THE STRUCTURE OF COCCULINE AND COCCULIDINE

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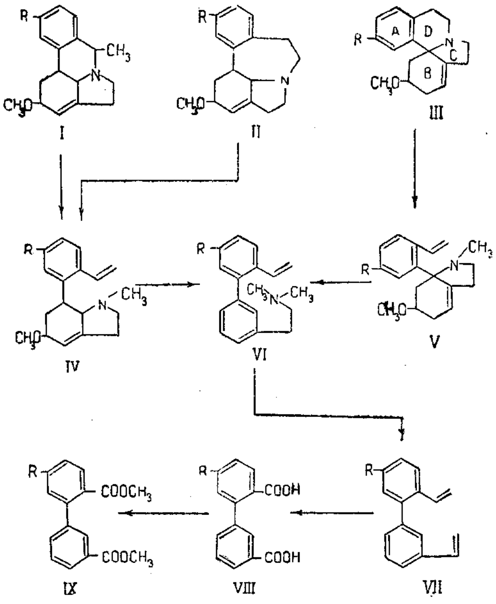
The alkaloids cocculine and cocculidine were first isolated by S. Yu. Yunusov from Cocculus laurifolius (family Menispermaceae) in 1950. On the basis of the results of chemical reactions, these substances were ascribed the structure of the indophenanthridine alkaloids Ia and Ib, respectively [2, 3].

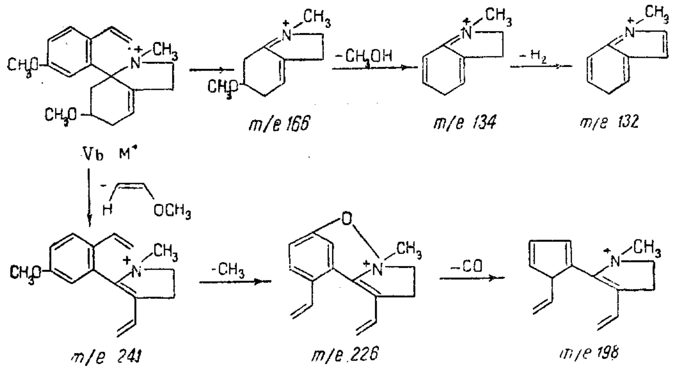


a, R=OH, b, R=OCH_3

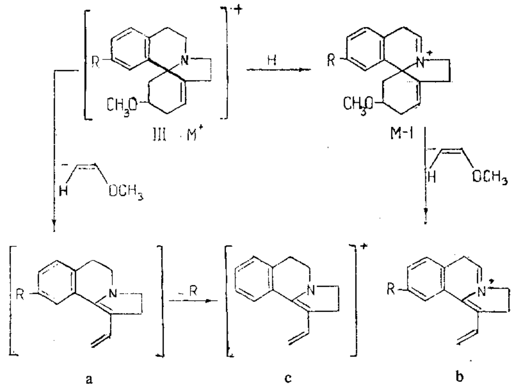
A mass spectrometric study of cocculine and cocculidine has shown that although the m/e values of the molecular ions correspond to the empirical formulas proposed previously (271 and 285, respectively), the peaks of the $(M - 15)^+$ ions in the spectra have extremely low intensities (3–5%) (Fig. 1). It is known that the elimination of a methyl radical is energetically considerably more favorable than the elimination of a hydrogen atom [4]. Since in the mass spectra of the indophenanthridine alkaloids [5] the peak of the $(M - 15)^+$ ion has a high intensity because of the extension of the system of conjugated double bonds, it was to be expected that in the mass spectra of cocculine and cocculidine the M – 15 peak should be one of the maximum peaks. The very low intensity of the M – 15 peak in the mass spectra of the alkaloids studied, and also their capacity for undergoing a three-stage Hofmann degradation, leading finally to a biphenyl derivative (VII–IX) [2] has given grounds for doubting the presence of a C-methyl group in these alkaloids and for proposing for them the probable structures II [6] and III. (see Scheme 1 on the following page).

The mass spectra of cocculine and cocculidine give no fundamental information on which of the two probable structures corresponds to these substances, since in both cases the occurrence of a retrodiene decomposition leading to the appearance of peaks of ions a and b is possible. If it is borne in mind that in the first stage of the Hofmann degradation of II and III the corresponding des-N-methyl derivatives with different structures, IV and V are formed [although the products of the further transformation (VII–IX) are identical in the two cases], it may be expected that under the conditions of mass spectrometry IV and V will behave specifically, which is explained by the nature of the linkage of rings B and C.

In actual fact, a study of the mass spectra of des-N-methylcocculidine showed that it corresponds completely to structure Vb (Fig. 2 and Scheme 1) and that it does not contain peaks of fragments with m/e 139 and 134 that are characteristic of compounds of type IV. Consequently, structure II for cocculine and cocculidine is excluded. Hence



Scheme 1



Scheme 2

they will have structures IIIa and IIIb respectively. The incorrectness of the structures I and II for cocculine and cocculidine and the correctness of the structures that we have now proposed (IIIa and IIIb) are also confirmed by the absence from the NMR spectrum of cocculine (Fig. 3) of the signals of protons of the C-methyl group and the signal of a benzyl proton.

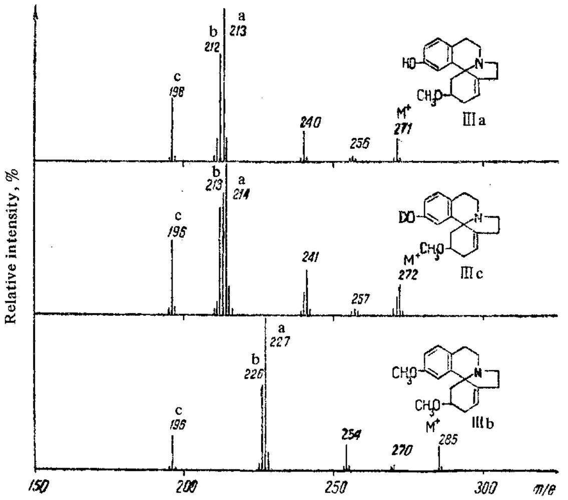


Fig. 1. Mass spectra of cocculine (IIIa), deuterococculine (IIIc), and cocculidine (IIIb).

The proposed structure Vb for des-N-methylcocculidine is completely reflected in its mass spectrum. The peak of the ion with m/e 166, containing rings B and C, has the maximum intensity. The subsequent splitting out of a molecule of methanol and water from this ion leads to ions with m/e 134 and 132 (see Fig. 2 and Scheme 1). The transitions 166 → 134 and 134 → 132 are confirmed by the presence of metastable peaks with m/e 180.0 (calculated 180.0) and 131.0 (calculated 130.0), respectively. The energetic suitability of this process is explained by the complete aromatization of rings B and C. The peaks of the other ions arising through the retrodiene decomposition of the molecular ion and the splitting out of substituents have low intensities (see Fig. 2 and Scheme 1).

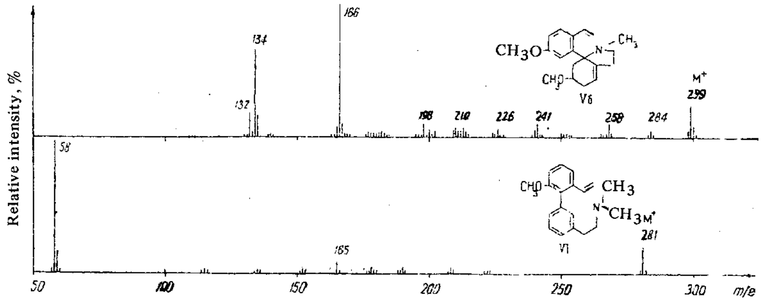


Fig. 2. Mass spectra of des-N-methylcocculidine (Vb) and of des-N-dimethylcocculidine (VI).

The main direction of the fragmentation of the molecular ions of cocculine (IIIa), its deutero analog (IIIc), and cocculidine (IIIb) consists in the retrodiene decomposition of the ions M^+ and $(M - 1)^+$, leading to the formation of fragments a and b. This route of decomposition is characteristic for the molecular ions of the Erythrina alkaloids [8]. On the subsequent elimination from the ion-radical a of the substituent in the aromatic ring in the form of a radical, the ion c is formed (Scheme 2). The peaks of the other fragments due to the elimination of substituents from M^+ are of low intensity (see Fig. 1).

The sequence of the fragmentation of the molecular ions of compounds IVa–IVc that has been given is confirmed by the presence in their spectra of the peaks of the metastable ions the m/e values of which are given in the table.

In the mass spectra of compound VI, the product of the two-stage Hofmann degradation of cocculidine, the peak of the ion with m/e 58 formed as a result of simple α-cleavage (see Fig. 2) has the maximum intensity.

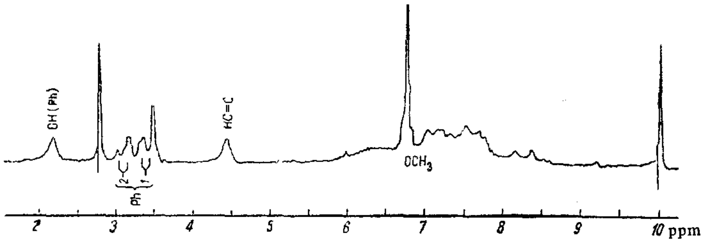


Fig. 3. NMR spectrum of cocculine (CDCl$_3$, 60 MHz).

Values of m/e of the Metastable Ions in the Mass Spectra of Compounds IIa–IIc

Compound	Metastable transition	Calculated	Found
a	$M^+ \rightarrow a$	$213^2/271=167.4$	167.4
	$a \rightarrow c$	$196^2/213=180.3$	180.4
b	$M^+ \rightarrow a$	$214^2/217=168.0$	168.0
	$a \rightarrow c$	$196^2/214=179.5$	179.5
c	$M^+ \rightarrow a$	$272^2/285=180.8$	180.8
	$a \rightarrow c$	$196^2/227=169.2$	169.2

The mass spectra were recorded on a standard MKh-1303 instrument fitted with a system for the introduction of the sample directly into the ion source at 100–140° C with an energy of the ionizing electrons of 30–50 eV.

CONCLUSIONS

1. The mass spectra of cocculine and cocculidine and of their derivatives, and the NMR spectrum of cocculine, have been studied.

2. It has been established that cocculine and cocculidine have the structures IIIa and IIIb, respectively.

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