TAUTOMERISM OF THE ACETATES OF THE QUATERNARY ALKALOIDS SANGUINARINE AND HELERITRINE

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The question of the tautomerism of quaternary bases of the type of sanguinarine and berberine has been repeatedly discussed in the literature. Although it has been shown on the basis of some indirect information obtained from the chemical behavior, their pK value, and their UV spectra that the reactivity of compounds of this type is due to carbinolamine–aminoaldehyde–immonium tautomerism, this information does not provide the possibility of interpreting the results obtained unambiguously [1, 2]. Furthermore, for salts of these alkaloids the existence has been shown of only the quaternary immonium form with a stable heteroaromatic structure. Exceptions are the cyanide alkaloids, which have been isolated in the pseudo form [3, 4].

The present paper gives information on the influence of the polarity of the medium on the spectra of sanguinarine and heleritrine. For this study we used the acetates of these alkaloids, which are soluble in organic solvents, since salts of the alkaloids with inorganic acids are practically insoluble in them.

The acetates of sanguinarine and heleritrine that were obtained, like other salts of these alkaloids, form colored aqueous solutions. In many organic solvents they give a coloration of lower intensity than in water, and their solutions in ether or dioxane are colorless. When the ether is removed, or on prolonged standing under ether, it is possible to isolate colorless forms of the acetates of the alkaloids considered.

In UV spectra (Table 1) of aqueous solutions of such salts a number of absorption maxima can be seen, one of which is present in the visible region. Conversely, in dioxane or ether solution the long-wave maximum is not observed, which can be explained by the absence of an aromaticity of ring B in the compounds present in ethereal solvents and, as a consequence of this, a break in the chain of conjugation between rings A and C.

The NMR spectrum ($CDCl_3$, freshly prepared solution) of heleritrine acetate with mp 235°C (Table 2) has the signals of two isomers, and on a chromatogram in a thin layer of silica gel (Silufol; petroleum ether–diethyl ether–methanol (15 : 35 : 3) system) two spots are found with R_f 0.3 and 0.49; the latter of them predominates, and when a chloroform solution is allowed to stand the intensity of the lower spot increases (with the corresponding deposition on the plate of an ethereal solution of heleritrine acetate, only one spot appears on the chromatogram with R_f 0.49). One of the compounds present in the chloroform solution is the acetate of a pseudo base, since the NMR spectrum shows the signal of a proton geminal to an acetoxy group at 6.55 ppm. The second compound in the mixture may be an acyclic tautomer of the alkaloid, as can be judged from the presence in the spectrum of the signal of an aldehyde proton at 9.92 ppm. In the IR spectrum of a chloroform solution of heleritrine acetate absorption bands appear of carbonyls of different intensities at 1710 and 1755 cm^{-1} ($OCOCH_3$ and CHO) with the second frequency predominating. The acylic amino aldehyde is apparently present in the salt form, since in its IR spectrum absorption bands appear in the 2700-2800 cm^{-1} region. An amino aldehyde can arise from the corresponding base on salt-formation. When a chloroform solution is allowed to stand, the equilibrium shifts to the more stable pseudo acetate form, which crystallizes out from the solution in the form of yellow acicular crystals more sparingly soluble in chloroform with mp 225-226°C. In an IR spectrum the intensity of their 1710 cm^{-1} frequency is reduced. In dioxane solution heleritrine acetate likewise has two absorption bands at 1728 and 1750 cm^{-1} of almost equal intensity; on standing, the second of them disappears and the first increases in intensity. In deuteropyridine solution the presence of the aldehyde form was not observed. The two com-

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TABLE 1. UV Spectra of Sanguinarine and Heleritrine Acetates

Alkaloid	Solvent	λ_{max}, nm (log ε)						
		I	II	III	IV	V	VI	VII
Heleritrine	Dioxane	213(4,3835)	287(4,6308)	323(4,1321)	335(inflection)	351(inflection)	405(3,8430)	
	Water		268(4,6471)	280(inflection) (4,5163)	(4,0573) 317(4,4499)	(3,7060) 340(4,2906)		
Sanguinarine	Dioxane	213(3,9963)	288(4,6106)	328(4,2238)	337(inflection)	352(inflection)	402(3,2947)	476,(3,3092)
	Water		275(4,0878)	283(inflection) (4,0086)	(4,1711) 329(3,9629)	(3,7936) 350(inflection) (3,7619)		

TABLE 2. Chemical Shifts and Spin–Spin Coupling Constants in the NMR Spectra of Heleritrine and Sanquinarine Acetates

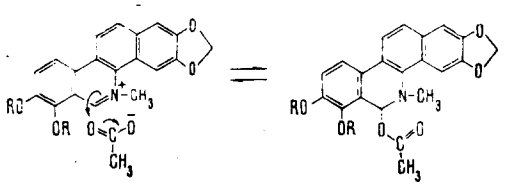
Compound	Solvent	NCH_3	$(OCH_3)_4$	CH_2O_2	OAc	H–C–OAc	Aromatic protons
Heleritrine acetate	$CDCl_3$	2,35 s	2,99 s 3,66 s	6,05 s	1,97 s	6,55 s	7,10 s, 7,86 s, 6,77 d, 7,63 d, 7,38 d, 7,41 d (J=8 Hz)
	C_5D_5N a	2,54 s	2,83 s 3,65 s	5,88 d J=3 Hz	1,96 s	6,28 s	7,08 s, 7,67 s, 6,86 d, 7,62 d, 7,43 d, 7,76 d (J=8 Hz)
	b	2,58 s	3,45 s 3,96 s	5,97 d J=4, Hz	1,96 s	6,69 s	7,23 s, 7,04 s, 6,96 d, 7,56 d, 7,41 d, 7,80 d (J=8 Hz)
	D_2O	4,40 s	3,93 s 4,06 s	6,08 s 6,05 s	1,99 s	—	6,63 s, 7,30 s (2H), 7,61 s (2H), 7,43 m, 9,22 s - $C_{(11)}$–H
Sanguinarine acetate	$CDCl_3$	2,91 s	—	6,01 s	1,97 s	6,26	7,04 s, 7,88 s, 6,62 d, 7,66 d, 7,55 d, 7,32 d (J=8 Hz)
	D_2O	4,40 s	—	6,17 s 6,40 s	1,99 s	—	6,85 s, 7,32 s, 7,60 s (2H), 7,45 s, 9,23 s–$C_{(11)}$–H

Note: s – singlet; d – doublet; m – multiplet.

pounds present in solution were ascribed to the acetates of two isomeric pseudo bases apparently differing by the mutual positions of the $N-CH_3$ and OAc groups (from their NMR spectra).

In the NMR spectrum of an aqueous (D_2O) solution of heleritrine acetate the signal of the protons of the $N-CH_3$ group is present in a weaker field as compared with a solution in $CDCl_3$ (4.3 and 2.35 ppm, respectively), which shows the salt-like nature of the compound in aqueous solution. Furthermore, in aqueous solution seven aromatic protons can be seen, one of which is heteroaromatic (9.1 ppm). Similar changes in the spectra are also observed for solutions of sanguinarine acetate.

Thus, for sanguinarine and heleritrine acetates the existence of an equilibrium of tautomeric forms may be assumed: immonium salt–pseudo base salt, the ratio between them being determined by the polarity of the medium.



EXPERIMENTAL

The NMR spectra were taken on a Varian HA-100D instrument. As internal standards we used HMDS (for chloroform and deuteropyridine solutions) and tert-butanol (for aqueous solutions). The IR spectra were obtained on a UR-10 spectrophotometer and the UV spectra on a Hitachi EPS-3T spectrophotometer. The acetates of the alkaloids were prepared by mixing the corresponding bases with an excess of glacial acetic acid, followed by washing out the excess of acid with ether and drying the salt obtained in the air. The washing with ether must be done in small portions in order to avoid the dissolution of the acetate.

SUMMARY

The spectra of sanguinarine and heleritrine acetates in various solvents have been studied. It has been shown that an equilibrium exists of the tautomeric forms of the acetates which depends on the polarity of the medium.

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