New Combinations of Some Basic Drugs with Dodecaphosphowolframic Acid

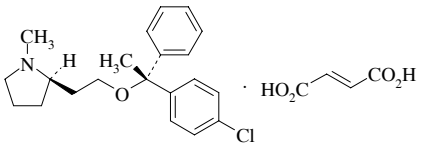
I. IR and thermal characterization

ALEXANDRA FILARETA NEAGU*#, IOANA CLEMENTINA CONSTANTINESCU#
University of Medicine and Pharmacy "Carol Davila" Bucharest, Faculty of Pharmacy, Department of Analytical Chemistry, 6 Traian Vuia Str., 020956, Bucharest, Romania

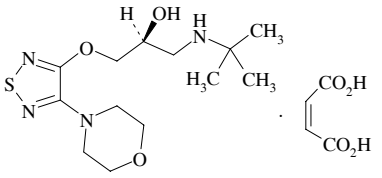
Clemastine and timolol react with dodecaphosphowolframic acid ($H_3PW_{12}O_{40}$) and form hardly soluble ion-associations. The structures of the obtained complexes were confirmed by IR spectral analysis and thermogravimetric analysis coupled with differential calorimetric analysis. Caloric effects were determined by thermal analysis and the conditions for processing the complex combinations were established in order to further assay of drugs. The chemical formula, molecular weight and solubility in water for the two complexes were determined.

Keywords: Clemastine, Timolol, Dodecaphosphowolframic acid, Ion pairs

Clemastine, (2R)-2-[2-[I-1-(4-chlorophenyl)-1-phenyl-ethoxy] ethyl-1-methyl pyrrolidine (fig. 1), is an antihistaminic drug used for diminution of the effects of histamine at H_1 receptors and timolol 1-[1,1-dimethylethyl-(amino)]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol – 3-yl] oxy] 2-propanol (fig. 1) is a drug with antihypertensive effect helpful in ocular hyper pressure and glaucoma [1].



Clemastine fumarate



Timolol maleate

Fig. 1 Chemical structures of clemastine fumarate and timolol maleate

Several methods have been reported for the quantitative determination of the clemastine (CL) and timolol (TM). Chemical and physico-chemical methods (electrochemical, spectrometric and chromatographic) have been used for the assay of these drugs from bulk, pharmaceuticals and biological fluids [2-15].

We have studied the chemical structure and analytical properties of CL and TM in order to develop new methods for quantitative determination of these drugs.

CL shows basic properties due to its pyrrolidinic nucleus, which is easily protonable and has the capacity to form salts and ion-pairs with some voluminous complex anions.

TM is characterized by the same analytical properties. The secondary amino group of the molecular structure of TM confers the basic character of this drug. The ether and secondary alcohol functions from its molecule influence intrinsic properties of the two heterocyclic rings, morpholinyl and thiadiazol.

Dodecaphospowolframic acid (PWo) behaves like a polyprotic acid. It has a high molecular weight and his voluminous anion forms ion-pairs with basic drugs, with a low solubility in water. It is a reagent with a high sensibility which has been used for the assay of basic substances from batch (like alkaloids and basic drugs) and for the separation of drugs from their dosage forms [16, 17, 18].

CL and TM react with PWo and form hardly soluble ion-associations. The complexes compounds were obtained, purified and dried at ambient temperature and then were further used for IR and thermal analysis who are useful for characterization of the new synthesized compounds [19, 20].

Experimental part

Reagents

All reagents were of analytical grade and used without further purification. The water used in all reactions was distillated water. Clemastine fumarate (CLF) was provided by Promedic and timolol maleate (TMM) by Merck. A 3% (w/v) of PWo solution was prepared by dissolving the accurate weighed amount of 3.00g in 100mL distillated water. A 2M chlorhydric acid was prepared by diluting a 38% HCl (Merck) solution with distillated water. Ethylic alcohol (Merck) was used.

Procedure for the preparation of the complexes

An appropriate amount (accurate weighed) of substance was dissolved in alcohol (CLF) or water (TMM). The *p*H value was adjusted at 1 using HCl 2M and then PWo was added in order to precipitate the drug. The reagent solution was added in small portions and under continuous stirring until the precipitation was completed, and then a small volume of reagent was added in excess. The precipitate was separated by a filtering crucible G_4 and purified by washing at first with a saturated solution of precipitate and in the end with distillated water until the washing waters show a negative reaction with $AgNO_3$.

* *email: lxndr_neagu@yahoo.com*

# *Authors with equal contribution*

The precipitate was dried in vacuum desicator to constant weight.

IR spectra were registered using a Bio-Rad-Win IR spectrophotometer. IR spectra of the ion-pairs were performed comparative with those of drugs and PWo on KBr disks, at frequency 4000- 400cm^{-1}.

Thermal analysis: the thermal behavior of reagent, drugs and ion-pairs was examined using thermogravimetry (TG), differential thermal analysis (DTG) and differential scanning calorimetry (DSC) in a temperature range of 20 – 700 and 20 – 600°C. The heating rate was 20°C/min. A Du Pont 2000 derivatograph instrument was used.

Procedure for the formula weight determination: has been used a spectrophotometric method established by Lee Kum Tatt [21], using the maximum absorbances of the two complexes in acetonitril at 269 nm for CL-PWo, and in methanol at 267.3nm for TM-PWo, respectively.

Procedure for the solubility in water determination: has been determined the absorbances for the saturated solutions of the complexes CL-PWo and TM-PWo in water at 25°C using a Perkin Lambda 2 UV-VIS spectrometer.

Results and discussions

IR spectral analysis shows important changes in the characteristic bands of functional groups which are involved in the complexation process (table 1).

The IR spectrum of wolframophosphoric acid is presented in figure 2. The large band with maximum at 3399.64 cm^{-1} was attributed to the water of crystallization. The IR spectrum shows characteristic bands for reagent at 1080.43 cm^{-1}, 982.562 cm^{-1}, 893.16 cm^{-1}, 799.219cm^{-1}, 595.007 cm^{-1}, 523.767cm^{-1}.

The IR spectrum of clemastine fumarate (fig. 3) shows a large number of absorption bands. We attribute the most important bands to the functional groups from its structure. We attribute the bands from 3500-3400cm^{-1} and 2675 cm^{-1} to hydrogen fumarate ion. The band from 3500 - 3400 cm^{-1} has a large maxim at 3435.19 cm^{-1} and it results from several bands. We attribute the other bands as follow: >C=O group from fumaric acid at 1702.57cm^{-1} (valence vibration) and at 1396.6 cm^{-1} (deformation vibration for chain OH); -COO- group: 1505 cm^{-1} and 1398.6 cm^{-1}; >N+H%CH_3 group (pyrrolidinic nucleus): 2355 cm^{-1}; two benzene nucleus: 3062 cm^{-1} (ϑ_{CH}), 979.107 cm^{-1} (ϑ_{C-C}), 648.913 cm^{-1} (γ_{CH}),1585 cm^{-1}(ϑ_{C-C}), 1656.09 cm^{-1} (γ_{CH}); %H_2C%O%CH<:1100.73cm^{-1} ; >C-O : 1243.03 cm^{-1}; >CH_2 : 2918cm^{-1} ($\vartheta_{CH2\ asim}$) and 2875cm^{-1} ($\vartheta_{CH\ asim}$),1446.43 cm^{-1} (deformation vibration), 720.84 cm^{-1} (skeleton vibration); C%N:1362 cm^{-1} (valence vibration).We attribute the bands from 1945.43cm^{-1} and 1144 cm^{-1} to ring vibration (ϑ_{ring}), respectively ring pulsation.

The IR spectrum of clemastine phosphowolframate (Cl-PWo) (fig. 4) shows characteristic bands for anion and protonated CL, with small deviations, shape and magnitudine modifications. There are present bands at

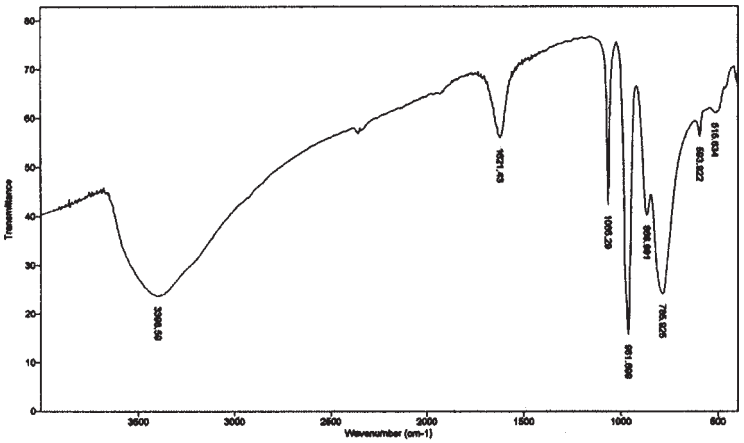


Fig. 2 IR spectrum of wolframophosphoric acid

Compound	IR (KBr) ν (cm^{-1})
Wolframophosphoric acid	3399.64 ; 1080.43; 982.562; 893.16; 799.219; 595.007; 523,767
Clemastine fumarate	3435.19; 3062; 2918; 2875; 2355; 1945.43; 1702.57; 1656.09; ; 1585; 1505; 1446.43; 1398.6; 1396.6; 1243.03; 11441100.73; 979.107; 720.84; 648.913; 362
Clemastine phosphowolframate	2360.06; 1445; 1095; 1979.95; 979.299; 896.157; 811,47; 590; 521.985
Timolol maleate	3305; 3082; 2968; 2891.3; 2855.3; 1698.45; 1204; 1055; 1025.28; 864.487; 769.693; 654.467; 448,946;
Timolol phosphowolframate	3082; 2977; 2964; 2922; 1620; 1080.1; 979.404; 896.331; 814.761; 595.442; 522.527

Table 1
IR SPECTRAL DATA

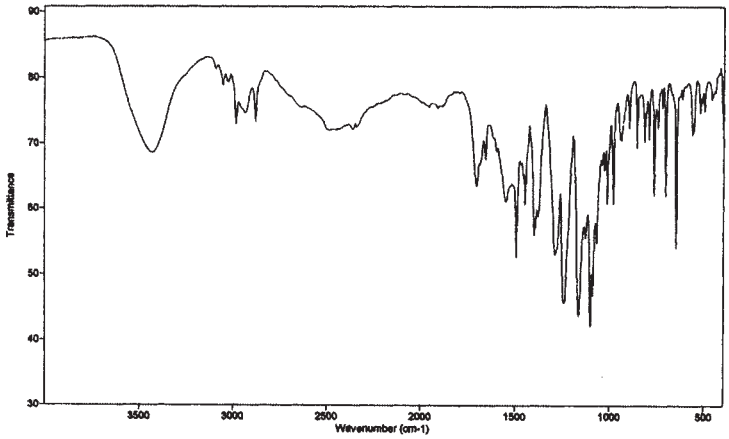


Fig. 3 IR spectrum of clemastine fumarate

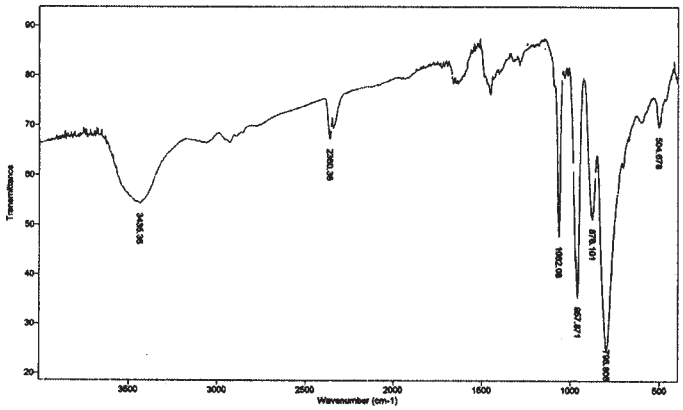


Fig. 4 IR spectrum of clemastine phosphowolframate

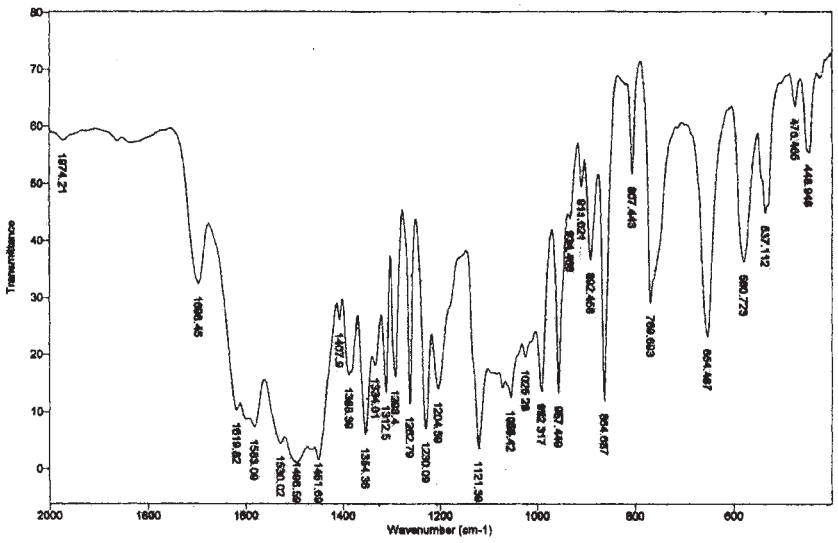


Fig 5. IR spectrum of timolol maleate

2360.06cm^{-1} 1095 cm^{-1} and 1445 cm^{-1} (for CL) and at 1079.95cm^{-1}, 979.299cm^{-1}, 896.157cm^{-1}, 811.47 cm^{-1}, 590 cm^{-1} and 521.985 cm^{-1} (for PWo anion). The IR spectrum of complex shows some differences comparative with the IR spectrum of CL due to the complexation process.

IR spectrum of timolol maleate (fig. 5) is characterized by the presence of the bands from 3305cm^{-1} and 1204cm^{-1} which are attributed to valence vibrations of the OH group (ϑ_{OH}) and C-OH group (ϑ_{C-OH}). The band from 3082cm^{-1} that characterizes the valence vibration for HN group (ϑ_{NH}) and the absorption band of valence vibrations from 1698cm^{-1} are attributed to the C=N group. The IR spectrum shows characteristic bands for valence vibrations of CH_3 group ($\vartheta_{CH3\ as}$) at 2968cm^{-1}. The valence vibrations of C-O-C group ($\vartheta_{C-O-C\ as}$) are characterized by the absorption band from 1055cm^{-1}.

The IR spectrum of timolol phosphowolframate (TM-Pwo) (fig. 6) shows some differences comparative with the IR spectrum of TM due to the complexation process. These changes are demonstrated from disappearance of the absorption bands ϑ_{NH} from 3082 cm^{-1} and 2964 cm^{-1} in the IR spectrum of timolol and by presence of the deformation vibration band of the group NH(σ_{NH}) from 1620 cm^{-1} in the IR spectrum complex. Also, there are presents characteristics bands of protonated amino group from ion-pair molecule at 2977-2922 cm^{-1}. The very intense bands for reagent from 1079 cm^{-1} and 981 cm^{-1} appear with same intensity in the IR spectrum complex.

Thermal analysis

The thermogravimetric curve (TG) of CL-PWo (fig. 7) has an almost horizontal plate up to 100°C, with a loss of 0.06179% of weight; later on, a pronounced variation in mass can be seen up to 280°C, with a maximum at 200°C (with a loss of 14.15% of weight) and a smaller variation up to 458°C with a maximum at 360°C (with a loss of

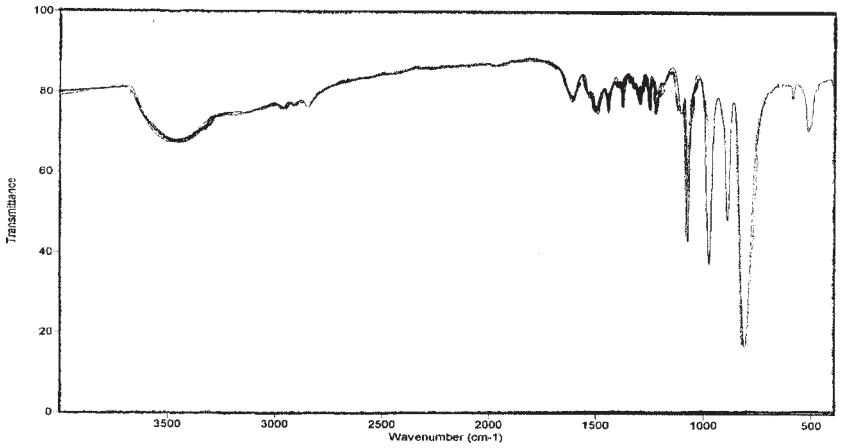


Fig. 6 IR spectrum of timolol phosphowolframate

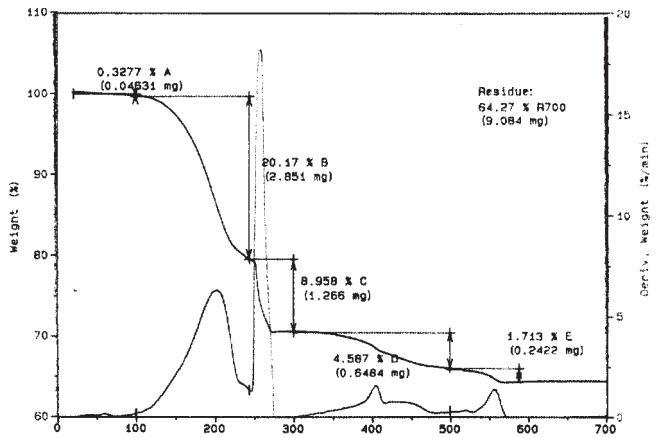


Fig. 7 TG and DTG curves of clemastine phosphowlframate

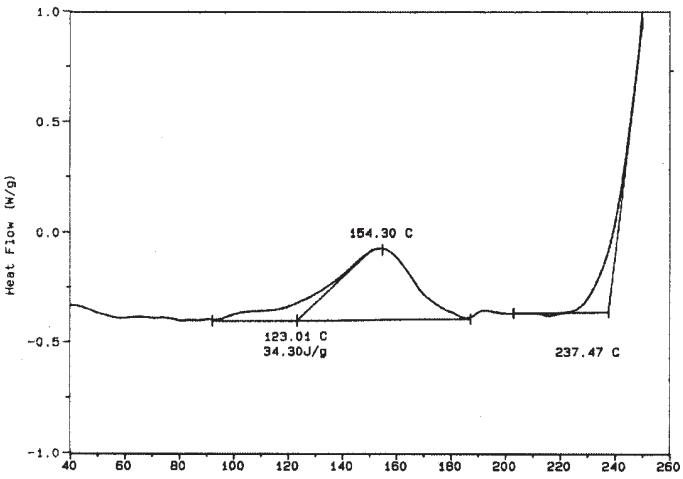


Fig. 8 DSC curve of clemastine phosphowolframate

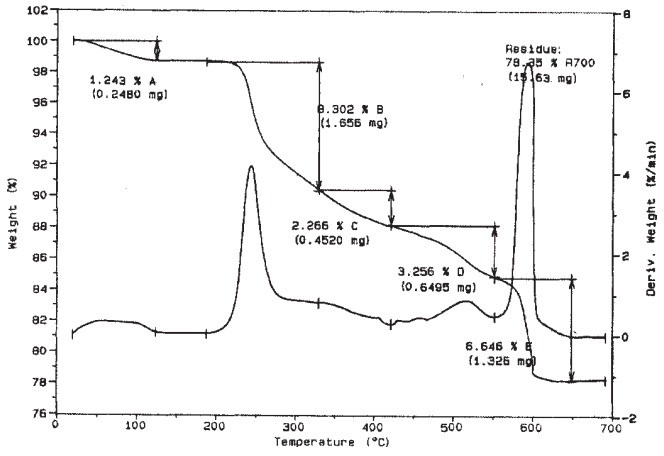


Fig. 9 TG and DTG curves of timolol phosphowolframate

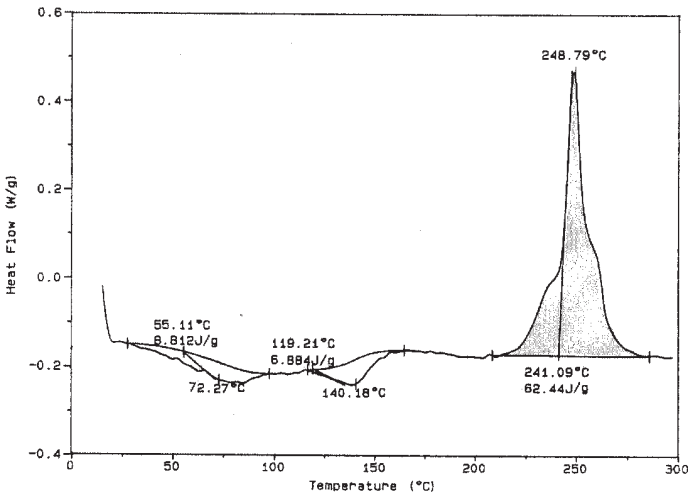


Fig. 10 DSC curve of timolol phosphowolframate

4.163% of weight). In the range of temperature from 458°C to 660°C a pronounced loss of mass takes place (7,714%) after which the mass remains constant. The residuum represents 73.88% of the start mass. DSC curve of Cl-PWo (fig. 8) shows small endothermic effects up to 160°C and a pronounced endothermic effect with a maximum at 250°C.

TG and DTG curves of TM-PWo (fig. 9) show a progressive variation of mass; it observes a small loss of mass between 95-150°C, and between 210-330°C it produces a decrees of mass with a loss of 8.302 % of weight. Between 550-650°C it observes a severe decree, with a loss of 6.646%. DSC curve of TM-Pwo (fig. 10) shows two endothermic peaks: one very small at 72.27°C and another one at 140.18°C. The DSC curve evidences a molecular arrangement by a pointed exothermic peak up to 248.79°C with a pronounced enthalpy (62.44 J/g).

For the determination of formula weight we used the formula established by Lee Kum – Tatt:

$$F = \frac{a \cdot \varepsilon}{A \cdot v}$$

where:

F= formula weight of the complex;
a = weight (g) of the complex;
ε = molar absorbtivity of the complex;
A = experimental absorbance;
v= solution volume (mL).

Formula weight for CL-PWO is 3989.13 (experimental) and 3989.92 (theoretical), witch correspond to chemical formula $[C_{21}H_{26}ClNOH]^{3+}[PW_{12}O_{40}]^{3-}4H_2O$, and for TM-Pwo

Complex	Chemical structure	Formula weight	Solubility	
			mg/L	mol / L
CL-PWo	$[C_{21}H_{26}ClNOH]^{3+}[PW_{12}O_{40}]^{3-}\exists 4H_2O$	3989.13	40.20	$1.00\exists 10^{-5}$
TM-PWo	$[C_{13}H_{25}N_4O_5S]^{3+}[PW_{12}O_{40}]^{3-}\exists 4H_2O$	3900.03	37.13	$9.52\ 10^{-6}$

Table 2
COMPLEXES CHARACTERISTICS

is 3900.03 (experimental) and 3900.17 (theoretical) corresponding to chemical formula $[C_{13}H_{25}N_4O_5S]^{3+}[PW_{12}O_{40}]^{3-}4H_2O$.

The solubility in water at 25°C (S(mg/vmL)) was calculated from relation:

$$S = \frac{A \cdot v \cdot F}{\varepsilon}$$

where:

S= the solubility in water at 25°C (mg complex dissolved in v mL);

A = experimental absorbance; v= volume of distilled water (mL);

F= formula weight of the complex;

ε = molar absorbtivity of the reagent in water .

The results were: 40.20 mg/L or 1.00 10^{-5} mol/L for CL-PWo and 37.13 mg/L or 9.52 10^{-6} mol/L for TM-PWo, respectively, that demonstrated the low solubility of these complexes [22].

Conclusions

The intrinsic basic character reflected the capacity of the monoprotonated cations of CL and TM to form complex compounds by ionic associations with various reagents with voluminous complex anions. The molecular structural formulas of the hardly soluble complex compounds were confirmed by physical and physico-chemical analysis: IR spectra and thermogravimetric analysis coupled with differential calorimetric analysis.

Thus, IR spectral analysis shows important changes in the characteristic bands of functional groups witch are involved in the complexation process.

The thermal behaviour is a physico-chemical characteristic which has great importance from an analytical viewpoint. Using the data provided by the thermal analysis, the caloric effects were determined, and the conditions for processing the complex combinations were established, in order to further assay the drugs. Also the obtained data through thermal and IR spectra analysis were corroborated. The formula weight and the solubility of the examined ion pairs were determined by spectrophotometric method (table 2).

New ion association combinations of clemastine and timolol were obtained and the study performed showed that they may be used to develop new methods for the assay of these drugs.

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