PREPARATION OF A STABLE INJECTION SOLUTION OF BARVINKAN HYDROCHLORIDE

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The medicinal form proposed previously [2] for barvinkan hydrochloride [tetradehydrocuran-17-al hydrochloride] [1] has proved to be extremely labile: During storage the color of the preparation changes and its concentration and pharmacological activity decrease.

Various stabilizers have been used to obtain a stable injection solution [3, 4]. The stability of the injection solutions was tested by the "accelerated aging" method at a high temperature [5]. The most effective stabilizer proved to be a composite one consisting of sodium sulfite (0.1%), sodium metabisulfite (0.1%), ascorbic acid (0.2%), and sodium chloride (0.6%). The solution was saturated with carbon dioxide for 30 min. Variation of the composition of the stabilizers both qualitatively and quantitatively showed that the medicinal form that we have developed is the most stable (Table 1).

EXPERIMENTAL

To prepare a stable injection solution, all the components were weighed out and were diluted with water until dissolution was complete. The solution was filtered, saturated with carbon dioxide for 30 min, filled into ampuls of neutral glass by the vacuum method, and sealed. Tyndallization was carried out twice at 70-80°C for 60 min each time with an interval of 24 h.

The storage time was determined by the "accelerated aging" method at 60°C for 44 days, which corresponds to storage at room temperature for two yr. The injection solution was analyzed every 11 days. For this purpose, the tubes were opened and an aliquot of the solution was taken and was made alkaline to pH 8-9, and the base (vincanine) was extracted with chloroform. The chloroform was distilled off to dryness, and the residue was dissolved in glacial acetic acid and was titrated with perchloric acid in the presence of Crystal Violet

TABLE 1. Influence of Stabilizers on the Stability of a Solution of Barvinkan Hydrochloride

Composition of the solution	pH		Concentration, g/ml	
	after tyndallization	after "accelerated aging" for 44 days	after tyndallization	after "accelerated aging" for 44 days
1. Barvinkan hydrochloride (1.0%) Sodium metabisulfite (0.1%) Sodium chloride (0.8%) Hydrochloric acid, 0.1 N (3.3 ml) Water for injection (to 100 ml)	3,15	—	0,0095	—
2. Barvinkan hydrochloride (1.0%) Sodium metabisulfite (0.5%) Sodium chloride (0.3%) Water for injection (to 100 ml) Saturation with CO_2, 30 min	4,65	2,85	0,0095	0,0046
3. Barvinkan hydrochloride (1.0%) Sodium sulfite (0.1%) Sodium metabisulfite (0.1%) Ascorbic acid (0.2%) Sodium chloride (0.6%) Water for injection (to 100 ml) Saturation with CO_2, 30 min	4,40	3,95	0,0102	0,0097

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as indicator until the color changed from red-violet to green. The result was calculated to barvinkan hydrochloride.

SUMMARY

A method has been developed for obtaining a stable 1% injection solution of barvinkan hydrochloride with the aid of a complex stabilizer.

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SOME REACTIONS OF α-HYDROXYMETHYLENE- AND α-DIMETHYLAMINOMETHYLENE-2,3-POLYMETHYLENE-3,4-DIHYDROQUINAZOLIN-4-ONES

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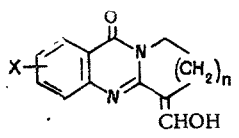
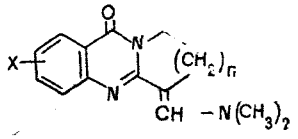
Many quinazoline derivatives have biological activities of various types. Thus, 2-perfluoro(chloro)alkyl-6,7-disubstituted 4-quinazolones possess a selective herbicidal action [1], and 2-alkyl-3-aryl-6(7)-substituted quinazolones are acaricides [2]. 2-Mono(di)alkylaminomethylene-1H(alkyl)-4-quinazolones and 2-tert-butyl-3-hydroxy-6-iodo-4-quinazolones have been proposed as fungicides [3, 4].

We have previously developed a method of synthesizing α-hydroxymethylene- and α-dimethylaminomethylene-2,3-polymethylene-3,4-dihydroquinazolin-4-ones and their 6- and 7-nitro derivatives (I, II), which are close analogs of the dialkylaminomethylene-4-quinazolones mentioned above, by the Vilsmeier–Haack formulation of 2,3-polymethylene-3,4-dihydroquinazolin-4-one [5].



I a-c

a) x=H, n=1
b) x=H, n=2
c) x=6—NO2, n=3



II a-c

a) x=H
b) x=6—NO2
c) x=7—NO2
n=1

In order to synthesize potential pesticides and to investigate the reactivity of the α-hydroxymethylene and α-dimethylaminomethylene groups we have studied some transformations of the above-mentioned compounds.

The α-hydroxymethylene- and α-dimethylaminomethylene-2,3-polymethylene-3,4-dihydroquinazolin-4-ones can be considered as enols and enamines. They should be capable of acylation

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