MEDICINAL PLANTS

ON THE MECHANISM OF THERMOLYSIS OF THE BENZO[c]PHENANTHRIDINE ALKALOID CHELERYTHRINE

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During our previous investigations of the benzo[c]phenanthridine alkaloids from *Macleaya microcapra* and *Macleaya cordata*, it was establish that the total extracts contain, besides sanguinarine (I) and chelerythrine (II), an admixture of a tertiary phenolic alkaloid of the same series. The properties of this component corresponded to those of the alkaloid fagaridine, which was earlier assigned the structure of a 2,3-methylenedioxy-N-methyl-7-hydroxy-8-methoxybenzo-[c]phenanthridinium salt (III) [1]. However, this structure assignment met objections [2] because of the obvious discrepancy with the observed color (yellow), which was demonstrated by comparison with a model compound (N-methyl-7-hydroxy-8-methoxybenzo[c]phenanthridinium salt) forming intensely colored betaine. Study of the two-dimensional ^{1}H NMR spectra of compound III measured in the COSY and NOESY modes showed that this alkaloid has a hydroxyl group in position 8 and, hence, is essentially a 2,3-methylenedioxy-N-methyl-7-methoxy-8-hydroxybenzo[c]-phenanthridinium salt (IV) [3, 4].

In order to compare alkaloid IV to compounds with formula III, we have synthesized the former salt by thermolysis of chelerythrine [3, 4]. Data on the N-demethylation of benzo[c]phenanthridine alkaloid chlorides, including chelerythrine, were reported in [5 – 7]. Our study of the products of chelerythrine sulfate thermolysis showed that the process is rather ambiguous, leading to the formation of a mixture of several compounds with the component ratio depending on the reaction conditions (temperature and duration). We have separated these substances by preparative TLC on silica gel eluted in a chloroform – methanol system (10 : 1) and obtained five bands. These spots were cut out and the corresponding fractions were extracted with chloroform. The structures of these compounds were determined with the aid of 1H NMR spectroscopy. It was established that the compounds were arranged on the TLC chromatogram in the following sequence (in order of decreasing mobility): N-norchelerythrine (V); isodecarine (VI); initial chelerythrine (II); 7-O-demethylchelerythrine (III), and a nonidentified starting compound (see the scheme and Table 1). We failed to accumulate the latter starting compound in an amount sufficient for the spectroscopic investigation because of its large affinity to the sorbent. However, proceeding from theoretical prerequisites and the known properties, we may suggest that this substance is O,O′-bisdemethylchelerythrine (VII). The observed properties (chromatographic mobility, coloration of solutions, solids, and protonated forms on acid sorbents) agreed with the proposed structures.[2]

N-Norchelerythrine (V) forms colorless solutions in chloroform (base), but is manifested as a yellow spot on silica gel (protonated form, Va). 7-O-Demethylchelerythrine (III) both in the solid state and in aqueous solutions exhibits a violet color corresponding to a zwitter-ion structure, but converts into a protonated form (yellow 7-hydroxy derivative) when dissolved in a strong acid such as CF_3COOH (trifluoroacetic acid, TFA). Compound VI (isodecarine) has a brick-red color on silica gel (N-protonated form) and is light-yellow in solutions (tertiary base). Compound VII appears as a brown spot on the starting line, but turns violet (characteristic of zwitter-ion compounds) in a chloroform solution. This behavior agrees with the proposed structure of O,O′-bisdemethylchelerythrine – quinoid on the TLC chromatogram (VII) and zwitter-ion in solution (VIIa).

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[2] Reported quaternary derivatives of these alkaloids are colored both in the solid state and in aqueous and water – ethanol solutions, while the corresponding pseudobases (N-demethylated derivatives – pyridine bases) are colorless. The colors of the alkaloid spots observed on the surface of silica gel (which is a weak acid) correlate with the coloration of their quaternary salts – in agreement with our experimental results and the published data of other researchers. The spots of these quaternary alkaloids on a thin silica gel layer (TLC) are well distinguished without using special chromogenic reagents or UV illumination.

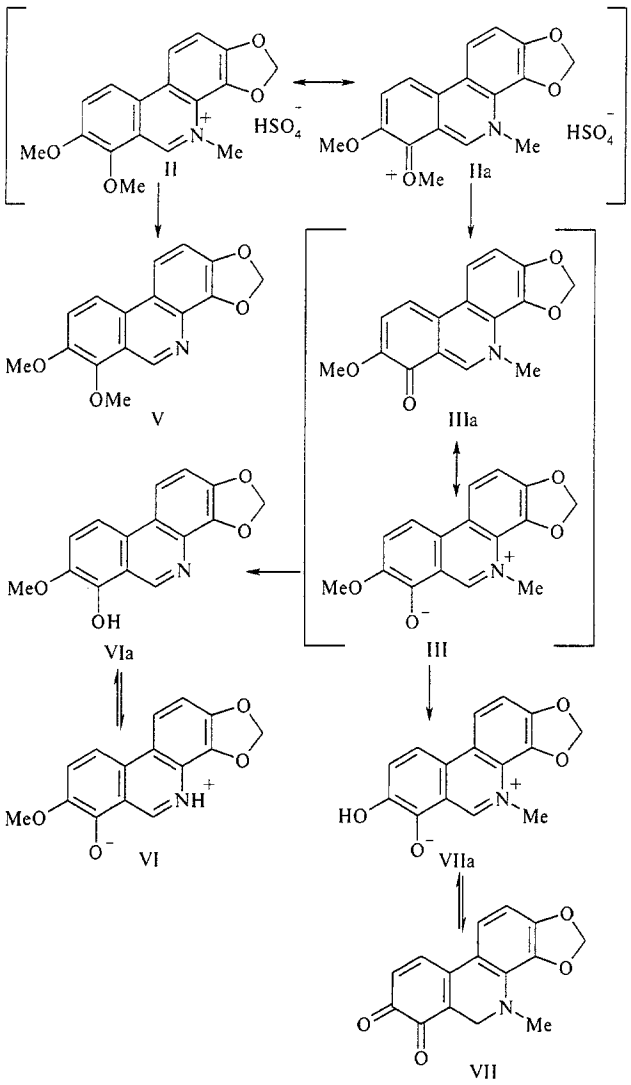

TABLE 1. Characteristics of the ^{1}H NMR Spectra of Chelerythrine (II), N-Norchelerythrine (V), 7-O-Demethylchelerythrine (III) and Isodecarine (VI)

Proton position	Chemical shift δ, ppm (J, Hz)				
	II*	V**	VI*	III*	III**
1	7.46 s	7.28 s	7.27 s	7.47 s	7.31 s
4	7.95 s	8.72 s	8.74 s	7.91 s	7.71 s
6	9.74 s	9.75 s	9.80 s	9.80 s	9.67 s
9	8.08 d (J 9.32)	7.61 d (J 9.12)	7.54 d (J 9.0)	7.94 d (J 8.7)	7.35 d (J 7.9)
10	8.51 d (J 9.32)	8.37 d (J 9.12)	8.15 d (J 9.0)	8.48 d (J 8.7)	7.41 d (J 7.9)
11	8.49 d (J 8.89)	8.36 d (J 8.96)	8.35 d (J 8.9)	8.31 d (J 9.2)	8.22 d (J 8.8)
12	8.18 d (J 8.89)	7.86 d (J 8.96)	7.85 d (J 8.9)	8.15 d (J 9.2)	7.83 d (J 8.8)
7-OCH_3	4.34 s	4.12 s	–	–	–
8-OCH_3	4.14 s	4.07 s	4.07 s	4.14 s	3.98 s
OCH_2O	6.26 s	6.13 s	6.14 s	6.27 s	6.18 s
N-CH_3	5.06 s	–	–	4.96 s	4.53 s

* Solvent $CDCl_3$ – TFA.

Thus, an analysis of the experimental data suggests that the thermolysis of chelerythrine proceeds by two competitive pathways (O- and N-demethylation) corresponding to heteroatoms possessing maximum positive charges (which follows from their resonance structures containing N-methylimmonium and methyloxonium groups as depicted in the scheme).

In the molecule of chelerythrine (II), the O-methyl group in position 7 (in contrast to the O-methyl group in position 8) is displaced from the plane of the aromatic ring A, as follows from the ^{1}H NMR data. Our previous investigations on alkaloids from the isochondrodendrine series [8, 9] showed that OCH_3 groups not conjugated to the aromatic ring plane are susceptible to protonation in acids, association with reagents possessing a paramagnetic shift, and easy chemical and thermal demethylation.

Compound V (O-methyldecarine or N-demethylchelerythrine) is a natural alkaloid isolated from *Xanthoxylium arnottianum Maxim.* [10], *Chelidonium japonicum* [11], and *Xanthoxylium cupsidatum Champ.* [12]; reported spectroscopic parameters agree with our data. This compound was also obtained by methylation (CH_2N_2) of decarine [13].

Thermal O-demethylation of quaternary heteroaromatic compounds was also described for the conversion of berberine (a protoberberine alkaloid) chloride into berberrubine (berberoline) [14, 15] and oxoglaucine (an aporphine alkaloid) methyl iodide into corunnine [16].

EXPERIMENTAL PART

The ^{1}H NMR spectra were measured on a Gemini 200 (Varian, USA) spectrometer operated at a working frequency of 200 MHz, using TMS as the internal standard. The purity of compounds was checked by TLC on Silufol UV-254 plates, with the spots distinguished by visible colors or under UV illumination.

Thermolysis of chelerythrine (II) bisulfate. A sample of chelerythrine bisulfate weighing 20 mg was heated to melting in a device for the melting point determination (m.p., 235 – 237°C) until cessation of the gas evolution (2 – 3 min). Then the sample was cooled, dissolved in methanol, applied as a band onto the starting line of a silica gel plate, and neutralized with a 25% aqueous ammonia solution. Then the plate was dried and chromatographed in a chloroform – methanol system (10 : 1). The spots were cut out, extracted with chloroform, and evaporated to obtain the following fractions (in the order of decreasing mobility): A (yellow band), N-norchelerythrine (V); B (brick-red band), isodecarine (VI); C (yellow band), chelerythrine (II); D (violet band), 7-O-demethylchelerythrine (III); E (brown band), nonidentified compound (apparently, O,O′-bisdemethylchelerythrine).

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