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NOVEL REARRANGEMENTS DURING PYROLYSIS OF COCAINE

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Abstract – Pyrolysis of cocaine at 600°C in a nitrogen atmosphere yields a mixture of compounds, sixteen of which were identified. The structural isomers methyl phenylacetate and methyl *o*-, *m*- and *p*-toluates are the products of a new skeletal rearrangement of cocaine.

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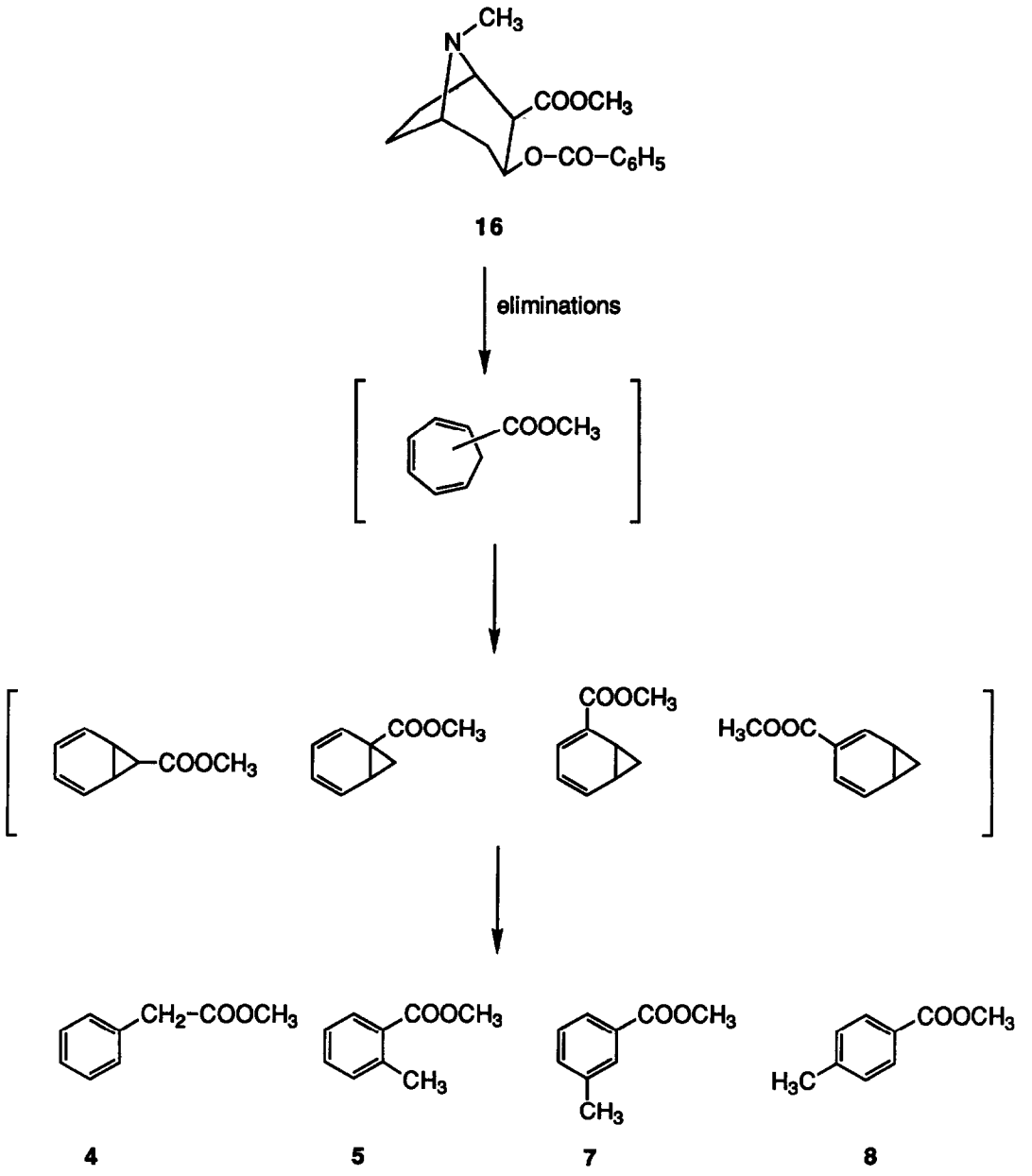
Investigating the chemical changes which occur during cocaine base smoking, this alkaloid was pyrolysed at 600°C in a nitrogen atmosphere. In a previous paper[1] the isolation and structure elucidation of methyl 4-(3-pyridyl)butanoate (**15**) as one of the main components from the cocaine pyrolysate was described. We now wish to report a detailed analysis of the pyrolysate.

RESULTS AND DISCUSSION

Gas chromatographic screening showed that the compounds formed by pyrolysis of cocaine are much more volatile than the starting material. Therefore it was expected that the pyrolytic products are formed by simple fragmentations and eliminations. The pyrolysate was analysed by capillary gas chromatography and GC/MS. The components identified in the pyrolysate are listed in Table 1. It is clear that the majority of the identified products is formed by eliminations of benzoic acid, ethene, and methylamine, by N-demethylations, C-C bond fragmentations, and aromatization. However, six compounds are not formed by these reactions and have to be considered rearrangement products of the cocaine molecule. The rearrangements by which the methyl pyridylbutanoates (**13** and **15**) are formed will be discussed in detail in a following publication. Another rearrangement is involved in the formation of the four structural isomers methyl phenylacetate (**4**), and methyl *o*-, *m*- and *p*-toluates (**5**, **7** and **8**).

We propose a reaction pathway for the formation of these four isomers assuming a methyl cycloheptatrienecarboxylate as an intermediate, which rearranges into the four products, see Scheme 1. A somewhat similar rearrangement is known to occur during the pyrolysis of methylcycloheptatrienes in the temperature range between 300 and 400°C yielding a mixture of all


CH3
N
COOCH3
O-CO-C6H5
16
eliminations
COOCH3
COOCH3
COOCH3
COOCH3
H3COOC
CH2-COOCH3
COOCH3
CH3
COOCH3
CH3
COOCH3
H3C
4
5
7
8

Scheme 1.

Table 1. Components identified in the pyrolysate of cocaine[a]

RRT[b]	Compound	%
0.31	Phenol (**1**)	0.2
0.71	Methyl benzoate (**2**)	0.06
0.79	Methyl nicotinate (**3**)	0.1
1.00	Methyl phenylacetate (**4**)	0.7
1.05	Methyl *o*-toluate (**5**)	0.04
1.24	Benzoic acid (**6**)	52.0
1.24	Methyl *m*-toluate (**7**)	0.07
1.30	Methyl *p*-toluate (**8**)	0.2
1.35	Methyl 2-methylnicotinate (**9**)[c]	trace
1.47	A methyl cycloheptatrienecarboxylate (**10**)[c]	trace
1.61	Methyl 6-methylnicotinate (**11**)[c]	0.05
2.23	(2-*exo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-ene-2-carboxylic acid methyl ester (**12**)[c]	0.2
2.99	Methyl 2-(3-pyridyl)butanoate (**13**)[c]	trace
3.76	Methylecgonidine (**14**)	0.3
5.67	Methyl 4-(3-pyridyl)butanoate (**15**)	7.0
-	Cocaine (**16**)	37.6

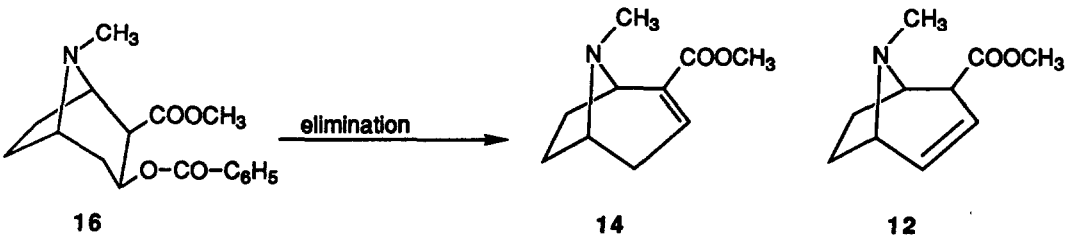
[a] The naturally occurring form *l*-cocaine was investigated.

[b] RRT = Relative retention time on CP-Sil 5.

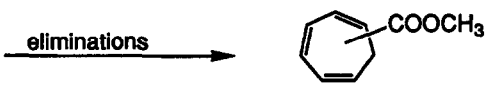
[c] Tentatively identified.

the isomeric methylcycloheptatrienes, ethylbenzene, *o*-, *m*- and *p*-xylenes, styrene, and toluene.[2] In our case, however, no isomerisation of the methyl cycloheptatrienecarboxylates was observed. Only one methyl cycloheptatrienecarboxylate (**10**) could be detected as a trace, see Table 1. Moreover, the relative quantities of methyl phenylacetate (**4**) and the methyl toluates (**5**, **7** and **8**) formed by this skeletal rearrangement are not compatible with the reaction scheme proposed by Egger.[2]

The formation of methyl phenylacetate (**4**) and the methyl toluates (**5**, **7** and **8**) includes the eliminations of benzoic acid and methylamine from the cocaine molecule, yielding a methyl cycloheptatrienecarboxylate as an intermediate, followed by skeletal rearrangements probably occurring *via* methyl bicyclo[4.1.0]hepta-2,4-diene-carboxylate intermediates.



16 14 12



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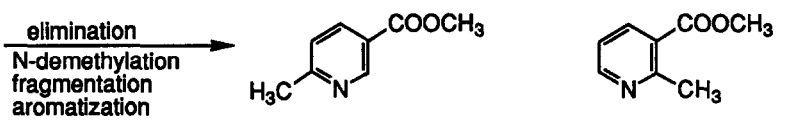

11 9

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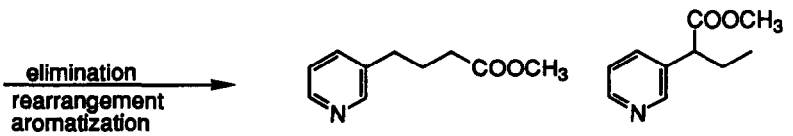

15 13

Scheme 2.

In Scheme 2 the pyrolytic products are arranged according to the type of reaction involved in their formation process. To determine the origin of the methyl group on the pyridine nucleus in the methyl methylnicotinates (**9** and **11**) cocaine-[*N*-CD_3] was pyrolysed under the same conditions as the unlabelled material. Of the sixteen products listed in Table 1 only the methyl pyridylbutanoates (**13** and **15**), methylecgonidine (**14**), and its unconjugated isomer (**12**) showed incorporation of the label. Methylation of the pyridine nucleus by the N-methyl is thus excluded. Therefore the methyl group on the pyridine nucleus originates from C-C bond fragmentation in the pyrrolidine moiety of cocaine.

When cocaine was pyrolysed in air the obtained pyrolysate was qualitatively the same as the nitrogen-pyrolysate; only small quantitative differences were observed.

It should be noted that the pyrolytic products of cocaine could be of importance in explaining the severe physiological effects of smoking cocaine base mixed with tobacco or marihuana[1,3].

EXPERIMENTAL

^{1}H NMR spectra were measured on a Varian EM-390 spectrometer with TMS as an internal standard. Mass spectra (GC/MS) were recorded on a Kratos MS 80 spectrometer at 70eV, values in *m/z* (rel. int.). The GC oven was programmed from 80 to 230°C at 6°C/min. Relative retention times (RRT) were determined at 110°C on a Packard Becker 417 gas chromatograph equipped with a capillary CP-Sil 5 fused silica column (Chrompack); length: 25 m; i.d.: 0.24 mm. The percentage composition was determined with a Varian CDS 111 integrator.

The compounds were identified by comparison of the mass spectra and retention times with those of reference samples. The tentative identifications, see Table 1, are mainly based on the similarities of the observed mass spectra with those published before. However, mass fragmentation patterns and reaction mechanistic considerations were also useful.

l-Cocaine was supplied by Diosynth, Apeldoorn, The Netherlands. Methyl iodide-d_3 was obtained from Merck, Darmstadt. *l*-Methylecgonidine (**14**) was prepared from *l*-cocaine according to literature procedure.[4] *l*-Cocaine-[*N*-CD_3] was synthesized by N-methylation of *l*-norcocaine which was obtained by N-demethylation[5] of *l*-cocaine.

l-Cocaine-[*N*-CD_3] was prepared in analogy to literature procedure[6] by stirring a mixture of 200 mg (0.692 mmol) of *l*-norcocaine, 174 mg (2.076 mmol) of $NaHCO_3$, 105 mg (0.727 mmol) of methyl iodide-d_3, and 5 ml of dry DMF at room temperature for 3 days. The DMF was removed by warming *in vacuo* (rotatory evaporator; waterbath 60°C), water (10 ml) was added, and the mixture was extracted with Et_2O (3 x 8 ml). The Et_2O layer was extracted with 1 N HCl (3 x 5 ml). The H_2O layer was made alkaline (pH 7-8) with dilute NH_4OH and extracted with $CHCl_3$ (3 x 5 ml). The organic layer was dried (Na_2SO_4) and concentrated to give 116 mg of white crystals, pure by GC (yield 55%). Found: M^+ 306.1674. $C_{17}H_{18}D_3NO_4$ requires 306.1659. ^{1}H NMR (90 MHz,

$CDCl_3$): 8.0 (2H, *m*), 7.4 (3H, *m*), 5.25 (1H, *m*), 3.7 (3H, *s*), 3.6 (1H, *m*), 3.3 (1H, *m*), 3.0 (1H, *m*), 2.6-1.7 (6H, *m*).

Methyl 2-methylnicotinate (**9**): MS *m/z* 151 (M^+, 90), 120 (100), 119 (95), 93 (19), 92 (93), 91 (54), 65 (50), 64 (14), 63 (21), 39 (35).

Methyl 6-methylnicotinate (**11**): MS *m/z* 151 (M^+, 85), 120 (78), 94 (15), 93 (12), 92 (100), 91 (11), 65 (44), 64 (9), 63 (12), 39 (33).

A methyl cycloheptatrienecarboxylate (**10**): MS *m/z* 150 (M^+, 20), 135 (10), 119 (27), 92 (10), 91 (100), 90 (11), 89 (11), 65 (20), 63 (9), 39 (9). Compare lit.[7]

(2-*exo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-ene-2-carboxylic acid methyl ester (**12**): MS *m/z* 181 (M^+, 26), 152 (14), 123 (10), 122 (100), 107 (13), 106 (5), 94 (10), 81 (5), 79 (4), 42 (5). Compare lit.[8]

Methyl 2-(3-pyridyl)butanoate (**13**): MS *m/z* 179 (M^+, 25), 164 (20), 149 (21), 132 (16), 120 (86), 105 (19), 92 (100), 91 (17), 77 (26), 65 (14).

The pyrolysis apparatus was described earlier.[1] In each experiment 20 mg of *l*-cocaine or *l*-cocaine-[*N*-CD_3] was deposited as a thin film in a quartz tube (i.d. 1 cm) and pyrolysed for 5 min at 600°C in a stream of nitrogen (25 ml/min). The pyrolytic products were extracted with abs. EtOH and the solvent concentrated to give 11.6 mg of dark brown oil. During the pyrolysis some gas evolution was observed.

Prior to 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.

At 400°C, using the same conditions as mentioned above, pyrolysis of 20 mg of *l*-cocaine yielded 18.5 mg of light yellow oil which consisted of almost pure starting material. Of the pyrolytic products only methylecgonidine (**14**) could be identified by GC/MS.

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