Anal. Calcd. for $C_{11}H_{12}ON_3$: C, 66.36; H, 6.92. Found: C, 66.40; H, 7.05.

3-Methyl-1-naphthol,† previously synthesized by Fittig,[16] was prepared by dehydrogenation of the methyltetralone. Heating with selenium at 310–330° for twenty hours or with sulfur at 250° for thirty minutes afforded the methylnaphthol in yields of 25 and 30%, respectively. By brominating the methyltetralone in carbon bisulfide, removing the solvent, and then boiling the oily residue with dimethylaniline, the methylnaphthol was obtained in a satisfactory condition in 65% yield. The substance crystallized from petroleum ether in fine needles which melted initially at 91–93.5°, solidified, and remelted at 93.5–94°. The **benzoate** melted at 75–76°.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.44; H, 5.34. Found: C, 82.22; H, 5.38.

2-Methyl-1-tetralone† was prepared by cyclization of α-methyl-γ-phenylbutyryl chloride according to Schroeter, *et al.*,[17] and also, in 75% yield, by heating the acid with 80% sulfuric acid. The ketone boiled at 136–137° at 16 mm. pressure.

The **oxime** melts at 98–99°; the **semicarbazone** forms needles, m. p. 205–206°.

Anal. Calcd. for $C_{11}H_{12}ON_3$: C, 66.36; H, 6.92. Found: C, 66.49; H, 6.77.

2-Methyl-1-naphthol† was prepared from 2-methyl-1-tetralone by dehydrogenation with bromine (41% yield) and from 2-methyl-1-naphthylamine according to Lesser[18] (55% yield). The substance crystallized from petroleum ether as fluffy needles, m. p. 63–64°. The **benzoate** formed needles from ether–petroleum ether, m. p. 94–95°.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.44; H, 5.34. Found: C, 82.40; H, 5.69.

(16) Fittig, *Ann.*, **255**, 270 (1889); **314**, 73 (1901).
(17) Schroeter, Lichtenstadt and Irineu, *Ber.*, **51**, 1600 (1918).
(18) Lesser and Aczél, *Ann.*, **402**, 30 (1914).

The **acetate** separates from ether–petroleum ether as needles, m. p. 81–82°.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. Found: C, 78.15; H, 5.93.

Summary

By partial hydrogenation under suitable conditions vitamin K_1 and 2-methyl-3-cinnamyl-1,4-naphthoquinone can be converted into the corresponding β,γ-dihydrides. More drastic hydrogenation of the former compound affords the β,γ,5,6,7,8-hexahydride. The products are conveniently purified through their solid hydroquinones.

The 2,3-oxides of 2-substituted and 2,3-disubstituted 1,4-naphthoquonones having both saturated and β-unsaturated groups are easily prepared by the action of hydrogen peroxide and sodium carbonate. Vitamin K_1 oxide is a stable, colorless oil. The oxides of the 2-substituted series are easily cleaved by alkali, in part with elimination of the substituent group.

Piperylene adds to toluquinone in both possible directions, but one of the isomeric addition products is easily isolated and affords a ready source of 2,8-dimethyl-1,4-naphthoquinone.

Details are given of the preparation of the various methylnaphthols and methyltetralones assayed for antihemorrhagic activity.

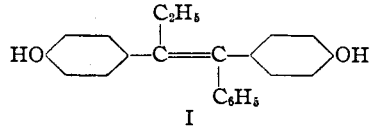
RAHWAY, NEW JERSEY
CAMBRIDGE, MASSACHUSETTS RECEIVED AUGUST 10, 1940

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Studies on the Preparation of Synthetic Sex Hormones. I. Hexoestrol

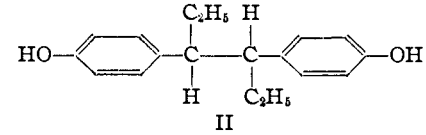
BY SEYMOUR BERNSTEIN AND EVERETT S. WALLIS

That relatively simple, synthetic organic compounds exhibit an oestrogenic activity is now well known. The number of oestrogens is amazingly large. Considerable interest has been centered upon diethylstilboestrol (I). The preparation of this highly interesting compound has been accomplished by Dodds, Robinson, *et al.*[1]



I

In 1938, Campbell, Dodds and Lawson reported the isolation, in poor yields, of a highly potent oestrogen from the products of the demethylation of anethole.[2] Later, it was shown that this compound was in reality *p,p'*-dihydroxydiphenylhexane (II) and was named *hexoestrol.*[1b,3]



II

It is evident that diethylstilboestrol, I, and

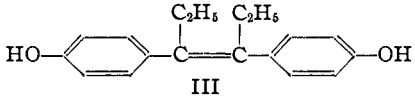
(1) E. C. Dodds, R. Robinson, *et al.*, (a) *Nature*, **141**, 247 (1938); (b) *Proc. Roy. Soc.* (London), **B127**, 140 (1939).

(2) N. R. Campbell, E. C. Dodds and W. Lawson, *Nature*, **142**, 1121 (1938).

(3) N. R. Campbell, E. C. Dodds and W. Lawson, *Proc. Roy. Soc.* (London), **B128**, 253 (1940).

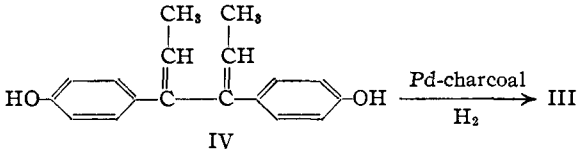
hexoestrol, II, differ chemically in degree of saturation. They also differ in their oestrogenic activity, hexoestrol being the more potent. Dodds, *et al.*,[3] report that 0.0002 mg. of hexoestrol produces response in a rat as compared with 0.0003–0.0004 mg. for diethylstilboestrol.

The English workers have succeeded in preparing hexoestrol in several other ways. Catalytic hydrogenation of pseudodiethylstilboestrol (III) gives hexoestrol along with some diethylstilboestrol (I).[1b]



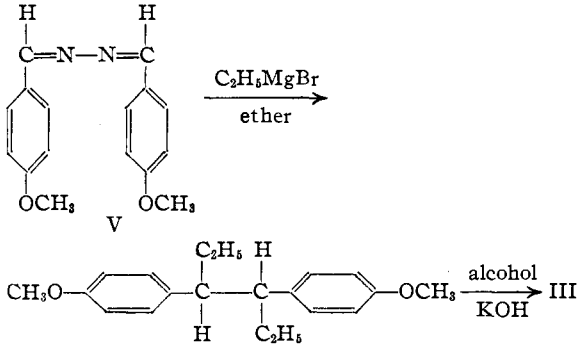
III

Similar hydrogenation of the dimethyl ethers of diethylstilboestrol and pseudodiethylstilboestrol (III), with subsequent demethylation, affords excellent yields of the oestrogen.[1b] Also, hydrogenation with a palladium charcoal catalyst of 4,4′-dihydroxy-γ-δ-diphenyl-β-δ-hexadiene (IV) gives the compound in almost quantitative yield.[1b]

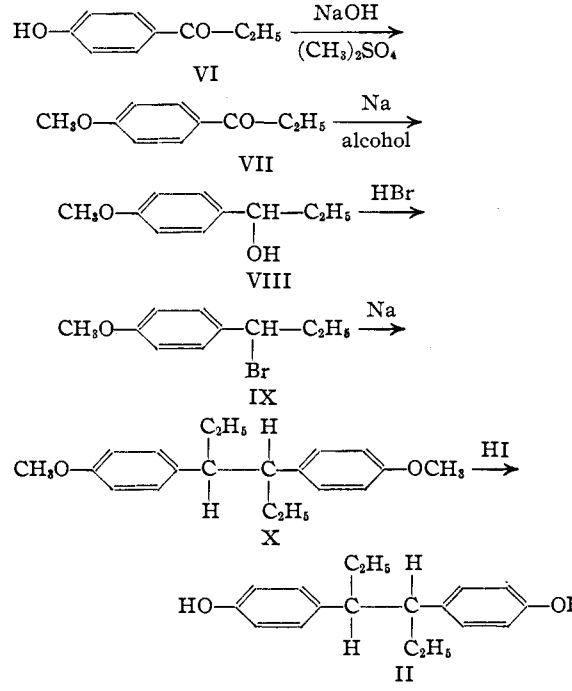


IV

In all these methods, however, the starting materials are more or less expensive and are not obtained in excellent yields. Lastly, hexoestrol may be prepared by the action of ethylmagnesium bromide on anisaldazine (V) with subsequent demethylation.[3]



A study of the various preparative methods for hexoestrol described above indicated that a better synthesis was desirable. In this paper we wish to report certain experiments which have resulted in the development of a new synthesis for hexoestrol. The starting material (*p*-oxypropiophenone (VI)) is inexpensive. It is methylated with dimethyl sulfate to give the methyl ether *p*-methoxypropiophenone (VII) (yield 88%). Reduction of the ketone with sodium and alcohol gives *p*-methoxyphenylethylcarbinol (VIII) (yield 60%). The carbinol is converted into the corresponding bromide (IX) with dry hydrogen bromide at 0°. An ether solution of the bromide (dried with anhydrous sodium sulfate and calcium chloride) is allowed to stand in contact with sodium wire at room temperature. On working up the product the dimethyl ether of hexoestrol (X) is obtained (yield 15% based on the carbinol (VIII)). Demethylation with hydriodic acid gives hexoestrol (II) (m. p. 184–185°, yield 87%). A much lower yield of dimethylhexoestrol is obtained if the corresponding chloride is used in the coupling reaction with sodium.



Experimental Part

Preparation of *p*-Methoxypropiophenone (1′-Oxo-4-methoxy-1-propylbenzene) VII.—A mixture of 57 g. of *p*-oxypropiophenone (VI) and 30 g. of dimethyl sulfate was heated to 80°. A solution of sodium hydroxide was then added until the reaction mixture became alkaline. Maintaining the same temperature, more dimethyl sulfate was added, and in turn more sodium hydroxide until the mixture was again alkaline. This procedure was repeated several times until a total of 92 g. of dimethyl sulfate was used. The alkaline reaction mixture was then refluxed for two hours, and allowed to cool to room temperature. The

reaction mixture, now acid, was made alkaline and taken up in ether. The ether extract was washed with water until neutral, dried with anhydrous sodium sulfate, and evaporated. The yellow liquid residue was distilled under diminished pressure; yield 56 g. (88%), b. p. 151–152 at 19 mm.

Preparation of *p*-Methoxy-phenylethylcarbinol[4] VIII (1'-Oxy-4-methoxy-1-propylbenzene).—Seventy-six grams of *p*-methoxy-propiophenone (VII) was dissolved in 500 cc. of absolute ethyl alcohol. The solution was heated to the reflux point, when 75 g. of sodium, cut in small pieces, was added, all at once, through the top of the condenser (150 cm. long, internal diameter, 3.3 cm.). A vigorous reaction resulted but it subsided rapidly. The reaction mixture was allowed to cool and stand overnight. Four hundred cc. of water was then added and complete solution resulted with the formation of two immiscible layers. The upper layer was yellow and the lower water-white. The ethyl alcohol was removed by distillation and the heterogeneous liquid residue taken up in ether. The ether extract was washed with water until neutral, dried with anhydrous sodium sulfate, and evaporated. The residue was a yellow oil (wt. 76 g.) which was fractionally distilled under diminished pressure in an atmosphere of nitrogen. The fraction boiling at 137–140° (11.5 mm.) was used, $n^{20}D$ 1.5245, yield 46 g. (60%).

Preparation of *p*-Methoxyphenylethylmethyl Bromide (IX) (1'-Bromo-4-methoxy-1-propylbenzene).—Dry hydrogen bromide was passed for four hours into 15 g. of *p*-methoxyphenylethylcarbinol kept at 0° by an ice-bath. The reaction mixture became turbid at first and then gradually assumed a light red color; at this stage it was heterogeneous, consisting of two liquid layers. Ice-cold absolute ether was added, and the resulting ether solution poured into ice-water contained in a separatory funnel. On shaking both layers became water-white. The water layer was extracted twice more with small amounts of cold absolute ether. The combined ether extracts were dried with sodium sulfate and then with anhydrous calcium chloride for ten minutes, and used immediately in the following reaction.[5]

Preparation of Dimethylhexoestrol (X) [3,4-Di-(*p*-methoxyphenyl)-hexane].—The ether solution of the bromide (volume, 200 cc.) previously described, and freed from calcium chloride, was added to 15 g. of sodium wire. A slight evolution of gas resulted, but subsided quickly. The reaction mixture was allowed to stand for forty-five hours. Within four and one-half hours of the start of the reaction an appreciable amount of blue solid was formed. Throughout the course of the reaction the surface of the sodium wire was kept "fresh" by frequent stirring. After the reaction has gone twenty-one hours a small amount of fresh sodium wire was added. At the end of the reaction time a considerable amount of blue solid was formed.

The ether solution was decanted, the residual sodium was destroyed with alcohol and then water was added. The resulting solution was extracted with ether which was then added to the main ether fraction. The combined ether extracts were washed until neutral, and dried with anhydrous sodium sulfate. The ether solution possessed a yellow color.

Evaporation of the ether leaves a sweet smelling yellow-brown oil (wt. 13 g.) which partially solidified on cooling. It was steam distilled to remove volatile impurities (anethole, etc.), and was then taken up in ether. The ether extract had a yellow color which persisted after treatment with animal charcoal. The ether solution was dried with anhydrous sodium sulfate and evaporated. The residue (wt. 10 g.) was a yellow-brown oil which crystallized partially on cooling. After cooling in the icebox it was filtered, and the crystals so obtained washed with cold methyl alcohol: wt. 2.6 g., m. p. 124° unsharply. Evaporation of the methyl alcohol from the mother liquor left a halogen-free yellow-brown, fairly viscous oil (wt. 7.5 g.). The nature of this material is being investigated. The crystals described above were dissolved in acetone and methyl alcohol and the solution concentrated until crystallization took place. After two such recrystallizations 1.9 g. of brittle plates was obtained; m. p. 142–143.5° (uncor.). From the mother liquors were obtained 0.1 g. more of the same material; yield 2.0 g., 15% (based on carbinol).

Preparation of Hexoestrol (II) [3,4-Di-(*p*-oxyphenyl)-hexane].—A mixture of 500 mg. of dimethylhexoestrol, 2 cc. of glacial acetic acid, and 10 cc. of hydriodic acid (sp. gr. 1.7) was heated at 135–140° for two hours. Water was then added and the product worked up in ether. The ether extract had a yellow color which could be removed with sulfurous acid. The extract was dried with anhydrous sodium sulfate and evaporated, leaving 0.4 g. of the product, m. p. 178–180°. Recrystallization from benzene gave needles, m. p. 184–185°; yield 0.39 g., 87%.

We wish to take this opportunity to express our thanks to Merck & Company, Inc., Rahway, N. J., for a grant-in-aid for this work.

Summary

A new method for the preparation of hexoestrol m. p. 185° has been described.

PRINCETON, N. J. RECEIVED AUGUST 1, 1940

(4) See A. Klages, *Ber.*, **35**, 2262 (1902); A. Klages and P. Allendorf, *ibid.*, **31**, 998 (1898).

(5) In the above preparation, it is necessary to work up the product as rapidly as possible and to use ice-cold solvents, since the bromide is not very stable.