TEBROPHEN, A NEW ANTIVIRUS PREPARATION

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Tebrophen (3,5,3',5'-tetrabromo-2,4,2',4'-tetrahydroxydiphenyl) is an original preparation used for the treatment of virus diseases of the eyes as a 0.1 and 0.25% ointment on a petroleum jelly base. It is a white powder with a cream tint, mp 283-284° (decomposes), is virtually insoluble in water but readily soluble in acetone and soluble in ethanol and isopropanol. Tebrophen possesses high activity against influenza virus (type A strain PR-8) in vitro and in experiments on chick embryos.

Tebrophen has undergone successful clinical trials for the treatment of virus diseases of the eyes (herpetic keratitis and adenovirus keratoconjunctivitis) and has been accepted for use in medical practice by the Pharmacological Committee, Ministry of Health of the USSR. Tebrophen ointment is recommended for local application. In the treatment of adenovirus keratoconjunctivitis and various forms of herpetic keratitis, the ointment must be applied into the conjunctival sac 2-3 times during the day and once at night. Treatment is continued until a cure is effected.

As the original compound for synthesis of tebrophen, the readily accessible pentabromoresorcinol (I) is used [1]. By thermal decomposition of this compound, tribromoresoquinone (II) is formed [2]. The writers found that if this process is carried out in an invert solvent with high boiling point, such as bromobenzene, the reaction takes place without special complications and the yield of II is 51%. By reduction of II with sodium hydrosulfite, tebrophen (III) was obtained with a yield of 84%:



Methods of reduction of II to tebrophen suggested in the literature gave only low yields and are of no practical interest [2, 3].

EXPERIMENTAL

<u>Tribromoresoquinone (II).</u> A mixture of 101 g pentabromoresorcinol (I) and 800 ml distilled bromobenzene is heated with mixing for 25-30 min to 143-145°, kept at this temperature for 30 min, after which the solvent is evaporated off completely in vacuo (at a residual pressure of 400 mm, to begin with, then at 20-25 mm). The residue is treated with methylene chloride cooled to -5° . The orange-red crystals of II thus formed are separated by filtration, washed with cold methylene chloride, and dried in air. Yield 35.36 g (51%), mp 202-203°. Found, %: C 20.79; H 0.4; Br 69.27. $C_{12}H_2Br_6O_4$. Calculated, %: C 20.90; H 0.23; Br 69.52.

3.5.3'.5'-Tetrabromo-2.4.2'.4'-tetrahydroxydiphenyl (Tebrophen) (III). To a suspension of 69 g II in a mixture of 276 ml isopropanol and 195 ml water, 65.25 g sodium hydrosulfite (80% content) is added with vigorous stirring. The reaction mixture is stirred for 20 min at room temperature. Under these circumstances the reaction mass changes color from orange-red to dark green, and then to white. The suspension

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thus obtained is treated with 2 liters water and mixed for 2-3 min, after which the precipitate thus formed is separated by filtration. The technical tebrophen (III) thus obtained is dissolved in 490 ml acetone; 1 g sodium hydrosulfite and 4.8 g charcoal are added to the solution, the mixture is stirred and filtered, and tebrophen is precipitated from the filtrate with 2.45 liters water warmed to 45°. The precipitate is separated by filtration, washed with water, and dried for 20 h at 80°. Yield 44.9 g (84.1%), mp. 283-284° (decomposes). Found, %: C 27.01; H 1.15; Br 59.77. $C_{12}H_6Br_4O_4$. Calculated, %; C 26.99; H 1.13; Br 59.88.

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