IMPROVED METHOD FOR THE PREPARATION OF DIETHYLSTILBESTROL FROM 4,4-BIS(p-ACETOXYPHENYL)-3-HEXANONE

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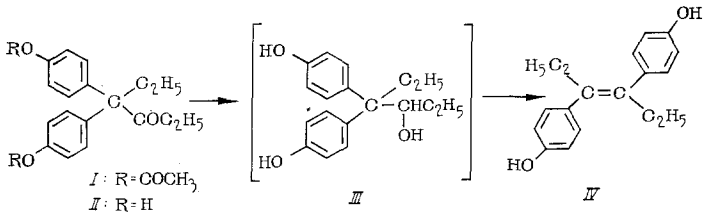
Of the large number of extant methods for preparation of diethylstilbestrol [1], that of Adler et al., [2], in which the starting compounds are phenol and propionic acid, has acquired practical significance. Technically the most complex stage in this method is the reduction of the keto group in 4,4-bis(p-acetoxyphenyl)-3-hexanone (I) to the pinacolyl alcohol (III), which gives diethylstilbestrol (IV) by retropinacol rearrangement.



The recommended procedure for reduction specifies forcing conditions (sodium in refluxing butyl or isopropyl alcohol) because of the low reactivity of the keto group, which is sterically shielded by the two phenyl and the ethyl groups, in pinacolin ketone diacetate I.

We have examined the stage of the reduction of I to III and the stage of retropinacol rearrangement of III to IV. We used complex metal hydrides with the aim of developing a method of reduction more suitable for use under industrial conditions. We found that only calcium borohydride, which, in contrast to the majority of alkali-metal and alkaline earth metal borohydrides, has high reducing activity [3] and does not form solvates, is capable of reducing this sterically hindered keto group to form carbinol III. The reaction was carried out in solution in aqueous isopropyl alcohol in the cold. Thin-layer chromatography revealed that the reaction gives almost quantitative yield. Because carbinol III is an oily product, we carried out the subsequent reaction without isolating compound III.

We selected the conditions for the preparation of transdiethylstilbestrol by retropinacol rearrangement of III on the basis of gas-chromatographic analysis of the reaction mixture. The method is based on the chromatography of trimethylsilyl (TMS) ethers of the cis- and trans-isomers of IV, derived by reaction with bis-(trimethylsilyl)acetamide (BSA) [4].

We examined the behavior of the trans-isomer IV in various solvents to reduce the possible isomerization of trans-IV to the cis-isomer during treatment of samples of the reaction mixture and preparation of the TMS ethers. We found that the most suitable solvents for preparing the TMS ethers of IV present in the reaction mixture are tetrahydrofuran and acetone. We extracted the reaction products from the reaction mixture with ethyl acetate, in which only 2% isomerization of trans-IV takes place in a short time [4].

We used this GLC method to analyze the composition of the reaction mixture in the course of the retropinacol rearrangement by adding hydrochloric acid to the solution of III in isopropyl alcohol and then stripping off the isopropyl alcohol.

We found that the diethylstilbestrol content (80-81%) of the reaction solution is a maximum when removal of isopropyl alcohol is complete, i.e., when the vapor temperature rises to 90-93°C. Under the conditions of the rearrangement we detected almost no isomerization of trans-IV; GLC revealed that the content of the cis-isomer did not exceed 3-4%.

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EXPERIMENTAL

The GLC analyses were carried out on an LKhM-8MD model 5 with a double flame-ionization detector. Chromatographic conditions were: column length 60 cm and internal diameter 0.3 cm, packed with 2.5% NSKT-50 on Chromosorb HMDS 80-100 mesh; column temperature 149-150°C.

Sample Preparation for Chromatography. The dry residue containing a mixture of cis- and trans-isomers of IV (about 0.5 g), derived by treatment of a sample of the reaction mixture, was dissolved in anhydrous acetone (10 ml). This solution (0.5 ml) was transferred to a 5-ml graduated flask and BSA (0.5 ml) was added. The solution was brought to the mark with anhydrous tetrahydrofuran, stirred, and left at room temperature for 30 min (by this time the formation of TMS ethers was complete). This solution (1-1.2 ml) was chromatographed. The order of elution of the components was: solvent and excess BSA; TMS ether of cis-IV; an unidentified impurity, possibly the TMS ether of 3,4-bis(p-hydroxyphenyl)-2-hexene [4]; and the TMS ether of trans-IV.

Treatment of Samples of the Reaction Mixture. The reaction mixture (about 30 ml) was diluted with water (fivefold quantity), transferred to a separating funnel, and extracted with ethyl acetate. The organic layer was washed with water until neutral, dried, and evaporated to dryness at a temperature not higher than 30°C. The residue was dried in a vacuum dessicator over calcium chloride for 24 h.

3,4-Bis(p-hydroxyphenyl)-3-hexene (IV, Diethylstilbestrol). Compound I (16.25 g, 0.044 mole) was hydrolyzed in refluxing 1% sodium hydroxide solution in isopropyl alcohol (325 ml) for 1 h. After the reaction calcium chloride (28 g, 0.25 mole) was added. The mixture was cooled to a temperature between −10 and −12°C and sodium borohydride (8.64 g, 0.22 mole) was added. The mixture was stirred at a temperature between −10 and −12°C for 16 h. After the usual treatment a solution of III in isopropyl alcohol was separated and concentrated hydrochloric acid (25 ml) was added. The solution was evaporated until the vapor temperature reached 90-93°C. Crystallization from aqueous isopropyl alcohol gave IV (8.3 g) with mp 170-171°C [1]. The yield was 70% based on I.

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