α-methyl-β-phenylpropionamide, m. p. 104–106°; when this was mixed with an authentic sample of the amide (m. p. 108.5°) the mixture melted at 106–108°. No solid separated from the oil obtained from the carbinol. The Skelly A was removed by distillation and the oil was extracted with boiling water. Concentration of the aqueous extract to a small volume, followed by refrigeration, yielded *ca.* 100 mg. of crystalline amide, m. p. 105–107°, undepressed when mixed with an authentic sample of α-methyl-β-phenylpropionamide.

Summary

A mechanism has been proposed for the Willgerodt reaction. This mechanism has been supported by experimental results and it has been demonstrated how all of the previously existing data on the reaction fit into this mechanism.

The reaction has been extended to a number of ketones, alcohols and olefins to which the Willgerodt reaction has not previously been applied.

RENSSELAER, NEW YORK RECEIVED SEPTEMBER 22, 1945

[CONTRIBUTION FROM THE ARMOUR LABORATORIES]

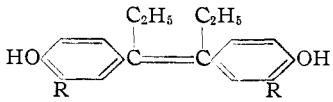
Preparation of New Derivatives of Diethylstilbestrol and Hexestrol by the Claisen Rearrangement[1]

BY EMIL KAISER AND J. J. SVARZ

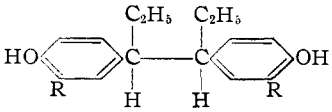
The influence of various aliphatic radicals and unsaturated groups on the estrogenic activity of α,α′-substituted stilbestrol has been thoroughly investigated by Dodds, Golberg, Lawson and Robinson[2]; however, the introduction of these groups into the aromatic nuclei of diethylstilbestrol and hexestrol has not been described. Therefore we decided to prepare a new series of 3,3′-allyl, propenyl and propyl substituted synthetic estrogens by applying the Claisen rearrangement[3] to the diallyl ethers of diethylstilbestrol and hexestrol. The diallyl ethers of diethylstilbestrol and hexestrol, not previously described, were prepared by reacting diethylstilbestrol and hexestrol with allyl bromide in the presence of potassium carbonate in methyl ethyl ketone. The Claisen rearrangement of the diallyl ethers yielded 3,3′-allyldiethylstilbestrol (I) and 3,3′-allylhexestrol (II). Both compounds were benzoylated and the benzoic esters were found to be insoluble in ether. By heating the 3,3′-allyldiethylstilbestrol and 3,3′-allylhexestrol in a solution of potassium hydroxide in diethyleneglycol according to Fletcher and Tarbell,[4] a shifting of the double bonds in the side chains occurred and the corresponding propenyl derivatives were formed. The reaction did not proceed smoothly. The solution turned dark and the product was mostly resinified even when the heating was carried out in an atmosphere of nitrogen. The 3,3′-propenyldiethylstilbestrol (III) and 3,3′-propenylhexestrol (IV) were obtained in low yields. To improve the yields a small amount of concentrated sodium hydrosulfite solution was added to the reaction mixture. Although little of the sodium hydrosulfite dissolved in the diethyleneglycol, losses due to discoloration and resinification were greatly reduced and the yields improved.

The 3,3′-propenyldiethylstilbestrol and 3,3′-propenylhexestrol have the double bonds of the side chains in a conjugated position to the double bonds of the aromatic nuclei. This configuration renders both compounds susceptible to light. Exposed to light the 3,3′-propenyldiethylstilbestrol turns yellow much faster than the 3,3′-propenylhexestrol.

The 3,3′-allylhexestrol was hydrogenated over platinum oxide and the saturated 3,3′-propylhexestrol (V) isolated and crystallized.



I, R = $CH_2CH{=}CH_2$
III, R = $CH{=}CHCH_3$



II, R = $CH_2CH{=}CH_2$
IV, R = $CH{=}CHCH_3$
V, R = $CH_2CH_2CH_3$

The estrogenic activities of the new compounds, compared with estrone as a standard, are shown in Table I.

Introduction of the propenyl groups into the aromatic nuclei of diethylstilbestrol results in the greatest loss of activity in this series. The 3,3′-propenyldiethylstilbestrol is $^1/_{1250}$ to $^1/_{2500}$ as strong in estrogenic activity as the diethylstilbestrol. Dodds, Golberg, Lawson and Robinson[2] found that the substitution of the α,α′-ethyl groups by propenyl groups causes a 150-fold drop of estrogenic activity. This loss is only about one-tenth as much as the loss of estrogenic activity caused by the substitution into the aromatic nuclei.

(1) Paper given at the November, 1945, meeting of the Chicago Section of the American Chemical Society at the Northwestern Institute of Technology, Evanston, Illinois.

(2) (a) Dodds, Golberg, Lawson and Robinson, *Nature*, **141**, 247 (1938); (b) *ibid.*, **142**, 34 (1938); (c) *Proc. Roy. Soc.* (London), **127B**, 140 (1939).

(3) "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 1.

(4) Fletcher and Tarbell, THIS JOURNAL, **65**, 1431 (1943).

TABLE I

Substance	Assay method[a,b] Immature mice, %	Spayed rats, %
Estrone (standard)	100	100
Diethylstilbestrol	250	150-200
Diallyl ether of diethylstilbestrol	1-2	0.5-0.8
3,3'-Allyldiethylstilbestrol	10-20	6-7
3,3'-Propenyldiethylstilbestrol	0.1-0.2	.....
Diallyl ether of hexestrol	1	1
3,3'-Allylhexestrol	<4	1-2
3,3'-Propenylhexestrol	<4	<1
3,3'-Propylhexestrol	>0.5	.....

[a] Evans, Varney and Koch, *Endocrinology*, **28**, 747 (1941). [b] Koch, *ibid.*, **31**, 162 (1942).

Acknowledgment.—The authors wish to thank Professor F. C. Koch for his helpful advice during the course of this work and Mr. E. G. King for performing the biological assays reported in this paper.

Experimental[5]

Preparation of the Diallyl Ether of Diethylstilbestrol.—This compound was prepared in the same manner as described for allyl phenyl ether.[6] The diallyl ether of diethylstilbestrol was crystallized from isopropanol; m. p. 93-93.5°.

Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.76; H, 8.05. Found: C, 82.47; H, 8.24.

Preparation of 3,3'-Allyldiethylstilbesterol.—Nine grams of the diallyl ether of diethylstilbestrol was dissolved in 30 cc. of diethylaniline and the solution refluxed for four hours in an atmosphere of nitrogen. After cooling 400 cc. of 2 *N* hydrochloric acid was added and the emulsion extracted with ether. The ether layer was washed with *N* hydrochloric acid followed by a water washing and then evaporated to dryness. The residue was treated with a 10% potassium hydroxide solution and the cloudy alkaline solution clarified by filtration with a small amount of charcoal. The filtrate was acidified with hydrochloric acid and an oily precipitate settled out. The precipitate solidified after standing overnight and was filtered off. The substance was dried in a vacuum desiccator, then dissolved in 20 cc. of ether, and low boiling petroleum ether added until cloudiness developed. The cloudy solution was kept overnight at −5°. A sticky brown precipitate settled out and was removed by filtration. The almost colorless filtrate was concentrated and several volumes of petroleum ether added. By cooling to 5-10° a crystalline precipitate was formed which was filtered off. In a similar manner more material was crystallized out from the mother liquor. The combined fractions weighed 5.3 g. and melted at 101-101.5°. By fractional crystallization of this material 2.25 g. of 3,3'-allyldiethylstilbestrol was obtained with a melting point of 103-104°.

Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.76; H, 8.05. Found: C, 82.41; H, 7.94.

Preparation of the Dibenzoate of 3,3'-Allyldiethylstilbestrol.—In 5 cc. of methyl ethyl ketone 0.35 g. of 3,3'-allyldiethylstilbestrol and 0.30 g. of benzoyl chloride were dissolved, 0.40 g. of anhydrous potassium carbonate added and the solution refluxed for eight hours. The cooled solution was poured into 100 cc. of water and the mixture was allowed to stand at room temperature until the oily precipitate solidified. The solid was filtered off and dried in a desiccator. The dry substance was washed several times with ether, and then dissolved in a small amount of hot benzene. Ether was added and the ester crystallized out at −5°. The shiny crystals were recrystallized from an ether-benzene mixture; m. p. 187-188°.

Anal. Calcd. for $C_{38}H_{36}O_4$: C, 81.98; H, 6.52. Found: C, 82.25; H, 6.78.

Preparation of the Diacetate of 3,3'-Allyldiethylstilbestrol.—In 5 cc. of methyl ethyl ketone 0.7 g. of 3,3'-allyldiethylstilbestrol and 0.35 g. of acetyl chloride were dissolved. To the solution 0.85 g. of anhydrous potassium carbonate was added and the solution refluxed for eight hours. Then water was added and the precipitated oil extracted with ether. The ether layer was washed with alkali and with water, dried and the ether evaporated. The residue was crystallized twice from a mixture of ether and petroleum ether; m. p. 122-123°.

Anal. Calcd. for $C_{28}H_{32}O_4$: C, 77.74; H, 7.46. Found: C, 77.34; H, 7.94.

Preparation of 3,3'-Propenyldiethylstilbestrol.—Nine grams of potassium hydroxide was dissolved by heating and stirring in 50 cc. of diethylene glycol. Four and one-half grams of 3,3'-allyldiethylstilbestrol and 0.3 g. of sodium hydrosulfite dissolved in 2 cc. of water were added to the diethylene glycol solution. The reaction mixture was kept in an oil-bath of 170-180° for two hours in an atmosphere of nitrogen. After cooling the solution was diluted with water, acidified with hydrochloric acid and extracted with ether. The ether layer was washed with water, dried and concentrated by heating and bubbling nitrogen through the solution. To the concentrated ether solution petroleum ether was added until cloudiness developed. A dark oil separated after the solution was allowed to stand overnight at room temperature. This oil was discarded. The yellow upper layer was poured off and treated again with petroleum ether. This procedure was repeated until the upper layer became colorless. This was then concentrated in an nitrogen atmosphere to a small volume. Petroleum ether was added and the solution kept at 5-10°. The 3,3'-propenyldiethylstilbestrol crystallized out and was recrystallized from a mixture of ether-petroleum ether; m. p. 120-121°.

Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.76; H, 8.05. Found: C, 81.19; H, 8.30.[7]

From the 3,3'-propenyldiethylstilbestrol melting at 120-121° a very small amount of a fraction was obtained which softened at 122°, melted at 143-144°. This fraction crystallized out when a diluted ether-petroleum ether solution of the material melting 120-121° was kept at −5° for several days.

Preparation of the Diallyl Ether of Hexestrol.—This compound was prepared in the same manner as the diallyl ether of diethylstilbestrol; m. p. 81.5°.

Anal. Calcd. for $C_{24}H_{30}O_2$: C, 82.25; H, 8.62. Found: C, 82.05, 82.42; H, 8.37, 8.91.

Preparation of 3,3'-Allylhexestrol.—This compound was prepared in the same manner as the 3,3'-allyldiethylstilbestrol; m. p. 107°.

Anal. Calcd. for $C_{24}H_{30}O_2$: C, 82.25; H, 8.62. Found: C, 82.30; H, 8.67.[7]

Preparation of the Dibenzoate of 3,3'-Allylhexestrol.—This compound was prepared in the same manner as the dibenzoate of the 3,3'-allyldiethylstilbestrol. The crystals are insoluble in ether, m. p. 192°.

Anal. Calcd. for $C_{38}H_{38}O_4$: C, 81.69; H, 6.85. Found: C, 81.94; H, 7.05.

Preparation of 3,3'-Propenylhexestrol.—This compound was prepared in the same manner as the 3,3'-propenyldiethylstilbestrol. The compound softens at 148° and melts completely at 153-154°.

Anal. Calcd. for $C_{24}H_{30}O_2$: C, 82.25; H, 8.62. Found: C, 82.01; H, 8.54.

Preparation of 3,3'-Propylhexestrol.—Two-tenths of one gram of platinum oxide was suspended in 100 cc. of isopropanol and shaken with hydrogen at 45 lb. pressure. Then 0.5 g. of 3,3'-allylhexestrol was added and shaken

(5) Microanalyses were made at the California Institute of Technology, Pasadena, California.

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

(7) Analysis made by J. Alicino, Metuchen, New Jersey.

with hydrogen at 45 lb. pressure for eight more hours. The solution was filtered off and evaporated. The residue was crystallized from ether–petroleum ether in the same manner as the 3,3′-allyldiethylstilbestrol; m. p. 123.5–124.5°.

Anal. Calcd. for $C_{24}H_{34}O_2$: C, 81.31; H, 9.63. Found: C, 81.58; H, 9.49.

Summary

The Claisen rearrangement has been applied to the diallyl-ethers of diethylstilbestrol and hexestrol. The 3,3′-allyldiethylstilbestrol and 3,3′-allylhexestrol obtained in the rearrangement were transformed to 3,3′-propenyldiethylstilbestrol and to 3,3′-propenylhexestrol, respectively. The 3,3′-propylhexestrol has been prepared by hydrogenation of the 3,3′-allylhexestrol. All of the new compounds are weak estrogens.

CHICAGO, ILLINOIS RECEIVED DECEMBER 29, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF NELIO RESIN PROCESSING CORPORATION]

Nopol. I. The Reaction of β-Pinene with Formaldehyde

BY J. P. BAIN

There is described in the literature the addition of formaldehyde to numerous terpenes to yield mono- and polyhydric alcohols. The purity and structure of such products is questionable with the exception of 8-camphene carbinol prepared by Langlois[1] by condensation of paraformaldehyde and camphene in acetic acid solution.

Kriewitz[2] reported that pinene of boiling point 156–159° reacts with an alcoholic solution of paraformaldehyde at 170–175° to give an alcohol $C_{11}H_{18}O$ in 15% yield. He reported for this alcohol the following constants, b. p. 232–236°, d^{22}_4 0.961, strongly dextrorotatory. We have been unable to isolate an alcohol from α-pinene using the Kriewitz procedure though traces of alcohols seem to be formed.

In this Laboratory it has been found that β-pinene (nopinene) (I) and formaldehyde in the form of one of its substantially anhydrous polymers readily condense in equimolecular quantities to form a new optically active bicyclic primary alcohol, 6,6-dimethylbicyclo-(1,1,3)-hept-2-ene-2-ethanol, which has been named nopol (II). The pure alcohol possesses the following physical properties, $n^{25}D$ 1.4920, d^{25}_4 0.9647, b. p. 110.5° (10 mm.), $\alpha^{25}D$ −36.5° (10-cm. tube).

While β-pinene readily yields nopol under the conditions used by Kriewitz, the product is always levorotatory and is therefore not identical with the product reported by Kriewitz. Further, the densities of the two products are not in close agreement.

β-Pinene occurs to the extent of about 30% in American gum turpentine, its most important source, and is a constituent of numerous other volatile oils. Regardless of its source, it occurs almost without exception as the optically pure levo form, while α-pinene which generally accompanies it is found in either optically pure form or as a mixture of optical isomers. Like β-pinene, nopol is also an optically pure levo compound.

Nopol may be prepared by three general methods. (1) β-Pinene and paraformaldehyde in acetic acid solution at 120° yield nopyl acetate which is readily saponified to nopol. A number of side reactions occur during the condensation of hydrocarbon and formaldehyde, such as isomerization of nopol to monocyclic isomers, hydration of the β-pinene to fenchol and borneol, isomerization of β-pinene to α-pinene, camphene and *l*-limonene and formation of polyhydric alcohols by (a) hydration of nopol, (b) condensation of the monocyclic isomers of nopol with further formaldehyde, and (c) reaction of two or more molecules of formaldehyde with the various terpenes formed by isomerization of β-pinene. While fair yields of nopyl acetate and nopol are obtained by this method, it is evident that the separation of pure compounds is possible only by efficient fractionation.

(2) A better method for preparation of nopol consists of heating a mixture of β-pinene and paraformaldehyde in the presence of a small quantity of catalyst such as zinc chloride for several hours at 115–120°. Here the reaction is smooth and may be carried out at atmospheric pressure. While the yields are rather good some higher boiling monocyclic isomers of nopol are formed together with polymeric material.

(3) Almost quantitative yields of pure nopol, practically free of higher boiling isomers and polymers, are obtained by autoclaving paraformaldehyde and β-pinene at 150 to 230° for several hours. Unreacted β-pinene and nopol are readily separated from the reaction mixture by fractionation. Since other terpenes including α-pinene, camphene and dipentene show practically no reaction with formaldehyde under these conditions, nopol of high purity may be obtained readily from even quite crude β-pinene such as gum turpentine. While crude β-pinene may be used, or the reaction mixture may be diluted with such inert solvents as alcohol or benzene without appreciable sacrifice in purity of the nopol produced, lower yields are obtained even when the β-pinene is in considerable excess over that required by the formaldehyde. It is interesting to note that when 37–40% aqueous formaldehyde is used

(1) Langlois, *Ann. Chim.*, **12**, 265 (1919).
(2) Kriewitz, *Ber.*, **32**, 57 (1899).