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SPECTROPHOTOMETRIC DETERMINATION OF PAPAVERINE HYDROCHLORIDE BY REACTION WITH PHLOXIN

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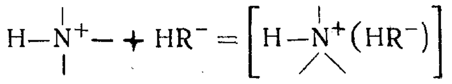
The optimum conditions for the formation of a complex of papaverine hydrochloride with phloxin have been determined: pH 2.5-3.2. A procedure has been developed for the spectrophotometric determination of papaverine hydrochloride. The sensitivity of the determination is 0.4 μg/ml.

Papaverine [1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline] is present in opium. Papaverine hydrochloride (I) is widely used in medicine as a spasmolytic drug [1]. The quantitative determination of (I) in pharmaceutical preparations (papaverine hydrochloride, papaverine hydrochloride tablets) is carried out by titrimetric methods [2]. The procedure is distinguished by a high accuracy, but it requires considerable amounts (0.3-0.5 g) of the preparation for analysis. Procedures have been described for the extraction-photometric determination of (I) [3-5], the main disadvantages of which are their lengthiness and the necessity for working with harmful organic solvents.

Our aim was to develop a fairly sensitive procedure simple in use for the quantitative determination of (I) by converting it into a colored compound. It was found that with the organic reagent phloxin (PL), (I) forms an intensively red-violet-colored complex compound. The optical density of solutions of the complex of (I) with phloxin depends on the pH and on the concentrations of (I) and of the reagent. Analysis of the absorption spectra of (I)–PL solutions containing various amounts of (I) showed the possibility of using the complex-forming reaction for the quantitative determination of (I).

The maximum value of the optical densities of solutions of the complex are reached after 3-5 min and then remain constant for not less than 5 h. The optical reaction conditions have been established: temperature 15-30°C; pH 2.5-3.2; 1.5-2.0 ml of a 0.076% solution of phloxin and 1-2 ml of a 0.1% solution of polyvinyl alcohol in 25 ml.

The maximum of the absorption spectrum of the complex lies in the 542-547 nm region. The molar extinction coefficient is $5.33 \cdot 10^4$. The ratio of (I) to PL in the complex has been established as 1:1 by the methods of physicochemical analysis (isomolar series, equilibrium shift). Since the pK_1 and pK_2 values of phloxin are, respectively, 2.41 and 3.13 [6], in the pH 2.4-3.1 interval the singly-charged phloxin anion is present. Under the conditions of interaction with phloxin, (I) is present in solution in the protonated form. On this basis it is possible to give the following reaction equation for the formation of the complex of papaverine hydrochloride with phloxine:



$$H-\overset{|}{\underset{|}{N}}{}^{+}- + HR^{-} = \left[H-\overset{|}{\underset{/\,\backslash}{N}}{}^{+}(HR^{-})\right]$$

Papaverine hydrochloride interacts with the eosin form of the phloxin molecule dissociated at the hydroxy group symmetrical to the carbonyl oxygen. The interaction of (I) at the carboxy group of phloxin is unlikely, since its π-electronic system is isolated and the ioni-

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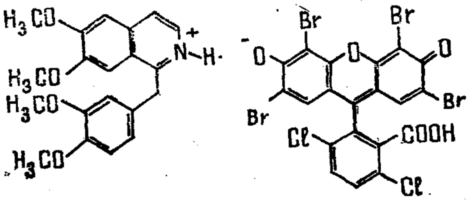
zation of the carboxy group does not affect the electronic spectrum of the phloxin molecule. Such a mechanism of the reaction is confirmed by the fact that (I) forms a colored compound with 6-hydroxy-9-phenylfluorone (containing no carboxy group) and with a dye in which the carboxy group has been esterified (ethyleosin). The electrostatic interaction between papaverine and phloxin is intensified by a H-bond. Hydrophobic interaction also plays a role, since the plane chromophoric system with a delocalized charge (HR^-) is stabilized through van der Waals effects in the complex with a cation.

The following may be given as the most probable structural formula of the complex:



The procedure for the quantitative determination of (I) that has been developed has been used for its determination in tablets to within 0.01 g. Preliminary experiments established that the fillers and auxiliary substances (talc, sugar, starch, calcium stearate) do not interfere with the determination of papaverine hydrochloride by the reaction with phloxin.

EXPERIMENTAL

Determination Procedure. About 0.13 g (accurately weighed) of a powder of ground tablets is placed in a measuring flask (100 ml), distilled water to 1/3 of the volume is added, the mixture is shaken for 3-5 min, and it is then diluted to the mark with water and is filtered. Of the resulting solution, 1 ml is transferred to a measuring flask (25 ml) and 2 ml of a 0.1% solution of polyvinyl alcohol, 1.5 ml of a 0.076% solution of phloxin, 2.5 ml of a 0.01 N solution of hydrochloric acid, and water to the mark are added, and the mixture is stirred. To prepare a solution of a standard sample of the complex, 1 ml of standard solution of (I) (100 µg/ml) is added to a measuring flask (25 ml) and the subsequent procedure is as described above. The optical densities of the solution are measured in a spectrophotometer at 545 nm in cells with a layer thickness relative to a comparison solution containing all the ingredients apart from the (I).

The amount of (I) in grams (X) in one tablet is calculated from the formula

$$X=\frac{0.0001\cdot A_X\cdot 100\cdot M}{A_{st}\cdot H}=\frac{0.01\cdot A_X\cdot M}{A_{st}\cdot H},$$

where H is the weight of the sample; M is the mean weight of one tablet; A_X and A_{st} are the optical densities of the solution to be analyzed and the standard solution; and 0.0001 is the amount of (I) in grams in 1 ml of standard solution (prepared from a pharmaceutical preparation "papaverine hydrochloride").

Below we give the results of the spectrophotometric determination of (I) by the reaction with phloxin:

Sample, g	(I) determined on one tablet		Metrological characteristics
	g	%	
0,1209	0,0098	98,0	$\bar{X}=99{,}0\%$
0,1284	0,0099	99,0	$S=1{,}225$
0,1312	0,0101	101,0	$S_{\bar{X}}=0{,}548$
0,1252	0,0098	98,0	$\varepsilon_{0,95}=1{,}52$
0,1324	0,0099	99,0	$A_{rel},\%=1{,}54$

CONCLUSIONS

The procedure developed is characterized by high sensitivity, accuracy, and simplicity of performance and does not require the use of harmful reagents and solvents. It can be used in the analysis of pharmaceutical preparations containing papaverine hydrochloride (tablets, solutions).

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HAPLODIMERINE – A NEW TYPE OF DIMERIC QUINOLINE ALKALOIDS

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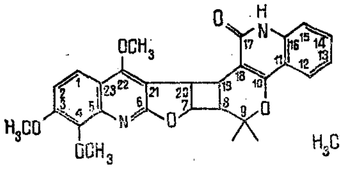
A base, which has been called haplodimerine, has been isolated from the fruit of the plant *Haplophyllum foliosum* Vved. It has been established by x-ray structural analysis that haplodimerine includes fragments of the known alkaloids skimmianine and flindersine attached to one another through the double bonds of furan and dimethylpyran rings with the formation of a four-membered ring.

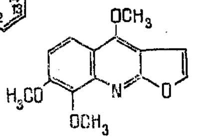
In an investigation of the fruit of the plant of *Haplophyllum foliosum* Vved. (family Rutaceae) growing in the environs of Alimtai (TadzhSSR), in addition to known alkaloids [1] we have isolated a minor base with the composition $C_{28}H_{26}N_2O_6$ (M^+ 486.1706 HRMS), mp 292-293°C, which we have called haplodimerine (I). The substance is optically inactive and sparingly soluble in organic solvents, water, and dilute alkali. It dissolves in mineral acids and gives the reaction for alkaloids with tungstosilicic acid.

The structure of the base isolated was first studied by the methods of IR, UV, NMR, and mass spectroscopy. The spectral material taken all together enabled us to determine the following fragments as components of the alkaloid (I): unsubstituted and ortho-substituted benzene rings, one of which formed part of a 2-quinolone nucleus, and three methoxy and two $C-CH_3$ groups [2, 3].

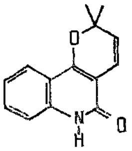
However, the spectral characteristics proved to be insufficient to determine the structure of haplodimerine. We performed an x-ray structural investigation which showed that the base isolated had structure (I), i.e., the haplodimerine molecule includes fragments of skimmianine (II), and flindersine (III) linked with one another through the double bonds of furan and dimethylpyran rings with the formation of a four-membered ring.



I



II



III

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