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QUATERNARY BENZOPHENANTHRIDINE ALKALOIDS

9,10-DEMETHYLENE DERIVATIVES OF SANGUINARINE

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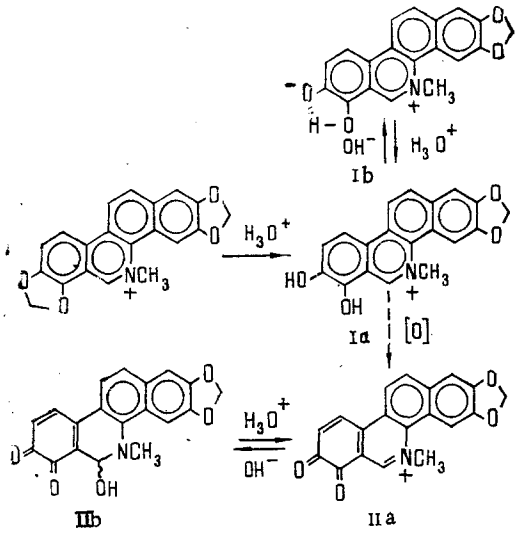
In the process of isolating quaternary benzophenanthridine alkaloids from the herb *Macleaya cordata* Mil. R. Br. and *M. microcarpa* (Maxim.) Fedde, together with the acid sulfates of sanguinarine and chelerythrine (on chromatograms the spots are orange and yellow, respectively), we observed the presence in the mixture of two minor components, one of which on a thin layer of alumina appears in the form of a starting spot (compound B) colored violet, while on silica gel it is represented by a lilac or violet coloration (for the base). Compound A, which in chromatography on silica gel is about half as mobile as chelerythrine, appears in the form of an orange-yellow spot. The intensity of the starting spot increases when the bisulfates of the alkaloids are stored for a long time, but it has been found that the amount of this impurity does not exceed 1-2%.



In a comparative study of chromatograms of a series of samples of the alkaloids on prolonged storage, we observed a starting spot as impurity only in samples of sanguinarine bisulfate. This shows that compound B is a product of the transformation of the latter. Since the sanguinarine molecule differs from the chelerythrine molecule by the presence of a methylenedioxy group in the 9-10 position in place of two methoxy groups in the same positions, its transformation can be explained by the participation of just this group in the process.

In order to determine the nature of the impurity, the total acid sulfates of the alkaloids that had been stored for a long time were subjected to preparative chromatography in a thin layer or on a column of alumina. This led to the isolation of the two components mentioned above together with sanguinarine and chelerythrine. On the other hand, a mixture of sanguinarine and chelerythrine was subjected to saponification by heating with dilute sulfuric acid. In this case, a gradual decrease in the amount of sanguinarine in the reaction mixture was observed with the formation, after alkalinification, of an intensely violet-

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TABLE 1. Comparative Characteristics of the PMR Spectra of the Compounds Obtained

Compound	Chemical shifts (δ, ppm) in CF_3COOH, 0 – TMS				
	N^+CH_3	$(OCH_3)_2$	CH_2O_2	Aromatic protons	$CH=N^+$
Chelerythrine sulfate	5,10	4,21 4,39	6,25	7,52 s, 8,05 s, 8,16 d, 8,20 d, 8,57 d, 8,64 d (J=8Hz)	9,79 s
Sanguinarine chloride	5,02	—	6,24 6,48	7,48 s, 7,98s, 7,90d, 8,17 d, 8,49 d, 8,52 d, (J=8 Hz)	9,55 s
Base B	5,01	—	6,24	7,48 s, 8,00s, 7,96 d, 8,16 d, 8,30 d, 8,52 d (J=8 Hz)	9,76 s
Base A	5,06	—	6,36	7,61 s, 8,17 s, 8,34 s, (2H), 7,26 d, 8,59 d (J=10Hz)	9,51 s

colored spot of compound B identical with a sample isolated preparatively from the combined alkaloids after prolonged storage. The saponification product was also subjected to chromatographic separation on a column of alumina. As a result, compound B was isolated, this forming a crystalline trifluoroacetate $C_{19}H_{13}NO_4 \cdot CF_3COOH$ with mp 217.5-220°C. Compound A was isolated in the form of a brown powder with mp 183°C.

The structures of the compounds were confirmed with the aid of their PMR spectra, which showed the presence of the benzophenanthridine skeleton that is characteristic for sanguinarine and chelerythrine with substitution in the same positions (the signals of seven aromatic protons, one of which is heteroaromatic, two one-proton singlets corresponding to para substitution in the nucleus, and two pairs of one-proton doublets with ortho spin–spin coupling constants belonging to the protons of rings A and C, see Table 1).

The spectra of both compounds contain the signals of the protons of a methylimmonium group and of one methylenedioxy group, the positions of the signals of the latter in the spectrum corresponding to the signal of this group in chelerythrine, and also to one of the signals in sanguinarine. Since chelerythrine remains practically unchanged under the conditions of the saponification reaction, the signal of the methylene protons in the spectra of compounds A and B must be assigned to the OCH_2O group in the 2-3 position. The increased sensitivity of the 9,10-methylenedioxy group to acid hydrolysis is explained by the presence of the electron-accepting $CH=\overset{+}{N}CH_3$ group adjacent to it. In the rapid preparation of the acid sulfates of the alkaloids or in the extraction of the alkaloids from the raw material with a weak organic acid such as citric, the formation of base B can be reduced to a minimum.

In compound A, one of the aromatic protons in ring A (C_9–H), adjacent to an oxygen function, undergoes a diamagnetic shift in relation to the corresponding proton of compound B (about 90 Hz), and the spin–spin coupling constant is 10 Hz, which shows its o-quinoid structure. When chromatograms on plates coated with silica gel were treated with alkali, the spots corresponding to compound A were colored pink, although the initial substances are insoluble in alkalis. Thus, the pink coloration corresponds to the carbinolamine structure of compound (IIb) and a yellow coloration to the o-quinoid anhydro salt (IIa).

Compound B is 9,10-demethylenesanguinarine (I) and has a tendency to undergo tautomeric transformations. The violet-colored compound apparently has the zwitterionic formula (Ib), and its yellow salt with acids the structure (Ia). Compound B, like corrunine [1, 2], is practically insoluble in alkalis, does not change its coloration in an alkaline medium, and does not show a phenolic shift in the UV spectrum.

Thus, compound B formed in the process of isolation is an artefact, and compound A – its oxidized form – is 9,10-demethylene-9,10-dehydrosanguinarine. However, in a study of extracts of freshly collected Madeaya leaves, the presence of compound A was also detected. On the other hand, this compound was not detected in the total sulfates of quaternary alkaloids isolated from the roots of *Corydalis sewerzowii*. In view of this, it may be assumed that the quinoid compound is a normal product of metabolism in the plants.

EXPERIMENTAL

The PMR spectra of the compounds were measured on a Varian HA-100 spectrometer (CH_3COOH, O — TMS). The melting points were determined in evacuated capillaries in an electric heating apparatus, and also on a Boetius micro hot stage. The determination of the degree of purity of the compounds and the investigation of their properties were performed in a thin layer of alumina (activity II, chloroform system) and also in silica gel [Silufol, diethyl ether—petroleum ether—methanol (35:15:3) system]. When samples of the alkaloids were deposited on the silica gel plates in the form of the disulfates, ammonia solution was added to the same spot for neutralization (without neutralization by ammonia, the salts of the quaternary ammonium derivatives do not migrate from the starting line in the systems mentioned).

Separation of the Alkaloids. A mixture of 2 g of the combined bisulfates of the quaternary alkaloids sanguinarine and chelerythrine was heated with 70 ml of 5% sulfuric acid on the water bath for 4 h, whereupon the solid matter partially dissolved. After cooling, the reaction mixture was treated with 25% ammonium hydroxide solution and with chloroform. The organic layer was separated off and, after being dried with sodium sulfate, was concentrated to small volume and was then deposited on a column of alumina (activity II). After washing with chloroform, the column was divided into four zones. The upper, violet, zone was washed with a mixture of chloroform and methanol (1:1) and was then extracted with a mixture of chloroform and acetic acid (3:1) with heating. The solvents were distilled off, the residue was again treated with chloroform, and the extract was filtered from inorganic impurities and, after drying with sodium sulfate, was evaporated in vacuum. According to the results of chromatography in a thin layer of silica gel, the sample consisted of an individual substance — 9,10-demethylenesanguinarine with mp 226-227°C. After drying in a pistol with heating, the compound had changed, having been converted into an infusible and sparingly soluble compound. When it was mixed with trifluoroacetic acid, the crystalline trifluoroacetate with the composition $C_{19}H_{14}NO_4^+ \cdot CF_3COO^-$ was formed, and this was separated off and washed with ether. mp 217.5-220°C.

After the drying of the adsorbent, the other zones were extracted with a mixture of chloroform and methanol (2:1), and the extract was filtered and concentrated in vacuum. The dry residue from the second and third zones from the top was treated with chloroform, and the insoluble part, which consisted mainly of 9,10-demethylene-9,10-dehydrosanguinarine, was dissolved in chloroform with heating, and the solution was filtered and was re-evaporated mp 183°C (Kofler).

SUMMARY

In the isolation and purification of the benzophanthridine alkaloids sanguinarine and chelerythrine two minor bases — 9,10-demethylenesanguinarine and 9,10-demethylene-9,10-dehydrosanguinarine — were isolated, and it was shown that the former is an artefact produced from sanguinarine in the process of isolation and also when the sulfates of the alkaloids are subjected to prolonged storage.

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