

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Synthesis of Dihydrodiethylstilbestrol

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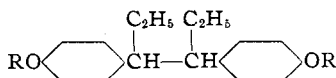
Dihydrodiethylstilbestrol (I) is an interesting estrogenic agent whose potency is of the same order as that of estrone and estradiol. A lower melting diastereomer (II) is relatively inert although biologically active in large doses.¹ The high-melting form was required in quantity for a project in endocrinology, and the present paper describes the synthesis which was developed.

There are several published methods of preparing dihydrodiethylstilbestrol (I), but none is satisfactory. It was first discovered in the de-

yield the desired isomer when hydrogenated in acetone over palladized charcoal. 3,4-Di-(*p*-hydroxyphenyl)-2,4-hexadiene is reported to give I in almost quantitative yield, but the parent diene is made by a difficult procedure involving *p*-hydroxypropiophenone pinacol. In another laboratory¹ diethylstilbestrol dimethyl ether has been converted to the corresponding oxide which on subsequent catalytic reduction leads to the proper phenol ether (III) in 30% yield. The method has much to recommend it, but the large number of steps in the synthesis, beginning with anisaldehyde, make it too prolonged to be practical.

Hydrogenation methods, in our hands, proved to be disappointing. Contrary to the finding of Dodds and co-workers, the hydrogenation of diethylstilbestrol dimethyl ether in acetone over palladized charcoal, due to an inexplicable difference in catalyst,⁴ gave the low-melting diastereomer (IV) exclusively. Identical results were obtained with Raney nickel and with copper chromite. Diethylstilbestrol, hydrogenated in alcohol over Raney nickel, produced the wrong isomer (II) quantitatively.

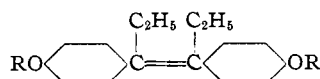
As an entirely different approach to the problem we have found that dihydrodiethylstilbestrol can be prepared by a short and direct method from the oily, unstable, hydrogen bromide addition product of anethole described long ago by Orndorff and Morton.⁵ The structure of anethole hydrobromide is not known with certainty because rapid decomposition, even at room temperature, makes purification impossible. However, along with polymeric material, it undoubtedly contains a great deal of the α -bromo derivative (XI). We have demonstrated this by coupling the product by means of magnesium in dry ether. There is formed an oil from which the high-melting ether (III) may be recovered in 15–20% yield. Smaller amounts of the low-melting form (IV) are found in the residue of higher polymers. The ether (III) is smoothly demethylated with alcoholic potassium hydroxide³ to give dihydrodiethylstilbestrol in nearly quantitative yield.



II R = H, m. p. 128°

III R = CH₃, m. p. 146°

IV R = CH₃, m. p. 56°

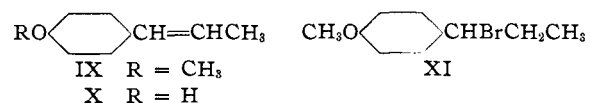


VI R = H, m. p. 142°

VII R = CH₃, m. p. 124°

VIII R = CH₃, liquid

methylation products of anethole (IX)² where its presence as a persistent impurity led to the erroneous conclusion that anol (X), the normal demethylation product, has estrogenic action. The yield is negligible.



Campbell, Dodds and Lawson² have synthesized it in about 1% yield by the action of ethylmagnesium bromide on anisaldehyde. Methods of hydrogenation have also been investigated,³ since diethylstilbestrol (V), its geometrical isomer (VI) and the respective dimethyl ethers (VII and VIII) are now available compounds. Hydrogenation of diethylstilbestrol gives a mixture in which the low-melting isomer (II) predominates. Pseudo-diethylstilbestrol (VI) also gives a mixture. The dimethyl ether (VII) is said to

(1) Kirschbaum, Kleedorfer, Prillinger, Wessely and Zajic, *Naturwissenschaften*, **27**, 131 (1939).

(2) Campbell, Dodds and Lawson, *Proc. Roy. Soc. (London)*, **B128**, 253 (1940).

(3) Dodds, Golberg, Lawson and Robinson, *ibid.*, **127**, 140 (1939).

(4) Our catalyst was prepared by the method of Hartung, *This Journal*, **50**, 3370 (1928).

(5) Orndorff and Morton, *Am. Chem. J.*, **23**, 194 (1900).

The many modifications of the method which were tried are mentioned in the Experimental Part. The over-all yield of dihydrodiethylstilbestrol is 10–15%, based on the anethole. This is not large, but the cheapness of the starting material and the shortness of the working time give the procedure many advantages.

Experimental Part

3,4-Dianisylhexane.—Dry hydrogen bromide was passed into a solution of 50 g. of anethole in 200 cc. of petroleum ether (b. p. 40–60°) cooled in an ice-salt-bath. A part of the anethole crystallized but soon redissolved. After twenty minutes a sample showed no evidence of unsaturation when tested with bromine in chloroform. The flask was removed from the cooling bath, connected to the water pump, and a capillary tube was arranged so that a current of dry air was drawn through the solution. The petroleum ether was evaporated until the volume was down to about 70 cc. The yellow solution was decanted from a small amount of insoluble material and taken up in 300 cc. of dry ether. It was added to 5.4 g. of magnesium covered with 50 cc. of ether in the conventional Grignard apparatus at such a rate that gentle refluxing was maintained. After addition was complete, a warm water-bath was used for an additional hour of refluxing. At this point a sample on dilution with water was acid in reaction, and hence no Grignard reagent was present. Water was cautiously added until no more reaction occurred, and the ether layer was separated. The water layer was extracted once with ether; the combined ether fractions were washed with water and dilute sodium bicarbonate, dried over sodium sulfate and evaporated to a sirup. Fifty cc. of petroleum ether (b. p. 60–68°) was added and the solution was left in the refrigerator overnight. The crystals were removed by filtration, washed with petroleum ether, and dried. The yield of crude product in this fraction, melting at 137–140°, was 8 g.

The product as isolated at this stage is suitable for demethylation because the phenol is very easy to purify. However, it crystallized well with little loss from alcohol or petroleum ether. A sample for analysis melted at 144–145°.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8. Found: C, 80.4; H, 9.0.

The petroleum ether mother liquors were concentrated and distilled at low pressure. The yield of distillable oil

varied considerably from one run to another. Usually 5–15 g. was obtained boiling at 155–190° at 0.2 mm. This was diluted with 3 cc. of petroleum ether and after twelve hours in the refrigerator 1–3 g. more of dianisylhexane separated.

The residual oil was obviously a mixture. A 10-g. fraction when allowed to stand in the refrigerator for a month deposited 3.1 g. of the low-melting isomer (IV) which after crystallization from methanol melted at 55–57° and did not depress the melting point of the same product obtained by the hydrogenation of diethylstilbestrol dimethyl ether.

Further evidence for the presence of the isomer in the residual oil was obtained by demethylation with alcoholic potassium hydroxide as described below. The phenol fraction from a 10-g. lot gave, after crystallization from benzene-petroleum ether, 1 g. of the low-melting phenol (II). It was identical with the hydrogenation product of diethylstilbestrol; m. p. and mixed m. p. 128°.

Modifications of the dianisylhexane synthesis were as follows. In the addition of hydrogen bromide to anethole, methylene chloride was also found to be a suitable solvent. The final yield was the same. Substitution of hydrogen chloride for hydrogen bromide was a complete failure. Sodium, as a coupling agent, gave a very small yield, due, probably, to the prolonged heating necessary for complete reaction. Coupling at low temperatures offered no advantage nor did a reversal of the order of the reaction by the slow addition of magnesium to the hydrogen bromide addition product. The use of copper chloride to promote coupling⁶ did not improve the yield, and the practice was given up when it was discovered that no Grignard reagent was formed.

Dihydrodiethylstilbestrol.—Dianisylhexane was demethylated by the published method.² For example, 10 g. of the phenol ether was placed in a steel bomb with 20 g. of potassium hydroxide and 40 cc. of alcohol and heated to 225° for eighteen hours. There was an insignificant neutral fraction. The phenol was crystallized from benzene. The yield was practically quantitative; m. p. 185–186°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2. Found: C, 79.6; H, 8.5.

Summary

A procedure is described for the synthesis of dihydrodiethylstilbestrol (m. p. 186°) from anethole.

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(6) Conant and Blatt, *THIS JOURNAL*, **50**, 555 (1928).