solution was transferred to a 100-ml volumetric flask and brought up to the mark with the buffer solution. The procedure was continued as shown above.

Chromatographic Determination. A sample of about 0.2 g was dissolved in 3 ml of ethanol, and 0.4 μl of the solution was placed on the chromatograph.

Isolation of the Salt of I from the Reaction Mixture

A sample of the "reaction product" was diluted with water in 1:5 ratio. Compound I was extracted 20 times with benzene. The concentrated aqueous solution was treated with acetone. After separation of the precipitated sodium chloride, acetone was distilled. To remove traces of I, a saturated alcoholic solution of picric acid (3:1) was added to the residue. After dilution with water, the picrates which separated out were filtered, and the aqueous solution was purified from the residue of picric acid by fivefold extraction with benzene and treatment with activated charcoal. After distillation of water in vacuo (1 mm Hg), a syrup was obtained containing 85% of the salt (spectrophotometrically).

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PREPARATION OF FLUOCINOLONE ACETONIDE

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Fluocinolone acetonide, Synalar, acetonide of 6α,9α-difluoropregna-1,4-diene-11β,16α,17α,21-tetraol-3,20-dione (IV) is a highly active preparation with antiinflammatory and antiallergic properties.

In the literature, including patent literature [1-5], methods for the preparation of fluocinolone acetonide are described using the 21-acetate of 6α-fluoropregna-1,4,9(11)-triene-16α,17α,21-triol-3,20-dione and its acetonide (I) as the key intermediates. The 9β-11-epoxy ring necessary for further transformations was introduced by successive addition of the elements of hypobromous acid to the corresponding $\Delta^{9(11)}$-olefin and closing of the bromhydrin formed. To introduce fluorine into the 9-position of the molecule, the trans-diaxial opening of the 9β,11-epoxy ring by anhydrous hydrofluoric acid was used, in accordance with the Fried method.

The methods described for the preparation of fluocinolone acetonide were characterized by the introduction of the acetonide grouping at various stages of the synthesis. The introduction of the acetonide grouping at the last stage of the synthesis is preceded by shielding the 16α,17α-diol grouping in the form of 16-acetate before the reaction with hydrogen fluoride.

For the synthesis of IV, we used a compound already containing the acetonide grouping, i.e., the 21-acetate of 6α-fluoropregna-1,4,9(11)-triene-16α,17α,21-triol-3,20-dione (I). The acetonide group served as a reliable shielding of the labile 16α,17α-dioxy-20-keto grouping, which tends to undergo a D-homorearrangement under the conditions of acid and alkaline catalysis. We chose a sequence of reactions including the formation of bromhydrin II, the closing of the ring into the epoxy compound III, with simultaneous hydrolysis of the 21-acetoxy group, as well as the opening of the epoxy ring with concentrated hydrofluoric acid.

The sequence of reactions chosen by us is described for several other fluorinated corticosteroids [6], but because of the specific structure of the starting compound, a detailed study of the process was required.

For the preparation of bromhydrin II, we used dibromantin as the source of hypobromous acid. In contrast to previous investigations of the preparation of 5,6-bromhydrins [7], in this case the reaction proceeds stereospecifically with the formation of the 9α-bromo-11β-hydroxy compound II in a yield of 82-85%. The reaction proceeds equally well in different solvents: dioxane, ethyl acetate, tetrahydrofuran. When the reaction was carried out in acetone [8], we observed a reaction of the solvent with dibromantin, which led to a considerable expenditure of the reagent.

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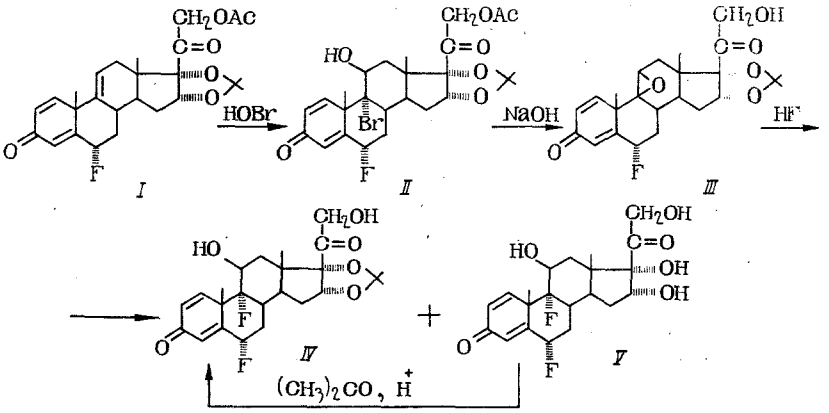

The closing of the epoxy ring in the bromhydrin II containing the 21-acetoxy group was effected in the presence of sodium hydroxide (pH about 9.0). By means of thin layer chromatography, it was found that under the action of alkali the hydrolysis of the 21-acetoxy group and the closing of the ring with the formation of the 21-hydroxy compound III take place simultaneously. The yield of the last compound is 84-86% based on II.

To open the epoxy ring of III with the formation of vicinal fluorhydrin IV, we used 70% hydrofluoric acid, a solution of hydrogen fluoride in dimethylformamide, and a complex of hydrogen fluoride with urea.

From the technical point of view, 70% hydrofluoric acid was the simplest to use. In other cases, the reaction does not proceed to completion, and after a prolonged period of the reaction, resinification products are formed.

During treatment of the epoxy compound III with 70% hydrofluoric acid, together with the formation of fluocinolone acetonide IV, its partial hydrolysis is observed, leading to the formation of tetraol V. When this compound is heated in acetone in the presence of 57% perchloric acid, it is readily converted into IV.

Temperature substantially influences the character of the reaction of the epoxy compound III with hydrofluoric acid. Thus, if the reaction is carried out above 0°C, appreciable resinification of the products takes place. At a lower temperature (−30°C), the rate of the reaction noticeably decreases, which leads to an increase in the content of tetraol V in the reaction mixture. We found the optimal conditions for carrying out the reaction of III with hydrofluoric acid, the yield of fluocinolone acetonide IV, including also the amount obtained from the tetraol V, amounts to more than 60% in this case.

Thus, our scheme for the synthesis of fluocinolone acetonide from I is optimal, since it ensures the highest yield of the end product.

EXPERIMENTAL

Chromatographic analysis of compounds II, III, IV was carried out on Silufol UV-254 plates in benzene–acetone (4:1), benzene–acetone (2:1), and benzene–acetone (7:3) systems, respectively; the chromatograms were developed with a 1% solution of vanillin in a 10% solution of perchloric acid, and a solution of phosphomolybdic acid in alcohol. The values of $[\alpha]_D^{20}$ were determined on an A1-EPL polarimeter.

21-Acetate of 6α-Fluoro-9α-bromo-16A,17α-isopropylidenedioxypregna-1,4-diene-11β,21-diol-3,20-dione (II). A 24.6 ml portion of 10% perchloric acid is added at 15°C to a solution of 22 g of I in 220 ml of tetrahydrofuran, and 8.6 g of dibromantin is added in four portions during 30 min. To complete the process, the reaction mixture is stirred for another 40 min at the same temperature, and then 4.6 ml of a 10% solution of sodium bisulfite is added, and 220 ml of water for complete separation of the steroid. The residue is filtered, washed with water to a neutral reaction, and used in the following stage without drying.

6α-Fluoro-9β,11-epoxy-16α,17α-isopropylidenedioxypregna-1,4-diene-21-ol-3,20-dione (III). A solution of 33 g of crude bromhydrin II in 1.32 liter of methanol is cooled to 2-4°C, and 4.4 ml of 5% sodium hydroxide is added. The reaction is carried out in an inert gas current. After stirring for 1 h, the reaction mixture is acidified with 0.2 ml of acetic acid, and methanol is evaporated in vacuo to dryness. The residue is ground with water and filtered. Yield, 15 g (72.3%), mp 218.5°C (decomp.), $[\alpha]_D^{20}$ +63° (c 1, chloroform), $E_{1cm}^{1\%}$ 356 at 246 nm. An analytical sample was obtained by purification of the epoxy compound III from acetone. (Found, %: C 66.30; H 6.85; F 4.5. $C_{24}H_{29}FO_6$. Calculated, %: C 66.65; H 6.76; F 4.39.

6α,9α-Difluoro-16α,17α-isopropylidenedioxypregna-1,4-diene-11β,21-diol-3,20-dione (IV, Fluocinolone Acetonide). A 4.6-g portion of epoxy compound III is added in portions, with stirring, to 30 ml of 70% hydrofluoric acid placed in a polyethylene beaker and cooled to −15°C. The reaction mixture is stirred for 1 h at the same temperature, and then for 1.5 hours at 0°C, and poured onto a mixture of 25% aqueous ammonia with ice. The reaction product which precipitated is extracted with methylene chloride (3 times with 100 ml), and the extract washed twice with water. The unextracted tetraol V, which separated out in the aqueous washings, is filtered and washed with a small amount of cold acetone. Thus, 1.83 g of tetraol V is obtained, mp 263-267°C (ethyl acetate−methanol) (according to literature data [3], mp 266-268°C.) A suspension of 1.83 g of V in 50 ml of acetone is heated to boiling with 0.5 ml of 57% perchloric acid. After cooling, 170 ml of methylene chloride is added to the reaction mixture, which is then washed twice with water and combined with the main extract of IV. The combined extract is filtered through 16 g of aluminum oxide, and the filtrate is treated with 1 g of activated charcoal. After distillation of the solvent in vacuo (to beginning of crystallization), the residue is diluted with an equal volume of hexane. The precipitate is filtered and dried under vacuo at 100°C for 1 h. Thus, 3.12 g of fluocinolone acetonide IV is obtained. Yield 67%, mp about 260°C, $[\alpha]_D^{20}$ +96° (c 1, dioxane), $E_{1cm}^{1.5\%}$ 0.523 at 242 nm (according to literature [3], mp 265-266°C, $[\alpha]_D^{20}$ +95°).

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INDUSTRIAL HYGIENE IN THE MANUFACTURE OF MEDICINAL PREPARATIONS FOR INJECTIONS (REVIEW)

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According to present-day requirements on the quality of medicinal preparations for intravenous administration, it is necessary to remove from the production area the sources of mechanical and microbiological particles, since these particles, present in the atmosphere of the premises, may contaminate the preparations. The results of numerous studies carried out on such premises show that one of the main sources of dust are the working personnel [1-3].

It has been found that man constantly discharges aerosol particles in a number varying from 1000 to 30,000,000 per minute, depending on the nature of the movements performed by him [4]. The source of the particles separating out from a working man is mainly his skin [5], through which up to 7 g of dense perspiration substances, 20 g of fat [6], as well as several thousand dry particles of skin coating containing microorganisms [7] pass per day into the surrounding environment. Studies [1] have shown that an especially active source of aerosol particles is the hairy part of the head. Moreover, there are data on an abundant separation of microbiological particles during expiration (11,600 microorganisms per hour), and especially during speaking (up to 5000 bacteria per minute) [7].

Since it is impossible to completely remove all the personnel from the production areas, it is important to protect the atmosphere of the production area from particles emitted by man. The problem arises of the preparation of the personnel before entering the production area so that they will emit the smallest possible number of aerosol particles.

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