

[CONTRIBUTION FROM THE ARMOUR LABORATORIES]

Preparation of New Derivatives of Diethylstilbestrol and Hexestrol. II. Extension of the Claisen Rearrangement

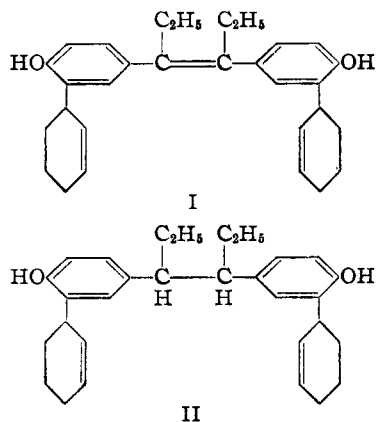
BY EMIL KAISER, A. L. ANDERSEN, JR., AND J. J. SVARZ

Rearrangement of the diallyl ethers of diethylstilbestrol and hexestrol to the corresponding 3,3'-disubstituted derivatives has been reported.¹

These investigations were extended to the study of the behavior of the di-2-cyclohexene-1-yl ethers of synthetic estrogens. Heretofore only one other application of the Claisen rearrangement to 2-cyclohexene-1-yl phenol ethers has been described.² The 2-cyclohexene-1-yl ether of phenol was pyrolyzed at 215° yielding 5% of *o*-cyclohexene-2-phenol.

The di-2-cyclohexene-1-yl ether of diethylstilbestrol was prepared by two different methods: Method I, the reaction between 1-bromocyclohexene-2, diethylstilbestrol and potassium carbonate in methyl ethyl ketone; Method II, the reaction between 1,2-dibromocyclohexane and diethylstilbestrol in the presence of sodium alcoholate. Method I yielded 12% of the theoretical amount of di-2-cyclohexene-1-yl ether of diethylstilbestrol. Method II, an adaptation of the procedure of Solonina,³ yielded 25 to 35% of the same compound. Method II was therefore used to prepare the dicyclohexene ether of hexestrol.

The di-2-cyclohexene-1-yl ethers were rearranged to the 3,3'-disubstituted derivatives by refluxing in diethylaniline in an atmosphere of nitrogen. 3,3'-Di-(2-cyclohexene-1-yl)-diethylstilbestrol (I) was isolated in a 25% yield and 3,3'-di-(2-cyclohexene-1-yl)-hexestrol (II) in a 38% yield.



A better yield of rearrangement products averaging 65 to 67% was obtained by the use of benzoic anhydride in the reaction mixture. The dibenzoates of the 3,3'-disubstituted products were formed in this reaction. Saponification of

the dibenzoates yielded 3,3'-di-(2-cyclohexene-1-yl)-diethylstilbestrol and 3,3'-di-(2-cyclohexene-1-yl)-hexestrol, respectively. These compounds were identical to those formed by the rearrangements of the di-2-cyclohexene-1-yl ethers without the use of benzoic anhydride.

Experimental⁴

Di-2-cyclohexene-1-yl Ether of Diethylstilbestrol. **Method I.**—Diethylstilbestrol and 1-bromocyclohexene-2 were treated in the same manner as described for allyl phenyl ether.⁵

The di-2-cyclohexene-1-yl ether of diethylstilbestrol was crystallized from methanol, m. p. 118–119°, yield 12.1%.

Method II.—Twenty grams of 1,2-dibromocyclohexane was added to a solution prepared by dissolving 4 g. of sodium and 10.72 g. of diethylstilbestrol in 100 ml. of absolute ethanol and the mixture refluxed for twenty-four hours. The solution was then concentrated under reduced pressure and treated with a solution of 10 g. of sodium hydroxide in 100 ml. of water. The alkaline solution was extracted with ethyl ether and the ether layer washed with 100 ml. of 10% aqueous sodium hydroxide and water. The ether was removed by distillation and the residue crystallized twice from 100-ml. portions of 95% ethanol; m. p. 117–119°; yield 4.43 g. (25.3%).

Anal. Calcd. for $C_{30}H_{36}O_2$: C, 84.08; H, 8.46. Found: C, 84.08; H, 8.57.⁶

Preparation of 3,3'-Di-(2-cyclohexene-1-yl)-diethylstilbestrol.—Two grams of the di-2-cyclohexene-1-yl ether of diethylstilbestrol was dissolved in 15 ml. of diethylaniline and the solution refluxed for seven hours in an atmosphere of nitrogen. The diethylaniline was removed and the product crystallized from an ethyl ether-petroleum ether mixture as described for 3,3'-diallyldiethylstilbestrol.¹ The substance was recrystallized by dissolving in 10 ml. of ethanol and adding 10% of water to the hot solution; yield 0.5 g. (25%), m. p. 154–156°.

Anal. Calcd. for $C_{30}H_{36}O_2$: C, 84.08; H, 8.46. Found: C, 83.62; H, 8.86.⁷

Preparation of the 3,3'-Di-(2-cyclohexene-1-yl)-diethylstilbestrol Dibenzoate.—One and a half grams of the di-(2-cyclohexene-1-yl)-diethylstilbestrol and 3 g. of benzoic anhydride were dissolved in 15 ml. of diethylaniline and refluxed for six hours in an atmosphere of nitrogen. After cooling 100 ml. of 2 *N* hydrochloric acid was added and the mixture extracted with ether. The ether layer was washed with 2 *N* acid, water, and dried over sodium sulfate. It was then concentrated to about 15 ml. and 30 ml. of methanol added. The dibenzoate crystallized in the cold. It was recrystallized by dissolving in 15 ml. of carbon tetrachloride and adding 30 ml. of methanol; yield 1.5 g., m. p. 188–199°.

(4) All melting points uncorrected.

(5) Claisen, *Ann.*, **418**, 69 (1919).

(6) Analysis made at the California Institute of Technology, Pasadena, California.

(7) Figures obtained for the percentage of carbon were consequently lower than the calculated values, regardless whether the compound was obtained by rearrangement of the ether or by saponification of the dibenzoate. The carbon values of the dibenzoate checked well with the calculated values. Such irregularities have been reported previously for 4,4'-dioxo-2,2-methyl- α,β -diphenylbutane by Bretschneider, de Ionzee Bretschneider and Ajtai, *Ber.*, **74**, 571 (1941).

(1) Kaiser and Svarz, *THIS JOURNAL*, **68**, 636 (1946).

(2) Cornforth, Hughes and Lions, *J. Proc. Roy. Soc., N. S. Wales*, **71**, 323 (1938).

(3) W. Solonina, *J. Chem. Soc.*, **76**, I, 681 (1899).

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 82.98; H, 6.97. Found: C, 82.96; H, 7.15.⁶

Saponification of 3,3'-Di-(2-cyclohexene-1-yl)-diethylstilbestrol Dibenzoate.—One-half gram of 3,3'-di-(2-cyclohexene-1-yl)-diethylstilbestrol dibenzoate was refluxed for two hours in an atmosphere of nitrogen with 10 ml. of a 10% potassium hydroxide-isopropanol solution. After cooling the mixture was diluted with 30 ml. of water and acidified with *N* hydrochloric acid. An oil precipitated which solidified on standing at room temperature. This was filtered, washed with water and dissolved in 10 ml. of ethanol. The solution was clarified with a small amount of charcoal. After filtration 10% of water was added and the solution cooled. Crystals were obtained which melted at 153–156° and were identical to the 3,3'-di-(2-cyclohexene-1-yl)-diethylstilbestrol obtained by rearrangement of the ether; yield 0.15 g.

Anal. Calcd. for $C_{30}H_{38}O_2$: C, 84.08; H, 8.46. Found: C, 83.25; H, 8.56.⁸

Di-2-cyclohexene-1-yl Ether of Hexestrol.—Ten and eight-tenths grams of hexestrol was treated in the same manner as described in Method II for the preparation of the di-2-cyclohexene-1-yl ether of diethylstilbestrol. The product obtained after treatment with alkali was crystallized twice from 95% ethanol; m. p. 123–124°, yield 5.86 g. (34.1%).

Anal. Calcd. for $C_{30}H_{38}O_2$: C, 83.66; H, 8.89. Found: C, 83.57; H, 8.68.⁶

3,3'-Di-(2-cyclohexene-1-yl)-hexestrol.—This compound was prepared in the manner described for 3,3'-di-(2-cyclohexene-1-yl)-diethylstilbestrol. One and a half grams of the di-2-cyclohexene-1-yl ether of hexestrol yielded 0.58 g. of rearranged product; m. p. 169–171°.

Anal. Calcd. for $C_{30}H_{38}O_2$: C, 83.66; H, 8.89. Found: C, 83.4; H, 9.06.⁶

3,3'-Di-(2-cyclohexene-1-yl)-hexestrol Dibenzoate.—This compound was prepared in the manner described for

3,3'-di-(2-cyclohexene-1-yl)-diethylstilbestrol dibenzoate. One gram of the di-2-cyclohexene-1-yl ether of hexestrol when treated with 2 g. of benzoic anhydride in diethyl-aniline and crystallized from a carbon tetrachloride-methanol mixture yielded 0.98 g. of a product melting at 198–201°. Repeated analysis showed the existence of one mole of methanol of crystallization.

Anal. Calcd. for $C_{44}H_{56}O_4 \cdot CH_3OH$: C, 80.56; H, 7.51. Found: C, 80.64,⁶ 80.51,⁸ 80.80⁹; H, 7.06,⁶ 7.25,⁸ 6.95.⁹

The methanol of crystallization was removed by drying in high vacuum.

Anal. Calcd. for $C_{44}H_{56}O_4$: C, 82.72; H, 7.29. Found: C, 82.04; H, 7.47.⁹

3,3'-Di-(2-cyclohexene-1-yl)-hexestrol Dipropionate.—Twenty-seven hundredths of a gram of 3,3'-di-(2-cyclohexene-1-yl)-hexestrol was refluxed with 10 ml. of propionic anhydride for two and one-half hours. The product obtained after hydrolysis of the mixture with water was crystallized twice from 95% ethanol; yield 0.15 g., m. p. 133.5–135°.

Anal. Calcd. for $C_{38}H_{46}O_4$: C, 79.66; H, 8.54. Found: C, 79.5; H, 8.46.⁸

Summary

The di-2-cyclohexene-1-yl ethers of diethylstilbestrol and hexestrol have been prepared by two methods. Application of the Claisen rearrangement to these compounds produced the corresponding 3,3'-disubstituted derivatives. Use of benzoic anhydride in the rearrangement of the ethers increased the yield considerably.

(9) Analysis made by Dr. Joseph F. Alicino, Metuchen, New Jersey.

(8) Analysis made by Dr. Charles W. Beazley, Skokie, Illinois.

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Structure Determination and Synthesis of a Plant Growth Inhibitor, 3-Acetyl-6-methoxybenzaldehyde, Found in the Leaves of *Encelia Farinosa*

BY REED GRAY AND JAMES BONNER

Introduction

In a recent publication¹ it was demonstrated that the leaves of *Encelia farinosa* when applied to tomato and to other plants exert a marked inhibition of growth. The toxic principle was removed by extracting the dry *Encelia* leaves with purified ether. Water and ether extracts of the *Encelia* leaves, when fed to tomato seedlings in solution culture, caused death of the plants within one day. Fractionation of the leaf extracts led to the isolation of a pure crystalline compound which was toxic when fed to tomato seedlings in solution culture. It was suggested that the presence of the growth inhibitor in the leaves may be responsible for the fact that only few individuals of desert annuals are found growing in close relationship with the *Encelia* shrub on the desert.

The present work is concerned with the charac-

terization and synthesis of this new toxic compound which was isolated from the *Encelia* leaves.

Experimental

Physical and Chemical Properties.—The toxic material crystallizes in colorless needles from ether or alcohol, m. p. 144°. Sublimation causes no change in melting point. The compound has no odor but when the crystals are heated a pleasant perfume-like odor is detected. It burns with a smoky flame leaving no residue after ignition. A sodium fusion showed the absence of nitrogen, sulfur and halogens. Evidently the compound is composed only of the elements carbon, hydrogen and oxygen. The compound is soluble in hot water, warm ether, alcohol, acetone, benzene and chloroform. It is insoluble in cold water, 5% hydrochloric acid, 5% sodium hydroxide, petroleum ether and carbon tetrachloride. It dissolves in

(1) Gray and Bonner, *Am. J. Bot.*, Jan. (1948).