrolysis of (–)-cocaine (**1**) gave both the isomers methylisoecgonidine (**3**) [7.2%, corrected for the formation of the rearrangement product methyl 4-(3-pyridyl)butanoate (**9**)] and methylecgonidine (**2**) (0.3%), while at 400 °C only methylecgonidine (**2**) (<0.1%) was identified as pyrolytic product. Thus, we have results indicating temperature-dependent mechanisms in (–)-cocaine (**1**) pyrolysis. In the temperature range of 500-600 °C our results are consistent with a *cis*-elimination mechanism leading to methylisoecgonidine (**3**)[11,14] (Scheme 1). In the temperature range of 200-600 °C still another elimination mechanism must operate resulting in the formation of methylecgonidine (**2**). Since a *trans*-elimination in the pyrolysis of esters is only observed in very few cases[21] and only when a *cis*-elimination is impossible on stereochemical grounds, we were surprised to observe a reaction, which looked like a *trans*-elimination, at a lower temperature (400 °C) than the common *cis*-elimination, that takes place at 600 °C as the main reaction of (–)-cocaine (**1**).



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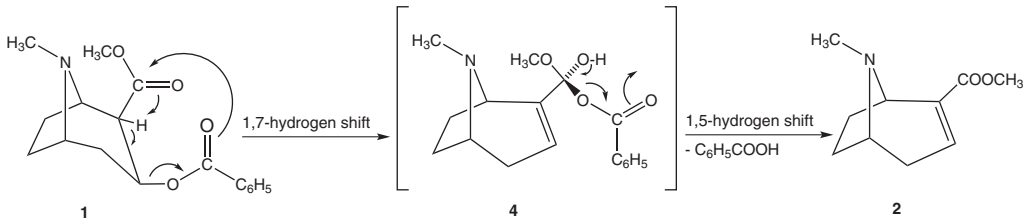
Scheme 1. *Cis-elimination of benzoic acid from (–)-cocaine (**1**)*

Careful literature search revealed the possibility of a two-step *trans*-elimination mechanism occurring in a diester.[15] Application of this two-step process to (–)-cocaine (**1**) leads to methylecgonidine (**2**) (Scheme 2). The first step is a 1,7-hydrogen shift yielding an ortho acid derivative **4** as intermediate which undergoes a 1,5-hydrogen shift giving methylecgonidine (**2**) and the eliminated benzoic acid. The relatively low activation energy of a 1,7-hydrogen shift[16,17] makes the appearance of the *trans*-elimination at a rather low temperature possible. The antarafacial character of a 1,7-hydrogen shift[16,18] is in accordance with the stereochemistry of the observed *trans*-elimination. The next step in this elimination, a suprafacial 1,5-hydrogen shift, is not relevant for the stereochemistry of this reaction. The proposed mechanism is in agreement with the calculated atomic charges for (–)-cocaine (**1**) in the gas phase,[23] i.e. the most positive hydrogen

*e-mail: novakmk@hotmail.com

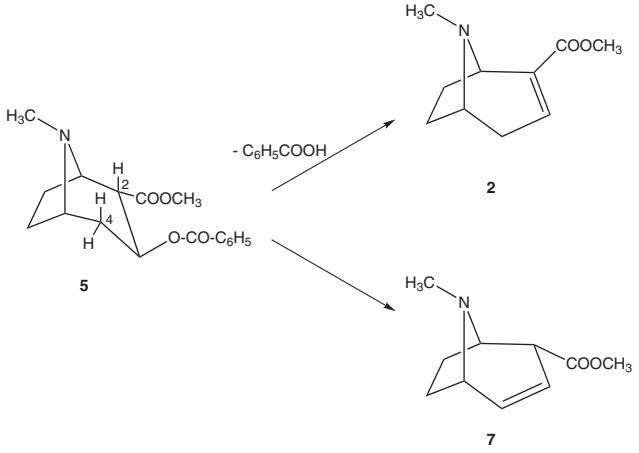


Scheme 2. *Two-step trans-elimination of benzoic acid from (−)-cocaine (**1**)*

moves to the most negative oxygen. The facile rotation of the carbonyl group on C-2 in (−)-cocaine (**1**)[24] makes the antarafacial character (the oxygen atom positioned above the hydrogen atom on C-2) of the 1,7-hydrogen shift possible. The activation energy of a 1,7-hydrogen shift is lower than that of a 1,5-hydrogen shift (*cis*-elimination).[16,17] Moreover, the 1,7-hydrogen shift in (−)-cocaine (**1**) includes two carbonyl groups which lower the activation energy.[16]

To support our mechanistic proposal (+)-pseudococaine (**5**) was pyrolyzed at different temperatures. At 600 °C, besides the starting material (60%), the main decomposition products were benzoic acid (34%), methylecgonidine (**2**) (0.5%), and methyl 2-(3-pyridyl) butanoate (**6**) (0.5%). The latter compound is a rearrangement product of the primary pyrolysate methylecgonidine (**2**). At 240 °C (gas chromatographic conditions) methylecgonidine (**2**) and benzoic acid were the only thermal decomposition products of (+)-pseudococaine (**5**). The *cis*-elimination mechanism leading to methylecgonidine (**2**) is depicted in Scheme 3. The availability of an axial α-hydrogen atom[19] makes the *cis*-elimination of benzoic acid a facile reaction. Of the two axial α-hydrogen atoms only the more acidic C-2 hydrogen reacted yielding the conjugated, thermodynamically more stable isomer **2**. The possible, but improbable *trans*-elimination[19-21] of benzoic acid using the equatorial C-4 hydrogen atom and leading to the unconjugated isomer methylpseudoisoecgonidine (**7**) could not be detected (Scheme 3).

Additional experiments showed that the formation of methylecgonidine (**2**) from (−)-cocaine (**1**) is catalyzed by acid, but the formation of methylisoecgonidine (**3**) is not, indicating a polar transition state



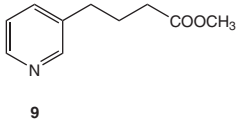
Scheme 3. *Eliminations of benzoic acid from (+)-pseudococaine (**5**)*

in the formation of **2** and an apolar one in the formation of **3**. These results are in accord with the available literature data.[21]

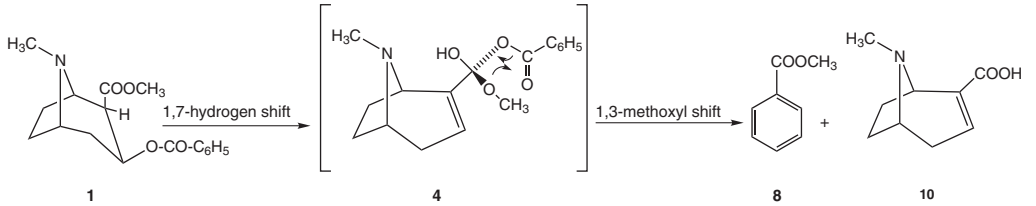
Furthermore, methyl benzoate (**8**) (0.06%) was identified in the (−)-cocaine (**1**) pyrolysate at 600 °C.[13] A plausible mechanism for the formation of methyl benzoate (**8**) involving the rare thermal 1,3-methoxyl shift[22] is given in Scheme 4. The occurrence of this shift supports in this way the structure of the postulated ortho acid derivative **4**. In this respect it is important to note that at 600 °C the pyrolysis of (+)-pseudococaine (**5**) does not involve the 1,7-hydrogen shift and hence the intermediate **4** is not produced. Consequently, the pyrolysate of (+)-pseudococaine (**5**) contains no methyl benzoate (**8**) and this has been confirmed by GC-MS analysis.

The above mentioned results indicate that chemical activation[25-29] is involved in the pyrolyses of (−)-cocaine (**1**) and of (+)-pseudococaine (**5**) at 600 °C. In both cases chemically activated (vibrationally excited) methylecgonidine (**2**) is formed containing, however, different amounts of excess energy which is defined as activation energy minus heat of reaction.[26] As shown in Scheme 5, chemically activated methylecgonidine (**2**)** from (+)-pseudococaine (**5**) possesses more internal energy than methylecgonidine (**2**)* formed from (−)-cocaine (**1**). In the former case the methylecgonidine (**2**)** rearranges further to the major compound methyl 2-(3-pyridyl)butanoate (**6**), while methylecgonidine (**2**)* from (−)-cocaine (**1**) rearranges only in trace amounts to the same compound **6**;[13] the quantity of the rearrangement product being a measure[30] of the internal excess energy. This is another indication that there are two distinct elimination mechanisms with different activation energies operative.

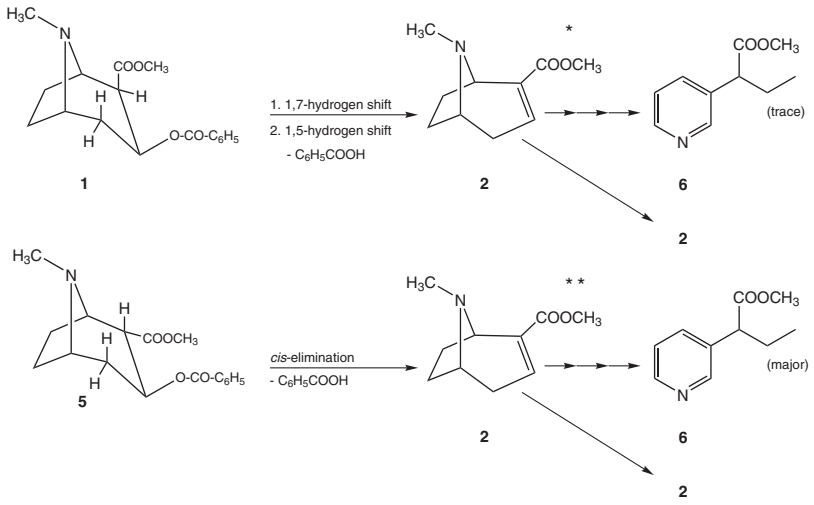
By analogy, at 600 °C *cis*-elimination of benzoic acid from (−)-cocaine (**1**) gives chemically activated methylisoecgonidine (**3**)* which rearranges further to the major compound methyl 4-(3-pyridyl) butanoate (**9**).[14,31]



At 400 °C (pyrolysis in quartz tube under nitrogen) (−)-cocaine (**1**) gives chemically activated methylecgonidine (**2**) which does not react further to methyl 2-(3-pyridyl)butanoate (**6**). It is clear that at 400 °C the chemical activation is not high enough to enable the rearrangement; the applied temperature is of crucial importance. At 600 °C the added kinetic energy is high enough to make the rearrangement possible.



Scheme 4. *Formation of methyl benzoate (**8**) from (−)-cocaine (**1**) including a 1,3-methoxyl shift*



Scheme 5. *Formation of chemically activated methylecgonidine (**2**) containing different amounts of excess energy*

It is interesting to note that in contrast to the most literature on chemical activation[25,26] our example is the result of an endothermic reaction (benzoic acid elimination).

Mass spectrometry

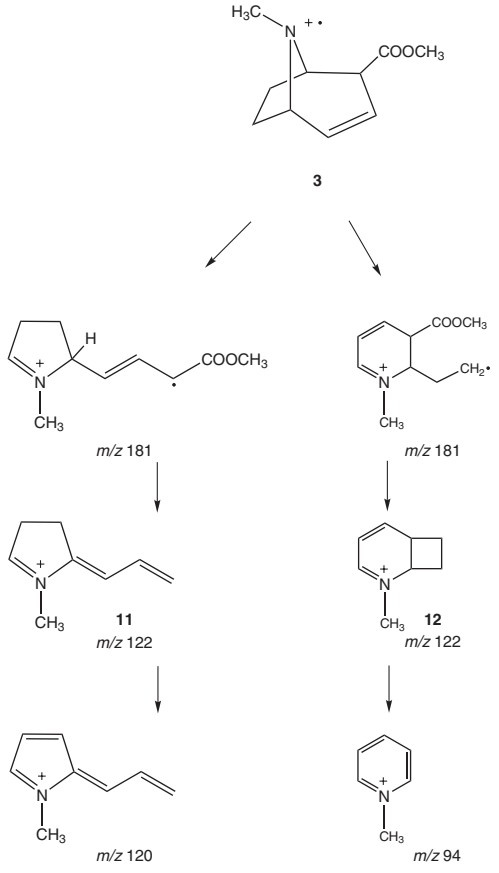
The structure of methylisoecgonidine (**3**) was ascertained by the interpretation of its mass spectrum[13] and by comparison with the mass spectrum of the conjugated isomer methylecgonidine (**2**).[7,32] Two main fragmentation pathways can be distinguished in the mass spectrum of **3**. Allylic cleavage in the tetrahydropyridine moiety of methylisoecgonidine (**3**) is the major fragmentation pathway leading to a dihydropyrrole derivative **11** at *m/z* 122 (base peak) (Scheme 6). The minor fragmentation pathway is the result of an allylic cleavage in the pyrrolidine moiety of compound **3** giving a dihydropyridine derivative **12** at *m/z* 122 (base peak) (Scheme 6). The fragmentation pathways clearly indicate the location of the double bond in the unconjugated olefin **3**.

CONCLUSIONS

Pyrolysis of (−)-cocaine (**1**) gives a rather unexpected result. In the temperature range of 200-500 °C only the two-step *trans*-elimination is observed. This is a slow reaction having a low frequency factor due to the reaction geometry (antarafacial 1,7-hydrogen shift). Above ca. 500 °C competing[17] elimination mechanisms are operative. At 600 °C the *cis*-elimination predominates. Thus, the elimination mechanisms are temperature-dependent. Accordingly, there are two primary pyrolysates, the ortho acid derivative **4** and methylisoecgonidine (**3**), depending on the appropriate mechanism of benzoic acid elimination from (−)-cocaine (**1**). In practice, this means that the formation of methylecgonidine (**2**) in cocaine base (crack) smoking follows the two-step *trans*-elimination, often catalyzed by acid from adulterants.

EXPERIMENTAL

Mass spectra (GC-MS and HRMS) were recorded on a Kratos MS 80 spectrometer at 70 eV, values in *m/z* (rel. int.). The GC analysis was performed on a Packard Becker 417 equipped with a capillary CP-Sil 5 fused silica column (Chrompack); length: 25 m; i.d.: 0.24 mm. The oven temperature was programmed from 110 to 230 °C at 10 °C/min. The injection port temperature was 240 °C. The percentage composition was determined with a Varian CDS 111 integrator.



Scheme 6. *Fragmentation pathways in the EI mass spectrum of methylisoecgonidine (**3**)*

The compounds were identified by comparison of their mass spectra and retention times with those of reference samples.

(−)-Cocaine (**1**) was supplied by Diosynth, Apeldoorn, The Netherlands. (+)-Pseudococaine (**5**) was prepared from (−)-cocaine (**1**) according to literature procedure.[33]

The pyrolysis apparatus was described earlier.[31] (+)-Pseudococaine (**5**) (20 mg) was deposited as a thin film in a quartz tube (i.d. 1 cm) and pyrolyzed for 5 min at 600 °C in a stream of nitrogen (12 mL/min). The pyrolytic products were extracted with abs. EtOH and the solvent concentrated to give 11.5 mg of brown oil. During the pyrolysis some gas evolution was observed. Prior to the GC-MS analysis

benzoic acid was removed from the pyrolysate by washing a $CHCl_3$ solution of the pyrolysate with a saturated aqueous $NaHCO_3$ solution.

Methylisoecgonidine (**3**) [*Chem. Abstr.* name: (2-*exo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-ene-2-carboxylic acid methyl ester]: MS *m/z* 181 (M^+, 26), 152 (14), 124 (4), 123 (10), 122 (100), 120 (3), 108 (3), 107 (13), 106 (5), 94 (10), 93 (3), 81 (5), 80 (3), 79 (4), 77 (3), 65 (3), and 42 (5); HRMS (EI, M^+) calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1108.

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