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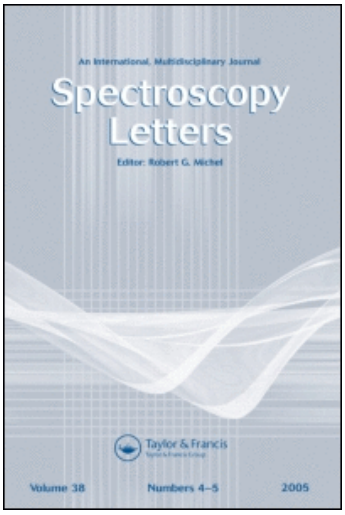

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A New Sensitive Spectrophotometry Method for the Analysis of Some Antihistamines

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A NEW SENSITIVE SPECTROPHOTOMETRIC METHOD FOR THE ANALYSIS OF SOME ANTIHISTAMINES

Keywords: astemizole, cinnarizine, mequitazine, terfenadine, Picrolonic acid, spectrophotometry

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ABSTRACT

A simple and sensitive spectrophotometric method is developed for the assay of some antihistamines. The method is based on the interaction of these basic compounds with picrolonic acid in chloroform to give a yellow color exhibiting maximum absorption at 359 nm.

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The drugs determined are astemizole, cinnarizine, mequitazine and terfenadine. Beer's Law is valid for the investigated antihistamines.

The drugs are determined either in pure form or in their pharmaceutical formulations. The sensitivity of the proposed procedure is discussed and the results are compared with reported ones.

INTRODUCTION

There are three histamine receptors; H_1, H_2, and H_3.The investigated drugs - astemizole, cinnarizine, mequitazine and terfenadine - are H_1 antihistamines. They competitively antagonize the effects of histamine at receptor sites but they do not block the release of histamine. Most of these agents are effective in allergic rhinitis and as adjuncts to conventional therapy in anaphylactic reaction. Cinnarizine is also used in the treatment of vascular disorders. In fact; all antihistamines are amine derivatives and belong to different chemical classes [1].

Several methods have been reported for the determination of the investigated compounds. These methods include titrimetric [2,3], colorimetric [4 - 15], spectrophotometric [16,17], high pressure liquid chromatographic [18-22] and radioimmunoassay methods [23,24]. In addition; comprehensive reviews are also published for some of the chosen compounds [25,26].

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Picrolonic acid is 3-methyl-4-nitro-1- (p-nitrophenyl)-2-pyrazoline-5-one (scheme 1). It is regarded as nitrophenol owing to its similarity to picric acid [27]. It yields very sparingly, soluble salts which in their properties show a close resemblance to picrates[27].

Picrolonic acid is often used in place of picric acid for the isolation and quantitation of nitrogenous bases[28]. It is also used for the detection and estimation of calcium[29].

Recently picrolonic acid was used for the spectrophotometric determination of zinc through the formation of a ternary system with either 1,10-phenanthroline or 2,2`- bipyridyl [30,31].

A spectrophotometric determination of carbocromen (chromonar) using picrolonic acid was also reported [32].

The objective of the present work is to study the possible chemical reactions between some H_1 antagonists as astemizole, cinnarizine, mequitazine and terfenadine (Scheme 1) and picrolonic acid reagent, hoping to develop a suitable method for the quantitative analysis of these drugs.

EXPERIMENTAL

Apparatus

UV-VIS-spectrophotometer (Shimadzu, Model 160A), was used for the spectroscopic analysis. Quartz cells of 1-cm path length were used.

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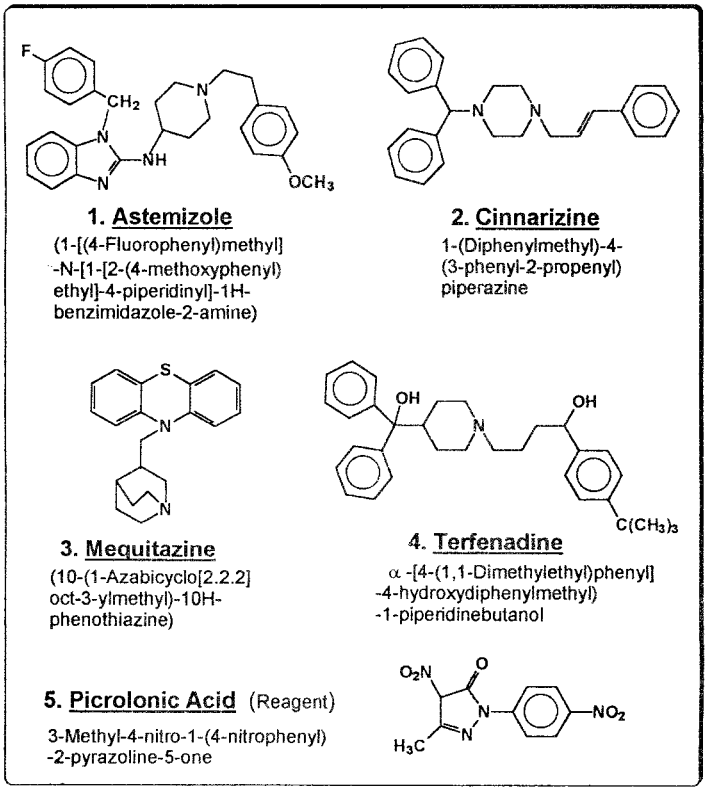
Scheme 1.

Chemistry of the investigated drugs and reagent



Materials and reagents:

1. Astemizole authentic sample (Pharco Pharm., Alex. Egypt).

2. Astemizole tablets ®, labeled to contain 10 mg astemizole / tablet.

(South Drugs Ind. Co., 6 October City, Egypt.) Batch No. 896102.

3. Cinnarizine authentic sample, (Alex. Co. for Pharm. and Ind., Alex., Egypt).

4. Stugeron tablets ®, labeled to contain 25 mg cinnarizine / tablet. (Glaxo Wellcome Egypt S.A.E., El Salam City, Cairo, Egypt) Batch No. 61247A.

5. Mequitazine authentic sample, (Amriya, Rhone-Poulenc, Alex., Egypt).

6. Primalan tablets ®, labeled to contain 5 mg mequitazine / tablet. (Amriya Rhone-Poulenc, Alex., Egypt) Batch No. 106703.

7. Terfenadine authentic sample, (Amoun Pharm. Ind. Co., El Salam City, Cairo, Egypt).

8. Histadine tablets ®, labeled to contain 60 mg terfenadine / tablet. (Amoun Pharm. Ind. Co., El Salam City, Cairo, Egypt).

9. Picrolonic acid reagent (B.D.H.Laboratory Chemicals Division). A 0.02 % of picrolonic acid in chloroform is to be freshly prepared.

10. A chloroformic solution of each drug was prepared so as to contain: 0.02 mg % astemizole / ml, 0.05 mg % cinnarizine / ml or 0.04 mg % of mequitazine or terfenadine / ml.

11. A chloroformic solution containing 5×10^{-4} M of astemizole, cinnarizine, mequitazine or terfenadine.

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12. A chloroformic solution containing 5×10^{-4} M of picrolonic acid.

PROCEDURE

Development of calibration curves

Serial volumes (1 – 5 ml) of each chloroformic solution of the antihistamines were transferred to a series of 10 ml volumetric flasks, and the volume was adjusted to about 5 ml with chloroform. Each flask was treated with 1 ml picrolonic acid reagent and then completed to volume with chloroform. The flasks were set aside for 5 minutes, then the developed yellow color was measured spectrophotometrically at 359 nm against a reagent blank treated similarly.

Procedure for tablets

Twenty tablets of each drug were weighed, powdered and mixed. An accurately weighed quantity of the powder, equivalent to 20 mg astemizole, 50 mg cinnarizine or 40 mg of mequitazine or terfenadine was transferred to a 100 ml volumetric flask. The content was treated with 70 ml chloroform and extracted by shaking for 15 minutes. The flask was then completed to volume with chloroform, mixed and filtered. A volume of the filtrate was diluted with chloroform to obtain 0.02 mg ml^{-1} of astemizole, 0.05 mg ml^{-1} of cinnarizine or 0.04 mg

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ml^{-1} of mequitazine or terfenadine. An aliquot volume of the diluted solution was transferred to a 10 ml volumetric flask and treated as mentioned under the development of the calibration curves.

Determination of the stoichiometric ratio

Using the continuous variation method (Job's method [33]).

In 10 ml-calibrated flasks, a series of equimolar chloroformic solutions (5×10^{-4} M) of each antihistamine and the reagent, in different complementary volumes, totaling 1 ml (0.1 + 0.9 to 0.9 + 0.1 inclusive) were prepared. The flasks were diluted to volume with chloroform and set aside for 5 minutes. The absorbances were measured at the specified λ max and a graph was then plotted.

Results And Discussion

Absorption Spectra

The chloroformic solution of picrolonic acid is very slightly yellow and having an absorption band at 315 nm. Despite of the structural variation; each of the drugs Astemizole, Cinnarizine, Mequitazine and Terfenadine reacted with picrolonic acid – in chloroform – to give a yellow colored product exhibiting a major band at 359 nm (Fig. 1).

Optimum Conditions

The influence of different parameters on the color development

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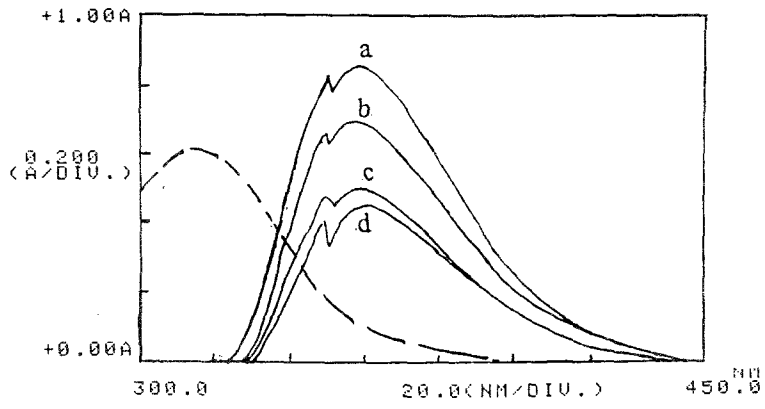

Figure 1. Absorption spectra of picrolonic acid (-----) with:
a-1mg% astemizol b-1.6mg% mequitazine
c-1mg% cinnarizine d-1mg% terfenadine

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was studied to determine the optimal conditions for the assay procedure.

The course of the reaction was studied as a function of the reagent concentration, selectivity of the solvent and stability. Maximum spectral absorption was obtained when using 1 ml of 0.02 % w / v of picrolonic acid, in a total volume of 10 ml.

Different solvents were tested so as to select the proper one that would lead to the highest absorption intensity. Polar solvents as methanol, ethanol, isopropanol, acetonitril and dimethylformamide were tried; but found unsuitable. Nonpolar solvents, on the other hand,

as chloroform and carbon tetrachloride were found ideal as they offer high yield of the reaction product and low color intensity for the blank. It has been observed that the rate of the reaction between the drug and reagent (in chloroform) is fast and the color attained its maximum intensity within 5 minutes, and remains stable for at least 30 minutes.

Quantification

Under the described experimental conditions; the standard calibration graphs were constructed for the color reactions between the drugs astemizole, mequitazine, cinnarizine or terfenadine and the reagent picrolonic acid. The absorption of the colored product at 359 nm was plotted vs. the concentration of the drug in mg %.

Concentration ranges, slopes, intercepts, correlation coefficients and molar absorptivities are given in Table 1.

The reproducibility of the proposed method was checked through the analysis of 5 replicate samples of each of the different investigated drugs. The different volumes of the samples chosen contained different drug concentrations within the Beer's law limit.

The standard deviation for the assay results was between ± 1.12 and ± 1.88 . This range would recommend the use of the procedure for the quality control analysis of the cited drugs either in their bulk forms or in tablet preparations.

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Table 1

Some spectral characteristics for the investigated drugs and color reaction

Base	Linear range mg %	Intercept a	Slope	Corr. Coeff.	A (1%, 1cm)	ε*
Astemizole	0.2 – 1.0	- 0.005	0.85	0.9996	845	38750
Cinnarizine	0.5 – 2.5	- 0.004	0.521	0.9998	516	19015
Mequitazine	0.4 – 2.0	- 0.009	0.445	0.9997	436	14060
Terfenadine	0.4 – 2.0	0.002	0.456	0.9958	458	21603

ε^* = Apparent Molar Absorptivity (1 mol^{-1} cm^{-1}).

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Application

The proposed procedures were used to determine the investigated drugs in pure form and in tablet preparations. The results obtained as shown in Table 2 are comparable to some reported procedures [4,11,16] or to the USP 1995 procedure [2].Student's t and F tests show no significant difference between the proposed and the other procedures that were taken for comparison.

Interference

The common tablet excipients such as glucose, lactose, starch, magnesium trisilicate and sodium laurylsulphate, were found not to

Table 2

Assay results of the investigated antihistamines in pure form and in pharmaceutical preparations

Drug	Recovery % ± Standard Deviation [a]			
	Picrolonic Acid	Reference Method[b]	F[c]	t[d]
Astemizole powder	98.74 ±1.12	98.38 ± 1.2	1.25	0.48
Astemizole tablets ®	100.8 ±1.37	100.9 ±1.18		
Cinnarizine powder	99.02 ±1.88	98.66 ± 1.54	1.49	0.33
Stugerone tablets ®	99.2 ± 1.29	99.0 ± 1.31		
Mequitazine powder	100.1 ± 1.26	99.7 ± 0.83	2.31	0.69
Primalan tablets ®	100.6 ± 1.37	101.0 ± 1.64		
Terfenadine powder	100.8 ± 1.21	100.9 ± 1.36	1.26	0.15
Histadine tablets ®	99.75 ± 1.2	99.65 ± 1.74		

(a) Each result is the mean of 5 experiments.

(b)- Astemizole was determined using $FeCl_3$ / 1,10-phenanthroline [4].

-Cinnarizine was determined spectrophotometrically [16].

-Mequitazine was determined using p-chloranilic acid [11].

-Terfenadine was determined by the USP 1995 method [2].

(c) Theoretical value of $F = 6.39$ ($p = 0.05$).

(d) Theoretical value of $t = 2.78$ ($p = 0.05$).

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interfere with the color formation or intensity. This is due to their insolubility in chloroform.

Reaction involved

In a trial to understand the nature of the reaction between the handled drugs and the reagent, the following was tested or observed:

a) Some antihistamine drug salts that are soluble in chloroform as doxylamine succinate, diphenhydramine hydrochloride and chlorpheniramine maleate were found to react with picrolonic acid in a manner similar to the investigated drugs.

b) Some antihistamine drug salts that are insoluble in chloroform as phenylephrine hydrochloride and phenylpropanolamine hydrochloride should be treated with silver oxide, followed by an extraction of the freed drug with chloroform to enable a reaction with picrolonic acid.

c) The consistency of the 359 nm spectral band for the reaction products of all tested drugs despite their structural variation with picrolonic acid, is probably due to the formation of a charge transfer complex.

This suggestion is based on the fact that polynitro compounds are characterized by forming complexes rather than ordinary salts with aromatic compounds possessing electron donating properties [34]. Accordingly, the binding in these complexes would be due to the attractive forces between an electron rich partner (drug) and an electron poor substance (picrolonic acid).

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d)The shift in the spectrum of the reaction product to a longer wavelength relative to the reactants (drug and picrolonic acid) is indicative to a charge transfer complex formation. This is due to the enhanced possibility for resonance stabilization of an excited state involving both reactants.

e) Job's continuous variation method [33] was applied by using equimolar concentration of drug and picrolonic acid (5×10^{-4} M). The molar ratio as shown in Fig. 2 and 3, as representative, was found to be 1 : 1 for all the antihistamines analyzed, regardless of the number of the basic centers present in the molecule of each drug.

Conclusion

The proposed method is characterized by being simple, easy and time saving. So it could be recommended to be used for routine analysis of the investigated drugs whether in pure form or in their pharmaceutical tablet preparations. However, the method is not recommended for the analysis of cinnarizine when it is combined with heptaminol acefylinate (Sureptil tablets), since the latter shows positive reactivity with picrolonic acid. This obstacle may be solved by a pre-separation of components by a suitable separation technique as paper chromatography, partition column chromatography or thin

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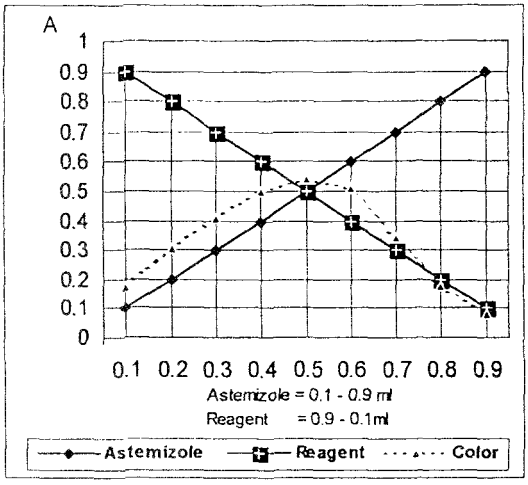

Figure 2: Absorbances at 359 nm for the color reaction of Astemizole and picrolonic acid using equimolar complementary volumes

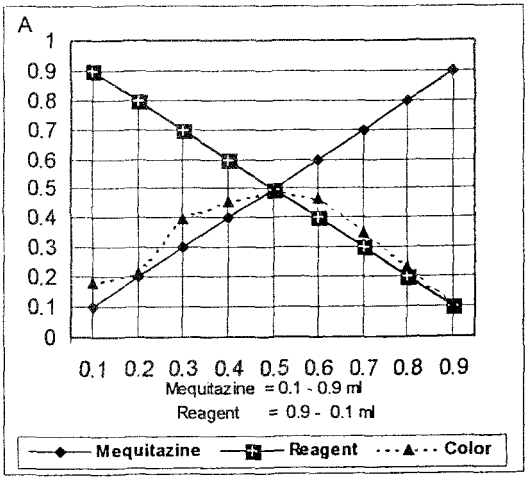

Figure 3: Absorbances at 359 nm for the color reaction of Mequitazine and picrolonic acid using equimolar complementary volumes.

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layer chromatography. This defect does not affect the use of the proposed method for the routine analysis and content uniformity determination of singly prescribed antihistamines.

REFERENCES

1. Wilson and Gisvold's ' Text Book Of Organic And Pharmaceutical Chemistry ' 9th ed. J.B.Lippincott. New York. 1991 pp.418 – 428.
2. The USP XXIII, USP Convection, Inc., Twinbrook Parkway Rockville, MD,USA, p. 1494, 1995.
3. A.A. Bodwan, A. Abu Malooh, L. Owais, M.S. Salem and H. Alkaysi; Anal. Lett. 24 (2) ,217 (1991).
4. C.S.P. Sastry and P.y. Naidu; Indian drugs 34 (3), 140 (1997).
5. S.Z. Qureshi and M.A. Khan; Analusis, 24 (5), 190 (1996).
6. A.A. Alwarthan and A.M. Alobaid; J. Pharm. Biomed. Anal. 14 (5), 579 (1996).
7. S.B.Patil, S.P. Nemade, G.N. Chaudhari and H.V. Kotle; Indian Drugs, 30 (9), 438 (1993).
8. B.P. Zorya and S.G. Solomonova; Farm. Zh, 669 (1991).
9. G.A. Saleh and H.F. Askal; Pharmazie, 45 (3), 220, (1990).
10. N. Purohit and S.G. Kaskhedikar; Indian Drugs, 34 (7), 414 (1997).

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11 .M.M. Ayad, H.M. Saleh, M. El Maamli, S. El Adl and M. El Henawee; Alex. J. Pharm. Sci., 6, 173 (1992).

12. M. Ayad, H. Saleh, M. El Maamli, M. El Bolkini and M. El Henawee; Anal. Lett. 26 (5), 913 (1993).

13. R.T. Sane, J.K. Ghadge, A.B. Jani, S.S. Kotwal and A.J. Vaidya; Indian Drugs, 29, (5), 236 (1992).

14. M.M.Abdel-Khalek and H.G. Daabees; Alex. J. Pharm. Sci., 8 (1), 13 (1994).

15. M.M. Abdel-Khalek, M.S. Mahrous and H.G. Daabees; Alex. J. Pharm. Sci., 7 (3), 201 (1993).

16. L. Sun; Zhongguo-yiyuan-yaoxue-zazhi 13, (4), 165 (1993).

17. H. Cai and X. Yang; yaowu-fenxi-zazhi 6 (1), 31, (1986).

18. G.S. Sadana and A.J. Potdar; Indian Drugs 27, 140, (1989).

19. M.T. Rosseel and R.A. Lefebvre, Chromatographia 36356 (1993).

20. H.K.L. Hundt; J. Chromatogr-Biomed Appl.; 21 (2 (J. Chromatogr 232) 465 (1982).

21. S. Surapaneni and S.K.W. Khalil; J. Liq. Chromatogr 17 (11), 2419 (1994).

22. S.K. Gupta, P.R. Gwilt, J.K. Lim and D.H. Waters; J. Chromatogr 361403 (1986).

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23. R. Woestenborghs, I. Geuens, M. Michiels, R. Hendriks and J. Heykants; Drug-Dev-Res. 8 (1-4), 63 (1986).

24. C.E Cook, D.L. Williams; M. Myers, C.R. Tallent, G.A. Lesson, R.A. Okerholm, G.J. Wright; J. Pharm. Sci. 69 (12), 1419 (1980).

25. A.A. Badwan, H.N. Alkaysi, L.B. Owais, M.S. Salem and T.A. Arafat, "Analytical Profile Of Drug Substances and Excipients" K. Florey (Ed.) Academic Press, New York pp. 627 – 662 (1990).

26. A.M. Alobaid and M.S. Mian, Ibid, vol. 20, pp. 173 –208 (1991).

27. J. Scmidt and H.G. Rule, A Text Book Of Organic Chemistry, 5th ed., Revised and edited by N. Campbell (Edin), p 676 (1964).

28.T. Higushi and E.B. Hanseen. Pharmaceutical Analysis, Interscience Publishers, John Wiley and Sons p. 379 (1961).

29.The Merck Index. 12th ed., An Encyclopedia of Chemicals, Drugs and Biologicals. Merck & Co., Inc. White House Station, N.J. USA (1996).

30. N. Dumitrescu and V. Dumitrescu; Rev. Chim. 39 (3), 262 (1988).

31. N. Dumitrescu and V. Dumitrescu; Rev. Chim. 39 (9), 794 (1988).

32. L. Przyborowski and A. Zygmut; Farm-Pol 40 (12), 717 (1984).

33. P. Job, Ann. Chim., 9, 113, 1928. Through G.G. Guilbault and

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L.G. Hargis, " Instrumental Analysis Manual " Marcel Dekker Inc., (1970).

34. J. Roberts and M. Caserio, Basic Principle Of Organic Chemistry. Published by W.A. Benjamin, Inc. New York, Amsterdam (1965).

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